# Enantioselective Total Synthesis of a *trans*-Hydrindane Rings/Side-Chain Building-Block of Vitamin D − Asymmetric Induction in an Acid-Catalyzed Conjugate-Addition Reaction

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**Keywords:** Total synthesis / Vitamin D / Diastereoselectivity / Induced diastereoselectivity / Asymmetric synthesis

For the enantioselective total synthesis of 1α,25-dihydroxyvitamin $D_3$ (**3**), we have developed an enantioselective approach to the "northern" portion building-block **8**, starting from the optically active hexanoic acid derivative **44**, 2-methylcyclopent-2-en-1-one (**10**) and 1-(phenylthio)but-3-en-2-one (**9**). The steric course of the addition reaction of homochiral (*S*)-ketene acetals **28**, **40**, **44** and **58** with **10** was examined. We found that in the cases of **28**, **44** and **40**, the reactions occur with high simple and induced (facial) diastereoselectivities.
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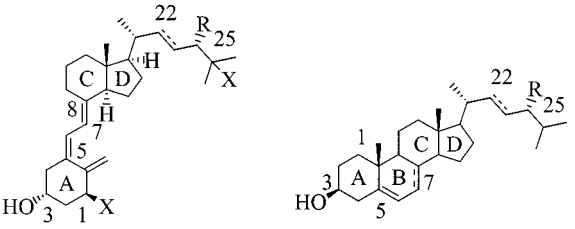
## Introduction

Various strategies have been developed for the synthesis of vitamin $D_3$ and its congeners (Figure 1, **1**−**3**) in decades of studies on the chemistry and therapeutic applications of these compounds. In the pioneering approaches, 7-dehydrocholesterol **4** or ergosterol **5** were subjected to a UV-induced rearrangement, followed by thermal rearrangement, to afford vitamin $D_3$ (**1**) or vitamin $D_2$ (**2**), respectively.[1,2]

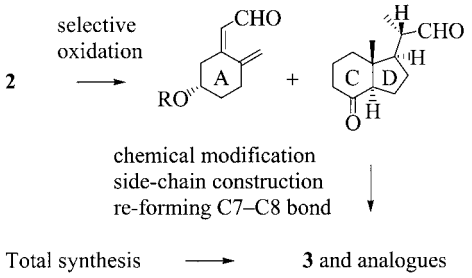


**1**, R = H, X = H, vitamin $D_3$
**2**, R = Me, X = H, 22-ene, vitamin $D_2$
**3**, R = H, X = OH, 1α,25-dihydroxyvitamin $D_3$

**4**, R = H, cholesterol
**5**, R = Me, 7,22-diene, ergosterol

Figure 1. The most important representatives of the vitamin D group, and their respective biosynthetic and synthetic precursors

The discovery of 1α,25-dihydroxyvitamin $D_3$ (**3**), and other biologically active metabolites of vitamin $D_3$, focused chemical research onto transformations of the sterol side chain and A-ring prior to or after the photochemical rearrangement. The rapid expansion of medicinal applications of vitamin D-metabolites and their analogues for the treatment of human diseases related to bone-metabolism, immune effects, cell differentiation and hormone secretion[3,4] has been paralleled by progress in the development of convergent synthetic methodologies.[5−8] In the most efficient syntheses of compound **3**, the requisite precursors to the ring A and/or the CD-rings/side chain building blocks could be conveniently acquired from commercially available vitamin $D_2$ (**2**), by regioselective oxidative cleavage of the appropriate double bond(s),[9] as outlined in Scheme 1. Total synthesis provides a complementary and more versatile approach to vitamin metabolites and their analogues. Several methods for the total synthesis of vitamin D are presently available. However, the development of an efficient and enantioselective total synthesis of the CD-rings/side-chain building-block (i.e. the "northern" portion) presents an ongoing challenge to organic chemists.[10−15]




Scheme 1. Convergent synthetic approaches to 1α,25-dihydroxyvitamin $D_3$ and its derivatives

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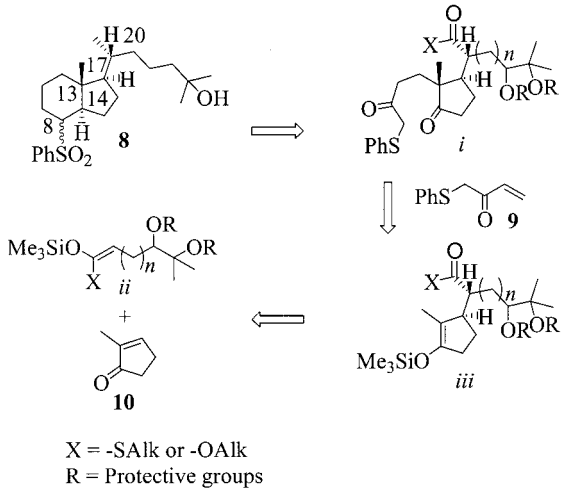
Recently, we reported[16] a concise diastereoselective synthesis of the northern building-block of 25-hydroxyvitamin $D_3$ **8** (Scheme 2), in which we utilized two tandem Mukaiyama−Michael reactions. Herein, we present the results from our efforts to combine diastereoselectivity and efficiency in carbon−carbon bond-forming reactions with the demands of enantioselectivity in the generation of four contiguous stereogenic centers, at C-13, C-14, C-17 and C-20 (steroid numbering), in **8**. The configuration of the fifth stereogenic center at C-8 is of no consequence for the further synthesis, since the phenylsulfonyl group will serve as a handle for the coupling of **8** to an appropriate A-ring building-block, using the Julia olefination reaction.[17−19]




Scheme 2. General plan for the synthesis of **8** from ketene acetals *ii* and Michael acceptors **10** and **9**

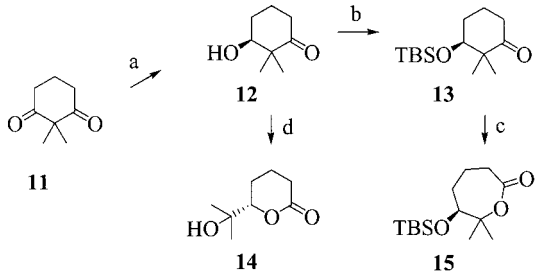
Reports of enantioselective reactions of cyclic α,β-unsaturated ketones and silyl enol ethers are scarce. The reaction of cyclopent-2-en-1-one with ketene acetals derived from acetic acid, promoted by chiral titanium/BINOL complexes, has been reported to afford the respective adducts (with one stereogenic center) with significant enantioselectivities.[20] Relevant studies using propionic acid-derived ketene acetals have suggested that additional activation of the electrophile by an α-alkoxycarbonyl group is required.[21,22] Due to the generation of two new asymmetric centers, stereochemical control of the reaction becomes more complex.[23−26] More promising approaches involve optically active reagents. Thus, reaction of a propionamide ketene acetal with an ephedrine-derived chiral auxiliary and various alkyl vinyl ketones in the presence of $TiCl_4$ afforded the respective adducts with significant simple and induced (facial) diastereoselectivities.[27,28] A high degree of induced diastereoselectivity has also been reported in the case of the $TrSbCl_6$ (Tr = trityl) catalyzed addition of an achiral propionate-derived ketene acetal to optically active 4-methoxy-2-methylcyclopent-2-en-1-one.[29]

Analysis of various enantioselective approaches to compound **8** and some preliminary experiments focused our attention on optically active ketene acetals bearing a protected diol functionality, of general structure *ii* (Scheme 2). The choice of compounds *ii* as optically active precursors to the vitamin D building-block **8** was particularly appealing because, firstly, the required optically active dihydroxy derivatives of fatty acids are readily accessible and inexpensive, and secondly, C-24 and C-25 hydroxylated metabolites and analogues of vitamin D could be synthesized directly from these starting materials. We expected that the acid-catalyzed reaction of *ii* and enone **10** would occur with simple diastereoselectivity, to afford the respective *like* (*l*) adduct.[30] Induced diastereoselectivity favoring one of the diastereomeric pairs (17*R*,20*R* or 17*S*,20*S*) of the silyl enol ether *iii* was anticipated. However, there was no literature precedent to allow us to estimate the magnitude of induction or predict the facial selectivity. Further reaction of silyl enol ether *iii* with **9** would afford intermediate *i*. It is well documented that the formation of the stereogenic center (at C-13) in this process is controlled by the stereogenic center already present in the five-membered ring[31] (C-17). Stereoselective transformation of *i* into **8** has already been reported.[16,32]

## Results and Discussion

### Synthesis of Optically Active Side-Chain Precursors

Several optically active dihydroxy esters and their derivatives were needed for the present studies. 2,2-Dimethylcyclohexan-1,3-dione (**11**) (Scheme 3) was subjected to baker's yeast reduction[33,34] to give the hydroxy ketone **12**.



Scheme 3. Synthesis of optically active building-blocks by microbiological reduction of 2,2-dimethylcyclohexan-1,3-dione (**11**). Reagents and conditions: (a) Baker's yeast; (b) TBSCl/imidazol/DMF; (c) *m*CPBA/$NaHCO_3$/$CH_2Cl_2$, 87% yield in two steps; (d) *m*CPBA/$CH_2Cl_2$, 82%

The seven-membered ring lactone **15** was then obtained in an excellent yield via protection of the hydroxy group in **12** followed by oxidation with *m*CPBA. In contrast, direct oxidation of **12** with the same reagent yielded the product that showed spectral properties suggestive of a six-membered ring derivative. A diagnostic piece of evidence was provided by a lower field shift of the C-6 signal (δ = 88.6 ppm) in the $^{13}C$ NMR spectrum, compared to that recorded in **15** (δ = 75.3 ppm). We surmised that the Baeyer−Villiger oxidation of **12** was accompanied by a ring-contraction, affording **14**. Indeed, all our attempts to transform the alcohol **14** into its TBS derivative failed, thus

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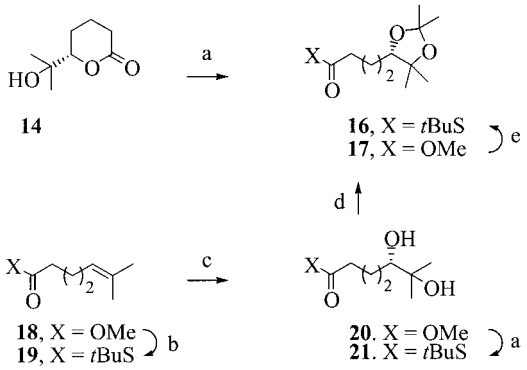
confirming the hydroxyl group bound to a tertiary carbon atom.

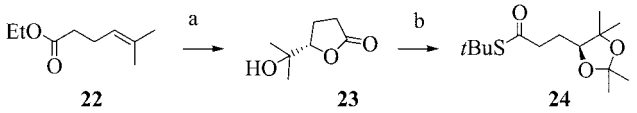
Lactone **14** was treated with a reagent prepared from trimethylaluminum and *tert*-butylmercaptan to afford the respective dihydroxy thioester.[35] This compound was transformed, without isolation, into the isopropylidene derivative **16** (Scheme 4). The product **16**, purified by consecutive column chromatography and distillation, was obtained in 56% yield, 96% *ee* (as determined by HPLC, Chiralcel OD column). The enantiomeric excess determined for **16** is indicative of the enantioselectivity achieved in the microbiological reduction of **11**, and of the *ee*'s of all the chiral derivatives shown in Scheme 3.




Scheme 4. The synthesis of optically active side-chain precursors; C20−C27 unit. Reagents and conditions: (a) 1. $AlMe_3$/*t*BuSH; 2. 2,2-dimethoxypropane, TsOH, 56%, 96% *ee*; (b) as reported;[36] (c) Sharpless asymmetric dihydroxylation, **18** into **20**: AD-mix-α, 76% yield (after distillation), > 95% *ee*; **19** into **21**: DHQ-PHAL, $K_3Fe(CN)_6$, $K_2CO_3$, $OsO_4$, 54%, 96% *ee* and **14**, 8%; (d) 2,2-dimethoxypropane, TsOH, **16**, 89%, **17**, 96%; (e) $AlMe_3$/*t*BuSH, 76%

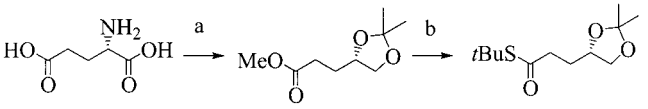
In an alternative approach to **16**, we used 6-methylhept-5-enoic acid as starting material.[36] The methyl ester **18** was subjected to the Sharpless asymmetric dihydroxylation (AD), using either commercially available AD-mix-α[37,38] or an oxidant prepared in situ,[39] to afford the dihydroxy derivative **20**. When AD-mix-α was used, the dihydroxy ester **20** was formed along with the hydroxy lactone **14**, in a ratio of 89:11 (as determined by GC). The dihydroxylation product was allowed to react with 2,2-dimethoxypropane in the presence of TsOH, affording **17**. Then, thioester **16** was obtained from **17** using the trimethylaluminum sulfide reagent. The order of the transformations on the route from **18** to **16** could be reversed since thioester **19** was smoothly dihydroxylated to give **21**. When the commercially available reagent was used, the dihydroxy derivative **21** was accompanied by a small amount of a side product, presumably lactone **14**. On all routes involving AD, ester **16** was obtained uniformly with over 95% *ee*.

In order to prepare the subsequent side-chain precursor, the unsaturated ester[40] **22** (Scheme 5) was subjected to the dihydroxylation procedure to give the five-membered lactone[41] **23** (70% yield, 96% *ee*). Lactone **23** was transformed into the thioester **24** in an analogous manner to that described above for its homologue.




Scheme 5. The synthesis of optically active side-chain precursors; C20−C23 unit. Reagents and conditions: (a) AD-mix-α, 70%, 96% *ee*; (b), 1. $AlMe_3$/*t*BuSH, 2. 2,2-dimethoxypropane, TsOH, 60% in 2 steps

Finally, the thioester **27** (Scheme 6), lacking geminal methyl groups at the chain terminus, was obtained from the methyl ester **26**, itself synthesized from the L-glutamic acid (**25**), essentially following literature procedures.[42,43]




Scheme 6. The synthesis of optically active precursors of the side chain lacking *gem*-dimethyl groups. Reagents and conditions: (a) as reported[42,43] (b) $AlMe_3$/*t*BuSH, 47%

### Synthesis of CD-Rings/Side-Chain Building-Blocks Starting from Optically Active Side-Chain Precursors

With all the required optically active precursors to vitamin D in hand, the stage was set for studies on asymmetric induction in the conjugate-addition reaction. We started with the ketene acetals that contained all the carbon atoms of the ultimative vitamin D side chain.

The thioester **16** was transformed into the ketene acetal **28** (Scheme 7) in the usual way,[44] and the product was purified by a short-path distillation. A mixture of (*E*)- and (*Z*)-isomers in a ratio of 89:11 was obtained.[45] Reaction of **28** with the enone **10** in the presence of $TrSbCl_6$ (7 mol %) in dichloromethane at −78 °C afforded the adduct, which was treated in situ with the enone[32] **9**. The product of tandem conjugate-addition was obtained in 55% yield. HPLC analysis and spectroscopic data indicated that two diastereomers had been obtained in a ratio of 76:24. All our attempts to separate the diastereomers by column chromatography failed. Fortunately, the major diastereomer crystallized (m.p. 103 °C, methanol), and was isolated from the mixture by crystallization (ca. 27% yield from **28**). A single-crystal X-ray analysis revealed it to be the (13*R*,17*R*,20*R*,24*S*) diastereomer[46] **29**. It is noteworthy that the absolute configuration of **29** is consistent with our plans for the synthesis of natural vitamin $D_3$ derivatives. After some time, a further quantity of crystals was obtained from the mother liquors (m.p. 69−70 °C). This material proved to be a 1:1 mixture of **29** and its minor diastereomer, to which the structure **30** (13*S*,17*S*,20*S*,24*S*) was assigned later (vide infra). Exposure of the 1,5-diketone **29** to methanolic potassium hydroxide afforded the bicyclic derivative **31**.

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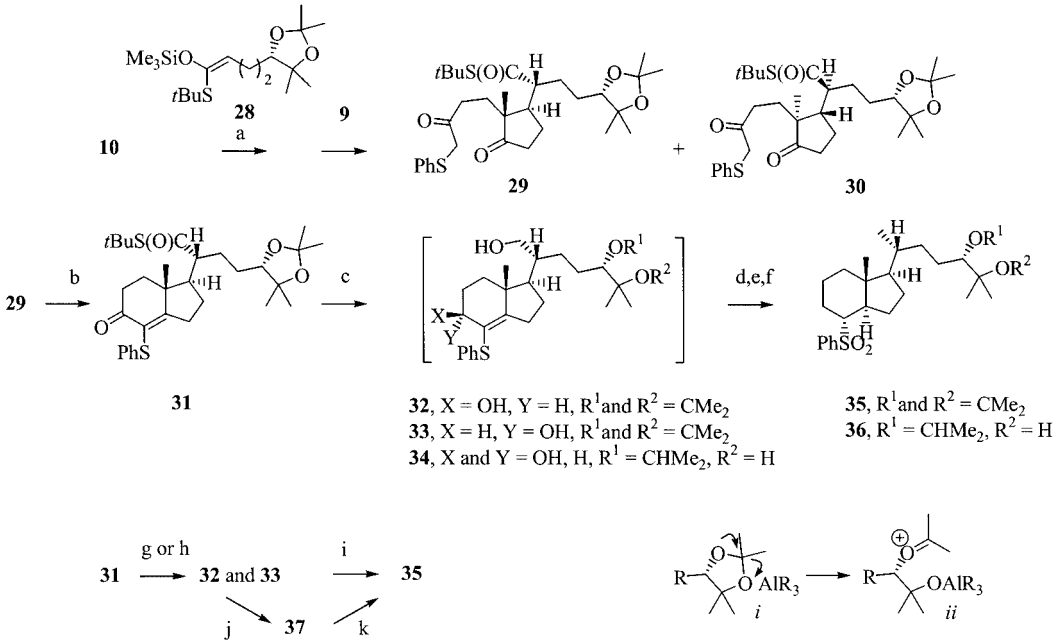


Scheme 7. Synthesis of the CD-rings /side-chain building-block **35**. Reagents and conditions: (a) $TrSbCl_6$, cat., 55% yield, then crystallization of **29**; (b) KOH/MeOH, 84%; (c) DIBALH/$CH_2Cl_2$, −78 °C; (d) TsCl/$Et_3N$; (e) *m*CPBA; (f) $LiAlH_4$, **35**, 36% and **36**, 16% from**31**; (g) 1. $CsCl_3{\cdot}H_2O/NaBH_4$, 2. $LiAlH_4$, **32**, 87% and **33**, 5%; (h) as (f), **32**, 73% and **33**, 15%; (i) 1. TsCl, $Et_3N$, 2. *m*CPBA, 3. $LiAlH_4$, 70% from **31**; (j) as (d), 89%; (k) *m*CPBA and then $LiAlH_4$, 72%

Various synthetic pathways from **31** to the *trans*-hydrindane derivative **35** were then explored. First, DIBALH was used to simultaneously reduce the *tert*-butylthioester and the keto groups. The crude product (a mixture of diastereomers) was treated with TsCl, which resulted in the selective esterification of the primary hydroxy groups. Then, the intermediates were oxidized with *m*CBPA to form the corresponding sulfones. Finally, the tosyloxy/sulfone derivatives were reduced with $LiAlH_4$.[47] A mixture of two compounds was obtained. The major product, separated by column chromatography (36% yield from **31**), was identified as the required acetonide **35**. Structure **36** was assigned to the minor product (16% yield) on the grounds of analytical and spectral properties. We concluded that the multi-step transformation of **31** into **35**, without purification of the intermediates, could be handled smoothly. However, the first step of the sequence, DIBALH reduction of **31**, afforded the expected diols **32** and **33** along with a side product **34** (presumably as a mixture of isomers). Mechanistically, reductive opening of the dioxolane ring is likely to involve a Lewis acid-catalyzed formation of the oxonium ion (*ii*, Scheme 7). All our attempts to minimize the amount of the side product **36** formed, by diminishing the excess of DIBALH or by altering the reaction conditions, failed.

In a subsequent approach, **31** (Scheme 7) was reduced with the Luche reagent[48] and then the intermediate allylic alcohols, with their unaffected thioester groups, were treated with $LiAlH_4$. After chromatography, the 9β,21-diol **32** was obtained (87% yield) along with a small amount of its C-9 epimer **33** (5% yield). Diol **32** was tosylated to give the 21-mono-tosylate **37** (not shown), and the tosylate was transformed into **35** (72% yield) using the aforementioned sequence of steps. Finally, **31** was reduced in one step with $LiAlH_4$ to afford a mixture of diols **32** and **33** (88% yield), and the mixture was transformed further, without isolation, to give **35** in 54% overall yield from **31**.

Both of the routes where DIBALH was not used provided the saturated sulfone **35** in high yields. The diastereoselectivities in the reduction of **31** are noteworthy; 9β- and 9α-hydroxy derivatives were formed in ratios as follows: DIBALH − ca. 70:30; $LiAlH_4$ − 83:17; the Luche reagent − 95:5.

Deprotection of acetal **35** using Amberlyst-15H in methanol gave the diol **38** (Scheme 8). This compound was treated with mesyl chloride and triethylamine, and the crude mesylate was reduced with $LiAlH_4$. The target product **8** was obtained (66% yield in 2 steps) and was found to be identical to an authentic sample.

All that remained to be done for the completion of the study on the synthesis of **8** from the ketene acetal **28** was the clarification of the structure of the minor diastereomer generated along with **29** in the conjugate-addition reaction. Since the minor diastereomer could not be separated, we thought it would be reasonable to subject the mixture to a sequence of operations that would eventually transform **29** into **8**. We anticipated that the diastereomer of then unknown structure would, under these conditions, afford the respective isomer of **8**, and that this would be easier to identify. The mixture (a sample enriched in the minor diastereomer by crystallization, *dr* 1:1) was subjected to the annulation procedure (Scheme 8), and the crude product was acidified with HCl in order to remove the acetal protec-

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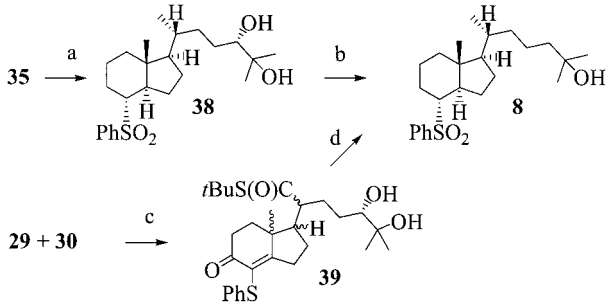
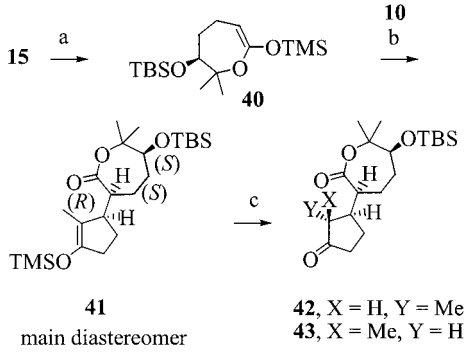



Scheme 8. Transformation of **35** into **8**; correlation of the structures of diastereomers **29** and **30**. Reagents and conditions, (a) Amberlyst-15H/MeOH, 81%; (b) 1. $MsCl/Et_3N$, 2. $LiAlH_4$, 87%; (c) 1. KOH/MeOH, 2. HCl, 70%; (d) 1. DIBALH, 2. $MsCl/Et_3N$, 3. *m*CPBA, 4. $LiAlH_4$, 26% in 4 steps

tive group. Intermediates **39** were treated with an excess of DIBALH to produce the respective tetrols, which were used without purification. The tetrols were treated with two molar equivalents of mesyl chloride in the presence of triethylamine, and then consecutively with *m*CPBA and $LiAlH_4$. A single product identical in all respects with racemic **8** was obtained. It was evident that the diastereomer accompanying **29** contributed to the racemate with its (13*S*,17*S*,20*S*) enantiomer; structure **30** was assigned to this compound.

These results demonstrate that readily accessible chiral ketene acetals can be conveniently used as precursors to the optically active vitamin D building block **8**. However, the diastereoselectivity observed in the generation of **29** and **30** (76:24) left room for improvement. To this end, we became interested in examining the use of the ketene acetal **40** derived from lactone **15**. The ketene acetal function in **40** (Scheme 9) is clearly more sterically hindered than that in **28**. It has been found that a stereogenic center in the α-position to the reaction-site in cyclic ketene acetals directs the addition.[49−51] Longer-range effects remain unclear.[52]




Scheme 9. Attempted use of ketene acetal **40** for the synthesis of **8**. Reagents and conditions: (a) LDA and then TMSCl, 92%; (b) $TrSbCl_6$, 69%; (c) Amberlyst-15H, crystallization

Lactone **15** was transformed into the silyl enol ether **40** (Scheme 9), and the latter was allowed to react with the enone **10** in the presence of the trityl catalyst. The initial adduct was formed as expected, however, it failed to react with the "second" acceptor **9**. After the usual work-up, a mixture of three isomers was obtained in a ratio of 80:12:8 (as shown from integration of the methyl group signals in the $^1H$ NMR spectrum). Further experiments showed that reaction-quenching and work-up procedures affect the ratio of the two major diastereomers, indicating that these products differ by a stereogenic center labile to epimerization. The major component of the mixture was obtained in a crystalline form (51% yield from **40**). Its structure was determined to be **42** by X-ray analysis.[53] Consequently, structure **41** was assigned to the immediate adduct and **43** to the major side product.

At this stage, it was also established that the conjugate-addition reaction of **40** and **10** occurred with relatively high diastereoselectivity, *dr* ca. 90:10. However, the relative configuration of the newly formed stereogenic centers was *unlike* (*u*), which was at odds with the synthetic plan (for some comments on the stereochemistry of the reaction, vide infra). This line of research was subsequently abandoned. It should be mentioned that we attributed the failure of the attempted reactions of **41** with **9** to steric hindrance.

Next, we turned our attention to the ketene acetal **44** (Scheme 10) derived from the thioester **24**.

A shorter distance between the stereogenic center and the reaction site (i.e. in a 1,3-relationship) was expected to be advantageous for asymmetric induction.[54] It should be noted that **24** does not include all the carbon atoms of the vitamin D side chain, and that a routine extension of the side chain would be required in the course of the synthesis of **8**. The reaction of the ketene acetal **44** consecutively with the enones **10** and **9** afforded a mixture of products, in a ratio of 85:11:4 (as determined by HPLC), in 75% yield. The major constituent of the mixture **45** was isolated in a pure form by preparative TLC, and its gross structure was confirmed by spectroscopic methods. However, its NMR spectra were too complex for us to attempt stereochemical assignments. In contrast to the earlier discussed synthesis, no crystalline material could be obtained.[55] The crude mixture was subjected to the annulation procedure to afford the enones, **49** and its respective diastereomer. The major product **49** was isolated, but no crystals suitable for X-ray analysis could be gained. In an attempt to obtain a derivative of **45** that would be helpful in structural elucidation, the five-membered lactones **47** and **48** (Scheme 10) were prepared. The isomeric products were separated by column chromatography, but the high-field signals corresponding to the lactone ring-protons in the $^1H$ NMR spectra of both isomers were poorly resolved.

In a search for evidence that would allow us to assign the stereochemistry, CD spectra of adduct **45** and its homologue **29** were taken. The spectra were similar in shape, but the Cotton effect was of the opposite sign, suggesting that **45** and **29** differed in configuration at C-13. Assuming a (13*S*) configuration for **45**, it could be deduced that the center at C17 has the (*S*) configuration (see the discussion of the synthetic plan). For the third newly generated stereogenic center, the (20*S*) configuration would be expected on

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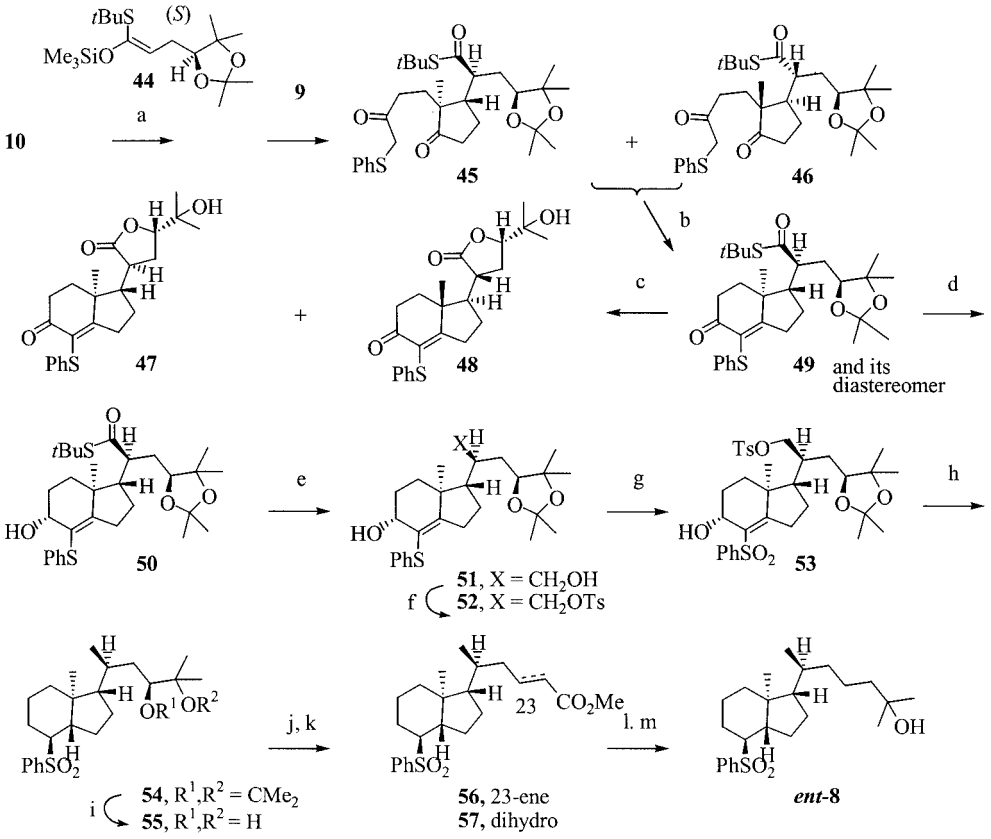


Scheme 10. Synthesis of *ent*-**8** from ketene acetal **44**. Reagents and conditions: (a) $TrSbCl_6$, 7 mol %; 75%, isomer ratio 85:11 4; (b) KOH/MeOH, 79%; (c) Amberlyst-15H/MeOH; (d) $CeCl_3 \cdot 7H_2O/NaBH_4$/MeOH and crystallization, 66%; (e) $LiAlH_4$; (f) TsCl/DMAP/$Et_3N$; (g) *m*CPBA; (h) $LiAlH_4$, 63% in 4 steps; (i) as in (c) 80%; (j) $Pb(OAc)_4$; (k) $(Ph)_3PCHCO_2Me$, 80%; (l) $H_2$/Pd; (m) MeMgI, 88% in 2 steps

the grounds of the preference of *l* products in the Mukaiyama−Michael reaction. For these reasons, the (13*S*,17*S*,20*S*,23*S*) configuration appeared to be the most likely for **45**.

The synthesis was continued with the premise that the structure of **45** and its derivatives would be confirmed at later stages. Reduction of the enone **49** and its accompanying isomers (the crude product of an annulation reaction) with the Luche reagent afforded the respective allylic alcohols in an almost quantitative yield. The major component of the mixture crystallized, and was isolated in 66% yield by crystallization. Single crystal X-ray analysis[53] of the isolated allylic alcohol revealed its structure as **50**. Consequently, structures were established as **45** for the major product of the conjugate-addition reaction, **47** for the major isomer of the lactonization, and **49** for the major diastereomer of the annulation product.

For the second major product of the conjugate-addition step, structure **46** appeared to be most likely (as the alternative *l* diastereomer). Accordingly, structure **48** was tentatively assigned to the isomeric lactone. The minor product (4%) presumably represents one of the *u* diastereomers.

Isomerically pure **50** was transformed into **54** (47% overall yield), as indicated in Scheme 10. Next, the protective group was removed, and the resulting diol **55** was cleaved with lead tetraacetate to afford the respective aldehyde. The latter was allowed to react with methyl (triphenylphosphoranylidene)acetate, without isolation, to afford the unsaturated ester **56**. Finally, **56** was hydrogenated, and the isolated dihydro derivative **57** was treated with an excess of the Grignard reagent to afford the enantiomer of the previously prepared building-block: *ent*-**8**. The specific rotation of the enantiomers is inconclusively low; the enantiomeric nature of the synthesized compounds was confirmed by their CD spectra.

The synthesis we accomplished involved seven isolated intermediates, and afforded *ent*-**8** in 14% overall yield from **44**. Obviously, for the synthesis of natural enantiomers of vitamin D derivatives by this route, the (*R*)-enantiomer of the protected dihydroxy ester **24** must be used.

Not all of the carbon atoms of the dihydroxy ester derivative **24** were incorporated into the target compound *ent*-**8** in the above approach. The terminal isopropyl group was cleaved off after all of the stereogenic centers had been installed. Therefore, it was tempting to examine the dihydroxy ester derivative **27**, which is devoid of the geminal methyl groups. Replacement of **44** by **58** (Scheme 11) would contribute to "atom economy". Additionally, we believed that a comparison of **44** and **58** would contribute to our understanding of the steric effects in the conjugate-addition reaction.

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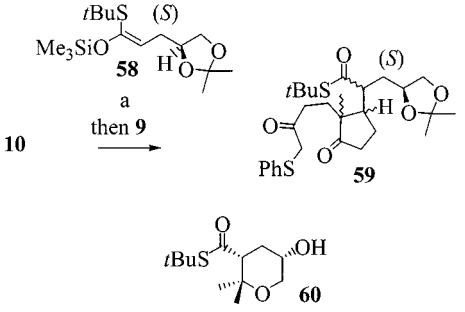



Scheme 11. Attempted synthesis of **8** using ketene acetal **58**. Reagents: (a) $TrSbCl_6$, 39%.

Thioester **27** was treated consecutively with LDA and trimethylsilyl chloride to give ketene acetal **58** as a mixture of (*E*) and (*Z*) isomers, in a ratio of 82:18. The reaction of **58** with enones **10** and then **9** turned out to be less effective than expected. After some experimentation, the tandem addition product **59** was obtained in 39% yield. It is noteworthy that the pyran derivative **60** was isolated from one of the experiments in which **58** reacted with cyclopent-2-en-1-one, thus demonstrating that **58** is susceptible to cyclization.

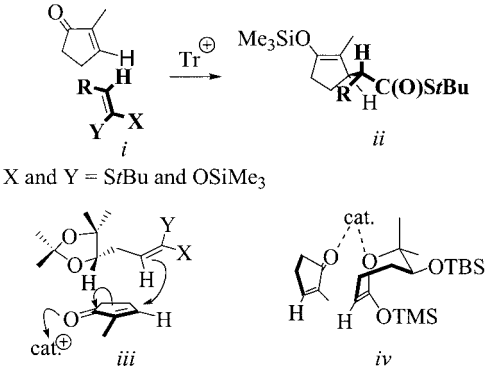
$^1H$ and $^{13}C$ NMR spectral analysis of **59** showed the presence of two diastereomers in a ratio of ca. 1:1. Hence, it is clear that the geminal methyl groups at the terminus of the ketene acetal chain are crucial for the diastereoselectivity of the conjugate-addition reaction.

### Comments on the Stereochemistry of Conjugate-Addition Reactions

In our studies aimed at the enantioselective synthesis of the hydrindane derivative **8**, we examined the reactions of four homochiral ketene acetals of (*S*) configuration with 2-methylcyclopent-2-en-1-one and, where applicable, with the subsequent Michael acceptor **9**. In reviewing the stereochemical outcome of these reactions, we assume that the ratio of diastereomers isolated from a tandem conjugate-addition reaction reflects well the stereoselectivity in the initial step.

Reaction of the acyclic ketene acetals **28** and **44** with the enone **10** occurred with a high simple diastereoselectivity, affording respective adducts of *like* (*l*) configuration [(17*S*,20*S*) or (17*R*,20*R*)], as virtually the only products. The cyclic ketene acetal **40** reacted with **10**, again to give predominantly a single diastereomer of the adduct (*dr* ca. 90:10), but in this case, the main product was of *unlike* (*u*) configuration (17*R*,20*S*). Initial experiments in which ketene acetal **58** reacted with **10** indicated a lack of diastereoselectivity in this reaction.

We conclude that ketene acetals **28** and **44** react in accordance with the general stereochemical model of the Mukaiyama−Michael conjugate-addition involving 2-methylcyclopent-2-en-1-one (Scheme 12, *i*). The major features of this model are as follows:[30] firstly, the configuration of the ketene acetal double bond has no effect on the reaction course, since two sterically bulky groups *t*BuS and $Me_3SiO$ are involved; secondly, the ethylenic bonds participating in the reaction are in the relative *anti*-periplanar orientation; thirdly, the ketene acetal vinylic proton is directed towards the enone methyl group.




Scheme 12. Stereochemistry of the conjugate-addition reactions

The highest induced diastereoselectivity was recorded for the ketene acetal **44** in which the stereogenic center and the reaction site have a 1,3-relationship. The diastereomers of (17*R*,20*R*) and (17*S*,20*S*) configuration were formed in a ratio of 12:88. The one-carbon-longer ketene acetal **28** afforded diastereomers (17*R*,20*R*) and (17*S*,20*S*) in a ratio of 76:24. Formally, reversal of facial selectivity occurred.

An inspection of molecular models suggests that the *Re*,*Re* approach (*l*) of **44** to **10**, in which the dioxolane ring is essentially perpendicular to the cyclopentenone ring, and the dioxolane proton is orientated towards the enone methyl group, is favored (Scheme 12, *iii*). In this arrangement, the interaction of the dioxolane methyl groups with the enone is minimal. With the extension of the ketene acetal chain, the difference in stereofacial approaches of **28** and **10** diminishes. The *Si*,*Si* approach, presumably with the dioxolane proton located in the vicinity of enone carbonyl, accounts for the observed selectivity.

The cyclic ketene acetal **40** afforded a (17*R*,20*S*) product **41** and its minor diastereomer in a ratio of ca. 87:13. Analysis of the model indicates that a half-boat conformation of the seven-membered ring, with the *tert*-butyldimethylsilyloxy group in a pseudo-equatorial orientation, is favored (Scheme 12, *iv*). The *Re*-side (*exo*) of the ketene acetal is exposed to the attack of the reagent. As regards the enone, addition occurs on its *Si*-side. This favors the approach of the carbonyl group orientated towards the silyloxy group, and with the enone methyl group eclipsed by the ketene acetal vinylic proton. This reaction may be viewed as substrate-controlled,[56] in the sense that the specific requirements of one the reactants imposes simple and induced diastereoselectivity.

## Conclusion

In conclusion, enantioselective synthetic approaches to the vitamin D building-block **8**, starting from optically ac-

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tive derivatives of fatty acids, were developed. Simple and induced diastereoselectivity in the Mukaiyama−Michael reaction of selected optically active ketene acetals with 2-methylcyclopent-2-en-1-one were examined.[63]

## Experimental Section

Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer model 141 polarimeter using a 1-mL capacity cell (5-cm path length) in $CHCl_3$. NMR spectra were recorded in $CDCl_3$ solutions, $^1H$ at 200 MHz and $^{13}C$ at 50 MHz unless otherwise indicated, with a Varian Gemini instrument. $^1H$ spectra at 500 MHz and $^{13}C$ spectra at 125 MHz were recorded with a Bruker AMX spectrometer. Chemical shifts are quoted on the δ scale with the solvent signal as an internal standard ($CDCl_3$, $^1H$ NMR: δ = 7.26 ppm. $CDCl_3$; $^{13}C$ NMR: δ = 77.00 ppm). In $^{13}C$ NMR spectra, the multiplicities of the signals were assigned using the DEPT technique. IR spectra were recorded with a Perkin−Elmer 1670 FT spectrophotometer. MS (electron impact, 70 eV) were recorded with an AMD 604 (AMD Intectra GmbH) mass spectrometer. HPLC analyses were performed using a Shimadzu LC-8A system provided with a SPD-6A variable UV detector; flow rate 0.5 to 1 mL/min. Column chromatography was performed with gradient elution on Merck silica gel 60, 230−400 mesh. TLC was performed on aluminum sheets, Merck 60F 254 and preparative TLC on glass plates, 20 × 20, covered with Merck silica gel FG 254. Anhydrous solvents were obtained by distillation from benzophenone ketyl (THF) or calcium hydride ($CH_2Cl_2$, benzene). Air-sensitive reactions were performed in oven- or flame-dried glassware under argon. Organic extracts were dried with anhydrous $Na_2SO_4$ or $MgSO_4$, and solvents were evaporated using a rotary evaporator. Microanalyses were performed at our analytical laboratory. DHQ: dihydroquinine; PHAL: phthalazine.

**(3*S*)-3-Hydroxy-2,2-dimethylcyclohexan-1-one (12):** This compound was prepared following the reported procedure.[33] In a typical run, 2,2-dimethylcyclohexa-1,3-dione (**11**) (4.00 g, 28.17 mmol), commercially available baker's yeast (150 g), sucrose (80 g), water (1 L), ethanol (96%, 10 mL) and Triton X-100 (0.2%, 40 mL) were used. The mixture was stirred at 30 °C for 48 h. The crude product was purified by chromatography on silica gel to give the unchanged dione **11** (1.28 g, 32%) and the ketol **12** (1.23 g, 31%): $[\alpha]_D^{22}$ = +23.7 (*c* = 2.0). Reported:[33] $[\alpha]_D^{22}$ = +23.0 (*c* = 2.0).

**(6*S*)-*O*-(*tert*-Butyldimethylsilyl)-6-hydroxy-7,7-dimethyloxepan-2-one (15):** Imidazole (3.63 g, 53.38 mmol) and TBSCl (3.81 g, 25.28 mmol) were added to a solution of **12** (1.365 g, 9.61 mmol) in DMF (18 mL). The mixture was stirred at room temperature for 16 h, then at 50 °C for 9 h, and then poured into water. The product was extracted with dichloromethane. The organic extract was washed consecutively with ice-cold 1% HCl, 5% $NaHCO_3$ and water. The so-obtained solution of the TBS derivative of **12** was concentrated to ca. 25 mL, and powdered $NaHCO_3$ (10 g), and *m*CPBA (70%, 4.00 g, 16.23 mmol) were added. The mixture was stirred for 6 h, and then the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The product was extracted with dichloromethane. The solvent was evaporated. The residue was purified by chromatography on silica gel (80 g, hexanes/EtOAc, 25:1, 5:1) and then distilled in a kugelrohr apparatus (200°/1.0 Torr) to give **15** (2.26 g, 87%) as a crystalline solid: m.p. 41 °C. $[\alpha]_D^{22}$ = +29.9 (*c* = 2.0). $^1H$ NMR: δ = 0.06 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, $SiCMe_3$), 1.40 (s, 3 H), 1.43 (s, 3 H), 1.45−2.05 (m, 4 H, C5-H and C4-H), 2.54−2.73 (m, 2 H, C3-H), 3.72−3.63 (m, 1 H, C6-H) ppm. $^{13}C$ NMR: δ = −4.9 (SiMe), −4.2 (SiMe), 17.9 ($SiCMe_3$), 18.5 (C4), 24.3 (C7-*Me*), 25.7 ($SiCMe_3$), 27.6 (C7-*Me*), 32.5 (C5), 36.6 (C3), 75.3 (C6), 83.7 (C7), 174.3 (C2) ppm. $C_{14}H_{28}O_3Si$ (272.45): calcd. C 61.72, H 10.36; found C 61.49, H 10.43.

**(6*S*)-6-*O*-(*tert*-Butyldimethylsilyl)-7,7-dimethyl-2-*O*-(trimethylsilyl)-4,5,6,7-tetrahydrooxepine-2,6-diol (40):** A solution of LDA was prepared from diisopropylamine (0.410 mL, 3.13 mmol) and BuLi (1.35 M in hexanes, 1.315 mL, 3.13 mmol) in THF (6 mL) at 0 °C, and cooled to −78 °C. A solution of the lactone **15** (695 mg, 2.56 mmol) in THF (3 mL) was added, followed, after 45 min, by TMSCl (0.570 mL, 4.51 mmol). The mixture was set aside at room temperature for 12 h, and then the solvent was evaporated. The residue was diluted with hexanes (15 mL) and filtered through a pad of Celite. The solvent was evaporated, and the residue was distilled in a kugelrohr apparatus (220°/1.0 Torr) to give **40** (875 mg, 92%): $[\alpha]_D^{22}$ = −34.7 (*c* = 2.0). $^1H$ NMR: δ = 0.05 (s, 6 H, *t*Bu$Me_2$Si), 0.19 (s, 9 H, $SiMe_3$), 0.88 (s, 9 H, $SiCMe_3$), 1.24 (s, 3 H), 1.33 (s, 3 H), 1.41−1.77 (m, 2 H, C4-H), 1.81−2.02 (m, 2 H, C5-H), 3.47 (dd, *J* = 9.8, 3.9 Hz, 1 H, C3-H), 4.21−4.31 (m, 1 H, C6-H) ppm. $^{13}C$ NMR: δ = −4.8 (*t*Bu$Me_2$Si), −3.9 (*t*Bu$Me_2$Si), 0.3 ($SiMe_3$), 17.9 ($SiCMe_3$), 18.1 (C7-*Me*), 19.8 (C5), 25.8 ($SiCMe_3$), 27.9 (C7-*Me*), 31.4 (C4), 79.0 (C6), 80.5 (C7), 86.7 (C3), 154.5 (C2) ppm. $C_{17}H_{36}O_3Si_2$ (344.64): calcd. C 59.25, H 10.53; found C 59.17, H 10.31.

**(6*S*)-6-(1-Hydroxy-1-methylethyl)tetrahydro-2*H*-pyran-2-one (14):** Powdered $NaHCO_3$ (8 g) and *m*CPBA (70%, 2.132 g, 8.67 mmol) were added to a solution of **12** (985 mg, 6.94 mmol) in dichloromethane (25 mL). The mixture was stirred for 6 h, and then poured into saturated aqueous $Na_2S_2O_3$. The product was extracted with dichloromethane. The solvent was evaporated. The residue was filtered through silica gel (30 g, hexanes/acetone, 5:1) and then distilled in a kugelrohr apparatus (150 °C/1.5 Torr) to give **14** (900 mg, 82%): $[\alpha]_D^{22}$ = +17.1 (*c* = 2.0). IR (film): $\tilde{\nu}$ = 3445, 1769, 1185 $cm^{-1}$. $^1H$ NMR: δ = 1.19 (s, 3 H, Me), 1.24 (s, 3 H, Me), 1.42−2.06 (m, 4 H), 2.68−2.26 (m, 3 H), 4.03−4.13 (m, 1 H, C6-H) ppm. $^{13}C$ NMR: δ = 18.4, 22.4, 24.3, 25.6, 29.4, 71.4 (C1′), 88.6 (C6), 171.5 (C2) ppm. $C_8H_{14}O_3$: calcd. C 60.74, H 8.92; found C 60.49, H 9.17.

***S*-*tert*-Butyl 4-[(3*S*)-2,2,5,5-Tetramethyl-1,3-dioxolan-4-yl]butanethioate(16). a. From Lactone 14:** *t*BuSH (2.25 mL, 19.87 mmol) was added dropwise to a solution of trimethylaluminium (2.0 M in heptane, 9.94 mL, 19.88 mmol) in dichloromethane (25 mL) at 0 °C. The solution was warmed to room temperature, and, after 30 min, a solution of lactone **14** (1.39 g, 8.80 mmol) in dichloromethane (8 mL) was added. The mixture was stirred for 14 h and then poured into 10% aqueous tartaric acid. The product was extracted with dichloromethane. The solvent was evaporated. The residue was dissolved in 2,2-dimethoxypropane (7 mL), and TsOH (5 mg) was added. The mixture was set aside for 12 h and then filtered through silica gel (2 g), and the solvent was evaporated. The residue was purified by chromatography on silica gel (50 g, hexanes/EtOAc, 15:1) and the main fraction was distilled in a kugelrohr apparatus (165 °C/1.5 Torr). Thioester **16** (1.42 g, 56%) was obtained, 95.9% *ee* by HPLC (Chiralcel OD, 10% *t*BuOH in hexanes, $t_R$ = 6.14 min, for the minor (*R*) enantiomer, $t_R$ = 6.82 min): $[\alpha]_D^{22}$ = +1.6 (*c* = 2.0). $^1H$ NMR: δ = 0.99 (s, 3 H, Me), 1.05−1.89 (m, 4 H) overlapping 1.15 (s, 3 H, Me), 1.23 (s, 3 H, Me), 1.31 (s, 3 H, Me), 1.37 (s, 9 H, $CMe_3$), 2.30−2.56 (m, 2 H, C2-H), 3.53−3.63 (m, 1 H, C*H*O−) ppm. $^{13}C$ NMR: δ = 22.7, 22.9, 25.9, 26.7, 28.3 28.4, 29.7 ($CMe_3$), 44.1, 47.6, 79.9, 82.8, 106.4 (O−C−O), 199.7 (CO) ppm. $C_{15}H_{22}O_3S$: calcd. C 62.46, H 9.78; found C 62.19, H 10.01.

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**b. From Ester 17:** *t*BuSH (3.37 mL, 29.99 mmol) was added dropwise to a solution of trimethylaluminium (2.0 M in heptane, 2.0 M 15.00 mL, 30.00 mmol) in dichloromethane (20 mL) at 0 °C. The solution was warmed to room temperature, and, after 30 min, a solution of ester **17** (3.40 g, 14.78 mmol) in dichloromethane (10 mL) was added. The mixture was stirred for 14 h and then poured into 10% aqueous tartaric acid. The product was isolated as described above, purified by chromatography on silica gel (100 g, hexanes/ EtOAc, 25:1 and 10:1) and then distilled in kugelrohr apparatus to give **16** (3.235 g, 76%).

**c. From diol 21:** TsOH (15 mg) was added to a solution of diol **21** (1.19 g, 4.80 mmol) in 2,2-dimethoxypropane (15 mL). After 5 h, the reaction was quenched with triethylamine (1.0 mL), and the mixture was filtered through silica gel (2 g). The solvent was evaporated and the residue was purified by chromatography on silica gel (20 g, hexanes/ EtOAc, 20:1) to give **16** (1.23 g, 89%).

**Methyl 6-Methylhept-5-enoate (18):** A mixture of 6-methylhept-5-enoic acid[36] (10.50 g, 73.94 mmol), dry methanol (150 mL) and sulfuric acid (98%, 0.5 mL) was heated at reflux temperature for 4 h. After cooling, triethylamine (3 mL) was added, and the mixture was filtered through silica gel (25 g). The filtrate was evaporated. The residue was distilled. The fraction at 82−85 °C/30 Torr was collected to give ester **18** (9.46 g, 82%). $^1$H NMR: δ = 1.55 (s, 3 H, C=C-Me-*trans*), 1.57−1.70 (m, 5 H, C3-H and C=C-Me-*cis*), 1.88−2.04 (m, 2 H, C4-H), 2.26 (m, 2 H, C2-H), 3.62 (s, 3 H, OMe), 4.98−5.11 (m, 1 H, C5-H) ppm. $^{13}$C NMR: δ = 17.6 (3), 25.0 (C3), 25.6 (3), 27.3 (C4), 33.4 (C2), 51.3 (O*Me*), 123.3 (C5), 132.3 (C6), 174.0 (CO) ppm. $C_9H_{16}O_2$ (156.22): calcd. C 69.19; H-10.32; found C 69.28, H 10.37. Reported:[57] $^1$H NMR: δ = (60 MHz, $CDCl_3$): δ = 5.07 (m, 1 H), 3.63 (s, 3 H), 1.68 (br. s, 3 H), 1.58 (br. s, 3 H) ppm.

**Methyl (5*S*)-5,6-Dihydroxy-6-methylheptanoate (20). Asymmetric Dihydroxylation of the Unsaturated Ester 18 with $(DHQ)_2$-PHAL and $OsO_4$:** The reaction was carried out according to the procedure of Crispino and Sharpless.[39] Ester **18** (1.56 g, 10.00 mmol) was added to a well stirred solution of $(DHQ)_2$-PHAL (400 mg, 5.0 mol %), $K_3Fe(CN)_6$ (9.90 g, 30 mmol), $K_2CO_3$ (4.2 g, 30 mmol), and $OsO_4$ (25 mg, 1.0 mol %) in *t*BuOH/water (l:1, 100 mL) at 0 °C. The mixture was stirred for 8 h, then $Na_2SO_3$ (15 g) was slowly added, and the suspension was warmed to room temperature. The product was extracted with dichloromethane (5 × 30 mL). The extract was dried with and the solvent was evaporated. The residue was purified by chromatography on silica gel (70 g). Elution of the column with hexanes/EtOAc, 5:1 and then 1:1 gave the fraction containing the diol **20** (TLC, EtOAc/hexanes, 1:1, $R_f$ = 0.19). Further elution with hexanes/EtOAc, 1:2 afforded a side product with the same $R_f$ (0.10) as lactone **14** (TLC, EtOAc/hexanes, 1:1). The main fraction was distilled in a kugelrohr apparatus (175 °C/ 1.5 Torr) to give the diol (−)-**20** (1.06 g, 56%): $[\alpha]_D^{22}$ = −22.4 (*c* = 1.65). $^1$H NMR: δ = 1.07 (s, 3 H, Me), 1.12 (s, 3 H, Me), 1.20−1.98 (m, 4 H, C3-H and C4-H), 2.25−2.38 (m, 2 H, C2-H), 2.75 (br. s, 1 H, C6-O*H*), 3.12 (br.d, 1 H, *J* = 4.1 Hz, C5-O*H*), 3.22−3.35 (m, 1 H, C5-H), 3.61 (s, 3 H, O*Me*) ppm. $^{13}$C NMR: δ = 21.9 (2), 23.1 (3), 26.2 (3), 30.8 (2), 33.6 (2), 51.4 (OMe), 72.9 (C6), 77.8 (C5), 174.2 (CO) ppm. $C_9H_{18}O_4$ (190.24): calcd. C 56.82, H 9.54; found C 56.78, H 9.51.

The diol (5*S*)-(−)-**20**, over 95% *ee*, was also obtained from the unsaturated ester **18** in 76% yield using commercially available AD-mix α and the reported procedure.[37,38] The crude product consisted of the diol **18** and the lactone **14** in a ratio of 89:11.

**Methyl 4-[(3*S*)-2,2,5,5-Tetramethyl-1,3-dioxolan-4-yl]butyrate (17):** TsOH (10 mg) was added to a solution of the diol **20** (950 mg, 5.00 mmol) in 2,2-dimethoxypropane (10 mL). After 5 h, the reaction was quenched with triethylamine (0.5 mL), and the mixture was filtered through silica gel (2 g). The solvent was evaporated. The residue was purified by chromatography on silica gel (25 g, hexanes/EtOAc, 15:1), and the main fraction was distilled in a kugelrohr apparatus (165°/1.5 Torr) to give **17** (1.104 g, 96%): $[\alpha]_D^{22}$ = +3.9 (*c* = 1.65). $^1$H NMR: δ = 1.05 (s, 3 H, Me), 1.21 (s, 3 H, Me), 1.27 (s, 3 H, Me), 1.20−1.96 (m, 4 H, C3-H and C4-H) overlapping 1.37 (d, *J* = 0.6 Hz, 3 H, Me), 2.24−2.49 (m, 2 H, C2-H), 3.64 (dd, *J* = 4.0, 8.6 Hz, 1 H, CHO−), overlapping 3.64 (s, 3 H, OMe) ppm. $^{13}$C NMR: δ = 22.4 (2), 22.8 (3), 26.0 (3), 26.8 (3), 28.4 (3), 28.6 (2), 33.8 (2), 51.4 (OMe), 80.0 (C5′), 83.0 (C4′), 106.5 (O−C−O), 173.7 (CO) ppm. $C_{12}H_{22}O_4$ (230.30): calcd. C 62.58, H 9.63; found C 62.56, H 9.40.

***S*-*tert*-Butyl (5*S*)-5,6-Dihydroxy-6-methylheptanethioate (21). Asymmetric Dihydroxylation of the Unsaturated Thioester 10 with the Use of $(DHQ)_2$-PHAL and $OsO_4$:** The reaction was carried in an analogous way to the asymmetric dihydroxylation of ester **18**, as described above. The reagents were used as follows: $(DHQ)_2$-PHAL (400 mg, 5%mol), $K_3Fe(CN)_6$ (9.90 g, 30 mmol), $K_2CO_3$ (4.2 g, 30 mmol), $OsO_4$ (25 mg, 1%mol), *t*BuOH/$H_2O$ (1:1) 100 mL, thioester[36] **19** (2.14 g, 10.00 mmol), $Na_2SO_3$ (15 g). Reaction time 6 h. The product was extracted with dichloromethane (5 × 30 mL) and purified by chromatography on silica gel (100 g, hexanes/ EtOAc, 5:1 and then 3:1) to give diol (−)-**21** as the main fraction (TLC, EtOAc/hexanes, 1:1, $R_f$ = 0.29) and a side product ($R_f$ = 0.10, same as the lactone **14**). The crude diol was distilled using a kugelrohr apparatus (210 °C/1.0 Torr) to give the diol (−)-**21** (1.34 g, 54%): $[\alpha]_D^{22}$ = −19.5 (*c* = 2.5). HPLC analysis, Chiralcel OD, 10% *t*BuOH in hexanes, (*R*)-**21** ($t_R$, 15.64 min): (*S*)-**21** ($t_R$, 16.52 min), 2.26:97.74. $^1$H NMR: δ = 1.08 (s, 3 H, Me), 1.14 (s, 3 H, Me), 1.15−2.22 (m, 4 H, C3-H and C4-H) overlapping 1.40 (s, 9 H, $CMe_3$), 2.40−2.51 (m, 2 H, C2-H), 2.60−3.15 (br. s, 2 H, C5−O*H* and C6-O*H*), 3.29 (dd, *J* = 2.4, 10.1 Hz, 1 H, C5-H) ppm. $^{13}$C NMR: δ = 22.6 (2), 23.1 (3), 26.3 (3), 29.7 ($CMe_3$), 30.5 (2), 44.0 (2), 47.8 ($CMe_3$), 73.0 (C6), 77.8 (C5), 200.8 (CO) ppm. $C_{12}H_{24}O_3S$ (248.38): calcd. C 58.03, H 9.74; found C 58.04, H 9.84.

Asymmetric dihydroxylation of the thioester **19** using commercially available AD-mix-β[37,38] gave the diol (+)-**21** in 73% yield, at least 95% *ee* by HPLC: $[\alpha]_D^{22}$ = +21.0 (*c* = 1.03).

**(1*E*)- and (1*Z*)-1-(*tert*-Butylthio)-4-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]-1-trimethylsilyloxy-but-1-ene (28):** A solution of LDA was prepared from diisopropylamine (0.475 mL, 3.63 mmol), and BuLi (1.35 M in hexanes, 2.68 mL, 3.62 mmol) in THF (5 mL) and cooled to −78 °C, and a solution of **16** (745 mg, 2.59 mmol) in THF (2 mL) was added. After 45 min, TMSCl was added (0.59 mL, 4.68 mmol). The mixture was set aside at room temperature for 12 h, and then the solvent was evaporated. The residue was diluted with hexanes (15 mL), and filtered through a pad of Celite. The solvent was evaporated, and the residue was distilled in a kugelrohr apparatus (180 °C/1.0 Torr) to give **28** (867 mg, 93%) as a mixture of *E*:*Z* isomers in a ratio of 89:11 (as determined by integration of the $SCMe_3$ signals in the $^1$H NMR spectrum). **Major Isomer:** $^1$H NMR: δ = 0.21 (s, 9 H, $SiMe_3$), 1.08 (s, 3 H, Me), 1.23 (s, 3 H, Me), 1.32 (s, 3 H, Me), 1.37 (s, 9 H, $CMe_3$), 1.41 (s, 3 H, Me), 1.28−1.80 (m, 2 H), 2.24−2.42 (m, 2 H, C3-H), 3.64−3.75 (m, 1 H, CHO−), 5.23 (tr, 1 H, *J* = 7.4 Hz, C2-H) ppm. $^{13}$C NMR: δ = 0.3 ($SiMe_3$), 22.8, 26.0, 26.5, 26.7, 28.5, 29.7, 31.7 ($CMe_3$), 46.3 ($CMe_3$), 80.1 (C5′), 82.6 (C4′), 106.4 (O−C−O), 119.5 (C2), 145.9 (C1) ppm. **Minor isomer:** $^1$H NMR: δ = 0.22 (s, $SiMe_3$), 1.33 (s,

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$CMe_3$) ppm. $^{13}C$ NMR: δ = 31.4 ($CMe_3$) ppm. $C_{18}H_{36}O_3SiS$: calcd. C 59.95, H 10.06; found C 59.71, H 10.21.

**Ethyl 5-Methylhex-4-enoate (22):** A solution of *t*BuOK (6.72 g, 60.0 mmol) in THF (50 mL) was added dropwise to a stirred suspension of (3-ethoxycarbonylpropyl)triphenylphosphonium bromide[58] (25.0 g, 54.7 mmol) in dry THF (70 mL) at 0 °C. After 30 min, dry acetone (4.77 mL, 65.0 mmol) was added, and the mixture was warmed to room temperature. Stirring was continued for 4 h, and then the solvent was evaporated. Water (100 mL) and hexanes (100 mL) were added to the residue. The solid was filtered off and washed with hexanes (3 × 20 mL). The layers were separated. The aqueous layer was washed with hexanes (3 × 20 mL). The combined organic extracts were dried, and the solvent was evaporated. The residue was distilled and fractions boiling at 83−87 °C/16 Torr were collected. Ester **22** was obtained (5.92 g, 69%). $^1H$ NMR: δ = 1.22 (tr, 3 H, *J* = 7.1 Hz, $OCH_2CH_3$), 1.59 (s, 3 H, C=C-Me-*trans*), 1.65 (s, 3 H, C=C-Me-*cis*), 2.25−2.31 (m, 4 H, C2-H and C3-H), 4.10 (q, *J* = 7.1 Hz, 2 H, $OCH_2CH_3$), 4.98−5.12 (m, 1 H, C4-H) ppm, in agreement with those reported.[40] $^{13}C$ NMR: δ = 14.2 ($OCH_2CH_3$), 17.6 (3), 23.6 (C3), 25.6 (3), 27.3 (C3), 34.4 (C2), 60.1 ($OCH_2CH_3$), 122.4 (C4), 132.8 (C5), 173.3 (C=O) ppm.

**(5*S*)-5-(1-Hydroxy-1-methylethyl)dihydrofuran-2(3*H*)-one (23):** This compound was obtained from unsaturated ester **22** (1.56 g, 10.00 mmol) following the general procedure[38] using AD-mix-α (14 g) in *t*BuOH/$H_2O$ (1:1) 100 mL, and then $Na_2SO_3$ (15 g). The reaction was carried out at room temperature for 6 h. The product was extracted with dichloromethane (5 × 30 mL). The crude material was purified by chromatography on silica gel (50 g, hexanes/*i*PrOH, 10:1, 3:1) and then distilled in a kugelrohr apparatus (150 °C/2.5 Torr) to give the lactone **23** (1.01 g, 70%): $[\alpha]_D^{22}$ = +41.4 (*c* = 2.0). $^1H$ and $^{13}C$ NMR spectra were in agreement with those recorded for racemic material.[41]

***S*-*tert*-Butyl 3-[(4*S*)-2,2,5,5-Tetramethyl-1,3-dioxolan-4-yl]propanethioate (24):** *t*BuSH (2.93 mL, 26.00 mmol) was added dropwise to a solution of trimethylaluminium (2.0 M in heptane, 12.94 mL, 25.88 mmol) in dichloromethane (30 mL) at 0 °C. The mixture was stirred at room temperature for 30 min, and then a solution of the lactone **23** (1.49 g, 10.35 mmol) in dichloromethane (8 mL) was added. After 18 h, the mixture was poured into 10% aqueous tartaric acid, and the product was extracted with dichloromethane (6 × 15 mL). The extract was dried and the solvents evaporated. The residue was dissolved in 2,2-dimethoxypropane (10 mL), and TsOH (10 mg) was added. The mixture was stirred for 15 h, and then triethylamine (0.5 mL) was added, and the solution was filtered through a pad of silica gel (2 g). The silica gel was washed with $Et_2O$ and the filtrates were evaporated. The residue was purified by chromatography on a silica gel column (50 g, hexanes/EtOAc, 15:1). The main fraction was distilled in a kugelrohr apparatus (160 °C/1.5 Torr) to give the thioester **24** (1.70 g, 60%): $[\alpha]_D^{22}$ = −9.6 (*c* = 2.2). HPLC analysis (Chiralcel OD column, 10% *t*BuOH in hexanes, showed enantiomeric ratio of 2.17:97.83 ($t_R$, 7.01 and 7.83 min) which corresponds to 95.7% *ee*. $^1H$ NMR: δ = 1.03 (s, 3 H, Me), 1.18 (s, 3 H, Me), 1.25 (s, 3 H, Me), 1.34 (s, 3 H, Me),1.40 (s, 9 H, $CMe_3$), 1.59−1.80 (m, 2 H, C3-H), 2.39−2.76 (m, 2 H, C2-H), 3.50−3.67 (m, 1 H, CHO−) ppm. $^{13}C$ NMR: δ = 22.8, 22.9 (C3), 25.8, 26.7, 28.4, 29.7 ($CMe_3$), 41.7 (C2), 47.8 ($CMe_3$), 80.0 (C4′), 82.(C5′), 106.7 (C2′), 199.6 (C1) ppm. $C_{14}H_{26}O_3S$ (274.42): calcd. C 61.27, H 9.55; found C 61.18, H 9.81.

**(1*E*)- and (1*Z*)-1-(*tert*-Butylthio)-3-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]-1-(trimethylsilyloxy)prop-1-ene (44):** The ketene acetal **44** was obtained as described above for its homologue using: diisopropylamine (0.84 mL, 6.42 mmol), BuLi (2.23 M in hexanes, 2.85 mL, 6.36 mmol) in THF (10 mL), then the thioester **24** (1.551 g, 5.66 mmol) in THF (4 mL) and then TMSCl (1.10 mL, 8.71 mmol). The crude product was distilled in a kugelrohr apparatus (210 °C/1.5 Torr) to give **44** (1.86 g, 95%) as a mixture of *E*:*Z* isomers in a ratio of 85:15 (as determined by integration of the $SCMe_3$ signals in the $^1H$ NMR spectrum). **(*E*) Isomer:** $^1H$ NMR: δ = 0.20 (s, 9 H, $SiMe_3$), 1.10 (s, 3 H, Me), 1.23 (s, 3 H, Me), 1.29 (s, 3 H, Me) 1.35 (s, 9 H, $CMe_3$), 1.38 (s, 3 H, Me), 2.21−2.62 (m, 2 H, C3-H), 3.62 (dd, *J* = 7.9, 5.6 Hz, 1 H, C4′-H), 5.25 (dd, *J* = 8.3, 6.4 Hz, 1 H, C2-H) ppm. $^{13}C$ NMR: δ = 0.3 ($SiMe_3$) 23.0, 26.2, 26.8, 28.5, 29.5 (C3), 31.7 ($CMe_3$), 46.3 ($CMe_3$), 79.4 (C2′), 82.9 (C4′), 116.4 (C5′), 115.9 (C2), 146.9 (C1) ppm. **(*Z*) Isomer:** $^1H$ NMR: δ = 0.22 (s, $SiMe_3$), 1.32 (s, $CMe_3$) ppm. $C_{17}H_{34}O_3SSi$ (346.60): calcd. C 58.91, H 9.89; found C 58.87, H 10.08.

***S*-*tert*-Butyl 3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]propanethioate (27):** Methyl 3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]propanoate[42,43] (**26**), $[\alpha]_D^{28}$ = −2.6 (*c* = 5.34) (97% *ee*) was transformed into **27** as described above for its homologues. The reagents were used as follows: **26** (6.5 g, 35 mmol) in dichloromethane (15 mL), trimethylaluminium (2 M solution in hexanes, 35 mL 70 mmol), *t*BuSH (7.9 mL, 70 mmol) and dichloromethane (50 mL). Thioester **27** was obtained (4.0 g, 47%): $[\alpha]_D^{28}$ = −1.15 (*c* = 4.84) (at least 97% *ee* by HPLC, Chiralcel OD-H column, hexanes/*i*PrOH, 320:1, $t_R$ **27** and its enantiomer 8.55 and 9.30 min, respectively). $^1H$ NMR: δ = 1.36 and 1.30 (2s, 6 H, $Me_2C$), 1.42 (s, 9 H, $Me_3C$), 1.85 (m, 2 H, C3-H), 2.54 (m, 2 H, C2-H), 3.49 (dt, *J* = 7.8, 1.1 Hz, 1 H, CHO−), 3.94−4.12 (m, 2 H, $CH_2O$−) ppm. $^{13}C$ NMR: δ = 25.62 and 26.91 ($Me_2C$). 29.11 (C3), 29.79 ($Me_3C$), 40.52 (C2), 47.91 ($CMe_3$), 69.0 (C5′), 74.82 (C4′), 108.85 (O−C−O), 199.40 (C=O) ppm. $C_{12}H_{22}O_3S$ (246.37): calcd. C 58.50, H 9.00; found C 58.31, H 9.02.

**(1*E*)- and (1*Z*)-1-(*tert*-Butylthio)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(trimethylsilyloxy)prop-1-ene (58):** A solution of LDA in THF was prepared from BuLi (2.2 M in hexanes, 2.47 mL, 5.44 mmol) and $(iPr)_2NH$ (0.77 mL, 5.5 mmol) in THF (6 mL) and cooled to −78 °C. A solution of the thioester **27** (1.0 g, 4.07 mmol) in THF (2 mL) was added, followed, after 45 min, by $Me_3SiCl$ (0.86 mL, 6.8 mmol). The mixture was left at room temperature for 12 h. The solvent was evaporated, and the residue was dissolved in hexanes (30 mL) and filtered through a pad of Celite (2 g). The filtrate was concentrated and the residue was distilled in a kugelrohr apparatus (150 °C/0.1 Torr) to give the ketene acetal **58** (1.09 g, 84% yield) as a mixture of (*E*) and (*Z*) isomers in a ratio of 82:18 (as determined by integration of the $SCMe_3$ signals in the $^1H$ NMR spectrum). $^1H$ NMR: δ = 0.20 (s, 9 H, $SiMe_3$), 1.33 (s, 3 H, C2′-Me), 1.34 (s, 9 H, $CMe_3$), 1.40 (s, 3 H, C2′-Me), 2.50 (m, 2 H, C3-H), 3.56 (m, 1 H, CHO−), 4.0 (m, 2 H, $CH_2O$−), 5.17 (t, *J* = 7.5 Hz, 1 H, C2-H) ppm. $^{13}C$ NMR: δ = 0.32 ($SiMe_3$) 25.67 and 26.87 ($O_2CMe_2$), 31.74 ($CMe_3$), 33.13 (C3), 46.72 ($CMe_3$), 68.65 (C5), 75.68 (C4), 108.69 (O−C−O), 114.27 (C2), 147.64 (C1) ppm. **(*Z*)-Isomer:** $^1H$ NMR: δ = 0.19 (s, 9 H, $SiMe_3$), 1.32 (s, 9 H, $CMe_3$) ppm. $^{13}C$ NMR: δ = 0.83 ($SiMe_3$), 31.11 ($CMe_3$), 31.40 ($CMe_3$), 46.0, 69.03 (C5′), 75.18 (C4′), 118.9 (C2), 145.50 (C1) ppm.

***S*-*tert*-Butyl (2*R*)-[(1*R*,2*R*)-3-Oxo-2-(3-oxo-4-phenylthiobutyl)cyclopentyl]-4-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]butanethioate (29) and *S*-*tert*-Butyl (2*S*)-[(1*S*,2*S*)-3-Oxo-2-(3-oxo-4-phenylthiobutyl)cyclopentyl]-4-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]butanethioate(30):** A solution of **28** (984 mg, 2.73 mmol) in dichloromethane (3 mL) was added to a solution of 2-methyl-2-cyclopent-

1-one (**10**) (0.29 mL, 2.96 mmol) and $TrSbCl_6$ (107 mg, 0.19 mmol, 7%) in dichloromethane (10 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h, and then a solution of 1-(phenylthio)but-3-en-2-one (**9**) (534 mg, 3.00 mmol) in dichloromethane (2 mL) was added. Stirring at −78 °C was continued for 3 h, then the mixture was warmed to room temperature, and, after 30 min, the reaction was quenched with water (0.5 mL). $Na_2SO_4$ (5 g) was added, and the mixture was filtered through a pad of Celite. The solvent was evaporated, and the residue was purified by chromatography on silica gel (140 g, hexanes/EtOAc, 30:1, 3:1) to give a mixture of **29** and **30** (850 mg, 55%) as an oil. The ratio of isomers **30** ($t_R$, 23.38 min) and **29** ($t_R$, 24.11 min) was determined to be 24:76 by HPLC (Nucleosil 50:5µm, hexanes/EtOAc, 83:17). After a few days, the mixture partly crystallized. Cold methanol was then added, and crystals were collected. Recrystallization of this material from methanol gave **29** (410 mg); m.p. 103 °C. $[\alpha]_D^{22}$ = +8.4 (*c* = 2.0). IR (film): $\tilde{\nu}$ = 1741, 1703, 1676 $cm^{-1}$. $^1H$ NMR: δ = 0.99 (s, 3 H, Me), 1.07 (s, 3 H, Me), 1.22 (s, 3 H, Me), 1.32 (s, 3 H, Me), 1.40 (s, 9 H, $CMe_3$), 1.41 (s, 3 H, Me), 3.64 (s, 2 H, $CH_2$−S), 3.51−3.68 (m, 1 H, CHO−), 7.12−7.39 (m, 5 H, SPh) ppm. $^{13}C$ NMR: δ = 18.6, 22.8, 22.9, 26.0, 26.8, 28.4, 29.1, 29.4 ($CMe_3$), 35.7, 36.5, 43.5, 43.9, 48.8, 51.1, 54.4, 80.0, 83.3, 106.6 (O−C−O), 126.6, 128.9 (2 C-*m*), 129.7 (2 C-*o*), 134.8, 203.3, 204.3, 221.0 ppm. $C_{31}H_{46}O_5S_2$: calcd. C 66.16, H 8.24; found C 66.15, H 8.33.

**X-ray Analysis:** A sample was crystallized from methanol, initially at 20 °C and then at 0 °C. A colorless crystal measuring 0.035 × 0.28 × 0.7 mm was used. Crystal data: monoclinic, space group $P2_1$, *a* = 11.1535, *b* = 6.353(1), *c* = 22.036(4) Å, β = 96.79(1)°, *V* = 1603.5(5) Å$^3$, *Z* = 2, $d_{calcd.}$ = 1.17 g/cm$^3$. Diffraction data were collected using an MCH3 diffractometer, Cu-$K_\alpha$ radiation, ω/2θ scan mode to $\theta_{max.}$ = 64.5°. The structure was solved using direct method program SHELXs.[59] The program SELXL-93[60] was used for refinement of the structure, which converged to $R_1$ = 0.0419, $wR_2$ = 0.1054 for reflection with [$I \geq \sigma(I)$], and $R_1$ = 0.0445, $wR_2$ = 0.1149, and GoodF = 1.05 for all 2134 data and 343 variables.

Crystallographic data for **29** has been deposited with the Cambridge Crystallographic Data Centre, the deposition No. CCDC-219369. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK. Fax: (internat.) +44(0)-1223-336033 or E-mail: deposit@ccdc.cam-.ac.uk. CD measurements, vide infra.

After crystallization of **29**, the mother liquors were evaporated. A crystalline material was collected and identified as a 1:1 mixture of **29** and **30**, m.p. 69−70 °C.
**30:** $^1H$ NMR: δ = (resolved signals) 1.26 (s, 3 H, Me), 1.34 (s, 3 H, Me), 3.61−3.71 (m, 1 H, CHO−) ppm. $^{13}C$ NMR: δ = 42.8, 53.4 ($CMe_3$), 82.2, 202.4 ppm.

***S*-*tert*-Butyl (2*R*)-2-[(1*R*,7a*R*)-7a-Methyl-5-oxo-4-phenylthio-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]-4-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]butanethioate (31):** KOH in methanol (30%, 0.5 mL) was added to a solution of **29** (610 mg, 1.09 mmol) in methanol (20 mL). The mixture was set aside at room temperature for 1 h, and the solvent was evaporated. The residue was purified by chromatography on silica gel (100 g, hexanes/EtOAc, 30:1, 10:1, 4:1) to give **31** (500 mg, 84%): $[\alpha]_D^{22}$ = +40.5 (*c* = 2.0). $^1H$ NMR: δ = 1.03 (s, 3 H, Me), 1.17 (s, 3 H, Me), 1.19 (s, 3 H, Me), 1.27 (s, 3 H, Me), 1.36 (s, 3 H, Me), 1.44 (s, 9 H, $CMe_3$), 2.38−2.85 (m, 5 H), 3.50−3.60 (m, 1 H, CHO−), 6.98−7.21 (m, 5 H, SPh) ppm. $^{13}C$ NMR: δ = 16.5, 22.8, 25.9, 26.0, 26.6, 26.7, 28.4, 29.4 ($CMe_3$), 30.0, 30.3, 33.9, 34.4, 47.1, 48.6, 52.4, 54.3, 79.9 (C5′′), 83.2 (C4′′), 106.5 (O−C−O), 125.1 (C4′), 125.3 (C-*p*), 127.0 (2C-*m*), 128.5 (2C-*o* ), 135.9 (C-*ipso*), 184.8 (C3′a), 193.3 (C5′), 203.1 (C1) ppm. HRMS calcd. for $C_{28}H_{40}O_4S_2$ [$M^+$]: 544.269562; found 544.268098. Calcd. for $C_{28}H_{38}O_3S_2$ [M − Me]$^+$: 486.22623; found 529.244623.

**(3*R*)-3-[(1*R*,3a*R*,4*R*,7a*R*)-7a-Methyl-4-(phenylsulfonyl)octahydro-1*H*-inden-1-yl]-1-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]butane (35):** a. DIBALH (1 M in hexanes, 4.5 mL) was added to a solution of **31** (410 mg, 0.75 mmol) in dichloromethane (15 mL) at −78 °C. The mixture was stirred at room temperature for 5 h, and poured into 10% tartaric acid. The product was extracted with dichloromethane. The solvent was evaporated. The residue was dissolved in dichloromethane (10 mL), and triethylamine (2 mL) and DMAP (20 mg) were added. The solution was cooled to −25 °C, and TsCl (432 mg, 2.26 mmol) in dichloromethane (2 mL) was added dropwise. The mixture was stirred at room temperature for 9 h, and the solvent was evaporated. The residue was purified by chromatography on silica gel (30 g, hexanes/EtOAc, 10:1, 4:1). Fractions with $R_f$ = 0.25−0.5 (TLC, hexanes/EtOAc, 1:1) were collected. This product was dissolved in dichloromethane (12 mL), and the solution was cooled to 0 °C. *m*CPBA (70%, 450 mg, 1.83 mmol) was added, and the mixture was stirred at room temperature for 1 h, and then poured into 10% $Na_2S_2O_3$. The product was extracted with dichloromethane. The extract was washed with water and the solvent was evaporated. The residue was dissolved in THF (5 mL), and $LiAlH_4$ (1 M in THF, 7 mL, 7.00 mmol) was added. The solution was heated at the reflux temperature for 25 min. After cooling, methanol (2 mL) was added, and the mixture was poured into 10% tartaric acid. The product was extracted with dichloromethane. The extract was washed with water and dried. The solvent was evaporated and the residue was purified by chromatography on silica gel (6 g). Elution with hexanes/EtOAc, 20:1, 5:1 gave compound **35** (125 mg, 36%). Further elution with hexanes/EtOAc, 3:1 afforded **36** (56 mg, 16%). **35:** M.p. 57−58 °C (pentane). $[\alpha]_D^{27}$ = +3.4 (*c* = 1.0). $^1H$ NMR: δ = 0.68 (s, 3 H, C7′a-*Me*), 0.92 (d, *J* = 6.4 Hz, 3 H, C4-H), 1.06 (s, 3 H, Me), 1.22 (s, 3 H, Me), 1.30 (s, 3 H, Me), 1.38 (s, 3 H, Me), 3.01 (br. td, 1 H, *J* = 11.3, 3.1 Hz, CH−$SO_2$), 3.54−3.63 (m, 1 H, CHO−), 7.46−7.68 (m, 3 H, H-*o* and -*p* Ph), 7.78−7.91 (m, 2 H, H-*m* Ph) ppm. $^{13}C$ NMR: δ = 11.8 (C7′a-*Me*), 18.6, 21.1, 22.8, 25.3, 25.8, 26.2, 26.8, 27.3, 27.8, 28.5, 32.8, 35.5, 38.7, 44.6 (C3′a), 48.1, 54.8, 63.7, 80.0 (C4′′), 83.9 (C5′′), 106.2 (O−C−O), 128.6 (C-*o*), 128.9 (C-*m*), 133.3 (C-*p*), 138.3 (C-*ipso*) ppm. MS EI (70): *m*/*z* (%) = 447 (85) [M − Me]$^+$, 405 (6), 263 (61), 245 (100), 135 (45), 109 (42), 95 (50). $C_{27}H_{42}O_4S$ (462.70): calcd. C 70.09, H 9.15; found C 70.10, H 9.40.

**(3*S*,6*R*)-3-Isopropoxy-2-methyl-6-[(1*R*,3a*R*,4*R*,7a*R*)-7a-methyl-4-(phenylsulfonyl)octahydro-1*H*-inden-1-yl)heptan-2-ol (36):** M.p. 119 °C (benzene/pentane, 1:5). $[\alpha]_D^{25}$ = +10.3 (*c* = 1.0). IR (film): $\tilde{\nu}$ = 3580, 1149 $cm^{-1}$. $^1H$ NMR: δ = 0.66 (s, 3 H, C7′a-Me), 0.88 (d, *J* = 6.4 Hz, 3 H, C7-H), 1.13 (d, *J* = 6.1 Hz, 6 H, O-CH$Me_2$), 1.14 (s, 6 H, C$Me_2$OH), 2.15−2.45 (br. s, 1 H, O*H*), 2.85−3.18 (m, 2 H, CHO− and $CHSO_2$), 3.67 (sept., 1 H, *J* = 6.1 Hz, O−C*H*$Me_2$), 7.45−7.66 (m, 3 H, H-*o* and -*p* Ph), 7.74−7.92- (m, 2 H, H-*m* Ph) ppm. $^{13}C$ NMR: δ = 11.8 (C7′a-*Me*), 18.7, 21.0, 22.4, 23.2, 24.6, 25.3, 26.7, 27.2, 27.8, 28.0, 33.3, 35.9, 38.6, 44.5 (C3′a), 48.0, 54.8, 63.6, 71.8, 72.9 (O−*C*H$Me_2$), 84.4 (C2), 128.6 (C-*o* ), 128.8 (C-*m*), 133.3 (C-*p*), 138.2 (C-*ipso*) ppm. $C_{27}H_{44}O_4S$ (464.71): calcd. C 69.79, H 9.54; found C 69.86, H, 9.65.

b. *m*CPBA (70%, 953 mg, 3.870 mmol) was added to a solution of tosylate **37** (792 mg, 1.290 mmol) in dichloromethane (20 mL) at 0 °C. The mixture was stirred at room temperature for 2 h, and then poured into saturated aqueous $NaHCO_3$. The product was ex-

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tracted with dichloromethane (3 × 15 mL). The organic extract was washed with saturated aqueous $Na_2SO_3$ and water, and the solvent was evaporated. The residue was dissolved in THF (25 mL), and $LiAlH_4$ (343 mg, 9.030 mmol) was added. The mixture was heated under reflux for 20 min. After cooling, methanol (4.5 mL) was added, and then the mixture was poured into 10% aqueous tartaric acid. The product was extracted with dichloromethane (3 × 15 mL). The organic extract was evaporated and the residue was purified by chromatography on silica gel (100 g, hexanes/EtOAc, 20:1, 3:1). Sulfone **35** was obtained (429 mg, 72%), which was identical to the sample described above.

c. $LiAlH_4$ (97 mg, 2.663 mmol) was added to a solution of enone **31** (279 mg, 0.513 mmol) in THF (10 mL). The mixture was heated under reflux for 40 min, then cooled, and the reaction was quenched with methanol (1 mL). Workup with 10% tartaric acid solution and extraction with dichloromethane (3 × 15 mL) gave the crude product, which was purified by chromatography on silica gel (100 g, hexanes/EtOAc, 20:1, 2:1) to give the diol **32** (172 mg, 73%) and the diol **33** (35 mg, 15%), identical to the respective samples prepared by other methods (vide infra). The crude product from an analogous reduction (340 mg, 0.783 mmol) was added to a dichloromethane (4 mL) solution of triethylamine (1.5 mL) and DMAP (10 mg). The solution was cooled to −20 °C, and TsCl (187 mg, 0.981 mmol) in dichloromethane (1 mL) was added. The mixture was stirred at room temperature for 12 h, and then poured into water. The product was isolated by extraction with dichloromethane and purified by chromatography on silica gel (30 g, hexanes/EtOAc, 10:1, 4:1) to give tosylates **37** and its epimer (418 mg, 87%) in a ratio of 5:1 (determined by $^1$H NMR spectroscopy). This product was dissolved in dichloromethane (10 mL). The solution was cooled to 0 °C and *m*CPBA (70%, 503 mg, 2.043 mmol) was added. The mixture was stirred at room temperature for 1 h, and then poured into aqueous $NaHCO_3$. The product was isolated by extraction with dichloromethane, dissolved in THF (12 mL) and treated with $LiAlH_4$ (152 mg, 4.00 mmol). The mixture was heated under reflux for 25 min, then cooled, and the reaction was quenched with methanol (2 mL). Work-up as described above gave the crude product which was purified by chromatography on silica gel (6 g, hexanes/EtOAc, 20:1, 5:1) to give sulfone **35** (219 mg, 70%), identical to the sample described above.

**(3*R*)-4-Hydroxy-3-[(1*R*,5*S*,7a*R*)-5-hydroxy-7a-methyl-4-(phenylsulfonyl)-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]-1-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]butane (32) and (3*R*)-4-Hydroxy-3-[(1*R*,5*R*,7a*R*)-5-hydroxy-7a-methyl-4-(phenylsulfonyl)-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]-1-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]butane (33):** Powdered $NaBH_4$ (114 mg, 3.000 mmol) was added to a stirred solution of the enone **31** (1.386 g, 2.548 mmol) and $CeCl_3 \cdot 7H_2O$ (559 mg, 1.500 mmol) in methanol (20 mL) and THF (10 mL) at −78 °C. After 1 h, the mixture was warmed to room temperature, stirred for an additional 1 h and then poured into 10% aqueous tartaric acid. The product was extracted with dichloromethane (3 × 25 mL). The extract was washed with water, dried, and the solvent was evaporated. The residue was dissolved in THF (12 mL), and a solution of $LiAlH_4$ (494 mg, 13.00 mmol) in THF (15 mL) was added. The mixture was heated under reflux for 30 min. After cooling, methanol (2.5 mL) was added, and the mixture was poured into 10% aqueous tartaric acid. The product was extracted with dichloromethane (3 × 20 mL). The extract was washed with water and dried, and the solvent was evaporated. The residue was purified by chromatography on silica gel (350 g, hexanes/EtOAc, 20:1, 2:1) to give the diol **33** (61 mg, 5%) and diol **32** (1.022 mg, 87%).

**33:** M.p. 112 °C (benzene/hexanes, 1:1). $[\alpha]_D^{27}$ = +203.7 (*c* = 1.0). $^1$H NMR: δ = 1.03 (s, 3 H, C7′a-Me), 1.10 (s, 3 H, Me), 1.25 (s, 3 H, Me), 1.33 (s, 3 H, Me), 1.41 (s, 3 H, Me), 2.24 (br. s, 1 H, O*H*), 2.35−2.76 (m, 4 H), 3.57−3.83 (m, 3 H, C4′′- and C4-H), 3.93−4.04 (br. s, 1 H, C5′-H), 7.09−7.37 (m, 5 H, SPh) ppm. $^{13}$C NMR: δ = 17.2 (C7′a-*Me*), 22.9 (3), 25.2 (2),. 25.6 (2), 26.0 (3), 26.0 (2), 26.8 (3), 27.8 (2), 27.9 (2), 28.5 (3), 30.9 (2), 35.1 (2), 41.0 (3), 46.0 (C7′), 50.6 (C3), 62.4 (C4), 66.1 (C5′), 80.2 (C3), 83.9 (C1), 106.4 (O−C−O), 122.3 (C4′), 125.5 (C-*p*), 127.6 (C-*m*), 128.9 (C-*o*), 135.8 (C-*ipso*), 162.5 (C3′a) ppm. MS EI (70): *m*/*z* (%) = 460 (100) $[M^+]$, 445 (43) $[M - CH_3]^+$, 427 (4) $[M - CH_3 - H_2O]^+$, 383 (49), 351 (16), 257 (24), 171 (32), 85 (3). $C_{27}H_{40}O_4S$ (460.68): calcd. C 70.40, H 8.74; found C 70.27, H 8.75.

**32:** $[\alpha]_D^{26}$ = −85.3 (*c* = 2.7). $^1$H NMR: δ = 1.06 (s, 3 H, C7′a-Me), 1.08 (s, 3 H, Me), 1.23 (s, 3 H, Me), 1.31 (s, 3 H, Me), 1.39 (s, 3 H, Me), 2.73 (br. s, 1 H, O*H*), 3.56−3.77 (m, 3 H, C4- and C4′′-H), 4.00−4.15- (m, 1 H, C5′-H), 7.06−7.30 (m, 5 H, SPh) ppm. $^{13}$C NMR: δ = 17.9 (C7′a-Me). 22.8 (3), 25.6 (2), 26.0 (3), 26.1 (2), 26.2 (2), 26.8 (3), 28.3 (2), 28.3 (2), 28.5 (3), 35.1 (2), 41.0 (3), 46.0 (C7′a), 50.8 (C6), 62.5 (C7′), 67.8 (C5′), 80.1 (C2), 83.8 (C1), 106.4 (O−C−O), 124.1 (C4′), 125.6 (C-*p*), 127.5 (C-*m*), 128.9 (C-*o*), 134.9 (C-*ipso*), 162.2 (C3′a) ppm. MS EI (70): *m*/*z* (%) = 460 (100) $[M^+]$, 445 (39) $[M - CH_3]^+$, 427 (3) $[M - CH_3 - H_2O]^+$, 383 (46), 257 (17), 171 (21), 85 (53). HRMS calcd. for $C_{27}H_{40}O_4S$ $[M^+]$: 460.26473; found 640.26543.

**(3*R*)-3-[(1*R*,5*S*,7a*R*)-5-Hydroxy-7a-methyl-4-(phenylsulfonyl)-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]-1-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]-4-tosyloxybutane (37):** Diol **32** (830 mg, 1.804 mmol) and DMAP (15 mg) were dissolved in a mixture of dichloromethane (7.5 mL) and triethylamine (2.5 mL), and cooled to −20 °C. A solution of TsCl (477 mg, 2.435 mmol) in dichloromethane (5 mL) was added. The mixture was stirred at 0 °C for 12 h, and then at room temperature for 6 h, and then poured into water. The product was extracted with dichloromethane (3 × 15 mL). The extract was washed consecutively with 3.5% aqueous HCl, saturated aqueous $NaHCO_3$ and water, and then dried. The solvent was evaporated, and the residue was purified by chromatography on silica gel (100 g, hexanes/EtOAc, 10:1, 2:1). Tosylate **37** was obtained (986 mg, 89%): $[\alpha]_D^{24}$ = −58.6 (*c* = 2.18). $^1$H NMR: δ = 0.96 (s, 3 H, Me), 0.97 (s, 3 H, Me), 1.16 (s, 3 H, Me), 1.28 (s, 3 H, Me), 1.36 (s, 3 H, Me), 2.42 (s, 3 H, Ph-*Me*), 2.65 (s, 1 H, OH), 3.44−3.55 (m, 1 H, C4′′-H), 3.94−4.18 (m, 3 H, C4- and C5′-H), 7.09−7.32 (m, 5 H, SPh), 7.33 (d, *J* = 8.2 Hz, 2 H, H-*m* Ts), 7.79 (d, *J* = 8.2 Hz, 2 H, H-*o* Ts) ppm. $^{13}$C NMR: δ = 17.8 (C7′a-*Me*), 21.6 (3), 22.6 (3), 25.9 (3), 26.0 (2), 26.1 (2), 26.7 (2), 26.8 (3), 28.1 (2), 28.2 (2), 28.5 (3), 34.8 (2), 38.5 (1), 45.9 (C7′a), 50.3 (1), 67.4 (C4), 70.0 (C5′), 79.9 (C5′′), 83.5 (C4′′), 106.4 (O−C−O), 124.7 (C4), 125.7 (C-*p*, Ph), 127.6 (C-*m*, Ph or Ts), 127.9 (C-*m*, Ts or Ph), 129.0 (C-*o* , Ph), 129.7 (C-*o* , Ts), 132.6 (C-*p*, Ts), 134.7 (C-*ipso*, Ph), 144.8 (C-*ipso*, Ts), 161.1 (C3′a) ppm. MS EI (70): *m*/*z* (%) = 614 (19) $[M^+]$, 599 (9) $[M - CH_3]^+$, 581 (2) $[M - CH_3 - H_2O]^+$, 307 (8), 257 (17), 43 (100). HRMS calcd. for $C_{34}H_{46}O_6S_2$ $[M^+]$: 614.27358; found 614.27378.

**(3*S*,6*R*)-2-Methyl-6-[(1*R*,3a*R*,4*R*,7a*R*)-7a-methyl-4-(phenylsulfonyl)octahydro-1*H*-inden-1-yl)heptane-2,3-diol (38):** Amberlyst-15H® (500 mg) was added to a solution of **35** (120 mg, 0.26 mmol) in methanol (5 mL), and the mixture was stirred at room temperature for 48 h. After this time, the solid was filtered off. The filtrate was concentrated, and the residue was purified by chromatography on silica gel (5 g, hexanes/acetone, 10:1, 3:1) to give **38** (89 mg, 81%): m.p. 141 °C (benzene/hexane, 1:2). $[\alpha]_D^{26}$ = −13.9 (*c* = 0.6). $^1$H NMR: δ = 0.65 (s, 3 H, C7′a-Me), 0.88 (d, *J* = 6.5 Hz, 3 H,

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C7-H), 1.10 (s, 3 H, Me), 1.16 (s, 3 H, Me), 2.42 (br. s, 1 H, −OH), 2.61 (br. s, 1 H, −OH), 3.00 (br. td, $J$ = 11.4, 3.2 Hz, CH−$SO_2$), 3.22 (br. d, $J$ = 8.3 Hz, 1 H, CHO−), 7.46−7.66 (m, 3 H, H-*o* and -*p* Ph), 7.76−7.92 (m, 2 H, H-*m* Ph) ppm. $^{13}$C NMR: δ = 11.8, 18.8, 21.0, 23.1, 25.2, 26.4, 27.2, 27.8, 28.0, 33.1, 35.6, 38.7 (C7′a) 44.5, 48.0, 54.8, 63.6, 73.0 (C2), 79.2 (C3), 128.5 (C-*m*), 128.8 (C-*o* ), 133.3 (C-*p*), 138.1 (C-*ipso*) ppm. $C_{24}H_{38}O_4S$ (422.63): calcd. C 68.21, H, 9.06; found C 68.37, H, 8.94.

**(6*R*)-2-Methyl-6-[(1*R*,3a*R*,4*R*,7a*R*)-7a-methyl-4-(phenylsulfonyl)octahydro-1*H*-inden-1-yl)heptan-2-ol (8):** MsCl (0.042 mL, 0.540 mmol) was added to a stirred solution of the diol **38** (180 mg, 0.427 mmol) and triethylamine (1.5 mL) in dichloromethane (10 mL) at −20 °C. After 1 h, the mixture was poured into water, and the product was extracted with dichloromethane. The extract was washed consecutively with water, 3% HCl and water. The solvent was evaporated. The residue was dissolved in THF (10 mL), and $LiAlH_4$ (228 mg, 6.00 mmol) was added. The mixture was heated under reflux for 30 min. After cooling, the reaction was quenched with methanol (4 mL), and the mixture was poured into 10% tartaric acid. The product was extracted with dichloromethane. The extract was washed with water and the solvent was evaporated. The residue was purified by chromatography on silica gel (20 g, hexanes/EtOAc, 20:1, 5:1) to give **8** (151 mg, 87%), identical with the authentic sample ([α], m.p., NMR).

***S*-*tert*-Butyl (2*R*,5*S*)-5,6-Dihydroxy-6-methyl-2-[(1*R*,7a*R*)-7a-methyl-4-(phenylthio)-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]-heptanethioate and *S*-*tert*-Butyl (2*S*,5*S*)-5,6-Dihydroxy-6-methyl-2-[(1*S*,7a*S*)-7a-methyl-4-(phenylthio)-5-oxo-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]heptanethioate (39):** A mixture of **29** and **30** (1:1, mother liquors after crystallization of **29**, see above)(181 mg, 0.322 mmol) was dissolved in methanol (10 mL), and KOH (30% in methanol, 0.3 mL) was added. After 1 h, 36% HCl (0.5 mL) was added, and the mixture was set aside for 15 h. After this time, the bulk of the solvent was evaporated. The residue was filtered through silica gel (10 g, hexanes/EtOAc, 1:1) to give a mixture of enones **39** (114 mg, 70%). $^1$H NMR: δ = 1.11 (s, 3 H, Me), 1.19 (s, 1.5 H, Me), 1.14 (s, 1.5 H, Me), 1.45 (s, 9 H, C*Me*$_3$), 1.21 (s, 3 H, Me), 2.40−2.88 (m, 5 H), 3.18−3.47 (m,1 H, C5-H), 6.96−7.24 (m, 5 H, SPh) ppm. $^{13}$C NMR: δ = 16.5 (split), 23.0 and 23.1 25.9, 26.0, 26.5, 27.7, 28.7, 29.1, 29.5 (C*Me*$_3$), 30.1, 30.5, 34.0, 34.5, 47.2, 48.7 and 48.8, 52.2 and 52.5, 53.4 and 54.6, 73.0 and 73.1 (C6), 77.2 and 78.6 (C5), 125.1 (C4′), 125.4 (C-*p*), 127.1 (2C-*m*), 128.8 (2C-*o* ), 135.9 (C-*ipso*), 185.4 (C3′a), 193.8 (C5′), 203.1 and 203.6 (C1) ppm. HRMS calcd. for $C_{28}H_{40}O_4S_2$ [$M^+$]: 504.23679; found 504.23746. Calcd. for $C_{28}H_{38}O_3S_2$ [$M - H_2O$]$^+$: 486.22623; found 486.22617.

**Transformation of 39 into *rac*-8:** The product described above (**39**) (114 mg, 0.23 mmol) was dissolved in dichloromethane (8 mL) and cooled to −78 °C, and DIBALH (1 M in hexanes, 3 mL, 3 mmol) was added. The mixture was stirred at room temperature for 12 h, and then poured into 10% tartaric acid. The product was extracted with dichloromethane (5 × 10 mL). The extract was washed with brine and the solvent was evaporated. The so-obtained crude tetrol was dissolved in a mixture of dichloromethane (3.5 mL) and triethylamine (0.1 mL, 0.712 mmol). The solution was cooled to −20 °C, and MsCl (0.04 mL, 0.515 mmol) was added. Stirring was continued for 30 min and then the mixture was poured into water. The product was extracted with dichloromethane. The extract was washed with 1%HCl and water, and concentrated to ca. 5 mL. This solution was cooled to 0 °C, and *m*CPBA (70%, 223 mg, 0.905 mmol) was added. The mixture was stirred at room temperature for 45 min, and then poured into 10% $Na_2S_2O_3$. The product was extracted with dichloromethane. The extract was washed with water and the solvent was evaporated. The residue was dissolved in THF (5 mL), and $LiAlH_4$ (1 M in THF, 7 mL) was added. The solution was heated under reflux for 25 min. After cooling, methanol (1.5 mL) was added, and the mixture was poured into 10% tartaric acid. The product was extracted with dichloromethane. The extract was washed with water and dried. The solvent was evaporated and the residue was purified by chromatography on silica gel (6 g, hexanes/EtOAc, 20:1, 5:1) to give *rac*-**8** (24 mg, 26% from **39**). This product was identical with a sample prepared before ($^1$H and $^{13}$C NMR spectra) but showed no measurable optical rotation.

**(3*S*,6*S*)-6-*tert*-Butyldimethylsilyloxy-7,7-dimethyl-3-[(1*S*,2*R*)-2-methyl-3-oxocyclopentyl]oxepan-2-one (42) and (3*S*,6*S*)-6-*tert*-Butyldimethylsilyloxy-7,7-dimethyl-3-[(1*S*,2*S*)-2-methyl-3-oxocyclopentyl]oxepan-2-one (43):** Ketene acetal **40** (670 mg, 1.79 mmol) was added to a stirred solution of **10** (0.210 mL, 2.14 mmol) and $TrSbCl_6$ (87 mg, 0.15 mmol) in dichloromethane (6 mL) at −78 °C. After 1 h, the reaction was quenched with pyridinemethanol (0.250 mL). The mixture was warmed to room temperature, and water (0.5 mL) and Amberlyst-15H (500 mg) were added. After 48 h, the mixture was filtered through a pad of Celite and $Na_2SO_4$. The solvent was evaporated and the residue was purified by chromatography on silica gel (80 g, hexanes/EtOAc, 25:1, 4:1). A mixture of isomers **42**, **43** and an undefined diastereomer was obtained as a colourless oil (476 mg, 69%): MS EI (70): *m*/*z* (%) = 368 (0.8), 353 (2), 311 (58), 253 (100), 215 (48), 173 (46), 117 (64), 97 (72), 75 (99). HRMS calcd. for $C_{20}H_{36}O_4Si$ [$M^+$]: 368.23829; found 368.23871. Calcd. for $C_{16}H_{27}O_4Si$ [$M^+ - t$Bu]: 311.16786; found 311.16778. $^1$H NMR (500 MHz): δ = 0.90 (d, $J$ = 7.4 Hz), 0.98 (d, $J$ = 6.5 Hz), 0.99 (d, $J$ = 6.9 Hz) ppm, of relative integration 80:12:8.

After standing for a few weeks in a refrigerator, the product solidified. Pentane was added, crystals were collected and recrystallized from pentane. Product **42** was obtained: m.p. 104−105 °C. $[\alpha]_D^{27}$ = −29.9 ($c$ = 0.6). $^1$H NMR: δ = −0.01 (s, 3 H, $SiMe_2$), 0.00 (s, 3 H, $SiMe_2$), 0.83 (s, 9 H, $SiCMe_3$), 0.99 (d, $J$ = 6.9 Hz, 3 H, C2′-Me), 1.34 (s, 3 H, Me), 1.43 (s, 3 H, Me), 3.66−3.75 (m, 1 H, C6-H) ppm. $^{13}$C NMR: δ = −5.2 (Si*Me*), −4.4 (SiMe), 13.7 (3), 17.9 (Si*C*Me$_3$), 21.4 (2), 23.2 (2), 24.4 (3), 25.6 (SiC*Me*$_3$), 28.9 (3), 30.8 (2), 36.8 (2), 46.1 (1), 46.7 (1), 47.6 (1), 73.6 (C6), 82.9 (C7), 173.7 (C2), 220.3 (C3′) ppm. $C_{20}H_{36}O_4Si$ (368.59): calcd. C 65.17, H 9.84; found C 65.16, H 9.88. X-ray analysis has been reported[53]

**Isomer 43:** $^1$H NMR: δ = 0.99 (d, $J$ = 6.9 Hz, C2′-Me) ppm. $^{13}$C NMR: δ = 73.9 (C6), 174.6 (C2). **Minor Isomer:** $^1$H NMR: δ = −0.02 (s), 0.00 (s), 0.90 (d, $J$ = 7.4 Hz, C2′-Me), 1.47 (s). $^{13}$C NMR: δ = 73.6, 82.6, 174.2 (C2) ppm.

***S*-*tert*-Butyl (2*S*)-[(1*S*,2*S*)--3-Oxo-2-(3-oxo-4-phenylthiobutyl)cyclopentyl]-3-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]propanethioate (45):** A solution of the ketene acetal **44** (4.58 g, 13.2 mmol) in dichloromethane (6 mL) was added dropwise to a stirred solution of **10** (1.47 g, 15.3 mmol) and $TrSbCl_6$ (415 mg, 0.72 mmol) in dichloromethane (30 mL) at −78 °C. After 1 h, **9** (2.2 g, 12.3 mmol) was added. The mixture was stirred at −78 °C for 1 h, and then warmed to room temperature (over ca. 1 h). The reaction was quenched with 10% aqueous $NaHCO_3$ (2 mL). The mixture was diluted with hexanes (30 mL) and filtered through a pad of Celite. The Celite was washed with dichloromethane, and the combined filtrates were evaporated. The residue was purified by chromatography on silica gel (250 g, hexanes/EtOAc, 4:1, 3:1) to give dione **45**, along with two of its diastereomers (5.45 g, 75% yield, isomer ratio: 85:11:4 by HPLC, Nucleosil 50:5 μm, hexanes/EtOAc, 3.4:1, $t_R$

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11.3, 10.2, and 9.7 min). A sample of **45** was isolated by preparative TLC (hexanes:EtOAc, 30:1, 5 developments): $[\alpha]_D^{22} = -8.2$ ($c$ = 1.5). $^1$H NMR: δ = 1.05 (s, 3 H, Me) 1.07 (s, 3 H, Me), 1.19 (s, 3 H, Me), 1.36 (s, 3 H, Me), 1.43 (s, 9 H, $CMe_3$), 1.44 (s, 3 H, Me), 3.65 (s, 2 H, C*H*−SPh), 3.71−3.86 (m, 1 H, CHO−), 7.12−7.41 (m, 5 H, Ph) ppm. $^{13}$C NMR: δ = 18.4, 22.2, 22.6, 25.0, 26.3, 28.2, 28.8, 29.1 (C*Me*$_3$), 31.3, 35.5, 36.0, 43.3, 43.5, 48.5 (*C*Me$_3$), 51.0, 51.2, 78.7 (C*C*Me$_2$O−), 79.6 (*C*HO−), 106.5 (O−C−O), 126.3 (C-*p*), 128.7 (C-*m*), 129.3 (C-*o*), 134.6 (C-*ipso*), 203.2, 203.9, 220.7 ppm. HRMS calcd. for $C_{30}H_{44}O_5S_2$ [M$^+$]: 548.26302; found 548.26535.

To **46** (tentative structure, $t_R$ = 10.2 min) the following signal were assigned. $^1$H NMR: δ = 1.34, 1.27, 1.39 ppm. $^{13}$C NMR: δ = 48.3 (*C*Me$_3$), 53.2, 79.8, 80.6, 106.0 (O−C−O), 201.2 ppm.

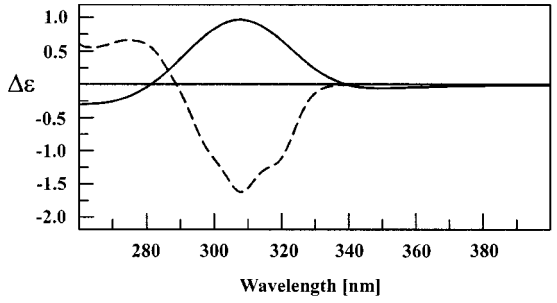


Figure 2. CD spectra of **45** (solid line) and **29** (dashed line)

An analogous reaction in which racemic ketene acetal **44** was used (prepared from 2,2-dimethylcyclopentan-1,3-dione[61]) afforded a mixture of racemic diketones **45** and **46** in a ratio of 8:1. *rac*-**45**: m.p. 92 °C (methanol). $C_{30}H_{44}O_5S_2$ (548.79): calcd. C 65.66, H 8.08; found C 65.67, H 8.10.

***S*-*tert*-Butyl (2*R*)-2-[(1*R*,7a*R*)-7a-Methyl-5-oxo-4-phenylthio-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]-4-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]propanethioate (49):** A mixture of **45** and its diastereomers, prepared as described above (1.64 g, 2.99 mmol), was dissolved in methanol (20 mL), and a solution of KOH (0.15 g) in methanol (1 mL) was added. The mixture was stirred at room temperature for 1 h, and then the solvent was evaporated. The residue was purified by chromatography on silica gel (90 g, hexanes/EtOAc, 4:1) to give a mixture of **49** and two other isomers (1.25 g, 79% overall yield) in a ratio of 86:10:4 by HPLC ("Nucleosil 50:5", hexanes/EtOAc, 12:1, $t_R$ = 43.2, 37.8 and 36.4 min, respectively).
**49:** $^1$H NMR: δ = 1.03 (s, 3 H, Me), 1.16 (s, 3 H, Me), 1.27 (s, 3 H, Me), 1.34 (s, 3 H, Me), 1.42 (s, 3 H, Me), 1.48 (s, 9 H, $CMe_3$), 3.73−3.79 (m, 1 H, CHO−), 7.02−7.25 (m, 5 H, PhS) ppm. $^{13}$C NMR: δ = 16.63 (C7′a-Me), 22.45 (3), 25.28 (3), 25.88 (2), 26.58 (3), 28.40 (3), 29.45 (C*Me*$_3$), 30.35 (2), 32.50 (2), 33.96 (2), 34.51 (2) 47.24 (0), 48.79 (*C*Me$_3$), 51.41 (1), 52.69 (1), 79.03 (*C*HO−), 79.85 (*C*Me$_2$O−), 106.80 (O−C−O), 125.11 (C4′), 125.31 (C-*p*), 127.01 (C-*o*), 128.74 (C-*m*), 135.86 (C-*ipso*), 184.70 (C3′a), 193.38 (C5′), 203.31 (C1) ppm. HRMS calcd. for $C_{30}H_{42}O_4S_2$ [M$^+$]: 530.2525; found 530.2534.

**(3*S*,5*S*)-5-(1-Hydroxy-1-methylethyl)-3-[(1*S*,7a*S*)-7a-methyl-5-oxo-4-phenylthio-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]dihydrofuran-2(3*H*)-one (47) and (3*R*,5*S*)-5-(1-Hydroxy-1-methylethyl)-3-[(1*R*,7a*R*)-7a-methyl-5-oxo-4-phenylthio-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]dihydrofuran-2(3*H*)-one (48):** A mixture of **49** and its isomers, prepared as described above (860 mg, 1.62 mmol), was dissolved in methanol (25 mL) and Amberlyst-15H® (4.0 g) was added. The mixture was stirred at room temperature for 72 h, after which time, the solid was filtered off and washed with methanol. The combined filtrates were evaporated. The residue was purified by chromatography on silica gel (45 g, hexane/EtOAc, 1:1) to give: unchanged **49** (32 mg), **47** (334 mg) and a fraction containing **47** and **48** (148 mg, in a ratio of 52:48 by HPLC, Nucleosil 50:5μ, hexane/EtOAc, 1:1, $t_R$ = 21.2 and 22.8 min, respectively). The mixed fraction was re-purified by chromatography on silica gel (20 g, hexane/EtOAc, 1:1) to give **47** (58 mg, 63% combined yield), a mixture **47** and **48** (22 mg, 1:2), and **48** (38 mg, 6% yield, 97% pure by HPLC).

**47:** $[\alpha]_D^{25} = +6.73$ ($c$ = 3.25). $^1$H NMR: δ = 1.21 (s, 3 H, Me), 1.25 (s, 3 H, Me), 1.35 (s, 3 H, Me),1.70−1.80 (m, 2 H), 1.85−1.97 (m, 2 H), 2.09−2.23 (m, 2 H), 2.34−2.45 (m, 2 H), 2.56−2.63 (m, 1 H), 2.67−2.90 (m, 4 H), 4.28 (dd, $J$ = 6.8, 6.2 Hz, 1 H, CHO−), 7.08−7.13 and 7.18−7.23 (m, 5 H, Ph) ppm. $^{13}$C NMR: δ = 17.41 (C7′′a-*Me*), 24.65 (3), 24.75 (2), 26.28 (3), 26.53 (C2), 30.36 (C2), 33.69 (2), 33.80 (2), 39.53, 46.82 (C7′′a), 50.86, 71.16 (C1′), 84.06 (C5), 125.42 (C2), 125.52 (C-*p*), 127.14 (C-*o* ), 128.77 (C-*m*), 135.69 (C-*ipso*), 178.58 (C2), 184.23 (C3′′a), 193.71 (C5′′). HRMS: Calcd. for $C_{23}H_{28}O_4S$ [M$^+$]: 400.17083; found 400.17203.
**48:** $[\alpha]_D^{20} = +10.8$ ($c$ = 1.45). $^1$H NMR: δ = (500 MHz) 1.17 (s, 3 H, Me), 1.19 (s, 3 H, Me), 1.36 (s, 3 H, Me), 1.74−1.86 (m, 3 H), 1.98 (dt, $J$ = 13.7, 5.5 Hz, 1 H), 2.16−2.23 (m, 2 H), 2.30−2.40 (m, 2 H), 2.56−2.63 (m, 1 H), 2.57−2.86 (m, 5 H), 4.23 (dd, $J$ = 7.2, 7.3 Hz, 1 H, C5-H), 7.08−7.13 and 7.18−7.23 (m, 5 H, Ph) ppm. $^{13}$C NMR: δ = 18.14 (C7′′a-*Me*); 23.62, 23.87, 26.81, 26.86, 30.66, 33.81, 34.18, 40.07, 46.69 (C7′′a), 50.02, 70.19 (C1′), 83.92 (C5), 125.55 (C4′′), 125.74 (C-*p*), 127.30 (C-*o* ), 128.87 (C-*m*), 135.72 (C-*ipso*), 177.57 (C2), 183.90 (C3′′a), 193.64 (C5′′) ppm. HRMS Calcd. for $C_{23}H_{28}O_4S$ [M$^+$]: 400.17083; found 400.17022.

***S*-*tert*-Butyl (2*S*)-2-[(1*S*,5*R*,7a*S*)-5-Hydroxy-7a-methyl-4-phenylthio-2,3,5,6,7,7a-hexahydro-1*H*-inden-1-yl]-3-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]propanethioate (50):** A mixture of enone **49** and its isomers, obtained as described above (482 mg, 0.91 mmol), was dissolved in methanol (15 mL) and THF (10 mL). $CeCl_3 \cdot 7H_2O$ (189 mg, 0.51 mmol) was added, and the mixture cooled to −78 °C. $NaBH_4$ (75 mg, 1.99 mmol) was added. After 2 h, the mixture was warmed to room temperature. The reaction was quenched with 10% aqueous tartaric acid (5 mL), and diluted with water. The product was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with water and dried, and the solvent was evaporated. The residue was crystallized from benzene to give **50** (318 mg, > 99% pure by HPLC, 66% yield). A sample was recrystallized from benzene: m.p. 186 °C (dec.). $[\alpha]_D^{20} = +49.3$ ($c$ = 1.45). $^1$H NMR: δ = 1.06 (s, 3 H, Me), 1.18 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.49 (s, 3 H, Me), 1.51 (s, 9 H, $CMe_3$), 3.79 (dd, $J$ = 9.3, 2.5 Hz, 1 H, C4′-H), 4.05 (t, $J$ = 7.1 Hz, 1 H, C5′′-H), 7.10−7.35- (m, 5 H, PhS) ppm. $^{13}$C NMR: δ = 17.76 (C7′′a-*Me*), 22.44, 25.28, 26.59, 27.72, 28.34, 28.41, 29.47 (C*Me*$_3$), 32.46, 34.18, 46.08, 48.56 (*C*Me$_3$), 51.84, 52.96, 67.55, 79.13, 79.92, 106.79 (O−C−O), 124.52 (C4′′), 125.67 (C-*p*), 127.48 (C-*m*), 129.0 (C-*o* ), 134.71 (C-*ipso*), 161.33 (C3′′a), 203.91 (C1) ppm. $C_{30}H_{44}O_4S_2$ (532.81): calcd. C 67.63, H 8.32; found C 67.58, H 8.41. X-ray analysis of this compound has been reported.[53]

**(1*S*,5*R*,7a*S*)-1-{(1*S*)-1-(Hydroxymethyl)ethyl-2-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]}-7a-methyl-4-phenylthio-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-ol (51):** A solution of **50** (152 mg, 0.286 mmol) in THF (3 mL) was added to a clear solution of Li-

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$AlH_4$ (15.2 mg, 0.40 mmol) in THF (3 mL). The mixture was heated under reflux for 3 h. After cooling, the reaction was quenched with methanol (0.5 mL), and the mixture was poured into a 10% aqueous tartaric acid (6 mL). The product was extracted with dichloromethane (4 × 15 mL). The extract was dried and the solvent was evaporated. Diol **51** was obtained (128 mg, 100% yield). $^1$H NMR: δ = 1.07 (s, 3 H, Me), 1.08 (s, 3 H, Me), 1.23 (s, 3 H, Me), 1.35 (s, 3 H, Me), 1.42 (s, 3 H, Me), 1.4−2.75 (m, 12 H), 3.60−3.85 (m, 4 H, C*H*$_2$OH, C4′′-H, OH), 4.10 (t, *J* = 7.2 Hz, 1 H, C5-H), 7.05−7.30 (m, 5 H, PhS). $^{13}$C NMR: δ = 17.75 (C7a-Me), 22.48, 25.54, 26.50, 26.99, 28.22, 28.40, 28.44, 29.49, 35.12, 39.20, 46.01 (C7a), 48.91, 63.50, 67.82, 78.85, 80.72, 106.82 (O−C−O), 124.48 (C4), 125.61 (C-*p*), 127.55 (C-*o* ), 128.95 (C-*m*), 135.11 (C-*ipso*), 161.83 (C3a) ppm. HRMS calcd. for $C_{26}H_{38}O_4S$ [M$^+$]: 446.24908. Found: 446.24790. This material was used for the next step without purification.

**(1*S*,5*R*,7a*S*)-7a-Methyl-4-phenylthio-1-{(1*S*)-2-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]-1-(tosyloxymethyl)ethyl}-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-ol (52):** TsCl (224 mg, 1.17 mmol) was added to a solution of diol **51** (128 mg, 0.286 mmol), triethylamine (1.2 mL) and DMPA (15 mg, 0.12 mmol) in dichloromethane (8 mL) at 0 °C. The solution was left overnight, and then the solvent was evaporated at room temperature. The residue was purified by chromatography on silica gel (15 g, hexanes/EtOAc, 2:1) to give tosylate **52** (134 mg, 78% yield). $^1$H NMR: δ = 1.03 (s, 3 H, Me), 1.11 (s, 3 H, Me), 1.33 (s, 3 H, Me), 2.44 (s, 3 H, Ph*Me*), 3.43 (dd, *J* = 11.3, 2.1 Hz, 1 H, C4′′-H), 4.0−4.2 (m, 4 H, C5-H, C*H*$_2$OTs, OH), 7.10−7.30 (m, 5 H, PhS), 7.35 and 7.80 (d, *J* = 8.0 Hz, 4 H, *Ph*-Me) ppm. $^{13}$C NMR: δ = 17.93 (C7a-*Me*), 21.60 (Ph-*Me*), 22.96, 25.63, 26.32, 26.52, 28.14, 28.22, 28.47, 34.85, 35.69, 46.08 (C7a), 50.72, 67.44 (*C*OTs), 69.70, 78.83 (C4′′), 80.04, 106.68 (O−C−O), 124.82 (C4), 125.85 (Ph C-*p*), 127.72 (Ph C-*o* ), 128.07 (Ts C2,6), 129.11 (Ph C-*m*), 129.88 (Ts C3,5), 132.52 (Ts C4), 134.69 (Ph C-*ipso*), 145.12 (Ts C1), 161.30 (C3a) ppm. This material was used for the next step without purification.

**(1*S*,5*R*,7a*S*)-7a-Methyl-4-phenylsulfonyl-1-{(1*S*)-2-[(4*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl]-1-(tosyloxymethyl)ethyl}-2,3,5,6,7,7a-hexahydro-1*H*-inden-5-ol (53):** *m*CPBA (50%, 231 mg, 0.67 mmol,) was added to a solution of sulfide **52** (134 mg, 0.223 mmol) in dichloromethane (7 mL) at 0 °C. The mixture was warmed to room temperature, and, after 2 h, was poured into 10% aqueous $Na_2SO_3$ (10 mL). The products were extracted with dichloromethane (4 × 15 mL). The extract was dried and the solvent was evaporated. The residue was purified by chromatography on silica gel (15 g, hexanes/EtOAc, 1:1) to give the sulfone **53** (135 mg, 96%). $^1$H NMR: δ = 0.96 (s, 3 H, Me), 1.05 (s, 3 H, Me), 1.07 (s, 3 H, Me), 1.29 (s, 3 H, Me), 2.41 (s, 3 H, Ph*Me*), 3.35 (dd, *J* = 1.9, 11.2 Hz, 1 H, C4′′-H), 3.95−4.0 (m, 3 H, C*H*$_2$OTs and OH), 4.68 (t, *J* = 7.9 Hz, 1 H, C5-H), 7.3−7.9 (m, 9 H, arom. H) ppm. $^{13}$C NMR: δ = 17.98 (C7a-*Me*), 21.55 (*Me*Ph), 22.88 (3), 25.54 (3), 25.98 (C2), 26.45 (3), 27.45 (2), 27.78 (2), 28.12 (2), 28.38 (3), 34.22 (2), 34.70 (C1′), 47.33 (C7a), 49.54 (1), 65.59 (C5), 69.60 (*C*OTs), 78.73 (C4′′), 79.87 (C5′′), 106.59 (O−C−O), 126.90 (Ph C2,6), 127.84 (Ts C2,6), 128.97 (Ph C3,5), 129.80 (Ts C3,5), 132.24 (Ts C4), 133.14 (Ph C4), 133.24 (C4), 141.18 (Ph C1), 145.08 (Ts C1), 167.76 (C3a) ppm. This material was used for the next step without purification.

**(4*S*)-2,2,5,5-Tetramethyl-4-{(2*S*)-2-[(1*S*,3a*S*,4*S*,7a*S*)-7a-methyl-4-(phenylsulfonyl)octahydro-1*H*-inden-1-yl]propyl}1,3-dioxolane (54):** $LiAlH_4$ (120 mg, 3.2 mmol) was added to a solution of **53** (0.61 g, 0.96 mmol) in THF (4 mL). The mixture was heated under reflux for 20 min. After cooling, methanol (2 mL) and then 10% aqueous tartaric acid (20 mL) were added. The products were extracted with dichloromethane (4 × 20 mL). The combined organic extract was dried and the solvent was evaporated. The residue was purified by chromatography on silica gel (35 g, hexanes/EtOAc, 3:1) to give sulfone 54 (0.27 g, 63% yield): m.p. 139 °C (hexanes). $[\alpha]_D^{20}$ = −6.5 (*c* = 1.4). $^1$H NMR: δ = 0.73 (s, 3 H, C7′′a-Me), 0.96 (d, *J* = 6.4 Hz, 3 H, C3′-H), 1.04 (s, 3 H, Me), 1.19 (s, 3 H, Me), 1.31 (s, 3 H, Me), 1.39 (s, 3 H, Me), 3.03 (dt, *J* = 3.1, 11.2 Hz, 1 H, $CHSO_2$−), 3.75 (dd, *J* = 1.5, 10.6 Hz, 1 H, C4-H), 7.5−7.7 and 7.8−7.9 (m, 5 H, Ph) ppm. $^{13}$C NMR: δ = 12.04 (C3′), 18.52 (C7′′a-*Me*), 21.12 (C6′′), 22.94 (3), 25.36 (C5′′), 25.64 (3), 26.91 (3), 27.35 and 27.95 (C2′′ and C3′′), 28.64 (3), 33.12 (C2′), 35.16 (2), 38.82 (2), 44.80 (C7′′a), 48.15 and 55.84 (C1′′and C3′′a), 63.70 (C4′′), 79.88 (C4), 80.09 (C5), 106.43 ($Me_2CO_2$), 128.67 and 128.90 (C-*o* and C-*p*), 133.31 (C-*m*), 138.35 (C-*ipso*) ppm. $C_{26}H_{40}O_4S$ (448.26): calcd. C 69.60, H 8.99; found C 69.67, H 9.15.

**(3*S*,5*S*)-2-Methyl-5-[(1*S*,3a*S*,4*S*,7a*S*)-7a-methyl-4-phenylsulfonyl-octahydro-1*H*-inden-1-yl]hexane-2,3-diol (55):** A mixture of acetonide **54** (272 mg, 0.61 mmol), Amberlyst-15H® (1.5 g) and methanol (9 mL) was stirred at room temperature for 72 h. The solid was filtered off and washed with methanol (3 × 6 mL). The combined filtrates were evaporated and the residue was purified by chromatography on silica gel (30 g, hexanes/EtOAc, 2:1, 1:1) to give diol **55** (203 mg, 80% yield) and unchanged **54** (20 mg). **55**: m.p. 133 °C (benzene). $[\alpha]_D^{20}$ = −16.2 (*c* = 1.6). $^1$H NMR: δ = 0.71 (s, 3 H, C7′a-Me), 0.93 (d, *J* = 6.4 Hz, 3 H, C6-H), 1.11 (s, 3 H, Me), 1.16 (s, 3 H, Me), 3.03 (dt, *J* = 3.1, 11.2 Hz, 1 H, CH−$SO_2$), 3.43 (dd, *J* = 3.3, 7.2 Hz, 1 H, C3-H), 7.5−7.7 and 7.8−7.9 (m, 5 H, Ph) ppm. $^{13}$C NMR: δ = 11.94 (C6), 18.50 (C7′a-*Me*), 21.07 (3), 23.11 (2), 25.32 (2), 26.52 (3), 27.33 (3) 28.11 (3), 32.51 (C5), 37.73 (2), 38.74 (2), 44.78 (C7′a), 48.12 (1), 55.68 (1) 63.69 (C4′), 73.13 (C2), 75.29 (C3), 128.63 and 128.90 (C-*o* and C-*p*), 133.31 (C-*m*), 138.19 (C-*ipso*) ppm. $C_{23}H_{36}O_4S$ (408.23): calcd. C 67.61, H 8.88; found C 67.58, H 9.03.

**Methyl (2*E*,5*S*)-5-[(1*S*,3a*S*,4*S*,7a*S*)-7a-Methyl-4-(phenylsulfonyl)-ocatahydro-1*H*-inden-1-yl]hex-2-enoate and (2*Z*,5*S*)-5-[(1*S*,3a*S*,4*S*,-7a*S*)-7a-Methyl-4-(phenylsulfonyl)ocatahydro-1*H*-inden-1-yl]hex-2-enoate (56):** A solution of $Pb(OAc)_4$ (65 mg, 0.15 mmol) in dichloromethane (1 mL) was added dropwise to a stirred mixture of diol **55** (47 mg, 0.12 mmol), powdered $K_2CO_3$ (115 mg, 0.84 mmol) and dichloromethane (3 mL) at −15 °C. The mixture was warmed to room temperature, and, after 1 h, it was filtered through a pad of Celite. The Celite was washed with dichloromethane and the combined filtrates were evaporated. The residue was dissolved in dry $CH_3CN$ (1.5 mL), and $Ph_3P{=}CHCOO_2Me$ (98 mg, 0.29 mmol) in $CH_3CN$ (1.5 mL) was added. The mixture was heated under reflux for 3 h. The solvent was evaporated and the residue was purified by chromatography (5 g, hexanes/EtOAc, 2:1) to give **56** (48 mg, 98%, *E*:*Z*, 10:1 by $^1$H NMR). **(*E*)-56 (from the mixture):** $^1$H NMR: δ = 0.68 (s, 3 H, C7′a-Me), 0.91 (d, *J* = 6.6 Hz, 3 H, C6-H), 3.03 (dt, *J* = 3.1, 11.2 Hz, 1 H, $CHSO_2$), 3.70 (s, 3 H, MeO), 5.80 (d, *J* = 15.5 Hz, 1 H, C2-H), 6.89 (m, 1 H, C3-H), 7.5−7.7 and 7.8−7.9 (m, 5 H, Ph) ppm. $^{13}$C NMR: δ = 11.85 (C6), 18.94 (C7a-*Me*). 21.02 (2), 25.29 (2), 27.29 (2), 27.88 (2), 35.34 (C5), 38.52 (2), 38.85 (2), 44.64 (C7′a), 48.02 (C3′a), 51.33 (MeO), 54.48 (C1′), 63.64 (*C*−$SO_2$Ph), 122.33 (C2), 128.64 and 128.88 (C-*o* and C-*p*), 133.30 (C-*m*), 138.13 (C-*ipso*), 147.75 (C3), 166.76 (C1) ppm. **(*Z*)-56:** $^1$H NMR: δ = 6.20 (m, C3-H), 3.67 (s, MeO) ppm. HRMS (liquid SIMS) calcd. for $C_{23}H_{32}O_4SNa$ [M$^+$ + Na]: 427.1984; found 427.1914.

**Methyl (2*E*,5*S*)-5-[(1*S*,3a*S*,4*S*,7a*S*)-7a-Methyl-4-(phenylsulfonyl)-ocatahydro-1*H*-inden-1-yl]hex-2-enoate and (2*Z*,5*S*)-5-[(1*S*,3a*S*,4*S*,7a*S*)-7a-Methyl-4-(phenylsulfonyl)ocatahydro-1*H*-inden-1-yl]hexa-**

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**noate (57):** A solution of **56** (46 mg, 0.11 mmol) in EtOAc (4 mL) containing 10% Pd on charcoal (4 mg) was stirred under hydrogen for 4 h, and the product was isolated in the usual way. The dihydro derivative **57** was obtained (46 mg, 100%): $[\alpha]_D^{20} = +2.6$ ($c = 2.4$). $^1$H NMR: δ = 0.67 (s, 3 H, C7′a-Me); 0.89 (d, $J = 6.4$ Hz, 3 H, C6-H), 2.24 (dt, $J = 2.0$, 7.0 Hz, 2 H, C2-H), 3.03 (dt, $J = 3.1$, 11.2 Hz, 1 H, CH−$SO_2$), 3.63 (s, 1 H, MeO), 7.5−7.7 and 7.8−7.9 (m, 5 H, Ph) ppm. $^{13}$C NMR: δ = 11.79 and 18.56 (C7a-*Me* and C6); 21.04, 21.37, 25.28, 27.29, 27.78, 34.32, 35.22, 38.64, 44.57, 48.06 (C7′a), 51.36 (MeO), 54.70, 63.69 (*C*$SO_2$Ph), 128.62 and 128.84 (C-*o* and C-*p*), 133.24 (C-*m*), 138.19 (C-*ipso*),174.03 (C1) ppm. HRMS (liquid SIMS) calcd. for $C_{23}H_{34}O_4SNa$ [$M^+$ + Na]: 429.2076; found 429.2101.

**(6*S*)-2-Methyl-6-[(1*S*,3a*S*,4*S*,7a*S*)-7a-methyl-4-(phenylsulfonyl)octahydro-1*H*-inden-1-yl)heptan-2-ol (*ent*-8):** A solution of MeMgI in $Et_2O$ was prepared from Mg (0.61 g, 0.025 gram atom) and MeI (1.25 mL, 20 mmol) in $Et_2O$ (15 mL), and cooled to −20 °C. A solution of ester **57** (44 mg, 0.108 mmol) in $Et_2O$ (1.5 mL) was added dropwise. The mixture was warmed to room temperature, and after 2 h, it was poured into ice-cold 40% aqueous $NH_4Cl$. The product was extracted with dichloromethane (4 × 5 mL). The combined extracts were dried and the solvents evaporated. The residue was purified by chromatography on silica gel (6 g, hexanes/EtOAc, 4:1, 2:1) to give crystalline alcohol ***ent*-8** (39 mg, 88% yield): $[\alpha]_D^{20} = -0.9$ ($c = 2.1$); $^1$H and $^{13}$C NMR spectra with identical with those of **8**.[62] Since specific rotation of the enantiomers is too low for any comparisons, CD spectra of **8** and *ent*-**8** were taken.

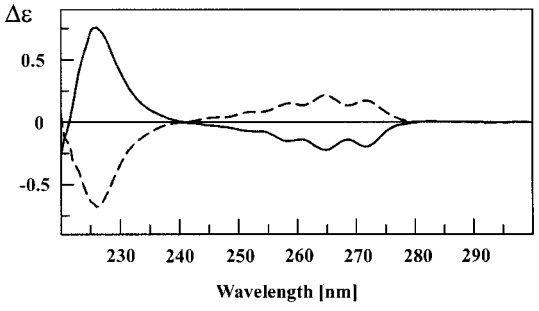


Figure 3. CD spectra of **8** (solid line) and *epi*-**8** (dashed line)

***S*-*tert*-Butyl (2ξ)-3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-[(1ξ,2ξ)-2-methyl-3-oxo-2-(3-oxo-4-phenylthiobutyl)cyclopentyl]propanethioate (59):** A solution of ketene acetal **58** (2.32 g, 7.3 mmol) in dichloromethane (3 mL) was added to a solution of **10** (0.77 g, 8.03 mmol) and $TrSbCl_6$ (250 mg, 0.43 mmol) in dichloromethane (15 mL) at −78 °C. The mixture was stirred for 30 min, after which time **9** (1.3 g, 7.3 mmol) was added. After 1 hour, the mixture was warmed to room temperature, and the reaction was quenched with water (1 mL). After 15 min, some $MgSO_4$ and hexanes (20 mL) were added, and the solution was filtered through a pad of silica gel (6 g). The silica gel was washed with dichloromethane (20 mL). The combined filtrates were evaporated, and the residue was purified by chromatography on silica gel (120 g, hexanes/EtOAc, 4:1) to give a mixture of diones **59** (1.48 g, 39% yield) as two diastereomers in a ratio of 50:50 by HPLC (Nucleosil 50:5, hexanes/EtOAc, 4:1, $t_R$ = 25.4 and 30.6 min). $^1$H NMR: δ = 1.03 (0.99, C7a′′-*Me*), 1.2−2.9 (m, 12 H) overlapping 1.34 and 1.35 (2s, 6 H, $Me_2C$), 1.40 and 1.41 (s, 9 H, $Me_3C$), 3.35−3.60 (m, 1 H, CHO−), 3.63 (s, 2 H, $CH_2S$), 3.95−4.25 (m, 2 H, $CH_2O$−), 7.1−7.4 (m, 5 H, Ph) ppm. $^{13}$C NMR: δ = 18.53 and 18.56 (C7a′′-*Me*), 22.82, 22.95, 25.45, 25.51, 26.81, 27.01, 29.35 (*Me*$_3$C), 29.05, 29.40, 35.65, 35.78, 36.32, 36.38, 43.07, 43.53, 43.81 (*C*$H_2$−SPh), 48.92 and 48.95, 51.14, 51.22, 51.39, 51.91, 69.19, 69.65, 72.87, 73.32, 108.72 and 108.77, 126.58 (C-*p*), 128.89 (C-*o* ), 129.61 (C-*m*), 134.74 (C-*ipso*), 201.64 and 203.06 (C1), 204.23 (C3′′′), 220.85 and 221.1 (C3′′) ppm. HRMS calcd. for $C_{28}H_{40}O_5S_2$ [$M^+$]: 520.23172; found 520.23262.

***S*-*tert*-Butyl (3*R*,5*S*)-5-Hydroxy-2,2-dimethyltetrahydro-2*H*-pyran-3-carbothioate (60):** A solution of ketene acetal **58** (1.48 g, 4.63 mmol) in dichloromethane (3 mL) was added to a solution of cyclopent-2-en-1-one (0.42 g, 5.1 mmol) and $TrSbCl_6$ (140 mg, 0.24 mmol) in dichloromethane (7 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h, and then warmed to room temperature. The product was isolated as described above and purified by chromatography on silica gel (20 g, hexanes/EtOAc, 2:1). The fraction corresponding to the unknown product (TLC) was collected (0.65 g) and distilled in a kugelrohr apparatus (160 °C/0.1 Torr). The pyran derivative **60** was obtained: $[\alpha]_D^{25} = +35.1$ ($c = 5.1$). $^1$H NMR: δ = 1.38 and 1.19 (2s, 6 H, $Me_2C$), 1.45 (s, 9 H, $Me_3C$), 2.10−1.95 (m, 1 H, C4-$H_{eq}$), 2.4−2.15 (m, 2 H, C4-$H_{ax}$, OH), 2.96 (dd, $J = 8.7$, 7.7 Hz, 1 H, C-3 H), 3.57 (dd, $J = 11.7$, 5.0 Hz, 1 H, C6-$H_{eq}$), 3.76 (dd, $J = 11.7$, 2.9 Hz, 1 H, C6-$H_{ax}$), 4.0−4.15 (m, 1 H, C5-*H*) ppm. $^{13}$C NMR: δ = 28.49 and 24.43 (C$Me_2$), 29.30 (*Me*$_3$C), 30.49 (C4), 47.94 (*C*$Me_3$), 61.53 (C3), 64.31 (C6), 77.06 (C5), 82.03 (C2), 198.56 (C=O) ppm. $C_{12}H_{22}O_3S$ (246.37): calcd. C 58.50, H 9.00; found C 58.07, H 8.95.

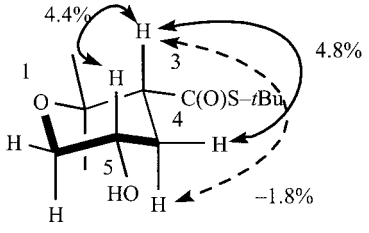


Figure 4. Diagnostic values from a nuclear Overhauser effect (NOE) experiment for **60**

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