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Review

Synthetic Routes to (+)-Cassiol and (-)-Cassioside

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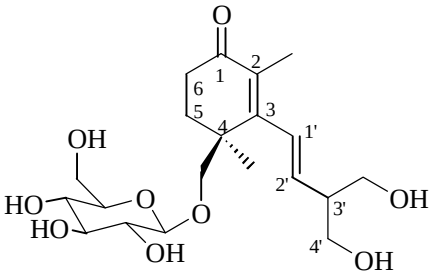
Esta revisão sumariza as seqüências desenvolvidas recentemente para a síntese total das substâncias antiulcerogênicas (+)-cassiol e seu glicosídeo (-)-cassiosídeo. A discussão está centralizada nas estratégias sintéticas e nas metodologias para a construção de centros carbônicos quaternários.

This review summarizes the sequences recently developed for the total synthesis of the antiulcerogenic compounds (+)-cassiol and its glucoside (-)-cassioside. The discussion is focused on synthetic strategies and on methodologies for the construction of quaternary carbon stereocenters.

Keywords: *enantioselective synthesis, construction of quaternary carbon stereocenters*

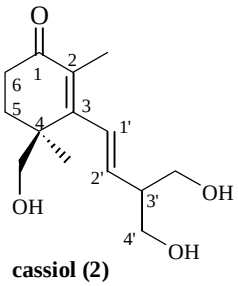
Introduction

As the result of a pharmacological analysis of the aqueous extract of the dried stem bark of *Cinnamomum cassia* Blume, one of the constituents of the traditional chinese prescription "goreisan" ("kennan keihi" in Japanese) that displayed a potent antiulcerogenic activity in rats, Fukaya *et al*.[1] isolated in 1988 three pure compounds responsible for this pharmacological effect. One of these compounds comprised 1 x 10^{-5}% of the stem bark and was named **cassioside** (**1**).



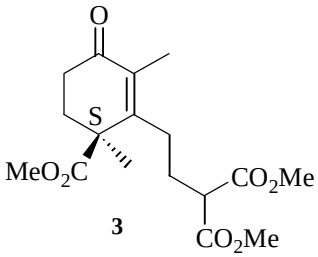
cassioside (1)

The structure of cassioside (**1**) {$[\alpha]_D$ -25.2 (c 0.5, MeOH)} was determined by extensive spectroscopic studies. In addition, the enzymatic hydrolysis of **1** with β-D-glucosidase afforded an aglycon named (+)-**cassiol** (**2**) {$[\alpha]_D$ 8.6 (c 0.25, MeOH)}, showing more potent antiulcer activity than cassioside itself.



cassiol (2)

The absolute configuration of (+)-cassiol (**2**) was shown to be *S* by comparison of the CD spectrum of the trimethyl ester **3**, prepared by selective hydrogenation, oxidation and methylation of **2**, with that of methyl tetrahydrotrisporate C (**4**), of known absolute configuration. As a consequence



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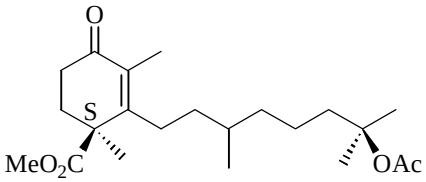
of this comparison, it can be conclude that the absolute configuration at C-4 of (-)-cassioside is also *S*.



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A careful analysis of the structure of (+)-cassiol (**2**) reveals a rather simple molecular framework that accommodates a functionalized cyclohexenone moiety with a quaternary stereocenter (C-4) and a 2-ethenyl-1,3-propanediol side chain which is connected at C-3. These structural features and pharmacological activity of cassiol have aroused the interest of synthetic organic chemists and several valuable contributions to its synthesis have appeared in the literature in recent years. In this Report we have summarized this body of published material, focusing our attention on synthetic strategies and on new methodologies for the construction of quaternary carbon stereocenters[2].

The discussion is organized into three primary sections: 1) strategies based on the assembly of a chiral cyclohexenone/cyclohexanone intermediate and its coupling with a side-chain precursor 2) the chiral Diels-Alder strategies and 3) the palladium catalyzed cycloisomerization strategy

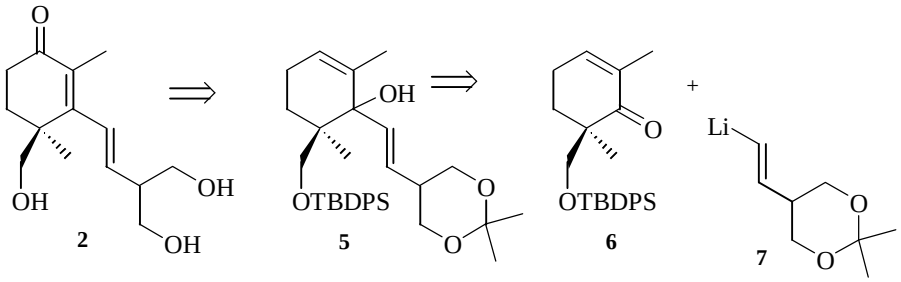
Strategies Based on the Assembly of a Chiral Cyclohexenone/Cyclohexanone Intermediate and its Coupling with a Side Chain Precursor

In 1989, Fukaya *et al.*, who had determined the structure of (+)-cassiol (**2**) just one year earlier, reported also its total synthesis. Fukaya's strategy[3], outlined retrosynthetically in Scheme 1, was based on the selective vinylation of the chiral enone intermediate **6** to furnish the allylic alcohol **5** which, through an 1,3-oxidative rearrangement and deprotection would afford (+)-(**2**).

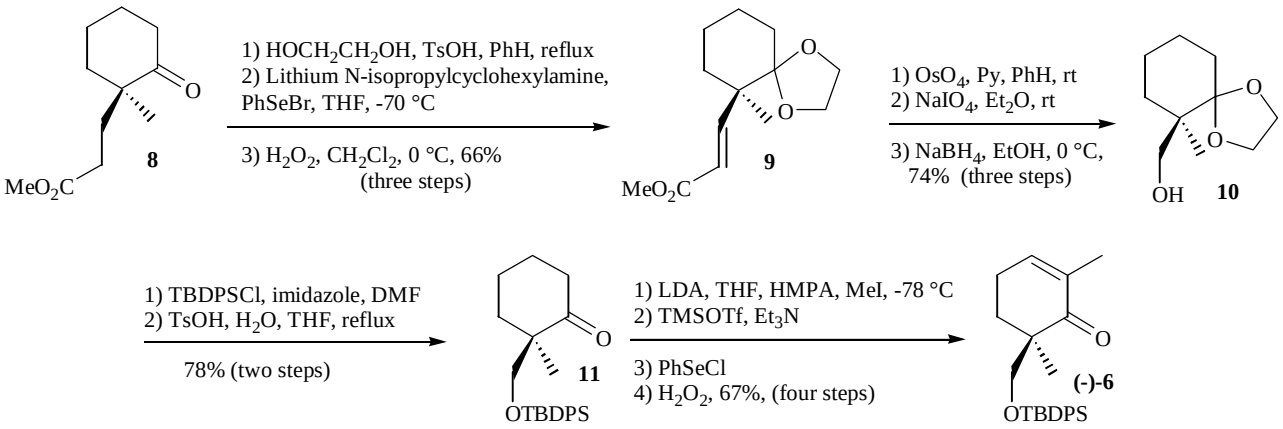
Starting with the commercially available chiral ketoester **8**, of known absolute configuration, and following the degradative sequence described in Scheme 2, the required enone **6** was obtained in enantiomerically pure form {$[\alpha]_D^{24}$ -23.6 (c 1.8, MeOH)}.

For the crucial selective vinylation reaction of (-)-**6**, the (*E*)-vinyllithium reagent **7** was generated *in situ* by the transmetalation of **14** with butyllithium, following the methodology previously described by Corey *et al.*[4], to afford the allylic alcohol **5** in 94% yield (see next page).

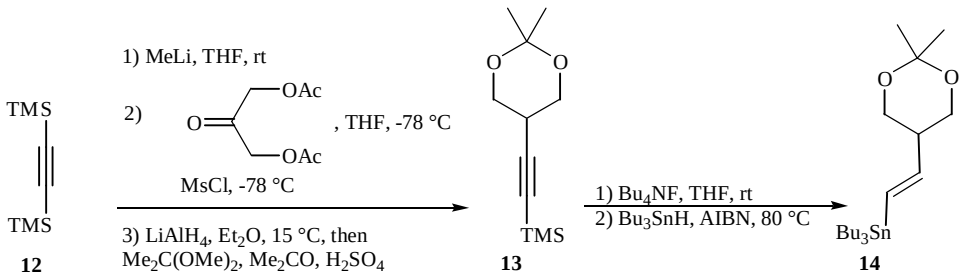
The vinylstannane **14** was, in turn, prepared in 29% overall yield starting with bis (trimethylsilyl)-acetylene (**12**) and following the sequence outlined in Scheme 3.



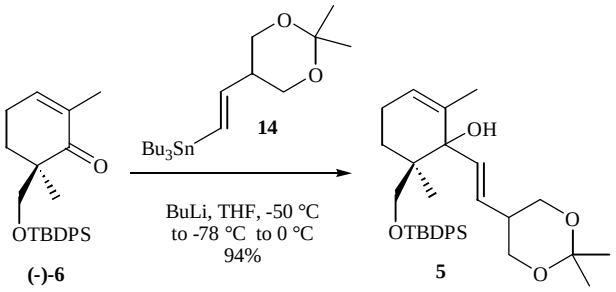
Scheme 1.



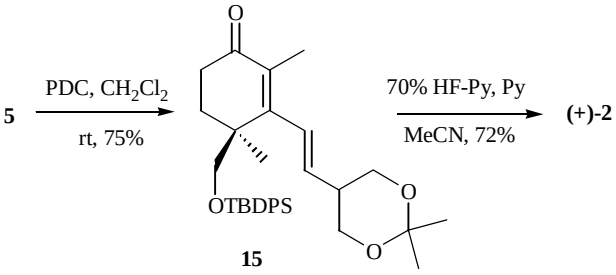
Scheme 2.



Scheme 3.



Finally, the oxidative rearrangement of the allylic alcohol **5**, induced by pyridinium dichromate, gave the expected enone **15** which, by deprotection, afforded (+)-cassiol (**2**) {$[\alpha]_D^{28.5}$ 8.63 (c 0.35, MeOH)} of more than 98% optical purity.

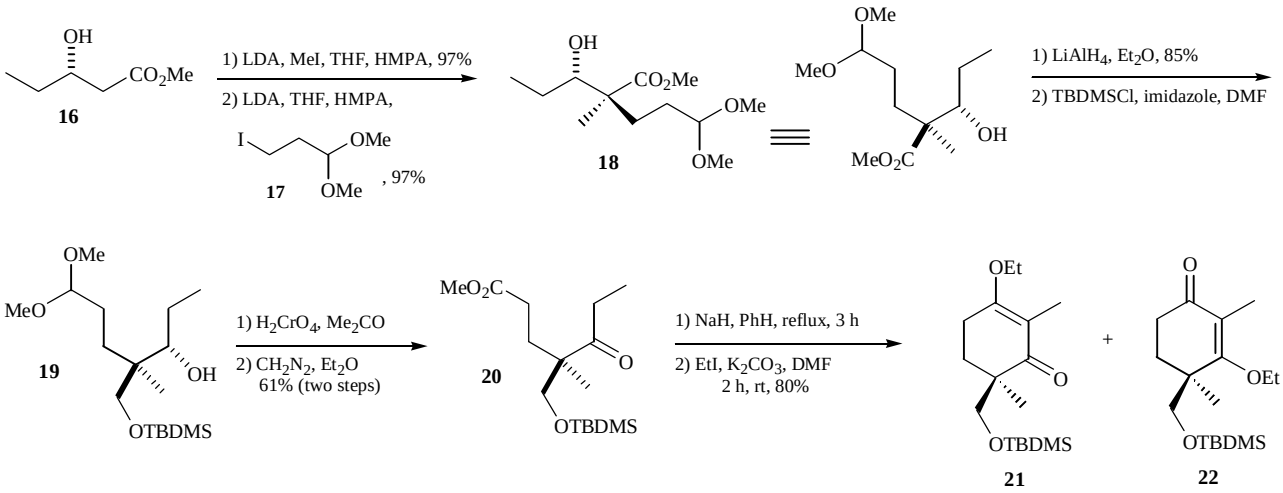


By following a strategy conceptually similar to that outlined in Scheme 1, several authors developed sequences towards cassiol (**2**), using, however, a variety of interesting methodologies for the construction of the quaternary stereocenter present in the required cyclohexenone/cyclohexanone intermediate.

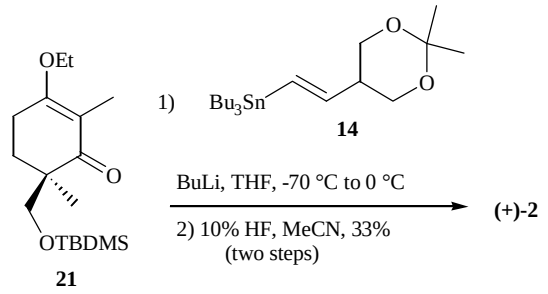
In 1990, Mori *et al.*[5] reported the enantioselective synthesis of the vinylogous ester **21**, and its transformation into (+)-cassiol (**2**), starting with the chiral β-hydroxyester **16**. By two successive alkylations of **16** with methyl iodide and with 3,3-dimethoxypropyl iodide (**17**) respectively, the ester **18**, with the required stereochemistry at the quaternary stereocenter, was obtained in excellent yield.

That the configuration of this ester is the one shown in **18**, was deduced on the basis of previous observations that the alkylation of the dianion of **16** (or its methylated product) gives preferentially the *anti*-product[6]. The ester **18** was then transformed into the vinylogous ester **21** by the sequence of functional group interconversions followed by Claisen condensation, esterification and column chromatography, as described in Scheme 4.

Finally, addition of **7**, generated from **14**, to **21** followed by cleavage of the protecting groups gave (+)-**2** in 5.6% overall yield and 99.2% ee.

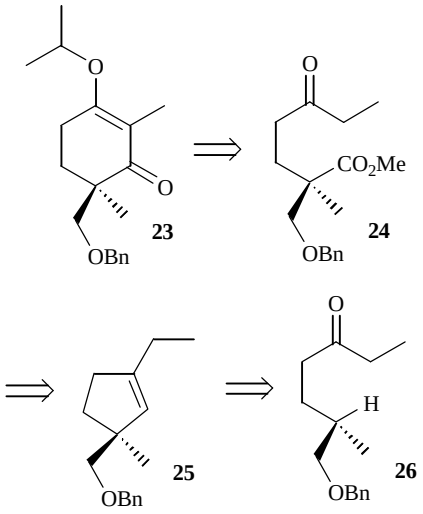


Scheme 4.

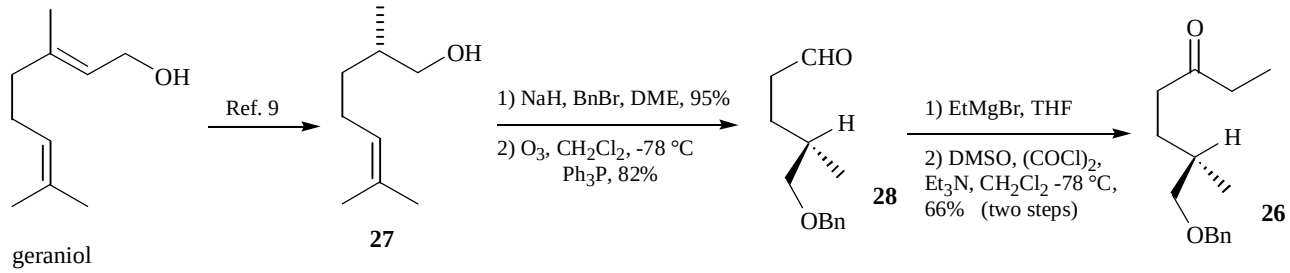


A similar strategy to that described by Mori e*t al*.[5] for the synthesis of (+)-cassiol (**2**) was reported in 1996 by Taber *et al.*[7] However, a completely different approach was used by these authors for the construction of the vinylogous ester **23**, with a defined absolute configuration, as illustrated in retrosynthetic format in Scheme 5. The key transformation in this approach is the stereospecific conversion of an acyclic stereocenter into a cyclic quaternary one (**26** → **25**) by an intramolecular alkylidene carbene methine insertion reaction[8].

Starting with (-)-norcitronellol (**27**) prepared from geraniol by a known procedure[9], and by a series of functional group manipulations, enantiomerically pure **26** was obtained (Scheme 6).



Scheme 5.

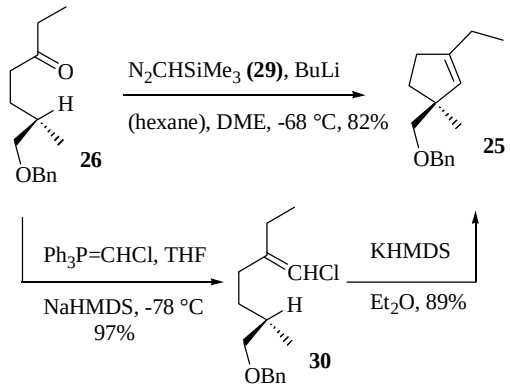


Scheme 6.

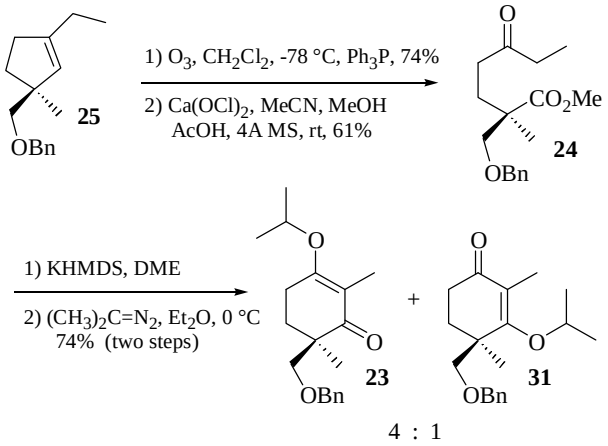
The cyclization of **26** into **25** was carried out with the lithium derivative of (trimethylsilyl)-diazomethane (**29**), generated *in situ*, and by α-elimination at the vinyl chlorides **30** according to Scheme 7. The yield of the two-step route was similar to that of the one-pot procedure with **29**.

For the preparation of **23**, cyclopentene **25** was first submitted to ozonolysis followed by oxidation to the methyl ester **24** which, upon Claisen condensation and esterification with 2-diazopropane, afforded a mixture of regioisomers (**23** and **31**) separable by column chromatography (Scheme 8).

The catalytic hydrogenation of **23** gave alcohol **32** which, by vinylation, under essentially the same conditions

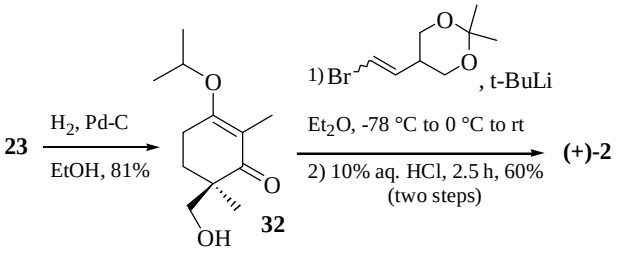


Scheme 7.



Scheme 8.

previously described, and cleavage of the protecting groups moiety, afforded (+)-cassiol (**2**) {$[\alpha]_D$ 9.1 (c 4.5, MeOH)}.

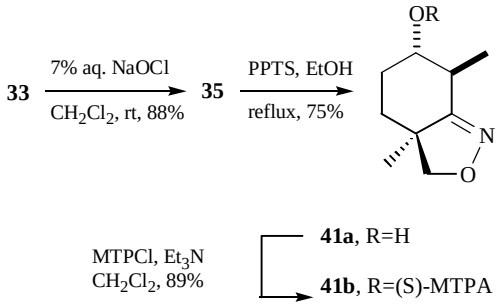


Also in 1996, Shishido and coworkers[10] took advantage of the highly diasteroselective intramolecular [3+2] dipolar cycloaddition of the nitrile oxide **34**, generated from oxime **33**, for the construction of isoxazoline **35**, a precursor of intermediate **36**, with a defined stereochemistry at the quaternary stereocenter, to be transformed into (+)-cassiol (**2**) (Scheme 9).

These authors envisioned, on the basis of molecular mechanic calculations, that the stereochemistry of the two contiguous chiral centers of oxime **33** was crucial to constraint the conformation of the transition state of the dipolar cycloaddition reaction to the more favorable chair-like one leading, consequently, to the diasteroselective formation of **35** (Fig. 1).

The preparation of oxime **33** with the required relative and absolute stereochemistry was carried out following the asymmetric aldol methodology of Evans[11] and further functional group interconversions, as shown in Scheme 10.

The nitrile oxide intermediate **34**, generated from oxime **33**, on treatment with sodium hypochlorite afforded, as expected, exclusively the isoxazoline **35** in 88% yield. That the stereochemistry of the newly generated center is *S* as depicted in **35**, was established by NOE experiments on the free alcohol **41a** and further, by analysis of the ^{1}H-NMR spectrum of the corresponding MTPA ester **41b**, it was shown that the optical purity of **35** was more than 99%.



The isoxazoline ring of **35** was smoothly cleaved by hydrogenolysis to afford **36** in good yield. By protection of the free hydroxyl group of **36** followed by vinylation, the intermediate **42** was obtained. Starting with **42** and following the sequence depicted in Scheme 11, the synthesis of (+)-cassiol (**2**) was completed.

More recently, in 1998, Banerjee *et al.*[12] reported a short and efficient synthesis of (-)-**6**, the key intermediate

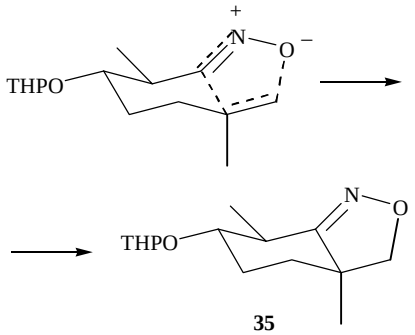
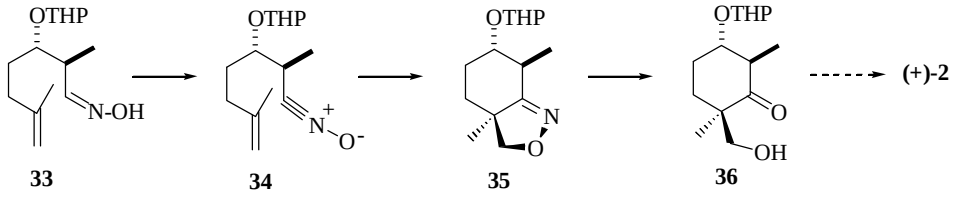
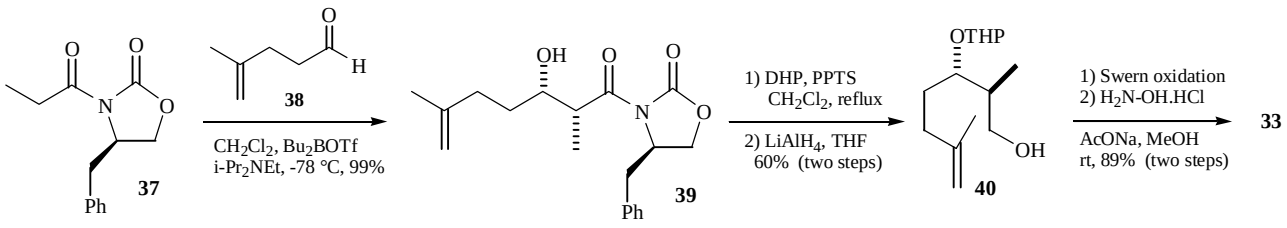


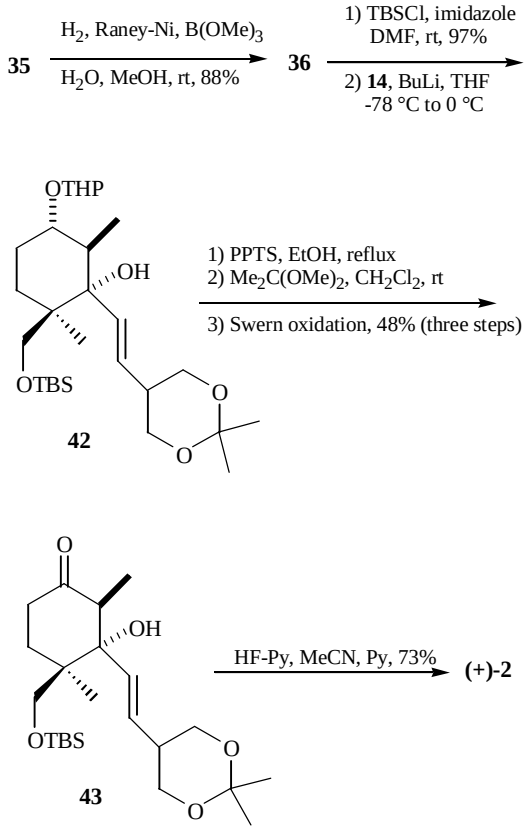
Figure 1.



Scheme 9.



Scheme 10.



Scheme 11.

enone which had been prepared by Fukaya an co-workers in the first synthesis of (+)-cassiol (**2**)[3].

The approach used by Banerjee *et al*. for the generation of the quaternary stereocenter of (-)-**6** was based on the asymmetric Michael addition of chiral imines /secondary enamines under neutral conditions to electrophilic alkenes, recently developed by d'Angelo and co-workers[13].

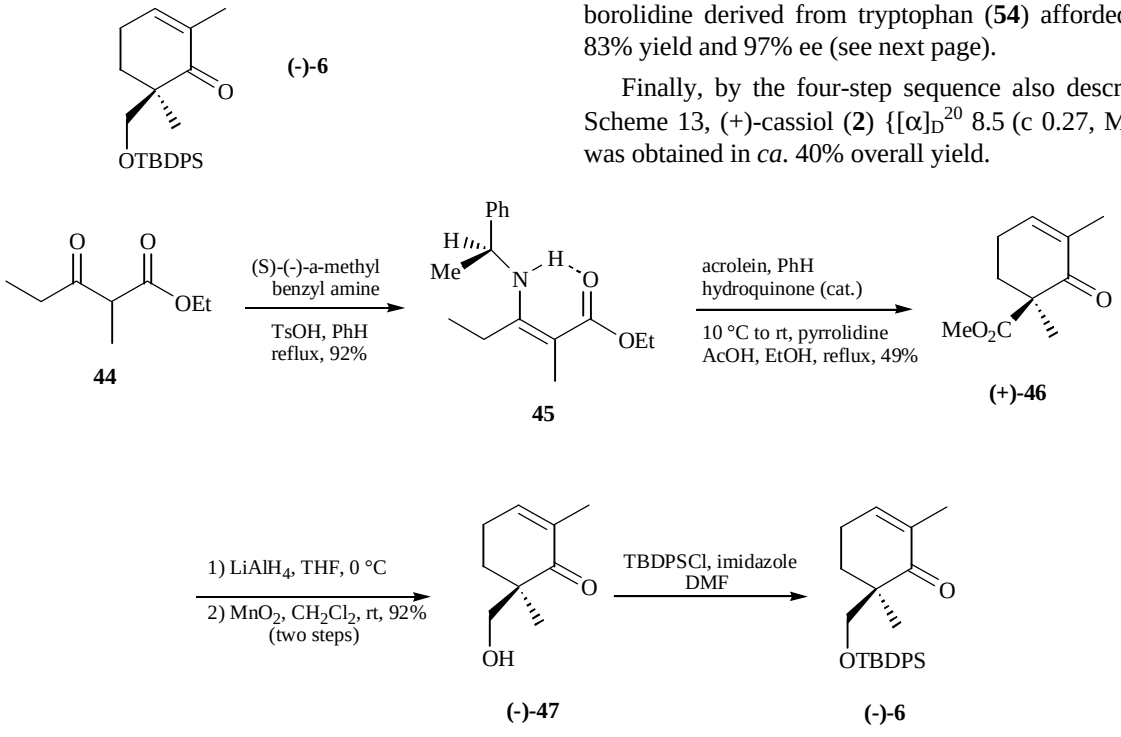
Condensation of β-ketoester **44** with (*S*)-(-)-α-methyl benzylamine furnished the chiral enamine **45** in excellent yield. The Michael addition of **45** to acrolein followed by hydrolysis and cyclization of the crude product afforded (+)-**46**. Finally, a sequence involving reduction, selective oxidation and protection gave enantiomerically pure (-)-**6** {$[\alpha]_D^{25}$ -22.75 (c 1.65, MeOH)}, this work represents a formal total synthesis of (+)-cassiol (**2**) (Scheme 12).

The Chiral Diels-Alder Strategies

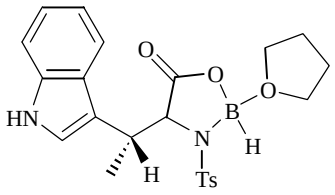
Two conceptually related enantioselective synthesis of (+)-cassiol (**2**) and (-)-cassioside (**1**) involving a chiral Diels-Alder reaction as the key step, have appeared in the literature.

In 1994, Corey and co-workers[14] demonstrated the synthetic power of their oxazaborolidine-catalyzed enantioselective Diels-Alder reaction[15] by the development of a remarkable short and efficient route to (+)-cassiol (**2**). After an appropriate choice of protecting groups for the diene, small structural modifications in the catalyst and an experimentally oriented selection of reaction solvents, Corey *et al*. discovered that the cycloaddition reaction of the electron-rich triene **51**, prepared as depicted in Scheme 13, and 2-methylacrolein in the presence of the chiral oxazaborolidine derived from tryptophan (**54**) afforded **52** in 83% yield and 97% ee (see next page).

Finally, by the four-step sequence also described in Scheme 13, (+)-cassiol (**2**) {$[\alpha]_D^{20}$ 8.5 (c 0.27, MeOH)} was obtained in *ca*. 40% overall yield.



Scheme 12.



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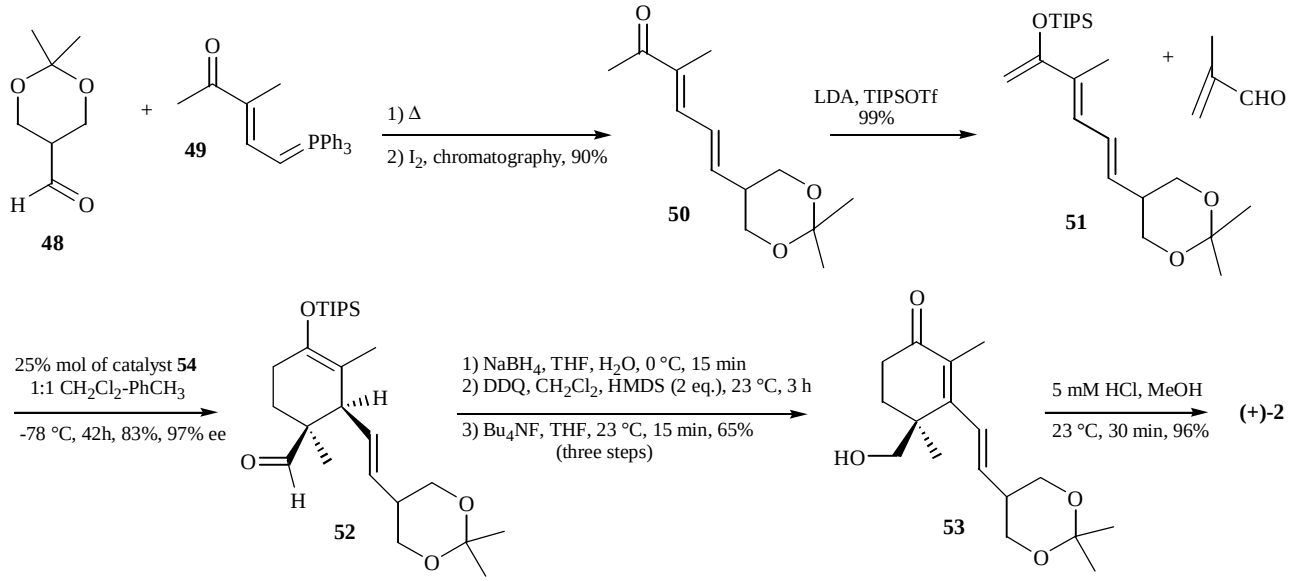
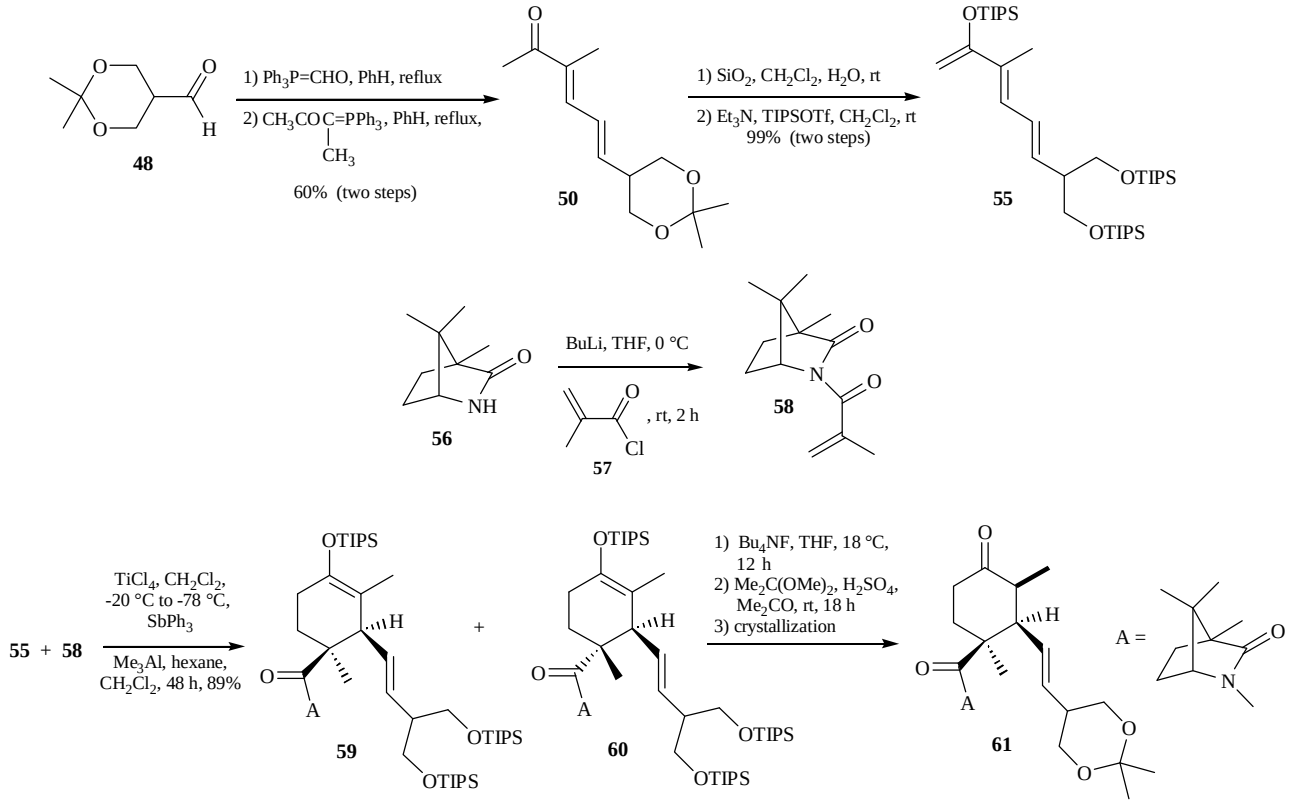
More recently, in 1996, Boeckman *et al.*[16] reported the construction of the quaternary carbon stereocenter present in (-)-cassioside (**1**) by an asymmetric Diels Alder reaction of the oxygenated triene **55**, identical to triene **51**, previously described by Corey *et al.*[14] except by the protecting group, and the chiral dienophile **58**.



Scheme 13.



Scheme 14.

The preparation of **55**, carried out by two consecutive Wittig reactions, is described in Scheme 14, together with the preparation of the chiral dienophile **58**.

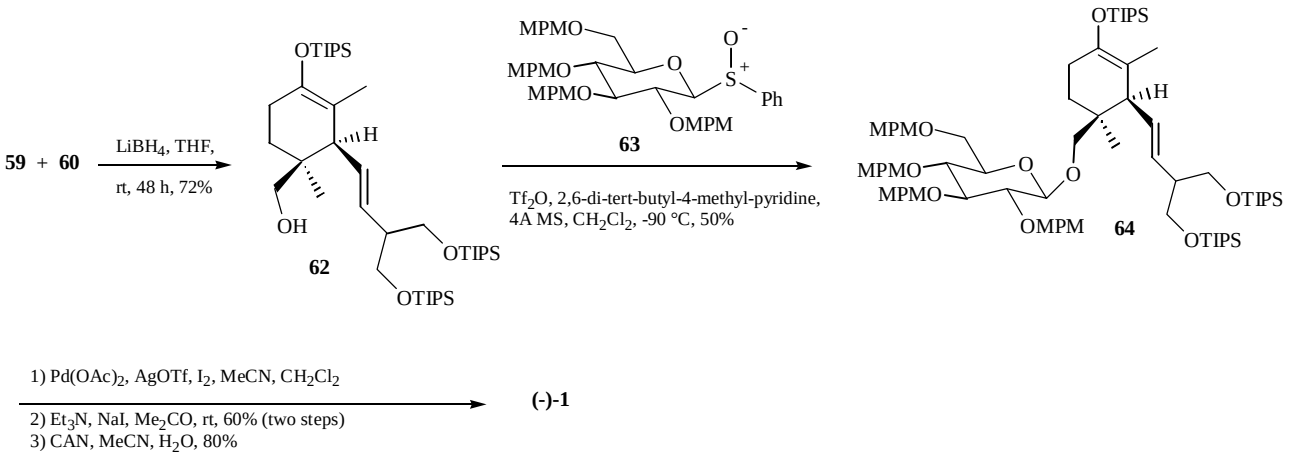
To avoid decomposition of the acid-sensitive triene **55**, under the usual conditions of the Lewis acid-catalyzed cycloaddition reaction, the $TiCl_4$-$SbPh_3$ complex was employed as promoter and further, one equivalent of trimethylalminum was added as proton scavenger. Under these conditions a 11:1 mixture of two diasteroisomeric cycloadducts **59** and **60**, *endo* and *exo* respectively, was obtained in 89% yield. The X-ray analysis of the crystalline acetonide derivative **61**, prepared as described also in Scheme 14, confirmed the structure and absolute stereochemistry of the major diastereoisomer.

The reduction of the mixture of cycloadducts **59** and **60** followed by column chromatography, allowed the isolation of the major alcohol **62** and recovery of the chiral auxiliary (**56**). Finally, glycosidation of the hydroxyl group of **62** following Kahne's procedure gave intermediate **64** which, by generation of the enone moiety and deprotection afforded (-)-**1** {$[\alpha]_D^{25}$ -25.1 (c 0.6, MeOH)}, this work represents the first total synthesis of (-)-cassioside (**1**) (Scheme 15).

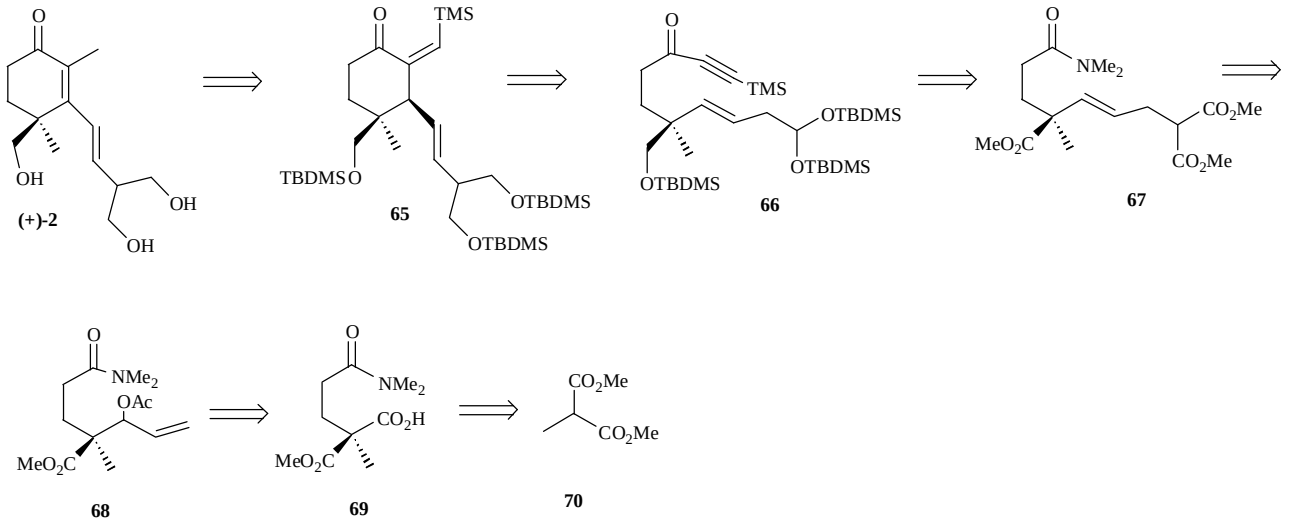
The Palladium Catalyzed Cycloisomerization Strategy

Also in 1996, based on the strategy outlined retrosynthetically in Scheme 16, Trost *et al.*[17] reported a new total synthesis of (+)-cassiol (**2**). The key features of Trost's cassiol synthesis are the new palladium catalyzed cycloisomerization of enyne **66** in an ene type fashion to the cyclohexanone derivative **65**, the elaboration of the side chain present in cassiol by a palladium (0) catalyzed reaction (**68** → **67**) and the generation of the quaternary carbon stereocenter by an enzymatic process.

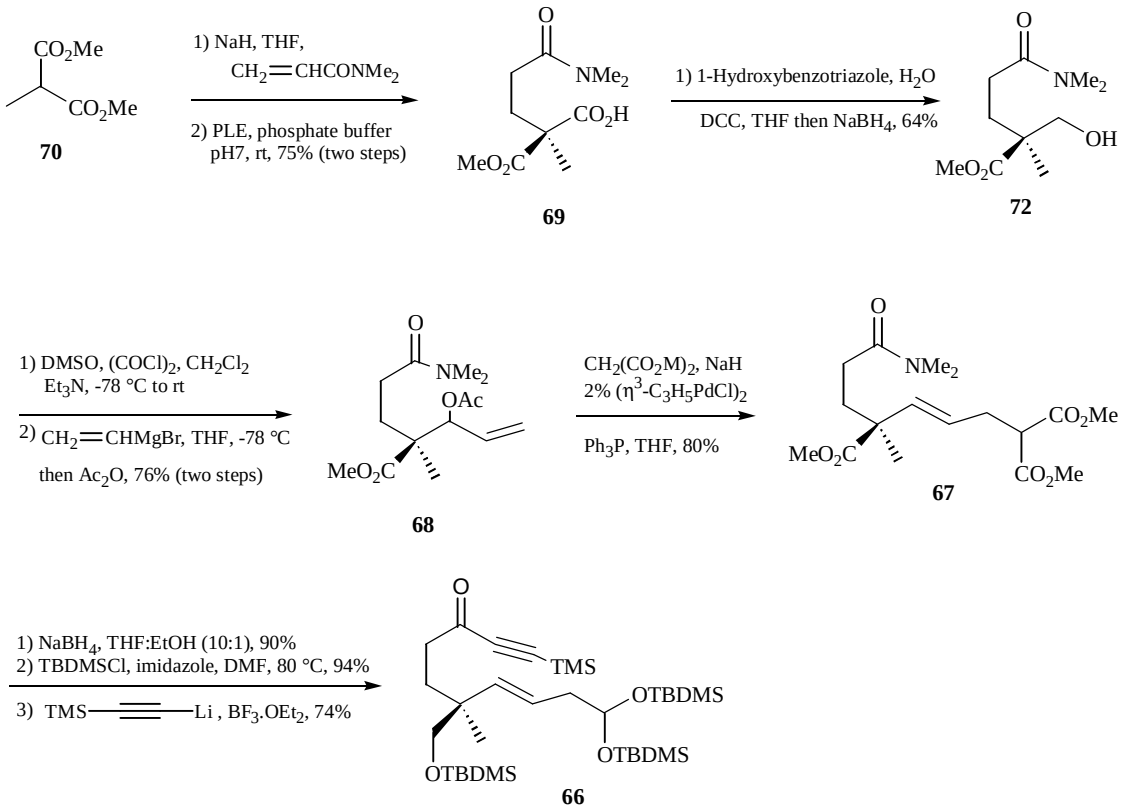
As shown in Scheme 17, the conjugate addition of the anion of dimethyl methylmalonate **70** to N,N-dimethy-



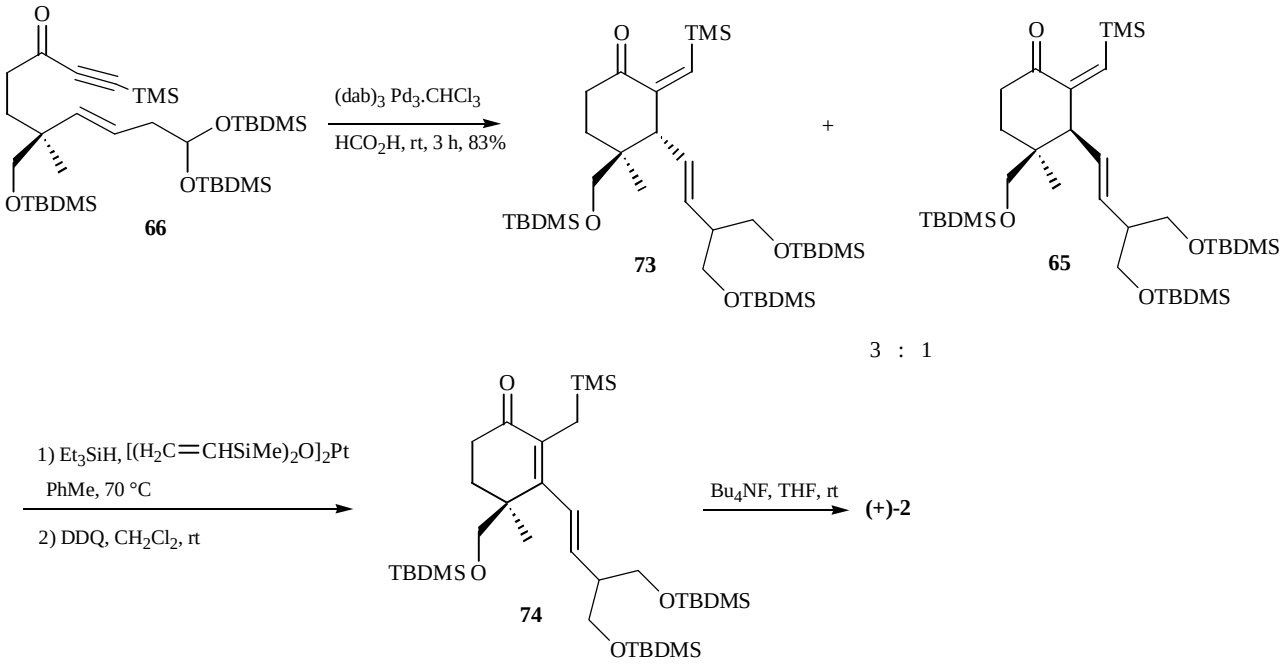
Scheme 15.



Scheme 16.



Scheme 17.



Scheme 18.

lacrylamide and desymmetrization of the resulting disubstituted malonate by pig liver esterase (PLE) catalyzed hydrolysis led to **69** of 92% ee after recrystallization. Although the absolute configuration of **69** was only tentatively assigned at this juncture, it was confirmed as *S* after completion of the synthesis.

Chemoselective reduction of the carboxylic acid group of **69** furnished alcohol **72** which, by oxidation and addition of vinylmagnesium bromide followed by acetylation gave **68**, the substrate required for the elaboration of the side chain of (+)-2. In fact, the Pd (0) catalyzed allylic alkylation of **68** with dimethyl malonate afforded triester **67** in good yield. Starting with **67** and by a sequence involving reduction of the ester groups and protection of the resulting triol, followed by conversion of the N,N-dimethylamide group into an alkynyl ketone, the cyclization precursor **66** was obtained in 18% overall yield in nine steps.

The key cycloisomerization reaction of **66**, under the conditions described in Scheme 18, afforded a 3:1 mixture of the diastereisomeric cyclization products **73** and **65** in 83% yield. Finally, by a two-step sequence involving a net double bond migration (**74**) followed by O and C desilylation (+)-cassiol (**2**) {$[\alpha]_D^{25}$ 16.1 (c 0.15, MeOH)} was obtained in 42% overall yield for the last three steps.

Concluding Remarks

The application of a variety of synthetic strategies and different methodologies for the construction of quaternary carbon stereocenters can be observed in the description of the sequences towards the synthesis of (+)-cassiol and its glucoside (-)-cassioside. The scarcity of (+)-cassiol together with its promising pharmacological activity and the interesting structural features are likely to stimulate a second generation of short and economical synthetic routes that will soon appear in the literature.

Acknowledgments

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