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# SYNTHESIS OF OPTICALLY ACTIVE FORMS OF SEUDENOL, THE PHEROMONE OF DOUGLAS FIR BEETLE[a]

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**Abstract**—(*R*)-(+)-Seudenol (3-methylcyclohex-2-en-1-ol) and its antipode were synthesized from optically active forms of 3-iodocyclohex-2-en-1-ol by treatment with $Me_2CuLi$. Their absolute configurations were determined by converting (+)-3-iodocyclohex-2-en-1-ol to the known (*R*)-(+)-cyclohex-2-en-1-ol.

Seudenol (3-methylcyclohex-2-en-1-ol, **1a** and **1a'**) is an aggregation pheromone isolated from female hindguts of the Douglas fir beetle, *Dendroctonus pseudotsugae*, by Vité *et al.*[1] Very recently Sivlerstein *et al.* showed that the natural seudenol is racemic.[2] This posed a very interesting problem as to the pheromone activity of the optically pure enantiomers of seudenol: is only one enantiomer responsible for the beetle aggregation or are the both enantiomers required for the aggregation? The latter was the case with sulcatol (6-methylhept-5-en-2-ol), an aggregation pheromone of *Gnathotrichus sulcatus*.[3,4] In order to answer this question, a synthesis of the pure enantiomers of seudenol is necessary so that one can carry out the bioassay. Moreover, the absolute configuration of optically active seudenol should be determined so that one can say something about the stereochemistry-pheromone activity relationship. Herein we describe our synthesis of optically pure (*R*)-(+)-seudenol **1a** and its antipode **1a'**.

At first sight the synthesis seemed quite easy, since three reports were available on the resolution of the closely related lower homolog, (±)-cyclohex-2-en-1-ol (**2a**+**2a'**).[5–7] Both Otzet *et al.*[5] and Hill and Morgan[6] converted the alcohol into the corresponding phthalic half ester (**2b**+**2b'**)). Otzet *et al.* resolved it with brucine to give (+)-cyclohex-2-en-1-ol **2a**, $[\alpha]_D$ + 110.6° ($CHCl_3$), while Hill and Morgan resolved it with dehydroabietylamine to give (−)-cyclohex-2-en-1-ol **2a'**, $[\alpha]_D$ − 15.2° ($CHCl_3$). The latter group determined the absolute configuration of the (−)-alcohol to be *S* (**2a'**).[6] Yamada *et al.* prepared the L-alanine ester (**2c**+**2c'**) of (±)-cyclohex-2-en-1-ol and resolved it by recrystallizing its benzoic acid salt to give finally (*S*)-(−)-**2a'**, $[\alpha]_D^{20}$ − 112° ($CHCl_3$).[7] We attempted to apply these methods for the resolution of (±)-seudenol.[8] However, neither the phthalic half ester nor the alanine ester of (±)-seudenol could be obtained owing to the extraordinary ease of elimination of the allylic hydroxyl group of seudenol during the manipulation.

We therefore turned our attention to the preparation under mild condition of the diastereomeric esters (**1b**+**1b'**) of (±)-seudenol with 3β-acetoxyetienic acid.[9,10] The crude product was chromatographed over alumina to give a crystalline ester (**1b** contaminated with **1b'**) and a gummy ester (**1b'** contaminated with **1b**). The recrystallized ester (**1b** contaminated with **1b'**) was reduced with $LiAlH_4$ yielding dextrorotatory seudenol (**1a** contaminated with **1a'**), $[\alpha]_D^{23}$ + 53.6° ($CHCl_3$). The gummy ester (**1b'** contaminated with **1b**) yielded levorotatory seudenol (**1a'** contaminated with **1a**), $[\alpha]_D^{23}$ − 44.6° ($CHCl_3$). The assignment of absolute configurations for these compounds as depicted in formulas will be described later in this paper.

The optical purities of the resolved seudenols were determined as follows. They were converted to (*S*)-(−)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid) esters (**1c** and **1c'**) in the standard manner.[11,12] Their NMR spectra were quite similar. However, the differences between the spectra of the two diastereomers (**1c** and **1c'**) became apparent upon addition of a small amount of the NMR shift reagent Eu(fod)$_3$ (europium 6,6,7,7,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate).[13] Especially the 3H singlet due to the methoxy protons separated into a pair of singlets at δ = 4.52 and 4.70. The area ratio of these two signals was 1 : 3. The signal at δ = 4.52 was assigned to that of the methoxy group of (−)-seudenol (*S*)-(−)-MTPA ester (**1c'**), while the other at δ = 4.70 was thought to be that of the methoxy group of its diastereomer (**1c**). Therefore our dextrorotatory seudenol was of *ca.* 50% optical purity. Similar NMR analysis revealed the optical purity of our levorotatory seudenol to be 36%. From these data, $[\alpha]_D$ value of pure (+)-seudenol **1a** was calculated to be *ca.* 100°. The resolution via the steroid ester was thus only partially successful resulting in the preparation of optically impure seudenols. Attempts to derive seudenol from optically pure (+)-3-hydroxycyclohexane-1-carboxylic acid[14] or (+)-cyclohex-2-en-1-ol were also unrewarding.

The successful synthesis of optically pure seudenol enantiomers was finally achieved as follows. Our failure to prepare the phthalic half ester of (±)-seudenol was due to the extreme ease of generation of an allylic carbonium ion by elimination of the hydroxyl group. The preparation of a phthalic half ester of an iodoalcohol **4** should be more feasible due to the presence of a vinylic iodine atom which would destabilize an allylic carbonium ion generated by dehydration. This was proved to be the case. 3-Idoocyclohex-2-en-1-one **3**[15] was reduced with $LiAlH_4$ to give 3-iodocyclohex-2-en-1-ol **4**. This was treated with phthalic anhydride in pyridine to give the

[a]Pheromone Synthesis XX: This work was presented at the EUCHEM Conference on Terpenes at Varenna, Lake Como, Italy, on 27 August 1977, as a part of K. M. 's lecture. Part XIX, S. Tamada, K. Mori and M. Matsui, *Agric. Biol. Chem.* **42**, 191 (1978).

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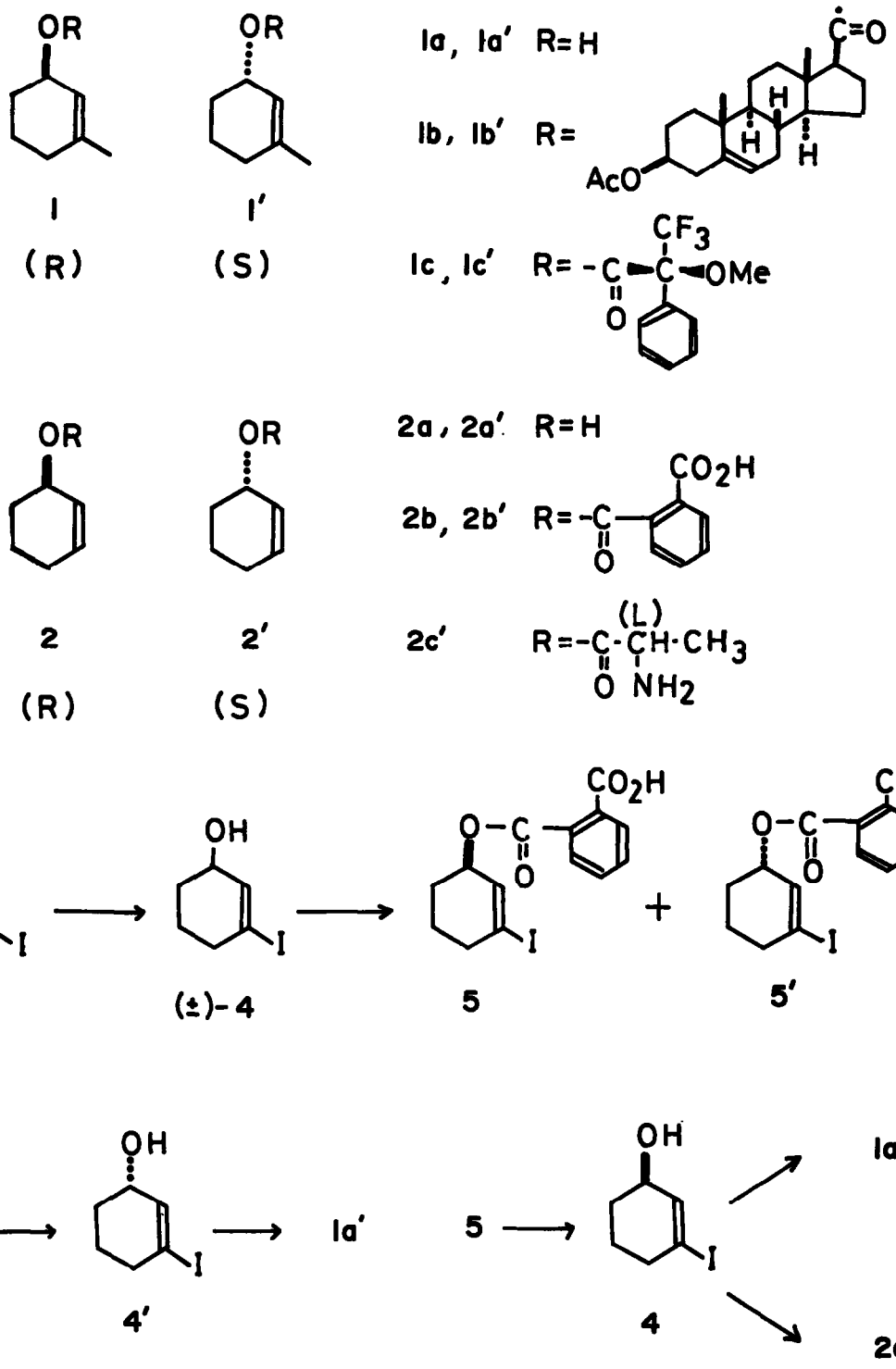


required half ester (5+5') as crystals in 83% yield. Resolution of the half ester with cinchonine in acetone gave dextrorotatory salt, m.p. 167–168°, $[\alpha]_D^{20}$ +64.3° (MeOH). Upon acidfication, this gave levorotatory half ester 5', $[\alpha]_D^{20}$ −34.7° (MeOH). The phthalic acid moiety was removed by reduction with $LiAlH_4$ to give (−)-iodocyclohex-2-en-1-ol 4, $[\alpha]_D^{20}$ −12.8° ($CHCl_3$). This was treated with an excess of $Me_2CuLi$ yielding (−)-seudenol 1a', $[\alpha]_D^{20}$ −96.3° ($CHCl_3$). (+)-Seudenol 1a was also obtained in a similar manner. Slightly levorotatory phthalic half ester of 3-iodocyclohex-2-en-1-ol was obtained by acidifying the mother liquor recovered after removal of the cinchonine salt of the half ester. This gave crystalline cinchonidine salt, $[\alpha]_D^{20}$ −28.6° (MeOH). The dextrorotatory half ester 5, $[\alpha]_D^{20}$ +34.7° (MeOH), was obtained by acidification of the cinchonidine salt. (+)-3-Iodochclohex-2-en-1-ol 4, $[\alpha]_D^{20}$ +12.8° ($CHCl_3$), and (+)-seudenol 1a, $[\alpha]_D^{20}$ +96.0° $CHCl_3$), were prepared in the same manner as described for the (−)-isomers. These optically active seudenols were further purified via their crystalline 3β-acetoxyetienates 1b (m.p. 95.5–96.5°) and 1b' (m.p. 91–92°). However, no increase

in optical rotation was observed with thus purified seudenol. The observed $[\alpha]_D$ value (+96.0°) of (+)-seudenol **1a** was in good accord with the value (*ca.* + 100°) calculated from the NMR analysis of the MTPA ester of partially resolved (+)-seudenol. Therefore our seudenol enantiomers could be regarded as optically pure. This conclusion was also supported by the careful NMR measurements on the corresponding MTPA esters **1c** and **1c'** in the presence of Eu(fod)$_3$. No splitting of the signal due to $OCH_3$ protons was observable within the limit of experimental error (<5%).

The absolute configuration of (+)-seudenol depicted as **1a** was determined by the conversion of (+)-3-iodocyclohex-2-en-1-ol **4** into (+)-cyclohex-2-en-1-ol **2a**, $[\alpha]_D^{20}$ + 108° ($CHCl_3$), with Masamune's hydride reagent obtainable by treatment of $LiAlH(OMe)_3$ with CuI.[16] Since the absolute configuration of (+)-cyclohex-2-en-1-ol is known to be *R* (**2a**),[6] (+)-seudenol also belongs to the *R*-series (**1a**). Comparison of our $[\alpha]_D$ value (108°) of **2a** with those of Otzet's **2a** (+ 110.6°)[5] and Yamada's **2a'** (− 112°)[7] supports the high optical purity (>96%) of our sample.

In conclusion highly optically pure seudenol enantiomers were synthesized in the quantities sufficient for biological tests. The biological work will be published in due course by Prof. J. P. Vité, University of Freiburg. It should be mentioned that the optically active iodides **4** and **4'** can serve as versatile intermediates for syntheses of optically active 3-alkylcyclohex-2-en-1-ols. This method may also be applicable to the preparation of other chiral 3-alkylcycloalk-2-en-1-ols.

## EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films unless otherwise specified and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer. Optical rotations were measured on a Jasco DIP-4 polarimeter. GLC analyses were performed on a Yanaco G80 gas chromatograph.

*Seudenyl 3β-acetoxyetienate* **1b** + **1b'**. Oxalyl chloride (17.5 ml) was added to an ice-cooled and stirred suspension of 3β-acetoxyetienic acid (10 g) in dry $C_6H_6$ (100 ml). After 30 min the acid dissolved completely. After another 30 min at room temp., the soln was concentrated *in vacuo*. The crystalline acyl chloride was dissolved again in dry $C_6H_6$ (50 ml) and concentrated *in vacuo* to remove the final trace of the excess oxalyl chloride. To an ice-cooled soln of the acyl chloride in dry pyridine (100 ml), a soln of (±)-seudenol (**1a** + **1a'**, 3.11 g; b.p. 90–92°/28 mm; $n_D^{23.5}$ 1.4825) in dry pyridine (10 ml) was added and the mixture was left to stand overnight at room temp. This was poured into ice-dil. HCl and the mixture was extracted with EtOAc. Insoluble materials were filtered off and the EtOAc soln was washed with dil. HCl, $H_2O$, $NaHCO_3$ soln and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 13.9 g of crude oily steroid ester. This was chromatographed over Woelm neutral $Al_2O_3$ (grade II, 332 g, 34 × 3.5 cm) in *n*-hexane employing *n*-hexane (1.5 l), 40%-$C_6H_6$–*n*-hexane (2 l), 60%-$C_6H_6$–*n*-hexane (0.5 l), $C_6H_6$ (1 l) and EtOAc (1 l) as eluants. Earlier fractions gave crystals which were recrystallized from 99% EtOH to give 1.4 g of solids (**1b** contaminated with **1b'**), m.p. 93–95°; $[\alpha]_D^{22}$ + 21.4° (c = 0.75, $CHCl_3$); $\nu_{max}$ (Nujol) 1740 (s), 1370 (m), 1260 (s), 1250 (s) $cm^{-1}$; δ ($CDCl_3$) 0.70 (3H, s), 1.02 (3H, s), 1.70 (3H, s), 2.02 (3H, s), 0.85–2.5 (26H), 4.4–4.9 (1H, m), 5.1–5.6 (3H, m). (Found: C, 76.54; H, 8.98. $C_{29}H_{42}O_4$ requires: C, 76.61; H, 9.31%). Later fractions contained only a small amount of crystals. After removal of crystals by filtration, the mother liquor (**1b'** contaminated with **1b**) weighed 1.8 g, $[\alpha]_D^{22}$ − 55.8° (c = 1.79, $CHCl_3$); $\nu_{max}$ 1730 (s), 1250 (s), 1200 (s) $cm^{-1}$.

*Optically impure* (+)-*seudenol* (**1a** contaminated with **1a'**). A soln of the crystalline (+)-etienate (0.75 g) in dry ether (15 ml) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (0.4 g) in dry ether (30 ml). The mixture was stirred for 2 h. Then $H_2O$ (0.4 ml) was added carefully to a stirred and ice-cooled mixture. Subsequently 15% NaOH soln (0.4 ml) and $H_2O$ (1.2 ml) were added to the mixture. The stirring was continued for 1 h. Then the mixture was filtered and the solid on the filter was thoroughly washed with ether. The combined filtrate and washings were dried ($K_2CO_3$) and concentrated *in vacuo*. The residue was mixed with *n*-hexane and filtered to remove the insoluble steroid alcohol. The filtrate was concentrated *in vacuo*. The residue was distilled to give 56.8 mg (31%) of optically impure (+)-seudenol (**1a** contaminated with **1a'**), b.p. (bath temp.) 95–115°/33 mm; $n_D^{23}$ 1.4795; $[\alpha]_D^{23}$ + 53.6° (c = 0.39, $CHCl_3$); $\nu_{max}$ 3350 (s), 3020 (w), 2960 (s), 2880 (s), 2840 (m), 1680 (w), 1460 (m), 1450 (m), 1390 (m), 1350 (w), 1290 (w), 1180 (m), 1160 (w), 1130 (w), 1120 (w), 1080 (m), 1070 (m), 1040 (s), 1020 (m), 1000 (m), 970 (s), 915 (m), 860 (w), 850 (w), 820 (w), 720 (w); δ ($CCl_4$) 1.65 (6H), 1.85 (3H, br. s), 3.64 (1H, s), 4.10(1H, br. s), 5.48 (1H, br. s). These IR and NMR data were identical with those of (±)-seudenol.

*Optically impure* (−)-*seudenol* (**1a'** contaminated with **1a**). Similarly the oily steroid ester (1.79 g) was reduced with $LiAlH_4$ (1.0 g) to give 202.7 mg (46%) of optically impure (−)-seudenol (**1a'** contaminated with **1a**), b.p. (bath temp.) 81–145°/16–19 mm; $n_D^{23}$ 1.4796; $[\alpha]_D^{23}$ − 44.6° (c = 0.73, $CHCl_3$). The IR and NMR data were identical with those of (±)-seudenol.

(S)-(−)-*MTPA ester of optically impure* (+)-*seudenol* (**1c** contaminated with **1c'**). This was prepared from the above described optically impure (+)-seudenol and (*S*)-(−)-MPTA-Cl by the standard procedure.[11] δ ($CCl_4$) 1.70 (3H, br. s), 1.37–2.10 (6H, m), 3.54 (3H, s), 5.50 (2H, m), 7.43 (5H, m); δ (MTPA ester 30.0 mg + Eu(fod)$_3$ 10.1 mg + $CCl_4$ 0.4 ml) 0.88, 1.72, ~1.95, two signals due to OMe at 4.52 and 4.70 (area ratio = 1 : 3), 5.65 (2H), 7.40–7.70 (3H, m), 8.15–8.40 (2H, m).

(S)-(−)-*MTPA ester of optically impure* (−)-*seudenol* (**1c'** contaminated with **1c**). This was also prepared according to the standard procedure.[11] δ ($CCl_4$) 1.74 (3H, br. s), 1.38–2.12 (6H, m), 3.58 (3H, s), 5.50-5.60 (2H, m), 7.48 (5H, m); δ (MTPA ester 27.3 mg + Eu(fod)$_3$ 10.3 mg + $CCl_4$ 0.4 ml) 0.84, 1.72, ~1.92, two signals due to OMe at 4.60 and 4.82 (area ratio = 7 : 3), 5.65 (2H, m), 7.35–7.70 (3H, m), 8.10–8.50 (2H, m).

(±)-3-*Iodocyclohex-2-en-1-ol* (**4** + **4'**). 3-Iodocyclohex-2-en-1-one (3, 15 g) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (5.62 g) in dry ether (100 ml). The mixture was stirred at 0–5° for 1 h and then for 2 h at room temp. Sat $Na_2SO_4$ soln was added dropwise to the ice-cooled mixture and the stirring was continued for 1 h. The insoluble material was filtered off and the filtrate was washed with $H_2O$ and sat NaCl soln, dried ($K_2CO_3$) and concentrated *in vacuo*. The residue was distilled to give 11.5 g (76%) of (±)-**4**, b.p. 89–90°/1 mm, $n_D^{20}$ 1.5835; $\nu_{max}$ 3300 (s), 3020 (w), 2920 (s), 2850 (m), 1630 (m), 1440 (m), 1420 (m), 1340 (m), 1320 (m), 1040 (s), 950 (s), 820 (w), 800 (w), 710 (m) $cm^{-1}$; δ ($CCl_4$) 1.40–2.20 (4H, m), 2.20–2.75 (2H, m), 3.95 (1H, s), 4.10 (1H, m), 6.45 (1H, m). (Found: C, 33.87; H, 4.30. $C_6H_9OI$ requires: C, 34.62; H, 4.34%).

*Phthalic half ester of* (±)-3-*iodocyclohex-2-en-1-ol* (**5** + **5'**). A mixture of (±)-**4** (17.5 g) and phthalic anhydride (11.6 g) in dry pyridine (61 ml) was stirred and heated at 80° for 5 h. After cooling, the mixture was poured into dil. HCl and ice and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with $H_2O$ and sat $NaHCO_3$ soln. The $NaHCO_3$ soln was acidified to pH 2–3 with dil. HCl and extracted with ether. The ether soln was washed with $H_2O$ and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from ether–light petroleum to give 24 g (83%) of (±)-**5** as needles, m.p. 101–103°, $\nu_{max}$ (Nujol) 2400–2700 (w), 1730 (s), 1705 (s), 1640 (w), 1610 (w), 1590 (w), 1470 (s), 1420 (w), 1390 (m), 1330 (m), 1310 (s), 1280 (m), 1140 (m), 940 (m), 920 (w), 750 (m), 730 (w), 710 (w), $cm^{-1}$; δ ($CDCl_3$) 1.6–2.2 (4H, m), 2.4–2.75 (2H, m), 5.25–5.65 (1H, m), 6.50–6.70 (1H, m) 7.50–7.80 (3H, m), 7.80–8.20 (1H, m). (Found: C, 45.18; H, 3.52. $C_{14}H_{13}O_4I$ requires: C, 45.34; H, 3.51%).

*Optical resolution of the phthalic half ester*

(a) *With cinchonine.* The racemic half ester (**5** + **5'**, 48.4 g) and cinchonine (38.3 g) was dissolved in hot MeOH (150 ml). The

for 1 h. The insoluble material was filtered off and the filtrate was left to stand for 3–4 days at room temp. The separated crystals were recrystallized 4 times from 99% EtOH to give 20.1 g (46%) of the cinchonine salt of **5'**, m.p. 167–168°, $[\alpha]_D^{20}$ + 64.3° (c = 1.04, MeOH); $\nu_{max}$ (Nujol) 1700 (m), 1630 (w), 1590 (m), 1570 (m), 1510 (w), 1470 (m), 1400 (m), 1380 (m), 1320 (m), 1295(m), 1290 (m), 1260 (w), 1130 (m), 940 (w), 920 (w), 780 (m), 730 (w), 700 (w), $cm^{-1}$. (Found: C, 59.52; H, 5.28. $C_{33}H_{35}O_3N_2I$ requires: C, 59.46; H, 5.28%). Thus obtained salt (20 g) was dissolved in 2N–HCl (to pH 2–3). The mixture was extracted with ether. The ether soln was washed with $H_2O$ and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give **5'** (9.7 g) as an oil, $[\alpha]_D^{20}$ − 34.7° (c = 0.528, MeOH); $\nu_{max}$ 3200 (s), 2640 (m), 2530 (m), 1750–1680 (s), 1630 (m), 1600 (m), 1580 (m), 1495 (m), 1410 (m), 1340–1240 (s), 1130 (m), 1070 (m), 1000 (m), 930 (m), 910 (m), 830 (m), 790 (m), 750 (m) $cm^{-1}$. This was employed for the next step without further purification.

(b) *With cinchonidine.* The slightly dextrorotatory phthalic half ester (29 g) was obtained by acidifying the mother liquor recovered after removal of the crystalline cinchonine salt. This oil and cinchonidine (22.9 g) was dissolved in acetone (100 ml) by stirring and heating at 50° for 1 h. The soln was left to stand in a refrigerator for 2–3 days. The separated crystals were recrystallized 4 times from acetone to give 13 g of the cinchonidine salt of **5**, m.p. 134–142°, $[\alpha]_D^{20}$ − 28.6° (c = 1.00, MeOH); $\nu_{max}$ (Nujol) 1710 (m), 1630 (w), 1590 (m), 1570 (m), 1470 (m), 1380 (m), 1370 (w), 1320 (w), 1270 (m), 1130 (w), 780 (w), 760 (w) $cm^{-1}$. (Found: C, 59.08; H, 5.50. $C_{33}H_{35}O_5N_2I_2I$ requires: C, 59.46; H, 5.28%). Thus obtained salt (13 g) was dissolved in 2N–HCl (to pH 2–3). The mixture was extracted with ether. The ether soln was washed with $H_2O$ and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give **5** (6.8 g) as an oil, $[\alpha]_D^{20}$ + 34.7° (c = 0.976, MeOH). The IR spectrum was identical with that of **5'**. This was employed for the next step without further purification.

*(S)-(−)-3-Iodocyclohex-2-en-1-ol* **4'**. A soln of **5'** (9.5 g) in dry ether (30 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (2.1 g) in dry ether (100 ml) under ice-cooling. The mixture was stirred at 0–5° for 1 h and for 2 h at room temp. Then sat $Na_2SO_4$ soln (8.5 ml) was gradually added to the stirred and ice-cooled mixture. After the addition, the mixture was stirred for 1 h and filtered to remove inorganic materials. The filter cake was thoroughly washed with ether. The filtrate and washings were combined, washed with $H_2O$ and sat NaCl soln, dried ($K_2CO_3$) and concentrated *in vacuo*. The residue was chromatographed over Woelm neutral alumina (grade III) and eluted with ether-*n*-hexane (5:1). The fractions containing **4'** were combined and concentrated *in vacuo*. The residue was distilled to give 3.32 g (58%) of **4'**, b.p. 91–92°/1 mm, $n_D^{20}$ 1.5811; $[\alpha]_D^{20}$ − 12.8° (c = 0.594, $CHCl_3$). The IR and NMR spectra were identical with those of the racemate. (Found: C, 35.15; H, 4.34. $C_6H_9OI$ requires: C, 34.62; H, 4.34%).

*(R)-(+)-3-Iodocyclohex-2-en-1-ol* **4**. A soln of **5** (6.6 g) in dry ether (20 ml) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (1.48 g) in dry ether (80 ml). Subsequent work-up as described for **4'** gave 2.47 g (62%) of **4**, $n_D^{20}$ 1.5798; $[\alpha]_D^{20}$ + 12.8° (c = 0.416, $CHCl_3$). The IR and NMR spectra were identical with those of the racemate.

*(S)-(−)-Seudenol (3-methylcyclohex-2-en-1-ol)* **1a'**. A soln of $Me_2CuLi$ in ether was prepared by adding 0.16 M-MeLi in ether (160 ml) to a stirred and cooled (−15 to −10°) suspension of CuI (15.8 g) in dry ether (100 ml) under Ar during 1 h. A soln of **4'** (3 g) in dry ether (30 ml) was added dropwise to the clear soln of $Me_2CuLi$ at −5 ~ 0° with stirring. After the addition, the mixture was stirred for 2 h at −5 ~ 0° and left to stand overnight in a refrigerator. Then the mixture was poured into ice-$NH_4Cl$ soln, dried ($K_2CO_3$) and concentrated. The residue was distilled to give 1.37 g (91%) of **1a'**, b.p. 82.5–83.5°/21 mm, $n_D^{20}$ 1.4817; $[\alpha]_D^{20}$ − 96.3° ± 0.3° (c = 0.458, $CHCl_3$). The IR and NMR spectra were identical with those of optically impure (+)-seudenol. (Found: C, 74.48; H, 10.73. $C_7H_{12}O$ requires: C, 74.95; H, 10.78%).

*(R)-(+)-Seudenol* **1a**. A soln of $Me_2CuLi$ in ether was prepared by adding 0.095 M-MeLi in ether(95 ml) to a stirred and cooled (−15 to −10°) suspension of CuI (9.31 g) in dry ether (80 ml) under Ar during 1 h. A soln of **4** (2.1 g) in dry ether (20 ml) was added dropwise to the clear soln of $Me_2CuLi$ at −5 ~ 0° with stirring. Subsequent work-up as described for **1a'** gave 0.95 g (90.5%) of **1a**, b.p. 83–84°/20.5 mm, $n_D^{20}$ 1.4818; $[\alpha]_D^{20}$ + 96.0° ± 0.3° (c = 0.423, $CHCl_3$). The R and NMR spectra were identical with those of (−)-seudenol. (Found: C, 74.62; H, 10.66. $C_7H_{12}O$ requires: C, 74.95; H, 10.78%).

*3β-Acetoxyetienate of (S)-(−)-seudenol* **1b'**. A soln of **1a'** (1.15 g) in dry pyridine (3 ml) was added to an ice-cooled and stirred soln of 3β-acetoxyetienoyl chloride (prepared from 4.66 g of 3β-acetoxyetienic acid) in dry pyridine (30 ml). The mixture was left to stand overnight at room temp. Then it was poured gradually to ice-cooled 3N-HCl (75 ml). To this was added EtOAc (100 ml). The insoluble material was filtered off through Celite. The filtrate was extracted with EtOAc. The extract was washed with sat $CuSO_4$ soln, $H_2O$, sat $NaHCO_3$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over Woelm neutral alumina (grade III). Elution with *n*-hexane-ether (20 : 1) gave **1b'** as crystals. The crude **1b'** was recrystallized from 99% EtOH to give 2.5 g (54%) of pure **1b'** as needles, m.p. 91–92°, $[\alpha]_D^{20}$ − 117.3° (c = 0.621, $CHCl_3$); $\nu_{max}$ (Nujol) 1740 (m), 1730 (s), 1665 (w), 1380 (m), 1360 (m), 1250 (s), 1200 (m), 1170 (w), 1150 (w), 1070 (w), 1050 (w), 1030 (m), 910 (m) $cm^{-1}$; δ ($CDCl_3$) 0.65 (3H, s), 1.03 (3H, s), 1.72 (3H, s), 1.95 (3H, s), 0.80–2.55 (26H), 4.30–4.70 (1H, m), 5.00–5.25 (1H, m), 5.25–5.60 (2H, m). (Found: C, 76.79; H, 9.33. $C_{29}H_{42}O_4$ requires: C, 76.61; H, 9.31%).

*3β-Acetoxyetienate of (R)-(+)-seudenol* **1b**. A soln of **1a** (0.8 g) in dry pyridine (2 ml) was added to an ice-cooled and stirred soln of 3β-acetoxyetienoyl chloride (prepared from 3.24 g of 3β-acetoxyetienic acid) in dry pyridine (30 ml). The mixture was left to stand overnight at room temp. Subsequent work-up as described for **1b'** including chromatographic purification and recrystallization from 99% EtOH gave 2.6 g (81%) of pure **1b**, m.p. 95.5–96.5°, $[\alpha]_D^{20}$ + 48.7° (c = 0.565, $CHCl_3$); $\nu_{max}$ (Nujol) 1740 (s), 1730 (s), 1680 (w), 1390 (m), 1370 (m), 1265 (s), 1200 (m), 1180 (w), 1060 (w), 1045 (m), 910 (w) $cm^{-1}$; δ ($CDCl_3$) 0.65 (3H, s), 1.04 (3H. s), 1.71 (3H, s), 1.95 (3H, s), 0.8–2.50 (26H), 4.20–4.75 (1H, m), 5.0–5.25 (1H, m), 5.25–5.50 (2H, m). (Found: C, 76.66; H, 9.24. $C_{29}H_{42}O_4$ requires: C, 76.61; H, 9.31%).

*(S)-(−)-Seudenol* **1a'** *from* **1b'**. A soln of **1b'** (2.52 g) in dry ether (20 ml) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (1.34 g) in dry ether (50 ml). The mixture was stirred for 2 h at 0–5° and then for 1 h at room temp. Subsequent work-up as described for the preparation of optically impure (+)-seudenol gave 0.46 g of **1a'**, b.p. 83–85°/23 mm, $n_D^{20}$ 1.4807; $[\alpha]_D^{20}$ − 93.9° ± 0.4° (c = 0.524, $CHCl_3$). The spectral data were identical with those of (±)-seudenol. GLC (5% SE-30 column at 94°, Carrier gas $N_2$, 1 $kg/cm^2$): Rt 1.65 min (96% purity) with an impurity at Rt 1.15 min (4%).

*(R)-(+)-Seudenol* **1a** *from* **1b**. A soln of **1b** (2.2 g) in dry ether (20 ml) was added to a stirred and ice-cooled suspension of $LiAlH_4$ (1.14 g) in dry ether (50 ml). The mixture was stirred for 2 h at 0–5° and then for 1 h at room temp. Subsequent work-up gave 0.38 g of **1a**, b.p. 83–85°/23.5 mm, $n_D^{20}$ 1.4804; $[\alpha]_D^{20}$ + 93.5° ± 0.4° (c = 0.491, $CHCl_3$). The spectral data were identical with those of (±)-seudenol. GLC (5% SE-30 column at 94°, Carrier gas $N_2$, 1 $kg/cm^2$): Rt 1.65 min (95%), 1.15 min (5%).

*(S)-(−)-MTPA ester of (S)-(−)-seudenol* **1c'**. This was prepared from **1a'** (41 mg) and (*S*)-(−)-MTPA-Cl (96.7 μl) in $CCl_4$ (0.9 ml) and pyridine (0.9 ml) by the standard procedure.[11] The product **1c'** weighed 0.105 g, $\nu_{max}$ 2940 (m), 2860 (w), 1740 (s), 1670 (w), 1490 (w), 1450 (m), 1380 (w), 1240–1280 (s), 1170 (s), 1120 (m), 1080 (w), 1020 (m), 990 (w), 900 (m), 830 (w), 760 (w), 715 (m), 700 (m) $cm^{-1}$. δ ($CCl_4$) 1.70 (3H, s), 1.30–2.10 (6H, m), 3.50 (3H, s), 5.20–5.70 (2H, m), 7.10–7.70 (5H, m); δ (MTPA ester 30 mg + Eu(fod)$_3$ 10.0 mg + $CCl_4$ 0.4 ml) 1.70 (3H, s), 1.75–2.19 (6H, m), 4.41 (3H, s, OMe), 5.43–5.75 (2H, m), 7.30–7.70 (3H, m), 7.95–8.40 (2H).

*(S)-(−)-MTPA ester of (R)-(+)-seudenol* **1c**. This was prepared from **1a** (40 mg) and (*S*)-(−)-MTPA-Cl (96.7 μl) by the standard procedure.[11] The product weighed 0.10 g, $\nu_{max}$ 2940 (m), 2860 (w), 1740 (s), 1670 (w), 1490 (w), 1450 (m), 1380 (w), 1240–1280 (s), 1170 (s), 1120 (m), 1080 (w), 1020 (m), 990 (w), 900 (m), 830 (w), 760 (w), 715 (m), 700 (m) $cm^{-1}$; δ ($CCl_4$) 1.69 (3H, s),

1.50–2.20 (6H, m), 3.50 (3H, s), 5.20–5.70 (2H, m), 7.10–7.70 (5H, m); δ (MTPA ester 30 mg + $Eu(fod)_3$ 10 mg + $CCl_4$ 0.4 ml) 1.57 (3H, s), 1.54–2.14 (6H, m), 4.64 (3H, s, OMe), 5.29–5.74(2H, m), 7.11–7.50 (3H, m), 7.94–8.40 (2H).

(S)-(−)-*MTPA ester of* (±)-*seudenol* **1c′** + **1c′**. This was prepared from (±)-seudenol by the standard procedure.[11] δ (MTPA ester 30 mg + $Eu(fod)_3$ 10.5 mg + $CCl_4$ 0.4 ml) 1.70 (3H, s), 1.68–2.93 (6H, m), 4.68 (1.5H, s, OMe), 4.93 (1.5H, s, OMe), 5.38–5.83 (2H, m), 7.28–7.68 (3H, m), 8.16–8.61 (2H, m).

(R)-(+)-*Cyclohex-2-en-1-ol* **2a**. A soln of $LiAlH(OMe)_3$ (70 millimoles) in THF (100 ml) was added dropwise under Ar to a stirred and ice-cooled suspension of CuI (6.84 g, 36 millimoles) in THF (14 ml). The mixture was stirred at 0° for 30 min. A soln of **4** (0.67 g) in THF (5 ml) was added to the reducing agent in one portion. The mixture was stirred at 0–5° for 2.5 h and then left to stand overnight at room temp. A mixture of ether (200 ml) and MeOH (14 ml) was added to the mixture. Then it was filtered through Celite. The filtrate was washed with sat $NH_4Cl$. The $NH_4Cl$ layer was extracted with ether. The combined organic soln was washed with sat $NaHCO_3$ soln, $H_2O$ and sat NaCl soln, dried ($K_2CO_3$) and concentrated. The residue was distilled to give 0.25 g (86%) of **2a**, b.p. 81–83°/40 mm, $[\alpha]_D^{20}$ + 108° ± 0.8° (c = 1.003, $CHCl_3$); $\nu_{max}$ 3360 (s), 3030 (m), 2940 (s), 2860 (m), 2840 (m), 1650 (m), 1455 (m), 1440 (m), 1395 (w), 1290 (w), 1170 (w), 1060 (s), 1000 (w), 960 (s), 900 (w), 810 (w), 730 (m) $cm^{-1}$. The IR spectrum was identical with that of authentic (±)-cyclohex-2-en-1-ol.

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## REFERENCES

[1]J. P. Vité, G. B. Pitman, A. F. Fentiman, Jr. and J. W. Kinzer, *Naturwiss.* **59**, 469 (1972).
[2]E. L. Plummer, T. E. Stewart, K. Byrne, G. T. Pearce and R. M. Silverstein, *J. Chem. Ecol.* **2**, 307 (1976).
[3]K. Mori, *Tetrahedron* **31**, 3011 (1975).
[4]J. H. Borden, L. Chong, J. A. McLean, K. N. Slessor and K. Mori, *Science* **192**, 894 (1976).
[5]R. Otzet, J. Pascual and J. Sistare, *An. Real. Soc. Espan. Fis. Quim., Ser. B* **62**, 965 (1966); *Chem. Abstr.* **66**, 85504$^c$ (1967).
[6]R. K. Hill and J. W. Morgan, *J. Org. Chem.* **33**, 927 (1968).
[7]S. Yamada, N. Takamura and T. Mizoguchi, *Chem. Pharm. Bull.* **23**, 2539 (1975).
[8]O. P. Vig, J. P. Salota, M. P. Sharma and S. D. Sharma, *Indian J. Chem.* **6**, 188 (1968).
[9]R. B. Woodward and T. J. Katz, *Tetrahedron* **5**, 70 (1959).
[10]J. Staunton and E. J. Eisenbraun, *Org. Synth. Col. Vol.* **5**, 8 (1973).
[11]J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.* **34**, 2543 (1969).
[12]J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.* **95**, 512 (1973).
[13]Cf. S. Iwaki, S. Marumo, T. Saito, M. Yamada and K. Katagiri, *J. Am. Chem. Soc.* **96**, 7842 (1974).
[14]D. S. Noyce and D. B. Denney, *J. Am. Chem. Soc.* **74**, 5912 (1952).
[15]E. Piers and S. Nagakura, *Synth. Commun.* **5**, 193 (1975).
[16]S. Masamune, P. A. Rossy and G. S. Bates, *J. Am. Chem. Soc.* **95**, 6452 (1973).