Functionalized Organolithium Compounds: New Synthetic Adventures

Carmen Nájera* and Miguel Yus*

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

Abstract: This review covers literature on non-stabilized functionalized organolithium compounds since 1997. In this overview, we consider intermediates with different separation between the functional group and the carbon-lithium bond (d^n-reagents) and having different hybridization at the carbanionic centre. Special emphasis is given to the synthetic applications of these intermediates in order to prepare polyfunctionalized molecules.

1. GENERAL INTRODUCTION

The use of carbanions as intermediates is a milestone in synthetic organic chemistry. Organometallic compounds are used for the formation of all kind of hybridized carbon-carbon bonds. The more polar organolithium compounds provide excellent electrophilic reactivity and are probably the most popular organometallics in contemporary organic chemistry [1]. Functionalized organolithium compounds are specially useful in order to transfer a functionality in only a synthetic operation [2]. However, obviously the functional group has to be compatible with the carbon-lithium bond. For this reason, the functionality should be protected and the organolithium reagent has to be prepared at low temperatures and in many cases in the presence of the electrophile (Barbier-type conditions) [3]. The preparation of organolithium compounds is based on (a) deprotonation with lithiated bases [4], (b) halogen-lithium exchange, (c) transmetallation reactions, mainly tin-lithium exchange, (d) carbon-heteroatom bond cleavage, and (e) carbolithiations [5].

The stability of functionalized organolithium compounds depends on the location and the nature of the functionality (or the heteroatom), the hybridization of the carbon bonded to the metal and their aggregation.

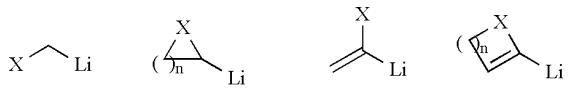
This review article deals comprehensively with the literature published from 1997, and it is the third part of our previous revisions [2a,b]. Stabilized organolithium compounds by electron-withdrawing groups or by heteroatoms such as sulfur, selenium, phosphorous, or silicon, as well as acyllithium or functionalized aryllithium compounds will be not consider.

This revision is ordered considering both, the relative position of the heteroatom (or the functional group) respect to the carbanionic centre and its hybridization.

*Address correspondence to this author at the Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain; Tel: (+34) 965 903548; Fax: (+34) 965 903549; E-mail: cnjera@ua.es; yus@ua.es

2. α−FUNCTIONALIZED ORGANOLITHIUM COMPOUNDS

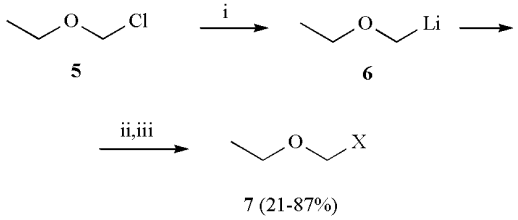
This type of non-stabilized reagents can bear oxygenated or nitrogenated functionalities at the α-position, either with sp^3 or sp^2 hybridization, mainly in acyclic (**1** and **3**) or cyclic systems (**2** and **4**).



1 **2** **3** **4**

2.1. sp^3-Hybridized α-Oxygenated Organolithium Compounds

Functionalized alkyllithiums **1** bearing an oxygen at the α-position can be generated by chlorine-lithium or tin-lithium exchange, as well as by α-deprotonation in the case of activated allylic or benzylic systems. Intermediate **6**, derived from chloromethyl ethyl ether **5,** was prepared by means of lithium powder and either di-*tert*-butylbiphenyl (DTBB; 5 mol%) [7], or naphthalene- (P_N) as well as biphenyl-supported (P_B) polymers [8], working either in a two-step process or under Barbier-type reaction conditions (Scheme 1).



5 **6** **7** (21-87%)

Scheme 1. *Reagents*: i, Li, DTBB (5 mol%), –90ºC; ii, E = RCHO, R_2CO, CO_2, PhCN, $PhCONMe_2$, CyNCO, PhN=CHPh; iii, H_2O.

Chiral lithiomethyl ethers **8-9** bearing the menthol unit were also prepared by chlorine-lithium exchange from the corresponding chloromethyl menthyl ethers. The metallation can be carried out with lithium powder and DTBB (5 mol%) in THF at 0ºC in the presence of carbonyl compounds, imines, DMF and Me_3SiCl as electrophiles. For the two-step process, the lithiation has to be carried out at –90ºC, followed by addition of the corresponding electrophile at the

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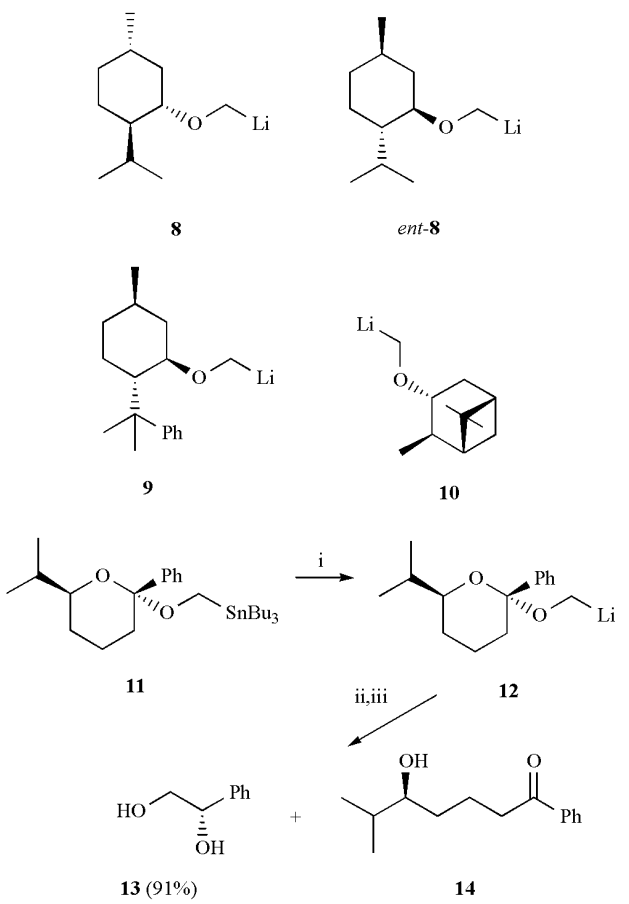
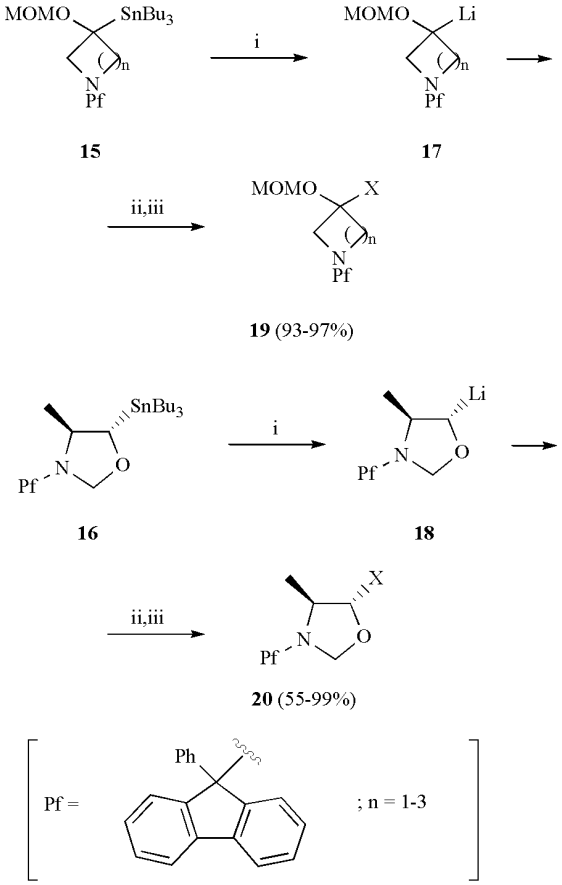
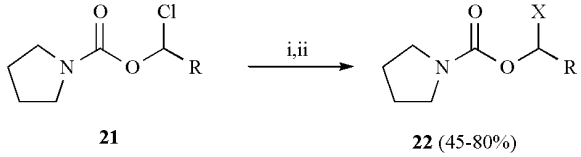


Scheme 2. *Reagents*: i, BuLi (2 equiv), 30% THF/Et_2O, –78ºC; ii, PhCHO; iii, CSA, MeOH, rt.



Scheme 3. *Reagents*: i, BuLi, THF, –78ºC; ii, E = MeOD, D_2O, RCHO, Me_2CO, DMF, MeI; iii, H_2O.



Scheme 4. *Reagents*: i, Li, DTBB (2.5 mol%), E = RCHO, R^1R^2CHO, Me_3SiCl, THF, –78ºC; ii, H_2O.

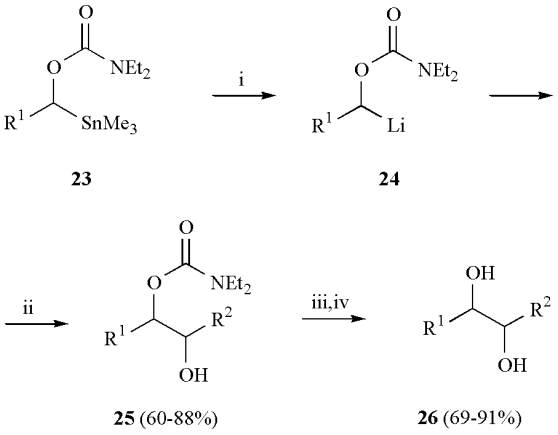
same temperature. When prochiral electrophiles are used, low asymmetric induction was obtained (up to 1:2) [9]. Intermediates *ent*-**8**, **9** and **10** were also prepared by tin-lithium exchange and gave similar level of asymmetric induction [10].

A chiral derivative of tributylstannylmethanol **11**, prepared from L-valine, provided after tin-lithium exchange a α-alkoxy organolithium compound **12** (Scheme 2). This chiral alkoxymethyl carbanion added to benzaldehyde with up to 91:9 diastereomeric ratio, depending on the solvent and the alkyllithium used for the transmetallation. Better results were obtained with 30% THF in ether providing the diol **13** in 91% yield and 88:12 er. Final hydrolysis of the adducts allowed the synthesis of 1,2-diols **13** and the recovery of the chiral auxiliary **14** [11].

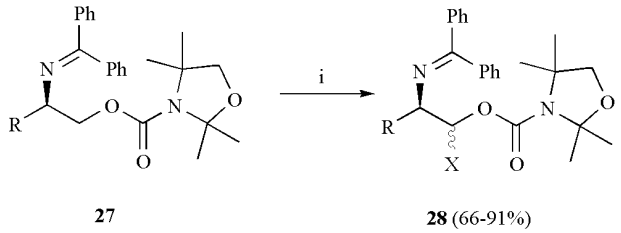
Cyclic α-alkoxy-β-aminoalkyllithium compounds **17** and **18** were prepared from the corresponding stannanes **15** and **16**, respectively, at –78ºC (Scheme 3). The stability of these organolithium compounds bearing a β-leaving group can be predicted by using the principle of microscopic reversibility along with Baldwin's rules, since their β-elimination decomposition is the reverse of n-*endo*-trig cyclization. The stability of intermediates **17** decreased with increasing ring size (up to n = 3). Oxazolidines **16** afforded after transmetallation and reaction with different electrophiles clean reactions to yield products **20** with retention of the configuration and with 2.6:1 dr in the case of benzaldehyde [12].

O-Chloroalkyl carbamates **21** were transformed into the corresponding dipole-stabilized lithiated species by DTBB-catalyzed lithiation under Barbier-type conditions at –78ºC and trapped with electrophiles (Scheme 4) [13]. However, attempts to carry out the stepwise lithiation failed or gave very low yields. After reduction with DIBALH or hydrolysis with LiOH, the corresponding diols can be obtained.

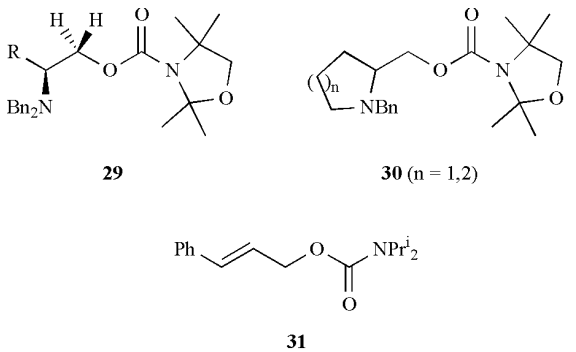
In the case of α-hydroxyalkyltrimethylstannanes, the tin-lithium transmetallation occurred when a carbamate is used as protecting group [14]. Surprisingly MOM-protected derivatives did not suffer transmetallation as in the case of α-hydroxyalkylstannanes [15]. Best results were obtained using *s*-BuLi at –95ºC to give intermediates **24**, which reacted with



Scheme 5. *Reagents*: i, *s*-BuLi, THF, –95ºC; ii, R^2CHO; iii, AlH_3, THF, rt; iv, H_2O

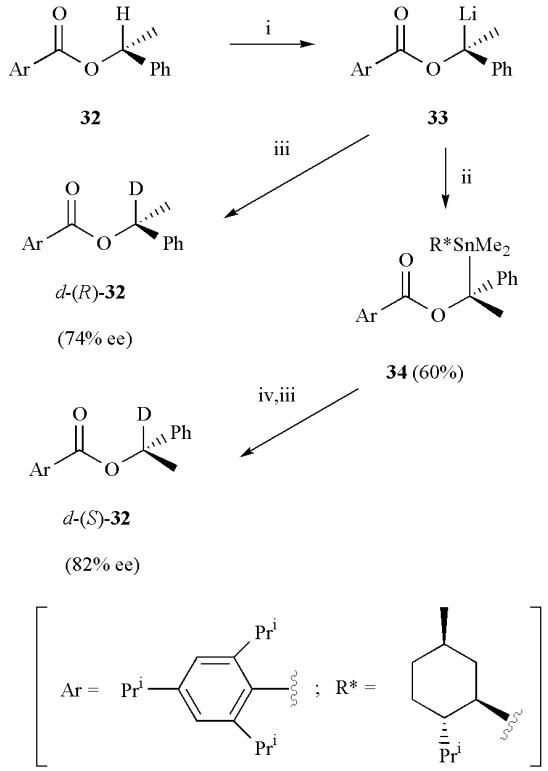


Scheme 6. *Reagents*: i, *s*-BuLi, TMEDA, Et_2O, –78ºC, E = Me_3SiCl, Me_3SnCl, R^1I.



aldehydes with good yields (Scheme 5). These adducts could be transformed into diols by AlH_3 reduction at room temperature [14].

Direct deprotonation of carbamates derived from β-aminoalcohols **27** by means of *s*-BuLi in the presence of TMEDA in ether at –78ºC afforded, after trapping with electrophiles, *anti/syn* mixtures of products **28** in *ca*. 3:1 ratio (Scheme 6) [16]. Deprotection with trifluoroacetic acid yielded the corresponding chain elongated β-aminoalcohols. Related 2-aminoalkyl carbamates **29** can be diastereoselectivity deprotonated in the presence of (–)-sparteine [17] at the pro-*S*-hydrogen, and with low selectivity in the case of TMEDA [18]. The lithio derivatives of carbamates **29** were used in the synthesis of 1,4-diamino-2,3-



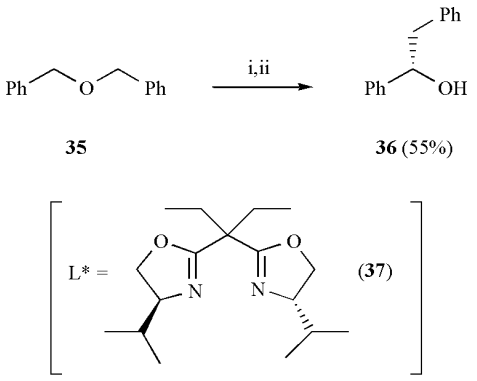
Scheme 7. *Reagents*: i, *s*-BuLi, PhMe/Et_2O, –78ºC; ii, Me_2R^*SnBr; iii, MeOD; iv, BuLi, TMEDA, hexane, –78ºC.

diols, which are the core unit of anti-HIV-1 protease agents by addition to α-aminoaldehydes or by dimerization with CuCl [19].

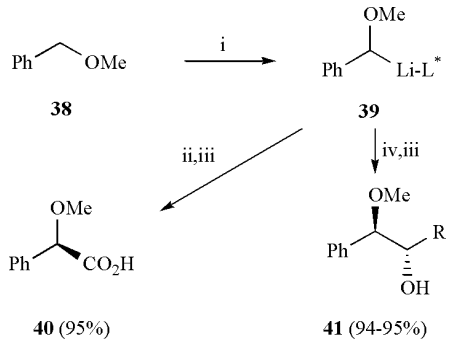
(*S*)-*N*-Benzylprolinol and *rac*-*N*-benzylpiperidine-2-methanol derived carbamates **30** were diastereoselectively lithiated in the presence of TMEDA or (–)-sparteine. An efficient kinetic resolution was observed by means of *s*-BuLi and (–)-sparteine in the case of **30** (n = 2) by abstraction of the *pro-S* hydrogen and further reaction with electrophiles. Enantioenriched (–)-(*S*)-**30** (n = 2) remains unchanged under the same conditions [20]. The stability of anions derived from all of these β-aminoalcohol carbamates is not related to the cyclic intermediates **17** and **18** [12] and may arise from their dipole-stabilized nature [21].

The allylic carbanion derived from (*E*)-cinnamyl alcohol carbamates **31** is configurationally unstable and equilibrates at temperatures below –50ºC. Carboxylation, acylation with acyl chlorides, stannylation, and silylation took place at the α-position with stereoinversion (79-86% ee) in the presence of (–)-sparteine [22a]. Related allylic anion derived from 9-chloro-5-aza-2,7-nonadienol carbamate was used in the asymmetric synthesis of 3,4-divinylpyrrolidine [22b].

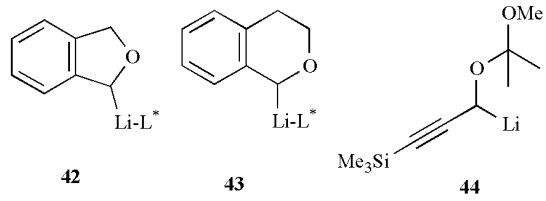
Benzyllithium compounds bearing an oxygenated substituent at the α-position were prepared by deprotonation and were configurationally stable. However, depending on the electrophile, inversion (RHal, MeOCOCl, CO_2, CS_2, RCN, RCOCl, Pr^iNCO) or retention [MeOH, AcOH, $(MeO)_2CO$, esters, anhydrides] was observed [23].



Scheme 8. *Reagents*: i, *t*-BuLi, Et_2O, L^*, –78ºC; ii, NH_4Cl.



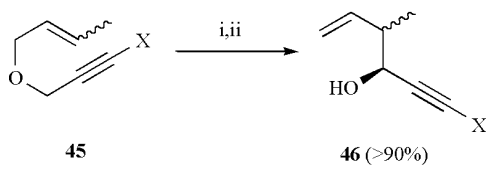
Scheme 9. *Reagents*: i, *t*-BuLi, Et_2O, **37**, –78ºC; ii, CO_2; iii, H_2O; iv, RCHO.



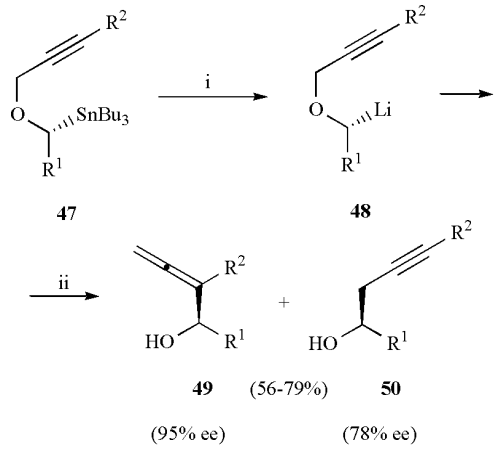
Inversion of the configuration during the stannylation of configurationally stable tertiary benzyllithium **33** was proven by X-ray diffraction analysis for compound **34** (Scheme 7). Lithio-destannylation and deuteration with MeOD of compound **34** gave deuterated (*S*)-**32** [24].

α-Alkoxybenzyllithium compounds suffered [1,2]-Wittig rearrangement to give the corresponding alcoholates [25]. The first enantioselective [1,2]-Wittig rearrangement was achieved by asymmetric lithiation of different benzyl ethers with *t*-BuLi in ether at –78ºC in the presence of (*S*,*S*)-bis(dihydroxoxazol) **37** as external chiral ligand [26]. Thus, in the case of dibenzyl ether **35**, the alcohol **36** was obtained in 55% yield and 60% ee (Scheme 8).

The intermediate organolithium **39** derived from benzyl methyl ether **38**, generated under the same reaction conditions as for compound **35**, was trapped with different electrophiles such as CO_2 [27] and aldehydes [28a] to afford α-methoxyphenylacetic acid and 1,2-diol monomethyl ethers, respectively, with good enantio- (up to 99%) and diastereoselectivity (up to 90% *anti*) (Scheme 9). The origin of the enantioselectivity was explained by a dynamic thermodynamic resolution mechanism. The same



Scheme 10. *Reagents*: i, *t*-BuLi, **37**, hexane, –78ºC; ii, H_2O.



Scheme 11. *Reagents*: i, BuLi, THF, –78ºC; ii, H_2O.

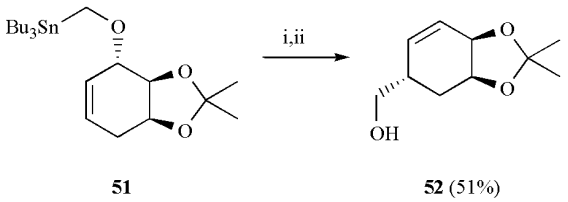
methodology was applied to isochroman and phthalan to give after lithiation α-substituted derivatives **42** and **43**, and finally the corresponding substitution products in 75-94% yield and 62-97% ee [28b]. The asymmetric induction is proved to occur at the postlithiation step, the epimerization being slower than the S_E reaction. The difference in rate depends upon the reactivity of the electrophile used. This protocol was applied to the asymmetric synthesis of U-10137, a selective dopamine D_4 antagonist.

The α-lithiated propargyl alcohol **44** was prepared by deprotonation with BuLi in THF at –78ºC and trapped with carbonyl compounds [29]. This reagent was used in the synthesis of a cyclic dienediyne related to the maduropeptin chromophore [29a] and of fused bicyclic [4.4.0] and [5.4.0] systems [29b].

α-(Allyloxy)alkyllithium compounds suffer [2,3]-Wittig rearrangement to give stereoselectively homoallylic alcohols [25a,c]. The use of the chiral bisoxazolidine **37** as external chiral ligand in asymmetric lithiation reactions was initially studied in the case of (*Z*)- and (*E*)-crotyl benzyl or propargyl ethers. High enantioselectivity (up to 89% ee) and diastereoselectivity were obtained with the propargyl derivatives **45** (Scheme 10) [30].

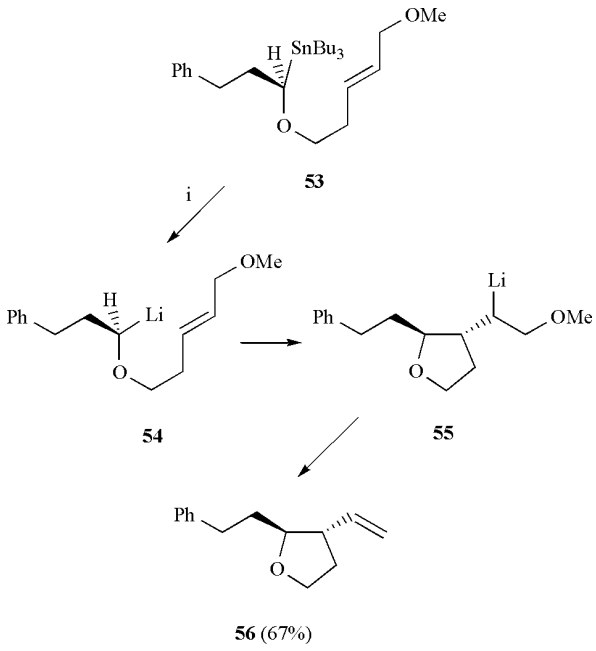
The rearrangement shown in Scheme 10 was also studied with enantiomerically enriched α-propargyloxy stannanes **47**, which lithiation showed to proceed with complete inversion of configuration (Scheme 11). The periselectivity [2,3] *versus* [1,2] of the rearrangement depends upon the nature of the substituents on the acetylenic moiety [31].

An application of this [2,3]-Wittig rearrangement was the synthesis of a *pseudo*-sugar with the hydroxymethyl group at C-5 [32]. The homoallylic alcohol **52** was obtained by tin-



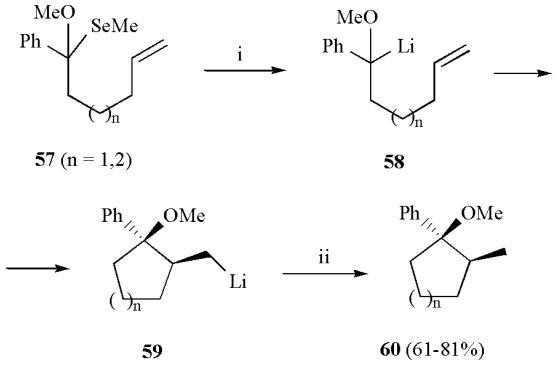
51 **52** (51%)

Scheme 12. *Reagents*: i, BuLi, THF, –78 to –60ºC; ii, H_2O.



53 **54** **55** **56** (67%)

Scheme 13. *Reagents*: i, BuLi, THF, –78 to 0ºC.



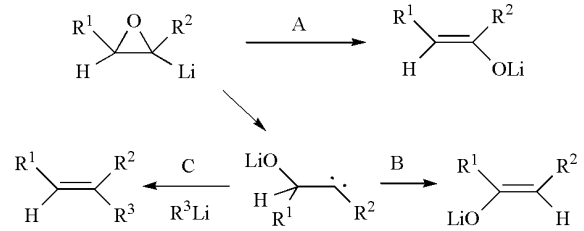
57 (n = 1,2) **58** **59** **60** (61-81%)

Scheme 14. *Reagents*: i, *t*-BuLi, THF, –78ºC; ii, MeOH.

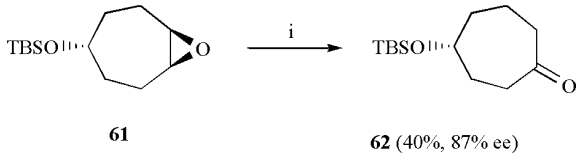
lithium transmetallation from the stannane **51** with BuLi through a *syn* mode and in moderated yield (Scheme 12).

α-(Homoallyloxy)alkyllithium **54**, prepared from compound **53** also by tin-lithium transmetallation with retention of the configuration, cyclized to compound **55** [33] by a 5-*exo* mode, also with retention, to give mainly the *trans*-disubstituted tetrahydrofuran **56**, after final β-elimination of the corresponding β-methoxy alkyllithium **55** (Scheme 13) [34].

ω-Alkenyl-α-methoxybenzyllithium derivatives **58**, prepared by selenium-lithium exchange, gave 5-*exo-trig* or 6-*exo-trig* cyclizations to give the corresponding cyclo-

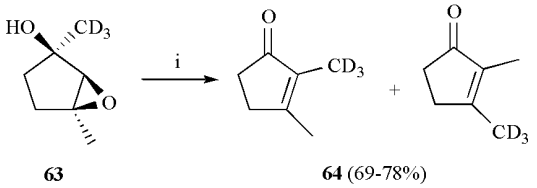


Scheme 15.



61 **62** (40%, 87% ee)

Scheme 16. *Reagents*: i, *i*-PrLi (2.4 equiv), Et_2O, (–)-sparteine, –98ºC to rt.



63 **64** (69-78%)

Scheme 17. *Reagents*: i, BuLi (2 equiv), rt.

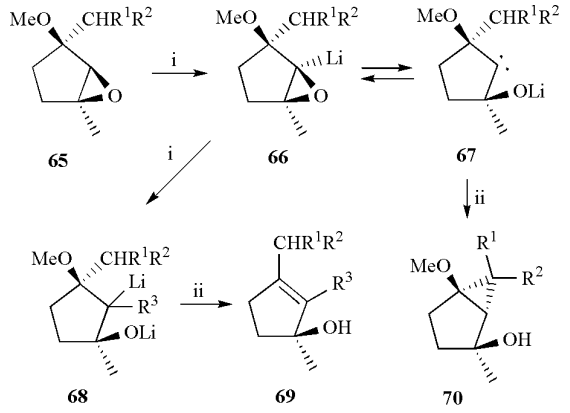
pentane or cyclohexane systems, respectively, with complete stereocontrol (Scheme 14) [35].

Oxiranyl anions **2** (X = O, n = 1) behave mainly as carbenoid species, only stabilized carbanions being able to be trapped by electrophiles. They can undergo β-elimination to give enolates (A), α-ring opening followed by a hydride 1,2-shift to afford a ketone enolate (B), or reductive alkylation by reaction with an organolithium reagent with concomitant lithium oxide elimination to provide alkenes (C) (Scheme 15) [36].

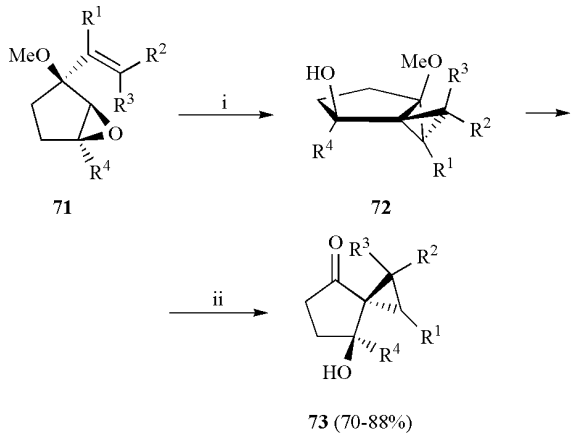
These oxiranyllithiums were usually generated by deprotonation with an alkyllithium reagent. Examples of a α-ring opening mechanism were described in the case of the enantioselective deprotonation of achiral epoxides (i.e. **61**) with chiral ligands, such as (–)-sparteine, (–)-α-isosparteine and bisoxazolines [37] and was applied to the synthesis of a ketone precursor **62** used in the synthesis of (S)-physoperuvine [37b] (Scheme 16). Competitive transannular reactions [38] and reductive alkylation [39] were also found to take place.

The reductive alkylation of epoxides, initially described by Crandall and Liu [40], was recently studied by Mioskowski et al. [36b]. They found that cis- and trans-epoxides were transformed into cis- and trans-alkenes when treated with an excess of organolithium reagents. However, when cyclic *syn*-β-hydroxy epoxides (*i.e.* **63**) were treated with BuLi, a 1,2-shift occurred to give a mixture of cycloalkenones (**64**) [41], depending on the reaction conditions (Scheme 17).

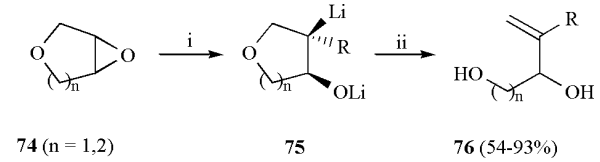
In the case of cyclic β-alkoxy epoxides, such as compounds **65**, the insertion of the organolithium reagent followed by alkoxide elimination was predominant to give



Scheme 18. *Reagents*: i, R^3Li (2 equiv), rt; ii, H_2O.



Scheme 19. *Reagents*: i, PhLi (2 equiv), cyclohexane/Et_2O, rt; ii, H_2O.



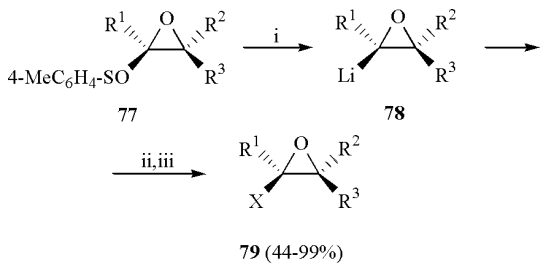
Scheme 20. *Reagents*: i, RLi (2.5 equiv); ii, MeOH.

allylic alcohols **69** through intermediates **66** and **68**. In some instances, insertion of the carbenoid **67** into an adjacent carbon-hydrogen bond took place to give cyclopropanes **70**, depending on the reaction conditions [42] (Scheme 18).

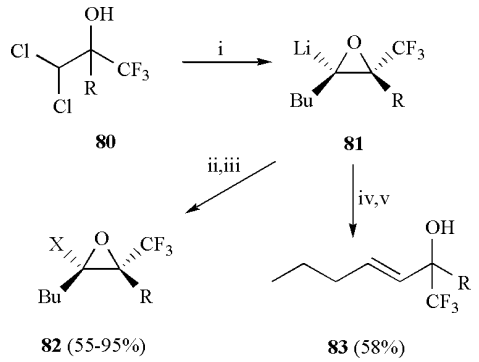
The intermediate carbenoid of the type **67** can be trapped in an intramolecular fashion when a vinyl substituent is at the β-position (*i.e.* **71**) to give tricyclo[4.1.0.0^{1,5}]heptane intermediates **72**, which after hydrolysis led to formation of spirocyclopropanes **73** [43] (Scheme 19).

Dihydrofuran and dihydropyran epoxides **74** underwent alkylative addition followed by β-elimination to give intermediate β-alkoxy organolithium compounds **75**, which after final β-elimination afforded alkenediols **76** [44] (Scheme 20).

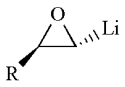
Non-stabilized oxiranyl anions substituted by an alkyl group at the α-position (*i.e.* **78**) were generated by desulfinylation of the corresponding precursors **77** with *t*-



Scheme 21. *Reagents*: i, *t*-BuLi (2 equiv), THF, –100ºC; ii, E = MeOH, CD_3OD, RCHO, R_2CO, RCOCl, Me_3SiCl; iii, H_2O.



Scheme 22. *Reagents*: i, BuLi (3 equiv), THF, –98ºC; ii, E = MeOH, Me_3SiCl, RCHO, RI; iii, MeOH; iv, –78ºC to rt (R = $PhCH_2CH_2$); v, H_2O.



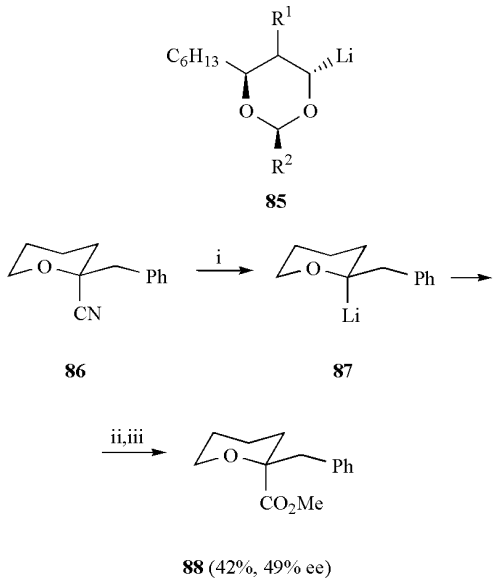
84

BuLi at –100ºC and were trapped stereospecifically with several electrophiles to give the expected products **79** in good yields [45] (Scheme 21). This methodology was applied to the asymmetric synthesis of epoxides and alcohols.

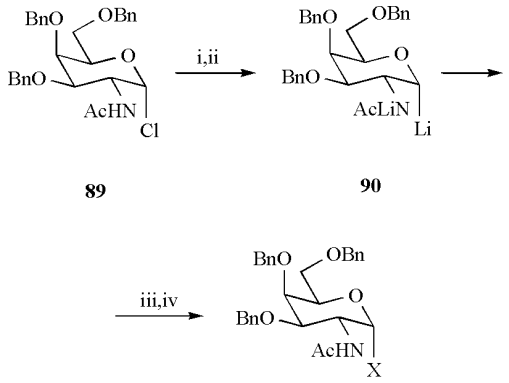
2-Lithio-3-(trifluoromethyl)oxiranes **81** can be prepared stereoselectively from dichlorohydrins **80** by reaction with BuLi at –98ºC and were trapped with electrophiles to give compounds **82**, or transformed into allylic alcohols **83** at room temperature by α-elimination followed by carbon-hydrogen insertion [46] (Scheme 22).

Direct lithiation at the less substituted position of terminal epoxides with *s*-BuLi in the presence of diamines at –90ºC and reaction with trimethylchlorosilane as electrophile was recently achieved, when the silylation agent is present during the generation of the oxiranyl anion **84**, affording epoxysilanes in 61-74% yield [47].

4-Lithio-1,3-dioxanes are cyclic compounds of the type **2**, which are useful 1,3-diol precursors because the kinetically preferred axial alkyllithium intermediates can be equilibrated to the corresponding equatorial ones [48]. Reductive lithiation of 4-(phenylsulfanyl)-1,3-dioxanes with LiDTBB in THF at –78ºC gave initially an axial radical, which is more stable than the equatorial one and a rapid



Scheme 23. *Reagents*: i, LiDTBB, THF, –78ºC; ii, CO_2; iii, CH_2N_2.

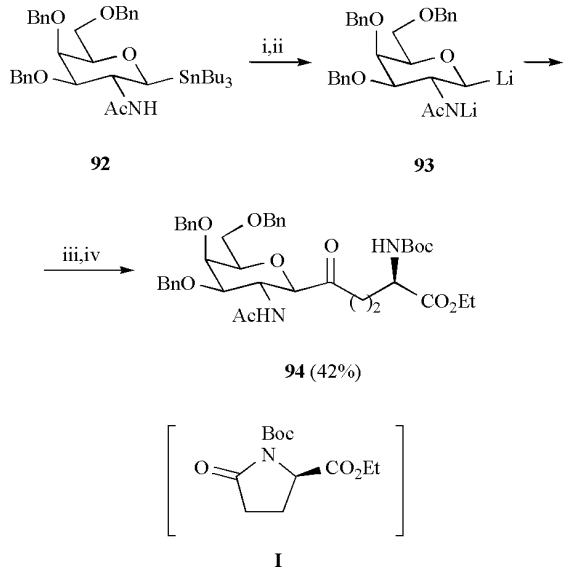


Scheme 24. *Reagents*: i, BuLi, THF, –90ºC; ii, $LiC_{10}H_8$ (2.2 equiv), –90ºC; iii, E = MeOD, RCHO, CO_2; iv, NH_4Cl-H_2O.

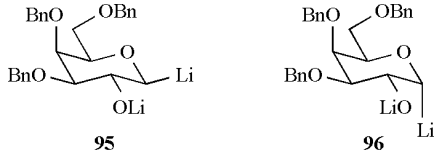
reductive lithiation generated axial alkyllithium reagents **85** [49]. Copper and zinc salts allowed alkylation, acylation and Michael additions in better yields (38-85%) than the corresponding organolithium compounds.

In the reductive decyanation of the tetrahydropyran **86** with LiDTBB, a configurational memory effect was observed up to 49% ee, in the case of the ester **88** [50] (Scheme 23).

The anomeric position of sugars was transformed stereoselectively into the corresponding organolithium compound by chlorine-lithium exchange [51] or by tin-lithium transmetallation [52]. Glycosyl dianion **90** derived from the galactopyranose **89** requires deprotonation of the amide moiety followed by reaction with lithium naphthalenide at –90ºC [51b] (Scheme 24). This dianion reacted with deuterated methanol, aldehydes and CO_2 to provide galactosamine α-*C*-glycosides.



Scheme 25. *Reagents*: i, MeLi, THF, –78ºC; ii, BuLi, –65ºC; iii, lactam **I**; iv, NH_4Cl-H_2O.



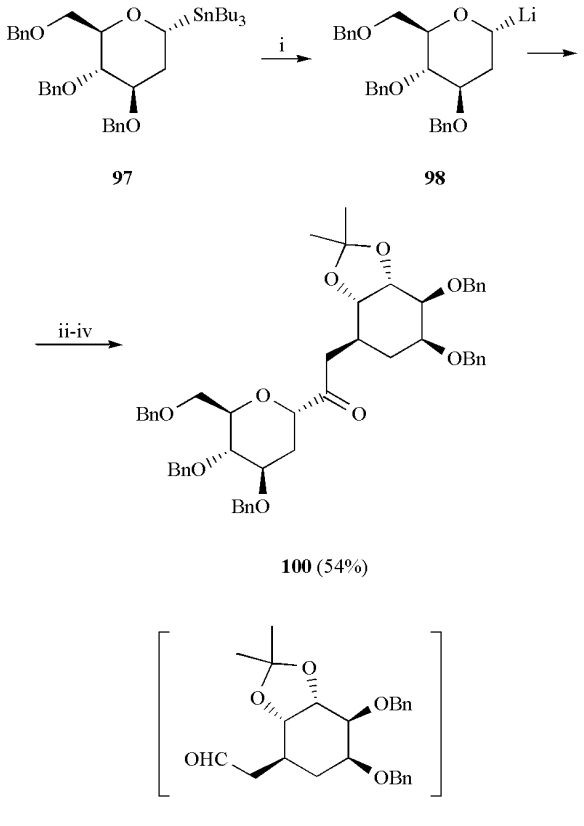
The β-configurated glycosyl dianions **93** can be prepared via deprotonation with methyllithium at –78ºC followed by transmetallation with butyllithium at –65ºC in THF [52]. This methodology was applied to the synthesis of *N*-glucoasparagine [52b], a *C*-glycosylated peptoid building block [52c] by using aldehydes as electrophiles. *C*-Glycosylated amino acids were prepared when lactams are used as electrophiles [52d] (Scheme 25).

β-*C*-Galactosides were prepared by tin-lithium exchange using BuLi in THF at –78 to –55ºC to give intermediates **95**, followed by reaction with deuterated methanol or aldehydes in 55-83% yield. The corresponding α-*C*-galactosides were prepared by reaction of the dianion **96** with these electrophiles. In this case, the glycosyl dianion **96** was prepared either by chlorine-lithium exchange or tin-lithium transmetallation. However, under the last conditions, the reaction with electrophiles gave α-*C*-galactosides in higher yields [53].

For the stereocontrolled synthesis of carba-*C*-disaccharides a 2-deoxyglucosyllithium **98**, generated from the corresponding tin intermediate **97** [54], reacted with the aldehyde **99** to provide aldols, which were oxidized to the ketone **100** [55] (Scheme 26).

2-Deoxy-D-ribofuranosyllithium was prepared by tellurium-lithium exchange with BuLi. It reacted with benzaldehyde to give the corresponding coupling product in moderate yield (52%) [56].

The vinylogous urethane lactone **101** was deprotonated at the α-position with *t*-BuLi at –78ºC and reacted with alkyl halides, aldehydes, and acid chlorides in good yields. Further



Scheme 26. *Reagents*: i, BuLi, THF, –78ºC; ii, **99**; iii, NH_4Cl-H_2O; iv, PDC.

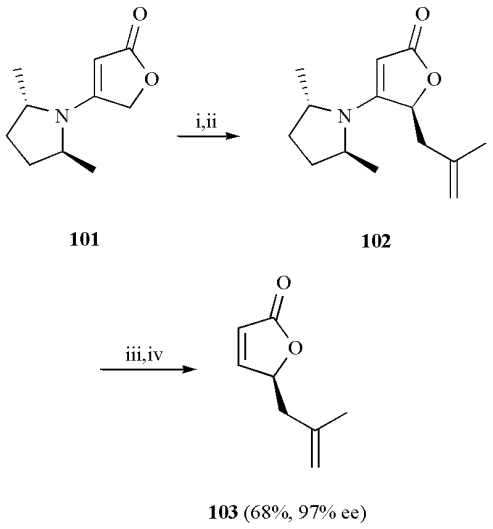
reduction of the double bond (*i.e.* in **102**) and Cope elimination provided enantiomerically pure γ-substituted butenolides (*i.e.* **103**) (Scheme 27). This γ-enolate was used in the synthesis of different fragments of okadaic acid [57].

In the enantioselective construction of A/C seco-B and A/B seco-C pro-taxol systems, the lithiolactone **104** was prepared by tin-lithium transmetallation at –90ºC [58]. On the other hand, phthalide anions **105** were prepared by deprotonation with LDA in THF at –78ºC and reacted with benzyl bromides in moderate yields [59].

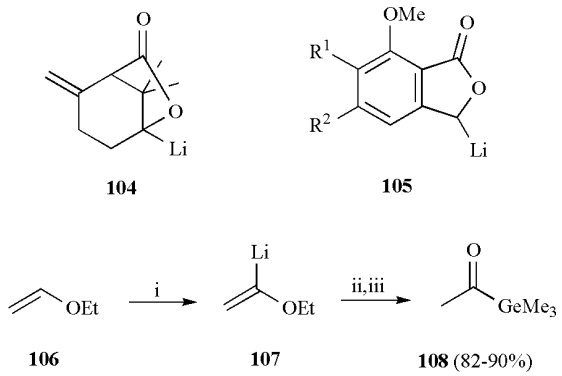
2.2. sp^2-Hybridized α-Oxygenated Organolithium Compounds

The generation and reactivity of α-metallated vinyl ethers were already reviewed for the period 1951-1996 [60]. These reagents **3** and the related cyclic ones **4** were used in organic synthesis as acyl anion equivalents [61]. They were prepared in general by deprotonation taking advantage of the kinetic acidity of the vinyl hydrogen at the β-position, compared to the β-one.

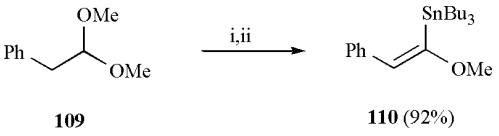
Simple vinyl ethers **3**, X = OMe [62] and X = OEt, as well as other systems with X = OMOM, OTHP, $OCHMeOEt$, $OCH{=}CH_2$, OPh, $OCOR$, $OSiR_3$ were prepared mainly by deprotonation with *t*-BuLi at very low temperatures and reacted with a variety of electrophiles. The use of chlorotrimethylgermane as electrophile in the case of



Scheme 27. *Reagents*: i, *t*-BuLi, THF, –78ºC; ii, $CH_2{=}CMeCH_2Br$; iii, $NaCNBH_3$, AcOH; iv, MCPBA.



Scheme 28. *Reagents*: i, *t*-BuLi, THF, –110ºC; ii, Me_3GeCl, –78ºC; iii, 3 M HCl.

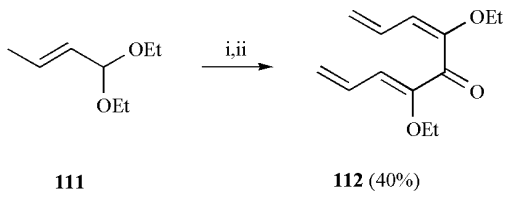


Scheme 29. *Reagents*: i, BuLi, KO-*t*-Bu, THF, –95ºC; ii, $ClSnBu_3$

1-ethoxyvinyllithium **107** (prepared from **106**) provided, after hydrolysis, the acylgermanane **108** [63] (Scheme 28).

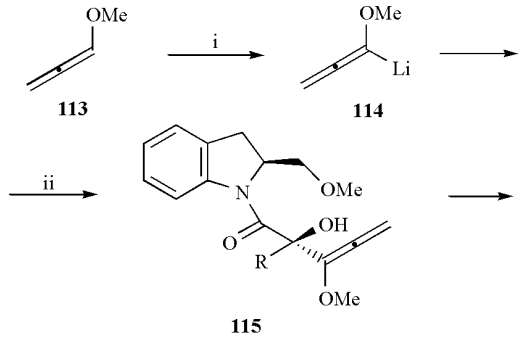
In the case of lithiated β-phenyl enol ethers, mixed superbase, BuLi and potassium *t*-butoxide (LIC-KOR) was used to promote β-elimination of methanol from the acetal **109** followed by α-deprotonation. Final reaction with chlorotributyltin allowed the synthesis of (*Z*)-methoxyvinylstannane **110**, suitable for Stille cross-coupling reactions [64] (Scheme 29).

The same strategy used in Scheme 29 was used with α,β-unsaturated aldehydes diethyl acetals **111** to give α-metallated α-ethoxy-1,3-dienes [64,65] in order to prepare dienyltin compounds [64]. In the case of using diethyl

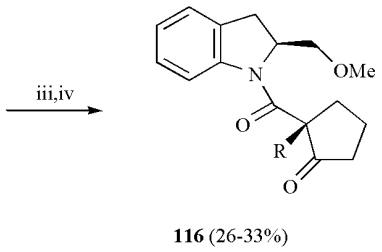


111 **112** (40%)

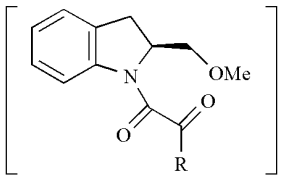
Scheme 30. *Reagents*: i, BuLi, *t*-BuOK, THF, –90ºC; ii, $(EtO)_2CO$.



113 **114** **115**



116 (26-33%)



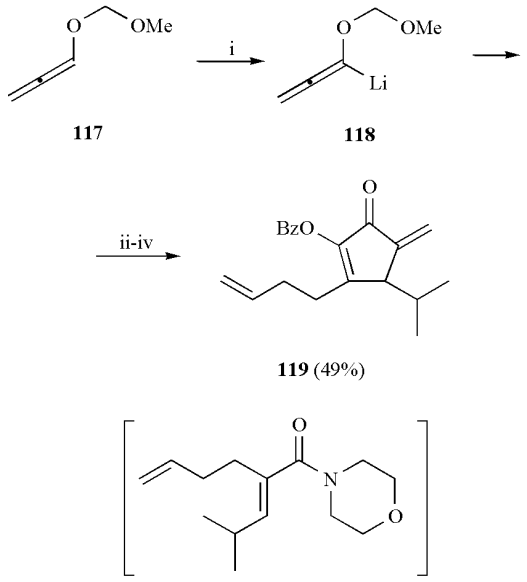
II

Scheme 31. *Reagents*: i, BuLi, THF, –78ºC; ii, **II**; iii, *t*-BuLi; iv, 5% HCl.

carbonate as electrophile, the corresponding ketone **112** was obtained [65b] (Scheme 30).

1,1-Dialkylbuta-1,3-dienes were prepared by reaction of α-metallated 1-ethoxybuta-1,3-diene with trialkyl boranes followed by palladium-catalyzed coupling with iodobenzene [65c]. The same anion was added to (*E*)-2,2,5-trimethylhexa-3,5-dienal and the corresponding adduct transformed into a *trans*-fused tetrahydroindanone ring system [65d].

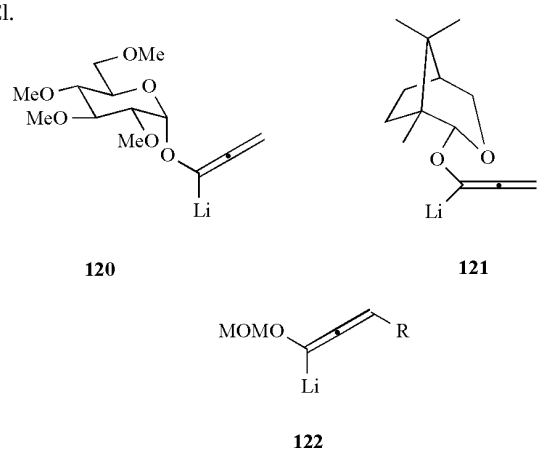
The lithiation of 1-methoxyallene **113** occurred in ether or THF with BuLi at –30 to –40ºC and the resulting anion **114** is stable at –30ºC for several days. Spectroscopic data and *ab initio* model calculations suggested a non-classical 1,3-bridged structure for this anion. It reacted with different electrophiles under kinetically controlled conditions at the α-position [60]. A recent stereoselective addition to chiral α-keto amides derived from (*S*)-indoline-2-carboxylic acid allowed the synthesis of the corresponding dihydrofuranones



117 **118** **119** (49%)

III

Scheme 32. *Reagents*: i, BuLi, THF, –78ºC; ii, **III**; iii, AcOH; iv, BzCl.

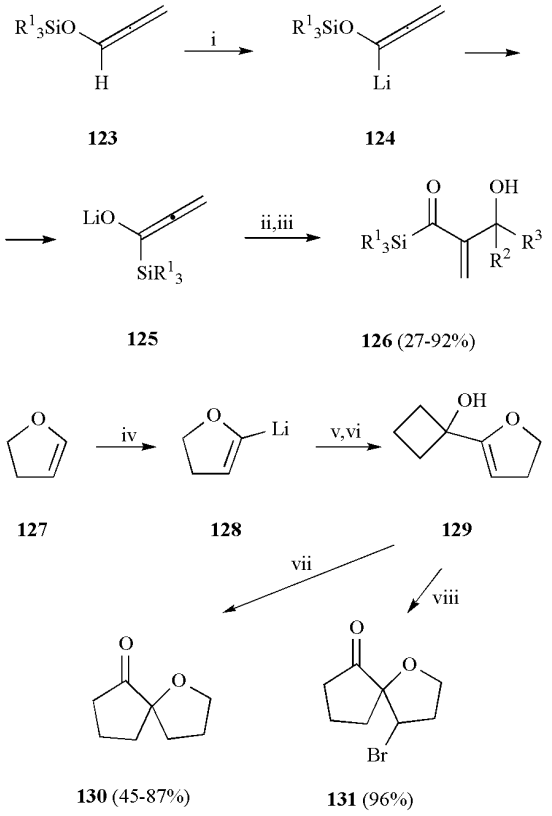


120 **121** **122**

116 [66] (Scheme 31). The addition of lithiated methoxyallene **114** to nitrones provided hydroxylamine derivatives, precursors of 1,2-oxazinones [67].

Recent applications of related α-lithiated methoxymethyl allenyl ethers in the synthesis of a cyclopentenone library [68] are based on the addition to α,β-unsaturated amides followed by spontaneous Nazarov-type cyclization. This strategy was also applied to the synthesis of a cyclopentenone precursor of roseophilin [69a] (Scheme 32).

The enantioselective variant of the former synthesis of cyclopentenones was carried out with the D-glucose-derived lithiated allene **120**, yields varying between 42 and 71% and ee between 41 and 67% [69b]. For the enantiospecific total synthesis of roseophilin, the (+)-camphoric acid derivative **121** gave the corresponding chiral cyclopentenone **119** in 86% ee [70]. For the synthesis of conjugated cyclopentenone prostaglandins related to Δ^7-PGA_1, anions **122** [R = Bu, *t*-Bu, $(CH_2)_5CO_2Me$, $(CH_2)_4C{\equiv}COEt$] derived from substituted allenes were added to a Weinreb amide [71a], to a trifluoromethyl ketone [71b], or to carbon dioxide [71c].



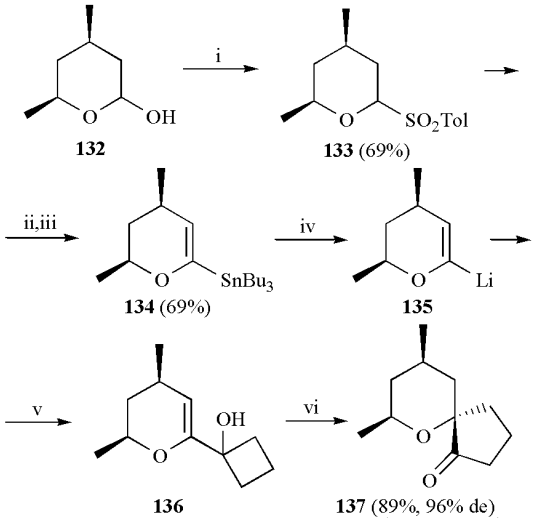
Scheme 33. *Reagents*: i, *t*-BuLi, THF, –78°C; R^2R^3CHO; iii, H_2O; iv, *t*-BuLi, THF, –78 to 0°C; v, Cyclobutanone, –78ºC; vi, $NaHCO_3$; vii, Dowex-50 or Amberlist- 15; viii, NBS, methyl-oxyrane, *i*-PrOH, –78°C.

In the deprotonation of trialkylsilyloxy allene **123** with *t*-BuLi at –78ºC resulted a reverse Brook rearrangement to give the lithium silaacrolein enolate anions **125**, which added to aldehydes and ketones to provide α,β−unsaturated TBS and TPS acylsilanes **126** (Scheme 33). Transmetallation from lithium to magnesium by adding $MgBr_2$ led to better yields in the case of ketones. For enolizable aldehydes, $ZnBr_2$ gave the best results [72].

α-Lithiated cycloalkenyl ethers of the type **4** derived from dihydrofuran and dihydropyran were formed by means of *t*-BuLi in a mixture of pentane and THF or with BuLi and a catalytic amount of TMEDA in hexane or pentane at 0ºC, and there are stable at this temperature for several hours. These reagents reacted with a great variety of electrophiles and were used as cyclic acyl anion equivalents [61a]. Recent applications of 2-lithio-4,5-dihydrofuran and pyran adducts to give cycloalkanones in pinacol rearrangement for the synthesis of spirocyclic ketones, were studied by Paquette *et al*. [73-76].

2-Lithio-4,5-dihydrofuran **128** reacted with cyclo-butanone to give the corresponding adduct **129**, which after treatment with acidic ion-exchange resins gave the spiroketone **130**. In the presence of NBS compound **129** afforded the bromoketone **131** [73] (Scheme 33).

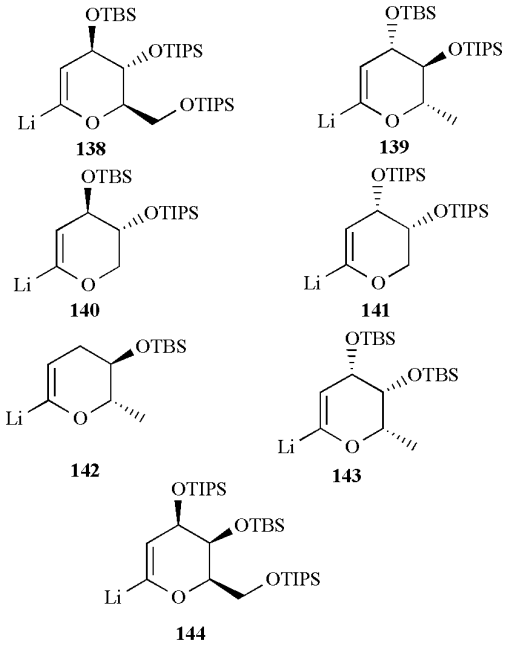
In the case of the substituted α−lithiated dihydropyran **135** (prepared from compound **132** through the sulfonyl



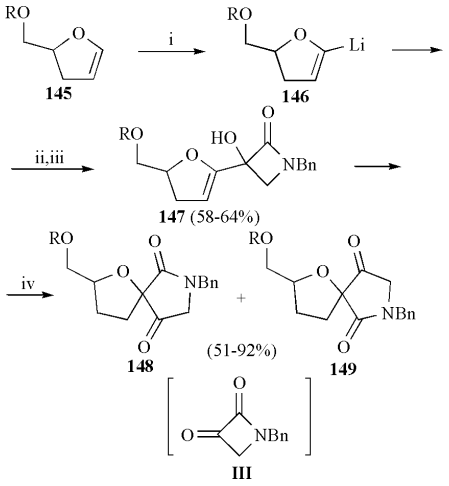
Scheme 34. *Reagents*: i, $TolSO_2H$, $CaCl_2$; ii, BuLi, then Bu_3SnCl; iii, DIPEA, $CHCl_3$, heat; iv, BuLi, THF, –78ºC; v, cyclobutanone; vi, CSA.

derivative **133** [77] and the tin compound **134**), a tin-lithium transmetallation was used. After reaction with cyclobutanone (to afford compound **136)** and final isomerization, the spirocompound **137** was isolated [74] (Scheme 34).

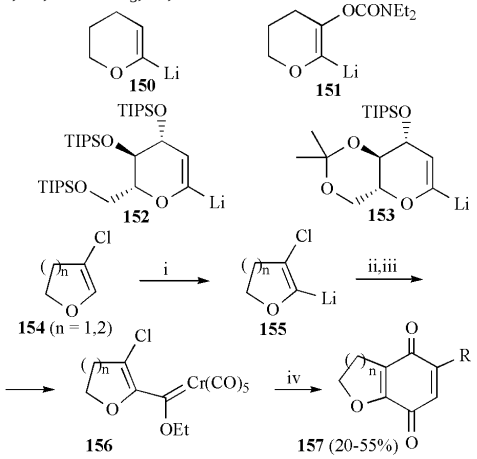
The rearrangement shown in Scheme 34 was used in the synthesis of spiro bis-*C*,*C*-glycosides by using adducts derived from cyclobutanone and cyclopentanone together with α-lithiated glucals **138-144** (prepared by C-1 lithiation with an excess of *t*-BuLi) [75].



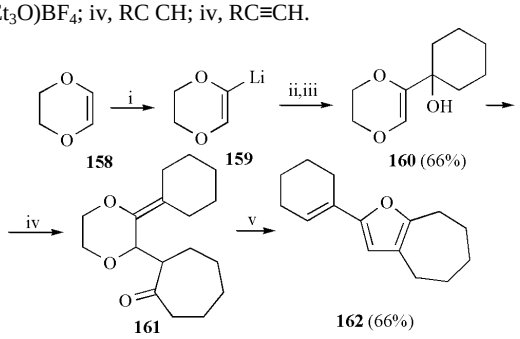
In the case of the organolithium compounds **146** derived from the furanoid glycals **145** (R = Tr, TBS), they were used in the synthesis of spirodiketopyrrolidines **148** and **149**, through compounds **147**, by reaction with a *N*-protected azetidinedione **III** as electrophiles [76] (Scheme 35).



Scheme 35. *Reagents*: i, *t*-BuLi, THF, –78 to 0ºC; ii, **III**, BF_3, –78 to –0°C; iii, $NaHCO_3$; iv, PPTS.

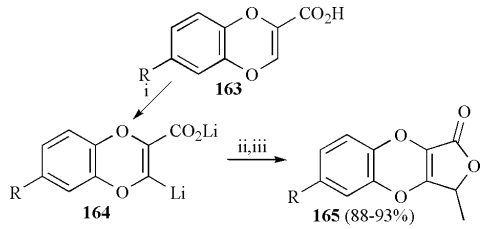


Scheme 36. *Reagents*: i, *t*-BuLi, THF, –78 ºC; ii, $Cr(CO)_6$, –78°C; iii, $(Et_3O)BF_4$; iv, RC CH; iv, RC≡CH.

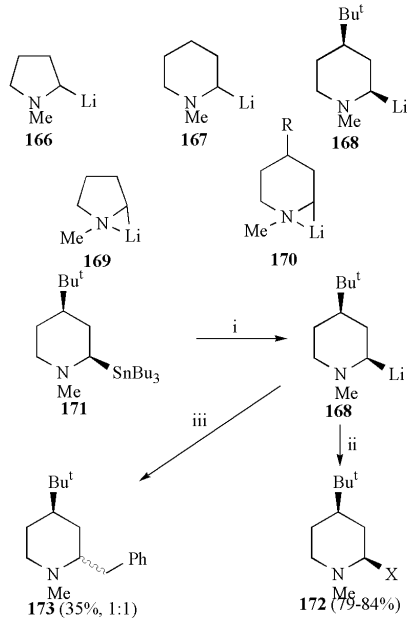


Scheme 37. *Reagents*: i, *t*-BuLi, THF, –30 to 0ºC; ii, Cyclohexanone; iii, H_2O; iv, Cycloheptanone trimethylsilyl enol ether, TMSOTf, –40ºC; v, CSA.

The tetrahydropyranyl derivative **150** was acetylated with a morpholine derived amide at 0ºC to give the corresponding ketone in 75% yield [78]. The β-(*N*,*N*-diethycarbamoyl)oxy substituted dihydropyranyllithium **151** was prepared by α-deprotonation with *t*-BuLi in THF at –78ºC and allowed to react with different electrophiles in 40-81% yields. The corresponding 2-iodo and 2-boronic acid derivatives underwent Suzuki-Miyaura coupling reactions to afford 2-aryl and 2-heteroaryl dihydropyran *O*-carbamates in high yields [79]. Lithiated glucals **152** and **153** were transformed into the corresponding vinyl chromates by reaction with $Cr(CO)_5$ [80].



Scheme 38. *Reagents*: i, LDA, THF/hexane, –78ºC; ii, MeCHO; iii, $EtCO_2H$, PhMe.



Scheme 39. *Reagents*: i, BuLi, THF, –78ºC; ii, E = Me_2CO, $(CH_2)_5CO$, *t*-BuCOCl; iii, BnBr.

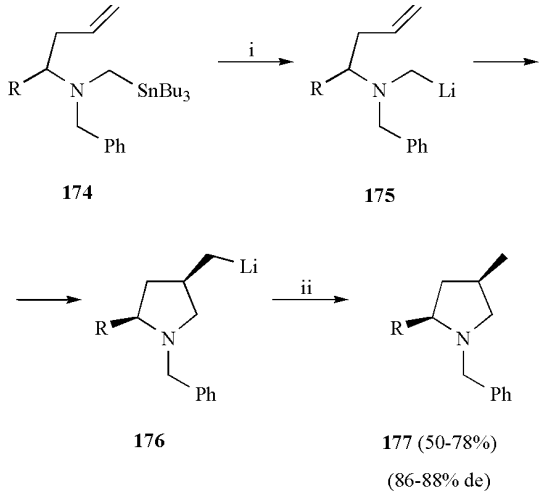
β-Chlorovinyl carbene complexes **156** were prepared from β-chloro dihydrofuranyl- and dihydropyranyllithium intermediates **155** (accessible by deprotonation of starting materials **154**), which underwent Dötz benzannulation reactions with alkynes to yield compounds **157** [81] (Scheme 36).

2,3-Dihydro-1,4-dioxin **158** can be lithiated with BuLi at 0ºC or *t*-BuLi at –30 to –20ºC to give 1,4-dioxen-2-yllithium **159**, which is a white solid stable at room temperature for one day and underwent alkylation, stannylation, aldol reactions and other transformations [60a]. Aldol adducts were used for the synthesis of spirocyclopropane derivatives [82], substituted furans (*i.e.* **162**, through intermediate **161**) [83] (Scheme 37) and oxabicyclo[4.2.1]nonene systems [84].

Benzocondensed systems **163** (and their carboxamides) were lithiated with LDA to generate intermediates **164**, which reacted with acetaldehyde being finally transformed into lactones **165** [85] (Scheme 38).

2.3. sp^3-Hybridized α-Nitrogenated Organolithium Compounds

α-Aminoalkyl organolithium compounds of type **1**, in which the lithium is located at a sp^3 carbon atom, can be derived from tertiary alkylamines (unstabilized) or from carbamates or amides (dipole-stabilized) [1d,4,17,86,87]. Considering first unstabilized α-amino organolithium systems [87], they were prepared mainly by tin-lithium transmetallation and are configurationally unstable [88a].



Scheme 40. *Reagents*: i, BuLi, THF, –78ºC; ii, MeOH.

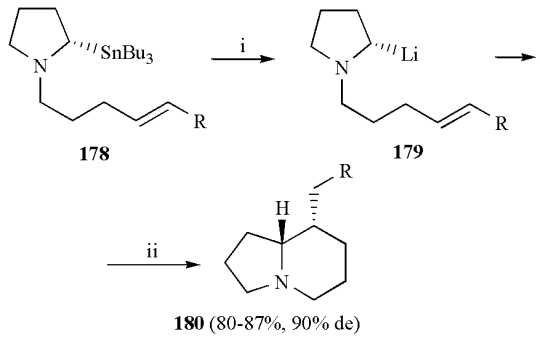
The structure of α-lithio-*N*-methylpyrrolidine **166**, as well of piperidines **167** and **168** were studied by ^{13}C, ^{15}N and ^{6}Li NMR, showing lithium bridging with the nitrogen atom as represented in **169** and **170** [88b]. The possible pathways in S_E2 reactions are (a) single electron transfer (SET) when products are completely racemic (E = Ph_2CO, BnBr, $BrCH_2CO_2Bu^t$), or (b) polar substitutions $S_E2$ret [E = CO_2, $ClCO_2Me$, $(MeO)_2CO$, ArCHO, R_2CO] *versus* $S_E2$inv (E = RX) [88b]. These descriptors were proposed by Gawley [88c]. Not easily reduced-electrophiles appear to react by a polar mechanism whereas easily reduced electrophiles prefer a SET mechanism.

Conformationally locked α-tributylstannyl-*N*-methylpiperidine **171** with a *t*-Bu substituent at the 4-position was evaluated in tin-lithium transmetallations, to give intermediate **168**, and further reaction with electrophiles [89]. When the lithium atom is equatorial, it reacted stereoselectively with carbonyl compounds ($S_E2$ret) to yield compounds **172**, whereas stereorandom alkylation was observed with benzyl bromide (SET), affording compound **173**, as well as β-elimination and reduction products resulting from a radical disproportionation. Axially oriented tin failed to transmetallate supporting that a synclinal relationship between the nitrogen lone pair and the carbon-tin bond was required for the transmetallation (Scheme 39).

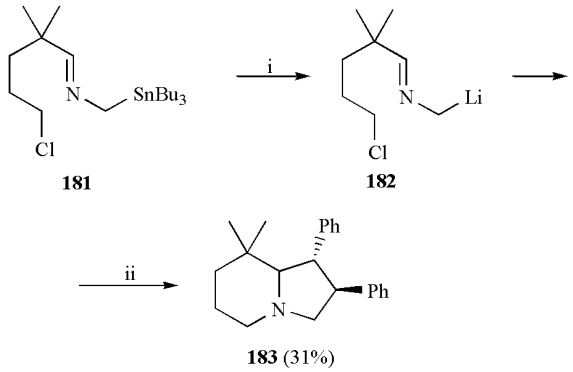
Intramolecular carbolithiation was studied with (α-amino)ethylstannanes **174** to give mainly *cis*-2,4-disubstituted pyrrolidines **177** by a 5-*exo*-*trig* mode involving intermediates **175** and **176** [90] (Scheme 40).

The use of chiral α-methylbenzyl auxiliary on the nitrogen atom gave 3-substituted pyrrolidines with up to 50% de. Very low enantioselectivities were obtained in the presence of (–)-sparteine. Related aminostannanes with pendant allylic ether, alkyne or carboxylic groups were transformed into 3-substituted pyrrolidines after transmetallation and anionic cyclization [91]

Enantiomerically enriched *N*-alkenyl 2-tributylstannyl-pyrrolidines were transformed into α-amino organolithium



Scheme 41. *Reagents*: i, BuLi, hexane/Et_2O (4/1), rt; ii, MeOH.

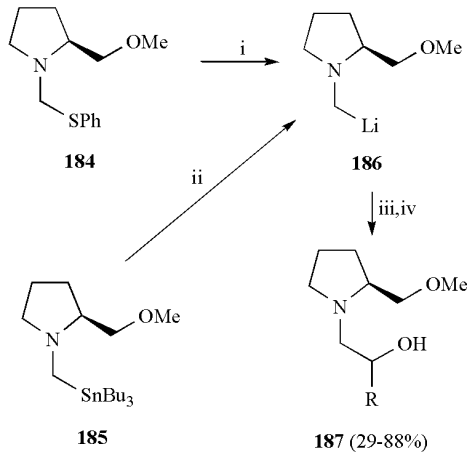


Scheme 42. *Reagents*: i, BuLi, THF, –78ºC; ii, *trans*-stilbene.

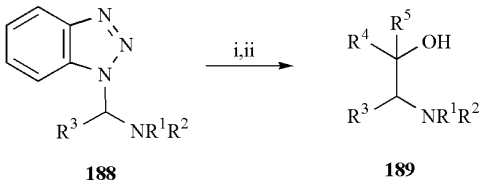
compounds, which cyclized to the corresponding pyrrolizidine and indolizidine derivatives [92]. Thus, transmetallation of compound **178** (R = H) in hexane/Et_2O with BuLi at room temperature gave the expected organolithium intermediate **179** (R = H), which after cyclization and quenching with methanol yielded the indolizidine **180** (R = H) with high diastereoselectivity (90% de) [92b] (Scheme 41). The addition of TMEDA reversed the diastereoselectivity and in all cases the racemization levels were rather high. When the same reaction was carried out with the (*E*)-phenylsulfanyl derivative **178** (R = PhS), compound **180** (R = PhS) was obtained predominantly (77% yield, 40% de) in 75% ee. The addition of TMEDA increased the rate of racemization *via* coordination to the lithium atom.

Transmetallation of the stannyl imine **181** generated unstabilized 2-azaallyl anion **182**, which in the presence of electron-rich alkenes as dipolarophiles gave indolizidines **183**, after cyclization and intramolecular *N*-alkylation [93] (Scheme 42). In the case of non-chlorinated stannyl imine, the cycloaddition reaction of the corresponding azaallyl anions afforded pyrrolidines [94]. This methodology was applied to the solid phase synthesis of a variety of substituted pyrrolidines [95].

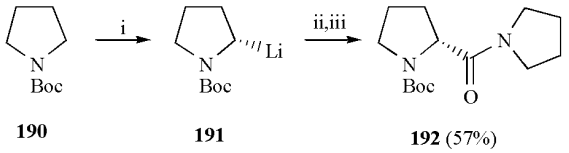
Chiral *N*-lithiomethylpyrrolidine **186** was prepared either by sulfur-lithium exchange or by tin-lithium transmetallation from the corresponding prolinol derivatives **184** and **185**, respectively, using lithium 4,4'-di-*tert*-butylbiphenyl (LiDTBB) or butyllithium, respectively [96] (Scheme 43).



Scheme 43. *Reagents*: i, LiDTBB, THF, –95ºC; ii, BuLi, THF, –78ºC; iii, RCHO; iv, H_2O.



Scheme 44. *Reagents*: i, Li, LiBr, R^4R^5CO, THF, –78ºC; ii, H_2O.



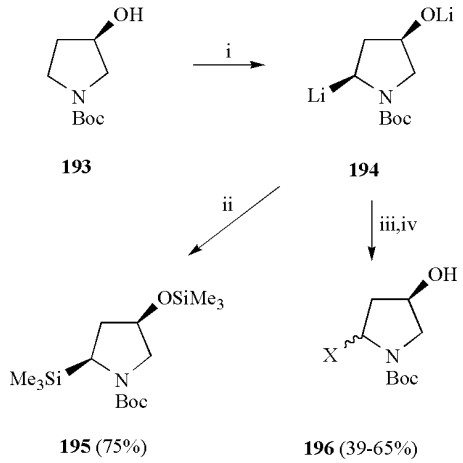
Scheme 45. *Reagents*: i, *s*-BuLi, Et_2O, –78ºC, (–)-sparteine; ii, $(CH_2)_4NCOCl$; iii, AcOH.

Condensation with aldehydes gave β-aminoalcohols **187** in good yields but modest diastereoselectivity.

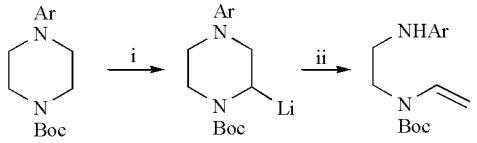
N-(α-Aminoalkyl)benzotriazoles **188** can be transformed into the corresponding carbanions *via* reductive lithiation with lithium metal in the presence of lithium bromide. The lithiation has to be carried out in the presence of ketones providing the corresponding β-aminoalcohols **189** [97] (Scheme 44).

Dipole-stabilized systems coordinated with the carbonyl oxygen showed lower reactivity than ustabililized α-amino organolithium compounds and greater resistence to racemization. They are prepared mainly by deprotonation and were used as chiral carbanions by ion pair formation with the bidentate ligand (–)-sparteine [4,17,86,87]. A recent application of the lithiated *N*-Boc pyrrolidine **191** [prepared from **190**) using (–)-sparteine] was the synthesis of chiral diamines, such as (*R*)-2-[(pyrrolidin-1-yl)methyl]pyrrolidine and its *N*-methyl derivative. In this case, 1-pyrrolidinecarbonyl chloride was used as electrophile giving the amide **192** in 85% ee [98] (Scheme 45).

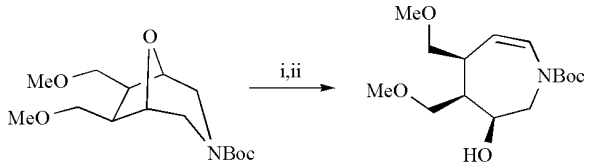
7-Azabicyclo[2.2.1]heptanes can be prepared from 5-allyl-2-(tributylstannyl)-*N*-Boc-pyrrolidine [99a]. On the other hand, the asymmetric lithiation of *N*-Boc-indoline at the 2-position followed by S_E2 reaction was applied to the synthesis of enantiomerically enriched 2-substituted indolines [99b]. Recently, chiral α-amino alkyllithium reagents derived from *N*-Boc-pyrrolidine **190** and from *N*-Boc-dimethylamine were transformed into the corresponding cuprates. These α-amino organocuprates were acylated with acyl chlorides [100a], being also used in vinylation reactions [100b,c], conjugate additions [101] and allenylation reactions with propargylic substrates [102].



Scheme 46. *Reagents*: i, *s*-BuLi, THF, TMEDA, –78 to –46ºC; ii, Me_3SiCl; iii, E = BuBr, n-$C_5H_{11}Br$, CH_2=$CHCH_2Br$, Bu_3SnCl, Me_2SO_4, n-$C_7H_{15}CHO$; iv, H_2O.



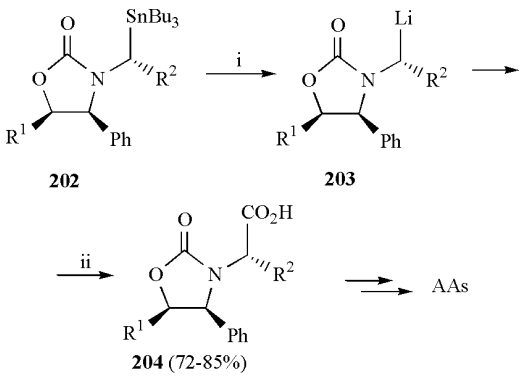
Scheme 47. *Reagents*: i, *s*-BuLi, THF, TMEDA, –78ºC; ii, NH_4Cl.



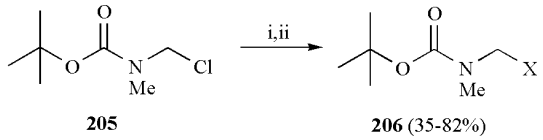
Scheme 48. *Reagents*: i, *s*-BuLi, Et_2O, (–)-sparteine, –105ºC; ii, H_2O.

N-Boc-3-hydroxypyrrolidine **193** underwent direct lithiation at C-5 (and not at C-2) by means of *s*-BuLi in THF/TMEDA to give intermediate **194** [103], as it was described previously [104]. The silylation of **194** gave *cis*-2,4-disubstituded adduct **195**, but the reaction with other electrophiles such as alkyl bromides, tributyltin chloride, dimethyl sulfate or octanal gave the corresponding 2,4-disubstituted pyrolidines **196** with low diastereoselectivity (Scheme 46).

In the case of the lithiation of *N*-Boc-*N'*-arylpiperazines **197** with *s*-BuLi and TMEDA, the corresponding intermediates **198** behave as typical β-functionalized



Scheme 49. *Reagents*: i, BuLi, THF, –78ºC; ii, CO_2; iii, 6 M HCl.



Scheme 50. *Reagents*: i, Li, DTBB (2.5 mol %), E = Me_3SiCl, RCHO, R^1R^2CO, THF, –78ºC; ii, H_2O.

organolithium compounds (see Section 3) suffering β-elimination, even at –78ºC [105a] (Scheme 47).

The same behaviour was observed in the deprotonation of 3-aza-8-oxabicyclo[3.2.1]octane **200** with *s*-BuLi in the presence of (–)-sparteine, which afforded the azepine **201** [105b]. The Boc group directs the removal of an equatorial proton α respect to the nitrogen atom from a chair-like conformation as in the case of *N*-Boc-piperidine [4], followed by subsequent β-elimination of the antiperiplanar bridging ether (Scheme 48).

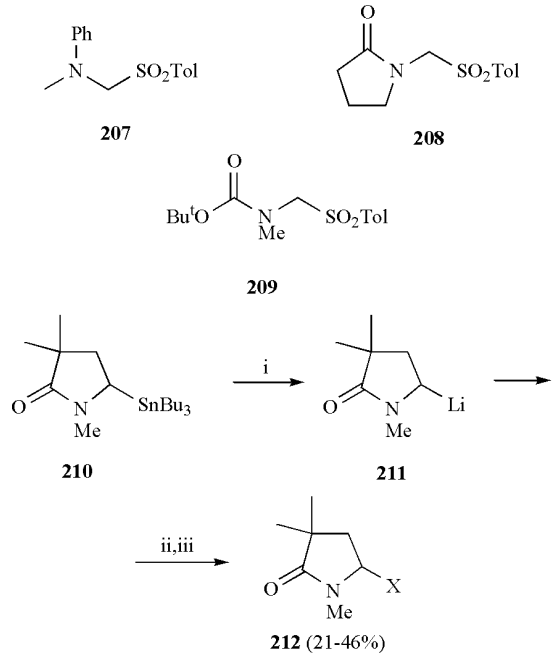
Tin-lithium transmetallation was used in the preparation of dipole-stabilized α-amino organolithium compounds derived from oxazolidinones. *N*-(α−Stannylalkyl)oxazolidinones **202** were transformed into the corresponding intermediates **203** and used in the synthesis of L-methionine labelled with ^{11}C [107a,b] and other L-amino acids (AAs) in good yields and ee up to 95% [107c] (Scheme 49).

The same methodology was used by Nakai *et al.* for the asymmetric synthesis of β−aminoalcohols by reaction of compounds **202** (R^1 = H) with aldehydes [108]. In the Michael addition to α,β-unsaturated carbonyl compounds, CuCN has to be added [109].

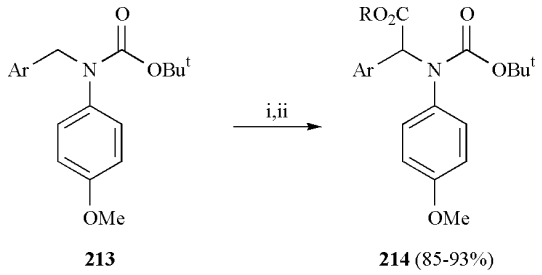
Arene-catalyzed lithiation of *O*-*t*-butyl-*N*-(chloromethyl)-*N*-methyl carbamates **205** under Barbier-type reaction conditions led to the corresponding adducts **206**, which were transformed into the expected β-aminoalcohols [110] (Scheme 50).

α-Amidomethyl and α-aminomethyl sulfones **207**-**209** were treated with lithium and a catalytic amount of naphthalene, also in the presence of carbonyl compounds as electrophiles, to give β-amido or β-amino alcohols [111].

Dipole-stabilized but unchelated α-amino organolithium compounds were prepared by tin-lithium exchange [112].



Scheme 51. *Reagents*: i, BuLi, THF, TMEDA, –78 to –50ºC; ii, E = Me_3SiCl, BnBr, $(CH_2)_5CO$, Ph_2CO; iii, H_2O.

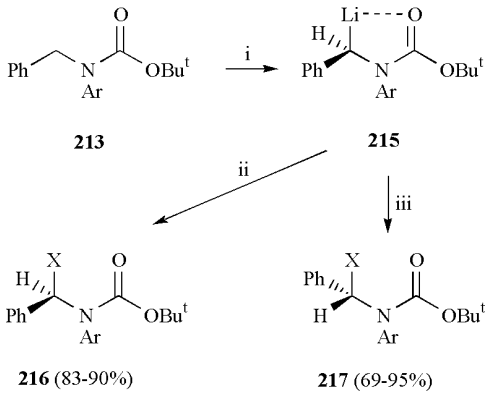


Scheme 52. *Reagents*: i, *s*-BuLi, (–)-sparteine, PhMe, –78ºC; ii, CO_2 or $ClCO_2Me$.

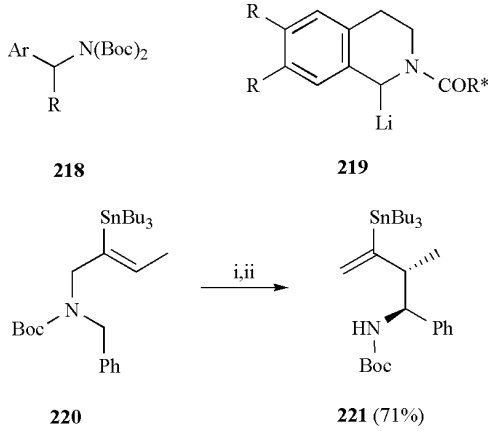
The lactam **210** was transmetallated with BuLi at –78ºC in the presence of TMEDA, being necessary to rise the temperature to –50ºC to give the intermediate **211** (Scheme 51). This reagent gave, after reaction with electrophiles, lower yields than the corresponding chelated dipole-stabilized α-amino organolithium compounds.

N-Boc-protected benzylamines can be deprotonated enantioselectively with *s*-BuLi in the presence of (–)-sparteine. The enantiomeric excess resulting from the electrophilic substitution depended not only on the solvent and the electrophile, but also on the reaction time [113]. Beak *et al.* found that when *N*-Boc-*N*-aryl benzylamines **213** were deprotonated by means of *s*-BuLi/(–)-sparteine at –78ºC in toluene for 8 h and further reaction with carbon dioxide or methyl chloroformate, enantioenriched phenylglycine derivatives **214** were obtained with *R* or *S* configuration, respectively [114] (Scheme 52).

The same authors demonstrated that the absolute configuration of α-aminobenzyllithium intermediates **215** (prepared from the carbamates **213**) is *R*. These dipole-stabilized carbanions maintain the configuration in the



Scheme 53. *Reagents*: i, *s*-BuLi, (–)-sparteine, PhMe, –78ºC; ii, E = $ClCO_2Me$, $BrCH_2CO_2Me$; iii, E = CO_2, $ClSnMe_3$, TfOR, CMe_2=$CHCH_2Br$, CH_2=CHCHO, RCHO, R^1CH=NR^2.

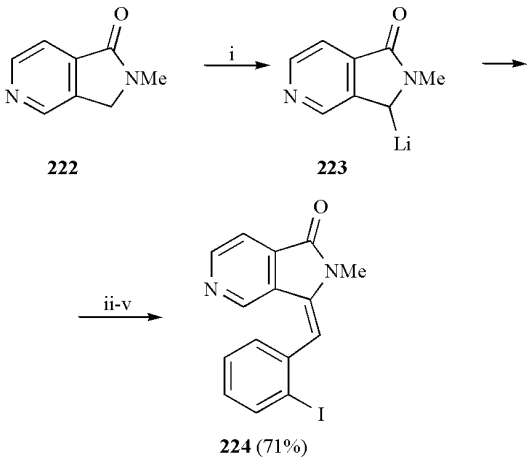


Scheme 54. *Reagents*: i, LDA, THF/HMPA (4/1), –78 to –40ºC; ii, H_2O.

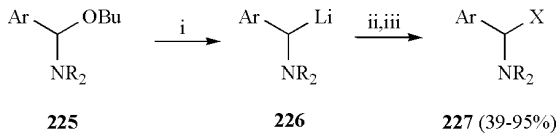
presence of (–)-sparteine before they reacted with electrophiles. Retention of the configuration was observed with other electrophiles (Scheme 53). Their proposal was that unreactive electrophiles, or those that coordinate to the lithium atom, react by $S_E2$ret to give compounds **216**, while fast-reacting and noncoordinative electrophiles react by $S_E2$inv affording compounds **217**. This methodology was an appropriate strategy for the enantioselective synthesis of α-, β-, and γ-aryl amino acids and esters. *N*-Boc-*N*-trimethylsilylbenzylamines were used for the enantioselective synthesis of arylglycines [115].

The *N*,*N*-di-Boc-protected benzylamines **218** underwent [1,2]-Boc migration with KDA/*t*-BuOLi (prepared from LDA and *t*-BuOK) in THF at –78ºC to provide *N*-Boc protected *t*-butyl phenylglycines in good yields (44-96%) [116a]. Tetrahydroisoquinoline gulonic amides were lithiated with *t*-BuLi in THF at –78ºC to give benzylic anions **219**, which were alkylated in 41-57% yield and up to 98% de. The diastereoselectivity was determined during the alkylation step [116b]

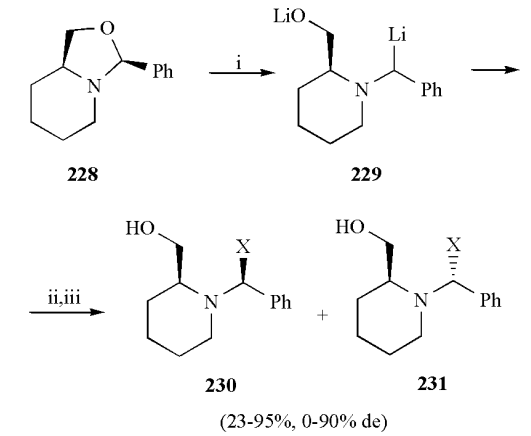
The aza-[2,3]-Wittig sigmatropic rearrangement was less studied than the corresponding oxy-process. Acyclic rearrangements were recently described with *N*-Boc protected allylbenzylamines **220** [117]. The presence of a tributyltin group at the 2-position of the allyl group improve



Scheme 55. *Reagents*: i, LiHMDS, THF, –78ºC; ii, *o*-iodobenzaldehyde; iii, Me_3SiCl; iv, LiHMDS, –78 to 0ºC; v, H_2O.



Scheme 56. *Reagents*: i, Li, naphthalene (5-10 mol %), THF, –20ºC; ii, E = H_2O, D_2O, RHal, *t*-BuCHO, R_2CO; iii, H_2O.

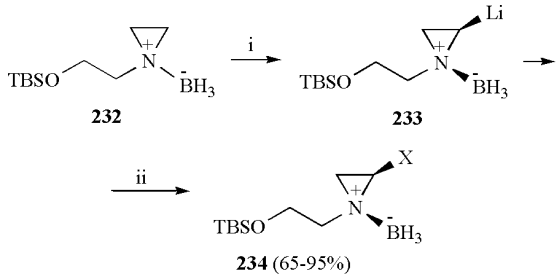


Scheme 57. *Reagents* i, Li, naphthalene (10 mol %), THF, –20ºC; ii, E = H_2O, D_2O, RHal; iii, H_2O.

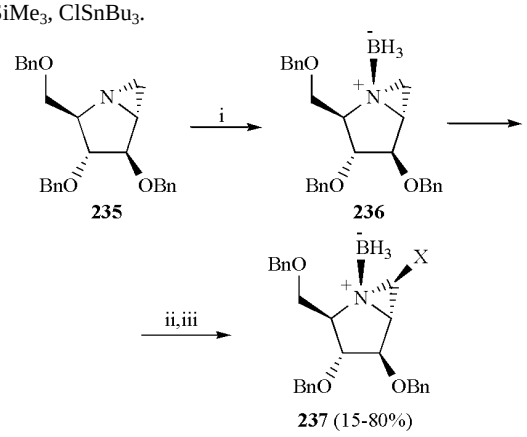
the diastereoselection giving product **221** in > 90% de [117b] (Scheme 54).

An unchelated dipole-stabilized α-aminobenzyl organolithium compound **223** (prepared by deprotonation of the starting material **222**) was used in the synthesis of the azaphenanthrene alkaloid eupolauramine, through the intermediate **224**. This compound was obtained after β-elimination of the β-alkoxide organolithium compound derived from the adduct resulting from the reaction of the carbanion **223** with *o*-iodobenzaldehyde [118] (Scheme 55).

Unstabilized α-aminobenzyllithium compounds **226** were prepared by reductive cleavage of α-*N*,*N*-dialkylamino substituted benzyl butyl ethers **225** using lithium and a catalytic amount of naphthalene. After reaction with different electrophiles, products **227** were isolated with variable yields [119a] (Scheme 56).



Scheme 58. *Reagents*: i, *s*-BuLi, THF, –78ºC; ii, E = D_2O, MeI, $ClSiMe_3$, $ClSnBu_3$.



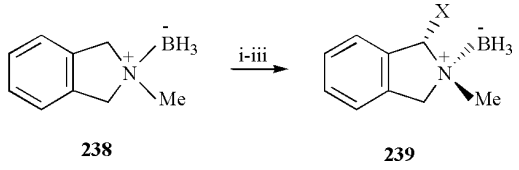
Scheme 59. *Reagents*: i, BH_3·THF; ii, *s*-BuLi, (–)-sparteine, cumene, –78ºC; iii, E = $ClSnBu_3$, $ClPO(OEt)_2$, $ClP(OEt)_2$.

In the case of a 2-phenyloxazolidine **228**, the corresponding organolithium compound was more stable due to the presence of an alkoxide group. Reductive lithiation of a 92:8 diastereomeric mixture of bicyclic oxazolidine **228** occurred with racemization at the benzylic position through the formation of the rapidly interconverting diastereomeric organolithium intermediate **229**. One of these organolithium compounds reacted preferentially with alkyl halides affording mainly *syn*-products **230** [119b] (Scheme 57).

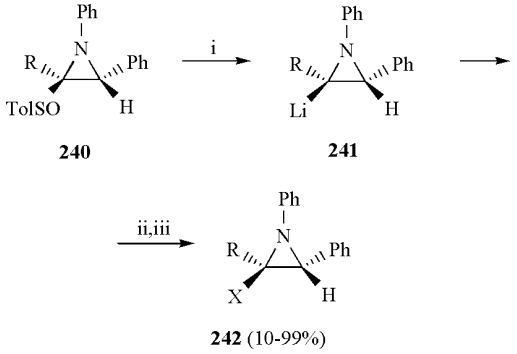
Unstabilized aziridine anions [36a] are reagents of the type **2** (X = NR, n = 1) and were prepared by previous nitrogen-borane complexation (see structure **232**) followed by deprotonation with *s*-BuLi (Kessar method). The lithiation took place diastereoselectively with *s*-BuLi in THF at –78ºC (lithium *syn* to boron; see **233**), probably due to steric effects. After reaction with different electrophiles, products **234** were mainly obtained [120] (Scheme 58).

Increased *s*-character in the carbon atom, which will be deprotonated, facilitates the lithiation in the case of the mentioned aziridine-borane complexes. This methodology was applied to the arabinose-derived aziridine **235**, which after complexation with borane, to give the complex **236**, lithiation in the presence of (–)-sparteine, and final reaction with electrophiles afforded mainly products **237**, with retention of the configuration in the lithiated aziridine [121] (Scheme 59).

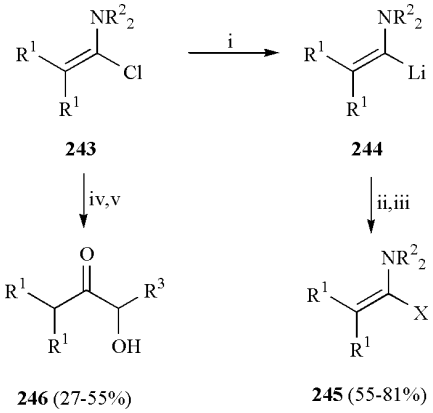
The isoindoline-borane complex **238** was also *syn*-lithiated and, in presence of (–)-sparteine, alkylated enantioselectively (up to 89% ee and 49:1 dr) to afford compounds **239** [122] (Scheme 60).



Scheme 60. *Reagents*: i, *s*-BuLi, Et_2O, (–)-sparteine, –78ºC; ii, E = Me_3SiCl, MeI, EtI, *n*-$C_5H_{11}Br$; iii, NH_4Cl-H_2O.



Scheme 61. *Reagents*: i, *t*-BuLi or RMgHal/*t*-BuLi, THF, –78ºC; ii, E = H_2O, MeOD, RCHO, R_2CO, $ClCO_2R$, $ClPO(OEt)_2$, PhNCO; iii, NH_4Cl-H_2O.

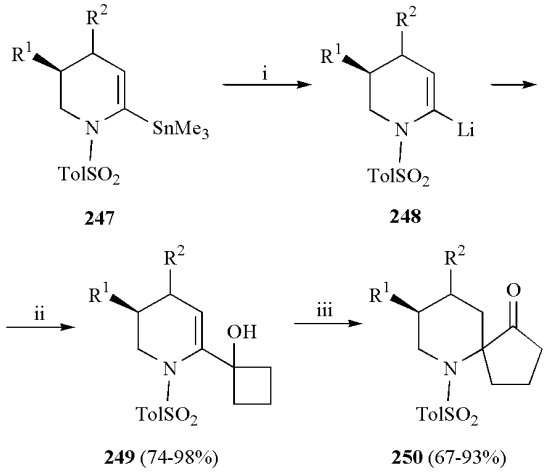


Scheme 62. *Reagents*: i, Li, DTBB (5 mol %), THF, –90ºC; ii, E = D_2O, Me_3SiCl, PhCOCH=CHPh/BF_3·OEt_2, CO_2, CyNCO; iii, H_2O; iv, Li, DTBB (5 mol %), R^3CHO, THF, –40ºC; v, 2 M HCl or silica gel.

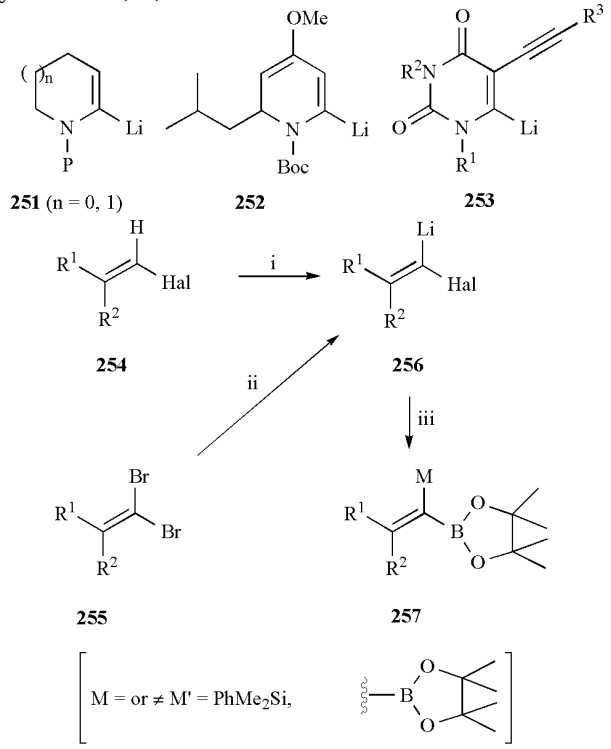
Satoh *et al.* have used the same methodology than in the case of the mentioned oxiranyl anions [45] (Scheme 21) for the preparation of aziridinyl anions. Sulfinylaziridines **240** suffered sulfoxide-lithium exchange with *t*-BuLi or a mixture of a Grignard reagent and *t*-BuLi at –78ºC to generate aziridinyllithiums **241** [123]. These intermediates were found to be stable below –30ºC and reacted stereoselectively with different electrophiles to yield products **242** (Scheme 61).

2.4. sp^2-Hybridized α-Nitrogenated Organolithium Compounds

α-Lithioenamines **244** were recently prepared by chlorine-lithium exchange from the corresponding α-chloroenamines **243**. Intermediates **244** can be generated with lithium and DTBB (5 mol %) at –90ºC and trapped with different electrophiles to afford products **245** [124] (Scheme 62). When the arene-catalyzed lithiation was performed at



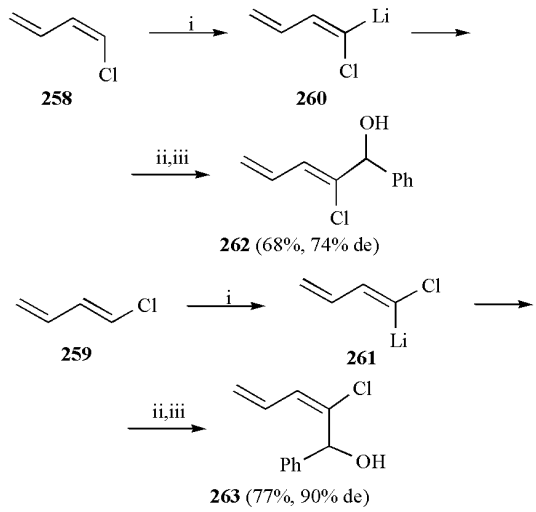
Scheme 63. *Reagents*: i, MeLi (2 equiv), Et_2O, –100ºC; ii, cyclobutanone; iii, CSA or HCl.



Scheme 64. *Reagents*: i, LiTMP, THF/Et_2O, –110ºC; ii, BuLi, THF/Et_2O, –110ºC; iii, M-M'.

–40ºC it was necessary to work under Barbier-type reaction conditions, that is, carrying out the lithiation in the presence of the corresponding electrophile. The final hydrolysis of aldol-type products with 2 M HCl afforded α-hydroxyketones **246** in moderate yields. This type of reagents can also be considered as acyl anion equivalents as in the case of α-metallated vinyl ethers [60a] (Section 2.2).

Cyclic enamides **247**, derived from piperidine lactams, were prepared by palladium-catalyzed cross-coupling of enol triflates with hexamethyldistannane. Tin-lithium transmetallation provided intermediates **248**, which were coupled with cyclobutanone to give compounds **249**. Final semipinacol-type rearrangement under acidic conditions



Scheme 65. *Reagents*: i, LiTMP (2 equiv), –90ºC; ii, PhCHO; iii, H_2O.

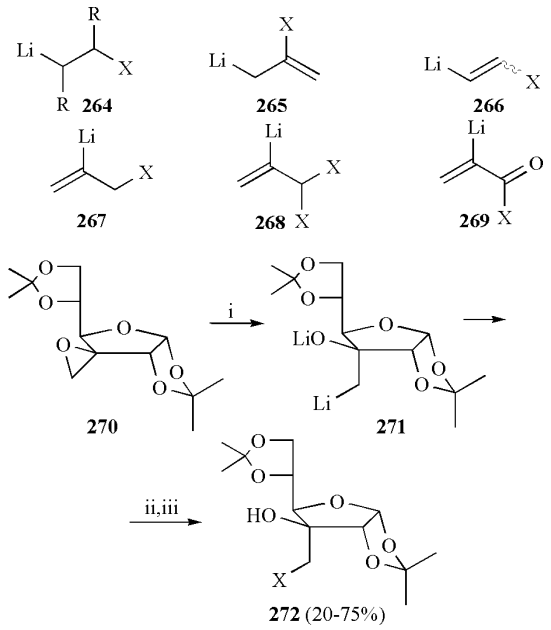
yielded the corresponding azaspiro cyclic ketones **250** [125] (Scheme 63), as it was before described by Paquette *et al.* using α−lithiated dihydropyrans [73-76].

Enecarbamates were lithiated with *t*-BuLi in THF at –78ºC to afford organolithium compounds **251** (P = Boc) [126a]. These intermediates and other vinyllithium reagents were added to dimethyl squarate and applied by Paquette *et al.* to the synthesis of polyquinanes [126a] (see Section 3.2). The seven membered ring **251** (n = 2, P = Boc) was prepared by deprotonation with BuLi in the presence of TMEDA and transformed into the corresponding acid by reaction with CO_2 in 56% yield [126b]. α-Lithiated enamidines **251** (P = CH=NBu^t) were alkylated with alkyl iodides in order to carry out intramolecular Heck reactions for the preparation of spiro compounds [126c].

Directed lithiation of a dihydropyridine with BuLi afforded intermediate **252**, which was transformed into 6-iodo-2,3-dihydro-4-pyridone in 75% yield by reaction with iodine. This strategy was applied to synthesize the spirocyclic core of the alkaloid spirolucidine [127]. In addition, lithiated pyrimidines **253** were prepared by LDA deprotonation at –78ºC and transformed into the corresponding 6-iodo derivatives in 46-82% yield. These iodides were used in the synthesis of nucleoside enediynes [128].

2.5. Other sp^2-Hybridized α-Functionalized Organolithium Compounds

α-Haloalkenyllithium species can be generated by α-deprotonation and by halogen-lithium exchange [60b]. Shimizu *et al.* have recently reviewed the application of different α-haloalkenylidene reagents **256**, prepared either by α-deprotonation of vinyl halides **254** with lithium 2,2,6,6-tetramethylpiperidine or by bromine-lithium exchange from 1,1-dibromoalkenes **255** at low temperatures (Scheme 64). They were used for the synthesis of *gem*-silylboryl and *gem*-diboryl compounds **257**, by migration of an intermediate ate complex [129]. A related α-bromovinyllithium compound of



Scheme 66. *Reagents*: i, Li, DTBB (5 mol %), THF, –78ºC; ii, E = H_2O, D_2O, Me_3SiCl, CO_2, R_2CO; iii, H_2O.

type **256** [Hal = Br; R^1 = (*S*)-CHCHMe(OMEM); R^2 = H] was added to sulfonylimines in order to give after ozonolysis *N*-protected α-amino esters [130].

The deprotonation of (*Z*)- or (*E*)-1-chlorobutadienes, **258** or **259**, with LiTMP at –90ºC gave stereoselectively (*Z*)- or (*E*)-1-chloro-1-lithio-1,3-butadienes **260** or **261**, respectively. After trapping with benzaldehyde, products **262** and **263** were regioselectively obtained mainly with retention of the configuration [131] (Scheme 65).

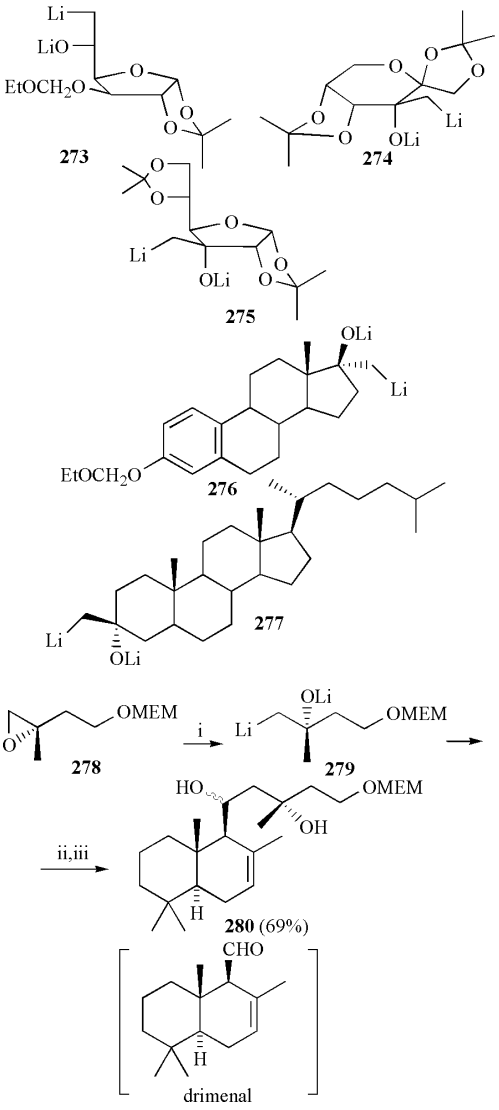
3. β-Functionalized Organolithium Compounds

Organolithium compounds with a functional group at the β-position are very unstable intermediates, specially compounds bearing a good leaving group. They have a great tendency to undergo β-elimination reactions. They can have sp^3 or sp^2 hybridization either with acyclic or cyclic structure of the type **264-269**.

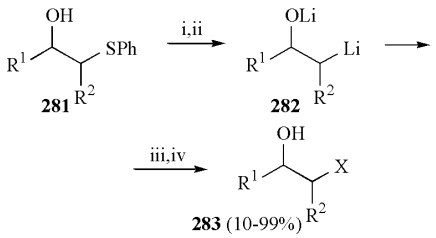
3.1. sp^3-Hybridized β-Functionalized Organolithium Compounds

β-Oxido and β-amino alkyllithium compounds of the type **264** are typical d^2-reagents, which are stabilized and trapped by electrophiles when the heteroatom bears a negative charge. The most used preparative method for β-oxido intermediates **264** (X = OLi) has been the reductive ring opening of chiral epoxides by lithium and an arene [6]. By a DTBB-catalyzed lithiation, the epoxide **270** (prepared from D-glucose) gave the intermediate **271**, which by reaction with different electrophiles afforded the expected compounds **272** [132a,b] (Scheme 66).

Related β-oxido organolithium compounds **273** and **274**, from D-glucose and D-fructose, respectively, were prepared



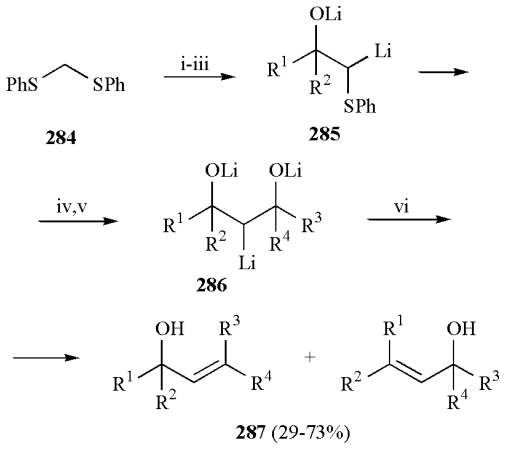
Scheme 67. *Reagents*: i, LiDTBB, THF, –78ºC; ii, drimenal; iii, H_2O.



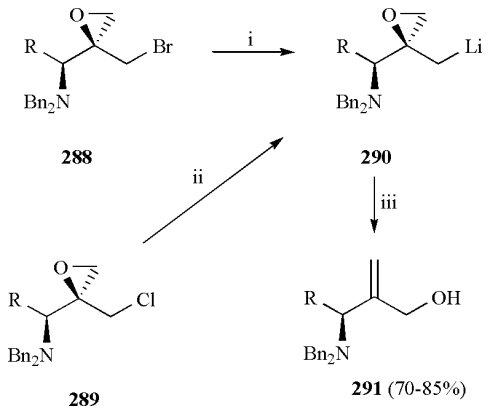
Scheme 68. *Reagents*: i, BuLi, THF, –78ºC; ii, Li, DTBB (5 mol %); iii, E = D_2O, RCHO, R_2CO; iv, H_2O.

from the corresponding epoxides. For the preparation of the intermediate **275**, the epimer of compound **271**, the corresponding chlorohydrin was lithiated under the same reaction conditions, previous deprotonation of the alcohol functionality. The use of intermediates **273-275** in the reaction with different electrophiles allowed the preparation of branched-chain functionalized carbohydrates [132a,b].

Intermediates **276** and **277**, derived from estrone and cholestanone, respectively, were prepared from the



Scheme 69. *Reagents*: i, BuLi, THF, 0ºC; ii, R^1R^2CO; iii, Li, DTBB (5 mol %), –78ºC; iv, R^3R^4CO; v, Li, DTBB (5 mol %), –78ºC to rt; vi, H_2O.



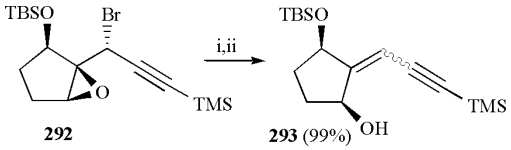
Scheme 70. *Reagents*: i, *t*-BuLi, THF, –78ºC to rt; ii, Li, –40ºC to rt; iii, H_2O.

corresponding epoxides and trapped with several electrophiles under the same reaction conditions as above [132c,d].

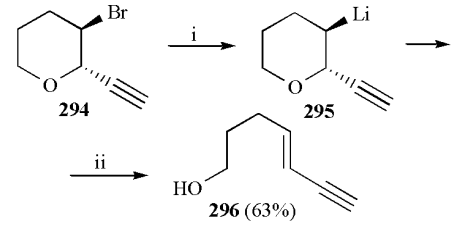
The optically active epoxide **278** was used for the preparation of the corresponding organolithium compound **279**, a new isoprenoid C_5-reagent, which was coupled with drimenal for the formation of an intermediate **280** used in the synthesis of the labdane diterpene forskolin [133] (Scheme 67).

β-(Phenylsulfanyl) alcohols **281** are appropriate starting materials for the preparation of acyclic and cyclic β-oxido functionalized organolithium compounds **282** by a DTBB-catalyzed lithiation. After reaction of these intermediates with different electrophiles the expected compounds **283** were isolated [134] (Scheme 68).

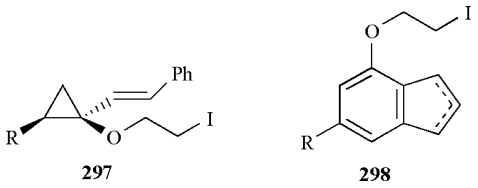
The same methodology (sulfur-lithium exchange) was used in the case of intermediates **286**, which were generated from bis(phenylsulfanyl)methane **284** through the β-functionalized organolithium compound **285**. These intermediates **286** suffered β-elimination to give a mixture of allylic alcohols **287** [135] (Scheme 69).



Scheme 71. *Reagents*: i, BuLi, THF, –90ºC; ii, H_2O.



Scheme 72. *Reagents*: i, BuLi, THF, –78ºC; ii, H_2O.



On Section 2.1 several α-alkoxy- β-amino organolithium compounds, such as **17** and **18** [12] derived from carbamates **27** [16], **29** [18, 19] and **30** [20], as well as from amino sugars **90** [51] and **93** [52] were described. Some β-oxido alkyllithium compounds have participated as intermediates in the lithiation of epoxides, such as **68** [42], **75** [44] and, in the case of sugar derivatives, **95** and **96** [53].

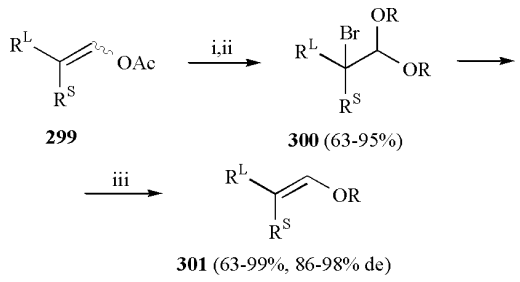
β-Elimination of β-alkoxy alkyllithium compounds is a convenient strategy for the synthesis of alkenes. Enantiomerically enriched β-bromo (**288**) or β-chloro epoxides (**289**) gave, after lithiation, intermediates **290**, which underwent β-elimination giving allylic amino alcohols **291** [136] (Scheme 70).

The bromoepoxide **292** gave, after bromine-lithium exchange with BuLi, a highly stereoselective elimination reaction (E2) through an *anti*-coplanar transition state for the Li-C-C-O bonds giving a 7:1 mixture of enynes **293**, possible intermediates in the synthesis of the maduropeptin chromophore [137] (Scheme 71).

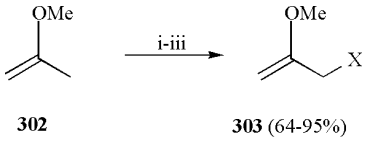
trans-Enyne **296** was prepared stereoselectively from *trans*-3-bromo-2-ethynyltetrahydropyran **294** by bromine-lithium exchange, to give the organolithium **295**, followed by β-elimination [138] (Scheme 72).

Iodoethyl cyclopropyl ethers **297** were transformed into cyclopropanols by treatment with *t*-BuLi at –78ºC [139a]. In the case of iodoethylindenes **298**, they also suffer spontaneous β-elimination after lithiation at –78ºC to give the corresponding phenols [139b].

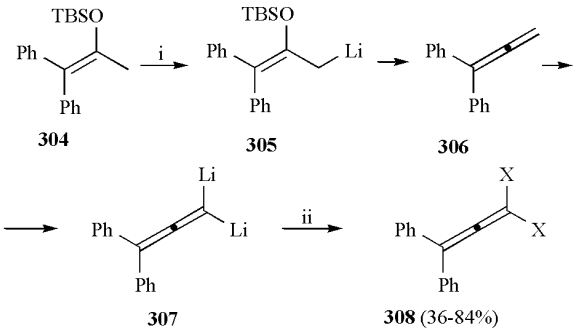
(*E*)-Enol ethers **301** can be prepared from the corresponding β-bromoacetals **300** (easily accessible from enol acetates **299**) by bromine-lithium exchange at –78ºC [140] (Scheme 73).



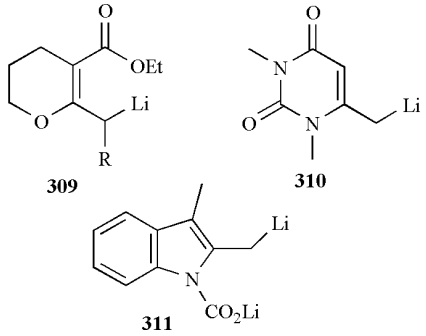
Scheme 73. *Reagents*: i, Br_2, CCl_4; ii, ROH; iii, BuLi, THF, –78ºC.



Scheme 74. *Reagents*: i, BuLi, *t*-BuOK, THF/hexane, –78 to –50ºC; ii, E = RHal, epoxides, R^1R^2CO, $ClSiEt_3$; iii, H_2O.

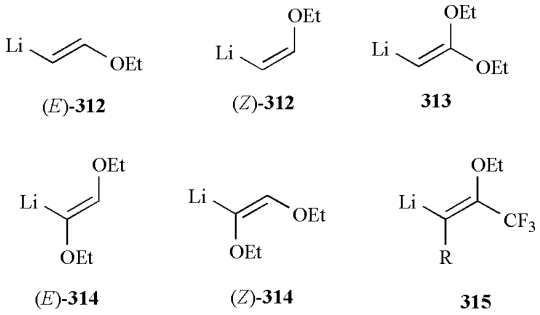


Scheme 75. *Reagents*: i, LDA (3 equiv), THF, 0ºC; ii, E = EtOH, R_3SiCl, Me_3SnCl, Ac_2O.



Allylic organolithium compounds of the type **265** decomposed easily to give allenes. However, methyl isopropenyl ether **302** was metallated with BuLi/*t*-BuOK at –78 to –50ºC and the corresponding intermediate trapped with electrophiles to afford products **303** in good yields, which after hydrolysis can be converted into the expected methyl ketones [141] (Scheme 74). Metallated intermediate derived from methyl isopropenyl ether **302** suffered β-elimination at –30ºC to give the corresponding allene.

In the direct transformation of the silyl enol ether **304** into a functionalized allene, a β-silyloxy alkyllithium **305** was involved. This intermediate was generated by LDA deprotonation and underwent β-elimination to the corresponding allene **306**, which was rapidly deprotonated to



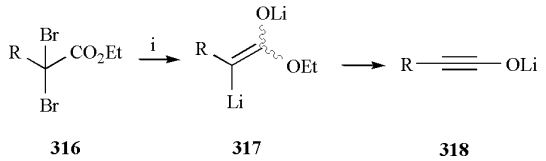
give a 1,1-bislithiated allene **307**. Final reaction of this intermediate with electrophiles yielded products **308** [142] (Scheme 75).

Cyclic allylic organolithiums of the type **265**, such as **309** [143a] and **310** [143b] were prepared by LDA deprotonation at –78ºC and used in the synthesis of tetrahydropyranones [143a] and uracil derivatives [143b], respectively. 2,3-Dimethylindole gave, after deprotonation with BuLi in the presence of CO_2 followed by lithiation with *t*-BuLi, the dianion **311**, which dimerized by treatment with diiodoethane in only 19% yield [143c].

3.2. sp^2-Hybridized β-Functionalized Organolithium Compounds

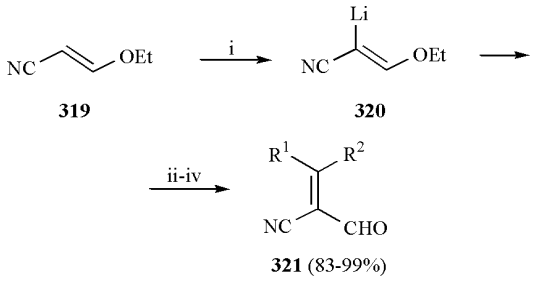
Alkenyllithium compounds of the type **266** were mainly prepared by bromine-lithium exchange. 2-Ethoxyvinyllithiums **312**, having *Z* or *E* configuration, present very different thermal stability. The *E*-isomer, prepared stereospecifically from (*E*)-1-bromo-2-ethoxyethylene and BuLi in THF at –75ºC, started to decompose at –50ºC through a favourable antiperiplanar elimination of lithium ethoxide. However, the *Z*-isomer is stable for 6 hours at –50ºC. In the case of 2,2-diethoxyvinyllithium **313**, it can be prepared by bromine-lithium exchange at –75ºC and was stable at 0ºC for 5 min due to the coordination of the metal with the oxygen atom. For the preparation of (*Z*)- or (*E*)-1,2-diethoxyvinyllithiums **314**, α-deprotonation of the corresponding 1,2-diethoxyethylenes took place at –75ºC using *t*-BuLi in THF. Compound (*E*)-**314** sustained after heating at 75ºC for 15 min, whereas the (*Z*)-isomer **314** can be kept at 0ºC for only 2 h. The inductive effect of the oxygen atom at the α-position also contributes to the stabilization of reagents **314** [144]. Reagent (*E*)-**312** was trapped stereospecifically with electrophiles such as alkyl iodides, carbonyl compounds, phenyl isocyanate, carbon dioxide, dimethyl disulfide, chlorotrimethylsilane and chlorotrimethyltin in 43-75% yield. (*Z*)-2-Ethoxyvinyllithium (*Z*)-**312** was transformed into the corresponding organocopper reagent for the conjugate addition to α,β−unsaturated lactones in good yields (65-92%) [145a]. When 2-bromo-2-cyclohexenone was allowed to react with (*Z*)-**312** at –70ºC, 1,2-addition took place giving the corresponding alcohol in 90% yield [145b].

2,2-(Diethoxy)vinyllithium **313** was prepared from its chlorinated precursor, which is more stable than the



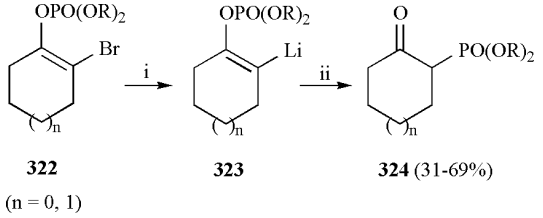
316 **317** **318**

Scheme 76. *Reagents*: i, *t*-BuLi, THF, –78 to 0ºC.



319 **320** **321** (83-99%)

Scheme 77. *Reagents*: i, LiTMP, THF, –78ºC; ii, R^1R^2CO; iii, H_2O; iv, TMSOTf.



322 **323** **324** (31-69%)

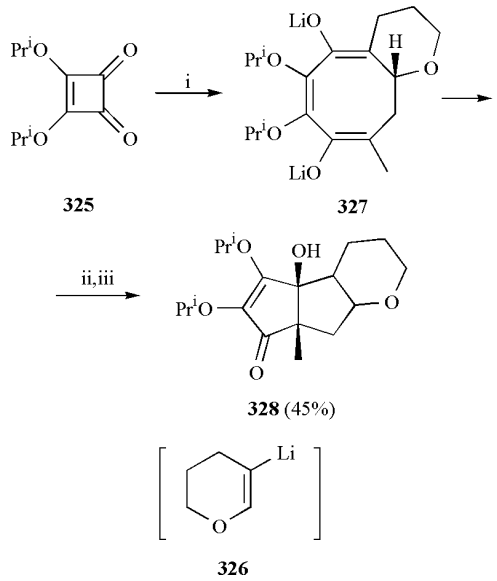
(n = 0, 1)

Scheme 78. *Reagents*: i, BuLi, THF, –78ºC to rt; ii, NH_4Cl-H_2O.

corresponding β-bromoketene acetal, The chlorine-lithium exchange was performed with lithium powder and DTBB (0.1 equiv) in THF at –20ºC, and the resulting reagent **313** was allowed to react with carbonyl compounds at the same temperature. Final hydrolysis with water at temperatures ranging between –40ºC and room temperature afforded β-hydroxy esters in 61-76% yield, and further treatment with 1 M HCl provided α,β-unsaturated esters [146]. β-Trifluoromethyl−β−ethoxyvinylliyhium compounds **315** were stereoselectively prepared by bromine-lithium exchange with *t*-BuLi (2 equiv) in ether and in the presence of TMEDA (1 equiv) at –78ºC. These reagents reacted with aldehydes and ethyl chloroformate to give the corresponding adducts in 30-60% yield [147].

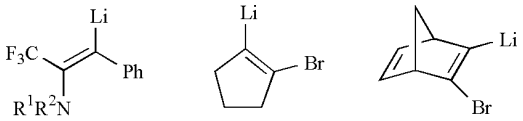
Ester dianions **317**, prepared from α,α-dibromoesters **316** by treatment with *t*-BuLi (4 equiv) at –78ºC, suffer β-elimination to give ynolate anions **318**, which were widely used as ketene anion equivalents [148a] (Scheme 76). The lithiation can also be carried out by a naphthalene-catalyzed lithiation at –78ºC, this method being more convenient, economical and practical [148b].

When the ethoxyethylene skeleton has a cyano group at the β-position (*i.e.* **319**), deprotonation took place in a regio and stereoselective manner using lithium 2,2,6,6-tetramethylpiperidine (LiTMP) at –78ºC. Further reaction of this anion **320** with carbonyl compounds gave the corresponding allylic alcohols (28-99%), which by treatment with trifluoromethanesulfonic acid trimethylsilyl ester



325 **327** **328** (45%) **326**

Scheme 79. *Reagents*: i, **326**, THF, -78ºC; ii, $MeC(Li)=CH_2$, –78ºC to rt; iii, NH_4Cl-H_2O.



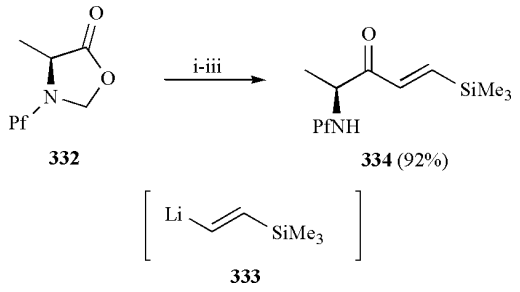
329 **330** **331**

afforded α,β−unsaturated α-cyano aldehydes **321** [149] (Scheme 77).

β-Bromovinyl phosphates **322** gave bromine-lithium exchange with BuLi at –78ºC affording β-lithiovinyl phosphates **323**, which suffered regiospecific 1,3-phosphorous migration to form α-keto phosphonates **324** [150] (Scheme 78).

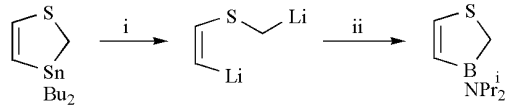
β-Lithiated dihydrofuran **326** was prepared by bromine-lithium exchange in Et_2O/THF at –100ºC and used in the synthesis of polyquinanes **328** by using compound **325** as starting material and involving the intermediate **327** [151] (Scheme 79). The double addition of alkenyl, cycloalkenyl and alkynyl lithium reagents to squarate esters studied by Paquette *et al.* constitutes a general methodology for the synthesis of polyquinanes [152].

Several vinyllithium reagents with other functional groups at the β-position were also described in the literature. Thus, the enamine derivatives **329** were prepared by deprotonation with *t*-BuLi in hexane in the presence of TMEDA at room temperature, reacting with aldehydes and ethyl chloroformate in 55-65% yield [153]. Cyclic β-bromovinyllithiums **330** and **331** were prepared by bromine-lithium exchange from the corresponding dibromides using *t*-BuLi in THF at –78ºC and reacted with the squarate ester **325** [151] and with different alkyl iodides [154], respectively.



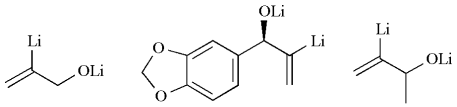
332 **334** (92%) **333**

Scheme 80. *Reagents*: i, **333**, THF/Et_2O, –78 to 10ºC; ii, HCO_2Et; iii, AcOH.



335 **336** **337** (33%)

Scheme 81. *Reagents*: i, BuLi, THF, –78ºC to rt; ii, *i*-Pr_2NBCl_2, –78 to –10ºC.



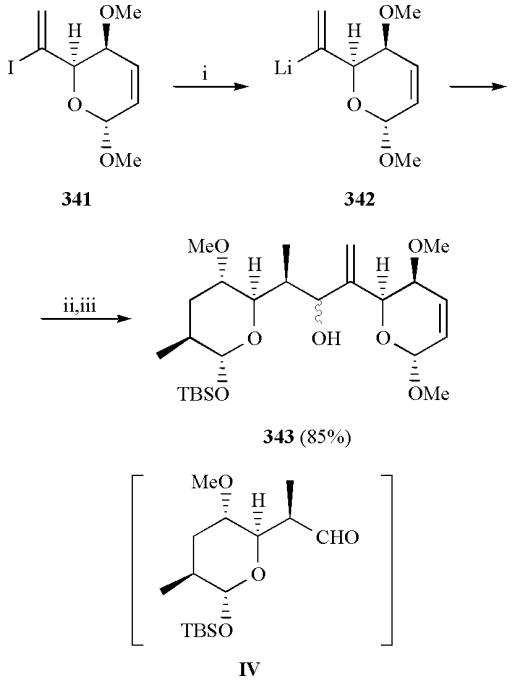
338 **339** **340**

β-(Trimethylsilyl)vinyllithium **333** was prepared from the corresponding bromo derivative by treatment with *t*-BuLi in Et_2O at –78 to –20ºC. Its reaction with the 9-phenyl-9-fluorenyl-protected oxazolidinone **332** afforded stereoselectively the α-amino ketone **334** [155] (Scheme 80).

The dianion **336** was prepared from the stannane **335** by transmetallation with BuLi in THF at –78ºC. It reacted with *i*-Pr_2NBCl_2 to give the thiaborolene **337** [156] (Scheme 81).

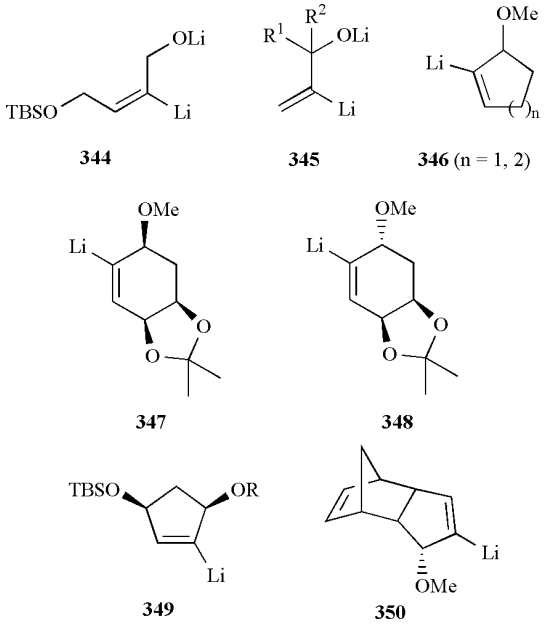
Allylic systems lithiated at the 2-position of the type **267** with acyclic or cyclic structures are usually prepared by halogen-lithium exchange. Lithium 2-lithioprop-2-en-1-olate **338**, prepared from the corresponding bromohydrin with BuLi in Et_2O [157] or with *t*-BuLi [158-160] at –78ºC, was recently used for the synthesis of the chiral sulfoxide (S_S)-2-(*p*-tolylsulfinyl)prop-2-en-1-ol using (–)-menthyl *p*-toluenesulfinate [157, 158]. The addition of intermediate **338** to chiral α-amino aldehydes gave a mixture of epimeric alcohols, which were used for the synthesis of (+)-epopromycin B [159]. Related dianions **339** [161] and **340** [162], prepared by bromine-lithium exchange with *t*-BuLi at –78ºC, were used in the total synthesis of (–)-wodeshiol [161] and all-*cis*-2,4,6-tetrasubstituted tetrahydropyrans [162], respectively.

For the asymmetric synthesis of the C3-C21 subunit [163] of the ansamycin antibiotic herbimycin A [164], the intermediate **343** was prepared from the β-alkoxy organolithium compound **342**. The iodo-lithium exchange was conducted at –95ºC with *t*-BuLi in ether, in order to



341 **342** **343** (85%)

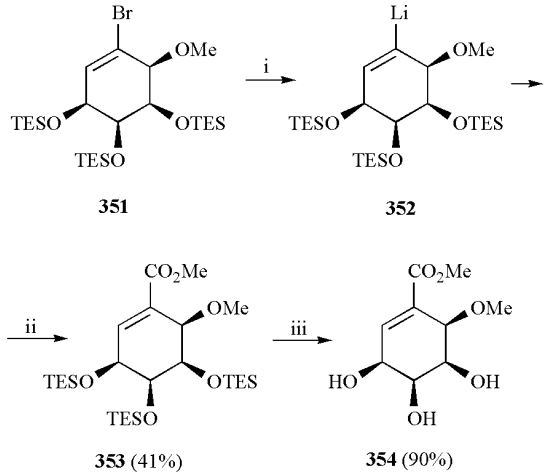
Scheme 82. *Reagents*: i, *t*-BuLi, Et_2O, –95ºC; ii, **IV**, –95 to –50ºC; iii, NH_4Cl.



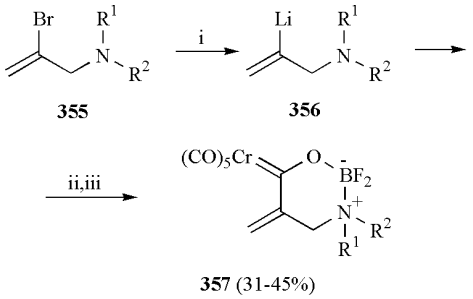
344 **345** **346** (n = 1, 2) **347** **348** **349** **350**

avoid possible β-elimination, to produce an allene (Scheme 82).

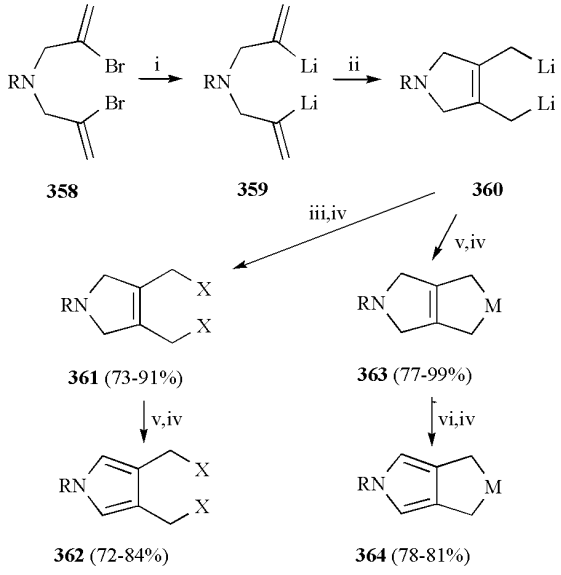
The β-oxide vinyllithium **344** was prepared by tin-lithium transmetallation with BuLi in THF at –78 to –35ºC and applied to the total synthesis of racemic taxifolial A and *iso*-caulerpenyne [165]. In the case of the organolithium **345**, the phenylsulfanyl precursor was lithiated with lithium in the presence of DTBB (5 mol %) at –78ºC [135]. Cyclic β-methoxyvinyllithiums **346** [151,166], **347** and **348** [167], and **349** and **350** [166a] were prepared by bromine-lithium



Scheme 83. *Reagents*: i, *t*-BuLi, Et_2O, –78ºC; ii, $ClCO_2Et$; iii, CF_3CO_2H.

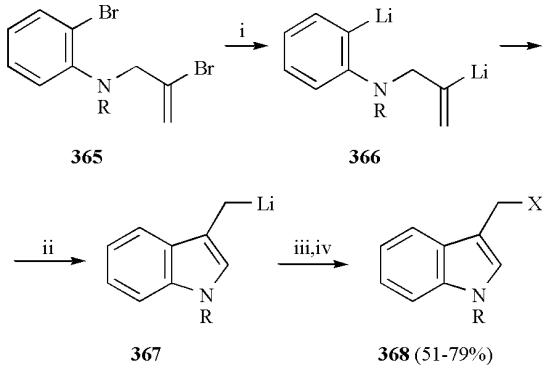


Scheme 84. *Reagents*: i, *t*-BuLi, Et_2O, –78ºC to rt; ii, $Cr(CO)_6$; iii, $BF_3{\cdot}Et_2O$.

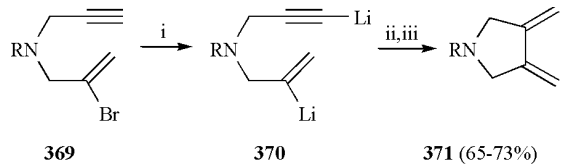


Scheme 85. *Reagents*: i, *t*-BuLi, Et_2O, –78ºC; ii, TMEDA; iii, E = D_2O, Me_3SiCl, PhCH=NPh; Me_2CO, CO_2; iv, H_2O; v, O_2 or DDQ; vi, Ph_2SiCl_2, Et_2GeCl_2, Me_2SnCl_2.

exchange at –78ºC from the corresponding bromoalkenes and used by Paquette *et al.* in the synthesis of triquinanes.



Scheme 86. *Reagents*: i, *t*-BuLi (2 equiv), Et_2O, –78ºC; ii, TMEDA; iii, E = D_2O, Me_3SiCl, $(RS)_2$, RCHO, R_2CO, PhCH=NCHMePh, RCN, PhNCO; iv, H_2O.



Scheme 87. *Reagents*: i, *t*-BuLi, Et_2O, –78ºC; ii, $Cp_2Zr(Me)Cl$, –78ºC to rt; iii, H_2O.

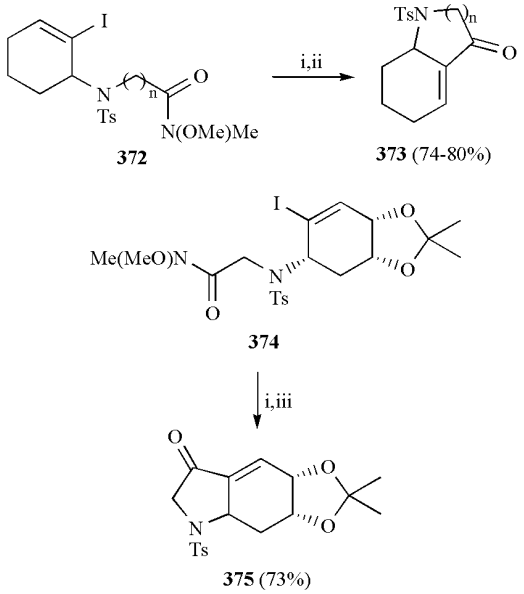
The total synthesis of (+)-pericosine B **354** was carried out by carboxylation of intermediate **352**, prepared from **351** by bromine-lithium exchange with *t*-BuLi, to give the ester **353** followed by removal of the protecting silyl groups [168] (Scheme 83).

2-Bromoallylamines **355** gave after bromine-lithium exchange with *t*-BuLi in ether at –78ºC the corresponding β-aminovinyllithium compounds **356**. They were used for the preparation of chelate chromium boroxycarbene complexes **357**, useful dienophiles in *exo*-Diels-Alder reactions with 2-amino-1,3-dienes [169] (Scheme 84). Intermediates of type **356** [169] were used by Paquette *et al.* in the addition to squarate esters for the synthesis of polyquinanes [152].

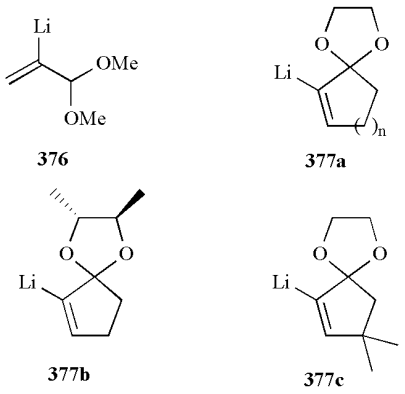
Treatment of *N,N*-bis-(2-bromoallyl)amines **358** with *t*-BuLi at –78ºC gave the corresponding dianions **359**, which after addition of TMEDA underwent intramolecular carbometallation to give dilithiated dihydropyrroles **360**. Final reaction of these dilithio derivatives with different electrophiles afforded dihydropyrrole **361** and **363,** and pyrrole derivatives **362** and **364**, after oxidation [170] (Scheme 85).

Related dianions **366**, prepared from the dibromo derivatives **365**, cyclized to give the lithiated indole derivatives **367**, which were used for the preparation of compounds **368** by reaction with different electrophiles [170] (Scheme 86).

Organodilithium compounds **370**, derived from allylamines **369**, were cyclized using a zirconocene derivative, giving heterocycles **371** [171] (Scheme 87). The same methodology was employed with other allylamines to provide seven and eight-membered heterocycles.



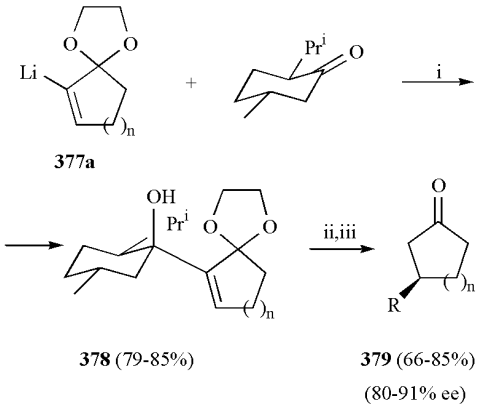
Scheme 88. *Reagents*: i, *t*-BuLi, THF, –78 to –30ºC; ii, 10% HCl; iii, NH_4Cl, 0ºC.



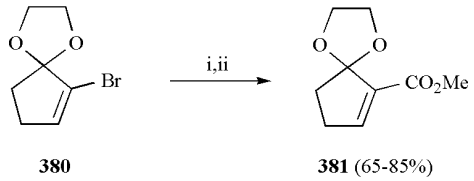
In the total synthesis of (–)-brunsvigine, intermediate **375** was prepared by intramolecular acylation of the vinylic organolithium compound derived from the iodinated system **374**. This cyclization was previously studied with different β-iodosulfonamides **372** to give the expected perhydroindolone, perhydroquinolone and perhydrobenzazepinone skeletons **373** [172] (Scheme 88).

Protected or unprotected α-acylvinyl anions [173] with structure **268** or **269** were prepared by halogen-lithium exchange or by deprotonation, respectively. 2-Lithioacrolein dimethyl acetal **376** [151] and 2-lithiocyclopentenone acetals **377a** (n = 1) [151] and **377b** [166], prepared by bromo-lithium exchange with BuLi at –78ºC, were added to diisopropyl squarate for the synthesis of triquinanes [152]. Following this methodology, the organolithium compound **377c** was used for the synthesis of jatrophatrione [174a]. This intermediate **377c** was transformed into the corresponding chiral sulfoxide by using (–)-menthyl *p*-toluenesulfinate as electrophile [174b].

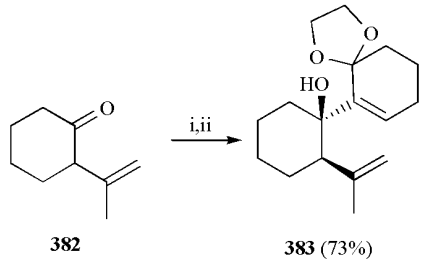
Cyclopentenone (n = 1) and cyclohexenone (n = 2) derivatives **377a** were added to (–)-menthone and the adducts used for an asymmetric Michael-type addition using cuprates



Scheme 89. *Reagents*: i, $(CO_2H)_2$; ii, $R_2Cu(CN)Li_2$, –60ºC; iii, MeOH.



Scheme 90. *Reagents*: i, BuLi, THF, –78ºC; ii, $ClCO_2Me$, –78 to 0ºC.



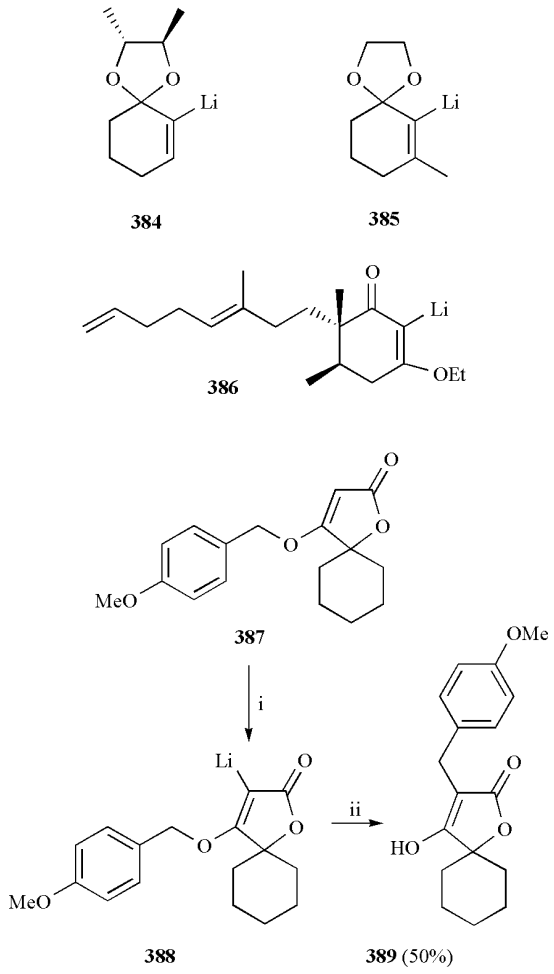
Scheme 91. *Reagents*: i, **377a** (n = 2), THF, –78ºC; ii, H_2O.

as the organometallic components, so products **379** were prepared in good yields and ee [175] (Scheme 89).

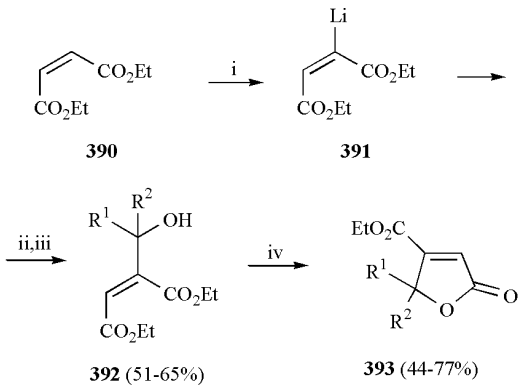
The enoate **381** was prepared from the bromo derivative **380** through the intermediate **377a** (n = 1), by reaction of this organolithium compound with methyl chloroformate, the reaction having been applied to the synthesis of the phorbol skeleton [176] (Scheme 90).

Reagent **377a** (n = 1) was added diastereoselectively to the *exo* face of the oxo group of (benzocyclobutenone)tricarbonylchromium(0) in 80% yield [177]. The cyclohexenone derived organolithium compound **377a** (n = 2) was added to 2-(methylvinyl)cyclohexenone **382** giving diastereoselectively the 1,2-divinylcyclohexanol **383**, which was used in a tandem oxy-Cope/ene reaction for the synthesis of polycyclic compounds [178] (Scheme 91).

Cyclohexenone derivatives **377a** (n = 2) and the corresponding (2*R*,3*R*)-2,3-butanediol acetal **384** were prepared from the corresponding chloroacetals by reaction with lithium in the presence of DTBB (5 mol %) in THF at

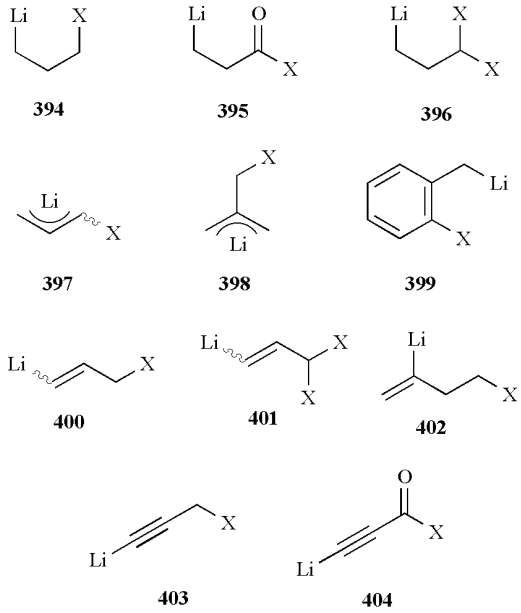


Scheme 92. *Reagents*: i, LDA, THF, –78ºC; ii, H_2O.



Scheme 93. *Reagents*: i, LiTMP, THF, –78 to 5ºC; ii, R^1R^2CO, –78ºC to rt; iii, H_2O; iv, $(PhS)_2$, hexane, reflux, hν.

–78ºC and allowed to react with electrophiles, such as carbonyl compounds and chlorotrimethylsilane, to afford the expected products in 51-98% yield [179]. 3-Methylcyclohexenone acetal organolithium derivative **385** added diastereoselectively to a α-trimethylsilyloxyaldehyde (52% yield, 90% de) for the construction of a *seco*-taxane [180].



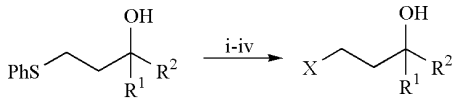
The phomactin A ring system was prepared from the reagent **386** by bromine-lithium exchange with *t*-BuLi at –78ºC and coupled with acrolein to give the corresponding alcohol in 76% yield [181].

When the benzyl tetronate **387** was deprotonated with LDA, and trying to perform the acylation with Ac_2O, an unexpected anionic [1,3]-sigmatropic rearrangement on intermediate **388** took place providing the tetronic acid **389** [182] (Scheme 92).

Maleate dimethyl ester **390** suffered α-deprotonation with LiTMP and the corresponding vinyllithium compound **391** reacted with carbonyl compounds to provide α, β−butenolides **393**, when the adducts **392** were exposed to thiyl radicals [183] (Scheme 93]. Under these radical reaction conditions intermediate maleates **392** suffered isomerization to give fumarate esters. The whole process is stereoselective and can be considered as related to the Baylis-Hillman condensation.

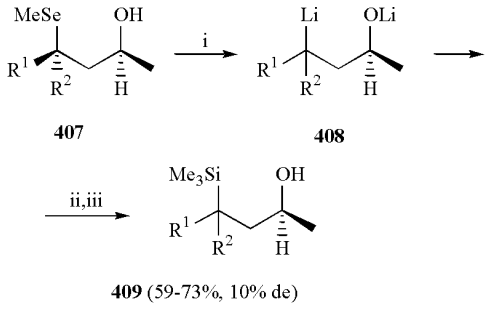
4. γ-FUNCTIONALIZED ORGANOLITHIUM COMPOUNDS

There are several types of γ-functionalized organolithium compounds depending on the hybridization of the carbon atom attached to the metal. In the case of alkyllithium compounds (Section 4.1), the functional group can be at a sp^3- (**394**) or sp^2-hybridized (**395**, homoenolates) carbon atom, as well as derivatives **396** (homoenolate equivalents). Allylic systems (Section 4.2) can bear the functional group at the 3-position (**397**) or at the 2-position (**398**). Benzylic derivatives bearing the functional group at the *ortho*-position of the aromatic ring (**399**) would also be considered (Section 4.3). sp^2-Hybridized organolithium compounds with (*Z*)- or (*E*)-configuration (**400**), β-acylvinyl anions (**401**) and vinylic intermediates **402** (Section 4.4), as well as sp-hybridized propargyl intermediates (**403** and **404**; Section 4.5) will be considered.



405 **406** (35-55%)

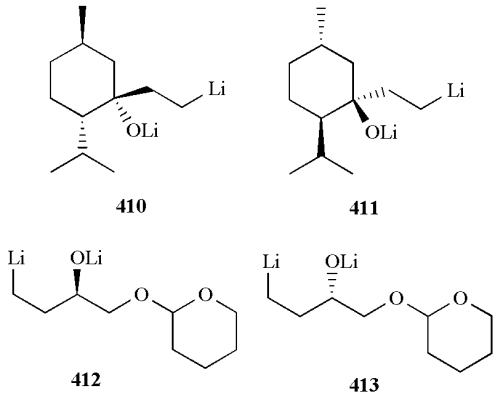
Scheme 94. *Reagents*: i, BuLi, $Mg(OCH_2CH_2OEt)_2$, THF, –78ºC to rt; ii, Li, THF, 0ºC to rt; iii, E = CO_2, R^3R^4CO; iv, H_2O.



409 (59-73%, 10% de)

[R^1, R^2 = Ph, Me]

Scheme 95. *Reagents*: i, BuLi (2 equiv), THF, –78ºC; ii, Me_3SiCl, –78 to –20ºC; iii, K_2CO_3-H_2O.



410 **411**

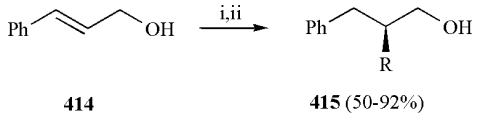
412 **413**

4.1. γ-Functionalized Alkyllithium Compounds

γ-Oxido functionalized organolithium compounds **394** can be prepared by halogen-, sulfur- or selenium-lithium exchange, tin-lithium transmetallation, reductive opening of oxetanes and by carbolithiation of cinnamyl alcohols. A recent work about the preparation and synthetic applications of these intermediates reported the lithiation of γ-(phenylsulfanyl)alcohols **405** with lithium to generate intermediates of the type **394**. These compounds were treated with magnesium 2-ethoxyethoxide in order to increase their stability in THF at room temperature, reacting then with different electrophiles to afford products **406** [184] (Scheme 94).

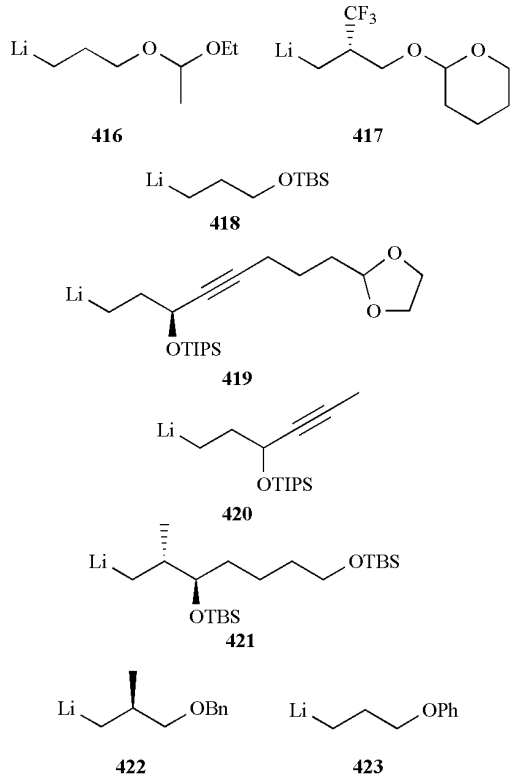
Benzyllithiums **408** were prepared by selenium-lithium exchange from the corresponding enantiomerically pure γ-hydroxybenzyl selenides **407** by means of BuLi at –78ºC. Epimerization took place before final trapping with chlorotrimethylsilane [185] (Scheme 95).

The reductive opening of chiral oxetanes with lithium powder and DTBB (5 mol%) in THF at 0 or –20ºC afforded



414 **415** (50-92%)

Scheme 96. *Reagents*: i, RLi, (–)-sparteine (1 equiv), cumene, –10 to 0ºC; ii, 1 M HCl.



416 **417**

418

419

420

421

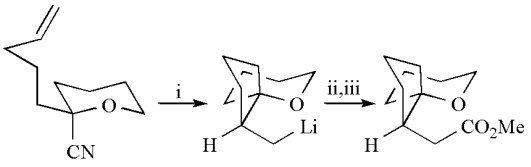
422 **423**

different enantiomerically pure γ-oxido alkyllithium compounds **410-413** [186]. Treatment of these intermediates with different electrophiles, such as H_2O, D_2O and carbonyl compounds, gave the corresponding products in 59-98% yield. When 2-phenyl substituted oxetanes were treated under the same reaction conditions, the ring opening took place at the benzylic position to give, after quenching with water, terminal alcohols [187].

The carbolithiation of cinnamyl alcohol **414** with alkyllithium compounds in the presence of (–)-sparteine [17,188] in cumene as solvent took place at –10ºC to give the corresponding alcohols **415** in high ee (up to 95% ee) [189] (Scheme 96).

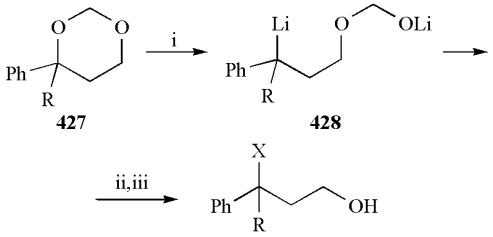
The protection of the hydroxy group of γ-halohydrins as acetal followed by bromine-lithium exchange (with lithium metal in ether at –20ºC) for compound **416** [190] or by iodine-lithium exchange (with *t*-BuLi in ether at –105ºC) for intermediate **417** allowed the preparation of the mentioned functionalized organolithium compounds [191]. The trapping of compound **416** with α-(phenylsulfanyl)cyclohexane-carbaldehyde took place in quantitative yield [190]. Intermediate **417** reacted with carbonyl compounds in 42-73% yield [191].

Silyl-protected γ-iodohydrins were lithiated with *t*-BuLi in ether at –78ºC providing intermediates **418-420**.



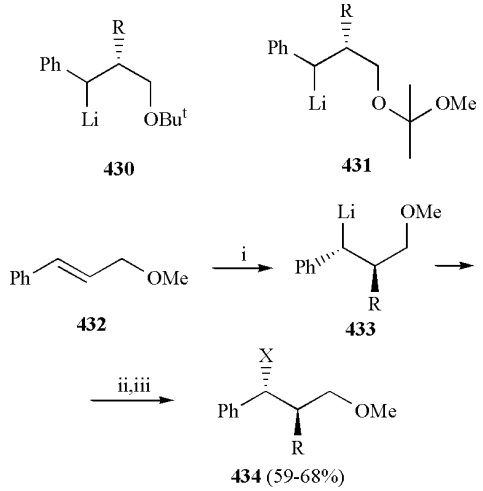
424 **425** **426** (65%)

Scheme 97. *Reagents*: i, LiDTBB, THF, –78ºC; ii, CO_2, –78ºC; iii, CH_2N_2.



427 **428** **429** (57-95%)

Scheme 98. *Reagents*: i, Li, $C_{10}H_8$ (5 mol %), THF, –40ºC; ii, E = H_2O, MeOD, RBr, Me_3SiCl, CO_2, *t*-BuCHO; iii, H_2O.

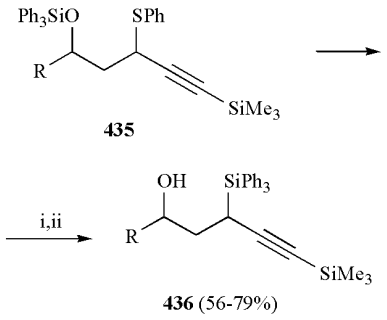


430 **431** **432** **433** **434** (59-68%)

Scheme 99. *Reagents*: i, RLi, TMEDA, Et_2O, 0ºC; ii, E = MeOH, MeOD, CO_2, $(MeS)_2$, MeI, –78ºC to rt; iii, NH_4Cl-H_2O.

Compound **418** was used in the total synthesis of the neurotoxic alkaloid (–)-perhydrohistrionicotoxin [192] as well as of dendrobatic alkaloids indolizidine (–)-209I and (–)-223J [193]. Overman *et al.* used reagents **419** [194a] and **420** [194b] for the synthesis of (–)- and (+)-scopadulcic acid A, and the BCD ring systems of diterpenes stemodane and stemarane, respectively by coupling with a Weinreb amide in 70% yield. For confirming the stereochemistry of the core structure of the mycolactone, intermediate **421** (prepared from the corresponding iodide by means of *t*-BuLi in THF at –78ºC) was coupled with a vinyl iodide under Negishi conditions in 60% yield, so a synthetic sample of the natural compounds was obtained [195].

γ-Alkoxy alkyllithium intermediates of type **422** [196] and **423** [197] were prepared by iodine-lithium exchange with *t*-BuLi and by reductive lithiation of γ-chloropropyl phenyl ether with lithium and DTBB (5 mol %) at –78ºC,



435 **436** (56-79%)

Scheme 100. *Reagents*: i, $LiC_{10}H_8$, THF, –78ºC; ii, H_2O.

respectively. In the last case, a second lithiation with cleavage of the carbon-oxygen bond took place at room temperature to give a new organolithium compound, so allowing the synthesis of 1,5-diols after reaction with two equal or different carbonyl compounds as electrophiles. Intermediate **422** was used in the total synthesis of the diterpene chatancin [196].

The reductive lithiation of the enantiopure nitrile **424** led to an intramolecular cyclization to give the alkyllithium compound **425**, which was trapped with carbon dioxide to afford the ester **426** in 42% ee, due to isomerization of the radical formed prior to the formation of the α-alkoxy organolithium compounds [198] (Scheme 97).

Benzylic γ-alkoxy organolithium compounds **428** were prepared by reductive cleavage of 1,3-dioxanes **427** with lithium and naphthalene (5 mol %) at –40ºC [199]. They reacted with different electrophiles giving, after hydrolysis, the corresponding γ-substituted alcohols **429** (Scheme 98).

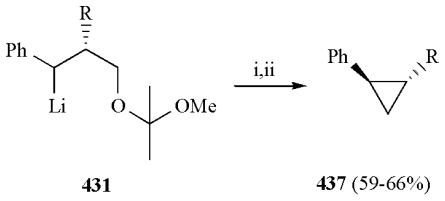
Carbolithiation of cinnamyl ethers or acetals with an alkyllithium in the presence of (–)-sparteine, previously described for cinnamyl alcohol **414** (Scheme 96), afforded organolithium intermediates of the type **430** and **431**, which were hydrolyzed to give the corresponding chiral 2-alkyl-3-phenylpropanols [189].

The carbolithiation of the cinnamyl methyl ether **432** with an alkyllithium at 0ºC in ether and in the presence of TMEDA gave intermediates **433**, which by reaction with electrophiles provided products **434** with good diastereoselectivities (up to 96% de) [200] (Scheme 99).

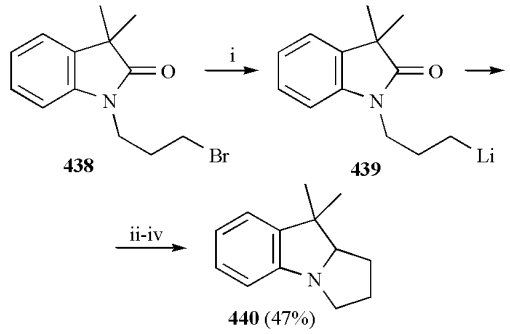
γ-Functionalized propargyllithiums were prepared by sulfur-lithium exchange from compounds **435** with lithium naphthalenide in THF at –78ºC. These intermediates were transformed into the corresponding propargylsilanes **436** by a diastereoselective retro-[1,4]-Brook rearrangement [201] (Scheme 100).

γ-Elimination reactions took place in the carbolithiation of the acetal derived from cinnamyl alcohol. Thus, when intermediates **431** were warmed to room temperature, 1,2-disubstituted cyclopropanes **437** are enantioselectively formed [189, 202] (Scheme 101).

γ-Nitrogenated alkyllithium compounds of the type **394** (X = NR_2) can be prepared by similar strategies as for the corresponding oxygenated systems. Recently, an intramolecular cyclization of the *N*-(bromopropyl)amide **438**



Scheme 101. *Reagents*: i, –50ºC to rt; ii, 2 M HCl.



Scheme 102. *Reagents*: i, *t*-BuLi, Et_2O, –78ºC; ii, –78 to 0ºC; iii, $LiAlH_4$; iv, NaOH.

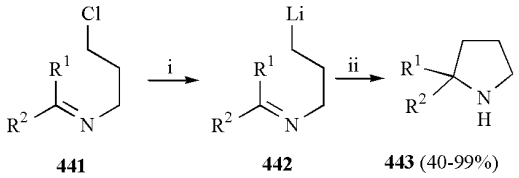
[203] and *N*-(3-chloropropyl)imine **441** [204] was used for the synthesis of pyrrolidines. Thus, bromine-lithium exchange, in the case of compound **438**, took place with *t*-BuLi at –78ºC in ether, giving the expected organolithium compound **439**, which by intramolecular cyclization followed by LAH reduction afforded the pyrrolo[1,2-*a*]indole **440** [203] (Scheme 102).

In the case of imines **441**, the corresponding organolithium compounds **442** were generated by reductive lithiation with lithium and DTBB at –78ºC. Intramolecular cyclization occurred at this temperature by an *endo-trig* process, giving after hydrolysis the corresponding 2-substituted pyrrolidines, including nornicotine [204] (Scheme 103).

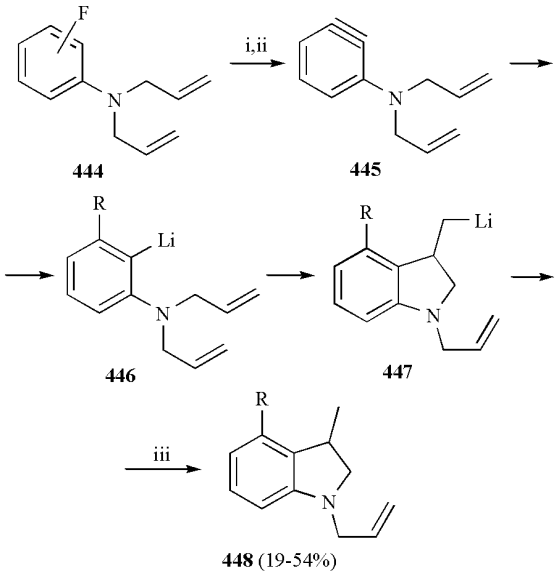
Regioselective *ortho*-lithiation of 2- or 3-fluoro-*N*,*N*-diallylaniline **444** with an excess of an organolithium reagent in methyl *t*-butyl ether (MTBE) initiated an anionic cascade providing the organolithium intermediates **447**, which after hydrolysis gave *N*-allyl 3,4-disubstituted indolines **448** [205] (Scheme 104). Initially, the benzyne derivative **445** was formed and, after addition of a molecule of the organolithium compound, resulted intermediate **446**, which underwent intramolecular cyclization forming the γ-nitrogenated alkyllithium compound **447**.

Intermolecular carbolithiation of secondary and tertiary cinnamyl amines **499** with BuLi in the presence of TMEDA or just in THF gave, after reaction with electrophiles, mainly products **501**, through the corresponding intermediates **500**. The same stereochemical outcome was obtained starting either from the (*E*)- or from (*Z*)-cinnamyl amines [189] (Scheme 105).

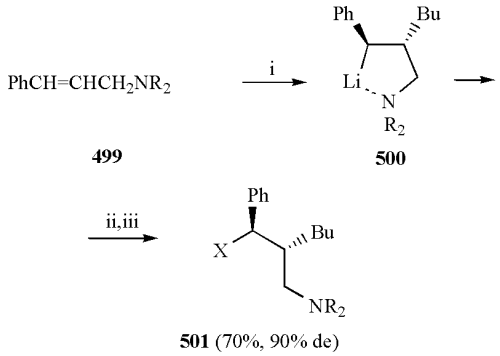
For the preparation of γ-sulfur-containing functionalized organolithium compounds, reductive methods were used. Thus, 2-phenylthietane **502** gave regioselectively the benzylic γ-thioxide intermediate **503** with lithium and DTBB at –78ºC. Treatment of this dianion with electrophiles afforded thiols **504** [206] (Scheme 106).



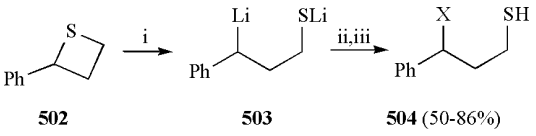
Scheme 103. *Reagents*: i, Li, DTBB (5 mol%), THF, –78ºC; ii, H_2O.



Scheme 104. *Reagents*: i, RLi (3 equiv), MTBE, 0ºC or rt; ii, rt; iii, H_2O.

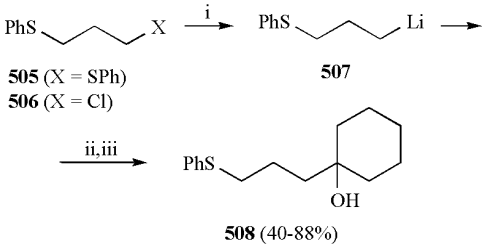


Scheme 105. *Reagents*: i, BuLi (1.5 equiv), –78 to 0ºC; ii, E = MeOD, $(MeS)_2$; iii, NH_3-H_2O.



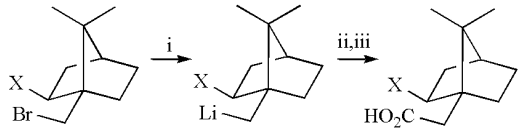
Scheme 106. *Reagents*: i, Li, DTBB (5 mol %), THF, –78ºC; ii, E = D_2O, R^1R^2CO, CO_2; iii, H_2O.

Similar reaction conditions were used for the preparation of the lithiated γ-thioether **507**. 1,3-Bis(phenylsulfanyl)-propane **505** or 1-chloro-3-(phenylsulfanyl)propane **506** gave intermediate alkyllithium **507**, which was trapped with



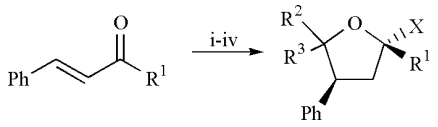
505 (X = SPh)
506 (X = Cl)
507
508 (40-88%)

Scheme 107. *Reagents*: i, $LiC_{10}H_8$, THF, –78ºC; ii, $(CH_2)_5CO$; iii, H_2O.



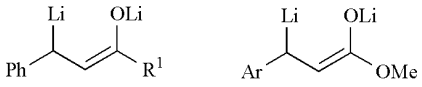
509 (X = Cl)
510 (X = F)
511 (X = Cl)
512 (X = F)
513 (X = Cl)
514 (X = F)

Scheme 108. *Reagents*: i, *t*-BuLi, –125ºC (X = Cl), –78ºC (X = F); ii, CO_2; iii, HCl.



515 **516** (23-51%)

Scheme 109. *Reagents*: i, Li, $C_{10}H_8$ (4 mol %), R^2R^3CO, $BF_3{\cdot}OEt_2$, THF, –78 to 0ºC; ii, H_2O; iii, Me_3SiH or Me_3SiCN or $Me_3SiCH_2CH{=}CH_2$, $BF_3{\cdot}OEt_2$, –78 to 20ºC; iv, $NaHCO_3$-H_2O.



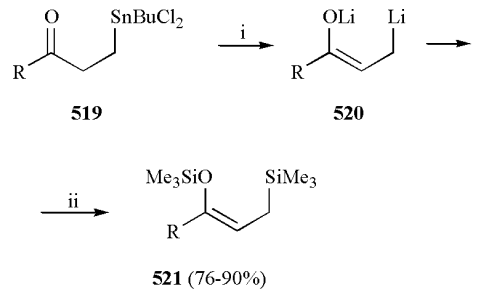
517 **518**

cyclohexanone to afford the product **508** in 40 or 88% yield, respectively [207] (Scheme 107).

γ-Halogenated functionalized organolithium compounds have a great tendency to undergo γ-elimination reactions. An exceptional case are intermediates **511** and **512**, which were prepared from the corresponding chloro or fluoro derivatives **509** and **510**, respectively. These intermediates were obtained by bromine-lithium exchange with *t*-BuLi at –125ºC and –75ºC, respectively. They could be trapped with carbon dioxide to afford carboxylic acids **513** and **514** in 7 and 47% yield, respectively [208] (Scheme 108).

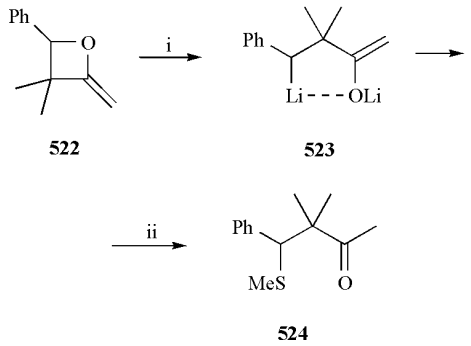
Lithium homoenolates **395** and **396** are very useful three-carbon homologating reagents with umpolung reactivity [2,209]. Unprotected carbonyl derivatives can be directly lithiated when a benzyllithium system is formed. Thus, α,β-unsaturated ketones **515** were treated with lithium powder in the presence of naphthalene (4 mol %) and working under Barbier-type conditions, that is, in the presence of the carbonyl compound activated with boron trifluoride, at –78ºC. The obtained lactols were finally transformed into the corresponding tetrahydrofurans **516** by reaction with silicon-containing nucleophiles [210] (Scheme 109).

In the case of cinnamates, the reduction with lithium in the presence of carbonyl compounds provided lactones in



519 **520**
521 (76-90%)

Scheme 110. *Reagents*: i, BuLi (4 equiv), THF, –78 to 0ºC; ii, Me_3SiCl.



522 **523**
524

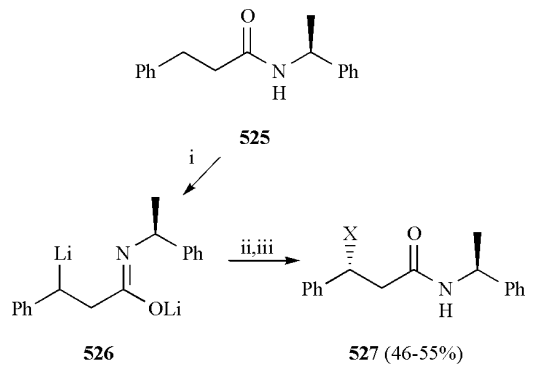
Scheme 111. *Reagents*: i, Li, DTBB (10 mol %), $(MeS)_2$, THF, –78ºC; ii, H_2O.

36-86% yield. These reactions can occur by a SET mechanism to give benzylic anions **517** and **518**. Intermediates of the type **517** were proposed in the reaction of aryllithiums with cinnamaldehyde in THF at room temperature and were trapped with alkyl halides in 33-99% yield [211].

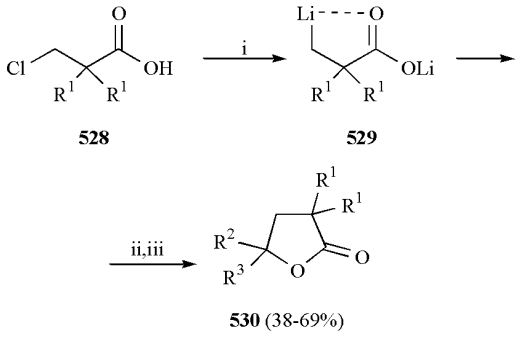
Similar α,β-unsaturated dianions **520** can be prepared from lithium enolates derived from β-tributylstannyl ketones by tin-lithium transmetallation [212]. It was recently proposed that in this process a α-deprotonation took first place forming a (*Z*)-enolate, which underwent then a transmetallation reaction [213]. Thus, γ-dichlorobutylstannyl ketones **519** reacted with an excess of BuLi in THF at temperatures ranging between –78 to 0ºC to give cleanly dianions **520**, which were trapped with chlorotrimethylsilane to afford products **521** [213a] (Scheme 110). Their corresponding cuprates were added to enones with formation of cyclic keto alcohols by subsequent attack of the enolate to the carbonyl group of the enone. However, in the case of the corresponding zincates, 1,6-diketones were obtained [213b].

The DTBB-promoted lithiation of 2-methylene-4-phenyloxetane **522** provoked the ring opening of the heterocycle giving the dianion **523**, which was trapped with dimethyl disulfide, to yield after hydrolysis the expected ketones **524** [214] (Scheme 111). However, in the presence of other electrophiles, such as carbonyl compounds or methyl iodide, only reaction of the enolate moiety was observed.

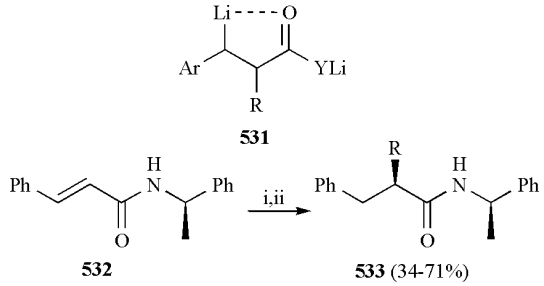
In the case of homoenolates derived from carboxylic acids or amides, it is simple to deactivate the functionality by deprotonation. Beak *et al.* have studied the direct γ-lithiation



Scheme 112. *Reagents*: i, *s*-BuLi (2 equiv), TMEDA, Et_2O, –78ºC; ii, E = $PhCH_2Br$, Me_3SiCl, MeI, BuI; iii, MeOH.



Scheme 113. *Reagents*: i, Li, DTBB (5 mol %), R^2R^3CO, THF, –78ºC; ii, H_2O; iii, PTSA.

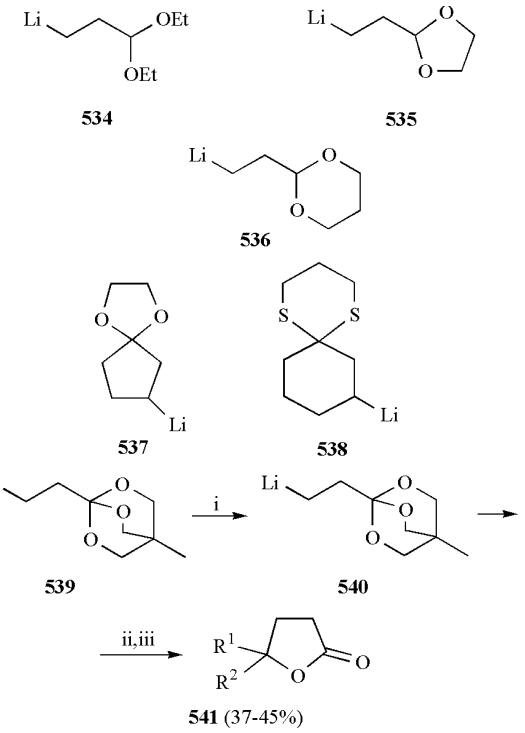


Scheme 114. *Reagents*: i, RLi (3 equiv), (–)-sparteine (3 equiv), cumene, –30 to –20ºC; ii, HCl.

of β-phenyl substituted carboxamides [215] by the so-called Complex Induced Proximity Effect (CIPE) [4]. Recently, chiral benzylic homoenolates were prepared by reaction of the corresponding amides derived from (*R*)- or (S)-1-phenylethylamine by deprotonation with *s*-BuLi in ether in the presence of TMEDA at –78ºC. For instance, the amide **525** gave a 1:1 mixture of diastereomers **526**, which reacted diastereoselectively with electrophiles to afford products **527** [216] (Scheme 112).

β-Chloropropanoic acids **528** (R^1 = H, Me) were first deprotonated and then lithiated in the presence of carbonyl compounds to give lactones **530**, after cyclization of the γ-hydroxy acids [217] (Scheme 113).

The carbolithiation of cinnamic acids and amides gave mixtures of 1,4- and 3,4-additions products. Only the last process gave homoenolates **531** as intermediates. In the case of the addition of organolithium compounds to cinnamic

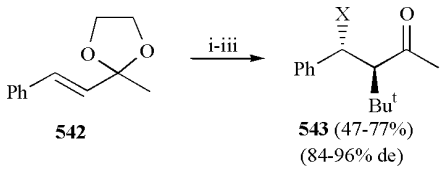


Scheme 115. *Reagents*: i, Li, DTBB (5 mol %), R^1R^2CO, THF, –78ºC; ii, phosphate buffer (pH = 7), –78ºC to rt; iii, PTSA.

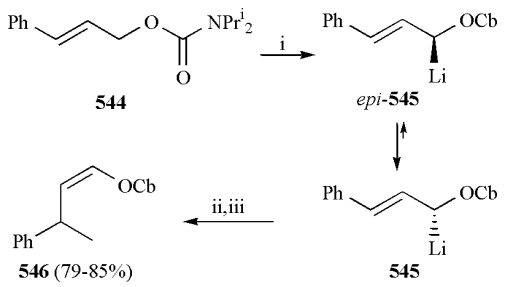
acids [218], electron-withdrawing groups at the aromatic ring increased the 3,4-addition. Mestres *et al.* proposed a polar addition mechanism, but a fast SET equilibrium followed by slow radical combination would also be possible [218c].

In the case of *N*-isopropylcinnamyl amide, the addition of BuLi complexed with (–)-sparteine gave preferentially the corresponding 3,4-addition product, working in cumene at temperatures ranging between –40 and –20ºC, but with low ee [219]. The addition of organolithium reagents to *N*-(1-phenylethyl)cinnamyl amides in the presence of (–)-sparteine afforded dianions of the type **531**. The amide **532** derived from (*R*)-α-methylbenzylamine was an appropriate substrate for the enantioselective preparation of products **533** [220] (Scheme 114). The *syn/anti* ratio obtained was between 75/25 and 95/5 with ee from 58 to 90%, BuLi, *n*-$C_6H_{13}Li$ and Me_3SiCH_2Li being the organolithium compounds used in these carbolithiation reactions.

Protected homoenolates derived from carbonyl compounds of the type **396** with acyclic structure **534-536** were mainly prepared by halogen-lithium exchange. Recent application of compound **534** to the reductive coupling with the aldehyde tosylhydrazone $PhCH_2CH_2CH$=NN-$(SO_2Ar)SiBu^tMe_2$, followed by treatment with acetic acid and trifluoroethanol gave, after molecular nitrogen elimination, $Ph(CH_2)_5CH(OEt)_2$ in 89% yield [221]. The same homoenolate **534** gave Michael addition to cyclohexenone in the presence of CuI and HMPA in THF at –78ºC in 40% yield, as well the corresponding dimerization product (72%) promoted by $CuCl_2$ [222]. The dioxolane derivative **535**, prepared by *t*-BuLi induced bromine-lithium exchange in ether at –78ºC, was acetylated with a Weinreb



Scheme 116. *Reagents*: i, *t*-BuLi, toluene, THF (1 equiv), 0ºC; ii, E = MeOH, MeOD, CO_2, $(MeS)_2$, MeI, –78ºC to rt; iii, NH_4Cl-H_2O.



Scheme 117. *Reagents*: i, BuLi, (–)-sparteine, toluene, –78ºC; ii, E = MeI, MeOTs; iii, H_2O.

amide and used for the preparation of the polypropionate C7-C16 subunit of zincophorin [223]. The 1,3-dioxane system **536** was used for the synthesis of highly functionalized porphyrins [224].

Cyclopentanone dioxolane **537** and cyclohexanone dithiane **538** lithium homoenolates were prepared from the corresponding β-phenylsulfanyl derivatives by reductive lithiation with LiDTBB in THF at –78ºC. They were alkylated with allylic bromides after transmetallation with the complex $CuBr{\cdot}SMe_2$ at –78ºC [225].

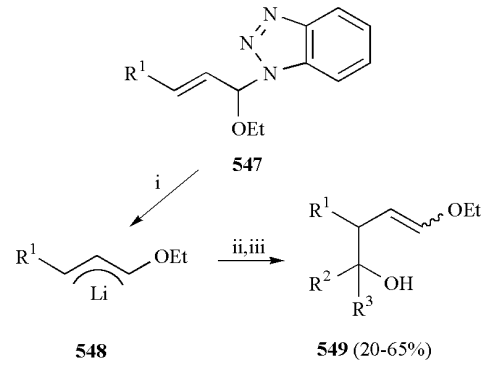
The masked propionic acid lithium homoenolate **540** was prepared from the β-chloro orthoester **539** by means of a DTBB-catalyzed lithiation. The coupling with carbonyl compounds was performed under Barbier-type conditions and applied to the synthesis of lactones **541** [226] (Scheme 115).

The cinnamyl acetal **542** underwent carbolithiation with *t*-BuLi in toluene at 0ºC and the corresponding lithium homoenolate reacted diastereoselectively with electrophiles yielding products **543** after hydrolysis [220] (Scheme 116).

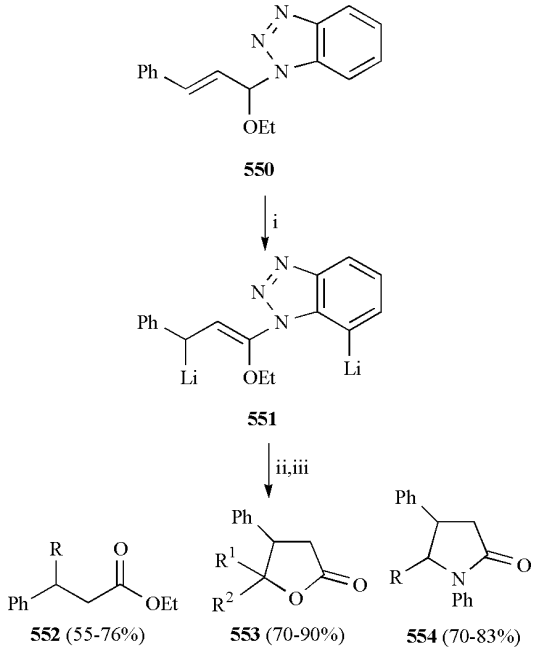
4.2. γ-Functionalized Allyllithium Compounds

Heterosubstituted allyl anions of the type **397** are also homoenolate anions equivalents (offensive strategy) [2,209,227]. The main problem with these reagents is the regioselectivity of the reaction with electrophiles. They can be prepared either by deprotonation of allylic systems or by tin-lithium transmetallation.

In a recent work about lithiated *O*-allyl carbamates [17] in enantioselective reactions, Hoppe *et al.* described that carbanion pairs resulting from the lithiation of (*E*)-cinnamyl *N*,*N*-diisopropylcarbamate **544** in the presence of (–)-sparteine were configurationally unstable and equilibrated even at temperatures below –50ºC [228]. The initially formed (1*S*)-*epi*-**545** was converted to the thermodynamically most stable (*R*)-intermediate **545** in toluene. Only methyl iodide and tosylate gave γ-attack with 50% ee for the iodide (anti-S_E2) and 48% for the tosylate (*syn*-S_E2). Acylation, silylation and stannylation took place at the α-position (Scheme 117).



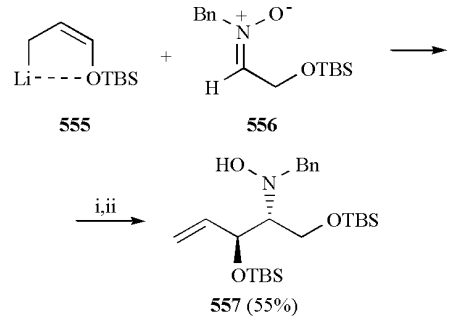
Scheme 118. *Reagents*: i, Li, $Br(CH_2)_2Br$, THF, –78ºC; ii, R^2R^3CO; iii, H_2O.



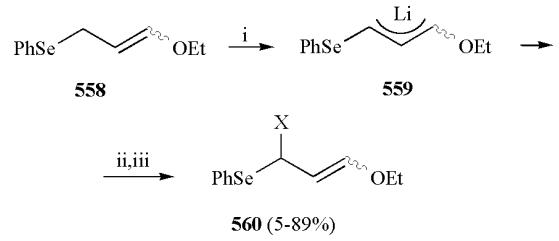
Scheme 119. *Reagents*: i, BuLi (2 equiv), THF, –78ºC; ii, E = RBr, R^1R^2CO, or R^1CH=NPh; iii, HCl-EtOH.

Carbon-nitrogen bonds of *N*-(α-ethoxyallyl)benzotriazoles **547** can be cleaved by lithium in the presence of lithium bromide in THF at –78ºC to afford delocalized intermediates **548**, which after addition of carbonyl compounds, gave mainly homoaldol products **549** [229] (Scheme 118). Alternatively the reaction can be performed under Barbier-type conditions. γ-Attack was observed with aromatic and also aliphatic aldehydes in the case of the γ-phenyl substituted benzotriazole **547** (R^1 = Ph). Compounds **549** were obtained as a *Z/E* mixture of diastereomers.

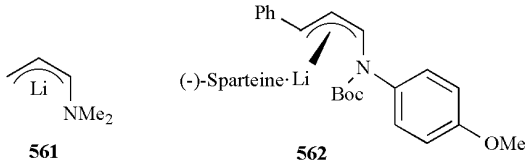
Related compound **550**, derived from benzotriazole, gave after deprotonation with BuLi dilithiated intermediate **551**, which reacted regioselectively with alkyl halides, carbonyl



Scheme 120. *Reagents*: i, THF, –40ºC; ii, H_2O.



Scheme 121. *Reagents*: i, LDA, THF, –78ºC; ii, E = D_2O, RHal, R^1R^2CO; iii, H_2O.

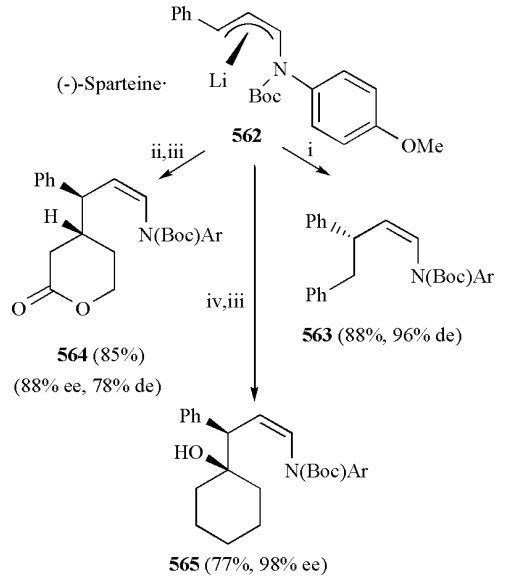


compounds and imines at the γ-position. Thus, compounds **551** were converted into β-substituted esters **552**, γ-lactones **553** and γ-lactams **554**, after final hydrolysis [230] (Scheme 119).

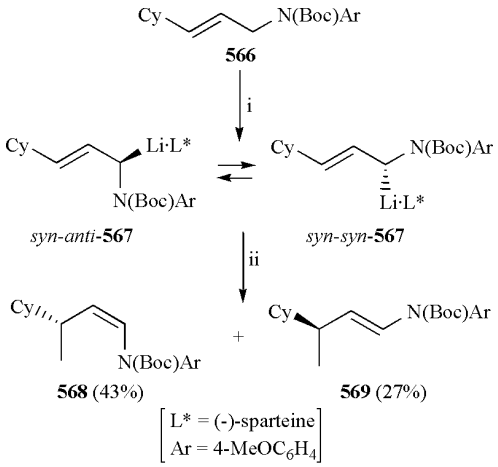
Allyl γ-silyl ethers derived carbanions are in rapid equilibrium with the corresponding α-silyl alkoxides, this behaviour being called the silyl-Wittig rearrangement. Intermediate **555**, prepared by deprotonation of the corresponding allyl silyl ether with *s*-BuLi in THF at –40ºC, reacted at the γ-position with the nitrone **556** to give the *anti*-hydroxylamine **557**, a precursor of 2-(hydroxymethyl)-3,4-pyrrolidinediol [231] (Scheme 120).

The 1,3-disubstituted allyllithium compound **559** was prepared by LDA deprotonation of 1-ethoxy-3-(phenylselenanyl)-1-propene **558** at –78ºC. It reacts with electrophiles at the α-position, respect to the selenium atom, to give products **560** as mixture (up to 5/1) of *Z/E*-diastereomers [232] (Scheme 121).

1-Aminoallyl organolithium compounds **397** (X = NR_2) are obtained either by deprotonation of enamines or allylic amines, or *via* tin-lithium transmetallation. They are useful homoenolate equivalents [2,209,227] because they react with different electrophiles regioselectively at the γ-position. Recent NMR studies show that 1-(dimethylamino)allyllithium **561**, as well as the corresponding potassium derivative, exists exclusively in the *endo*-conformation in THF, which is thermodynamically more stable than the *exo*



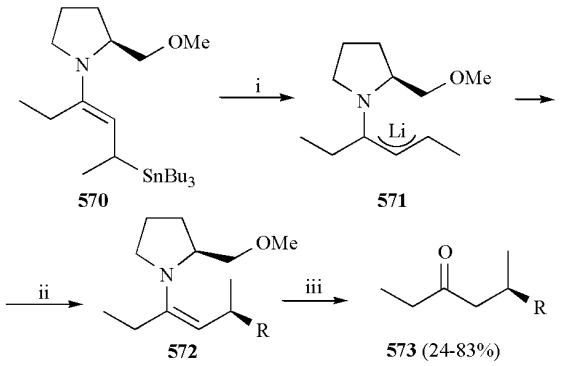
Scheme 122. *Reagents*: i, $PhCH_2Br$; ii, compound **V** (see text); iii, H_2O; iv, $(CH_2)_5CO$.



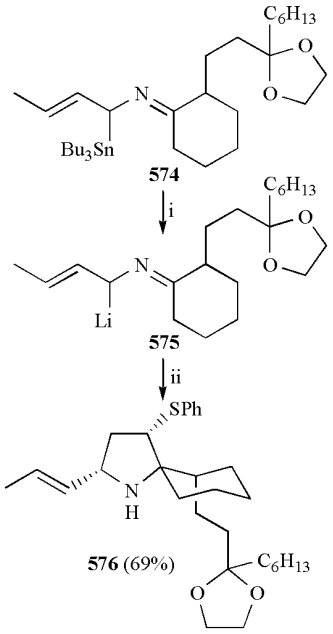
Scheme 123. *Reagents*: i, BuLi, (–)-sparteine, toluene, –78ºC; ii, MeI.

one according to ab initio calculations [233]. Cryoscopic measurements indicate that the lithium compound exhibits a monomer-dimer equilibrium shifted in favour of the dimer at higher concentrations. Solid-state structural investigation of the (–)-sparteine containing allyllithium compound **562**, prepared by deprotonation of the corresponding N-Boc-N-(p-methoxyphenyl)cinnamylamine with BuLi in the presence of (–)-sparteine, showed that the lithium atom is associated to the allyl moiety in a η^3-fashion [234]. This fact is in contrast to the analogous carbamoyloxy trimethylsilyl allyllithium·(–)-sparteine complex, in which the lithium atom is coordinated in a η^1-manner, lithium and sparteine being on the *Re* face of the allyl unit [235].

The alkylation of intermediate **562** with benzyl bromide took place with inversion yielding product **563**, whereas Michael addition to 5,6-dihydro-2H-pyran-2-one (**V**) and reaction with cyclohexanone occurred with retention of the configuration giving compounds **564** and **565**, respectively



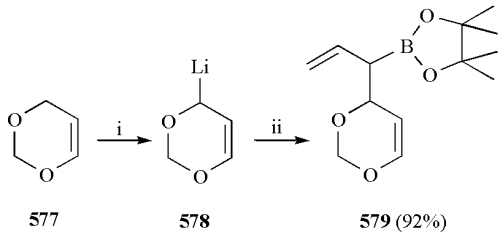
Scheme 124. *Reagents*: i, BuLi, THF, –78 to 20ºC; ii, RHal, –78ºC; iii, 4 M HCl.



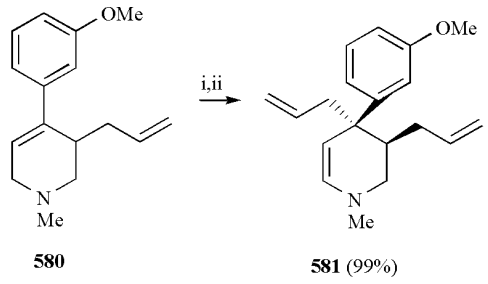
Scheme 125. *Reagents*: i, BuLi, CH_2=CHSPh, THF, –78ºC; ii, H_2O.

[234a,b] (Scheme 122). Solution structure of compound **562** was studied with ^{6}Li and ^{13}C NMR techniques showing that it has a monomeric η^3 *endo-syn-anti* structure [236]. Michael addition of compound **562** to α,β-unsaturated nitro compounds and alkylidene malonates or related activated olefins gave the expected products in good yields and high enantioselectivity and diastereoselectivity [237]. In the case of nitroalkenes, this methodology was applied to the synthesis of substituted piperidines, such as (–)-paroxetine, which hydrochloride is a selective seratonin reuptake inhibitor [237b]. After hydrolysis of γ-alkylated compounds of type **563** with 6 M HCl, β-substituted enantioenriched aldehydes are obtained [4]. They can be oxidized to β-substituted acids by means of sodium chlorite and esterified to the corresponding esters [238].

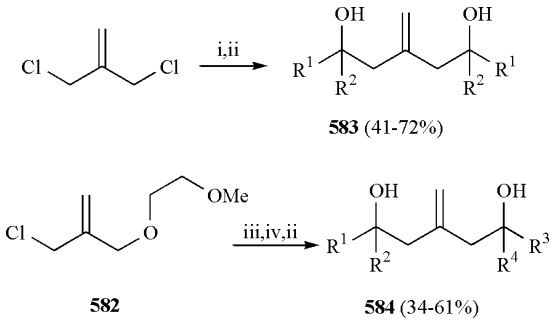
However, the organolithium compound **567** derived from 3-cyclohexylallylamine **566** is a configurationally stable η^1-coordinated monomer. From NMR studies, it was deduced that intermediate **567** exists as two rotamers and the electrophilic substitution afforded a mixture of *Z/E* products **568** and **569** [239] (Scheme 123).



Scheme 126. *Reagents*: i, *t*-BuLi, Et_2O, –78ºC; ii, CH_2=CHCH(Cl)B(OCMe$_2$)$_2$.



Scheme 127. *Reagents*: i, *s*-BuLi, THF, –45ºC; ii, CH_2=CHCH$_2$Br, –78ºC to rt.



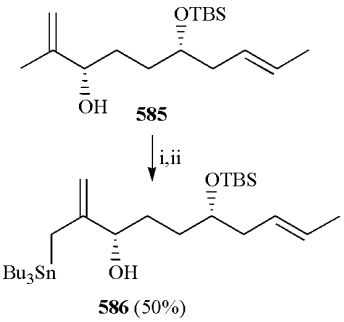
Scheme 128. *Reagents*: i, Li, $C_{10}H_8$ (5 mol %), E = R^1R^2CO, THF –78ºC to rt; ii, H_2O; iii, (2.5 Li, $C_{10}H_8$ mol %), E = R^1R^2CO, THF, –78 to –30ºC; iv, (2.5 Li, $C_{10}H_8$ mol %), E = R^3R^4CO, -30ºC to rt.

For the asymmetric synthesis of β-substituted aliphatic ketones **573**, chiral *endo*-aminoallyllithium **571** was prepared by tin-lithium transmetallation from the *O*-methylprolinol derivative **570**, and submitted to successive alkylation giving compounds **572** and final hydrolysis [240] (Scheme 124).

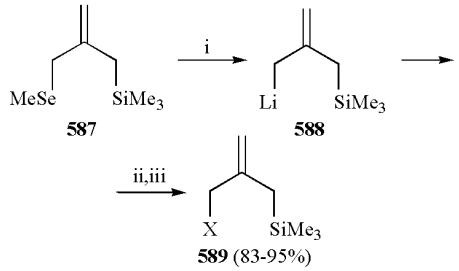
When α-(tributylstannyl)crotylamine was transformed into its corresponding imine **574**, the lithiation with BuLi afforded a 2-azapentadienyl anion **575**, which takes part in a cycloaddition reaction with phenyl vinyl sulfide affording regio and stereoselectively the pyrrolidine **576**, an intermediate used for the synthesis of 2,13-diepilepadiformine [241] (Scheme 125).

The cyclic allyllithium compound **578**, derived from 1,3-dioxene **577**, was alkylated with α-chloroallyl boronate to give the conjunctive reagent **579**, which was used in the synthesis of phenalamide A_2 [242] (Scheme 126).

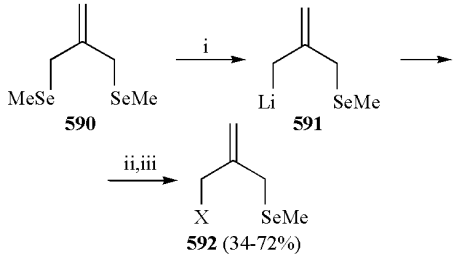
Tetrahydropyridine **580** was lithiated with *s*-BuLi and alkylated with allyl bromide at the γ-position to give quantitatively the cyclic enamine **581**, which was applied to



Scheme 129. *Reagents*: i, BuLi, Et_2O, THF, TMEDA; ii, Bu_3SnI.



Scheme 130. *Reagents*: i, BuLi, THF, –78ºC; ii, E = *n*-$C_{12}H_{25}I$, epoxides, R^1R^2CO, $R^1CH{=}NR^2$; iii, $KHCO_3$-H_2O.

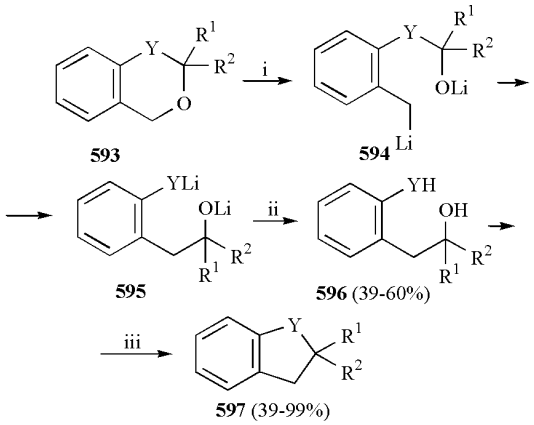


Scheme 131. *Reagents*: i, BuLi, THF, –78ºC; ii, E = R^1Br, R^1R^2CO; iii, H_2O.

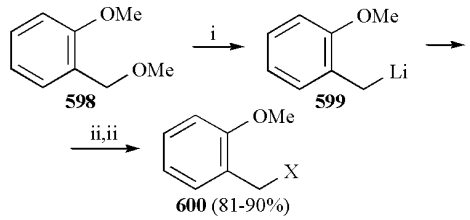
the synthesis of 4a-aryloxodecahydroisoquinolines [243] (Scheme 127).

Methallyllithium compounds of the type **398** were prepared by chlorine-lithium exchange. Thus, 3-chloro-2-(chloromethyl)-1-propene was submitted to a naphthalene-catalyzed lithiation in the presence of carbonyl compounds (Barbier-type conditions) at temperatures ranging between –78ºC and room temperature, giving, after hydrolysis the expected products **583**. In the case of the starting material **582**, after the first chlorine-lithium exchange at –78 to –30ºC in the presence of the first carbonyl compound, a second lithiation of the carbon-oxygen bond took place at room temperature, so a second carbonyl compound was added, allowing after hydrolysis the preparation of diols **584**, with different substitution at both sides of the molecule [244] (Scheme 128). This strategy was used for the synthesis of perhydrofurofurans [244] and perhydrofuropyrans [245].

Deprotonation of methallyl alcohols with BuLi in the presence of TMEDA took place by an alkoxide-assisted lithiation. In the case of compound **585**, the corresponding stannane **586** was prepared following this methodology, after lithium-tin transmetallation, and used in the total synthesis of (+)-amphidinolide K [246] (Scheme 129).



Scheme 132. *Reagents*: i, Li, DTBB (4.5 mol %), THF, rt (Y = O) or –78ºC (Y = S); ii, H_2O; iii, PTSA.



Scheme 133. *Reagents*: i, Li, $C_{10}H_8$ (5 mol %), THF, –10ºC; ii, E = D_2O, *t*-BuCHO; iii, H_2O.

Intermediate **588** bearing a trimethylsilyl group was prepared from compound **587** by selenium-lithium exchange, and applied to the synthesis of 2-substituted allyl silanes **589** [247] (Scheme 130). The mentioned intermediate **588** was used by other authors for the synthesis of different allylsilanes [248].

Related methylselenanyl methallyl anion **591** was also prepared by selenium-lithium exchange starting from the material **590** and using BuLi at –78ºC for that purpose. Further reaction with different electrophiles afforded products **592** [249] (Scheme 131).

4.3. γ-Functionalized Benzyllithium Compounds

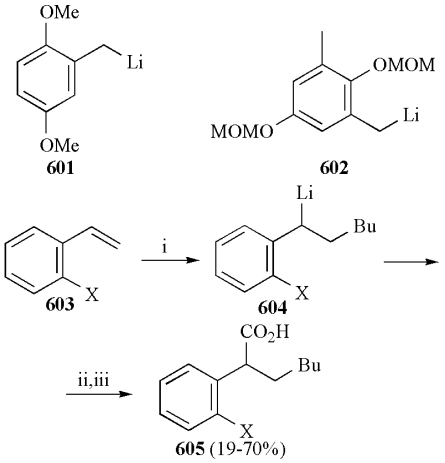
In this section it would be considered benzyllithium reagents of the type **399** with the functionality linked to the *ortho*-position of the aromatic ring being, in general, generated by a α-deprotonation reaction. Recently, 2-alkoxide and 2-thioalkoxide benzyllithiums **594** were proposed in the reductive lithiation of benzo-1,3-dioxanes and 1,3-oxathianes **593**, respectively, using lithium and a catalytic amount of DTBB at room temperature (Y = O) or –78ºC (Y = S). After involving rearranged intermediates **595**, homobenzyl alcohols **596** were obtained, which after treatment with *p*-toluenesulfonic acid gave heterocycles **597** [250] (Scheme 132).

Reductive lithiation of arylalkyl methyl ethers was also carried out with lithium and a catalytic amount of naphthalene giving different 2-, 3- and 4-substituted benzyllithium compounds. In the case of the *ortho*-methoxy derivative **598**, the reaction was carried out in THF at –10ºC

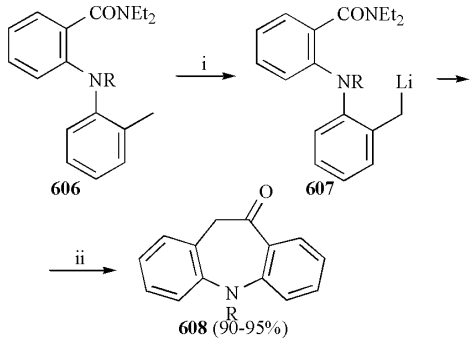
to give the intermediate **599**, which was trapped with electrophiles affording products **600** [251] (Scheme 133).

Alkoxy benzyllithiums **601** [252] and **602** [253] were prepared by reductive lithiation with lithium starting from the corresponding benzyl ether and benzyl chloride, respectively. Intermediate **601**, generated at –10ºC was added at –70ºC to a carbohydrate enone to give a mixture (*ca.* 1:2) of 1,2- and 1,4-addition products in 38% yield [252]. Intermediate **602** was prepared at 0ºC with lithium and reacted with a rather hindered ketone under sonication conditions in 70% yield, having been used in the synthesis of the diterpenes stypodiol and spistypodiol [253].

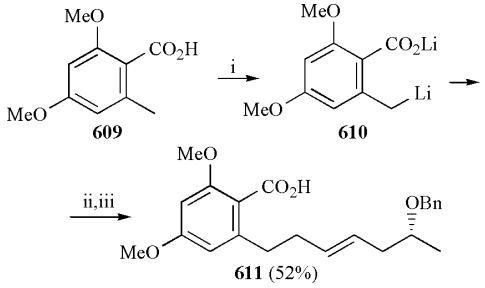
The carbolithiation [188] of *ortho*-substituted styrenes **603** with BuLi at –95ºC in the presence of (–)-sparteine was used for he synthesis of different γ-functionalized



Scheme 134. *Reagents*: i, BuLi, (–)-sparteine, cumene, -95°C; ii, CO_2; iii, 5% HCl.



Scheme 135. *Reagents*: i, LDA, TMEDA, THF, –20°C; ii, NH_4Cl-H_2O.



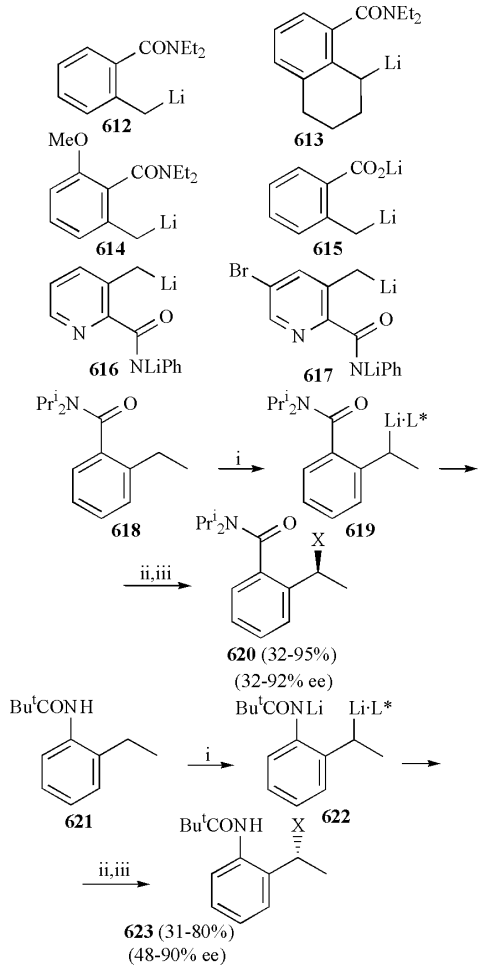
Scheme 136. *Reagents*: i, LDA (2 equiv), THF, –78 to –10ºC; ii, **VI** (see text), –30ºC to rt; iii, 2 M HCl.

benzyllithiums **604**, which were carboxylated to give the corresponding 2-arylalkanoic acids with up to 72% ee [254] (Scheme 134).

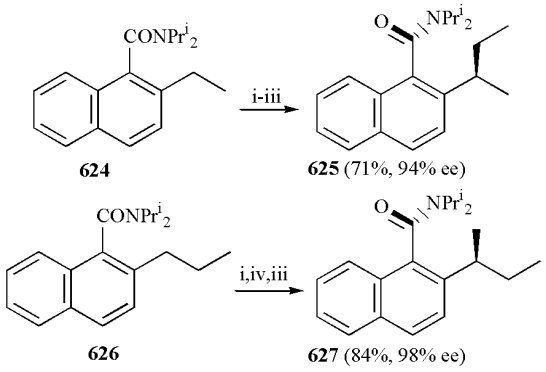
For the synthesis of the antiepileptic oxcarbazepine and analogues, *N*-benzyl allyl protected *N*-*o*-tolylanthranyl-amides **606** were deprotonated with different bases to give intermediate benzyllithiums **607**, which cyclized to the corresponding dibenzoazepinones **608** [255] (Scheme 135). Among the different bases essayed, LDA/TMEDA in THF at –20ºC gave the best results.

Benzyllithiums bearing a carboxylate at the *ortho* position such as compound **610** were used for the convergent synthesis of β-resorcylic acid derivatives [256]. Dianion **610** was prepared by deprotonation of the acid **609** with LDA at –78 to –10ºC and it was alkylated with (2*E*,5*R*)-5-benzyloxy-1-bromo-2-hexene (**VI**) to give the product **611** (Scheme 136).

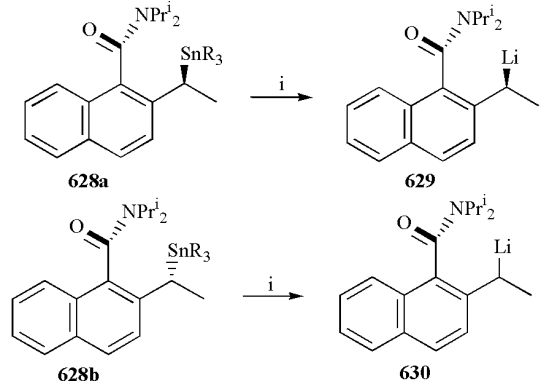
In a similar way, the amide **612**, prepared by deprotonation with LDA, was allylated with 1,1-dimethyl-3-chloropropene at the benzylic position to give an intermediate in the synthesis of the norsesquiterpenic lactone platyphyllide [257]. In the case of the anion **613**, the deprotonation of the starting amide was performed with



Scheme 137. *Reagents*: i, *s*-BuLi, MTBE, (–)-sparteine, –78ºC; ii, E = R_3SiCl, R_3SnCl, RHal, R_2CO; iii, H_2O.



Scheme 138. *Reagents*: i, *s*-BuLi, THF, –78ºC; ii, EtI; iii, H_2O; iv, MeI.



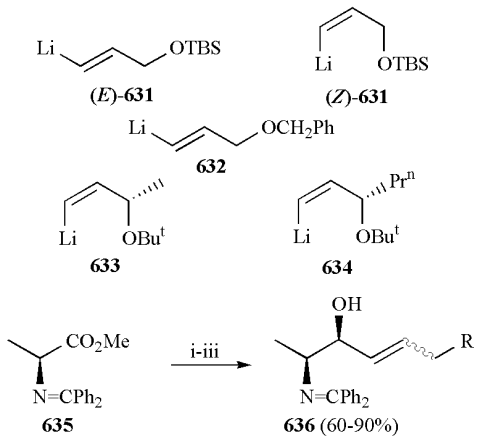
Scheme 139. *Reagents*: i, BuLi, THF, –78ºC.

BuLi at –70ºC, and reacted with DMF to afford the corresponding aldehyde in 92% yield [258]. The amide **614** was alkylated by coupling with an aldehyde tosylhydrazone [221]. In addition, different benzyllithiums **615-617** were prepared by deprotonation with *s*-BuLi or LDA, this strategy being applied to the synthesis of the anticancer agent Sch 66336 [259].

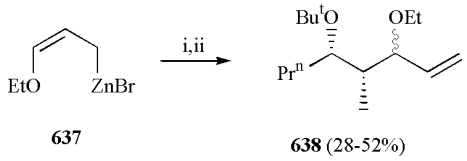
Lateral lithiation of *N*,*N*-diisopropyl(*o*-ethyl)benzamide **618** with *s*-BuLi in the presence of (–)-sparteine at –78ºC followed by electrophilic substitution gave products **620** with variable ee, intermediates **619**, being involved in the process. The enantiodetermining step occurred after deprotonation. The same happens in the case of *N*-pivaloyl-(*o*-ethyl)aniline **621** when the lithiation took place at –25ºC. Enantioenrichment in the first case arises from a dynamic kinetic resolution and a thermodynamic one in the second [260] (Scheme 137). The mentioned strategy was applied to the formal synthesis of (–)- and (+)-curcuphenol [261].

Tertiary 1-naphthamides are chiral compounds with the amide moiety perpendicular to the aromatic ring. Amide **624** can be resolved into the corresponding enantiomers, which racemized in solution at ambient temperature for some days. The lithiation with *s*-BuLi in THF at –78ºC followed by alkylation gave compound **625** almost as a single diastereomer. The other epimer **627** was prepared by methylation of the amide **626** [262] (Scheme 138). Both atropoisomers could be interconverted by heating at 65ºC.

The corresponding atropoisomeric stannanes **628** underwent tin-lithium transmetallation to give diastereomeric



Scheme 140. *Reagents*: i, *i*-Bu_5Al_2H, CH_2Cl_2, –78 to 0ºC; ii, **631** or **632**, –78ºC to rt; iii, $NaHCO_3$-H_2O.



Scheme 141. *Reagents*: i, **634**, Et_2O, rt; ii, NH_4Cl-H_2O.

benzyllithiums **629** and **630**, respectively. In the case of isomer **628a**, the transmetallation proceeded with retention but the other atropoisomer **628b** underwent unusual nonstereospecific tin- lithium exchange (Scheme 139). These type of benzyllithiums were used for the generation of new stereogenic centers [263].

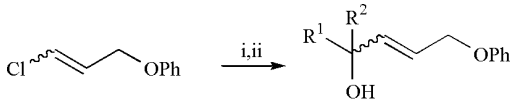
4.4. γ-Functionalized Alkenyllithium Compounds

Vinyllithium compounds of the type **400** can have *Z*- or *E*-configuration depending on the functional group and the structure of the starting material used in their preparation. Moreover, direct lithiation competes with the allylic deprotonation. In general, halogen- or tin-lithium exchange methodologies are preferred for the generation of these reagents in a stereospecific manner.

O-Protected γ-lithiated allyl alcohols **631** and **632** were prepared from the corresponding iodoalkenes (better than from bromoalkenes) in hexane by iodine-lithium exchange with *t*-BuLi at 0ºC. These reagents reacted with the *in situ* generated aldehyde derived from the benzophenone imine of methyl alaninate **635** to give the corresponding *threo*-alcohols **636** in good yields and high stereoselectivity (>20:1) [264] (Scheme 140).

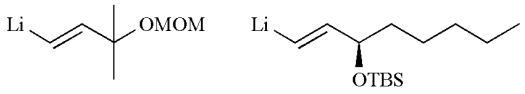
Lithiated allylic ethers **633** and **634**, also prepared by iodine-lithium exchange with *t*-BuLi in ether at –78ºC [265], were carbometallated [266] with the allylzinc reagent **637** to give, in the case of reagent **634**, linear 3,5-dialkoxy-4-methyl alkenes **638** [267] (Scheme 141). In the presence of magnesium bromide this reaction gave 1-vinyl-2-alkoxyalkyl cyclopropanes.

In the case of a 3/2:*Z*/*E*-mixture of 3-chloroallyl phenyl ethers **639**, the reductive lithiation with lithium and a catalytic amount of DTBB, in the presence of the



639 **640** (24-38%)

Scheme 142. *Reagents*: i, Li, DTBB (5 mol %), R^1R^2CO, THF, –78ºC; ii, H_2O.



641 **642**

corresponding carbonyl compound, gave a diastereomeric mixture of compounds **640** in moderate yields [268] (Scheme 142).

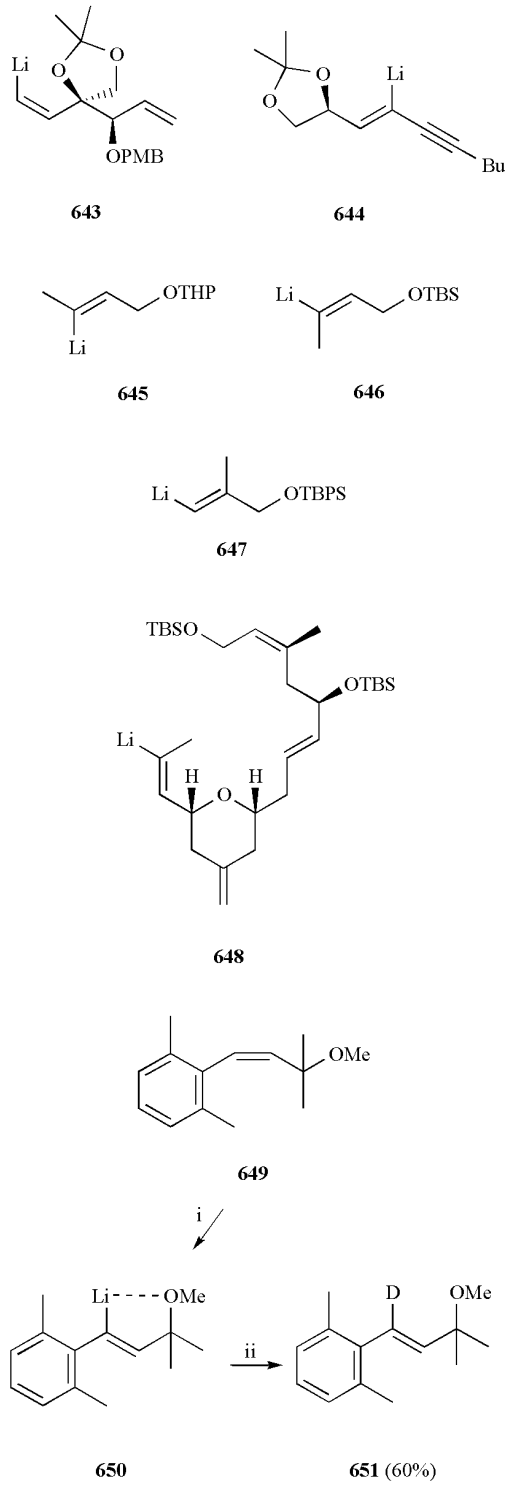
More substituted lithiated allylic alcohols such as intermediates **641** [269] and **642** [270] were prepared by tin-lithium exchange with BuLi in ether at –78ºC. In the first case, reagent **641** reacts with an aldehyde as electrophile in 87% yield, used for the synthesis of 1α,25-dihydroxyvitamin D_2 and the corresponding C-24 analogous [269]. Silylated reagent **642** [271] was transformed into the corresponding organozincate and added to a cyclopentenone for the synthesis of prostaglandins with neurotrophic activity [270].

Reagents **643** [272] and **644** [273] derived from the corresponding protected diols were prepared from the corresponding iodides by iodine-lithium exchange using *t*-BuLi in THF at –78ºC and from the corresponding bromides (4/1 *Z*/*E*-mixture of diastereomers) with *s*-BuLi in ether at –78ºC, respectively. Compound **643** reacted with a bicyclic ketone affording an alcohol in 85% yield, suitable for an anionic oxy-Cope rearrangement with formation of bicyclo[6.2.1]undecanes [272]. Intermediate **644** was used for the synthesis of the butenolide fugomycin [273].

Crotyl alcohol derivatives such as the organolithium compounds **645** [275] and **646** [276] were prepared from the (*Z*)-iodo derivatives by treatment with *t*-BuLi in ether at –100ºC and from the corresponding (*E*)-bromide at –78ºC, respectively. Both reagents reacted with aldehydes to give the corresponding alcohols as mixtures of diastereoisomers in 86 and 81% yield, respectively. The first case was applied to the synthesis of the lactones (5*R*)- and (5*S*)-polyandrane [275]. The second case was used in the synthesis of the polyene crassostreaxanthin B [276].

Methallyl alcohol derived organolithium **647** was prepared by iodine-lithium exchange and used for the synthesis of the corresponding tin compound [277] and the boronic acid [278] derivatives, for a Stille and Suzuki coupling reaction, respectively, with α,β-unsaturated α-haloesters.

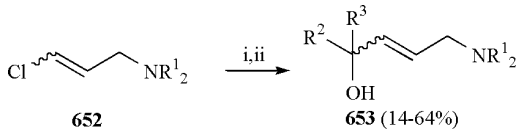
The more substituted γ-alkoxy vinyllithium **648** was prepared by bromine-lithium exchange with *t*-BuLi and transformed into a high-order cuprate for the coupling with an epoxide used in the total synthesis of the macrolide of the marine origin (+)-zampanolide [279].



643 **644** **645** **646** **647** **648** **649** **650** **651** (60%)

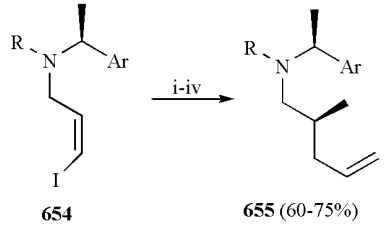
Scheme 143. *Reagents*: i, Li, DTBB (5 mol %), R^1R^2CO, THF, –78ºC; ii, H_2O.

A competitive deprotonation between a vinyl and a benzyl hydrogen was studied with twisted styrenes followed by D_2O quenching. It was found that the vinyl deprotonation is more favoured due to a σ-π* orbital interaction between the carbon-hydrogen bond to be cleaved and a π* of the ring. For instance, in the case of compound **649**, intermediate **650**



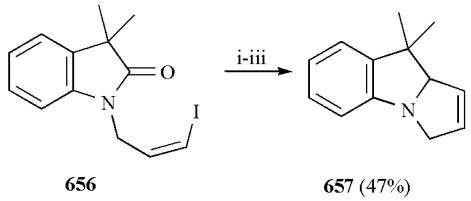
652 **653** (14-64%)

Scheme 144. *Reagents*: i, Li, DTBB (5 mol %), R^2R^3CO, THF, –78ºC; ii, H_2O.



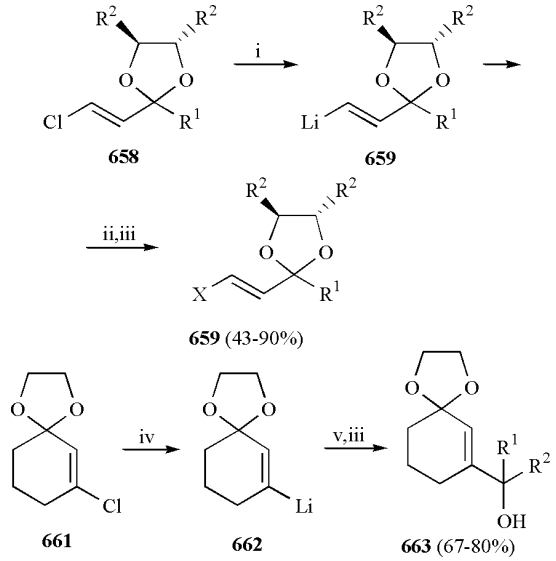
654 **655** (60-75%)

Scheme 145. *Reagents*: i, *t*-BuLi (2 equiv), Et_2O, –40ºC; ii, CH_2=$CHCH_2MgBr$ (2 equiv); iii, $ZnBr_2$ (2 equiv); iv, H_2O.



656 **657** (47%)

Scheme 146. *Reagents*: i, *t*-BuLi, Et_2O, –78 to 0ºC; ii, $LiAlH_4$; iii, 2 M NaOH.



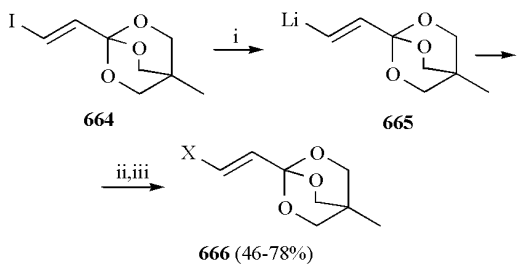
659 (43-90%)

661 **662** **663** (67-80%)

Scheme 147. *Reagents*: i, Li, DTBB (4 mol %), THF, –90ºC; ii, E = H_2O, D_2O, R^3R^4CO, –90 to –60ºC; iii, H_2O; iv, Li, DTBB (5 mol %), THF, –78ºC; v, E = R^1R^2CO, –78ºC.

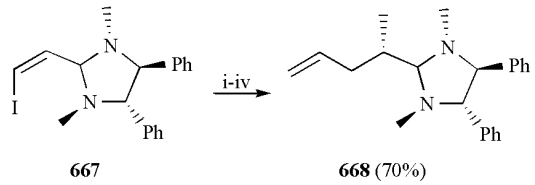
is mainly formed, which after deuterolysis afforded the labelled product **651** [280] (Scheme 143).

Allylamines lithiated at the γ-position have been less studied in the last time. Chlorinated allylamines **652** (as a 3/2:*Z*/*E* mixture of diastereoisomers) were reductively lithiated, as in the case of ether **639** (Scheme 142), and allowed to react with carbonyl compounds under Barbier-type conditions affording products **653** [268] (Scheme 144).



664 **665** **666** (46-78%)

Scheme 148. *Reagents*: i, *t*-BuLi, Et_2O, –78ºC; ii, E = R^1R^2CO, lactones, RCON(OMe)Me; iii, H_2O.



667 **668** (70%)

Scheme 149. *Reagents*: i, *t*-BuLi (2 equiv), Et_2O, –30ºC; ii, CH_2=$CHCH_2MgBr$ (2 equiv); iii, $ZnBr_2$ (2 equiv); iv, H_2O.

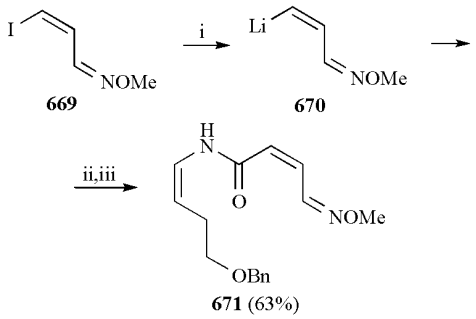
Chiral allylic amines **654** were lithiated, subsequently carbometallated [266] with allylmagnesium bromide, and treated with zinc bromide to give organobismetallic compounds, which were hydrolyzed providing diastereoselectively the amines **655** in up to 92% de [281] (Scheme 145).

The *N*-allyl amide **656** with an iodine atom at the γ-position was lithiated with *t*-BuLi and the intermediate vinyllithium reacted intramolecularly giving, after reduction with $LiAlH_4$, the pyrrolo[1,2-*a*]indole **657** [203] (Scheme 146).

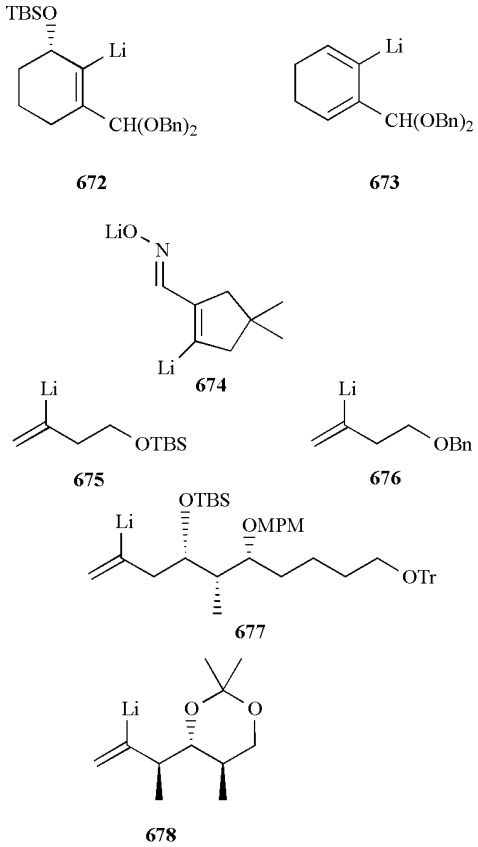
Reagents of the type **401** are considered β-acylvinyl anion equivalents [173]. Protected α,β-unsaturated carbonyl compounds with a halogen at the β-position were used as starting materials for the preparation of the corresponding vinyllithium intermediates. In the case of β-chloro α,β-unsaturated ketones with *E*-configuration, their corresponding acetals **658** were lithiated with lithium in the presence of DTBB to give stereoselectively organolithiums **659**, which were trapped with different electrophiles [180] (Scheme 147). No diastereoselection was observed in the case of the acetal derived from (2*R*,3*R*)-butanediol and prochiral aldehydes. On the other hand, 3-chloro-2-cyclohexenone acetal **661** was lithiated under similar reaction conditions giving adducts **663**, after reaction of the corresponding intermediates **662** with carbonyl compounds.

Protected *trans*-β-lithiated acrylic acid equivalent **665** was prepared for the first time from the corresponding iodide **664** by reaction with *t*-BuLi at –78ºC. This anion was allowed to react with carbonyl compounds, lactones and Weinreb amides, affording stereoselectively *E*-products **666** [283] (Scheme 148). This reagent **665** was used for the synthesis of (+)-brefeldin A.

(*Z*)-β-Iodo acrolein was derivatized to give the C_2-symmetric aminal **667** and submitted to lithiation with *t*-BuLi. Subsequent carbometallation with allylmagnesium



Scheme 150. *Reagents*: i, BuLi, hexane, –78ºC; ii, (*Z*)-$BnO(CH_2)_2CH=CHNCO$, –78ºC; iii, H_2O.

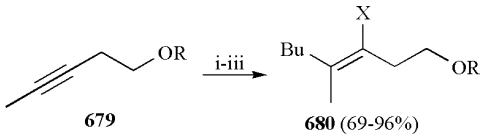


bromide and addition of zinc bromide (see Scheme 145) gave product **668** in 90% de [281] (Scheme 149).

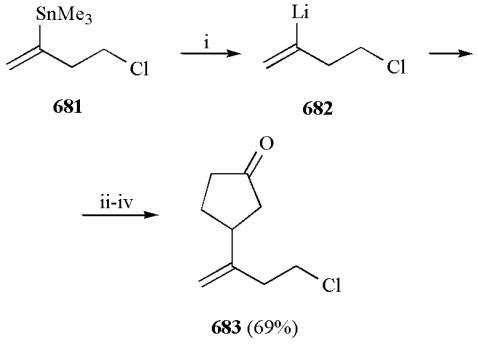
When (*Z*)-β-iodo acrolein was protected as *N*-methoxyimine **669**, after iodine-lithium exchange with BuLi give intermediate **670**, the amide **671** being isolated by reaction of this organolithium with a vinylic isocyanate [283] (Scheme 150).

Cyclic vinyllithiums derived from aldehydes **672** [284] and **673** [285] were used by Kuwajima *et al.* for the total synthesis of (+)-taxusin and taxol, respectively. They are prepared by bromine-lithium exchange with *t*-BuLi at –78ºC.

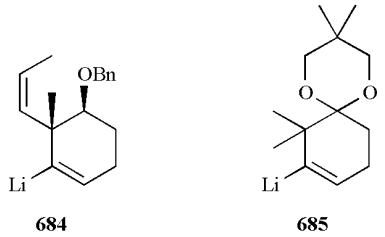
The oxime derived dianion **674** [286] was prepared by treatment of the corresponding vinyl bromide with an excess of *t*-BuLi (3 equiv) in THF at –78ºC. It was coupled with a



Scheme 151. *Reagents*: i, BuLi (3 equiv), $Fe(acac)_3$ (5 mol %), toluene, –20ºC; ii, E = D_2O, $ClSiHMe_2$, R^1R^2CO; iii, 1 M HCl.



Scheme 152. *Reagents*: i, MeLi, THF, –78ºC; ii, CuCN, LiCl, –78ºC; iii, cyclopentenone, $BF_3{\cdot}OEt_2$, –78ºC; iv, NH_4Cl.



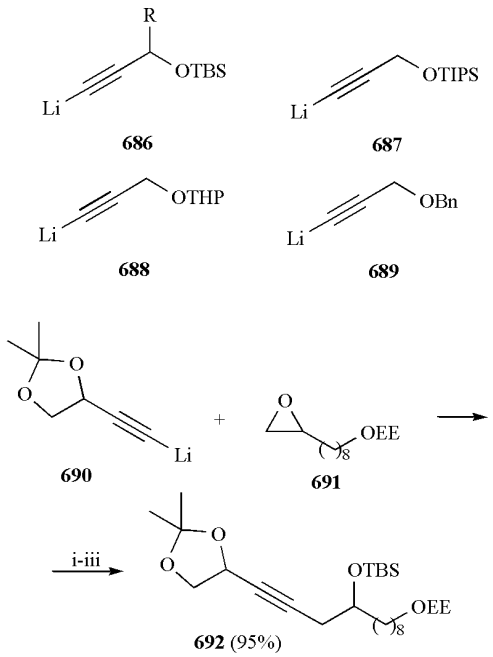
ketone in 68% yield and the corresponding product used in the total synthesis of the sesquiterpene (±)-illudin C.

Vinyllithium reagents derived from homoallylic systems of the type **402** are prepared mainly by halogen-lithium exchange. In general, protected γ-halogenated homoallylic alcohols were used for the preparation of γ-functionalized vinyllithiums **675**-**677**. The TBS-ether derived from 3-lithio-2-butenol **675** was used in the synthesis of the C1 alkyl side chains of Zaragozic acids A and C [287]. Benzyl ether **676** was transformed into the corresponding organoyterbium reagent and used for the preparation of the bicyclic core of pestalotiopsin [288].

Reagent **677**, prepared from the corresponding bromide by reaction with *t*-BuLi in ether at –78ºC was used as C29-C37 fragment for the synthesis of antitumor macrolides altohyrtins (spongistatins) [289]. In the total synthesis of the marine metabolites (+)-calyculin A and (–)-calyculin B, reagent **678** was transformed into its cuprate and coupled with an epoxide in 83% yield [290].

By means of an iron-catalyzed carbolithiation of alkynes, intermediates of the type **676** were prepared and trapped with electrophiles. The addition of BuLi takes place in the presence of a catalytic amount of $Fe(acac)_3$ at –20ºC with total diastereoselectivity, giving products **680** in high yields [291] (Scheme 151).

In the total synthesis of the marine origin sesquiterpenoid (±)-kelsoene, the chlorinated reagent **682** was prepared by tin-lithium transmetallation from the starting material **681**



Scheme 153. *Reagents*: i, $BF_3{\cdot}OEt_2$, –78ºC; ii, TBSCl, 2,6-lutidine, –78ºC; iii, H_2O.

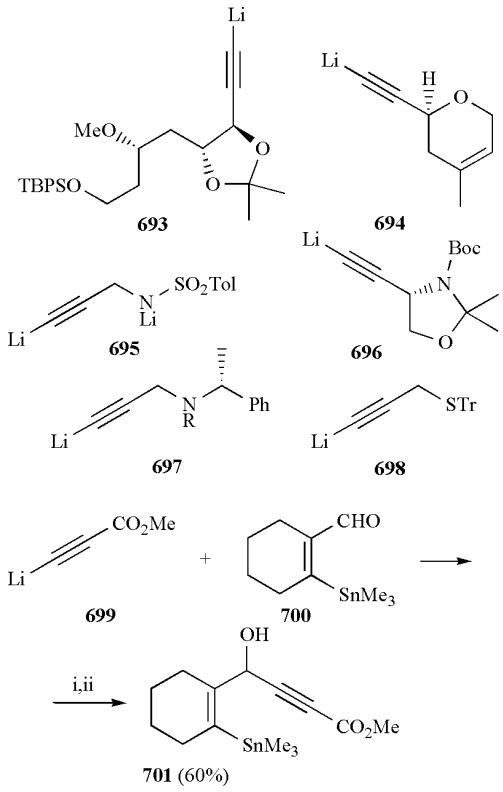
and transformed into the corresponding cuprate to be applied in the Michael addition to cyclopentenone, giving the expected product **683** [292] (Scheme 152).

Cyclohexyllithiums **684** and **685** were added to hindered α-trimethylsilyloxy aldehydes with high diastereoselectivity (> 95%) and used for the construction of *seco*-taxanes [180]. Reagent **684** was prepared using the Shapiro reaction starting from the corresponding ketone trisylhydrazone [293]. In the case of compound **685**, it can be generated either from the corresponding bromide or iodide by reaction with *t*-BuLi in THF at –78ºC, the best results in the reaction with benzaldehyde having been obtained with the first precursor [293].

4.5. γ-Functionalized Alkynyllithium Compounds

Lithiated alkynes bearing a functional group at the propargylic position, of the type **403**, are usually prepared by deprotonation with BuLi at low temperatures. Organolithium compounds **686** (R = H) [294] and **687** [295] derived from *O*-silyl-protected propargyl alcohols were alkylated or added to an aldehyde, and used in the synthesis of vitamin E and K analogues, as well as in the total synthesis of (+)-isolaurepinnacin. In addition, compound **686** (R = *n*-C_5H_{11}) was formylated using DMF as electrophile at temperatures ranging between –65 and –35ºC in 89% yield, and used for the synthesis of monofluorinated analogues of fatty acid metabolites [296].

The tetrahydropyranyl protected reagent **688** was alkylated with butadiene bis-epoxide in DMSO at 45ºC in 61% yield and employed for the synthesis of functionalized diene-diynes [297]. This reagent **688** was also condensed with 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone at –78ºC almost in quantitative yield [298]. On the other hand, the



Scheme 154. *Reagents*: i, THF, –78ºC; ii, H_2O.

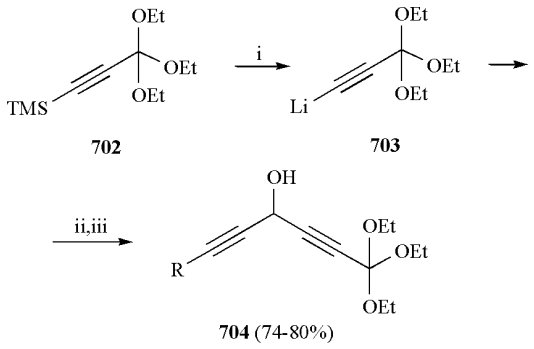
benzyl ether derivative **689** was acylated with (phenylpropanoyl)morpholine at –78ºC in 77% yield [78].

In the total synthesis of the oxidized phospholipid (11*E*)-9-hydroxy-13-oxotridec-11-enoate ester of 2-lysophosphatidylcholine, the epoxide **691** reacted with the alkynyldiol organolithium derivative **690** in the presence of $BF_3{\cdot}OEt_2$ at –78ºC to give after silylation the product **692** in 95% overall yield [299] (Scheme 153).

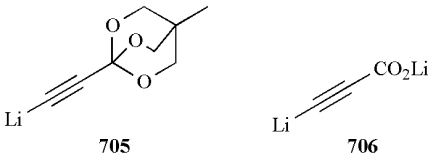
In the total synthesis of the macrolide of the marine origin (+)-phorboxazole A, reported by Smith *et al.*, compound **693** was prepared by deprotonation of the corresponding acetylene with *t*-BuLi, being then methylated with methyl iodide in quantitative yield [300]. The alkynyl anion **694** was prepared from the corresponding aldehyde under Corey-Fuchs homologation conditions followed by treatment of the corresponding vinyl dibromide with BuLi at –78ºC, and was used in the total synthesis of microtube-stabilizing agent (–)-laulimalide [301].

In the case of propargylamine, its sulfonamide was deprotonated with BuLi in THF at –78ºC to give the dianion **695**, which after treatment with paraformaldehyde gave the corresponding propargyl alcohol in 81% yield [302]. Starting from the Garner's aldehyde, the corresponding ethynyloxazolidine was prepared and lithiated with BuLi in THF at –100ºC, so the intermediate **696** was obtained, which was coupled with aldehydes in 62-96% yield [303] and with sugar lactones in 64-73% yield [304].

Lithiated propargylamines **697** were prepared by deprotonation with BuLi at –30ºC in ether and were



Scheme 155. *Reagents*: i, BuLi, THF, 0ºC; ii, RC≡CCHO; iii, H_2O.



carbozincated [266] to give dienylamines with good 1,3-diastereoselection [305]. 2-Propynyl trityl sulphide derived anion **698** was used for the synthesis of 17α-substituted mercapto alkynyl derivatives by addition to the corresponding TBS-protected estrone [306].

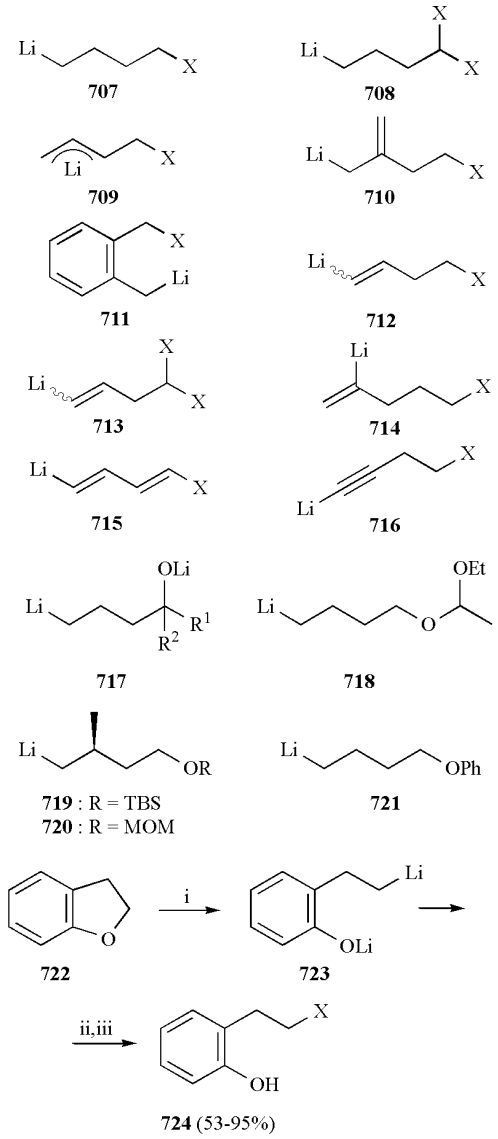
β-Lithiopropiolates of the type **404**, which are very unstable intermediates, were added to carbonyl compounds at very low temperature (–70 to –120ºC) [307]. Recently, methyl 3-lithiopropiolate **699** was used as nucleophile for the preparation of enyoates. For instance, compound **701** was prepared from the mentioned intermediate **699** and the stannylated aldehyde **700** [308] (Scheme 154).

In order to get more stable intermediates of type **404**, lithium orthopropiolate **703** and the orthoesters **705** were introduced as good alternatives. Compound **703** has to be prepared by reaction of trimethylsilyl orthopropiolate **702** with BuLi at 0ºC [309] by silicon-lithium exchange and was recently used for the preparation of diacetylenic ketones by coupling with acetylenic aldehydes followed by oxidation with manganese dioxide [310] (Scheme 155).

In the case of the orthoester reagent **705**, the lithiation was carried out with BuLi at –10ºC and it reacted with carbonyl compounds in good yields (61-93%), and with methyl iodide in 95% yield [311]. Lithium 3-lithiopropiolate **706** reacted with diethyl ketomalonate at temperatures ranging from–78ºC and room temperature in 45%, giving an adduct which was used in the synthesis of 5-substituted 3-pyrrolin-2-ones, potent inhibitors of cathepsin B [312].

5. δ-FUNCTIONALIZED ORGANOLITHIUM COMPOUNDS

As it was mentioned in Section 4, for γ-functionalized organolithium compounds, in the case of the corresponding δ −derivatives (umpoled d^4-reagents) they can be classified attending to the hybridization of the carbanion centre as (a) sp^3-hybridized **707** and **708** (Section 5.1), allylic **709** and

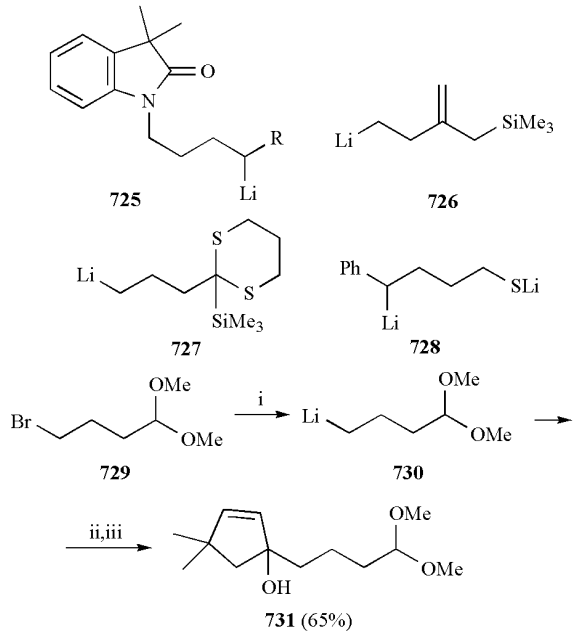


Scheme 156. *Reagents*: i, Li, DTBB (5 mol %), THF, rt; ii, E = H_2O, D_2O, Me_3SiCl, R^1R^2CO, –40ºC to rt; iii, H_2O.

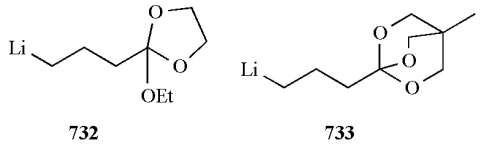
710 (Section 5.2) and benzylic compounds **711** (Section 5.3); (b) sp^2-hybridized derivatives **712-715** (Section 5.4); and (c) sp-hybridized systems **716** (Section 5.5).

5.1. δ-Functionalized Alkyllithium Compounds

4-(Phenylsulfanyl)alkanols were used for the preparation of 4-oxido alkyllithiums **717** by deprotonation with BuLi and magnesium 2-ethoxyethoxide at –78ºC followed by reductive lithiation with BuLi, as it was already described for the corresponding γ-reagents (see Scheme 94) [184]. Reagents **717** were also postulated as intermediates in the transformation of 1,3-bis(phenylsulfanyl)propane **505** into 1,5-diols by means of lithium and a catalytic amount of DTBB [207] (see Scheme 107). Protected 4-chlorobutan-1-ol, as the corresponding acetal, was transformed into the intermediate **718**, the homologous of the γ-derivative **417**, by chlorine-lithium exchange in ether at –20ºC [190].



Scheme 157. *Reagents*: i, *t*-BuLi (2 equiv), THF, –78 to 0ºC; ii, 4,4-dimethyl-2-cyclopenten-1-one, –78ºC; iii, NH_4Cl-H_2O.

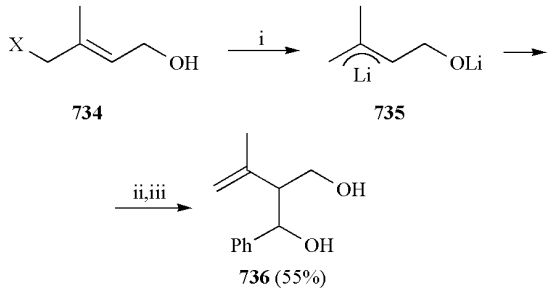


Optically active intermediates **719** [313] and **720** [314] were prepared by bromine- and iodine-lithium exchange, respectively, with *t*-BuLi in ether. They were used in the synthesis of the C28-C40 fragment of azaspiracids [313] and in the synthesis of (–)-cylindrocyclophanes A and F [314]. The phenyl ether **721** was prepared in a similar way than the corresponding γ-derivative **423** by an arene-catalyzed lithiation of the adequate chlorinated material [197].

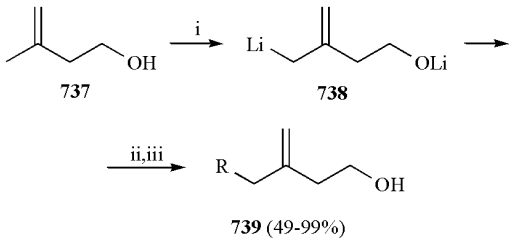
Reductive cleavage of 2,3-benzodihydrofuran **722** with lithium and a catalytic amount of DTBB (5 mol %) took place easily at room temperature affording intermediate **723**, which was trapped with different electrophiles in good yields [315] (Scheme 156). This reagent gave Michael addition to cyclohexenone in the presence of zinc bromide in 43% yield [316].

Other related δ−functionalized organolithium compounds such as **725** [203] and **726** [317] were prepared by bromine-lithium exchange with *t*-BuLi at –78ºC, as in the case of the corresponding γ-derivative **439** (see Scheme 102) and by reductive lithiation of the corresponding phenylsulfanyl precursor with lithium and a catalytic amount of DTBB at –78ºC, respectively. The last homoallylic reagent **726** was trapped with a *N*-phenethylimide in 83% yield [317].

The same strategy was employed in the preparation of the lithio thioacetals **727**, which was also coupled with an imide in 53% yield [317]. In the case of the benzylic dianion **728**, it was prepared from 2-phenyltetrahydrothiophene by an arene-catalyzed lithiation, as for the corresponding γ-derivatives [206] (see Scheme 106).



Scheme 158. *Reagents*: i, BuLi; ii, PhCHO; iii, H_2O.



Scheme 159. *Reagents*: i, BuLi, TMEDA, ether, 0ºC to rt; ii, RHal, –78ºC to rt; iii, NH_4Cl-H_2O.

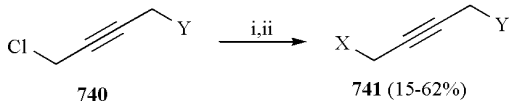
For the preparation of the bishomoenolate **730** [318], of the type **708**, the corresponding γ-bromo acetal **729** was lithiated with *t*-BuLi at –78ºC [319] (Scheme 157). The reaction of this intermediate with 4,4-dimethyl-2-cyclopenten-1-one led to a 1,2-addition giving the alcohol **731**, which was further elaborated for the synthesis of angular triquinanes.

Masked bishomoenolates **732** and **733** were prepared from the corresponding γ-chloro orthoesters by an arene-catalyzed lithiation in the presence of different electrophiles giving, after hydrolysis with methanol and a catalytic amount of *p*-toluenesulfonic acid, the corresponding methyl esters [226].

5.2. δ-Functionalized Allyllithium Compounds

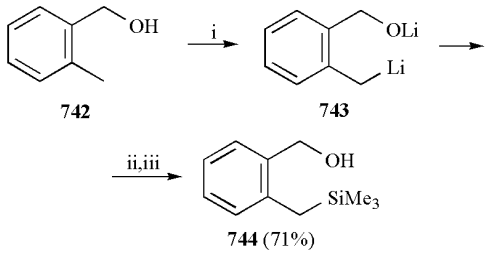
Allylic anions of the type **709** were only described in the synthesis of a forskolin intermediate [133,320]. The C_5 isoprenoid reagent **735** was generated by tin-lithium exchange from the allylic stannane **734** (X = $SnBu_3$) with BuLi. After addition of of benzaldehyde only products **736** from an allylic inversion were obtained (Scheme 158). When the anion **735** was generated from the corresponding chloride **734** (X = Cl) by successive reaction with BuLi and lithium naphthalenide, the Wurtz coupling product was the only one obtained in 66% yield [320].

3-Methyl-3-buten-1-ol **737** was regiospecifically lithiated to give the dianion **738**, a reagent of the type **710**, with BuLi in the presence of TMEDA [321]. Recent studies on alkylation reactions with alkyl halides revealed that the solvent plays an important role in this process. The best results were obtained using ether in both metallation and alkylation steps, the process being applied to the synthesis of a San Jose scale sex pheromone [322] (Scheme 159).



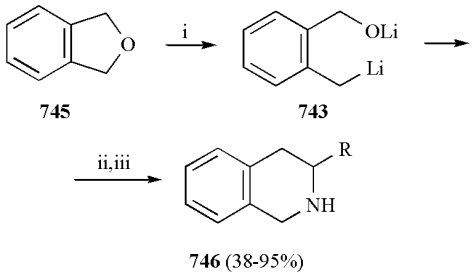
740 **741** (15-62%)

Scheme 160. *Reagents*: i, Li, DTBB (5 mol %), E = R^1R^2CO, Me_3SiCl, THF, –105ºC (Y = OTHP) or –78ºC [Y = $N(CH_2CH_2)_2O$, $N(CH_2CH{=}CH_2)_2$, OH, NHPh]; ii, H_2O.



742 **743** **744** (71%)

Scheme 161. *Reagents*: i, BuLi (2 equiv), Et_2O, 30-35ºC; ii, $ClSiMe_3$, –78ºC; iii, 10% H_2SO_4.



745 **743** **746** (38-95%)

Scheme 162. *Reagents*: i, Li, DTBB (5 mol %), THF, 0ºC; ii, $RCH{=}NSiMe_3$, –45ºC to rt; iii, HCl-H_2O; iv, Cl_2SO, 50ºC, then NaOH.

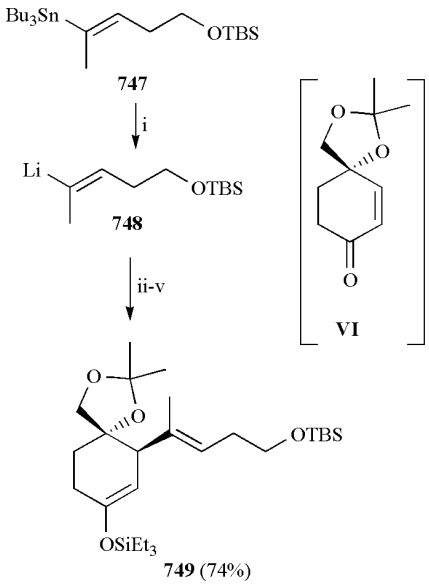
In the case of the propargyl systems **740** the corresponding anions were generated by an arene-catalyzed lithiation and coupled *in situ* with electrophiles to give the expected products **741** in moderate yields, without contamination with the corresponding allenic derivatives [323] (Scheme 160).

5.3. δ-Functionalized Benzyllithium Compounds

Benzyllithiums bearing a functionality at the δ-position of the type **711** were prepared by double deprotonation starting from 2-methylbenzyl alcohol **742** with BuLi under reflux, affording the dianion **743**. This intermediate was transformed into the corresponding silyl alcohol **744** [324] by reaction with $ClSiMe_3$ (Scheme 161).

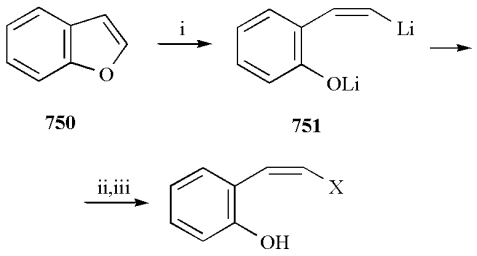
The reductive opening of phthalan **745** with lithium and a catalytic amount of DTBB generated the dianion **743** [325a], which reacted with *N*-trimethylsilylaldimines to give after cyclization tetrahydroisoquinolines **746** [325b] (Scheme 162). 3-Aryl substituted phthalans were also generated by reductive lithiation with lithium and naphthalene and the corresponding dianions of the type **743** were formylated with DMF in 68-74% yield to give the corresponding isochromans [326].

The dianion **743** was dimerized in 63% yield in the presence of $CuCl_2$ [222], gave Michael addition to



749 (74%)

Scheme 163. *Reagents*: i, BuLi, THF, –60 to –10ºC; ii, CuCN, –60 to –10ºC; iii, **VI**, –60ºC; iv, Et_3SiCl, Et_3N, –60ºC to rt; v, NH_3-H_2O, NH_4Cl.



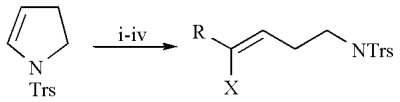
752 (45-94%)

Scheme 164. *Reagents*: i, Li, DTBB (5 mol %), THF, 0ºC; ii, E = H_2O, D_2O, R^1R^2CO, –78ºC; iii, H_2O, –78 to 0ºC.

electrophilic olefins (32-74%) and was acylated (45-65%) in the presence of CuI [222]. The Michael addition can also be carried out in the presence of other Lewis acids, such as $ZnHal_2$, $AlCl_3$, $FeCl_3$ and BF_3 in 17-79% yield [316]. The reaction of intermediate **743** with carbonyl compounds in the presence of $ClTi(OPr^i)_3$ (2 equiv) was chemoselective giving the expected adducts with aldehydes in the presence of ketones [327a]. Intermediate **743** was transformed into the corresponding organozinc compound, which was cross-coupled with aryl and alkenyl bromides under palladium catalysis in 30-78% yield [327b]. 5-Substituted resorcinols were prepared from 3,5-dimethoxybenzyllithium, generated from the benzyl trimethylsilyl ether by means of lithium powder and a catalytic amount of naphthalene [328].

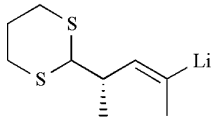
5.4. δ-Functionalized alkenyllithium compounds

The preparation of (*Z*)- or (*E*)-alkenyllithiums with a functional group at the δ-position of the type **712** was performed stereospecifically by halogen- or tin-lithium exchange from the corresponding precursors. Recently, the intermediate **748** was prepared from the tin compound **747** by tin-lithium transmetallation and the corresponding cuprate added to the enone **VI** affording the product **749** [329]

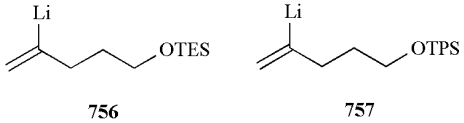


753 **754** (37-92%)

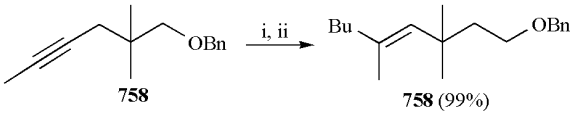
Scheme 165. *Reagents*: i, *t*-BuLi, Et_2O, –78 to 0ºC; ii, $R_2CuCNLi_2$; iii, E = H_2O, MeI, CH_2=$CHCH_2Br$, I_2, Me_3SnCl, HMPA, –78ºC to rt; iv, NH_4Cl, NH_3-H_2O.



755

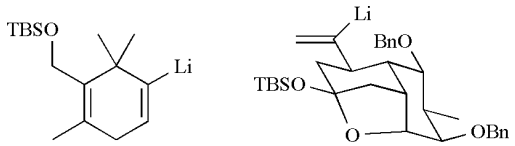


756 **757**



758 **758** (99%)

Scheme 166. *Reagents*: i, BuLi (3 equiv), $Fe(acac)_3$, toluene, –20ºC; ii, H_2O.



760 **761**

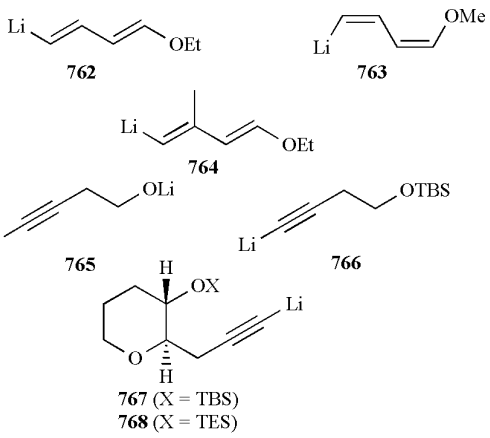
(Scheme 163). This strategy was used in the synthesis of (–)-fumagillin.

The (*Z*)-organolithium derivative **751** was prepared by reductive opening of 2,3-benzofuran **750** with lithium and a catalytic amount of DTBB at 0ºC. This intermediate was trapped with different electrophiles and applied to the synthesis of 2*H*-chromenes such as deoxycordiachromene [330] (Scheme 164).

For the synthesis of homoallylamines, the *N*-trisyl protected pyrrolidine **753** was lithiated with *t*-BuLi at low temperature followed by treatment with lithium cuprates to give vinylic intermediates, which reacted with electrophiles giving products **754** [331] (Scheme 165).

Dithiane protected vinyllithium **755** was stereoselectively prepared by iodine-lithium exchange with *t*-BuLi at –78ºC and coupled with enolizable aldehydes at –100ºC in 43-65% yield. This methodology was applied to the synthesis of the C1-C11 fragment of tedanolide and 13-deoxytedanolide [332].

Vinyllithium reagents of the type **714** with a silyloxy group at the δ−position **756** [333] and **757** [334] were prepared by bromine-lithium exchange with BuLi at –78ºC and were used in the preparation of the BC ring system of taxol by Mukaiyama *et al.* [333] and for the construction of the ABC ring system of the same molecule by Stork *et al.* [334], respectively.



762 **763** **764** **765** **766**

767 (X = TBS)
768 (X = TES)

The carbolithiation of the 4-hexynyl benzyl ether **758** with BuLi catalyzed by Fe(acac) gave, after protonation, the expected product **759** in quantitative yield [291] (Scheme 166).

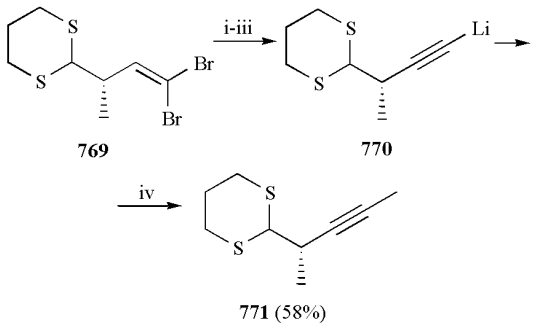
Other vinyllithiums **760** [335] and **761** [336] were prepared by means of the Shapiro reaction from the corresponding ketones and used in the synthesis of the C-ring of aryl taxoids [335] and the antibiotic nodusmicin, respectively [336].

δ-Functionalized (*E*,*E*)-dienyllithium **762**, of the type **715**, was prepared by tin-lithium transmetallation of the Wollenberg's 1-(tri-*n*-butylstannyl)-4-ethoxybutadiene [337] and, after transformation into the corresponding magnesium derivative, coupled with polyenals in the synthesis of the polyene macrolide roflamycoin [338]. (*Z*,*Z*)-Dienyllithium **763** was prepared by stereoselective tellurium-lithium exchange with BuLi in THF at –78ºC, and was trapped with benzaldehyde in 53% yield [339].

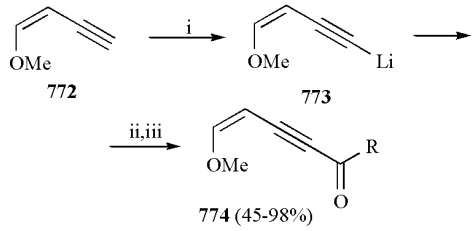
The C5 intermediate **764** was prepared from the corresponding chloride by reaction with lithium and a catalytic amount of DTBB at –78ºC and coupled with aldehydes in 50-99% yield. In the case of β-ionylidene acetaldehyde, retinal was prepared in 50% yield [146].

5.5. δ-Functionalyzed Alkynyllithium Compounds

The alkynyllithium compound derived from 3-butynol **765** was widely used in organic synthesis. It can be generated by reaction of the mentioned alcohol with BuLi (2 equiv) at –78ºC and reacted with a TBS-protected estrone for the synthesis of 17α-substituted mercaptoalkynyl estradiols [306]. By reaction of intermediate **765** with trimethylsilyl chloride, the corresponding protected acetylene was obtained in 95% yield [180,340], which was used in the synthesis of phomactin A. Protected reagent **766** was alkylated with 4-(benzyloxy)butyl iodide in 86% yield and used in the synthesis of the macrocyclic marine alkaloid haliclamine A [341]. In addition, compound **766** reacted with a lactone in 94% yield in the synthesis of the C28-C38 segment of



Scheme 167. *Reagents*: i, BuLi, THF, –78ºC; ii, MeOH, iii, *t*-BuLi; iv, MeI.



Scheme 168. *Reagents*: i, BuLi, THF, –78ºC; ii, RCOX; iii, NH_4Cl.

okadaic acid, using vinylogous urethane aldol chemistry [342].

Dihydropyran derivatives **767** and **768** were used by several groups for the convergent synthesis of *trans*-fused six-membered polytetrahydropyrans, common units in marine toxins, by efficient coupling with triflates [343].

The dithiane derivative **770** was obtained from the dibromide **769** and alkylated with methyl iodide in 91% yield [332] (Scheme 167).

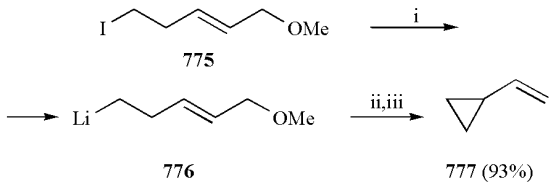
The enyne derivative **773** was prepared by deprotonation of compound **772** with BuLi at –78ºC and alkylated with different anhydrides or acyl chlorides to give the expected ketones **774**, precursors of 2-alkyl-4-aminopyridines, by an amination reaction [344] (Scheme 168).

6. REMOTE FUNCTIONALIZED ORGANOLITHIUM COMPOUNDS

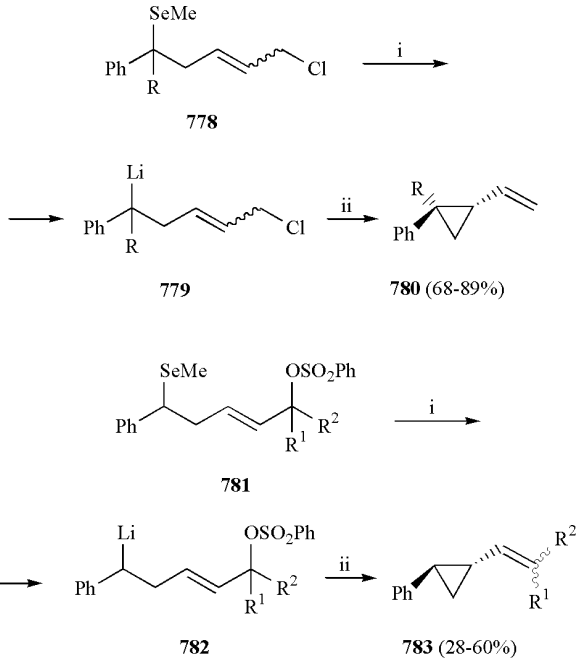
Organolithium compounds with a functionality at the ε-position or farer have in general very different skeleton and therefore they will be classified considering only their hybridization.

6.1. Remote Functionalized Alkyllithium Compounds

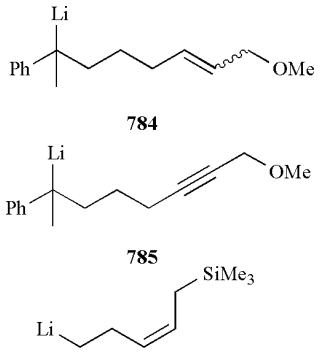
sp^3-Hybridized organolithium compounds with a leaving group at the ε-allylic position suffer intramolecular S_N' cyclizations [345] to give vinylcyclopropanes. This process was studied with the reagent **776**, prepared from the iodo compound **775** by means of *t*-BuLi in heptane at –78ºC. This intermediate cyclized by means of TMEDA at room temperature to give the product **777** [346] (Scheme 169).



Scheme 169. *Reagents*: i, *t*-BuLi (2 equiv), *n*-C_7H_{16}, –78ºC; ii, TMEDA; iii, rt.



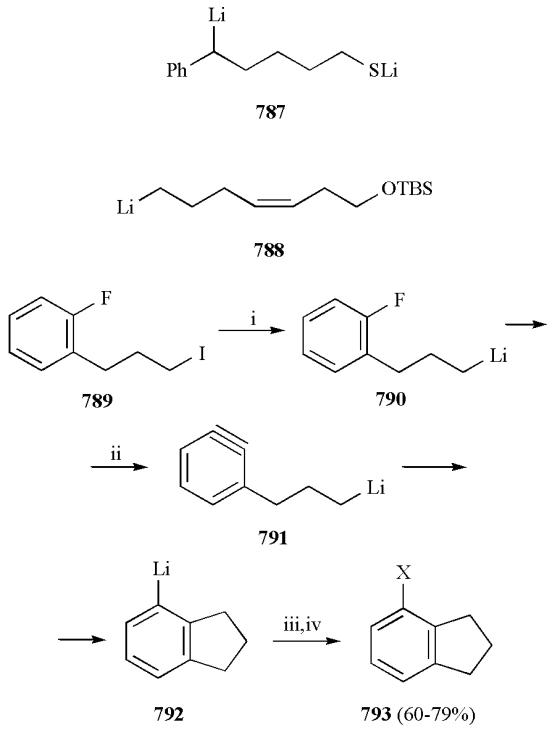
Scheme 170. *Reagents*: i, BuLi, THF, –78ºC to rt; ii, H_2O.



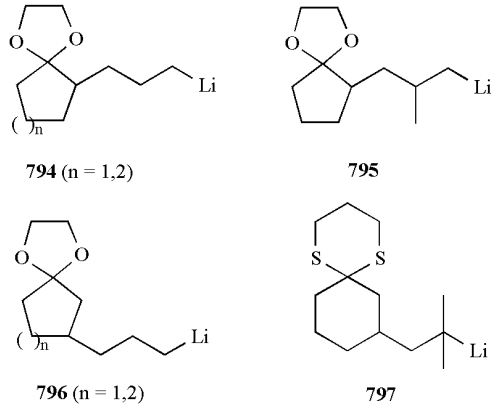
The benzyllithiums **779** and **782**, generated from the corresponding benzyl selenides **778** and **781** by selenium-lithium exchange, gave spontaneously the corresponding vinylcyclopropanes **780** and **783**, respectively, mainly having *trans*-configurations [347] (Scheme 170).

The former methodology has also been studied with the remote functionalized intermediates **784** and **785**, which cyclized giving 1-aryl-2-vinylcyclopentanes [348].

However, the silyl-substituted organolithium compound **786**, prepared by bromine-lithium exchange, did not cyclize and was coupled with 3-fluoro-3-buten-2-one to give the



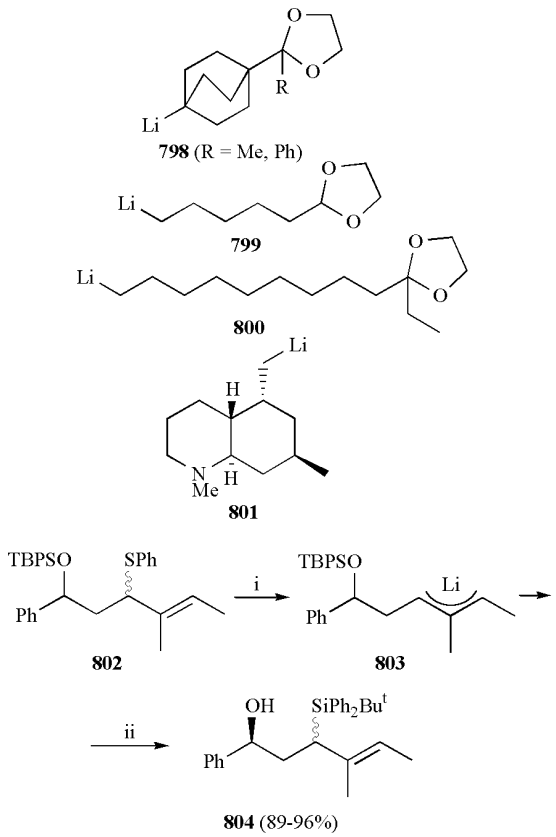
Scheme 171. *Reagents*: i, *t*-BuLi (3 equiv), pentane, Et_2O, –78ºC; ii, THF, –78ºC to rt; iii, E = H_2O, MeOD, $BrCH_2CH_2Br$, $ClCO_2Et$, DMF, PhCHO; iv, H_2O.



corresponding alcohol in 52% yield, which was used in the total synthesis of (±)dammarenediol [349].

The reductive opening of 2-phenyl substituted thiacyclohexane with lithium and a catalytic amount of DTBB (5 mol %) in THF at –78ºC led to the ε-functionalized organolithium intermediate **787** [206]. This reagent was trapped with D_2O, Me_3SiCl, CO_2 and carbonyl compounds in 58-80% yield, as it was previously described for the corresponding γ- (**503**) and δ-derivatives (**728**). The remote sp^3-hybridized organolithium compound **788** was prepared from the corresponding chloride by means of *t*-BuLi at –78ºC and coupled with 2-vinylcyclopropanecarbaldehyde in 51% yield [350].

A 5-*exo*-*dig* cyclization took place when the ε-functionalized organolithium compound **790**, prepared from the iodinated precursor **789**, was warmed in the presence of



Scheme 172. *Reagents*: i, $LiC_{10}H_8$, THF, –78ºC; ii, H_2O.

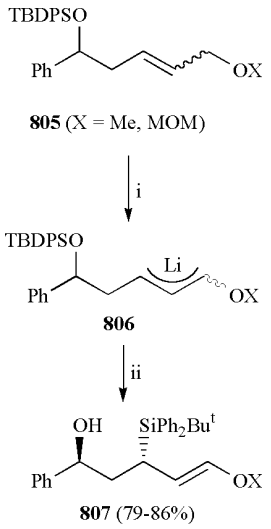
an excess of *t*-BuLi, through the benzyne derivative **791**. The resulting 4-lithioindan **792** was trapped with different electrophiles to give the corresponding products **793** [351] (Scheme 171).

Several masked δ- and ω-lithio enolates **794**-**797** were prepared by lithiation of the corresponding phenylsulfanyl substituted acetals or thioacetals with lithium 4,4'-di-*t*-butylbiphenylide (LiDTBB) at –78ºC. They were trapped with acyl chlorides in the presence of $CuBr{\cdot}SMe_2$ affording 1,6- and 1,7-diketones in 55-73% yield [225].

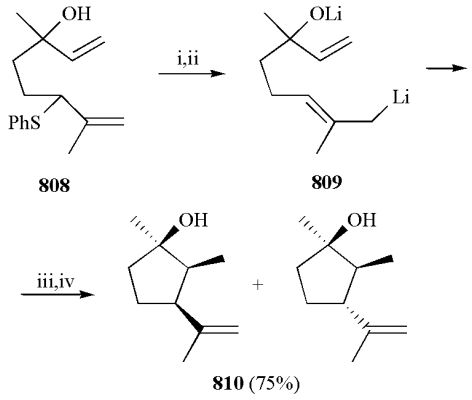
Dioxolane-protected organolithium compounds derived from bicyclic ketones **798** were prepared by inverse addition of the corresponding iodides to *t*-BuLi in ether at –70ºC for the preparation of rodlike molecules composed of bicyclo[2.2.2]octane units [352].

Remote lithium enolates **799** [353] and **800** [354] were prepared from the corresponding chlorides with lithium and a catalytic amount of naphthalene (4 mol %) and by bromine-lithium exchange with lithium, respectively. These reagents were used for the synthesis of naturally occurring hydroxyketones [353] and of the piperidine alkaloids (+)-prosopinine and (–)-deoxoprosophylline, respectively [354].

The cyclic perhydroquinoline derivative **801** was prepared from the corresponding iodide and applied, after lithium-magnesium transmetallation, to the synthesis of the *Lycopodium* alkaloid N_a-acetyl-N_b-methylphlegmarine [355].



Scheme 173. *Reagents*: i, *s*-BuLi, THF, –78ºC; ii, H_2O.



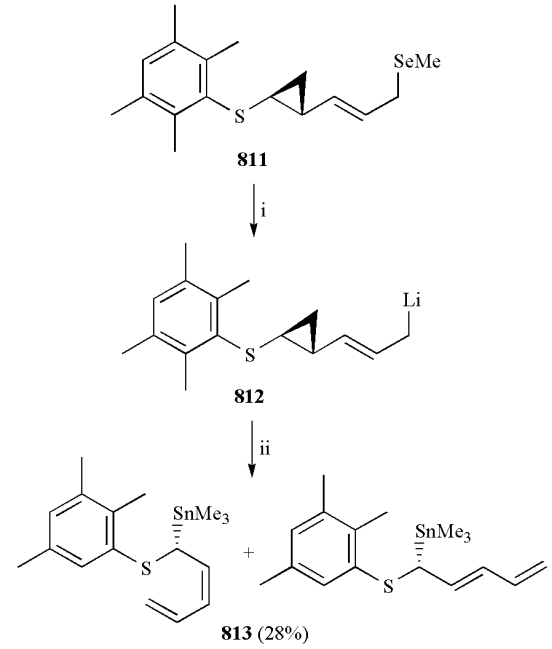
Scheme 174. *Reagents*: i, MeLi; ii, LiDTBB, THF, –78ºC; iii, –78ºC to rt; iv, H_2O.

6.2. Remote Allyl and Benzyllithium Compounds

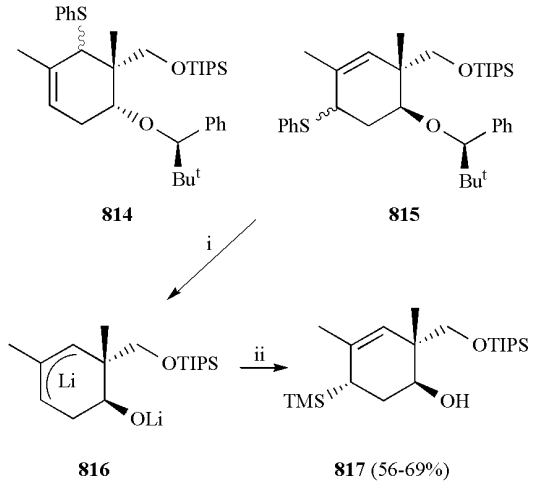
The allyllithium compound **803**, generated from the thioether **802** by reaction with lithium naphthalenide in the presence of TMEDA, suffered irreversible retro-[1,4]-Brook rearrangement giving rise to a 22:78 mixture of the *anti,trans* and *syn,trans* diastereomers **804** [356] (Scheme 172).

In the case of lithiated allylic methyl and MOM ethers **806**, prepared from compounds **805** by means of *s*-BuLi at –78ºC, the retro-[1,4]-Brook rearrangement occurred with 86-87% diastereocontrol affording mainly the *anti,trans*-allylsilanes **807** [357] (Scheme 173). This 1,3-asymmetric induction also took place with propargyllithium compounds derived from thioethers of the type **802** [358].

The lithium-ene cyclization of the ω-oxido allylic intermediate **809**, prepared from the alcohol **808** by sulfur-lithium exchange with LiDTBB, is reversible even at room temperature. The lithium oxyanionic group facilitated the double cyclization affording diastereoselectively products **810** as a 1:2.5 diastereomeric mixture [359] (Scheme 174). This organolithium compound **809** was transmetallated to the corresponding organomagnesium derivatives, which also gave a reversible magnesium-ene cyclization [359b].



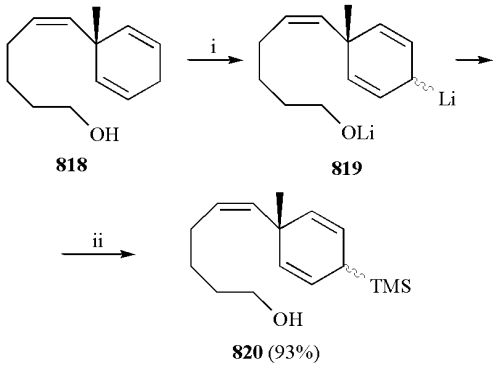
Scheme 175. *Reagents*: i, *t*-BuLi, THF, –108ºC; ii, Me_3SnCl, –108ºC.



Scheme 176. *Reagents*: i, LiDTBB, –45ºC; ii, TMSCl.

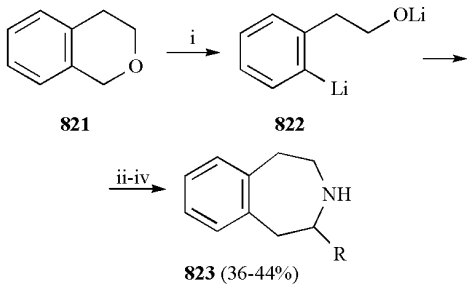
The ring opening of the enantiomerically pure ε-durylsulfanyl cyclopropylallyllithium **812**, prepared by selenium-lithium exchange from the selenide **811**, led to the formation of the corresponding homoallyllithium derivative **812**, which was trapped with trimethyltin chloride affording a 60:9 mixture of the diastereomers **813** [360] (Scheme 175).

Cyclic ω-functionalized allyllithiums **816** [361] and **819** [362] were used in syntheses of taxol. Thus, both thioethers **814** and **815** gave, after reductive lithiation and silylation, the same allylsilane **817** in 56 and 69% yield, respectively [361] (Scheme 176).



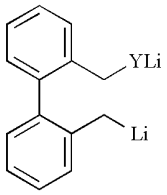
818 **819** **820** (93%)

Scheme 177. *Reagents*: i, BuLi, TMEDA, TMSCl, THF, 0ºC; ii, 2 M H_2SO_4.



821 **822** **823** (36-44%)

Scheme 178. *Reagents*: i, Li, DTBB (5 mol %), THF, 0ºC; ii, RCH=NSiMe$_3$, –45ºC to rt; iii, HCl-H_2O; iv, Cl_2SO, 50ºC, then NaOH.

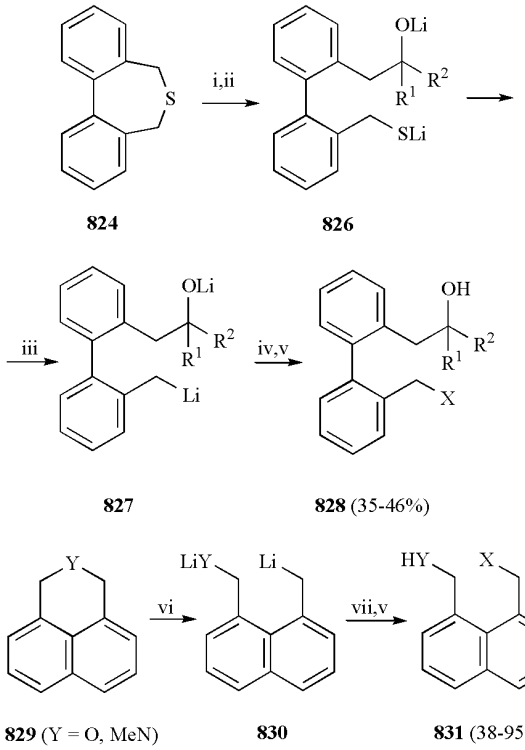


825 (Y = O, MeN, S)

The oxide pentadienyllithium **819**, generated from the alcohol **818** by deprotonation with BuLi in the presence of trimethylsilyl chloride, gave the corresponding product **820** as a 3:1 diastereomeric mixture, which was further cyclized to a bridged ten-membered ring compound [362] (Scheme 177).

The ring opening of isochroman **821** by the arene-catalyzed lithiation methodology gave the ε-oxido benzyllithium **822**, which was widely used in synthesis as it was previously described for the case of phthalan **745** (see Section 5.3). The reaction of this dianion **822** with *N*-silylimines led to the formation of amino alcohols, which were cyclized to the corresponding benzofused azepines **823** [326] (Scheme 178).

The dianion **822** was transformed into the corresponding organozinc compound and used in Negishi cross-coupling reactions [327a]. In the presence of $(Pr^iO)_3TiCl$ it reacted preferentially with aldehydes in the presence of ketones [327b]. For the Michael addition and acylation reactions, good yields are obtained with intermediate **822** in the presence of copper(I) iodide and HMPA, whereas



824 **826** **827** **828** (35-46%)

829 (Y = O, MeN) **830** **831** (38-95%)

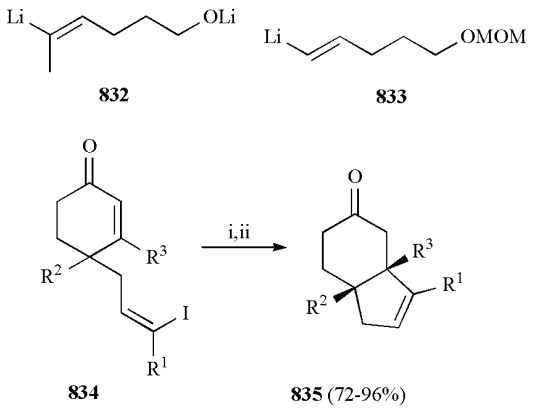
Scheme 179. *Reagents*: i, Li, DTBB (5 mol %), THF, –78ºC; ii, R^1R^2CO; iii, Li, DTBB (5 mol %), –78ºC to rt; iv, E = R^3R^4CO, $ClCO_2Et$, –78ºC; v, H_2O, –78ºC to rt; vi, Li, $C_{10}H_8$ (5-10 mol %), THF, –15ºC; vii, E = H_2O, D_2O, BuBr, *i*-PrBr, Me_2CO.

dimerization occurred by means of copper(II) chloride at –78ºC [222]. Other Lewis acids, such as $ZnHal_2$, $AlCl_3$, $FeCl_3$, and BF_3 also promoted the conjugate addition to α,β-unsaturated ketones and esters [316].

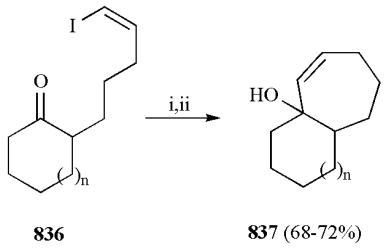
Remote functionalized benzyllithiums **825** were prepared by an arene-catalyzed lithiation of the corresponding cyclic diphenane systems, *N*-methyldibenzazepine [363] and 2,7-dihydrodybenzothiepine [364]. The oxygen- and nitrogen-containing intermediates were generated in the presence of naphthalene (10 mol %) at –15 and 0ºC, respectively, and coupled with electrophiles in 47-95% yield [363].

The lithiothioxide system **826** (Y = S) was generated from the heterocycle **824** at –78ºC in the presence of DTBB (5 mol %) with an excess of lithium powder and was allowed to react with carbonyl compounds to give the expected adducts in 47-82% yield, after hydrolysis [364]. However, when the reaction mixture was allowed to warm to room temperature, a new lithiation reaction took place giving dianions **827**, which reacted with a second electrophile affording biphenyls **828** in moderate yields [364] (Scheme 179).

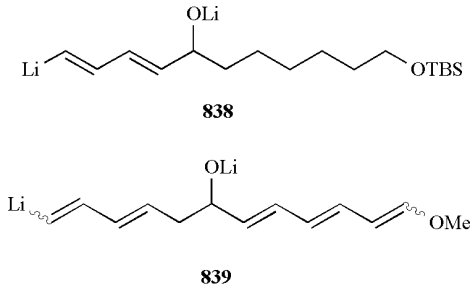
1,8-Disubstituted naphthalenes **831** can be prepared by ring opening of compounds **829** with lithium and a catalytic amount of naphthalene. ε-Functionalized benzyllithiums **830** were generated at –15ºC and trapped with electrophiles [363] (Scheme 179).



Scheme 180. *Reagents*: i, *t*-BuLi (2 equiv), HMPA (2 equiv), TMSCl (4 equiv), THF, –78ºC; ii, –78ºC to rt.



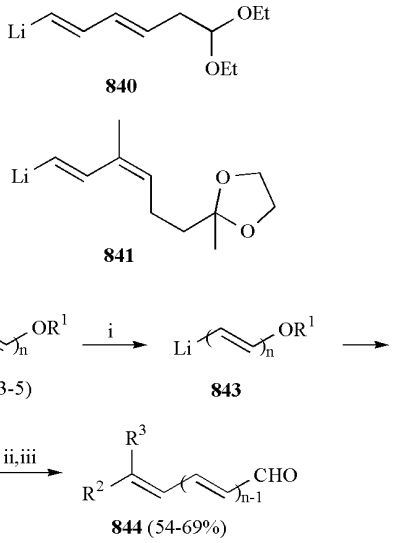
Scheme 181 *Reagents*: i, BuLi (2 equiv), THF, –78ºC; ii, H_2O.



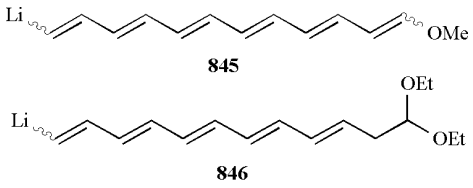
6.3. Remote Functionalized Alkenyl- and Alkynyllithium Compounds

Lithium (*Z*)-5-lithio-5-methyl-4-pentenol **832** was prepared stereoselectively from the corresponding bromo derivative by reaction with *t*-BuLi in THF at –78ºC and acylated with a Weinreb amide in 82% yield, being used in the synthesis of the enantiomer of the natural epolactaene [277]. A MOM-protected ε-alkoxy vinyllithium, (*E*)-5-lithio-4-pentenol **833** was synthesized from the corresponding (*E*)-iodo derivative by means of *t*-BuLi in THF, and alkylated with an allylic bromide in the presence of HMPA (53% yield) and used in the total synthesis of the antiviral marine natural product (–)- hennoxazole A [365].

Long-range functionalized vinyllithiums with a carbonyl group present in the molecule were used in intramolecular cyclization processes. Vinylic iodides **834** and other related systems were transformed efficiently into products **835** by iodine-lithium exchange with *t*-BuLi in THF in the presence of HMPA and TMSCl, followed by intramolecular conjugate addition [366] (Scheme 180).



Scheme 182. *Reagents*: i, *t*-BuLi, Et_2O, –70ºC; ii, R^2R^3CO; iii, 1 M HCl.

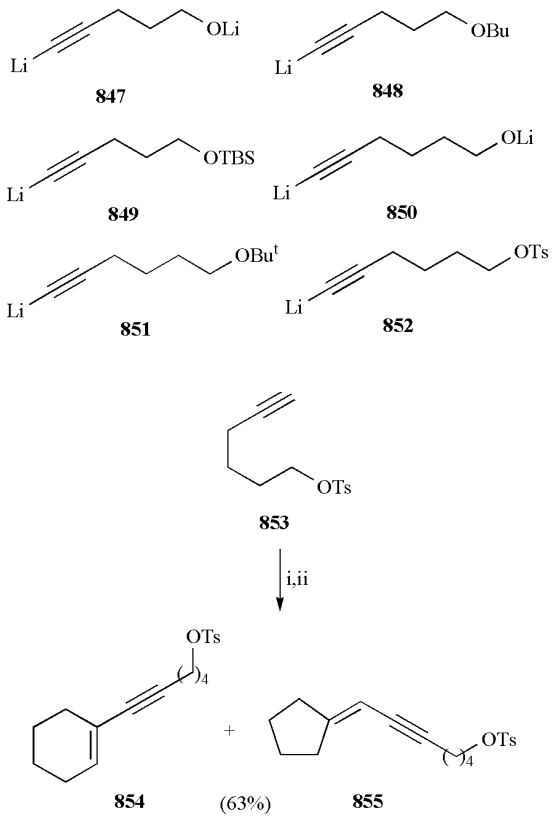


Intramolecular addition of vinyllithium reagents generated by iodine lithium exchange from compounds **836** was used for the preparation of seven-membered carbocycles **837** and other related systems [367] (Scheme 181).

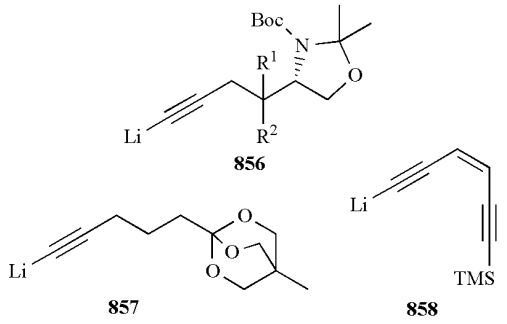
Dienyllithiums with an oxido functionality at the ε- [368] and ω-position (**838,839**) [369] were prepared from the corresponding bromo hydroxydienes by treatment with *t*-BuLi. The first intermediate **838** was coupled with heptanal affording a precursor of ostopanic acid in 91% yield [368]. In the case of reagent **839**, its coupling with benzaldehyde followed by hydrolysis gave a hexaenal in 10% overall yield [369].

The diethoxy acetal of (*E,E*)-6-bromohexa-3,5-dienal was lithiated with *t*-BuLi in ether at –78ºC to afford the corresponding ε-functionalized dienyllithium **840**. It reacted with ferrocenecarbaldehyde giving, after treatment with hydrobromic acid, 7-ferrocenyl-2,4,6-heptatrienal in 40% yield [370]. A related reagent **841** was also prepared by bromine-lithium under similar conditions than intermediate **840** and, after addition to a lactam, it was used in the synthesis of trisporic acids [371]

For the synthesis of polyenic conjugated compounds, several alkoxy functionalized polyenyllithiums **843** were prepared from the corresponding ω-bromo polyenol ethers **842** by treatment with *t*-BuLi in ether at –78ºC. These intermediates reacted with carbonyl compounds giving, after hydrolysis, polyenic aldehydes **844** [372] (Scheme 182). ω-



Scheme 183. *Reagents*= i, BuLi (0.5 equiv), THF, –85ºC; ii, rt.



Chloro and iodo polyenol ethers can also be used as starting precursors of these intermediates **843.**

The ω-lithio unsaturated intermediates **845** and **846** were prepared in a similar way than **843** and used as hexavinylogation reagents [369, 373].

sp-Hybridized organolithium compounds with an oxygenated functionality at the ω-position, such as compounds **847-849** derived from 4-pentyn-1-ol were prepared by deprotonation with MeLi or BuLi at –78ºC. The reagent **847** was used to prepare TBS-protected estrone [306]. The benzyl ether **848** was alkylated with propylene oxide in the presence of $BF_3{\cdot}Et_2O$ in 50% yield, and used for the synthesis of *iso*-cladospolide B [374]. The silyl ether **849** was used in the synthesis of (*Z*)-5-iodo-1-tributylstannylpent-1-ene by reaction with tributyltin chloride in 99% yield, followed by some functional group transformations [367]. The homologous reagent related to **847**, compound **850**, was used in the same reaction [306].

The *t*-butyl ether derivative **851** was used in the synthesis of perhydroindoles [375]. 6-Lithio-5-hexynyl tosylate **852**, prepared from the acetylene **853** with BuLi at –78ºC, reacted at room temperature in an intramolecular manner to give a cycloalkylidene carbene, which by reaction with another molecule of the starting material **853** afforded products **854** and **855**, as a 82:18 mixture [376] (Scheme 183).

Acetylides **856** were used in the synthesis of glycosylated amino acids by addition to sugar derived lactones [377]. In the synthesis of unsaturated polyazamacrocycles from the ladybird beetle *subcoccinella vigintiquatuorpunctata* the protected reagent **857** was alkylated in the presence of CuI [378]. Finally, the silyl enediyne reagent **858** was prepared by deprotonation with LiHMDS at –78ºC, being applied to the synthesis of the antitumor agent (±)-calicheamicinone [379].

ABREVIATIONS

AA	=	amino acids
Ac	=	acetyl
acac	=	acetylacetonate
Ar	=	aryl
Bn	=	benzyl
Boc	=	*tert*-butoxycarbonyl
Bu	=	*n*-butyl
Bu^t	=	(or *t*-Bu) *tert*-butyl
Bz	=	benzoyl
$C_{10}H_8$	=	naphthalene
Cb	=	*N*,*N*-di(isopropyl)carbonyl
CIPE	=	complex induced proximity effect
Cp	=	cyclopentadienyl
CSA	=	10-camphorsulfonic acid
Cy	=	cyclohexyl
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	=	diastereomeric excess
DIBALH	=	diisobutylaluminium hydride
DIPEA	=	diisopropylethylamine

DMF	=	dimethylformamide	NBS	=	*N*-bromosuccinimide
DMSO	=	dimethyl sulfoxide	PDC	=	pyridinium dichromate
dr	=	diastereomeric ratio	P_f	=	9-phenylfluorenyl
DTBB	=	4,4'-di-*tert*-butylbiphenyl	PGA	=	prostaglandin
duryl	=	2,3,5,6-tetramethylphenyl	Ph	=	phenyl
E	=	electrophile	PPTS=		pyridinium *p*-toluenesulfonate
E2	=	second order elimination	Pr^i	=	(or *i*-Pr) isopropyl
EE	=	1-ethoxyethyl	Pr^n	=	*n*-propyl
ee	=	enantiomeric excess	PTSA	=	*p*-toluenesulfonic acid
equiv	=	equivalent(s)	*rac*	=	racemic
er	=	enantiomeric ratio	ret	=	retention
et al.	=	and coworkers	R^L	=	large R
Et	=	ethyl	R^S	=	small R
h	=	hours	rt	=	room temperature
Hal	=	halogen	*s*-Bu	=	*sec*-butyl
HIV	=	human immunodeficiency virus	S_E	=	electrophilic substitution
HMDS	=	hexamethyldisilazane	SET	=	single electron transfer
HMPA	=	hexamethylphosphoric triamide	S_N	=	nucleophilic substitution
i. e.	=	for instance	TBDPS	=	(or TPS) *tert*-butyldiphenylsislyl
inv	=	inversion	TBS	=	(or TBDMS) *tert*-butyldimethylsilyl
KDA	=	potassium diisopropylamide	TES	=	triethylsilyl
LAH	=	lithium aluminium hydride	Tf	=	triflyl (trifluoromethanesulfonyl)
LDA	=	lithium diisopropylamide	THF	=	tetrahydrofuran
LIC-KOR	=	*n*-butyllithium + potassium *tert*-butoxide	THP	=	tetrahydropyranyl
			TIPS	=	triisopropylsilyl
M	=	molar	TMEDA	=	*N,N,N',N'*-tetramethylethylenediamine
MCPBA	=	*meta*-chloroperbenzoic acid			
Me	=	methyl	TMP	=	2,2,6,6-tetramethylpiperidine
MEM	=	(2-methoxyethoxy)methyl	TMS	=	trimethylsilyl
min	=	minute(s)	Tol	=	*para*-tolyl
MOM	=	methoxymethyl	Tr	=	trityl (triphenylmethyl)
MPM	=	(or PMB) *p*-methoxybenzyl	Trs	=	trisyl [2,4,6-6-tris(isopropyl)phenyl]
MTBE	=	methyl *tert*-butyl ether	Ts	=	tosyl (*para*-toluenesulfonyl)

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