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Detours en route to a total synthesis of (+)-cassiol

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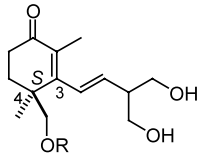
Abstract—A synthesis of the antiulcerogenic compound (+)-cassiol **1b** has been achieved in 43% yield starting with lactol (*S*)-**2** and sulfone **26**. This short and efficient synthesis features the one-pot Julia olefination reaction of the sodium anion of (*S*)-**2** with **26**, through the key intermediate (−)-**9**. This synthesis has been developed as a result of exploratory experiments including different olefination reactions on **2**. An attempt to synthesize the intermediate **9** by an intramolecular aldol condensation approach of the open chain precursor **4** is also described.

1. 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 potent serotonin-induced antiulcerogenic activity in rats, Fukaya et al. isolated the glucoside (−)-cassioside **1a**, whose enzymatic hydrolysis afforded the aglycone (+)-cassiol **1b**, exhibiting more potent antiulcer activity than cassioside itself.[1]

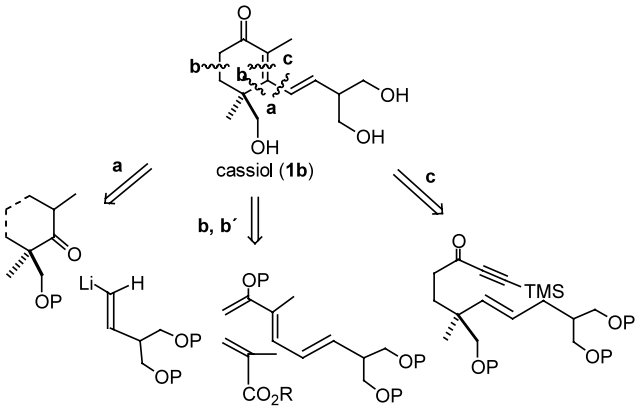


1a, R= β-D-glucopyranosyl
1b, R=H

A careful analysis of the structure of (+)-cassiol **1b** reveals a rather simple molecular framework that accommodates a functionalized cyclohexenone moiety with the (*S*)-C-4 quaternary stereocenter and a 2-ethenyl-1,3-propanediol side chain which is connected at C-3.

The 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.[2]

As depicted retrosynthetically in Scheme 1, three main strategies were used for the synthesis of (+)-cassiol.



Scheme 1.

The strategy involving disconnection **a**, based on the assembly of a chiral and adequately functionalized cyclohexenone/cyclohexanone intermediate, and its coupling with a side chain precursor, was used by several research groups.[3–9] Disconnection **bb′** involves a chiral Diels–Alder cycloaddition reaction,[10] and disconnection **c**, a cycloisomerization in an ene type fashion.[11] A comparative analysis of the approaches to cassiol indicates that the sequence reported by Corey et al.[10] in which the key step is a catalyzed enantioselective Diels–Alder reaction is, by far, the most efficient with respect to the number of synthetic steps and the overall yield (40%). It is worthwhile mentioning in connection with this, that the glucoside (−)-cassioside **1a** has also been synthesized. In fact, Boeckman et al.[12] obtained the

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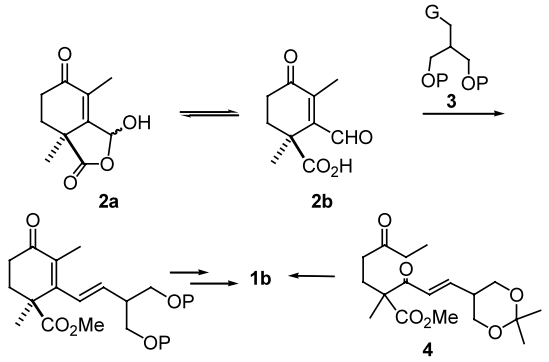
natural product following a sequence that includes an asymmetric Diels–Alder reaction and the glycosidation of an advanced intermediate. To the best of our knowledge, this is the only synthesis of (−)-**1a** so far reported.

Recently, as part of our project on the preparation of key intermediates for the synthesis of natural products, we have reported an efficient chemical resolution of lactol **2a**.[13] The availability of both enantiomers together with our interest on the use of the sequence involving a Michael addition followed by an aldol condensation in synthesis, prompted us to study two alternative routes toward (+)-**1b** that had not previously been explored: an intramolecular aldol condensation of the open chain substrate **4** already carrying the side chain present in cassiol and a convergent approach via olefination reaction of **2a** with a precursor of the side chain (**3**) (Scheme 2).[14]



Scheme 2.

The intramolecular aldol condensation approach has been used previously with varied success for the synthesis of the cyclohehexenone present in the trisporic acids.[15–18] The olefination approach has, in turn, also been used for their synthesis via Wittig reaction of the racemic lactol **2a** with appropriate phosphoranes.[19]

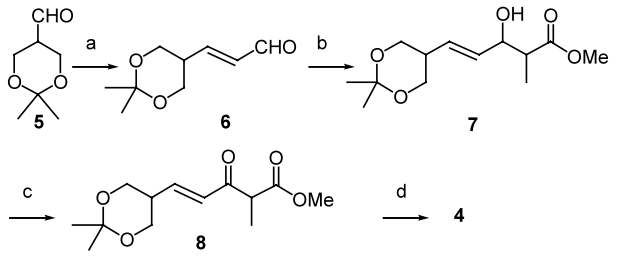
Although the antiulcerogenic activity of **1b** is probably due to the presence of a cyclohexenone moiety in the molecule,[20] the proposed synthetic sequences, if successfully developed, would allow the preparation of (+)- and (−)-cassiol and side chain analogues, in order to elucidate the role of these features in the pharmacological activity.

The results of our attempts to transform these ideas into reality are the basis of this report.

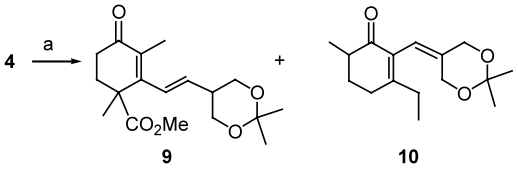
2. Results and discussion

For the synthesis of **4**, we followed the sequence described in Scheme 3, starting with the known aldehyde **5**.[21]

Unfortunately, the conversion of **4** into **9** in acceptable yields was more difficult than expected. After considerable experimentation we found that the treatment of **4** with 4% aqueous potassium hydroxide in refluxing methanol afforded **9** in only 9% yield, together with 56% of the unexpected compound **10** (Scheme 4). The structure and stereochemistry of the exocyclic double bond of **9** and the structure of **10** were defined by analysis of their ^{1}H and ^{13}C NMR spectra.

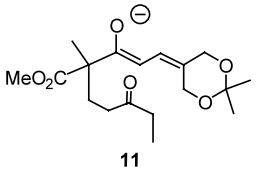


Scheme 3. *Reagents and conditions*: (a) (triphenylphosphoranylidene) acetaldehyde, PhH, reflux; (b) methyl propionate, THF, LDA, −78°C; (c) PDC, CH_2Cl_2, 24 h; (d) EVK, EtOH, NaOH.



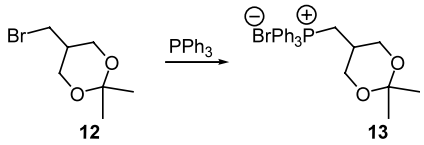
Scheme 4. *Reagents and conditions*: (a) 4% KOH (aq), MeOH, reflux.

Furthermore, the structure of **10** was confirmed by H,H and H,C COSY correlations and NOE experiments. Undoubtedly, the isolation of **10** indicates that the condensation step had occurred through the alternative enolate **11**. This is probably due to the poorly electrophilic character of the α,β-unsaturated carbonyl group together with the steric hindrance imposed by the neighboring neopentyl carbon in **4**. This could also be the reason why this approach gave low yields in most syntheses of the trisporic acids.



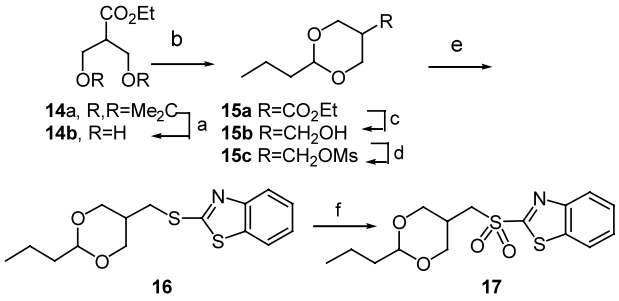
Our first choice for the synthesis of **1b** through the olefination approach was to use a simple Wittig reaction and the necessary reagent **13** was expected to be easily prepared by treatment of the known bromide **12**[22] with triphenylphosphine. However, all of our attempts to prepare **13** were unsuccessful and the treat-

ment of bromide **12** with triphenylphosphine under the usual conditions led to extensive cleavage of the protecting group.[†] The same result was obtained using a variety of hydroxyl protecting groups under several different reaction conditions.[23]



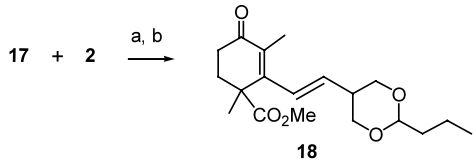
In view of these difficulties, we decided to apply the one-pot reaction recently reported by Julia et al.[24] and successfully used by Kociensky et al. in the synthesis of several natural products.[25,26]

The 2-benzothiazolylsulfone **17**, that was selected as the most adequate reaction partner, was prepared starting with the known ester **14a**,[21] as shown in Scheme 5, in which the protecting group has been changed to the butyraldehyde acetal, which is more resistant to deprotection than the acetone ketal present in **14a**.[23]



Scheme 5. *Reagents and conditions*: (a) 6N HCl, MeOH, 20°C; (b) $CH_3(CH_2)_2CHO$, TsOH, hexane, reflux; (c) LAH, Et_2O, 20°C; (d) MsCl, Et_3N, 0°C; (e) 2-mercaptobenzothiazole, KOH, EtOH, 20°C; (f) ammonium molybdate, H_2O_2, 0–20°C.

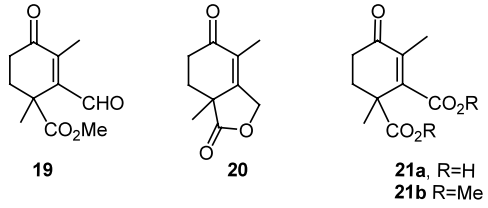
We have found that by the addition of lactol **2** to the anion of **17**, generated with LDA in THF at −80°C, the desired product **18** was obtained in only 18% yield after treatment of the crude product with excess diazomethane and purification by column chromatography (Scheme 6). The ^1H and ^{13}C NMR spectral data are in excellent agreement with the proposed structure and stereochemistry for **18**.



Scheme 6. *Reagents and conditions*: (a) LDA, THF, −80°C, **17**, 1 h, **2**, −80–15°C; (b) CH_2N_2, Et_2O.

Several attempts to improve the yield of **18** (longer reaction times, higher temperatures, order of addition of reagents, etc.) were unsuccessful, however, careful analysis of the reaction mixture allowed us to identify additional products, including **19**, **20** and **21a**, the formation of which deserve some comments.

The formation of **19** is readily explained through the reaction of unchanged starting material **2** with diazomethane during the work-up of the reaction and, the simultaneous formation of an alcohol and of a carboxylic acid, identified as the lactone **20** and the dimethyl ester **21b**, suggested that under the olefination reaction conditions, **2** would undergo a Cannizzaro-type reaction giving **20** and **21a**.



However, if a solution of **2** in THF was first treated with equimolar sodium hydride and then added to the anion of the benzothiazolylsulfone **17**, the coupling product **18** is obtained in ca. 78% yield, exclusively as the *E*-isomer, without formation of the side products.[‡]

We believe that under these conditions the carboxylate of **2b** predominates over the anion of **2a**, allowing in this way the rapid attack of the lithiated benzothiazolylsulfone to the carbonyl of the free aldehyde, leading to the coupling product. To the best of our knowledge, this is the first example of a Julia one-pot olefination reaction using a lactol in its anionic form as the reaction partner. We believe that this observation could extend the usefulness of this important reaction.

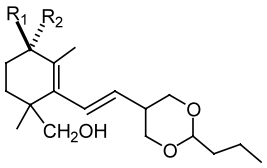
With compound **18** in hand, we turned our attention to the closing steps in the sequence towards cassiol. We envisioned that by reduction of **18** to a diol, followed by selective oxidation of the allylic alcohol and deprotection would furnish **1b**.

Reduction of **18** with LAH in Et_2O gave a 1.7:1 mixture of diols in good yield. The diols were then separated and analyzed by ^1H NMR spectroscopy. The minor diol was shown to be the pseudoaxial allylic alcohol **22a** and, the major one, was identified as the pseudoequatorial allylic alcohol **22b**. Our first choice for the oxidation of the mixture of allylic alcohols was to use manganese dioxide. We noted, however, that **22b**

[†] The easy cleavage of this ketal is probably due to the simultaneous presence of phosphonium and bromide ions in the reaction medium.

[‡] We thank Professor S. V. Ley (Cambridge) for this helpful suggestion.

was oxidized faster than **22a** to give **22c**. This observation was confirmed with the individual epimers. Diol **22a**, even after 16 h, gave a low yield of **22c** while unidentified products were detected in the reaction mixture (TLC).

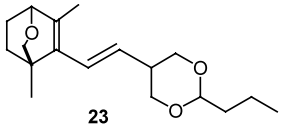


22a, R_1=OH, R_2=H
22b, R_1=H, R_2=OH
22c, R_1,R_2=O

To improve the yield of **22c**, we decided to study the oxidation of the epimeric allylic alcohols with DDQ under the conditions described by Burn et al.[27] In spite of the fact that under these conditions we obtained **22c** in a reasonable yield, a careful analysis of the reaction mixture allowed us to isolate a less polar compound in 32% yield.

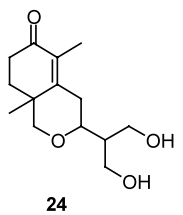
On the basis of its ^{1}H and ^{13}C NMR spectroscopic data, structure **23** was assigned to this compound. The formation of **23** was also detected working with the individual epimers.

We assume that the formation of **23** has occurred through an acid-catalyzed S_N1 type process, due to the low pK_a of the hydroquinone generated in the reaction mixture.[28]

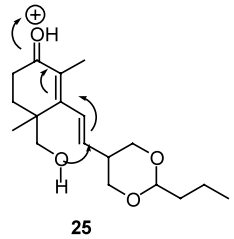


23

Attempts to hydrolyze the protecting group of **22c** to give **1b** also led us to problems. In fact, only unreacted starting material was detected (TLC) by treatment of **22c** with aqueous HCl in a solution of methanol at 20°C for several hours. However, after 40 min at reflux, a mixture of **1b** (42% yield) together with an unexpected product (35% yield), was obtained. The spectral data of **1b** were coincident with those reported in the literature[1] and the structure of the unknown product was established as **24** by analysis of its ^{1}H and ^{13}C NMR spectra. Apparently, the formation of **24**, through an acid-catalyzed intramolecular conjugate addition, as shown in **25**, is in competition with the hydrolysis of the butyraldehyde acetal. That is, we have paid the price of planning the sequence with a resistant protecting group.

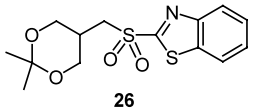


24



25

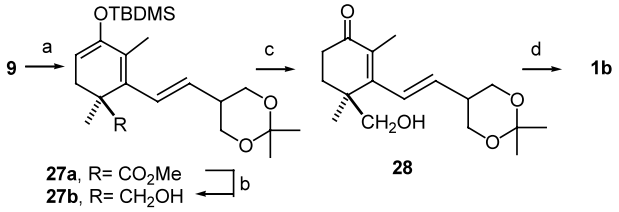
With the information obtained in the exploratory experiments described above, we were able to develop an efficient synthetic sequence to **1b** that could also be used for the synthesis of (+)-cassiol.



26

The sulfone **26**, carrying the more labile diol protecting group and prepared following a sequence very similar to that described for **17** (Scheme 5), when coupled with **2**, indeed afforded **9** in 78% yield.

To avoid the problems detected in the sequence of reduction and oxidation of **18**, we decided to protect the ketonic carbonyl group of **9** leaving the carbomethoxyl group free for reduction. On treatment with TBDMSOTf and Et_3N, **9** was transformed into the silyl enol ether **27a** which, on reduction with DIBALH at −78°C afforded **27b**. By deprotection with TBAF **27b** gave the known ketone **28**,[10] which, upon treatment with aqueous HCl in methanol at 20°C gave **1b** in good overall yield (Scheme 7).



Scheme 7. *Reagents and conditions*: (a) TBDMSOTf, Et_3N, CH_2Cl_2, 0°C then 20°C, 1 h; (b) DIBALH, THF, −78°C, 1 h; (c) TBAF, THF, 20°C, 1 h; (d) 6N HCl, MeOH, 20°C, 1 h.

Finally, starting with (*S*)-**2** and following the sequence used for racemic cassiol, (+)-**1b** was obtained in 43% overall yield. Its spectroscopic properties and specific rotation value matched those of naturally derived cassiol. The sequence with the optically active compounds was carried out without isolation and purification of the intermediates **27a**, **27b** and **28**, requiring only chromatographic purification of (−)-**9** and of (+)-**1b**.

The synthesis of (+)-**1b** described in this report, featuring an excellent approach for the olefination of lactols, is short and efficient and uses simple reactions that allow good reproducibility and material throughput.

3. Experimental

Melting points are uncorrected. IR spectra were measured in a Bruker FT-IFS25 spectrometer. The ^{1}H and

^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer for $CDCl_3$ solutions (except where noted) with Me_4Si as internal standard. For the 2D, COSY and NOE experiments Bruker standard software was employed. Column chromatography was performed on silica gel 60 H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of EtOAc in hexane as solvent. Analytical TLC was carried out using Kieselgel Merck GF_{254} with thickness 0.20 mm. The homogeneity of all intermediates prior to the high resolution mass spectral determination was carefully verified by TLC. Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. All chemicals were used as purchased or purified according to standard procedures. The enantiomeric purities were established via ^1H NMR analysis employing the shift reagent tris(3-[heptafluoropropyl-hydroxymethylene]-*d*-camphorato) europium(III) derivative [Eu(hfc)$_3$.

3.1. Preparation of compounds 9 and 10

Starting with the known aldehyde **5**,[21] and following the conditions described by Boeckman et al.[12] the enal **6** was obtained in 79%, as a yellowish oil. ^1H NMR δ: 9.53 (d, $J=7.7$ Hz, 1H), 6.85 (dd, $J=15.9$ and 7.8 Hz, 1H), 6.20 (ddd, $J=15.9$, 7.7 and 1.1 Hz, 1H), 4.05 (dd, $J=11.8$ and 4.3 Hz, 2H), 3.80 (dd, $J=11.8$ and 7.2 Hz, 2H), 2.67 (m, 1H), 1.45 (s, 6H).

3.1.1. Preparation of hydroxy ester 7. To a stirred solution of diisopropylamine (0.54 mL, 3.89 mmol) in THF (3 mL) at −30°C was added dropwise *n*-BuLi (2.85 mL, 3.89 mmol). The reaction was stirred for 15 min and cooled to −80°C. A solution of methyl propionate (0.37 mL, 3.88 mmol) in THF (2 mL) was added dropwise so that the internal reaction temperature remained below −78°C. When the addition of the methyl propionate was complete, the reaction was stirred for 50 min at −78°C. A solution of aldehyde **6** (0.60 g, 3.5 mmol) in THF (3 mL) was then added via cannula. The reaction was stirred for 5 min and quenched by the addition of saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue (1.05 g) was chromatographed to yield **7** as an oily solid mixture of diastereoisomers (0.58 g, 64%). ^1H NMR δ: 5.56 (m, 2H), 4.35 (br s, 0.4H), 4.15 (br s, 0.6H), 3.9–3.6 (m, 4H), 3.71 and 3.70 (s, 3H), 2.75 (m, 1H), 2.60–2.45 (m, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 1.16 and 1.15 (d, 3H) ^{13}C NMR δ: 175.63 (CO), 175.41 (CO), 132.55 (d), 131.96 (d), 129.41 (d), 128.66 (d), 97.43 (s), 74.04 (d), 72.50 (d), 63.85 (t, two carbons), 51.61 (q), 45.18 (d), 44.63 (d), 37.53 (d), 27.45 (q), 27.27 (q), 20.13 (q), 19.96 (q), 13.79 (q), 11.24 (q).

3.1.2. Preparation of keto ester 8. To a stirred solution of **7** (366 mg, 1.4 mmol) in anhydrous redistilled CH_2Cl_2 (30 mL) was added finely powdered PDC (1.2 g, 3.2 mmol). After 24 h, Celite was added, and the mixture was stirred for a further 20 min and filtered through a column of silica gel 60H with copious washings (EtOAc). Concentration of the filtrate afforded **8** as a colorless oil (273 mg, 74%), which showed to be a mixture of the keto and enol forms. ^1H NMR (keto form) δ: 6.84 (dd, $J=15.9$ and 7.9 Hz, 1H), 6.32 (d, $J=15.9$ Hz, 1H), 3.78 (m, 5H), 3.73 (s, 3H), 2.65 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.38 (d, $J=7.1$ Hz, 3H), signals of the enol form were also detected. ^{13}C NMR (keto form) δ: 194.28 (CO) 170.73 (CO), 144.61 (d), 129.02 (d), 97.80 (s), 62.83 (t, two carbons), 52.25 (q), 50.64 (d), 37.84 (d), 25.83 (q), 21.40 (q), 12.69 (q), signals of the enol form were also detected.

3.1.3. Preparation of diketo ester 4. To a stirred solution of the β-ketoester **8** (332 mg, 1.30 mmol) in EtOH (4 mL) was added 1 M aqueous NaOH (0.1 mL). To the resulting solution ethyl vinyl ketone (0.15 mL, 1.48 mmol) in EtOH (1.2 mL) was added dropwise (30 min). After 4 h at 20°C the solvent was evaporated, the residue dissolved in Et_2O, the organic phase was washed with brine, dried (Na_2SO_4) and evaporated to give essentially pure **4** as an oil (392 mg, 89%). ^1H NMR δ: 6.85 (dd, $J=15.0$ and 7.5 Hz, 1H), 6.30 (d, $J=15.0$ Hz, 1H), 4.0–3.6 (m, 4H), 3.70 (s, 3H), 2.75–2.55 (m, 1H), 2.40 (q, $J=7.3$ Hz, 2H), 2.55–2.30 (m, 1H), 2.30–1.90 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.04 (t, $J=7.3$ Hz, 3H). ^{13}C NMR δ: 209.91 (CO), 195.23 (CO), 173.09 (CO), 144.56 (d), 126.20 (d), 97.79 (s), 62.89 (t, two carbons), 57.37 (s), 52.34 (q), 37.87 (d), 37.04 (t), 35.78 (t), 28.31 (t), 26.00 (q), 21.32 (q), 19.13 (q), 7.65 (q).

3.1.4. Preparation of α,β-unsaturated ketone 9. To a stirred solution of compound **4** (198 mg, 0.60 mmol) in MeOH (8 mL) an aqueous 4% solution of KOH (0.28 mL) was added. The solution was heated at reflux for 7 h, until the TLC spot for the starting material had disappeared. The mixture was cooled and poured into brine. The aqueous phase was extracted with Et_2O, the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. The residue (128 mg) was chromatographed yielding **9** (17.2 mg, 9%) and **10** (85.6 mg, 56%). Compound **9** crystallized on standing, mp 74.5–75.5°C. IR (KBr) 1728, 1664, 1634 cm^{-1}. ^1H NMR δ: 6.27 (d, $J=16.4$, 1H), 5.67 (dd, $J=16.4$ and 8.2 Hz, 1H), 3.95–3.85 (m, 2H), 3.80–3.60 (m, 2H), 3.68 (s, 3H), 2.60–2.30 (m, 4H), 1.95 (m, 1H), 1.87 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H). ^{13}C NMR δ: 197.78 (CO), 175.85 (CO), 151.69 (s), 133.92 (d), 132.41 (s), 128.86 (d), 97.62 (s), 63.66 (t, two carbons), 52.22 (q), 46.78 (s), 39.33 (d), 34.05 (t), 33.39 (t), 26.59 (q), 22.66 (q), 20.92 (q), 12.39 (q). HRMS calcd for $C_{18}H_{26}O_5$ (M^+): 322.1780, found: 322.1784. Compound **10**: IR (neat) 1610, 1666 cm^{-1}. ^1H NMR δ: 5.76 (br s, 1H), 4.40 (s, 2H), 4.08 (s, 2H), 2.50–2.30 (m, 3H), 2.26 (q, $J=7.7$ Hz, 2H), 2.15–1.95 (m, 1H), 1.80–1.55 (m, 1H), 1.44 (s, 6H), 1.13 (d, $J=6.8$ Hz, 3H), 1.07 (t, $J=7.7$ Hz, 3H). ^{13}C NMR δ: 200.16 (CO), 162.82 (s), 136.04 (s), 129.57 (s), 116.06 (d), 98.58 (s), 64.46 (t), 61.03 (t), 40.94 (d), 30.07 (t), 28.75 (t), 28.50 (t), 23.91 (q), 23.78 (q), 15.42 (q), 11.52 (q). HRMS calcd for $C_{16}H_{24}O_3$ (M^+): 264.1725, found: 264.1727.

3.2. Preparation of sulfone 17

3.2.1. Preparation of diol 14b. To a solution of **14a**[21] (2.50 g, 13.3 mmol) in MeOH (18.3 mL) was added 6N aqueous HCl (1.15 mL). After 12 h at 20°C excess of solid $NaHCO_3$ was added and the resulting mixture was stirred for 30 min. The solvent was then evaporated and the residue was taken up in Me_2CO. The resulting slurry was filtered through a short pad of silica gel, washed copiously with EtOAc and the filtrate evaporated to yield **14b** (1.76 g). ^{1}H NMR δ: 4.23 (q, $J=7.1$ Hz, 2H), 4.10–3.90 (m, 4H), 2.80–2.65 (m, 1H), 1.30 (t, $J=7.1$ Hz, 3H). This product was used in the next step without further purification.

3.2.2. Preparation of acetal 15a. To a solution of crude **14b** (1.76 g) and butyraldehyde (1.28 g, 17.7 mmol) in hexane (13 mL) *p*-toluenesulfonic acid monohydrate (420 mg, 2.2 mmol) was added. The flask was fitted with a Dean–Stark trap connected to a reflux condenser and the mixture was heated under reflux for 4 h. The mixture was cooled and anhydrous NaOAc (356 mg, 4.33 mmol) was added. After stirring for 45 min, the mixture was taken up in Et_2O, washed with H_2O, dried (Na_2SO_4) and evaporated. The yellowish oily residue was purified by distillation to give **15a** (1.2 g, 45% for two steps) as a colorless oil. ^{1}H NMR δ: 4.44 (t, $J=5.0$ Hz, 1H), 4.28 (dd, $J=11.9$ and 5.0 Hz, 2H), 4.13 (q, $J=7.0$ Hz, 2H). 3.75 (t, $J=11.5$ Hz, 2H), 3.05–2.87 (m, 1H), 1.65–1.20 (m, 4H), 1.25 (t, $J=7.1$ Hz, 3H), 0.91 (t, $J=7.1$ Hz, 3H).

3.2.3. Preparation of alcohol 15b. To a stirred mixture of LAH (160 mg, 4.21 mmol) in anhydrous Et_2O (28 mL) at 0°C was gradually added a solution of **15a** (905 mg, 4.48 mmol) also in anhydrous Et_2O (9 mL). After stirring at 20°C for 40 min the reaction mixture was quenched by addition of H_2O (0.16 mL), 10% aqueous NaOH (0.32 mL) and saturated KF (0.5 mL). After stirring for 20 min, the mixture was filtered and the filtrate evaporated to give **15b** as a colorless oil (715 mg, 100%). ^{1}H NMR δ: 4.44 (t, $J=5.0$ Hz, 1H), 4.15 (dd, $J=11.7$ and 4.6 Hz, 2H), 3.51 (d, $J=18.5$ Hz, 2H). 3.46 (d, $J=11.4$ Hz, 2H), 2.35–2.13 (m, 1H), 1.65–1.20 (m, 4H), 0.92 (t, $J=7.2$ Hz, 3H).

3.2.4. Preparation of mesylate 15c. To a stirred solution of **15b** (200 mg, 1.25 mmol) in Et_3N (0.37 mL) at 0°C methanesulfonyl chloride (0.2 mL, 2.5 mmol) was gradually added. The mixture was stirred for 4 h at 0°C. After addition of H_2O (3 mL), the solution was made alkaline with Et_3N and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and evaporated to give **15c** (279 mg, 94%) as an oil. ^{1}H NMR δ: 4.41 (t, $J=5.0$ Hz, 1H), 4.15 (dd, $J=11.7$ and 4.6 Hz, 2H), 4.02 (d, $J=6.0$ Hz, 2H), 3.65–3.45 (m, 2H), 3.02 (s, 3H), 2.60–2.35 (m, 1H), 1.65–1.20 (m, 4H), 0.92 (t, $J=7.2$ Hz, 3H).

3.2.5. Preparation of 2-benzothiazolylsulfide 16. To a mixture of 2-mercaptobenzothiazole (215 mg, 1.29 mmol) in EtOH (1.8 mL) solid KOH (83 mg, 1.48 mmol) was added. The resulting orange solution was cooled to 0°C and a solution of **15c** (279 mg, 1.17 mmol) in EtOH (5.4 mL) was gradually added. The mixture was stirred for 68 h at 20°C and the solvent evaporated, the residue was taken up in H_2O and the aqueous phase extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, dried (Na_2SO_4) and evaporated. The residue (337 mg) was chromatographed affording pure **16** (218 mg, 56% for two steps), recrystallized from EtOH, mp 56.6–57.6°C. ^{1}H NMR δ: 7.88–7.72 (m, 2H), 7.42–7.26 (m, 2H), 4.45 (t, $J=6.0$ and 4.0 Hz, 1H), 4.25 (dd, $J=12.0$ and 4.0 Hz, 2H), 3.48 (t, $J=12.0$ Hz, 2H), 3.15 (d, $J=8.0$ Hz, 2H), 2.49 (m, 1H), 1.60–1.30 (m, 4H), 0.91 (t, $J=8.0$ Hz, 3H). ^{13}C NMR δ: 165.45 (s), 152.78 (s), 135.02 (s), 125.84 (d), 124.15 (d), 121.33 (d), 120.75 (d), 101.89 (d), 70.57 (t, two carbons), 36.55 (t), 34.08 (d), 30.95 (t), 27.06 (t), 13.75 (q).

3.2.6. Preparation of 2-benzothiazolylsulfone 17. To a solution of **16** (100 mg, 0.32 mmol) in anhydrous EtOH (3 mL) at 0°C ammonium molybdate (37 mg, 0.16 mmol) and 28% aqueous H_2O_2 (0.3 mL) were added. After stirring at 0°C for 3 h and at 20°C for 48 h, the majority of the EtOH was evaporated, H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed successively with 5% aqueous H_2SO_4, saturated aqueous $NaHCO_3$ solution, H_2O and brine, dried (Na_2SO_4) and evaporated to give a residue (113 mg) which was chromatographed to yield the sulfone **17** (103 mg, 93%), mp 114.6–115°C from Et_2O. IR (KBr) 1470, 1410, 1340, 980 cm^{-1}. ^{1}H NMR δ: 8.25–8.15 (m, 1H), 8.05–7.95 (m, 1H), 7.70–7.55 (m, 2H), 4.44 (t, $J=5.0$ Hz, 1H), 4.27 (dd, $J=11.8$ and 4.5 Hz, 2H), 3.48 (t, $J=11.5$ Hz, 2H), 3.26 (d, $J=8.0$ Hz, 2H), 2.80–2.60 (m, 1H), 1.60–1.25 (m, 4H), 0.90 (t, $J=6.0$ Hz, 3H). ^{13}C NMR δ: 165.24 (s), 152.24 (s), 136.39 (s), 128.00 (d), 127.55 (d), 125.14 (d), 122.15 (d), 101.89 (d), 69.88 (t, two carbons), 52.91 (t), 36.36 (t), 29.42 (d), 16.88 (t), 13.63 (q). Anal. calcd for $C_{15}H_{19}NO_4S_2$: C, 52.77; H, 5.61; N, 4.10, S, 18.78. Found: C, 52.81; H, 5.65; N, 4.16; S, 18.78%.

3.3. Preparation of diene 18 by Julia olefination reaction of 17 and 2

A solution of *n*-BuLi in hexane (1.65 M, 0.6 mL, 1 mmol) was added to a solution of diisopropylamine (0.15 mL, 1.08 mmol) in anhydrous THF (2 mL) at −80°C. After warming up to 0°C and stirred for 30 min, this solution was slowly added to a solution of **17** (341 mg, 1 mmol) in anhydrous THF (6 mL) at −80°C. Stirring was continued for 1 h after which a solution of **2** (100 mg, 0.51 mmol) in anhydrous THF (4 mL) cooled at −80°C was added. The mixture was allowed to warm to 15°C and then poured into brine and extracted with Et_2O. The aqueous phase, after acidification with 0.5N aqueous HCl (pH 4) was extracted with Et_2O and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in Et_2O, treated with an excess of ethereal diazomethane and the solvent evaporated. The residue was chromatographed to yield **18** (30.8 mg, 18%), **19** (18.8 mg, 20%) and a 1:1 inseparable mixture of **20** and **21b** (18

mg). Compound **18** is a colorless oil. IR (neat) 1720, 1660, 1629 cm^{-1}. ^1H NMR δ: 6.22 (d, $J=16.5$ Hz, 1H), 5.38 (dd, $J=16.2$ and 8.1 Hz, 1H), 4.45 (t, $J=5.0$ Hz, 1H), 4.09–3.90 (m, 2H), 3.67 (s, 3H), 3.50 (ddd, 2H), 2.80–2.50 (m, 1H), 2.60–2.30 (m, 3H), 2.00–1.90 (m, 1H), 1.85 (s, 3H), 1.70–1.30 (m, 4H), 1.47 (s, 3H), 0.92 (t, $J=7.2$ Hz, 3H). ^{13}C NMR δ: 197.70 (CO), 175.75 (CO), 151.42 (s), 132.60 (s), 132.13 (d), 129.49 (d), 101.77 (d), 70.40 (t, two carbons), 52.21 (q), 46.78 (s), 39.43 (d), 36.71 (t), 34.06 (t), 33.42 (t), 22.71 (q), 17.17 (t), 13.83 (q), 12.43 (q): HRMS calcd for $C_{19}H_{28}O_5$ (M^+): 336.1937, found: 336.1935. The ^1H NMR spectrum of compound **20** is coincident with that reported by White et al.,[19] δ: 4.98 (br s, 2H), 2.64–2.56 (m, 2H), 2.24–2.00 (m, 2H), 1.74 (br s, 3H), 1.50 (s, 3H). Compounds **19** and **21b** were identified by analysis of the ^1H NMR spectrum of the mixture and comparison with the spectra of the pure compounds independently prepared. The ^1H NMR spectrum of compound **19** is coincident with that reported by Secrist et al.,[29] δ: 10.30 (s, 1H), 3.67 (s, 3H), 2.70–1.90 (m, 4H), 2.22 (s, 3H), 1.50 (s, 3H). Compound **21b**: ^1H NMR δ: 3.81 (s, 3H), 3.73 (s, 3H), 2.60 (m, 2H), 2.45–2.05 (m, 2H), 1.93 (s, 3H), 1.52 (s, 3H). ^{13}C NMR δ: 197.66 (CO), 174.18 (CO), 167.55 (CO), 146.13 (s), 136.54 (s), 52.42 (q), 52.16 (q), 45.60 (s), 33.57 (t), 33.51 (t), 22.75 (q), 13.04 (q).

3.4. Improved preparation of 18

A solution of *n*-BuLi in hexane (2.1 mmol) was added to a stirred solution of diisopropylamine (0.29 mL, 2 mmol) in anhydrous THF (4 mL) at −30°C. After stirred for 30 min, this solution was slowly added to a solution of **17** (650 mg, 1.9 mmol) in anhydrous THF (13 mL) at −80°C. Stirring was continued for 1 h after which a solution of **2** (186.2 mg, 0.95 mmol) in anhydrous THF (8 mL) that was treated with NaH (76 mg, 60% dispersion in mineral oil, 1.9 mmol) and cooled at −80°C was added. The mixture was allowed to warm to −10°C and kept at this temperature for 12 h. The mixture was then poured into Et_2O and extracted with H_2O. The aqueous phase, after acidification with 0.5N aqueous HCl (pH 4) was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and treated with an excess of an ethereal solution of diazomethane. When the reaction was complete (TLC) a few drops of AcOH were added and the solvent was evaporated. The residue was chromatographed to yield the desired coupling product (250 mg, 78%) as an oil. The ^1H NMR and ^{13}C NMR of this product are coincident with those described above for **18**.

3.5. Preparation of diols 22a and 22b

To a stirred mixture of LAH (650 mg, 17 mmol) in anhydrous Et_2O (28 mL) at 0°C was gradually added a solution of **18** (305 mg, 0.91 mmol) also in anhydrous Et_2O (24 mL). After stirring at 20°C for 30 min (TLC) the reaction mixture was quenched by addition of H_2O (0.7 mL), 10% aqueous NaOH (1.4 mL) and saturated KF (2.1 mL). After stirring for 20 min, the mixture was filtered through a silica gel pad with copious washings with EtOAc, the filtrate was evaporated to give a mixture of diastereoisomeric diols as a colorless oil (233.2 mg, 82%). The residue was chromatographed to yield the more polar diol **22a** (56.6 mg, 19.7%) and the less polar diol **22b** (98.3 mg, 35%). Diol **22a**: IR (neat) 3569, 1670 cm^{-1}. ^1H NMR δ: 5.94 (dq, $J=16.1$ and 1.1 Hz, 1H), 5.14 (dd, $J=16.1$ and 7.8 Hz, 1H), 4.46 (t, $J=5.1$ Hz, 1H), 4.07 (dd, $J=11.5$ and 4.7 Hz, 2H), 3.94 (br t, $W_{1/2}=5.8$ Hz, 1H), 3.54 (d, $J=10.7$ Hz, 1H), 3.52 (t, $J=10.7$ Hz, 2H), 3.23 (d, $J=10.7$ Hz, 1H), 2.90–2.65 (m, 1H), 1.80 (s, 3H), 2.10–1.20 (m, 9H), 0.93 (t, $J=7.2$ Hz, 3H), 0.90 (s, 3H). ^{13}C NMR δ: 136.63 (s), 133.43 (s), 130.25 (d), 129.56 (d), 101.63 (d), 70.79 (t, two carbons), 69.30 (t), 68.66 (d), 39.60 (s), 38.69 (d), 36.68 (t), 27.44 (t), 27.17 (t), 21.45 (q), 19.03 (q), 17.12 (t), 13.75 (q). HRMS calcd for $C_{18}H_{30}O_4$ (M^+): 310.2144, found: 310.2148.

Diol **22b**: IR (neat) 3405, 1650 cm^{-1}. ^1H NMR δ: 5.94 (dq, $J=16.1$ and 1.0 Hz, 1H), 5.12 (dd, $J=16.1$ and 7.8 Hz, 1H), 4.46 (t, $J=5.0$ Hz, 1H), 4.07 (dd, $J=11.6$ and 4.8 Hz, 2H), 4.07 (m, 1H), 3.51 (t, $J=11.6$ Hz, 2H), 3.51 (d, $J=10.8$ Hz, 1H), 3.25 (d, $J=10.8$ Hz, 1H), 2.80–2.60 (m, 1H), 2.10–1.20 (m, 9H), 1.78 (s, 3H), 0.96 (s, 3H), 0.93 (t, $J=7.2$ Hz, 3H). ^{13}C NMR δ: 136.68 (s), 134.16 (s), 130.36 (d), 129.73 (d), 101.63 (d), 70.78 (t, two carbons), 69.81 (d), 68.98 (t), 39.63 (s), 38.67 (d), 36.69 (t), 28.94 (t), 28.24 (t), 22.83 (q), 17.67 (q), 17.11 (t), 13.74 (q). HRMS calcd for $C_{18}H_{30}O_4$ (M^+): 310.2144, found: 310.2149.

3.6. Oxidation of diols 22a and 22b

3.6.1. Method (a) with MnO_2. To a well stirred suspension of activated MnO_2 (750 mg, 8.6 mmol) in CH_2Cl_2 (10 mL) was added a solution of the mixture of diols **22a** and **22b** (76 mg, 0.24 mmol) in CH_2Cl_2 (2 mL). After 18 h of stirring at 20°C, the solvent was evaporated and the residue was taken up with EtOAc and filtered through a silica gel pad with copious washings. The filtrate was evaporated and the residue was chromatographed to give **22c** (38 mg, 50%) and the more polar diol **22a** (22 mg, 29%). (b) With DDQ: to a stirred solution of the mixture of diols **22a** and **22b** (58.4 mg, 0.19 mmol) in toluene (9 mL) DDQ (99.8 mg, 0.44 mmol) was added and the mixture was heated at 70°C. After 24 h (TLC) the mixture was filtered and the residue was washed with benzene and the filtrate evaporated. The residue was chromatographed to yield **22c**, as an oil, (28.0 mg, 47%) and **23** (18 mg, 32%) also an oil. Enone **22c**: IR (neat) 3500, 1663 cm^{-1}. ^1H NMR δ: 6.14 (dt, $J=16.3$ and 1.1 Hz, 1H), 5.25 (dd, $J=16.3$ and 7.9 Hz, 1H), 4.46 (t, $J=4.9$ Hz, 1H), 4.09 (dd, $J=11.6$ and 4.8 Hz, 2H) 3.67 (d, $J=10.8$ Hz, 1H), 3.55 (t, $J=11.5$ Hz, 2H), 3.41 (d, $J=10.8$ Hz, 1H), 2.95–2.70 (m, 1H), 2.58–2.50 (m, 1H), 2.30–2.20 (m, 1H), 1.77 (d, $J=1.1$ Hz, 3H), 1.76–1.60 (m, 4H), 1.55–1.30 (m, 2H), 1.07 (s, 3H), 0.92 (t, $J=7.2$ Hz, 3H). ^{13}C NMR δ: 198.80 (CO), 156.65 (s), 132.56 (s), 132.19 (d), 129.02 (d), 101.72 (d), 70.45 (t, two carbons), 68.90 (t), 40.45 (s), 38.87 (d), 36.62 (t), 33.60 (t), 31.37 (t), 21.30 (q), 17.06 (t), 13.70 (q), 13.42 (q). HRMS calcd for

$C_{18}H_{28}O_4$ (M^+): 308.1988, found: 308.1986. Compound **23**: IR (neat) 1722 cm^{-1}. ^1H NMR δ: 5.95 (d br t, $J=16.0$ Hz, 1H), 5.18 (dd, $J=16.0$ and 5.2 Hz, 1H), 4.47 (t, $J=5.1$ Hz, 1H), 4.15–4.03 (m, 3H) 3.56–3.44 (m, 3H), 3.05 (dd, $J=7.2$ and 3.2 Hz, 1H), 2.85–2.65 (m, 1H), 1.80 (s, 3H), 1.04 (s, 3H), 0.93 (t, $J=7.2$ Hz, 3H). ^{13}C NMR δ: 136.96 (s), 135.38 (s) 128.81 (d), 126.68 (d), 101.59 (d), 72.84 (t), 71.89 (d), 70.96 (t), 38.95 (d), 36.71 (s), 35.84 (t), 30.14 (t), 26.11 (t), 19.41 (q), 17.11 (t), 16.68 (q), 13.73 (q). HRMS calcd for $C_{18}H_{29}O_3$ (MH^+): 293.2117, found: 293.2122.

3.7. Preparation of cassiol

To a stirred solution of **22c** (29.8 mg, 0.097 mmol) in MeOH (5 mL) was added a 6N aqueous HCl and heated at reflux. After 40 min (TLC) solid $NaHCO_3$ was added and the stirring was continued for 15 min, the solvent was evaporated and the residue in Me_2CO was filtered through a silica gel pad with copious washings, the filtrate was evaporated and the residue was chromatographed to yield **1b** (10.4 mg, 42%) and **24** (8.6 mg, 35%). Cassiol **1b**: IR (neat) 3368, 1644, 1594 cm^{-1}. ^1H NMR (D_2O, 200 MHz) δ: 6.28 (d, $J=16.3$ Hz, 1H), 5.67 (dd, $J=16.3$ and 8.4 Hz, 1H), 3.76 (d, $J=11.4$ Hz, 1H), 3.75 (dd, A part of ABX, $J=11.5$ and 5.9 Hz, 2H), 3.66 (dd, B part of ABX, $J=11.1$ and 7.0 Hz, 2H), 3.43 (d, $J=11.5$ Hz, 1H), 2.71–2.55 (m, 3H), 2.17 (ddd, $J=13.4$, 9.8 and 6.0 Hz, 1H), 1.81 (d, $J=0.9$ Hz, 3H), 1.74 (ddd, $J=13.6$, 6.1 and 6.1 Hz, 1H), 1.12 (s, 3H). The signals at δ 3.75 and δ 3.66 simplify into an AB quartet upon irradiation at δ 2.67. This ^1H NMR spectrum is coincident with that reported by Fukaya et al.[1] for (+)-**1b** at 250 MHz. Compound **24**: IR (neat) 3402, 1656 cm^{-1}. ^1H NMR δ: 4.30 (ddd, $J=9.7$, 6.9 and 2.5 Hz, 1H), 3.93–3.70 (m, 4H), 3.40 (s, 2H), 2.83–2.47 (m, 5H) 1.90–1.33 (m, 4H), 1.76 (s, 3H), 1.33 (s, 3H). ^{13}C NMR δ: 198.02 (CO), 156.71 (s) 130.96 (s), 73.01 (t), 72.50 (d), 63.37 (t), 62.59 (t), 42.04 (d), 36.89 (s), 33.25 (t), 32.32 (t), 26.91 (t), 21.92 (q), 10.68 (q). HRMS calcd for $C_{14}H_{23}O_3$ (MH^+): 255.1596, found: 255.1585.

3.8. New preparation of cassiol 1b

Sulfone 26: mp 112.8–113.3°C from Et_2O. IR (KBr) 1465, 1325, 1140, 1040 cm^{-1}. ^1H NMR δ: 8.24–8.20 (m, 1H), 8.10–8.00 (m, 1H), 7.66–7.60 (m, 2H), 4.12 (dd, $J=12.0$ and 3.5 Hz, 2H), 3.81 (dd, $J=12.0$ and 4.6 Hz, 2H), 3.76 (d, $J=6.1$ Hz, 2H), 2.41 (m, 1H), 1.43 (s, 3H), 1.39 (s, 3H). ^{13}C NMR δ: 165.68 (s), 152.40 (s), 136.49 (s), 127.98 (d), 127.57 (d), 125.27 (d), 122.20 (d), 98.25 (s), 63.09 (t, two carbons), 54.30 (t), 29.45 (d), 25.75 (q), 21.56 (q). Anal. calcd for $C_{14}H_{17}NO_4S_2$: C, 51.36; H, 5.23; N, 4.28, S, 19.58. Found: C, 51.16; H, 5.23; N, 4.35; S, 19.56%.

Ester **9** was prepared in 78% yield following a sequence very similar to that described for **18**. The ^1H and ^{13}C NMR of this product are coincident with those described above for **9**.

3.8.1. Preparation of enol ether 27a. To a stirred solution of ester **9** (45.3 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) at 0°C was added freshly distilled (KOH) Et_3N (0.10 mL) and TBDMSOTf (0.11 mL, 0.48 mmol) in CH_2Cl_2 (1 mL). After 1 h at 20°C (TLC) the mixture was poured into aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and evaporated to give a residue (83.8 mg) that was chromatographed through a silica gel column with elution by hexane:EtOAc:Et_3N (95:5:1) to give pure **27a** (42.3 mg, 70%). ^1H NMR (benzene-d_6) δ: 6.43 (d, $J=16.3$ Hz, 1H), 5.72 (dd, $J=16.3$ and 8.3 Hz, 1H), 5.08 (dd, $J=5.9$ and 3.6 Hz, 1H), 4.11–3.75 (m, 4H), 3.59 (s, 3H), 3.27 (dd, $J=16.2$ and 3.6 Hz, 1H), 2.75–2.57 (m, 1H), 2.24 (dd, $J=16.2$. and 5.2 Hz, 1H), 2.13 (s, 3H), 1.72 (s, 6H), 1.55 (s, 3H), 1.21 (s, 9H), 0.36 (s, 3H), 0.34 (s, 3H). ^{13}C NMR (benzene-d_6) δ: 178.39 (CO), 150.52 (s), 135.62 (s), 130.36 (d), 130.30 (s), 129.18 (d), 100.21 (d), 96.24 (s), 65.17 (t), 64.99 (t), 52.27 (q), 48.14 (s), 40.56 (d), 35.45 (t), 28.40 (q), 26.63 (q, three carbons), 21.66 (q), 21.34 (q), 19.04 (s), 14.62 (q), −3.72 (q), −3.88 (q).

3.8.2. Reduction of enol ether 27a to alcohol 27b. To a stirred solution of ester **27a** (42.3 mg, 0.097 mmol) in THF (5 mL) at −78°C was added DIBALH 1 M in toluene (1.0 mL, 1 mmol). After 1 h (TLC) the reaction was quenched by the addition of H_2O (0.04 mL), 10% aqueous NaOH (0.11 mL) and saturated KF (0.60 mL). After stirring for 20 min, the mixture was filtered through a silica gel pad with copious washings with EtOAc and the filtrate evaporated to give pure **27b** (33.3 mg, 85%) as an oil. ^1H NMR (benzene-d_6) δ: 5.91 (d, $J=16.3$ Hz, 1H), 5.22 (dd, $J=16.3$ and 7.7 Hz, 1H), 4.88 (t, $J=4.7$ Hz, 1H), 3.78 (dd, $J=9.4$ and 4.8 Hz, 2H), 3.64–3.52 (m, 2H), 3.52 (d, $J=10.6$ Hz, 1H), 3.20 (d, $J=10.6$ Hz, 1H), 2.52 (dd, $J=16.7$ and 4.8 Hz, 1H), 2.45–2.30 (m, 1H), 1.92 (dd, $J=16.7$ and 4.8 Hz, 1H), 1.92 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H), 1.00 (s, 9H), 0.96 (s, 3H), 0.17 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (benzene-d_6) δ: 150.43 (s), 138.93 (s), 132.54 (d), 130.50 (d), 129.88 (s), 100.79 (d), 98.36 (s), 68.21 (t), 65.03 (t), 64.93 (t), 40.33 (d), 39.83 (s), 32.95 (t), 28.08 (d), 26.70 (q, three carbons), 22.17 (q), 21.73 (q), 19.09 (s), 15.99 (q), −3.72 (q, two carbons).

3.8.3. Preparation of enone 28. To a stirred solution of **27b** (33.3 mg) in THF (2 mL) at 20°C, TBAF 1 M in THF (0.25 mL, 0.25 mmol) was added. After 1 h (TLC) the mixture was poured into brine and extracted with Et_2O, the organic extracts were dried (Na_2SO_4) and evaporated to give a residue (28.6 mg) that was chromatographed through a silica gel column to give pure **28** (17.5 mg, 73%). IR (neat) 3462, 1654, 1607 cm^{-1}. ^1H NMR δ: 6.21 (dt, $J=16.3$ and 1.1 Hz, 1H), 5.57 (dd, $J=16.3$ and 7.6 Hz, 1H), 3.96 (dd, $J=12.0$ and 4.7 Hz, 2H), 3.85–3.75 (m, 2H), 3.71 (d, $J=11.0$ Hz, 1H), 3.42 (d, $J=11.0$ Hz, 1H), 2.65–2.50 (m, 3H), 2.32–2.15 (m, 1H), 1.81 (d, $J=1.0$ Hz, 3H), 1.76–1.63 (m, 1H), 1.44 (s, 6H), 1.11 (s, 3H). ^{13}C NMR δ: 199.17 (CO), 157.34 (s), 134.07 (d), 132.40 (s), 128.54 (d), 97.73 (s), 68.98 (t), 63.72 (t), 63.59 (t), 40.62 (s), 38.46 (d), 33.69 (t), 31.45 (t), 25.97 (q), 21.53 (q), 21.30 (q), 13.50 (q). These data are coincident with those reported by Corey et al.[10] for the optically active product.

3.8.4. Deprotection of 28. A solution **28** (17.5 mg, 0.059 mmol) in MeOH (2.0 mL) was treated with a 6N aqueous solution of HCl (0.1 mL) at 20°C and stirred for 1 h. The resulting solution was treated with excess solid $NaHCO_3$. The suspension was stirred for 15 min and concentrated under a nitrogen current. The residue was dissolved in Me_2CO and filtered through a silica gel pad, with copious washings. The filtrate was evaporated and the residue (47.8 mg) was chromatographed with EtOAc:Me_2CO (7:3) to afford pure **1b** (13.5 mg, 90%).

3.9. Preparation of (+)-1b

Starting with (*S*)-**2** and following the sequence used for racemic cassiol, (+)-**1b** was obtained in 43% overall yield. This sequence was carried out without isolation and purification of the intermediates **27a**, **27b** and **28**, requiring only chromatographic purification of (−)-**9** and of (+)-**1b**.

Compound (−)-**9**: colorless oil; the ^1H and ^{13}C NMR spectra of this product are coincident with those described for the racemic product; $[\alpha]_D^{27}$ −25.32 (*c* 3, $CHCl_3$), ee 97%, the enantiomeric purity was established by ^1H NMR. **(+)-Cassiol 1b**: colorless oil, $[\alpha]_D^{30}$ 8.34 (*c* 0.35, MeOH) (lit.[1] $[\alpha]_D$ 8.6 (*c* 0.25, MeOH). The ^1H NMR spectrum (200 MHz) of this compound is coincident with that described above for the racemic product and with that reported by Fukaya et al.[1] for (+)-**1b** at 250 MHz. ^1H NMR (D_2O, 500 MHz) δ 6.28 (dt, $J=16.3$ and 1.0 Hz, 1H), 5.67 (dd, $J=16.2$ and 8.4 Hz, 1H), 3.76 (d, $J=11.4$ Hz, 1H), 3.745 (dd, $J=11.2$ and 5.9 Hz, 1H), 3.740 (dd, $J=11.2$ and 5.9 Hz, 1H), 3.670 (dd, $J=11.2$ and 7.1 Hz, 1H), 3.666 (dd, $J=11.2$ and 7.1 Hz, 1H), 3.43 (d, $J=11.4$ Hz, 1H), 2.68–2.52 (m, 3H), 2.17 (ddd, $J=13.5$, 10.4 and 5.3 Hz, 1H), 1.81 (d, $J=0.9$ Hz, 3H), 1.75 (ddd, $J=13.5$, 6.6 and 5.8 Hz, 1H), 1.12 (s, 3H). This ^1H NMR spectrum is essentially identical with that reported by Corey et al.[10] for synthetic (+)-**1b** at 500 MHz. ^{13}C NMR (D_2O, 50 MHz) δ 207.12 (s), 164.87 (s), 139.17 (d), 134.35 (s), 131.37 (d), 70.44 (t), 64.55 (t, two carbons), 50.30 (d), 43.18 (s), 35.89 (t), 33.28 (t), 23.02 (q), 15.63 (q). These data are coincident with those reported by Corey et al.[10] for (+)-**1b** at 100 MHz.

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