Symmetry **2010**, *2*, 437-454; doi:10.3390/sym2020437

OPEN ACCESS

symmetry

ISSN 2073-8994

www.mdpi.com/journal/symmetry

Review

Diastereoselective Desymmetrization of Symmetric Dienes and its Synthetic Application

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Received: 30 January 2010; in revised form: 4 March 2010 / Accepted: 4 March 2010 / Published: 25 March 2010

Abstract: The desymmetrization of symmetric compounds is a useful approach to obtain chiral building blocks. Readily available precursors with a prochiral unit could be converted into complex molecules with multiple stereogenic centers in a single step. In this review, recent advances in the desymmetrization of symmetric dienes in the diastereotopic group differentiating reaction and its synthetic application are presented.

Keywords: desymmetrization; symmetric diene; chiral auxiliary; C_2-symmetric diol; acetal

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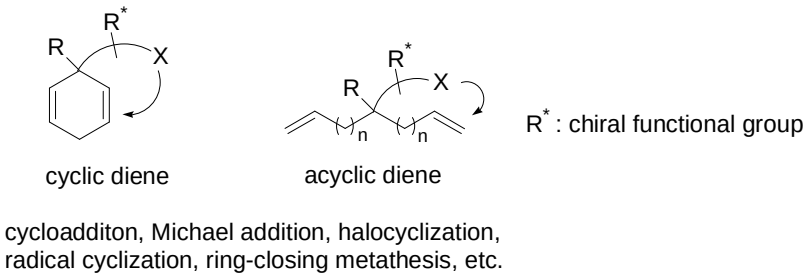
1. Introduction

The desymmetrization of *meso* compounds has become one of the most powerful strategies in organic synthesis [1]. It allows the formation of multiple chiral centers in a single step and offers an entry to a wide range of stereochemically complex molecules including natural products. The main advantage of the desymmetrization reactions is that symmetric precursors are readily accessible and easily synthesized. Therefore, there are numerous reports on asymmetric synthesis through desymmetrization reactions. Among them, the desymmetrization of diene substrates has been stereoselectively achieved by cycloaddition, Michael addition, halocyclization, radical cyclization, ring-closing metathesis, *etc*. A remaining olefin unit in the reaction products could be used for further transformations. Substrate-based asymmetric inductions from the latent stereogenic centers, namely, diastereotopic group differentiating reactions during the asymmetric syntheses have been explored [2]. In particular, substituted 1,4-cyclohexadienes have a great potential for the desymmetrization reactions [3,4]. These compounds are easily prepared by the Birch reduction/alkylation sequence of aromatic

compounds. A broad range of reactions have been developed for the desymmetrization of cyclohexadienes, and synthetic applications to natural product synthesis have been reported. The reviews on the desymmetrization of dienes before 2005 have already been reported [1-4]. We will then highlight the recent reports for the desymmetrization of dienes by diastereotopic group differentiating reactions in a stereoselective manner and its applications (Figure 1).

Figure 1. Diastereoselective desymmetrization of symmetric dienes.

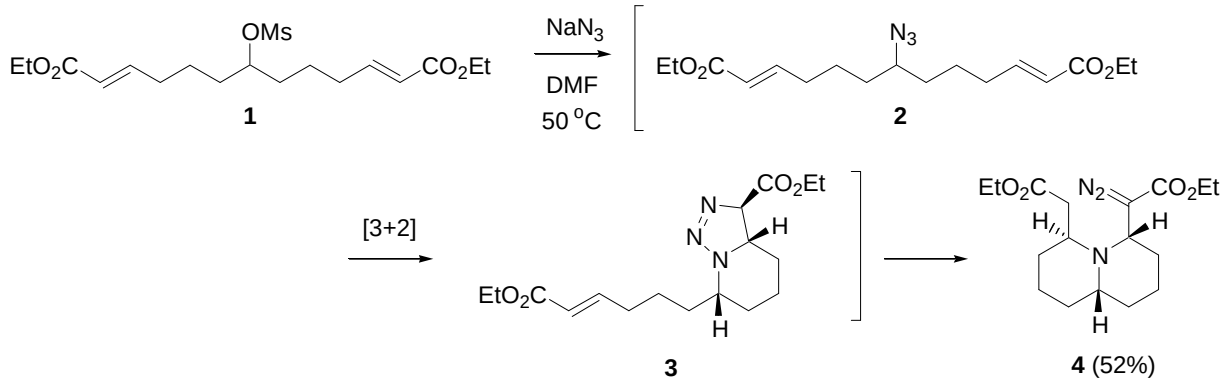


2. Desymmetrization of diene substrates by diastereotopic group differentiating reactions

2.1 Cycloaddition

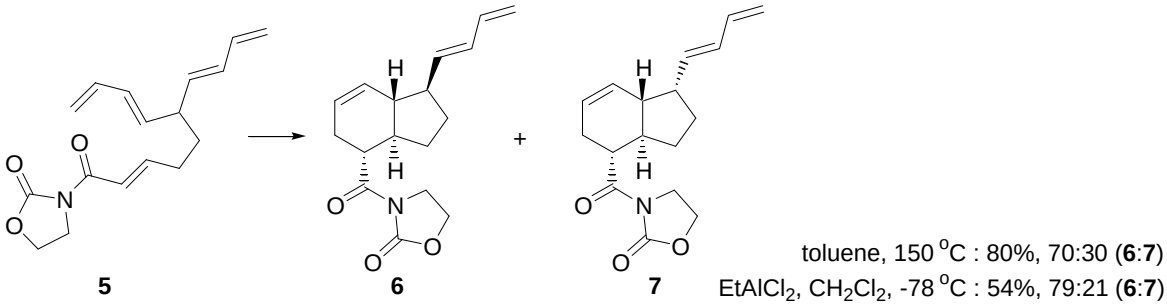
Stockman *et al*. reported the tandem intramolecular cycloaddition/triazoline fragmentation reaction [5]. The treatment of the mesylate **1** with sodium azide in DMF at 50 °C produced the azide **2**, and the subsequent [3+2] cycloaddition resulted in **3**. Fragmentation of the cycloadduct **3** followed by the ring closing reaction afforded the quinolizidine derivative **4** in 52% (Scheme 1). This reaction features a novel self-desymmetrizing cascade process.

Scheme 1. Intramolecular cycloaddition/triazoline fragmentation.



Linclau *et al*. developed the formation method of a C9-substituted *trans*-hydrindene ring by the intramolecular Diels-Alder reaction (IMDA) [6]. The reaction was conducted under thermal conditions (150 °C in toluene) and the bis(1,3-diene) unit of **5** was desymmetrized leading to a 70:30 mixture of **6** and **7**. The use of a Lewis acid ($EtAlCl_2$ in CH_2Cl_2 at -78 °C) as a catalyst afforded **6** and **7** with a higher selectivity (79:21) (Scheme 2).

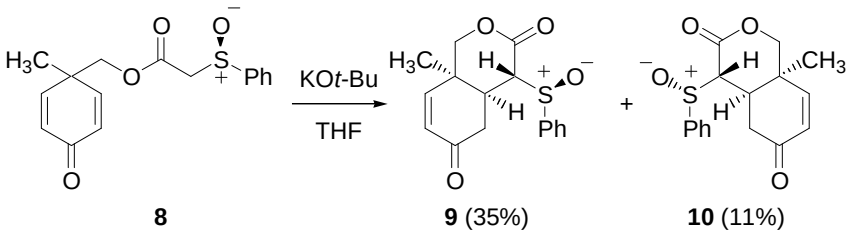
Scheme 2. Diastereotopic group selective intramolecular Diels-Alder reaction.



2.2 Michael addition

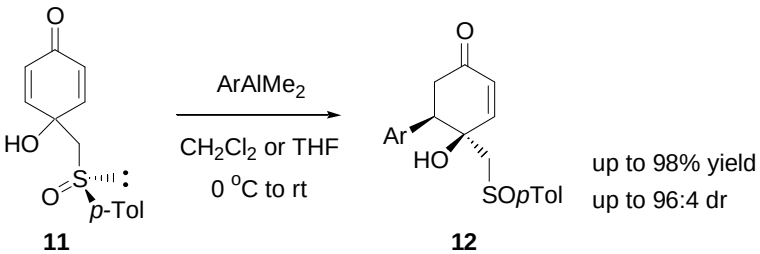
The sulfoxide-directed desymmetrization of cyclohexadienes was studied by Elliott *et al*. [7]. When the sulfoxide **8** was treated with KO*t*-Bu, the bicyclic compounds **9** and **10** were obtained in different yields (Scheme 3).

Scheme 3. Sulfoxide-directed desymmetrization of cyclohexadiene.



Carreño *et al*. reported the diastereoselective Michael addition on the cyclohexadiene with the chiral sulfoxide [8]. The chiral sulfoxide **11** was reacted with aryl organoaluminum reagents, leading to the addition products **12** (up to 98% yield, up to 96:4 dr) (Scheme 4). They envisaged that the hydroxyl group has an essential role in the asymmetric induction. They also applied this strategy to synthesize the aryl cyclitol derivatives.

Scheme 4. Diastereoselective Michael addition on cyclohexadiene with chiral sulfoxide.

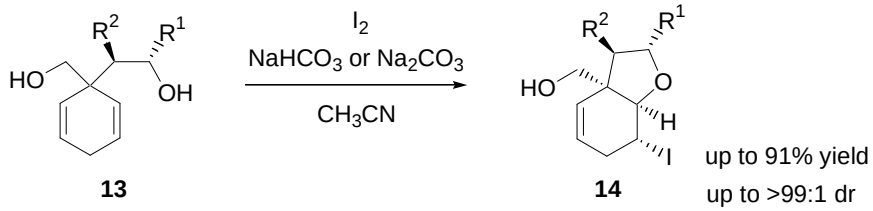


2.3 Iodocyclization

Elliott *et al*. employed the regio- and diastereoselective iodoetherification of 1,4-cyclohexadiene with a chiral tether [9]. Iodocyclization of the cyclohexadienes **13** having stereogenic centers adjacent to the oxygen atom with I_2 and $NaHCO_3$ or Na_2CO_3 smoothly proceeded to give 5-*endo* cyclization

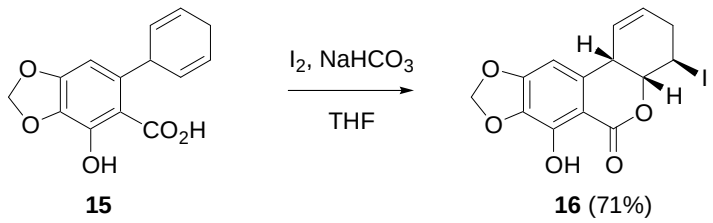
products **14** with a high selectivity (up to >99:1 dr) and up to 91% yield (Scheme 5). They also studied the competition between the 6-*exo* and 7-*endo* cyclization.

Scheme 5. Iodocyclization of 1,4-cyclohexadiene with a chiral tether.



Crich *et al*. developed the desymmetrization of aryl cyclohexadienes [10]. Iodocyclization of the aryl cyclohexadiene **15** provided the lactone **16** in 71% yield (Scheme 6). Compound **16** is a key intermediate in the synthsis of (±)-pancratistatin reported by Danishefsky *et al*. [11].

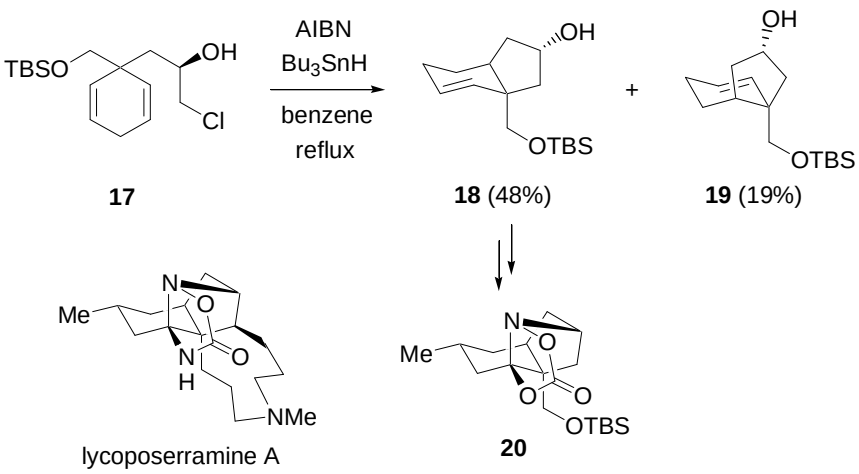
Scheme 6. Iodocyclization of aryl cyclohexadiene.



2.4 Radical cyclization / Epoxidation-cyclization

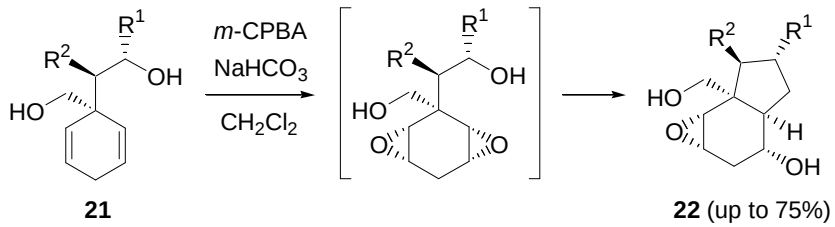
Recently, Elliott *et al*. reported the synthetic studies of lycopodium alkaloids, lycoposerramine A and S, by the desymmetrization of cyclohexadienes under radical conditions [12,13]. The radical cyclization of the mono-TBS compound **17** gave **18** and **19** as a separable mixture. The major isomer **18** underwent further transformations to give the heterocycle compound **20**, which is a model for the tetracyclic core of lycoposerramine A [12] (Scheme 7). They also carried out a synthesis towards lycoposerramine S by the same strategy [13].

Scheme 7. Synthesis of the tetracyclic core of lycoposerramine A.



They also described the stereoselective epoxidation and cyclization of 1,4-cyclohexadienes [14]. Epoxidation of the cyclohexadienes **21** with *m*-CPBA gave the cyclized products **22** (up to 75% yield) as single diastereoisomers, via the bis-epoxide intermediates (Scheme 8).

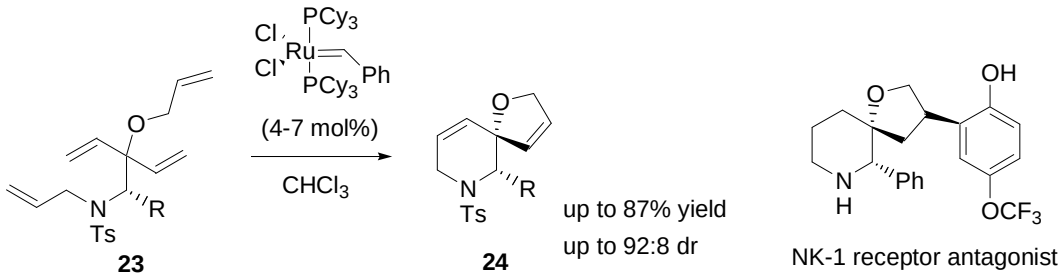
Scheme 8. Stereoselective epoxidation and cyclization of cyclohexadiene.



2.5 Ring-closing metathesis

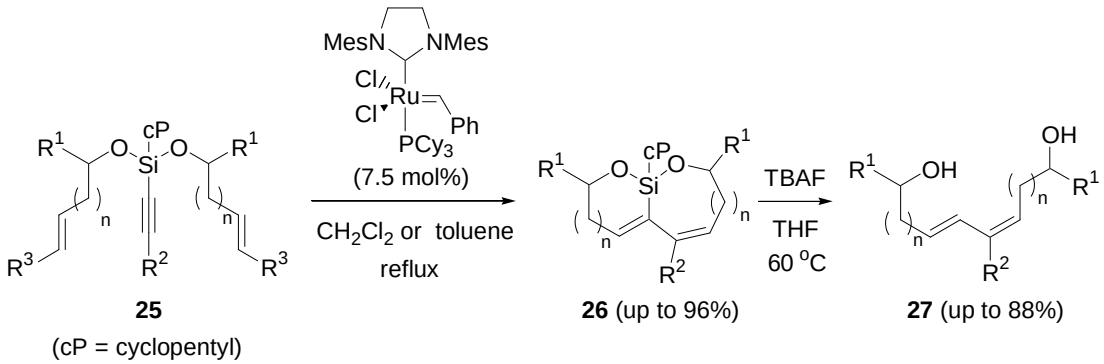
Wallace *et al*. studied the double ring-closing metathesis reaction of the tetraenes **23** with the first generation Grubbs' catalyst to stereoselectively form the spirocyclic rings **24** (up to 87% yield, up to 92:8 dr) [15]. They also applied this reaction to the enantioselective synthesis of the NK-1 receptor antagonist in 3 steps from **24** (R = Ph) [16] (Scheme 9). Recently, they revealed the reaction mechanism [17,18].

Scheme 9. Double ring-closing metathesis of tetraenes.



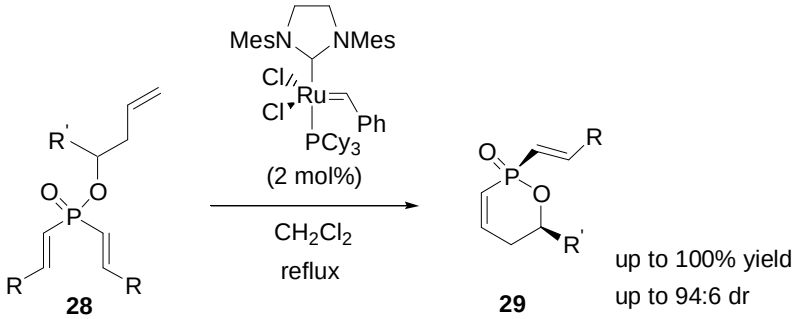
Lee *et al*. developed the dienyne ring-closing metathesis reaction of the alkynyl silaketals **25** with the second generation Grubbs' catalyst to afford the bicyclic siloxanes **26** in up to 96% yield. Removal of the silicon tether was achieved with TBAF to give the corresponding 1,3-dienes **27** [19,20] (Scheme 10). This methodology is an efficient tool to synthesize the 1,4-disubstituted 1,3-dienes.

Scheme 10. Dienyne ring-closing metathesis of alkynyl silaketals.



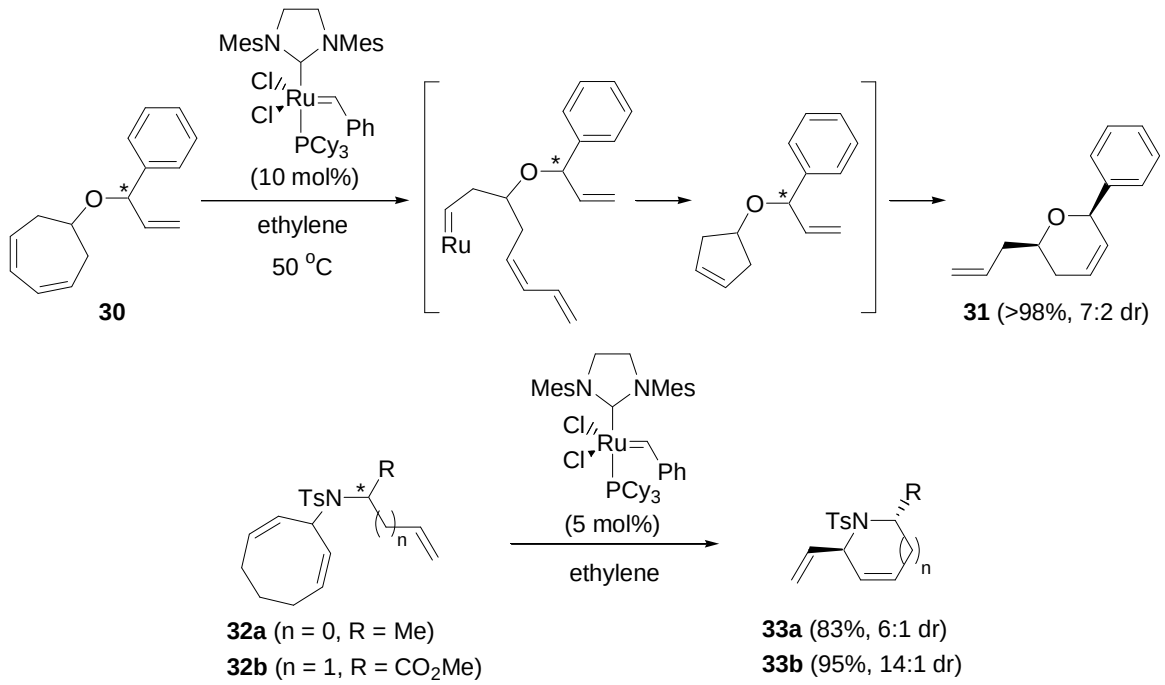
The diastereoselective ring-closing metathesis of phosphorus-containing trienes was reported by Gouverneur *et al*. [21]. The prochiral trienes **28** reacted with the second generation Grubbs' catalyst to give the P-stereogenic six-membered heterocycles **29** in up to 100% yield with a high diastereoselectivity (up to 94:6 dr) (Scheme 11).

Scheme 11. Ring-closing metathesis of P-containing trienes.



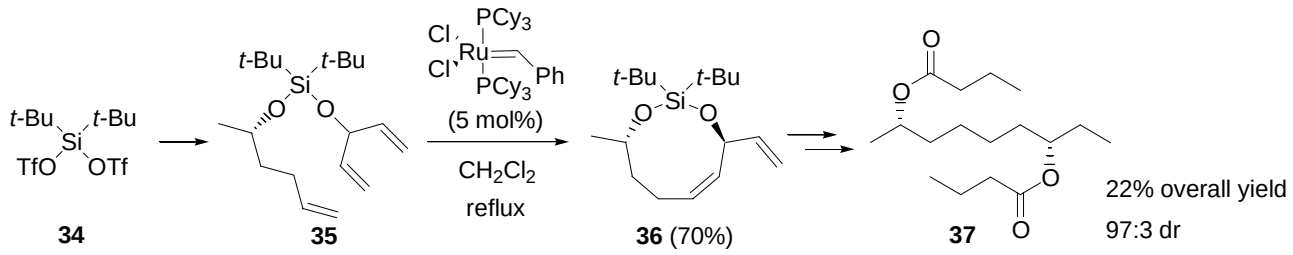
Blechert *et al*. employed the diastereoselective ring-rearrangement metathesis (RRM) [22]. Treatment of the cyclodiene **30** with the second generation Grubbs' catalyst gave the dihydropyran **31** in favor of the 2,6-*cis* product (>98% yield, 7:2 dr). They supposed that compound **30** reacted the precatalyst to produce the carbene complex and then RCM occurred to give the cyclopentene intermediate. This cyclopentene would rearrange to afford the isolated dihydropyran **31**. They also conducted the reactions of the cyclooctadienes **32a**,**b** under the same conditions, and obtained the dihydropyrrole **33a** (83% yield, 6:1 dr) and the piperidine derivative **33b** (95% yield, 14:1 dr), both of which are *trans* isomers (Scheme 12).

Scheme 12. Diastereoselective ring-rearrangement metathesis.



Pickett *et al*. explored the concise synthesis of the sex pheromone of *Sitodiplosis mosellana* by the silicon tethered ring-closing metathesis [23]. The di-*t*-butyl silaketal **35**, prepared from the chiral alcohol, prochiral 1,4-pentadien-3-ol and di-*t*-butylsilyl bis(trifluoromethanesulfonate) **34**, was subjected to metathesis conditions to give **36** in 70% yield from **34** over 2 steps. Removal of the silyl group and further transformations furnished the desired product **37** in 22% overall yield with 97:3 dr (Scheme 13).

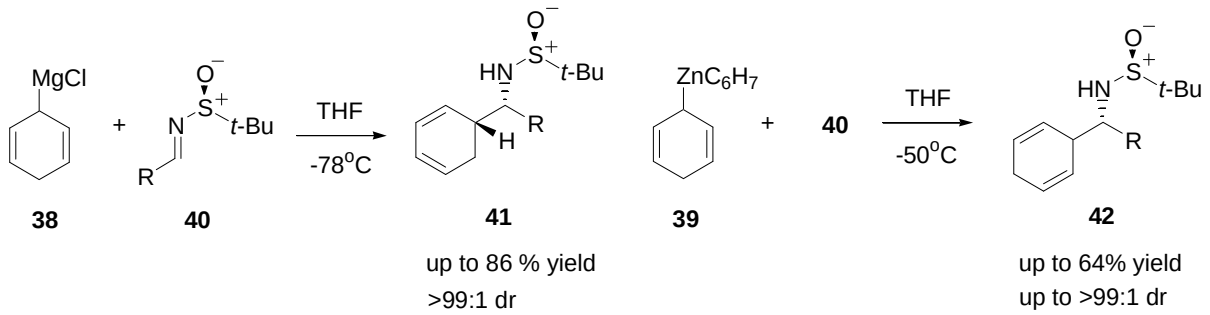
Scheme 13. Diastereoselective silicon-tethered ring-closing metathesis and synthesis of the sex pheromone of the orange wheat blossom midge.



2.6 Miscellaneous reactions

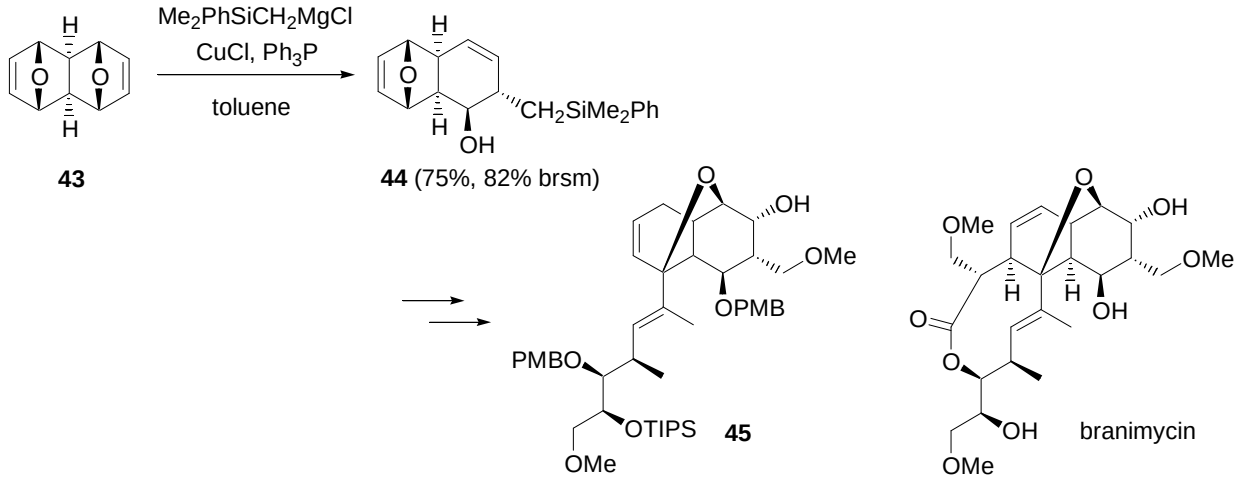
Studer *et al*. found that the chiral cyclohexadienyl-Ti complex reacted with aldehydes to afford chiral 1,3-cyclohexadienyl compounds with a high stereoselectivity [24,25]. They recently reported the desymmetrization of the metallated cyclohexadienes **38** and **39** with chiral *N-tert*-butanesulfinyl imines **40** [26]. The cyclohexadienyl-MgCl compound **38** provided the 1,3-dienes **41** with a high diastereoseletivity (>99:1 dr). When the metal on the cyclohexadiene was changed from Mg to Zn, the 1,4-dienes **42** were obtained (up to 99:1 dr) (Scheme 14). The 1,4-dienes **42** were readily oxidized to the corresponding diarylmethylamine derivatives, which are found in biologically active compounds.

Scheme 14. Desymmetrization of metallated cyclohexadienes with N-*tert*-butanesulfinyl imines.



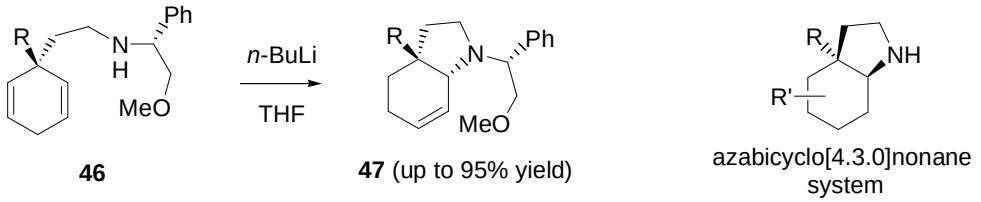
Gromov and Mulzer *et al*. developed a desymmetrization approach to construct the functionalized *cis*-decaline core of branimycin [27]. The treatment of the diepoxynaphthalene **43** with $Me_2PhSiCH_2MgCl/CuCl/Ph_3P$ resulted in an anti S_N' opening one of the oxa-bridges to stereoselectively give **44** in 75% yield (82% based on the recovered starting material **43**). Compound **44** underwent further transformations including the opening of the remaining oxa-bridge by hydride attack to synthesize the tricycle structure **45** (Scheme 15).

Scheme 15. Desymmetrization of diepoxynaphthalene and synthesis of *cis*-decaline core of branimycin.



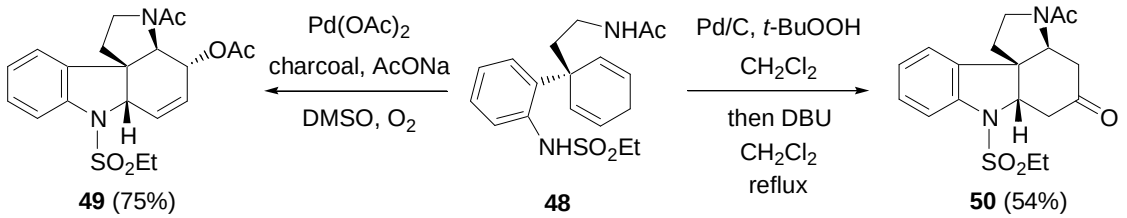
Landais *et al*. reported that the highly regio- and stereoselective intramolecular hydroamination of the cyclohexadienes **46** bearing the chiral secondary amine moieties led to the bicyclic allylic amines **47** (up to 95% yield). This cascade reaction is a useful method to provide a key structure, the azabicyclo[4.3.0]nonane system, found in various alkaloids [28] (Scheme 16) .

Scheme 16. Diastereoselective protonation-hydroamination cascade reaction.



The same group described two different approaches to the tetracyclic core of the aspidosperma alkaloids by a double oxidative amination and double conjugate addition process [29]. Treating the cyclohexadiene **48** with $Pd(OAc)_2$ and O_2 in DMSO provided the tetracyclic compound **49** as a single isomer in 75% yield. On the other hand, the allylic oxidation using Pd/C-*t*-BuOOH and subsequent double 1,4-addition in the presence of DBU led to **50** in 54% yield (Scheme 17).

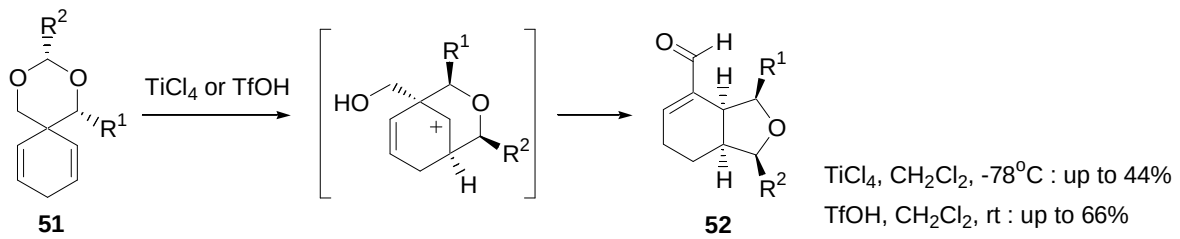
Scheme 17. Two approaches to tetracyclic core of aspidosperma alkaloids.



Prins reaction was also used for the desymmetrization of the 1,8-diene [30]. Elliott *et al*. reported the Prins desymmetrization of 1,4-cyclohexadienes [31,32]. The cyclohexadienes **51** were treated with $TiCl_4$ or TfOH to form the benzo[*c*]furan carboxaldehyde derivatives **52** via the oxocarbenium ion (up

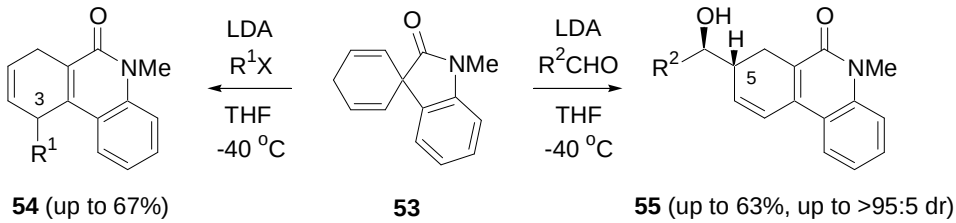
to 66% yield) (Scheme 18). TfOH is effective for this reaction due to its strong acidity with a non-nucleophilic counter-ion.

Scheme 18. Prins desymmetrization of 1,4-cyclohexadienes.



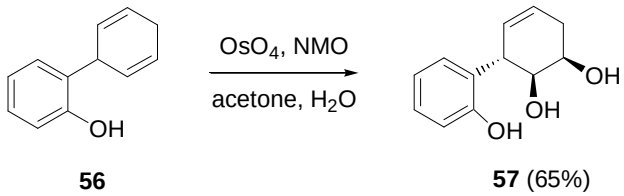
Landais *et al*. studied the rearrangement of spirocyclohexadienyl oxindoles [33,34]. Upon treatment of the spirooxindole **53** with LDA at -40 °C, the dienes rearranged to deliver the lithium enolate intermediate. The intermediate was then trapped by alkyl halides at the C3 center to afford **54** (up to 67%). On the other hand, the aldehydes were reacted at the C5 center to give **55** (up to 63%) with a high stereoselectivity (up to >95:5 dr) (Scheme 19).

Scheme 19. Rearrangement of spirocyclohexadienyl oxindoles followed by addition of alkyl halides or aldehydes.



Crich *et al*. reported the dihydroxylation of the aryl cyclohexadienes by the desymmetrization strategy [35]. Dihydroxylation of the cyclohexadiene **56** occurred exclusively with anti-selectivity to the substituted aromatic ring to minimize allylic strain to afford the triol **57** in 65% yield (Scheme 20).

Scheme 20. Dihydroxylation of aryl cyclohexadiene.

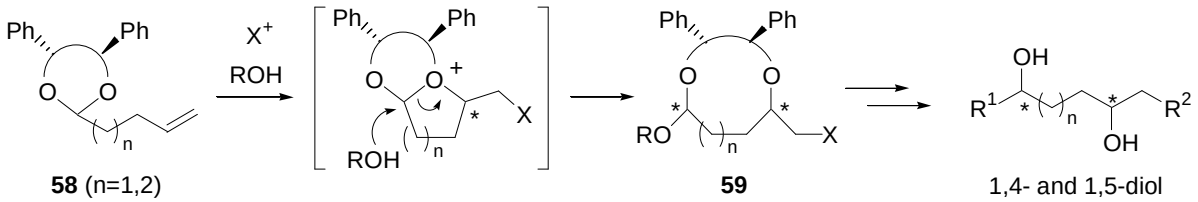


2.7 Asymmetric desymmetrization using C_2-symmetric acetal or aminal

We have developed an asymmetric synthesis of the chiral 1,4- and 1,5-diols by the diastereoselective intramolecular haloetherification reaction of the ene acetals **58**, easily prepared from the C_2-symmetric diols and ene aldehydes, involving the remote asymmetric induction [36,37]. This reaction stereoselectively proceeded via the chiral bicyclic cationic intermediates, and the subsequent nucleophilic addition of an alcohol to the oxonium ion intermediate afforded **59**, which have two

newly formed chiral centers on the prochiral atom and the acetal center of the starting materials **58**. The chiral auxiliary unit derived from the C_2-symmetric diol could be removed by various procedures, *i.e.*, Birch reduction, hydrogenolysis, and fragmentation promoted by CAN [38,39] (Scheme 21).

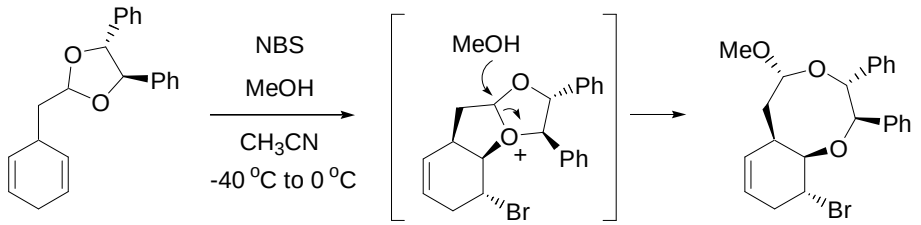
Scheme 21. Intramolecular haloetherification of ene acetals.



58 (n=1,2) **59**

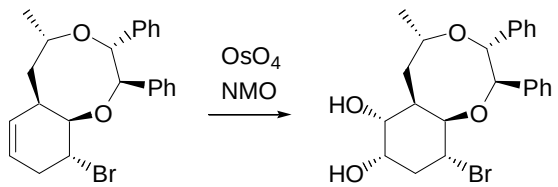
We then studied the intramolecular bromoetherification reaction of the substituted cyclohexadiene having the C_2-symmetric acetal **60** and found that the reaction successfully discriminated the two prochiral olefins in a stereoselective manner to provide **61** in 63% yield [40,41] (Scheme 22). This reaction was useful for constructing complex molecules because it could produce optically active cyclohexane derivatives bearing multiple chiral centers and the remaining olefin, which promised further transformations. The sterically hindered acetal moiety derived from the C_2-symmetric acetal could fix the cyclohexene ring conformation promising high regio- and stereoselective transformations. For example, the dihydroxylation of **62** with OsO_4 stereoselectively proceeded from the less hindered face to give the corresponding diol **63** in 85% yield as a single product [41] (Scheme 23).

Scheme 22. Intramolecular bromoetherification of cyclohexadiene acetal.



60 **61** (63%)

Scheme 23. Stereoselective dihydroxylation.

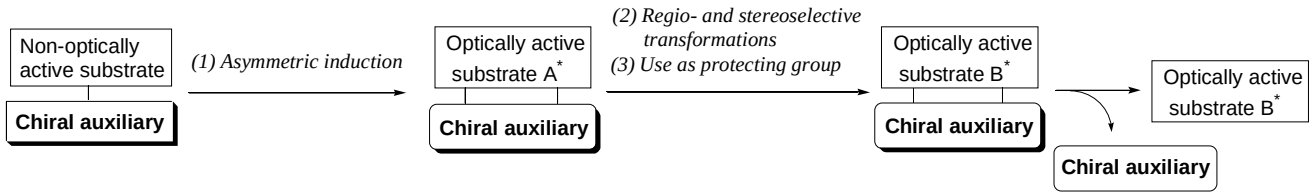


62 **63** (85%)

Enantioselective reactions with chiral catalysts are well-known as more powerful methods than diastereoselective approaches with chiral auxiliaries for asymmetric synthesis. The fatal drawback in diastereoselective reaction is that at least an equimolar amount of the auxiliary is necessary. However, for the synthesis of complex molecules including natural products, various reactions such as the regio-, stereo-, and chemoselective transformations must be considered. Recently, we have proposed a novel

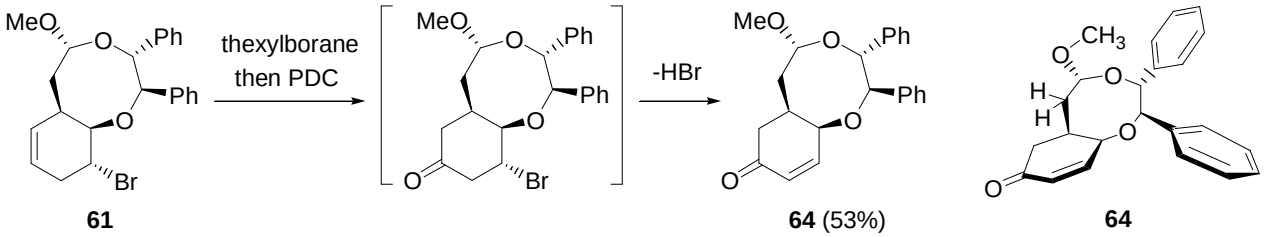
concept, the chiral auxiliary multiple-use methodology [42]. This is a new perspective in asymmetric synthesis utilizing a chiral auxiliary several times, namely, asymmetric induction, regio-, stereoselective transformation and protective group of the functional group (Figure 2).

Figure 2. Chiral auxiliary multiple-use methodology.



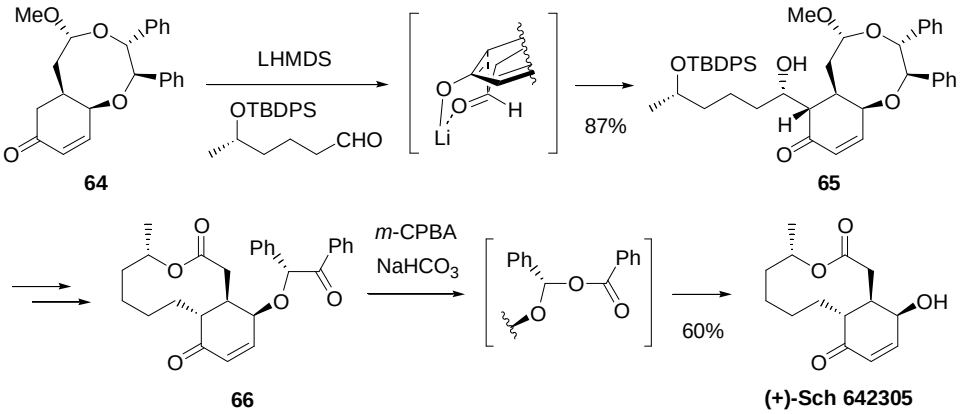
We achieved the concise synthesis of (+)-Sch 642305 by this methodology starting from the bromo acetal **61**, obtained by the bromoetherification of the cyclohexadiene acetal **60** [42]. First, the acetal **61** was subjected to the hydroboration-oxidation condition. The hydroboration reaction regioselectively proceeded and the subsequent oxidation gave the bromo ketone intermediate. This intermediate spontaneously converted to the enone **64** by elimination of HBr in 53% yield. The structure of **64** showed that the upper side of the cyclohexene ring was shielded by the axial C-C bond and methylene group of the acetal ring. Furthermore, the 8-membered acetal ring derived from chiral auxiliary fixed the conformation to prevent the cyclohexane ring inversion (Scheme 24).

Scheme 24. Hydroboration-oxidation procedure.



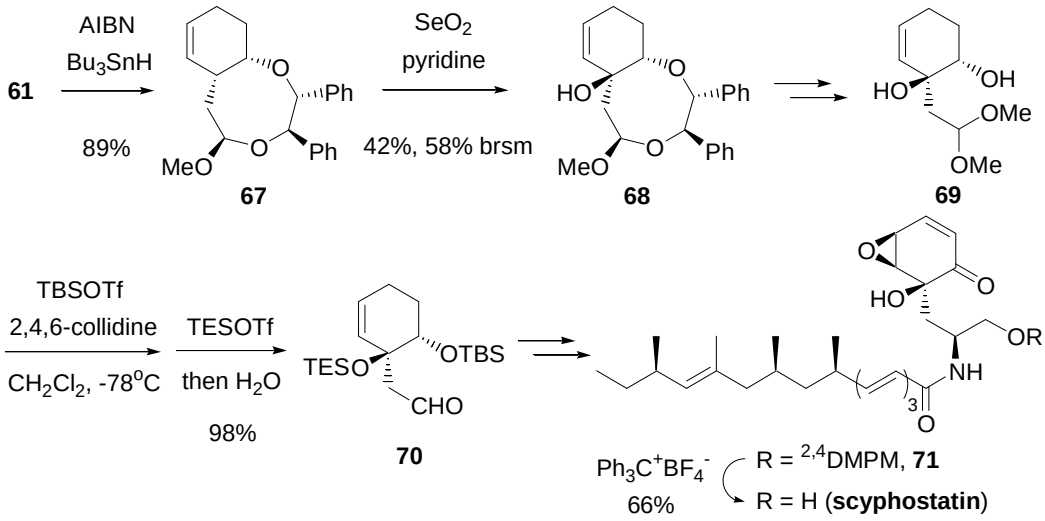
The aldol reaction of **64** with the chiral aldehyde proceeded from the sterically less hindered face to afford the alcohol **65** as a single diastereomer. Further transformations including the radical reduction and macrolactonization gave the macrolactone **66**. The chiral auxiliary was finally removed under oxidative conditions to furnish (+)-Sch 642305 via the ester intermediate (Scheme 25).

Scheme 25. Total synthesis of (+)-Sch 642305.



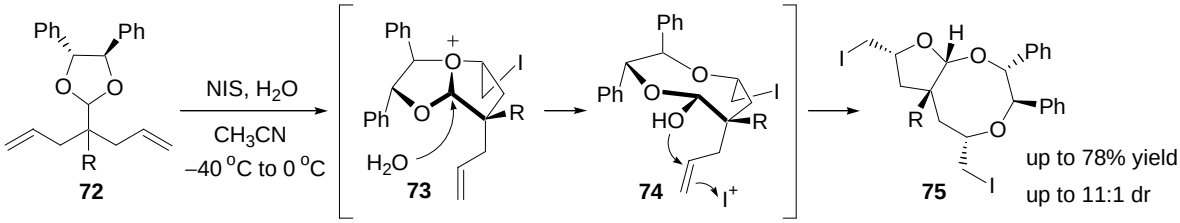
We also achieved the asymmetric total synthesis of scyphostatin, a potent inhibitor of neutral sphingomyelinase [43]. The radical reduction of **61** and stereoselective introduction of the tertiary alcohol with SeO_2 gave **68**. Further transformations afforded the dimethylacetal **69**. Deprotection of the acetal function by combination with silyl triflate/2,4,6-collidine under basic conditions gave **70** [44,45]. With **71** in hand, the deprotection of 2,4-dimethoxyphenylmethyl (^{2,4}DMPM) group with $Ph_3C^+BF_4^-$ then completed the total synthesis of scyphostatin (Scheme 26).

Scheme 26. Total synthesis of scyphostatin.



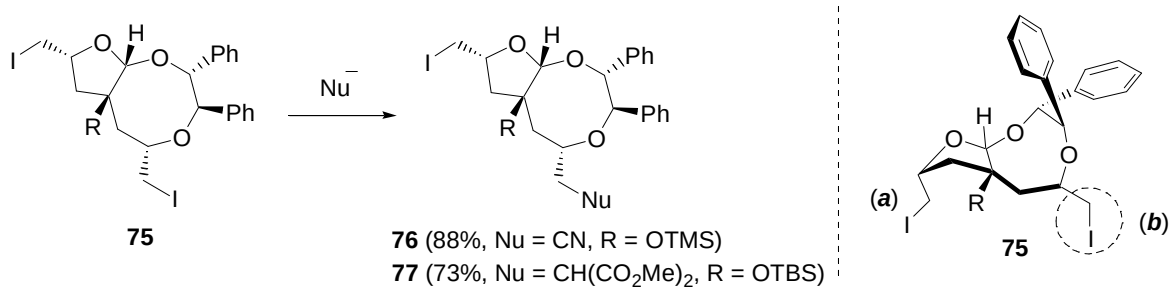
We have found that the novel double iodoetherification reaction of acyclic σ-symmetric diene acetals from the C_2-symmetric diol, *i.e.*, the chiral hydrobenzoin, afforded tetrahydrofurans with multiple chiral centers in a single operation [46,47]. Although discrimination of the two olefins of the σ-symmetric dienes with chiral auxiliaries by asymmetric intramolecular halolactonization have been reported, they do not have auxiliaries in the reaction products [48-53]. Compared with other reports, our method features that the chiral auxiliary remained in the product. Therefore, we could utilize the product for further regio- and stereoselective transformations. The acyclic diene acetals **72** with NIS and H_2O led to the optically active tetrahydrofuran derivatives **75** involving the newly installed four stereogenic centers (up to 78% yield, up to 11:1 dr). The reaction proceeded via the chiral hemiacetal intermediates **74** formed by iodoetherification of the acetal oxygen atoms and subsequent nucleophilic addition of H_2O to **73**, followed by a second iodoetherication to give **75** (Scheme 27). It is known that hemiacetal compounds could convert to hydroxyl aldehydes through a ring-opning reaction. Alternatively, the hemiacetal intermediates **74** have another double bond in the proper position and the second iodoetherification smoothly occurs.

Scheme 27. Double iodoetherification of diene acetals.



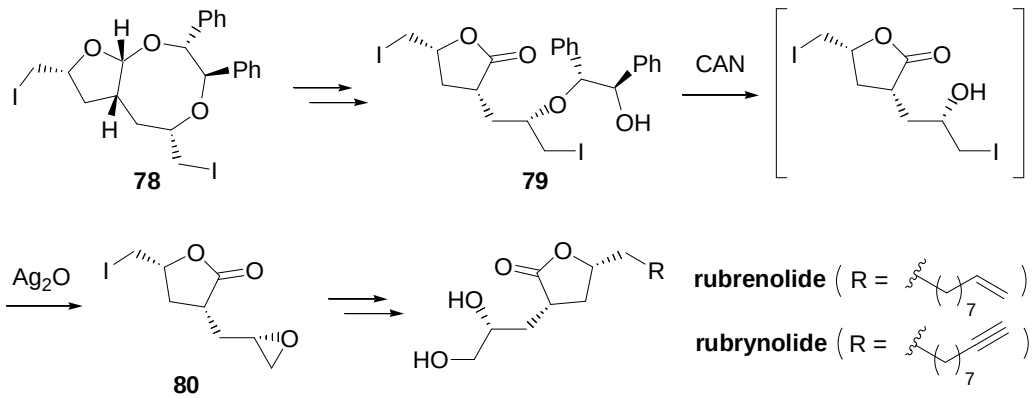
Since the acetals **75** have the iodomethyl functions, we tried to perform the regioselective nucleophilic substitution of iodine. The treatment of **75** with sodium cyanide or sodium malonate gave **76** (88% yield) and **77** (73% yield), the regioselective substitution products in the less hindered position (b) (Scheme 28). This result indicates that **75** could be a useful chiral synthon for the synthesis of optically active tetrahydrofurans or γ-lactones.

Scheme 28. Regioselective substitution.



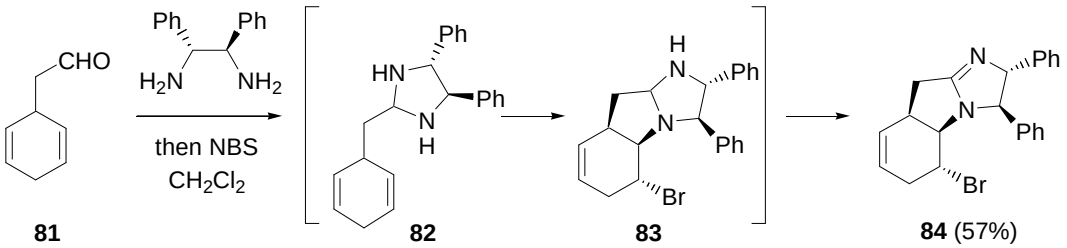
We applied this method to the asymmetric synthesis of rubrenolide and rubrynolide, which have the remote asymmetric center and substituted the γ-lactone ring. The 8-membered acetal **78** was converted to the lactone **79**. Removal of the chiral auxiliary with CAN, developed in our laboratory [38,39], followed by epoxidation of the resulting alcohol with Ag_2O afforded **80**. The treatment of the epoxide **80** with the corresponding Grignard reagent, and further transformation to furnish the synthesis of rubrenolide and rubrynolide (Scheme 29).

Scheme 29. Total synthesis of rubrenolide and rubrynolide.



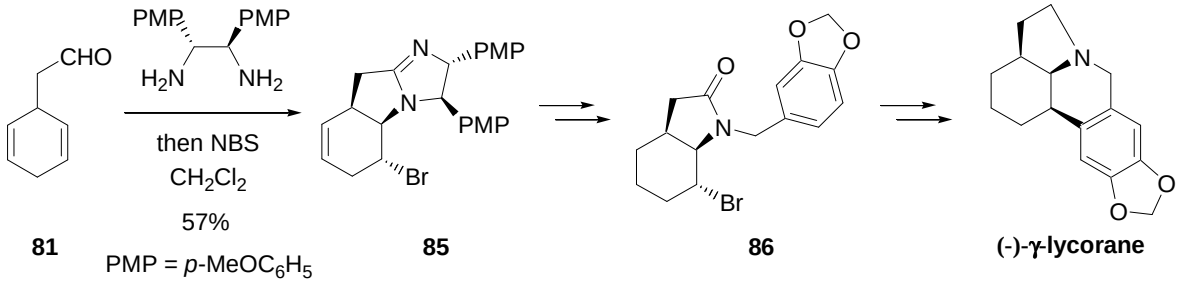
Our groups also employed the desymmetrization reaction using C_2-symmetric diene aminals in place of acetals to give compounds containing the nitrogen atom [54]. This reaction involves three steps, *i.e.*, the formation of aminal (**81**→**82**), stereoselective bromoamination (**82**→**83**), and oxidation of the aminal (**83**→**84**) in a cascade process (57% yield) (Scheme 30).

Scheme 30. Desymmetrization of diene aminal.



Furthermore, we applied this reaction to the concise synthesis of (–)-γ-lycorane. We proposed that the chiral imidazoline **85** derived from 1,2-di(4-methoxyphenyl)-1,2-diamine was an useful chiral synthon for achievement of the total synthesis. The compound **85** was converted to **86** via lactam formation and condensation of the aromatic unit. Finally, Friedel-Crafts reaction of **86** and subsequent reduction furnished (–)-γ-lycorane (Scheme 31).

Scheme 31. Total synthesis of (–)-γ-lycorane.



3. Conclusions

The desymmetrization reaction have enjoyed much popularity in organic synthetic chemistry. Among the many desymmetrization reactions, we focused on the symmetric dienes as a precusor. Differentiation of the diastereotopic diene group could be attained by cycloaddition, Michael addition, halocyclization, radical cyclization, ring-closing metathesis, *etc*. The alkene moiety in the reaction products could be used for further transformation. Therefore, the cyclic and acyclic dienes are promising precusors to obtain complex molecules with several chiral centers including biologically active natural products.

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