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Stereocontrolled synthesis of all eight stereoisomers of the putative anti-androgen cyoctol

Johann Mulzer,* Ulrich Kaselow, Klaus-Dieter Graske, Holger Kühne, Andreas Sieg and Harry J. Martin

Institut für Organische Chemie der Universität Wien, Währinger Strasse 38, A-1090 Wien, Austria

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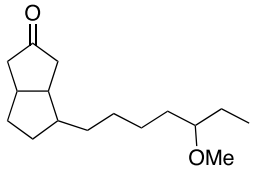
Abstract—All eight stereoisomers (**1**-**4** and enantiomers) of the putative anti-androgen cyoctol have been synthesized along stereochemically unambiguous routes. The biological tests of all isomers indicated that cyoctol is not an anti-androgen, contrary to the patent literature.

1. Introduction and biological background

The carbacyclin derivative cyoctol has been described as an androgen receptor blocker which induces a wide variety of interesting biological effects.



cyoctol

For instance, various forms of alopecia or male pattern baldness are treated by concomitant administration of potassium channel openers and cyoctol.[1] Another interesting phenomenon was that cyoctol was completely metabolized when passing through the skin as no unchanged cyoctol could be detected in ipsilateral plasma samples. This may eliminate the occurrence of adverse systemic effects after dermal application.[2] The effects of cyoctol or 13-*cis*-retinoic acid on binding of ^{3}H-labeled dihydrotestosterone (DHT) by human facial skin fibroblasts in culture were studied at final ratios of either cyoctol or 13-*cis*-retinoic acid to DHT between 0:1 and 104:1. 13-*cis*-Retinoic acid did not inhibit DHT binding even at ratios at 104:1. By contrast, cyoctol inhibited 78–93% of the DHT binding. Apparently, 13-*cis*-retinoic acid does not function as an anti-androgen, whereas cyoctol does.[3] Because cyoctol has in vitro efficacy and very low toxicity in experimental animals, investigations as to its clinical use as a topical anti-androgen for the treatment of acne and other diseases of localized androgen excess are indicated.[4] Fibroblast cultures were established from both frontal and occipital skin from patients with clinical diagnosis of androgenic alopecia undergoing hair transplantation. The DHT receptor activity from fibroblasts from the frontal region was 19.9 compared to 4.5 fmol per mg tissue protein in the occipital region. Cyoctol blocked a mean of 80% of the DHT binding in the fibroblasts derived from the frontal region and only 22% of that from the occipital region.[5] Anti-androgens, like cyoctol, may help in prevention and treatment of keloid and abnormal scar formation.[6] Cyoctol may have a role in anti-fungal therapy.[7] Intra-abdominal adhesions are the most common post-infective and postoperative complications. Cyoctol may be clinically useful in this problem.[8] Skin preparations for aging prevention contain cyoctol and at least one blood-circulation promoter selected from the group comprising γ-aminobutyric acid, vitamin E orotate, diisopropylamine dichloroacetate, hyaluronic acid, elastin, water-soluble collagen, Swertia japonica extract, and ginseng extract. The preparations stimulate skin functions, prevent dryness, and show anti-wrinkling effects in a short period of time.[9] A hair tonic was formulated containing Swertia extract 10.0, cyoctol 0.01, EtOH 60.0, polyoxyethylene hydrogenated castor oil 0.5 glycerin 5.0, perfume 0.1, and water to 100% by weight. The preparation significantly promoted the hair growth in mice and humans.[10] Cyoctol was effective in vitro as an anti-androgen without effect on either the estrogen or the progesterone receptors in carcinomas of the breast,

Keywords: Putative anti-androgen cyoctol; 13-*cis*-Retinoic; Cyoctol.
* Corresponding author. Tel.: +431427752190; fax: +431427752189; e-mail: johann.mulzer@univie.ac.at

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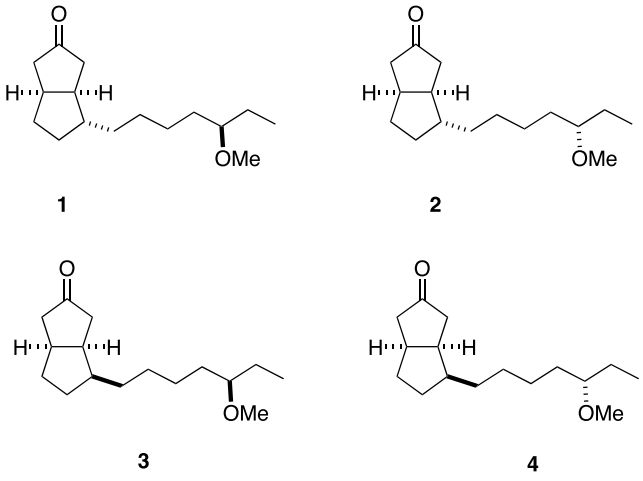
ovary, and prostate as well as in malignant melanomas. In a clonogenic assay, cyoctol was more effective against carcinomas of the breast, the kidney, the ovary, and the prostate than conventional anti-neoplastic agents in the majority of tumors tested.[11]



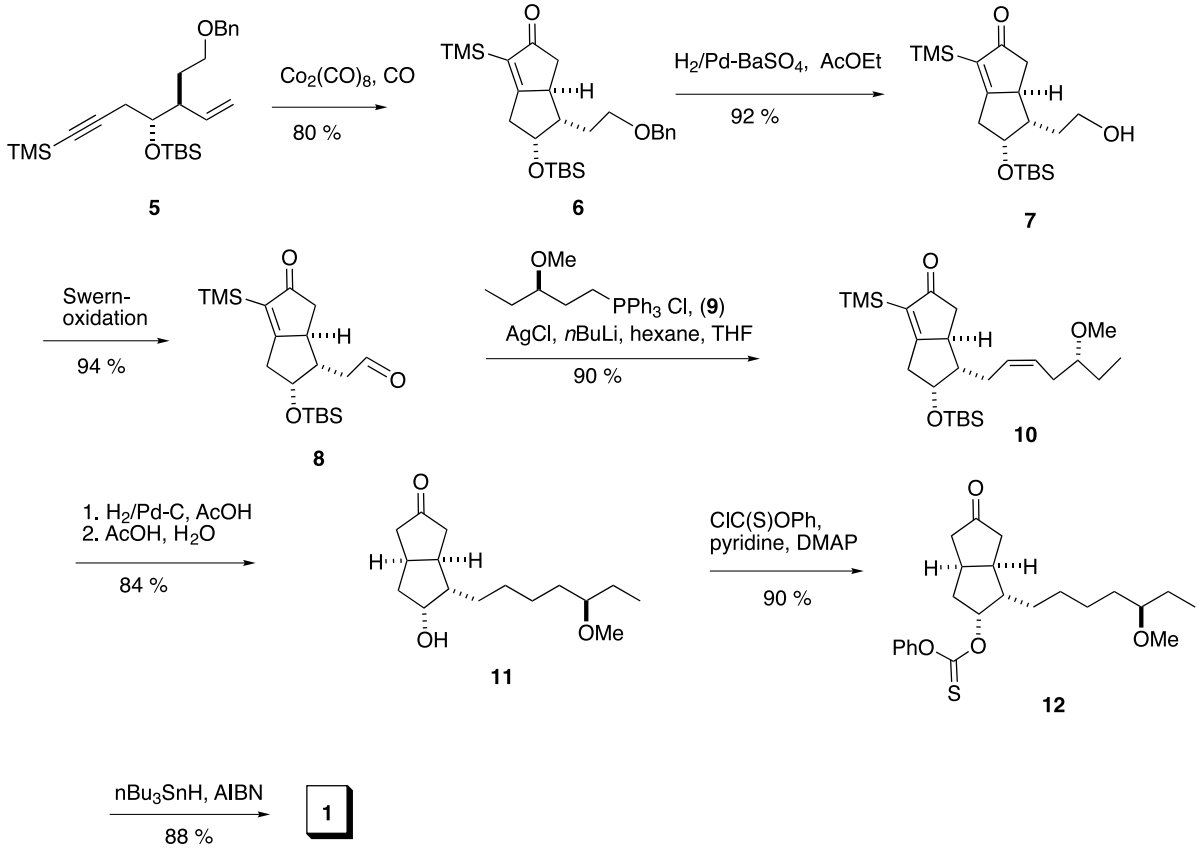
Intrigued by the manifold applicability of cyoctol we were puzzled by the fact that all biological data had been gained from a racemic mixture of diastereomers.[12] So it was unclear whether all stereoisomers or only a limited number thereof was responsible for the biological profile. Thus we decided to develop stereocontrolled approaches to all possible eight stereoisomers (**1**-**4** and enantiomers) of cyoctol and to subject these to conclusive biological testing in order to discriminate the influence of chirality on the biological activity.

1.1. Total synthesis

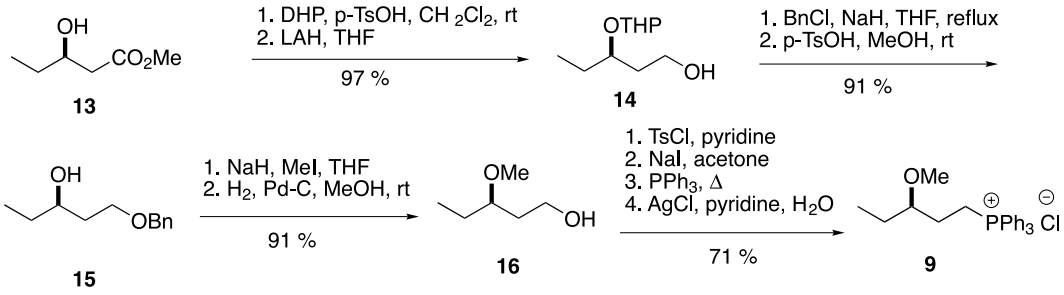
All our approaches are convergent. The carbacyclin core and an appropriately functionalized sidechain were prepared separately with defined stereochemistry and then united by efficient CC-connecting reactions.

In the first synthesis we made use of an intramolecular Pauson–Khand cyclization[13a] to prepare the carbacyclin core to which the sidechain was attached via a Wittig olefination. Specifically (Scheme 1) known enyne **5**[13b] was converted with $Co_2(CO)_8$ into the bicyclic enone **6** under forced Pauson Khand conditions (*n*-octane, 30 bar CO, 105 °C, 5d).[13b] Catalytic hydrogenation under controlled conditions removed the OBn protecting group without touching the endocyclic double bond to deliver alcohol **7** which was oxidized under Swern conditions to aldehyde **8**.

Wittig reaction with phosphonium chloride **9** (prepared along the straightforward route shown in Scheme 2) gave low yields, until silver(I)chloride was added in substoichiometric amounts. With this additive the yield rose to 90% obviously due to a catalytic effect of the silver salt which may act as a mild Lewis acid and facilitate the formation of the oxaphosphetane intermediate. Olefin **10** was formed *Z*-selectively and was converted into hydroxy cyoctol **11** in two steps. Reductive removal of the hydroxyl function via



Scheme 1.



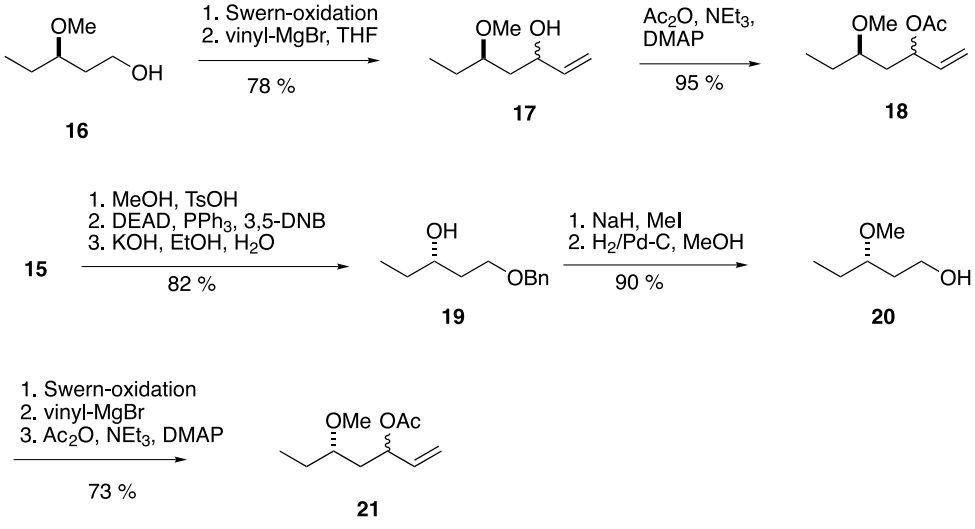
Scheme 2.

the Barton–McCombie protocol[14] furnished cyoctol **1** in stereochemically pure form (HPLC, ^{1}H and ^{13}C NMR) (Scheme 3).

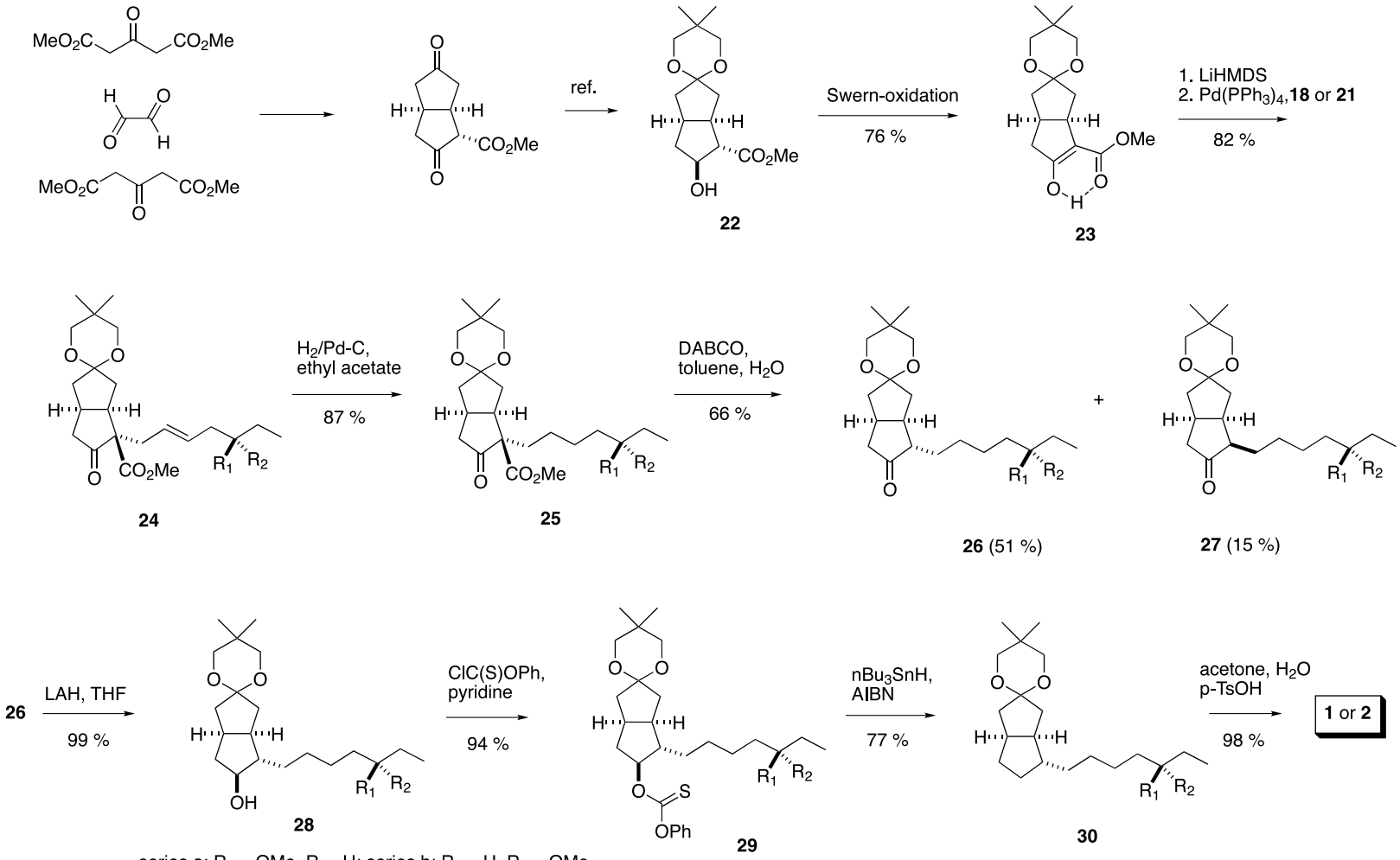
An alternative access to the bicyclic carbacyclin core (Scheme 4) was efficiently provided by the Weiss-reaction of dimethyl acetone dicarboxylate and glyoxal which, after enzymatic kinetic resolution and further transformation led to hydroxyester **22** in diastereo- and enantiopure form. Both enantiomers of **22** were thus available in multigram quantities.[15] Swern oxidation of **22** led to the keto-enol ester **23** which was subjected to a Trost–Tsuji allylation[16] with acetates **18** and **21**, respectively. Acetate **18** was prepared from alcohol **16** as shown in Scheme 3; Mitsunobu inversion[17] of alcohol **15** gave **19** which was transformed into allyl acetate **21** as shown. The allylation exclusively occurred from the less hindered *exo* face to furnish keto-ester **24** in diastereomerically pure form. Catalytic hydrogenation followed by Taber's decarbomethoxylation[18] generated ketones **26** and **27** in a 3:1—ratio, which means that the kinetic protonation of the corresponding enolate is not selective. After longer treatment with base, however, the ratio was shifted to 16:1 most likely due to thermodynamic control. After chromatographic separation diastereomer **26** was converted into cyoctol **1** via Barton–McCombie dehydroxylation and ketal hydrolysis.

To gain access to the *endo*-cyoctol series (Scheme 5) keto ester **24** was reduced with sodium borohydride to give hydroxyester **31** stereoselectively. Again the reagent attack occurred exclusively from the *exo*-face. Saponification of the ester led to hydroxy acid **32** which was treated with DEAD and triphenylphosphine to form olefin **33** via a dehydrative decarboxylation[19] Catalytic hydrogenation generated the *endo*-cyoctol derivative **34** stereoselectively, again via an *exo*-attack of the reagent. After ketal hydrolysis cyoctol **3** and **4** were obtained in stereochemically pure form (Scheme 6).

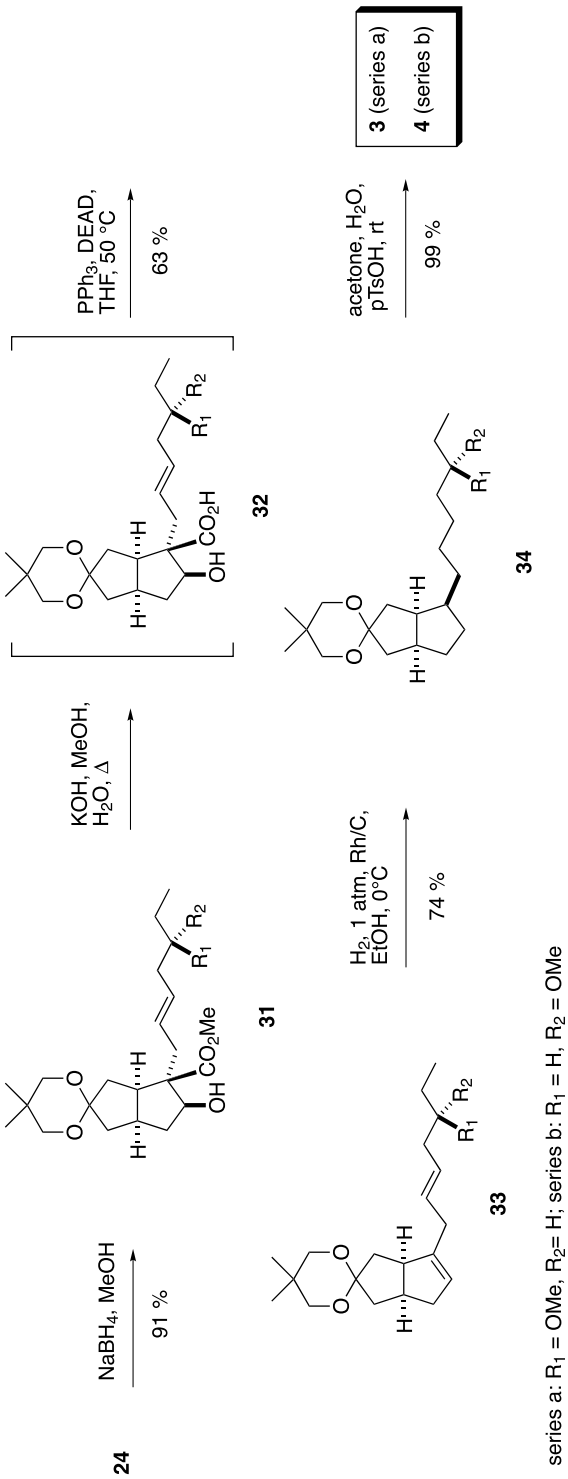
Instead of using the Trost–Tsuji reaction for attaching the cyoctol sidechain a stereocontrolled alternative route was developed (Scheme 7). Hydroxy ester **22** was reduced to the mono alcohol **40** via the mesylate. Alcohol **40** was then converted into the sulfone **41** which was deprotonated and alkylated with bromides (*R*)- or (*S*)-**39** to furnish **42**. Desulfonation with sodium amalgam led to a mixture of **43** and minor amounts of olefin **44**, which were transformed into cyoctols **1** and **2**. Alternatively (Scheme 8) **22** was dehydrated to the enoate **46**. This transformation involves a *syn* elimination of water which was not possible via the mesylate or tosylate. Instead, a Mitsunobu reaction was used to create bromide **45** under inversion of configuration,[20] which immediately underwent an *anti*-1,2-elimination of hydrogen bromide to form **46**. DIBALH-reduction generated the allylic alcohol **47** which was hydrogenated from the *exo* face to form the *endo* diastereomer **48**. Further



Scheme 3.


MeO2C
CO2Me
ref.
Swern-oxidation
76 %
1. LiHMDS
2. Pd(PPh3)4, 18 or 21
82 %
22
23
H2/Pd-C,
ethyl acetate
87 %
DABCO,
toluene, H2O
66 %
24
25
26 (51 %)
27 (15 %)
26
LAH, THF
99 %
ClC(S)OPh,
pyridine
94 %
nBu3SnH,
AIBN
77 %
acetone, H2O
p-TsOH
98 %
1 or 2
28
29
30
series a: R1 = OMe, R2= H; series b: R1 = H, R2 = OMe

Scheme 4.



Scheme 5.

manipulation as in the *exo* series led to cyoctol **4** in stereochemically pure form. The requisite bromide **39** were prepared via an enantioselective catalytic addition of diethyl zinc to aldehyde **36** (Scheme 6). According to a known protocol[21] diamine triflate (*R*,*R*)-**37** was treated with $Ti(OiPr)_4$ to form a titanium complex which was used for activating the diethylzinc. Alcohol **38** was formed with high yield and ee and was then transformed into the bromide (*R*)-**38** by routine operations. Analogously, (*S*)-**39** was prepared using (*S*,*S*)-**37** as the source of chirality.

In conclusion by combining the enantiomers of the *exo*- and *endo*-carbacyclin core with both enantiomers of the side-chain all eight stereoisomers of cyoctol have been prepared via totally stereocontrolled routes in quantities of ca. 1 g per stereoisomer. Catalysis has played a central role in all syntheses. The absolute and relative configurations of the products unambiguously follow from the individual synthetic routes. It can be seen that the ^1H NMR spectra of the *exo* (**1**)- and the *endo* (**3**)-cyoctols are significantly different (Figs. 1 and 2); however, the configuration of the sidechain is not reflected in the spectra. For further support, the crystal structure of sulfone **50** was elucidated via a single crystal diffraction.[22] (Fig. 3).

1.2. Biological tests

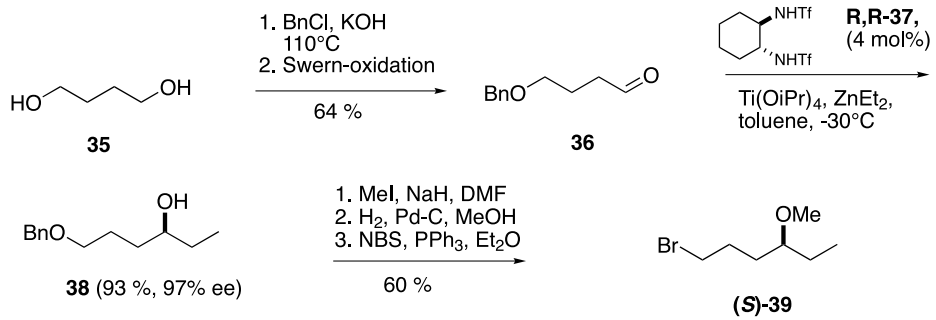
All eight stereoisomers of cyoctol were subjected individually to two different biological tests:

1. a receptor binding test should provide information about the affinity of the compounds to the binding site of the cytosolic androgen receptor of rat prostate
2. the effect of cyoctol as a topical anti-androgen was tested with the aid of the lipogenesis at the gold hamster ear

Ad 1. Androgen receptors was procured from rat prostate cytosol. 3H-Methyltrienolone was used as a reference for the binding affinity in presence of the test compound and the release of radioactivity would indicate a competitive binding of the cyoctol to the receptor. None of the eight stereoisomers showed any significant effect.

Ad 2. A 1% acetone solution of the test compound was applied to one ear of a castrated male Syrian gold hamster and as a reference, acetone was applied to the second ear. After 21 days the animals were killed and from each ear a segment of 8 mm diameter was removed and incubated with ^{14}C labelled acetate for 4 h. Then the tissue was digested proteolytically and the solutions were tested for their radioactivity. The higher the radioactivity the more lipids have been produced, and, hence, the higher the anti-androgenic effect of the substance. Again, none of the cyoctol stereoisomers had any significant effect on the lipogenesis.

These results were very confusing in the light of the patent literatur cited in the introduction. A possible explanation may be seen in the different sources of the androgen receptors applied, so that cyoctol may have a selectivity for certain kinds of receptors. Regarding the lipogenesis test the failure may be due to this particular kind of a biological test



Scheme 6.

and human skin cells may be different. All in all a discrepancy exists between our results and the patent literature, and it appears that additional biological tests will be needed to clarify the situation.

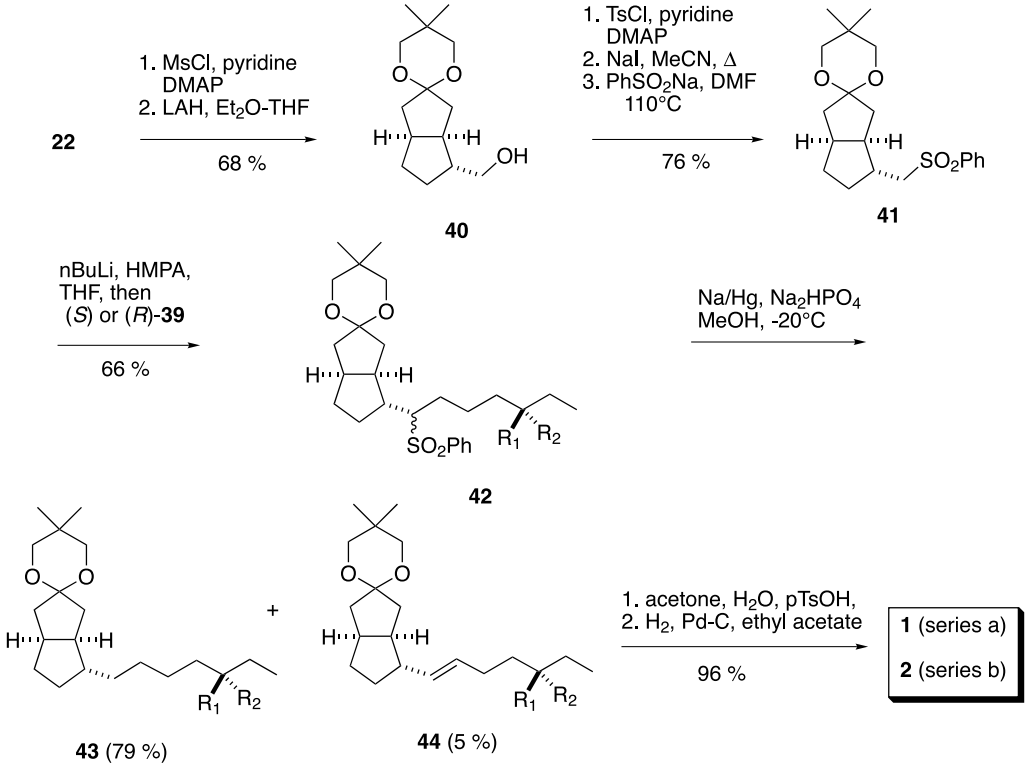
2. Experimental

2.1. General

Fourier transform infrared spectra were calibrated on an internal standard and are reported in wavenumbers (cm^{-1}). ^{1}H and ^{13}C NMR spectra were taken on 250, 400 and 600 MHz NMR machines. Proton chemical shifts are reported in δ, using the residual $CHCl_3$ as internal reference (7.26 ppm). Carbon chemical shifts are reported in δ, using $CDCl_3$ as an internal standard (77.0 ppm). Mass spectra were obtained under electron impact (EI).

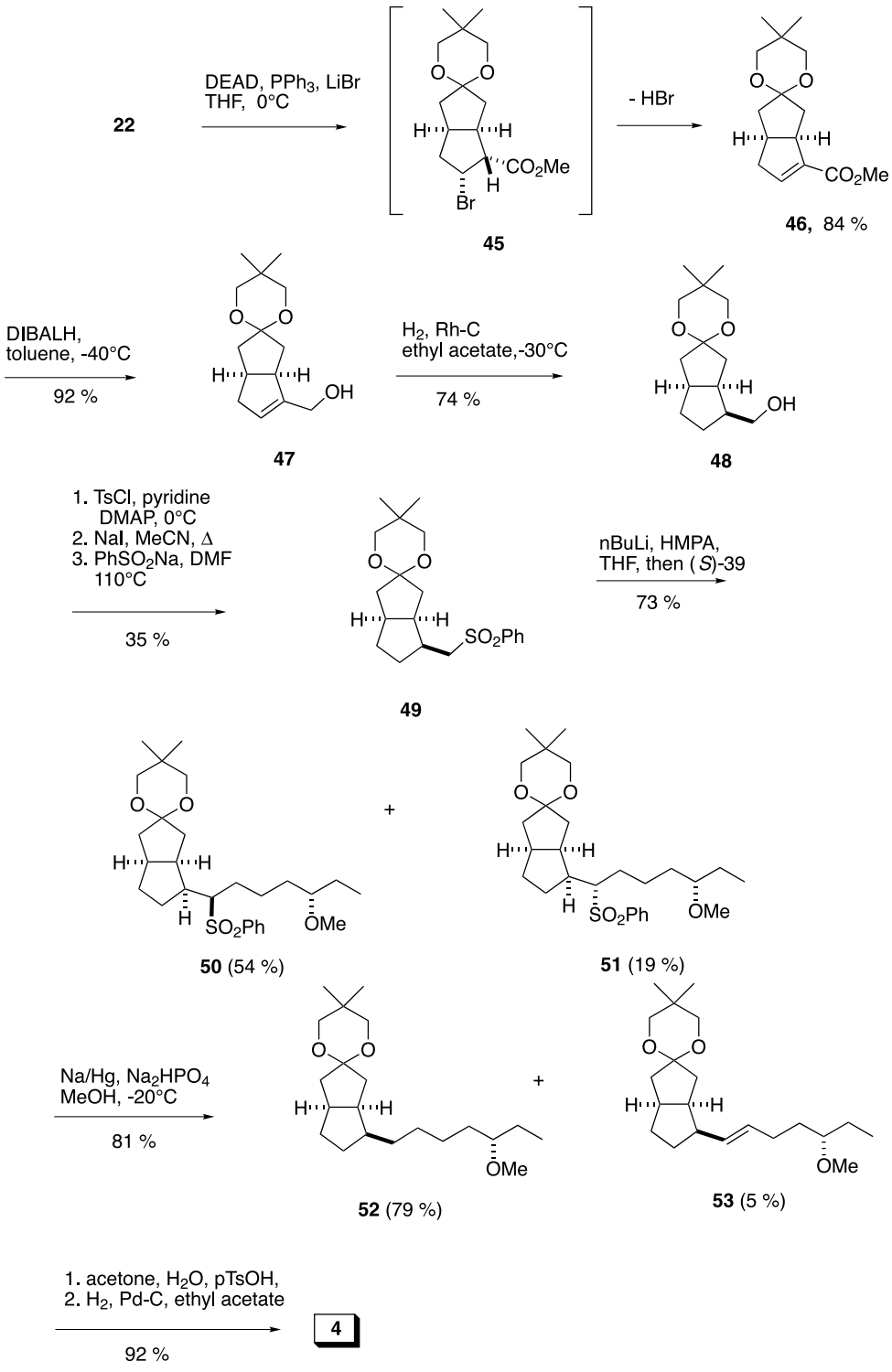
Commercially available chemicals were used without further purification. Where appropriate, reactions were performed in flame-dried glassware under an argon atmosphere.

Ether (Et_2O), tetrahydrofuran (THF) and toluene were freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Dichloromethane (DCM), diisopropylamine (iPr_2NH), triethylamine (Et_3N), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride. Hexanes and ethyl acetate (EtOAc) were distilled to remove higher boiling fractions.



series a: R_1 = OMe, R_2= H; series b: R_1 = H, R_2 = OMe

Scheme 7.



Scheme 8.

Silica gel 60 (230–400 mesh) was used for column chromatography. Precoated aluminium sheets 60 were used for analytical thin layer chromatography (TLC). Compounds were visualised with UV light, *p*-anisaldehyde stain, or phosphomolybdic acid in EtOH.

2.2. Typical procedures (TPs)

TP 1. Swern oxidation. Oxalyl chloride (1 mL, 11 mmol) in dichloromethane (25 mL) was treated with DMSO (1.7 mL, 25 mmol) at −78 °C. The mixture was stirred for 15 min at −78 °C, then the alcohol (10 mmol) in dichlorometane (10 mL) was added and the mixture was stirred at −78 °C for 1 h. NEt_3 (5.5 mL, 40 mmol) was added and the cooling was removed. The completeness of the reaction was checked via TLC. Water (25 mL) was added, the organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated

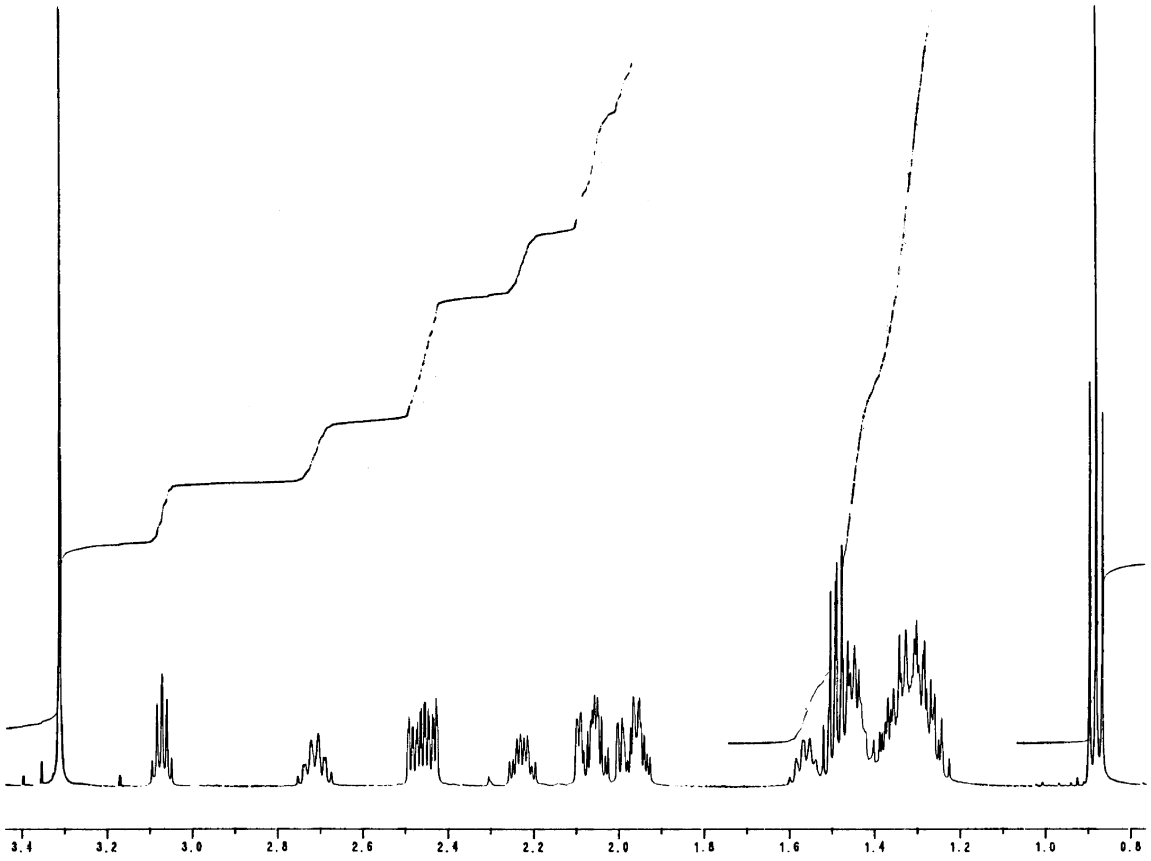


Figure 1. [1]H NMR spectrum of **1** (500 MHz).

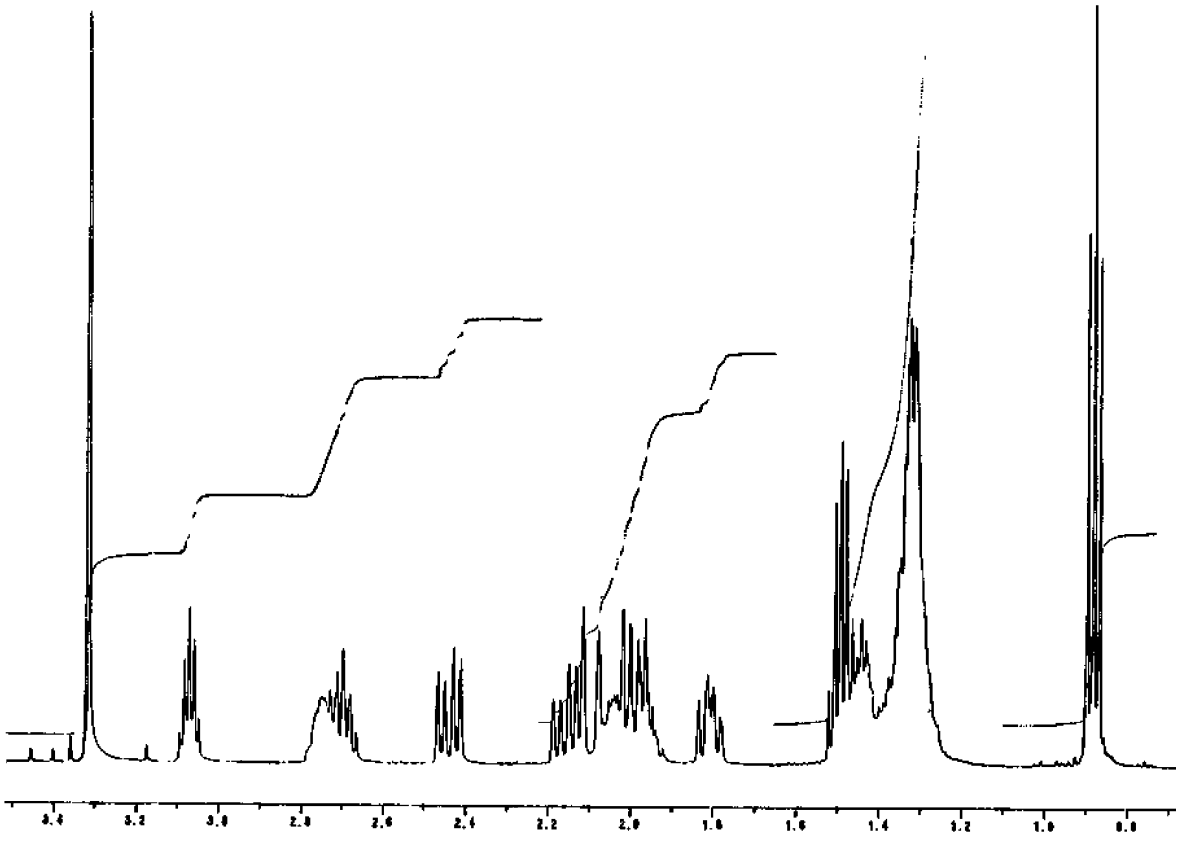


Figure 2. [1]H NMR Spectrum of **3** (500 MHz).

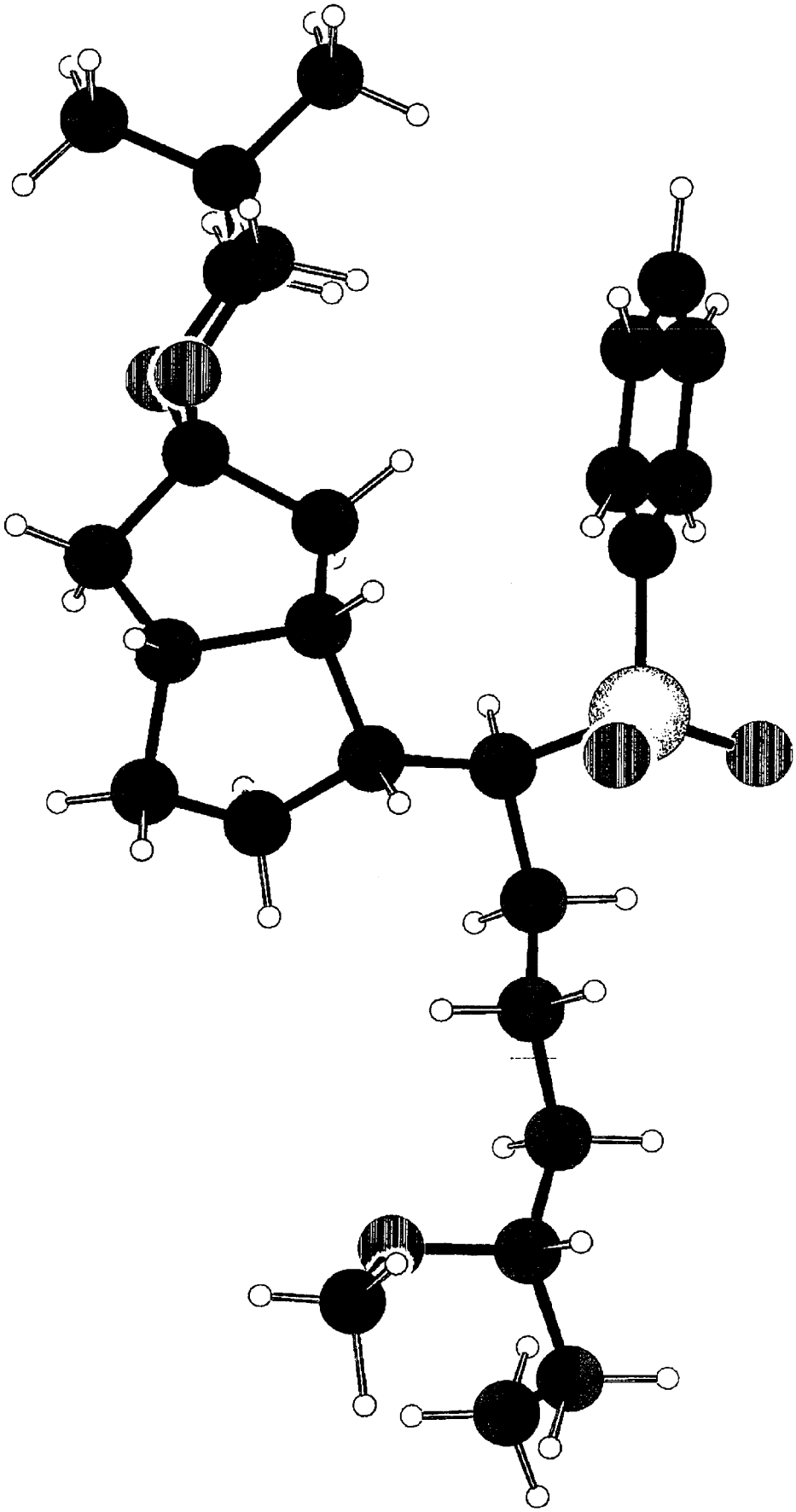


Figure 3. Crystal structure of sulfone **50**.

under reduced pressure. The residue was purified by chromatography.

TP 2. DIBALH reduction of esters. The ester (10 mmol) in diethylether (25 mL) was cooled to −90 °C and treated dropwise with a 1.2 M solution (10 mL, 12 mmol) DIBAL-H in toluene at a temperature of below −85 °C. The mixture was stirred for 2 h at −90 °C. A satd. aqueous solution of tartaric acid (10 mL) was added, the organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography.

2.2.1. Synthesis of 1 by Pauson–Khand-cyclization. Compound **6** (22.94 g, 50.0 mmol) in ethyl acetate (150 mL) was added dropwise to a suuspension of Pd/$BaSO_4$ (10%, 1.50 g) in ethyl acetate (60 mL) and stirred under a hydrogen atmosphere (1 bar) at 0 °C until no more hydrogen was absorbed. The mixture was filtered over silica gel, concentrated under reduced pressure and chromatographed (ethyl acetate/hexanes 1:2) to furnish **7** (16.98 g, 92%) as a colorless oil which crystallized in long needles of mp 77 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.08, 0.09 (two s, 6H), 0.17 (s, 9H), 0.90 (s, 9H), 1.48–1.61 (m, 1H), 1.67 (br. 1H), 1.79 (dq, J=14, 7 Hz, 1H), 1.92 (dq, J=14, 7 Hz, 1H), 2.06 (dd, J=18, 4.5 Hz, 1H), 2.54–2.63 (m, 2H), 2.91 (dd, J=19, 4.5 Hz, 1H), 2.96–3.07 (m, 1H), 3.72 (mc, 2H), 4.42 (t, J=4.5 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ [ppm]=−5.04, −4.47, −1.29, 17.92, 25.74, 31.63, 40.01, 42.58, 47.05, 49.97, 60.77, 75.02, 135.69, 196.23, 214.14 ppm. IR (KBr): ν=2955, 2928, 1691, 1608, 840, 777 cm^{-1}. $[\alpha]_D$=65.6 (c=1.4, $CHCl_3$). Anal. Calcd for $C_{19}H_{36}O_3Si_2$: C, 61.90; H 9.84. Found: C, 62.06, H, 9.86.

2.2.2. Swern-oxidation. Swern-oxidation of **7** (8.40 g, 22.8 mmol) was performed according to TP1. Aldehyde **8** (8.02 g, 96%) was obtained as colorless needles of mp 67 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.03, 0.07 (two s, 6H), 0.18 (s, 9H), 0.89 (s, 9H), 1.83–1.95 (m, 1H), 2.01 (dd, J=17, 4.5 Hz, 1H), 2.52 (dd, J=17, 7 Hz, 1H), 2.57 (d, J=19.5 Hz, 1H), 2.62 (dd, J=18, 5 Hz, 1H), 2.85–3.05 (m, 3H), 4.55 (t, J=5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=−5.09, −4.54, −1.30, 17.86, 25.72, 39.75, 41.79, 43.04, 44.49, 49.48, 74.26, 136.40, 193.95, 201.02, 212.88. IR (KBr): ν=2935, 1716, 1685, 1602, 840 cm^{-1}. $[\alpha]_D$=53.8 (c=1.4, $CHCl_3$). Anal. Calcd for $C_{19}H_{34}O_3Si_2$: C, 62.24; H 9.35. Found: C, 61.91, H, 9.44.

2.2.3. Wittig reaction of 8 with 9 to form 10. Phosphonium salt **9** (8.0 g, 18.5 mmol) and AgCl (0.85 g, 5.9 mmol) in THF (80 mL) was treated dropwise with *n*-butyllithium (1.6 M in hexane, 14.4 mL) at 26 °C. The mixture was cooled to −78 °C and **8** (2.70 g, 7.36 mmol) in THF (15 mL) was added dropwise and the mixture was stirred for 15 more min. Workup with water and hexanes furnished after chromatography (ethyl acetate/hexanes 1:10) olefin **10** (2.99 g, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.08 (s, 6H), 0.17 (s, 9H), 0.89 (t, J=7.5 Hz, 1H), 0.90 (s, 9H), 1.36–1.56 (m, 1H), 2.02 (dd, J=17.5, 4.5 Hz, 1H), 2.17–2.44 (m, 1H), 2.55 (dd, J=17.5, 6.5 Hz, 1H), 2.58 (d, J=19.5 Hz, 1H), 2.91 (dd, J=19.5, 4.5 Hz, 1H), 2.96–3.04 (m, 1H), 3.13 (quint, J=6 Hz, 1H), 3.35 (s, 3H), 4.41 (t, J=4.5 Hz, 1H), 5.40–5.56 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=−4.98, −4.44, −1.23, 9.43, 17.99, 25.79, 25.96, 26.85, 30.76, 40.06, 42.98, 50.23, 51.10, 56.56, 75.04, 81.95, 126.67, 129.36, 135.84, 195.66, 213.83. IR (KBr): ν=2926, 1690, 1606, 835, 774 cm^{-1}. $[\alpha]_D$=34.1 (c=1.1, $CHCl_3$). Anal. Calcd for $C_{25}H_{46}O_3Si_2$: C, 66.61; H 10.29. Found: C, 66.50, H, 10.21.

2.2.4. Catalytic hydrogenation of 10. To **10** (2.34 g, 5.19 mmol) in acetic acid (50 mL) was added Pd/C (10%, 120 mg) and the mixture was hydrogenated at 3 bar for 6 h. The mixture was filtered, 5 mL of water was added and the solution was heated to 50 °C for 15 h, concentrated under reduced pressure, diluted with ether, dried (MgSO4) and chromatographed (ethyl acetetae/hexanes 1:10) to give **11** (1.17 g, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 1.26–1.65 (m, 13H), 1.97 (ddd, J=19.5, 6.5, 1.5 Hz, 1H), 2.02–2.24 (m, 2H), 2.48–2.65 (m, 3H), 2.97 (m, 1H), 3.10 (quint, J=5.5 Hz, 1H), 3.33 (s, 3H), 4.30 (br, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.26, 25.50, 25.63, 28.28, 28.49, 32.74, 36.33, 42.87, 43.21, 43.35, 44.98, 52.65, 56.23, 74.74, 81.93, 220.60. IR (KBr): ν=2930, 1735, 1090. cm^{-1}. $[\alpha]_D$=−27.5 (c=1.1, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H 10.52. Found: C, 71.25, H, 10.52.

2.2.5. Barton–McCombie-dehydroxylation of 11 to give 1. *Compound* **11** (700 mg, 2.61 mmol), pyridine (619 mg, 7.83 mmol), and phenoxy-chlorothioformate (585 mg, 3.89 mmol) in methylene chloride (5 mL) were stirred at rt for 16 h. Workup with water and ether furnished after chromatography (ethyl acetate/hexanes 1:10) **12** (953 mg, 90%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 1.26–1.56 (m, 10H), 1.69–1.86 (m, 2H), 2.00 (ddd, J=19, 7, 1.5 Hz, 1H), 2.09–2.22 (m, 1H), 2.47–2.68 (m, 4H), 2.96 (mc, 1H), 3.09 (quint, J=5.5 Hz, 1H), 3.33 (s, 3H), 5.75 (t, J=4 Hz, 1H), 7.12, 7.31, 7.44 (three mc, 3H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.21, 25.36, 25.64, 28.05, 28.38, 32.73, 36.24, 40.03, 43.13, 43.90, 44.72, 51.13, 56.27, 74.74, 81.70, 88.82, 121.72, 126.37, 129.34, 153.10, 194.09, 219.15. IR (KBr): ν=2936, 1737, 1276, 692 cm^{-1}. $[\alpha]_D$=−29.8 (c=1.6, $CHCl_3$). Anal. Calcd for $C_{23}H_{32}O_4S$: C, 68.28; H 7.97. Found: C, 68.27, H, 7.93.

Compound **12** (750 mg, 1.85 mmol) and tributyltin hydride (646 mg, 2.22 mmol) and AIBN (5 mg) in toluene (10 mL) were heated to 90 °C for 2 h. Additional tributyl tinhydride (110 mg, 0.38 mmol) was added and the heating was continued for another 30 min. The mixture was concentrated under reduced pressure and chromatographed (ethyl acetate/hexanes 1:10). The eluate was treated with NaOH (7% in water, 10 mL), washed with water, dried ($MgSO_4$) and chromatographed (ethyl acetate/hexanes 1:10) to give **1** (416 mg, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 1.18–1.61 (m, 13H), 1.69–1.86 (m, 2H), 1.89–2.13 (m, 4H), 2.16–2.28 (m, 1H), 2.40–2.53 (m, 2H), 2.72 (mc, 1H), 3.08 (quint, J=5.5 Hz, 1H), 3.33 (s, 3H. ^{13}C NMR ($CDCl_3$): δ [ppm]=9.19, 25.43, 25.67, 28.61, 32.87, 35.4, 39.19, 43.85, 44.72, 46.16, 47.19, 56.21, 81.83, 220.64. IR (KBr): ν=2858, 1736, 1093 cm^{-1}. $[\alpha]_D$=−14.8 (c=1.6, $CHCl_3$). MS (80 eV, 40 °C): m/z=252, 223, 73. Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H 11.18. Found: C, 76.06, H, 11.15.

2.3. Trost–Tsuji-reaction for attaching the sidechain. Synthesis of 1, 2, 3, and 4

2.3.1. Synthesis of 23. Enantiomerically (>99% ee) pure carbacyclin **22** (40.45 g, 142 mmol) was oxidized under Swern oxidation (TP) to give, after chromatography (ethyl acetate/hexanes 1:3) ester **23** (60:40 keto-enol mixture) (32.21 g, 87%) as a yellowish oil which solidified to give waxy crystals of mp 60–63 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.94, 0.99 and 0.96, 0.97 (all s, 6H), 1.59–3.0 (m, 8H), 3.28 (m, 0.6H), 3.45, 3.49, 3.51 (all s, 4H), 3.76, 3.80 (all s, 3H), 10.26 (0.4H). ^{13}C NMR ($CDCl_3$): δ [ppm]= 22.34, 22.39, 22.50, 30.04, 33.53, 35.01, 37.68, 38.72, 38.89, 40.59, 41.00, 42.11, 44.63, 50.92, 52.38, 60.62, 71.63, 71.80, 72.29, 72.52, 101.07, 108.69, 109.15, 170.18. IR (KBr): ν=2960, 1665, 1615, 1440, 1325, 1275, 1250, 1110 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H 7.85. Found: C, 62.98, H, 7.62.

2.3.2. Synthesis of 24b. Ester **23** (8.00 g, 28.1 mmol) in THF (50 mL) was added dropwise to a suspension of NaH (60% in mineral oil) (1.24 g, 31 mmol) in THF (50 mL) at room temperature. The mixture was refluxed for 5 min and then added to a mixture of $Pd(PPh_3)_4$ (3.28 g, 2.80 mmol), triphenylphophine (15.2 g, 56.2 mmol) and allylacetate **21** (5.50 g, 29.5 mmol) which had previously been stirred at room temperature for 1 h. The new mixture was stirred at 70 °C for 4 h, concentrated under reduced pressure, diluted with DCM, chromatographed (ethyl acetate/hexanes 1:4) and purified by HPLC (*i*-PrOH/*n*-hexane 2:98) to obtain **24b** (6.90 g, 60%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.87 (t, J=7.5 Hz, 1H), 0.95, 0.97 (two s, 6H), 1.36–1.56 (m, 2H), 1.66–1.72 (m, 1H), 1.78 (dd, J=13.8, 4.5 Hz, 1H), 2.18 (t, J=7.5 Hz, 2H), 2.30 (t, J=7.5 Hz, 1H), 2.28–2.34 (m, 2H), 2.50–2.74 (m, 2H), 2.55 (t, 2H), 2.57–2.90 (m, 1H), 3.09 (m, 1H), 3.44, 3.48 (two s, 4H), 3.71 (s, 3H), 5.27–5.42 (m, 1H), 5.43–5.80 (m, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.28, 22.21, 22.29, 25.73, 29.95, 33.51, 35.95, 36.65, 38.38, 40.80, 44.79, 46.82, 56,.41, 63.41, 71.28, 72.68, 81.62, 108.79, 125.87, 131.65, 171.30, 214.26. IR (film): ν=2960, 1765, 1735, 1330, 1240, 1210, 1120, 1100, 1010 cm^{-1}. $[\alpha]_D$=−33.4 (c=1.4, $CHCl_3$). MS(EI, 80 eV, 40 °C): m/z=408, 393, 377, 349, 335, 128, 73, 41. HRMS Calcd for $C_{23}H_{36}O_6$: m/z=408.2512. Found: 408.2532.

2.3.3. Hydrogenation to 25b. Pd/C (10%, 258 mg) in ethyl acetate (30 mL) was treated with **24b** (2.58 g, 6.32 mmol) and then hydrogenated under normal pressure for 15 h. After filtration over celite the mixture was chromatographed (ethyl acetate/hexanes 1:3) to give **25b** (2.25 g, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.86 (t, J= 7.5 Hz, 1H), 0.95, 0.97 (two s, 6H), 1.08–1.56 (m, 8H), 1.54–1.96 (m, 4H), 2.24–2.48,2.58–2.82 (2m, 6H), 2.96–3.10 (m, 1H), 3.30 (m, 3H), 3.44, 3.48 (two s, 4H), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.15, 22.13, 22.19, 24.43, 25.41, 25.60, 29.87, 32.48, 33.56, 36.69, 40.78, 44.51, 48.22, 51.71, 52.20, 63.29, 71.25, 72.53, 81.62, 108.69, 171.32, 213.97. IR (film): ν=2960, 1745, 1730, 1330, 1240, 1205, 1120, 1095, 1010 cm^{-1}. $[\alpha]_D$=−36.1 (c=1.0, $CHCl_3$). Anal. Calcd for $C_{23}H_{38}O_6$: C, 67.29; H 9.33. Found: C, 67.09, H, 9.36.

2.3.4. Decarboxymethylation of 25b to 26b. *Compound* **25b** (2.18 g, 5.30 mmol) in *o*-xylene (10 mL) and water (0.9 mL) was treated with DABCO (6.00 g, 53 mmol) and refluxed for 16 h. The mixture solidified on cooling and was dissolved in toluene and chromatographed to give a 3:1 mixture of **26b** and **27b** (1.27 g, 67%) which was treated with NaOMe (0.077 mmol) in MeOH/THF (1:1, 4 mL) for 17 h at room temperature. The mixture was concentrated under reduced pressure, diluted with ether, extracted with satd. aq. ammonium chloride (10 mL), dried ($MgSO_4$) and purified by HPLC (hexane/*i*-PrOH 99:1) to give **26b** (1.16 g, 62%) and **27b** (70 mg, 4%) as colorless oils.

Compound **26b**. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J= 7.5 Hz, 1H), 0.92, 0.98 (two s, 6H), 1.18–1.58 (m, 9H), 1.60–1.80 (m, 2H), 1.90 (dd, J=13.5, 4.0 Hz, 1H), 2.02–2.15 (m, 1H), 2.16–2.54 (m, 5H), 2.66–2.84 (m 1H), 3.00–3.14 (m, 1H), 3.32 (s, 3H), 3.44, 3.48 (two s, 4H.). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.30, 22.39, 25.37, 25.80, 27.41, 30.01, 30.77, 32.80, 34.78, 41.11, 41.20, 43.64, 43.82, 54.34, 56.31, 71.93, 72.25, 81.94, 109.67, 221.13. IR (film): ν= 2940, 2860, 1730,1150, 1095 cm^{-1}. $[\alpha]_D$=27.4 (c=0.9, $CHCl_3$). Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H 10.29. Found: C, 71.40, H, 10.34.

Compound **b** ^{1}H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J= 7.5 Hz, 1H), 0.96, 0.98 (two s, 6H), 1.10–1.58 (m, 10H), 1.72–1.96 (m, 2H),2.04 (dd, J=18, 7 Hz, 1H); 2.24–2.41 (m, 2H), 2.50–2.77 (m, 2H), 2.80–2.96 (m, 1H), 3.07 (quint., 1H), 3.32 (s, 3H), 3.43 and 3.50 (two s, 4H): 2.24–2.48, 2.58–2.82 (2m, 6H), 2.96–3.10 (m, 1H), 3.30 (m, 3H), 3.44, 3.48 (two s, 4H), 3.72 (s, 3H).

2.3.5. Synthesis of 28b. $LiAlH_4$ (63 mg, 1.7 mmol) in THF (5 mL) at 0 °C was treated dropwise with **26b** (580 mg, 1.65 mmol) in THF (5 mL) for 15 min. The mixture was warmed to room temperature and stirred for additional 2 h. Workup with water and NaOH delivered after chromatography (ethyl acetate/hexanes 1:1) **28b** (581 mg, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J= 7.5 Hz, 1H), 0.95, 0.98 (two s, 6H), 1.10–1.88 (m, 15H), 1.96–2.28 (m, 4H), 2.30–2.50 (m, 1H), 3.08 (quint, 1H)), 3.32 (s, 3H), 3.46, 3.47 (two s, 4H.). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.32, 22.47, 22.50, 25.75, 28.14, 30.04, 32.86, 33.61, 36.12, 40.17, 40.75, 41.77, 44.38, 54.38, 56.28, 71.28, 72.25, 79.73, 82.01, 110.40. IR (film): ν=3430, 29940, 1460, 1325, 1110, 1040, 1015 cm^{-1}. Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.15; H 10.80. Found: C, 71.30, H, 10.95.

2.3.6. Synthesis of 29b. *Compound* **28b** (579 mg, 1.6 mmol) in DCM (5 mL) were treated at 0 °C with pyridine (0.4 g, 7.49 mmol) and *O*-phenylchlorothioformate (0.42 g, 2.42 mmol) in DCM (2 mL) at 0 °C. The mixture was stirred at room temp. for 3 h and then subjected to aqueous workup to give, after chromatography (ethyl acetate/hexanes 1:6) **29b** (748 mg, 94%) of a slightly yellow oil.

^{1}H NMR ($CDCl_3$): δ [ppm]=0.91 (t, J=7.5 Hz, 1H), 0.98, 1.00 (two s, 6H), 1.20–1.90 (m, 13H), 1.98–2.36 (m, 4H), 2.40–2.62 (m, 2H), 3.08 (quint, 1H)), 3.32 (s, 3H), 3.48 (s, 4H.), 5.10–5.28 (m, 1H), 7.00–7.16, 7.22–7.32, 7.34–7.48 (m, 5H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.33, 22.48, 22.50,

25.62, 25.80, 27.90, 30.08, 32.92, 33.28, 36.54, 36.70, 39.93, 40.40, 43.76, 50.55, 56.37, 71.78, 72.40, 81.99, 91.16, 109.94, 121.97, 126.38, 129.42, 153.37, 194.73.

IR (film): ν=2940, 1490, 1470, 1460, 1300, 1100, 1015 cm^{-1}. HRMS Calcd for $C_{21}H_{37}O_3$ ($M-C_7H_5O_2S$): m/z=337.27427. Found: 337.274160.

2.3.7. Synthesis of 2. *Compound* **28b** (1.29 g, 2.63 mmol) was reduced with tributyltin hydide as described for **12** to give **30b** (685 mg, 77%) as a colorless oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J=7.5 Hz, 1H), 0.95, 0.96 (two s, 6H), 1.06–1.68 (m, 15H), 1.76–1.94 (m, 2H), 1.95–2.09 (m, 1H), 2.22 (dd, J=13.5, 8.8 Hz, 2H), 2.36–2.58 (m, 1H), 3.08 (quint, 1H)), 3.32 (s, 3H), 3.44, 3.48 (two s, 4H.). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.32, 22.51, 25.83, 28.77, 30.05, 33.00, 33.84, 35.37, 40.08, 40.27, 47.47, 56.29, 71.63, 72.40, 82.07, 110.56. IR (film): ν=2940, 1460, 1115, 1040, 1015 cm^{-1}. $[\alpha]_D$=−18.9 (c=1.3, $CHCl_3$). Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H 11.31. Found: C, 74.69, H, 11.25. **30b** (650 mg, 1.92 mmol) in water/acetone (v/v 5:95, 130 mL) was stirred with *p*-TsOH (183 mg) at room temperature for 16 h and then neutralized with solid $NaHCO_3$, concentrated under reduced pressure, diluted with water, and extracted with ether. The ether phase was washed with water, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 1:10) to furnish **2** (484 mg, 99%) as a colorless oil. $[\alpha]_D$=−14.4 (c=1.1, $CHCl_3$). The spectral data are within the limits of detection identical with those of **1**.

2.3.8. Synthesis of 31a. Keto ester **24a** (4.90 g, 12.00 mmol) in methanol (80 mL) was treated in portions at −40 °C with solid sodium borohydride (240 mg, 6.2 mmol) and stirred for 2 h. after additional 1 h at room temperature the mixture was concentrated under reduced pressure and diluted with ether (200 mL), washed with water, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 1:1 to give **31a** (4.48 g, 91%) as a colorless oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.87 (t, J=7.5 Hz, 1H), 0.91, 1.00 (two s, 6H), 1.08–1.95 (m, 14H), 2.04–2.18 (m, 1H), 2.23–2.33 (m, 1H), 2.44–2.65(m, 3H), 2.99–3.08 (m, 1H)), 3.30 (s, 3H), 3.44, 3.45, 3.48, 3.50 (4s, 4H.). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.24, 22.35,22.49, 25.37, 25.67, 25.71, 30.60, 32.73, 37.59, 37.93, 38.15, 38.83, 40.04, 48.85, 51.38, 56.34, 61.45, 71.15, 72.89, 79.32, 81.82, 109.06, 176.35. IR (film): ν=2940, 1710, 1115, 1095, 1015 cm^{-1}. MS (EI, 80 eV, 80 °C): m/z=412, 397, 351, 335, 295, 284, 265, 181, 168, 128, 95, 69, 41. $[\alpha]_D$=7.7 (c=1.3, $CHCl_3$). Anal. Calcd for $C_{23}H_{40}O_6$: C, 66.96; H 9.77. Found: C, 66.67, H, 7.75.

2.3.9. Synthesis of 33a. *Compound* **31a** (4.80 g, 11.63 mmol) in methanol/water (v/v 2:1, 75 mL)) was treated with KOH (4.0 g, 7.13 mmol) in water (10 mL) and the mixture was stirred at 100 °C for 20 h, concentrated under reduced pressure and extracted with ether. The aqueous phase was acidified with 2 N HCl to pH 3 and extracted with ether. The ether phase was washed with water, dried ($MgSO_4$) and evaporated to dryness to give **32a** (4.30 g, 95%) as a colorless foam, which was dissolved in THF (250 mL) and treated with triphenylphosphane (2.83 g, 10.8 mmol). Diethyl azodicarboxylate (DEAD, 1.88 g, 10.8 mmol) was added dropwise at 50 °C, until no more carbon dioxide was evolved. The solvent was removed under reduced pressure and the residue was dissolved in ether (170 mL) and pentane (30 mL). The crystalline residue of hydrazo ester and phophine oxide was removed by filtration and the filtrate was chromatographed (hexanes/ethyl acetate) to give olefin **33a** (2.37 g, 61%) as a colorless oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.88 (t, J=7.5 Hz, 1H), 0.96 (s, 6H), 1.28–1.62 (m, 10H), 1.84–2.18 (m, 3H), 2.25–2.42 (m, 2H), 2.48–2.58 (m, 1H), 2.66–2.80 (m, 1H)), 2.92–3.16 (m, 2H), 3.32 (s, 3H), 3.46, 3.51 (2s, 4H., 5.16 (s, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.27, 22.45, 25.24, 25.80, 27.78, 29.38, 30.03, 32.86, 37.66, 38.04, 38.26, 41.04, 48.97, 56.27, 71.42, 72.49, 81.93, 109.49, 121.16, 146.60. IR (film): ν=3940, 3860, 1115, 1095 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=336, 218, 189, 176, 160, 147, 128, 105, 91, 79, 69, 55, 41. $[\alpha]_D$=−8.24 (c=1.5, $CHCl_3$). Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.96; H 10.78. Found: C, 74.75, H, 10.87.

2.3.10. Synthesis of 34a. Olefin **33a** (2.25 g, 6.69 mmol) in ethanol (100 mL) was hydrogenated with Rh/C (5%) (113 mg) at 0 °C under normal pressure for 8 h. The mixture was filtered over celite and evaporated under reduced pressure and chromatographed (hexanes/ethyl acetate 10:1) to furnish **34a** (1.69 g, 75%) as a colorless oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 0.94 and 0.98 (two s, 6H), 1.12–1.66 (m, 16H), 1.67–1.84 (m, 1H), 2.04 (m, 1H), 2.36–2.60 (m, 3H), 3.07 (m, 1H), 3.32 (s, 3H), 3.46, 3.49 (2s, 4H. ^{13}C NMR ($CDCl_3$): δ [ppm]=9.30, 22.48, 25.70, 25.84, 29.14, 29.54, 30.09, 30.83, 32.26, 33.04, 34.13, 39.05, 40.88, 42.59, 43.37, 56.33, 71.26, 73.06, 82.08, 109.15. IR (film): ν=2940, 1435, 1110, 1095 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=338, 323, 309, 265, 241, 223, 209, 181, 167, 141, 128, 95, 81, 73, 55, 41. $[\alpha]_D$=−35.2 (c=1.5, $CHCl_3$). Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H 11.31. Found: C, 74.19, H, 11.36.

2.3.11. Synthesis of 3. *Compound* **34a** (1.55 g, 4.58 mmol) in acetone/water (20:1, 250 mL) was treated with *p*-TsOH (220 mg, 1.15 mmol) for 20 h at room temperature. The mixture was neutralized with NaHCO3, concentated under reduced pressure and extracted with ether. The ether phase was washed with brine, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate (5:1) to give **3** (1.12 g, 97%) as a slightly yellow oil. ^1H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.5 Hz, 1H), 1.12–1.66 (m, 16H), 1.24–1.55 (m, 12H), 1.78–1.87 (m, 1H), 1.91–2.23 (m, 5H), 2.44 (ddd, J=19, 8, 2 Hz, 1H), 2.6–2.84 (m, 2H), 3.07 (m, 1H),3.32 (s, 3H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.19, 25.46, 25.72, 28.97, 30.07, 31.60, 31.48, 32.92, 37.68, 39.40, 43.48, 43.58, 45.46, 56.24, 81.90, 220.38. IR (film): ν=2930, 2850, 1740, 1465, 1400, 1200, 1155, 1090 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=252, 223, 191, 173, 133, 95, 81, 73, 67, 55, 41. $[\alpha]_D$=−113.4 (c=1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H 11.18. Found: C, 76.13, H, 11.24.

2.3.12. Synthesis of 4. The title compound was performed analogously from **24b**. The spectra were indistinguishable from those of **3**. $[\alpha]_D$=−105.4 (c=1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H 11.18. Found: C, 75.92, H, 10.99.

2.4. Synthesis of 1, 2 and 4 via sulfone-alkylation

2.4.1. Synthesis of 39. Butane-1,4-diol (443 mL, 5.00 mol) was treated with KOH (132.0 g, 2.00 mol). Water was removed under reduced pressure at 110 °C. Benzyl chloride (230 mL, 2.0 mol) was added dropwise, so that the temperature was above 90 °C. The mixture was stirred at 130 °C for 2 h, cooled to room temperature and diluted with water (1 L), extracted with ether. The ether phase was dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue was distilled at 0.5 mbar to give the monobenzyl ether (238 g, 66%) as a colorless oil, of which 18.00 g (99.9 mmol) were oxidized under Swern conditions (TP) to give aldehyde **36** (17.18 g, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.92 (t, J=7.8 Hz, 1H), 1.36–1.52 (m, 3H), 1.53–1.81(m, 3H), 2.63 (s, 1H), 3.49 (t, J=6 Hz, 2H), 3.49 (m, 1H), 4.50 (s, 2H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.89, 26.02, 30.04, 33.89, 70.42, 72.69, 72.82, 127.45, 128.24, 138.12.

2.4.2. Synthesis of (*S*)-38. Ditriflate (*R*,*R*-**37**) (927 mg, 2.45 mmol) in toluene (30 mL) was treated with Ti(O*i*Pr)$_4$ (21.9 mL, 73.6 mmol) and the mixture was stirred at 40 °C for 1 h. The mixture was cooled to −78 °C and diethylzinc (1 M in hexane, 135 mL) was added dropwise. A dark red solution was obtained which was treated dropwise with aldehyde **36** (10.93 g, 61.3 mmol) in toluene (10 mL) and the mixture was stirred at −30 °C for 5 h. The reaction was quenched with 2 N HCl (120 mL) and the ether phase was washed with brine, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 5:1) to furnish (*S*)-**38** (11.87 g, 93%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.92(t, J=7.8 Hz, 1H), 1.36–1.52 (m, 3H), 1.53–1.81 (m, 3H), 2.63 (s, 1H), 3.49 (t, J=6 Hz, 2H), 3.49 (m, 1H), 4.50 (s, 2H), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.89, 26.02, 30.04, 3.89, 70.42, 72.69, 72.82, 127.45, 128.24, 138.12. IR (film): ν=3415, 2934, 2858, 1495, 1453, 1362, 1099, 994, 962 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=208, 190, 179, 161, 147, 117, 107, 91, 71, 41. $[\alpha]_D$=7.1 (c=1.92, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H 9.68. Found: C, 74.22, H, 9.48.

2.4.3. Synthesis of (*S*)-39. *Compound* (*S*)-**38** (17.85 g, 85.7 mmol) in DMF (400 mL) was deprotonated with NaH (80%, 6.0 g, 214 mmol) at 0 °C.The mixture was stirred at room temperature for 1 h, cooled to 0 °C and treated dropwise with methyl iodide (21.3 mL, 343 mmol) in DMF (50 mL). The mixture was stirred overnight, quenched with water. The product was extracted with ether and the ether phase was dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 5:1) to give the methyl ether (18.72 g, 98%) as a colorless oil. For debenzylation the methyl ether (18.72 g, 84 mmol) in MeOH (300 mL) was hydrogenated over Pd/C (5%, 400 mg) at normal pressure. After filtration the solvent was removed under reduced pressure and the residue was chromatographed (hexanes/ethyl acetate 1:1) to give the mono alcohol (11.13 g, 100%) as a colorless oil. To prepare the bromide (*S*)-**39**, the alcohol (500 mg, 3.78 mmol) in DCM (8 mL) was added dropwise to mixture of triphenyl phosphine (2.78 mg, 10.58 mmol) and NBS (2.02 g, 11.34 mmol) in DCM (24 mL) and stirred overnight. The mixture was diluted with aqueous $NaHCO_3$ and extracted with ether. The ethereal extract was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was diluted with pentane, filtered and distilled (85–90 °C, 12 mbar) to give (*S*)-**39** (520 mg, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.90(t, J=7.6 Hz, 1H), 1.40–1.72 (m, 4H), 1.79–2.07 (m, 2H), 3.13 (quint, J=6 Hz, 1H), 3.32 (s, 3H), 3.44 (t, J=7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.30, 25.73, 28.62, 31.49, 34.20, 56.38, 81.14. IR (film): ν=2984, 2934, 2877, 1092 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=195, 193, 167, 165, 109, 107, 85, 73, 55, 45. $[\alpha]_D$=4.7 (c=3.03, $CHCl_3$). HRMS Calcd for $C_7H_{15}OBr$: 193.02281. Found: C, 193.02278.

2.5. Synthesis of 1 and 2

2.5.1. Synthesis of 40. Ester **22** (15.20 g, 53.4 mmol) in pyridine (60 mL) was treated with DMAP (100 mg) and then MsCl (8.3 mL, 107 mmol) was added dropwise. The mixture was stirred overnight at room temperature, water (50 mL) and ether (50 mL) were added. The phases were separated and the ethereal phase was washed with brine, dried ($MgSO_4$) and evaporated to give the mesylate as a colorless solid (18.09 g, 49.9 mmol) of mp 84–85 °C.

The mesylate (9.00 g, 24.8 mmol) in ether (150 mL) and treated dropwise at −20 °C with $LiALH_4$ (1.6 M in THF, 31.3 mL) for 15 min. The mixture was warmed to room temperature and stirred for another 90 min and quenched with *i*PrOH and then water. $MgSO_4$ and silicagel were added and the mixture was stirred overnight, filtered and chromatographed to furnish alcohol **40** (4.33 g, 73%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.94 (s, 3H), 1.36 (m, 2H), 1.63 (m, 3H), 1.87 (m, 3H), 2.21 (m, 3H), 2.51 (m, 1H), 3.46 (s, 2H), 3.50 (m, 1H). ^{13}C NMR ($CDCl_3$): δ [ppm]=22.46, 29.97, 30.04, 32.29, 39.60, 40.20, 40.28, 49.72, 66.31, 71.69, 72.34, 110.23. IR (film): ν=3428, 2949, 2866, 1109 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=240, 225, 209, 197, 181, 167, 155, 141, 128, 95, 81,69, 55. $[\alpha]_D$=22.6 (c=1.0, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}O_2$: C, 69.96; H 10.07. Found: C, 70.22, H, 9.88. For the preparation of the tosylate, alcohol **40** (9.13 g, 38.0 mmol) in pyridine (45 mL) was treated with DMAP (300 mg) and tosyl chloride (10.9 g, 57 mmol) was added in portions at 0 °C and the mixture was stirred for 16 h at room temperature. The reaction was quenched with water and the mixture was extracted with ether. The organic phase was washed with 2 N HCl, water, $NaHCO_3$ and brine, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 2:1) to give the tosylate (14.66 g, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.94 (s, 3H), 1.16–1.43 (m, 2H), 1.60 (m, 2H), 1.80 (m, 2H), 1.95–2.18 (m, 4H), 2.45 (s, 3H), 2.47 (m, 1H), 3.43 (s, 2H), 3.44 (s, 2H), 3.90 (d, J=7 Hz, 2H), 7.34 (d, J=9 Hz, 2H), 7.78 (d, J=9 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=21.62, 22.46, 30.08, 32.19, 38.97, 40.12, 40.25, 43.56, 46.06, 71.83, 72.20, 73.38, 109.96, 127.84, 129.78, 144.60. IR (film): ν=2952, 2867, 1362, 1109 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=394, 239, 223, 209, 167, 137, 91, 69, 41. $[\alpha]_D$=28.7 (c=1.4, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}O_5S$: C, 63.93; H 7.66. Found: C, 63.76, H, 7.45. To prepare the iodide, the tosylate (13.05 g, 33.1 mmol) in acetonitrile (130 mL) was treated with sodium iodide (10.91 g, 72.8 mmol) and the mixture was refluxed for 3 h. After cooling to room temperature water and ether were added and the ether phase was washed with

water, sodium thiosulfate and brine, dried ($MgSO_4$), and evaporated to give the iodide (11.58 g, 100%) as a slightly yellow oil ($[\alpha]_D=-20.1$ ($c=1.21$, $CHCl_3$)) which was used for the next step without purification. Sodium phenylsulfinate (8.15 g, 49.7 mmol) in DMF (200 mL) was added and the mixture was stirred at 110 °C overnight, cooled to room temperature, quenched with $NaHCO_3$ and extracted with ether. The ether phase was washed with brine, dried ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 2:1) to give sulfone **41** (9.49 g, 79%) along with the sulfinate (1.99 g, 17%).

Compound **41**. Solid with mp 60–61 °C: ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (s, 3H), 1.20–1.44 (m, 2H), 1.55–1.74 (m, 2H), 1.88 (m, 1H), 2.02 (m, 1H), 2.07–2.25 (m, 4H), 2.49 (m, 1H), AB-part of an ABX system: δ_A 3.05, δ_B 3.17, (J= 14, 7, 5.8 Hz, 2H), 3.41 (d, J=11 Hz, 1H), 3.46 (d, J= 11 Hz, 1H), 7.60 (m, 3H), 7.92 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=22.40, 22.58, 30.00, 32.58, 33.91, 39.55, 40.99, 47.29, 61.26, 71.86, 72.06, 109.84, 127.86, 129.22, 133.49, 140.06. IR (film): ν=2952, 2868, 1462, 1109, 1086 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=364, 279, 223, 209, 167, 137, 109, 95, 69, 55, 41. $[\alpha]_D=-30.2$ ($c=2.28$, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}O_4S$: C, 65.90; H 7.74. Found: C, 65.62, H, 7.51.

Sulfinate. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.95 (s, 3H), 0.96 (s, 3H), 1.13–1.43 (m, 2H), 1.60 (m, 2H), 1.81 (m, 2H), 1.92–2.21 (m, 4H), 2.46 (m, 1H), 3.42 (s, 2H), 3.44 (s, 2H), 3.45 (m, 1H), 3.92 (m, 1H), 7.54 (m, 3H), 7.70 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=22.50, 30.04, 30.33, 32.33, 39.24, 40.15, 43.79, 46.77, 46.85, 67.31, 71.79, 72.25, 110.06, 125.24, 128.98, 131.99. IR (film): ν=2867, 1444, 1132, 1108, 944 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=364, 279, 239, 223, 209, 208, 167, 137, 125, 95, 81, 69, 55.

2.5.2. Alkylation of sulfone 41. Preparation of 42a. Sulfone **41** (2.00 g, 5.49 mmol) in THF (8 mL) was treated dropwise with *n*BuLi (1.6 M in hexane, 3.95 mL, 6.31 mmol) at −20 °C. The mixture was slowly warmed to room temperature, then cooled to −20 °C and HMPA (3.82 mL) was added dropwise and the mixture was stirred at room temperature for 30 min. Then the mixture was cooled to −30 °C and treated dropwise with bromide (*S*)-**39** (1.29 g, 6.59 mmol) in THF (1 mL). Workup with water and ether furnished after HPLC (hexane/*i*PrOH 99.2:1) **42a** (1.58 g, 60%) as a diastereomeric mixture. First diastereomer: ^{1}H NMR ($CDCl_3$): δ [ppm]=0.80 (t, J=7.6 Hz, 3H), 0.90 (s, 3H), 1.01 (s, 3H),1.19–1.69 (m, 10H), 1.70–1.99 (m, 4H), 2.39 (m, 1H), 2.43 (m, 4H), 2.96 (m, 2H), 3.22 (s, 3H), AB-system: δ_A 3.42, δ_B 3.53, (J=11.6 Hz, 2H), 7.60 (m, 3H), 7.90 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.25, 22.36, 22.63, 24.37, 25.54, 26.54, 30.04, 32.61, 33.06, 34.18, 39.19, 40.89, 41.24, 42.60, 45.31, 56.29, 67.47, 71.70, 72.31, 81.20, 110.33, 128.45, 129.08, 133.33, 139.42. Second diastereomer: ^{1}H NMR ($CDCl_3$): δ [ppm]=0.84 (t, J=7.6 Hz, 3H), 0.86 (s, 3H), 0.96 (s, 3H),1.21–1.50 (m, 8H), 1.53–1.74(m, 3H), 1.83–2.27 (m, 7H), 2.42 (m, 1H), 3.00 (m, 2H), AB-system: δ_A 3.20, δ_B 3.27, (J=11.4 Hz, 2H), 3.27 (s, 3H), 3.40 (s, 2H), 7.60 (m, 3H), 7.90 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.18, 22.42, 22.55, 24.97, 25.16, 25.72, 29.35, 29.93, 32.92, 33.23, 37.40, 39.40, 40.63, 44.93, 45.40, 56.48, 66.63, 71.66, 72.05, 81.56, 110.07, 128.55, 129.08, 133.36, 139.03. IR (film): ν=2952, 2869, 1462, 1109, 1086 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=364, 279, 223, 209, 167, 137, 109, 95, 69, 55, 41. Anal. Calcd for $C_{27}H_{42}O_5S$: C, 67.75; H 8.84. Found: C, 67.51, H, 7.83.

2.5.3. Synthesis of 43a. The diastereomeric mixture of sulfones **42a** (1.54 g, 3.22 mmol) in methanol (35 mL) was treated at −20 °C with di-sodiumhydrogenphosphate (1.83 g, 12.88 mmol) and sodium amalgam (10 g, 6%) and stirred for 3 h. Water was added and the mixture was stirred for 30 min. The mercury was removed by decantation and the aqueous phase was extracted with ether. The ethereal phase was washed with brine, dried ($MgSO_4$), and chromatographed (hexanes/ethyl acetate 10:1) to give **43a** (910 mg, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, J=7.6 Hz, 3H), 0.95 (s, 3H), 0.97 (s, 3H),1.09–1.63 (m, 15H), 1.84 (m, 2H), 2.01 (m, 1H), 2.23 (dd, J=9.0, 13.0 Hz, 2H) 2.47 (m, 1H), 3.07 (quint, J= 5.6 Hz, 1H), 3.32 (s, 3H), 3.46 (s, 2H), 3.49 (s, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.34, 22.53, 25.64, 25.80, 30.08, 32.67, 32.98, 33.82, 35.38, 40.05, 40.25, 40.30, 47.07, 47.49, 56.35, 71.64, 72.42, 82.04, 110.55. IR (film): ν= 2934, 2854, 1462, 1111 cm^{-1}. MS (EI, 80 eV, 40 °C): m/z=338, 323, 309, 265, 241, 223, 209, 181, 167, 141, 128, 73, 69, 55. $[\alpha]_D=-19.3$ ($c=2.01$, $CHCl_3$). Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H 11.31. Found: C, 74.33, H, 10.75.

2.5.4. Synthesis of 1. *Compound* **43a** (2.66 g, 7.86 mmol) in acetone (450 mL) and water (22 mL) was treated with *p*-TsOH (373 mg, 1.96 mmol) and stirred at room temperature for 20 h. The mixture was neutralized with $NaHCO_3$ and concentrated under reduced pressure. The residue was extracted with ether, and the ether phase was washed with brine, dried ($MgSO_4$), and chromatographed (hexanes/ethyl acetate 10:1) to give **1** (1.90 g, 96%) as a colorless oil. All analytical data were fully in agreement with those reported above.

2.5.5. Synthesis of alcohol 48. Hydroxy ester **22** (5.00 g, 17.59 mmol) in THF was treated with triphenyl phosphane (4.73 g, 18.0 mmol), DEAD (3.13 g, 18.0 mmol) and lithium bromide (3.34 g, 18.0 mmol) at 0 °C for 5 h. The solvent was removed under reduced pressure and the residue was treated with ether to crystallize the hydrazo ester and the phosphine oxide. The mixture was filtered and the filtrate was chromatographed (hexanes/ethyl acetate 3:1) to give ester **46** (4.07 g, 85%) as a colorless oil, which was reduced with DIBALH (1.6 M in toluene, 12 mL) at −30 °C for 1 h (TP 2) to give, after aqueous workup allylic alcohol **47** (3.86 g, 92%), which was hydrogenated in ethyl acetate (700 mL) over Rh/C (5%, 1 g) at −30 °C for 6 h under normal pressure. The mixture was filtered and evaporated to dryness. The residue was chromatographed (hexanes/ethyl acetate 2:1) to give **48** (2.84 g, 74%) as a colorless solid of mp 58–59 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.95 (s, 3H), 0.97 (s, 3H),1.22–1.49 (m, 4H), 1.56 (s, 1H), 1.60–1.77 (m, 2H), 1.98–2.23 (m, 2H), 2.41 (m, 1H), 2.58 (m, 2H), 3.47 (s, 2H), 3.49 (s, 2H), AB-part of an ABX system: δ_A 3.60, δ_B 3.65, (J=10, 8, 7.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]= 22.41, 22.49, 26.63, 30.11, 32.14, 33.37, 39.18, 41.14, 41.22, 45.87, 64.04, 71.28, 73.06, 109.20. IR (film): ν= 3459, 2936, 2862, 1110, 1033, 999, 977 cm^{-1}. MS (EI,

80 eV, 40 °C): *m/z*=240, 225, 209, 197, 181, 167, 155, 141, 128, 95, 81, 69, 55. $[\alpha]_D=-28.6$ (*c*=1.05, $CHCl_3$). Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H 10.06. Found: C, 69.79, H, 9.88.

2.5.6. Synthesis of sulfone 49. Alcohol **48** (4.82 g, 20.0 mmol) in pyridine (25 mL) was treated with DMAP (300 mg) and tosyl chloride (5.72 g, 30.0 mmol). The mixture was stirred at room temperature overnight and then quenched with water. The mixture was extracted with DCM and the DCM phase was washed with brine, dried ($MgSO_4$) and the tosylate was crystallized by addition of hexane. 7.23 g (92%) was obtained as colorless crystals of mp 131–132 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.92 (s, 3H), 0.96 (s, 3H),1.08–1.30 (m, 3H), 1.38 (m, 1H), 1.62 (m, 2H), 1.97 (m, 1H), 2.17 (m, 1H), 2.35 (m, 1H), 2.45 (s, 3H), 2.53 (m, 2H), AB-system $\delta_A=3.37$, $\delta_B=3.42$ (*J*=11 Hz, 2H), 3.44 (s, 2H), ABX-system: $\delta_A=3.94$, $\delta_B=4.02$ (*J*=9.0, 9.0, 7.0 Hz, 2H), 7.34 (d, *J*=9.7 Hz, 2H), 7.82 (d, *J*=9.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=21.67, 22.52, 26.56, 30.15, 31.99, 33.12, 39.16, 41.27, 41.41, 42.17, 71.35, 71.68, 72.06, 108.93, 127.95, 129.86. IR (film): ν=2966, 2868, 1175, 1110, 951, 811 cm^{-1}. MS (EI, 80 eV, 40 °C): *m/z*=394, 309, 239, 223, 209, 167, 137, 91, 69. $[\alpha]_D=-13.4$ (*c*=1.04, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}O_5S$: C, 63.93; H 7.66. Found: C, 63.77, H, 7.43.

For the synthesis of the iodide, the tosylate (7.18 g, 18.2 mmol) and sodium iodide (6.00 g, 40 mmol) in acetonitrile (70 mL) was refluxed for 20 h. After cooling to room temperature water was added and the product was extracted with ether. The organic phase was washed with brine ($MgSO_4$) and chromatographed (hexanes/ethyl acetate 7:1) to give the iodide (5.62 g, 88%) as a slightly brown oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.97 (s, 6H), 1.18–1.54 (m, 4H), 1.64–1.83 (m, 2H), 2.26 (m, 2H), 2.43 (m, 1H), 2.59 (m, 2H), ABX-system: $\delta_A=3.07$, $\delta_B=3.24$ (*J*=9.8, 9.8, 7.0 Hz, 2H), 3.47 (s, 2H), 3.50 (s, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=7.29, 22.42, 30.08, 30.16, 32.47, 32.88, 39.12, 41.37, 43.35, 46.93, 71.28, 73.05, 108.65. MS (EI, 80 eV, 40 °C): *m/z*=350, 265, 223, 167, 137, 109, 95, 69, 55. $[\alpha]_D=-72.7$ (*c*=1.81, $CHCl_3$). HRMS *m/z* Calcd for $C_{14}H_{23}O_2$: 350.07416. Found 350.07414.

The iodide (5.60 g, 16.0 mmol) was converted into sulfone **49** (2.49 g, 43%) as described for **41**. Colorless solid of mp 144 °C. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.91 (s, 3H), 0.98 (s, 3H), 1.12–1.47 (m, 4H), 1.62 (m, 1H), 1.75 (m, 1H), 2.20–2.42 (m, 2H), 2.56 (m, 2H), AB-part of an ABX-system: $\delta_A=3.12$, $\delta_B=3.19$ (*J*=14.0, 6.6, 7.0 Hz, 2H), 3.43 (s, 4H), 7.64 (m, 3H), 7.95 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]= 22.33, 22.48, 29.41, 30.06, 31.80, 33.78, 37.04, 38.52, 41.86, 42.82, 57.98, 71.23, 73.05, 108.42, 127.90, 129.25, 133.58, 139.88. IR (film): ν=2953, 2865, 1444, 1290, 1148, 1109, 1012, 997 cm^{-1}. MS (EI, 80 eV, 40 °C): *m/z*=364, 279, 223, 167, 137, 109, 95, 69, 55. $[\alpha]_D=-37.1$ (*c*=2.45, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}O_4S$: C, 65.90; H 7.74. Found: C, 65.52, H, 7.59.

The sulfone **49** (2.33 g, 6.39 mmol) in THF (8 mL) was alkylated with bromide *S*-**39** as described for **42a** to give after HPLC (hexane/*i*PrOH 98:2) diastereomers **50** (crystals of mp 88 °C, 1.76 g, 58%) and **51** (colorless oil, 0.47 g, 15%).

Compound **50**. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.84 (t, *J*= 7.6 Hz, 3H), 0.89 (s, 3H), 1.02 (s, 3H), 1.10–1.83 (m, 14H), 2.31 (m, 3H), 2.55 (m, 1H), 2.79 (m, 1H), 2.98 (m, 2H), 3.27 (s, 3H), 3.44 (m, 4H), 7.60 (m, 3H), 7.92 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.18, 22.28, 22.60, 22.92, 25.62, 27.57, 29.43, 30.08, 31.25, 33.04, 33.72, 38.46, 42.30, 42.99, 56.35, 65.83, 71.20, 73.11, 81.37, 108.30, 128.69, 129.06, 133.45, 138.96. IR (KBr): ν=2963, 2924, 2862, 1445, 1297, 1145 1114, 1087 cm^{-1}. MS (EI, 80 eV, 40 °C): *m/z*=478, 463, 449, 393, 377, 361, 337, 219, 128, 95, 69. Anal. Calcd for $C_{27}H_{42}O_5S$: C, 67.75; H 8.84. Found: C, 67.38, H, 8.52.

Compound **51**. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.82 (t, *J*= 7.6 Hz, 3H), 0.88 (s, 3H), 1.02 (s, 3H), 1.10–1.81 (m, 13H), 1.94–2.14 (m, 2H), 2.25 (m, 1H), 2.50 (m, 2H), 2.63 (m, 1H), 2.96 (m, 2H), 3.26(s, 3H), 3.42 (d, *J*=11.0 Hz, 1H), 3.47 (d, *J*=11.0 Hz, 1H), 3.42 (d, *J*=11.0 Hz, 1H), 3.53 (d, *J*=11.0 Hz, 1H), 7.60 (m, 3H), 7.88 (m, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.27, 22.10, 22.26, 22.50, 25.67, 27.85, 29.25, 30.07, 32.51, 33.20, 36.21, 37.78, 39.52, 42.08, 42.76, 56.37, 66.87, 71.31, 73.04, 81.51, 108.55, 128.29, 129.03, 133.27, 139.96.

2.5.7. Synthesis of 52. The mixture of **50/51** (2.23 g, 4.66 mmol) in methanol (50 mL) was desulfonated as described for **43a** to furnish **52** (1.27 g, 81%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ [ppm]=0.89 (t, *J*=7.6 Hz, 3H), 0.95 (s, 3H), 0.99 (s, 3H), 1.17–1.66 (m, 16H), 1.74 (m, 1H), 2.04 (m, 1H), 2.47 (m, 3H), 3.07 (quint, *J*=5.8 Hz, 1H), 3.32 (s, 3H), 3.47 (s, 2H), 3.50 (s, 2H). ^{13}C NMR ($CDCl_3$): δ [ppm]=9.30, 22.46, 25.64, 25.78, 29.14, 29.49, 30.10, 30.79, 32.25, 33.00, 34.07, 38.95, 40.82, 42.29, 43.34, 56.35, 71.24, 73.06, 82.03, 109.10. IR (KBr): ν=2935, 2856, 1463, 1329, 1114, cm^{-1}. MS (EI, 80 eV, 40 °C): *m/z*=338, 323, 309, 295, 265, 241, 223, 209, 181, 167, 141, 128, 95, 81, 73, 69, 55. $[\alpha]_D=-26.7$ (*c*=2.35, $CHCl_3$). HRMS: *m/z* Calcd for $C_{16}H_{28}O_2$: 252.20893. Found 252.20889.

2.5.8. Synthesis of 4. *Compound* **52** (1.20 g, 3.55 mmol) in acetone (190 mL) and water (9 mL) was treated with *p*-TsOH (170 mg) at room temperature overnight. Workup was performed as described for the synthesis of **1** and the crude product was hydrogenated in ethyl acetate with Pd/C at room temperature and normal pressure. Chromatography (hexane/ethyl acetate 10:1) furnished **4** (820 mg, 92%) as a colorless oil. $[\alpha]_D=-112.6$ (*c*=1.33, $CHCl_3$). The analytical data were identical with those described above.

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22. Formula $C_{27}H_{42}O_5S$, molecular weight 478.70 g/mol, crystal system monoclinic space group $P2_1$, lattice constants: $a=$ 11.056(1) Å $b=5.941(1)$ Å $c=20.677(4)$ Å; $\alpha=98.71(1)^\circ$, cell volume 1342.5(7) $Å^3$, $Z=2$, density (Calcd) 1.184 g/cm^3, crystal size $0.03\times0.08\times1.2$ mm, radiation Cu K_α, linear absorption coefficient 13.0 cm^{-1}, number of reflexes 4770, number of independent reflexes 2817, Reflexes with $I>0$ 2803, *R*-value 0.042, *wR* 0.051, *S*-value 2.35. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Centre as supplementary publication number CCDC 237229. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).