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Ilicic Acid as a Natural Quiron for the Efficient Preparation of Bioactive α- and β-Eudesmol

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An efficient procedure for the isolation of the sesquiterpene ilicic acid (**3**) on a multigram scale of extracts obtained from aerial parts of *Inula viscosa* (Asteraceae) was developed. Acid **3** is an appropriate starting material for short, enantiospecific syntheses of β-eudesmol (**1**) and α-eudesmol (**2**), natural products featuring significant antiangiogenic and anti-Alzheimer properties. Synthesis of **1** was achieved in six steps and the synthesis of **2** in seven, producing overall yields of 52 and 41 %, respectively.

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Introduction

The use of appropriate natural products as starting materials in the synthesis of bioactive compounds is a powerful tool. In recent years, taxol, ecteinascidin known antitumourals and others[1] have been synthesized with great efficiency by using this strategy. β-Eudesmol (**1**) and α-eudesmol (**2**), two sesquiterpene isomers with interesting bioactivities, have been found in numerous essential oils,[2] although mostly in small quantities. Sesquiterpene **1** has an anticholinergic effect and exhibits antiangiogenic activity on the vascular endothelium, which thus makes it potentially useful in the treatment of different angiopathologies and cancers.[3] Moreover, it has recently been linked to the treatment of Alzheimer's disease.[4] Sesquiterpene **2** is a P/Q-type calcium channel blocker, which makes it effective in the treatment of cerebral poplexy and Alzheimer's disease.[5] Different approaches for the total syntheses of **1** and **2** in numerous steps have been published, including diastereoselective Simmons–Smith cyclopropanation,[6] Robison–Mannich condensation,[7] Diels–Alder cycloaddition[8] and radical cyclization.[9]

Dittrichia viscosa L. Greuter (sin. *Inula viscosa* L. Aiton, Asteraceae), a widespread Mediterranean plant, has proven to be a rich source of sesquiterpenes with an eudesmane skeleton;[10] ilicic acid (**3**) is one of the main components of the extracts of the aerial parts.[11] This acid is also found in other plants such as *Callitris glaucophylla*,[12] *Laggera alata*, *L. pterodonta*,[13] *Nectandra membranacea*[14] and so on, but in smaller proportions. The abundance of *Dittrichia viscosa L.* in central and southern Spain, and the ease with which it colonizes wasteland areas, led us to believe that it could be used as a renewable source of **3**. This compound has a structure and functionality that makes it a suitable starting material for the semisynthesis of **1** and **2** and other sesquiterpenes. The absence of an appropriate methodology to prepare this product on a preparative scale probably accounts for why there are no applications for this natural product. Continuing with our line of work on the development of new natural starting materials,[15] this paper focuses on the isolation of ilicic acid (**3**) from *Inula viscosa* and its use in the enantiospecific synthesis of **1** and **2**.

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Results and Discussion

The preparation of β-eudesmol (**1**) and α-eudesmol (**2**) from **3** was planned as indicated in Figure 1. Access to β-eudesmol (**1**) would be achieved via intermediate kudtdiol (**4**), a natural product isolated from *Jasonia glutinosa* D.C.[16] by selective deoxygenation of the primary hydroxy group. Sesquiterpene **4** would be obtained from ilicic acid (**3**) by regioselective dehydration and appropriate functionalization of the isopropyl group. A similar approach could be used to obtain α-eudesmol (**2**). In this case, the formation of a double bond at C3–C4 is necessary.

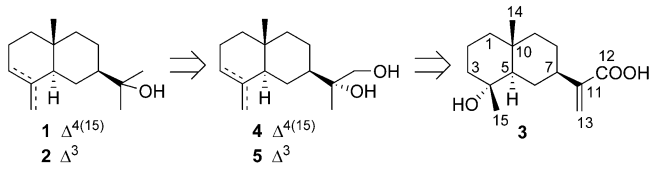

Figure 1. Retrosynthetic scheme for β- and α-eudesmol (**1** and **2**).

In order to obtain the natural starting product in sufficient quantities, it was necessary to conduct a study into the process of extraction and isolation of **3** from the aerial

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parts of *Inula viscosa* and its subsequent optimization. With this objective in mind, different methods of extraction and acid–base partition (methods A–C) were tested (Figure 2, Table 1). In method A, the extraction of dried and powdered plant material was carried out in a Soxhlet system for 5 h, whereas in methods B and C this was achieved by maceration (three times successively) of the fresh plant material for 30 min. In all cases the solvent employed for the extraction was *tert*-butyl methyl ether, which provided the best results in previous tests. The maceration of fresh plant material gave rise to extracts that were "cleaner" and richer in acid metabolites (seen by ^{1}H NMR spectroscopy).

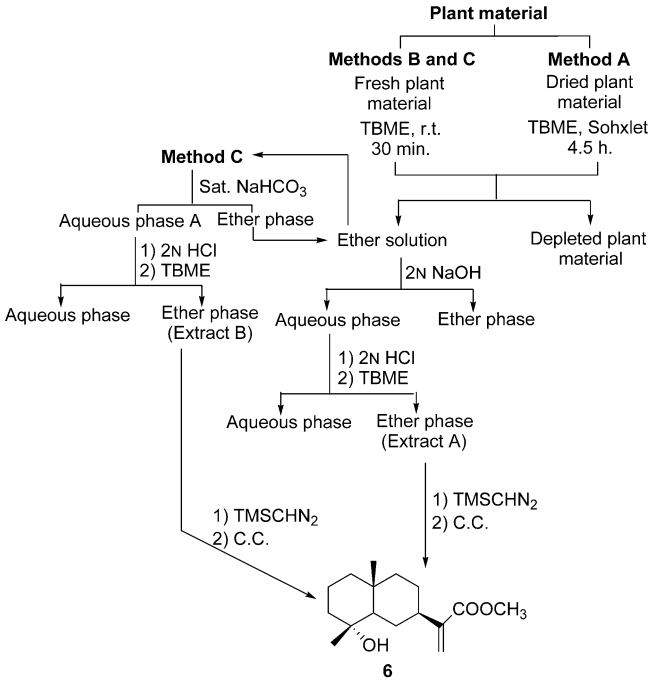


Figure 2. Extraction and isolation methods of **6**.

Table 1. Percentages obtained of **6** with the different isolation methods.

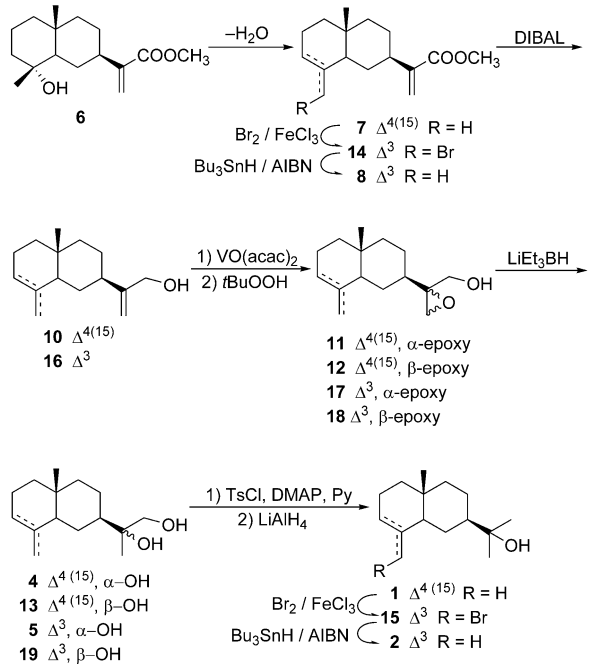
	April/May		August		September/October	
	Acid Phase [%][a]	**6** [%][a]	Acid Phase [%] [a]	**6** [%] [a]	Acid Phase [%][a]	**6** [%][a]
A[b]	2.49[e]	0.80	2.19[e]	0.41	2.60[e]	0.38
B[c]	2.60[e]	0.87	2.30[e]	0.50	2.70[e]	0.45
C[d]	1.27[f]	0.97	1.15[f]	0.79	0.90[f]	0.50

[a] Referred to dry plant weight. [b] Hot extraction (Soxhlet) and partition with 2 N NaOH. [c] Cold extraction and partition with 2 N NaOH. [d] Cold extraction and partition with saturate $NaHCO_3$ solution. [e] Total percentage of extract acid components (acid eudesmanes and polyphenols). [f] Percentage of acid eudesmanes.

In methods A and B, the acid–base partition of the extract was undertaken by using 2 N NaOH, which produced an acid fraction (extract A) consisting of acid eudesmanes together with polyphenolic compounds. Extract A was then methylated with $TMSCHN_2$[17] and then purified by column chromatography over silica gel to yield the methyl ester of **3**, that is, **6**.[18] In method C the acid–base partition was initially carried out with a saturated $NaHCO_3$ solution, which gave rise to an acid fraction comprising only acid eudesmanes (extract B), whose treatment with $TMSCHN_2$ and subsequent chromatographic separation produced **6**. As shown in Table 1, the best results were obtained by using method C.

The contents of **3** were then studied at different plant vegetative stages (Table 1), and the maximum production was found to occur in spring and at a level of nearly 1% with respect to the dry plant weight.

Having attained compound **6**, the synthesis of eudesmols **1** and **2** was achieved by following the synthetic sequence indicated in Scheme 1.



Scheme 1. Synthesis of eudesmols **1**, **2** and **4**.

The first step involved the regioselective formation of the double bond at the 4,15- or 3,4-positions. With this objective in mind, different dehydration methods were tested and the most significant are summarized in Table 2.

Treatment with iodine in benzene produced only isomer **9** with a tetrasubstituted double bond. Production of **7** with an exocyclic olefin was best performed by employing $POCl_3$ in pyridine at –20 °C (86%), whereas *p*-toluenesulfonic acid in benzene at reflux (35%) was used for **8**. The results in Table 2 show that in the *trans*-decalin of eudesmanes the presence of a double bond Δ^3 generates instability making this double bond difficult to obtain.

Reduction of α,β-unsaturated ester **7** with DIBAL in toluene led to allylic alcohol **10** with a yield of 96%, and the spectroscopic data correspond to those of the natural product β-costol.[23] Epoxidation of **10** with *t*BuOOH/$VO(acac)_2$ in benzene gave rise to a 1:1 mixture of epoxide epimers **11** and **12** in 92% yield. Subsequent reduction of this mixture with $LiEt_3BH$ in THF yielded a mixture of diol

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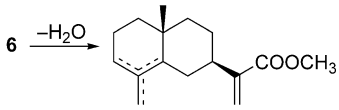
Table 2. Dehydration of **6** for the preparation of regioisomers **7**–**9**.



Dehydration agent	*T*	Percentage			
	[°C]	**7**	**8**	**9**	**6**
$POCl_3$/pyridine[19]	–20	86	2	2	–
$POCl_3$/pyridine[19]	100	57	17	16	–
I_2/Ph_3P[20]	r.t.	10	–	85	–
I_2/Ph_3P[20]	0	27	–	63	–
TsOH/C_6H_6[21]	80	15	35	43	–
TsOH/C_6H_6[21]	r.t.	7	3	5	73
I_2/C_6H_6[22]	r.t.	–	–	81	–
$SOCl_2$/pyridine[15c]	–40	48	23	24	–

epimers **4** and **13** in 98% yield. The Sharpless asymmetric epoxidation of **10**[24] with the use of diethyl L-(–)-tartrate as chiral auxiliary led to a 6:1 mixture of **11** and **12** as shown by ^{1}H NMR spectroscopy. Subsequent reduction of this mixture with $LiEt_3BH$ yielded **4** with a diastereomer excess of 70%. The spectroscopic data of **4** corresponded to those published for kudtdiol.[16] The preparation of **1** from the **4**/**13** mixture was carried out with good yield by reduction of their monotosylate with $LiAlH_4$.[16a]

The synthesis of α-eudesmol (**2**) was conducted following a sequence similar to that of **1** from methyl ester **6** (Scheme 1). However, all dehydration attempts of **6** led to the formation of the double bond in the 3,4-position in low yields (see Table 2). Because of this, isomerization of the double bond in the 4,15-positions of **7** to the 3,4-positions was attempted with $Br_2/FeCl_3$.[25] This reaction led to 15-bromoeudesmol **14**, whose immediate reduction with Bu_3SnH/AIBN yielded **8** in low yield (10%). In contrast, when this isomerization was carried out on the double bond of β-eudesmol (**1**) a yield of 80% was obtained, thus improving the synthesis of **2**. The spectroscopic data of **2** corresponded with those indicated in the bibliography for α-eudesmol.[26]

Conclusions

A convenient method for the extraction and isolation of ilicic acid (**3**) as its methyl ester (**6**) on a multigram scale from the aerial parts of *Inula viscosa* was developed. Compound **6** was used for the first time as a starting material to develop the enantiospecific synthesis of interesting and bioactive β- and α-eudesmol (**1** and **2**). Sesquiterpene **1** was obtained in six steps with an overall yield of 52%, and **2** was obtained via **1** plus one additional step in 41% overall yield. These results represent an improvement over the different approaches published up to now.

Experimental Section

General: IR spectra were recorded with a Mattson Satellite FTIR spectrometer. NMR spectra were performed with Varian Direct-Drive 400 (^{1}H 400 MHz/^{13}C 100 MHz) and 500 (^{1}H 500 MHz/^{13}C 125 MHz) spectrometers. High-resolution mass spectra were determined with an Autospec-Q VG-Analytical (FISONS) mass spectrometer. HPLC with UV detection was used. Semipreparative HPLC separation were carried out on a column (5 μm Silica, 10 × 250 mm) at a flow rate of 2.0 mL min^{-1}. All air- and water-sensitive reactions were performed in flame-dried flasks under an argon atmosphere. The solvents used were purified according to standard literature techniques and stored under an argon atmosphere.

Plant Material: *Dittrichia viscosa* L. Greuter was collected in October 2005, April 2006, May 2006 and August 2006 in the Parque Almunia zone (Granada, Spain). A voucher specimen is available for inspection at the herbarium of the Granada University.

Extraction and Isolation

Method A: Air-dried and finely powdered aerial parts of *Inula viscosa* (125 g) were extracted in a Soxhlet apparatus with *tert*-butyl methyl ether for 4.5 h. The solution obtained was washed with 2 N NaOH (3 × 150 mL) solution. The aqueous layer was acidified with 2 N HCl until pH 2 and extracted with *tert*-butyl methyl ether (3 × 150 mL). The ether layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford extract A (3.12 g, 2.49% with respect to the weight of dry aerial parts).

Method B: This method is similar to method A, but the extraction was made by maceration in *tert*-butyl methyl ether for 30 min (3 × 5 L). Extract A (6.5 g, 2.60% with respect to the weight of dry aerial parts) was obtained from 1.750 Kg of fresh aerial parts (250 g of dry aerial parts).

Method C: This method is similar to method B, but the ether solution was washed with saturated $NaHCO_3$ (4 × 600 mL) solution. The aqueous layer was acidified with 2 N HCl until pH 2 and extracted with *tert*-butyl methyl ether (4 × 400 mL). The ether layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford extract B (15.29 g, from 1.2 Kg of aerial parts, 1.27% with respect to the weight of dry aerial parts).

Extracts A and B were methylated with $TMSCHN_2$[17] to afford a crude product that was purified by column chromatography over silica gel to yield methyl ilicate (**6**)[18] (see Table 1; hexane/*tert*-butyl methyl ether, 50:50).

Dehydration of 6

Method A: Phosphorous oxychloride (11.5 mL) was added dropwise to solution of **6** (1033 mg, 3.90 mmol) in dry pyridine (80 mL) at –20 °C with vigorous stirring under an argon atmosphere. The mixture was kept at –20 °C for 5 h and then at room temperature for 2 h. It was then poured into ice and extracted with *tert*-butyl methyl ether (3 × 100 mL). The organic layer was washed with 2 N HCl (3 × 100 mL), saturated aqueous $NaHCO_3$ solution (3 × 100 mL) and brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield a mixture of methyl β-costate (**7**),[27] methyl α-costate (**8**)[28] and methyl γ-costate (**9**)[28a,29] (90%) in a 43:1:1 ratio.

Method B: This method is similar to method A, but the phosphorus oxychloride (1.2 mL) was added to a cold (0 °C) solution of **6** (107 mg, 0.40 mmol) in dry pyridine (8 mL), and the mixture was heated at 100 °C for 10 min to yield a mixture of **7**, **8** and **9** (90%) in a 3.5:1:1 ratio.

Method C: Iodine (130 mg) was added to a solution of Ph_3P (160 mg) in CH_2Cl_2 (2.5 mL), and the mixture was stirred at room temperature for 10 min. A solution of **6** (136 mg, 0.51 mmol) in

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CH_2Cl_2 (1.5 mL) was then added, and the mixture was further stirred at room temperature for 20 min. Aqueous 5% $NaHSO_3$ (5 mL) was added, and the mixture was stirred for 10 min. It was then diluted with CH_2Cl_2 (50 mL), and the organic layer was washed with water and brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield a mixture of **7** and **9** (95%) in a 1:8.5 ratio.

Method D: This method is similar to method C, but the reaction was carried out at 0 °C for 10 min to yield a mixture of **7** and **9** (90%) in a 1:2.3 ratio.

Method E: *p*-Toluenesulfonic acid (10 mg) was added to a stirred solution of **6** (120 mg, 0.45 mmol) in benzene (8 mL) at 80 °C, and the mixture was kept at reflux for 5 min. It was then diluted with *tert*-butyl methyl ether (50 mL) and washed with aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield a mixture of **7**, **8** and **9** (93%) in a 1:2.3:2.8 ratio.

Method F: This method is similar to method E, but the reaction was carried out at room temperature for 16 h to yield a mixture of **7**, **8** and **9** (15%) in a 2.3:1:1.6 ratio and **6** (73%).

Method G: Iodine (109 mg) was added to a stirred solution of **6** (114 mg, 0.43 mmol) in benzene (8 mL), and the mixture was kept at room temperature for 5 h. Aqueous 5% $NaHSO_3$ (5 mL) was added, and the mixture was stirred for 10 min. It was then diluted with *tert*-butyl methyl ether (50 mL), and the organic layer was washed with water and brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield only **9** (81%).

Method H: Thionyl chloride (0.90 mL) was added to a cold (–40 °C) solution of **6** (106 mg, 0.40 mmol) in dry pyridine (8 mL), and the mixture was kept at that temperature with stirring for 20 min. It was then poured into ice and extracted with *tert*-butyl methyl ether (3 × 100 mL). The organic layer was washed with 2 N HCl (3 × 100 mL), aqueous $NaHCO_3$ solution (3 × 100 mL) and brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield a mixture of **7**, **8** and **9** (95%) in a 2:1:1 ratio.

Preparation of β-Costol (9) by the Reduction of 7 with DIBAL: DIBAL (1 M in hexane, 0.65 mL, 2.4 equiv.) was added to a cold (–20 °C) solution of **7** (67 mg, 0.27 mmol) in dry toluene (5 mL) under an argon atmosphere with stirring. After 15 min, water (2 mL) was added to the mixture, and it was stirred at room temperature for 20 min. The mixture was filtered through a layer of silica gel/anhydrous Na_2SO_4 (2:1), and the layer was washed with *tert*-butyl methyl ether. The organic layer was concentrated in vacuo to yield a crude product that was purified by column chromatography over silica gel (hexane/*tert*-butyl methyl ether, 80:20) to obtain **10**[24] (57 mg, 96%).

Preparation of Epoxides 11 and 12 by the Epoxidation of 10 with $VO(acac)_2$/*t*BuOOH: $VO(acac)_2$ (4.4 mg) was added to a solution of **10** (121 mg, 0.55 mmol) in benzene (18 mL) under an argon atmosphere, and the mixture was heated at reflux for 10 min. *tert*-Butyl hydroperoxide (5.0–6.0 M in decane, 0.15 mL) was then added, and the mixture was kept at reflux whilst stirring for 30 min. After cooling to room temperature, the mixture was diluted with EtOAc (40 mL) and washed with aqueous $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield a crude product that was purified by column chromatography over silica gel (hexane/*tert*-butyl methyl ether, 80:20) to obtain a mixture of epimers **11** and **12** it a 1:1 ratio (120 mg, 92%).

(5*S*,7*R*,10*R*,11*R*)-11,13-Epoxyeudesm-4(15)-en-12-ol (11) and (5*S*,7*R*,10*R*,11*S*)-11,13-Epoxyeudesm-4(15)-en-12-ol (12): Colourless syrup. $[\alpha]_D$ = +44.9 (*c* = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3431, 3078, 2928, 2866, 2843, 1645, 1441, 1409, 1378, 1264, 1101, 1058, 886 cm^{-1}. HRMS (FAB): calcd. for $C_{15}H_{24}O_2Na$ $[M + Na]^+$ 259.1674; found 259.1673.

Compound 11: ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.69 (s, 3 H, 14-H), 1.16 (q, *J* = 12.4 Hz, 1 H, 6β-H), 1.18–1.66 (m, 10 H, 2 1-H, 2 2-H, 6α-H, 7α-H, 2 8-H, 2 9-H), 1.70 (br. s, 1 H, OH), 1.76 (br. d, *J* = 12.2 Hz, 1 H, 5α-H), 1.98 (br. dt, *J* = 6.8, 12.4 Hz, 1 H, 3α-H), 2.30 (br. d, *J* = 12.4 Hz, 1 H, 3β-H), 2.71 (d, *J* = 4.7 Hz, 1 H, 13a-H), 2.89 (d, *J* = 4.7 Hz, 1 H, 13b-H), 3.71 (dd, *J* = 8.9, 12.2 Hz, 1 H, 12a-H), 3.85 (dd, *J* = 2.2, 12.2 Hz, 1 H, 12b-H), 4.40 (s, 1 H, 15a-H), 4.70 (s, 1 H, 15b-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 16.4 (CH_3, C-14), 23.6 (CH_2, C-2), 23.9 (CH_2, C-8), 25.6 (CH_2, C-6), 36.3 (C, C-10), 37.0 (CH_2, C-3), 40.7 (CH, C-7), 40.8 (CH_2, C-1)*, 42.0 (CH_2, C-9)*, 49.0 (CH_2, C-12), 49.7 (CH, C-5), 61.3 (CH_2, C-13), 62.4 (C, C-11), 105.8 (CH_2, C-15), 150.7 (C, C-4) ppm (signals denoted with an * are exchangeable).

Compound 12: Distinct signals only: ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.72 (d, *J* = 4.7 Hz, 1 H, 13a-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.9 (CH_2, C-8), 26.6 (CH_2, C-6), 48.9 (CH_2, C-12), 61.4 (CH_2, C-13), 105.7 (CH_2, C-15) ppm.

Preparation of Kudtdiol (4) and 11-epi-Kudtdiol (15) by Reduction of the 11+12 Mixture with $LiEt_3BH$: $LiEt_3BH$ (1 M in THF, 0.66 mL) was added to a cold (0 °C) solution of the mixture **11+12** (78 mg, 0.33 mmol) in dry THF (1 mL) under an argon atmosphere. After 2.5 h, the mixture was hydrolyzed by the addition of water (0.1 mL), 6 N NaOH (0.1 mL) and water (0.3 mL), successively. The mixture was then stirred at room temperature for 10 min and filtered through a layer of silica gel/anhydrous Na_2SO_4 (2:1), and the layer was then washed with *tert*-butyl methyl ether. The organic layer was concentrated in vacuo to yield a crude product that was purified by column chromatography over silica gel (hexane/*tert*-butyl methyl ether, 95:5) to obtain a mixture of **4**[16] and **13** in a 1:1 ratio (77 mg, 98%).

Kudtdiol (4) and 11-epi-Kudtdiol (13): Colourless syrup. $[\alpha]_D$ = +45.1 (*c* = 1.0, CH_2Cl_2). IR (film): $\tilde{\nu}$ = 3425, 3079, 2964, 2934, 2906, 2844, 1646, 1461, 1380, 1364, 1284, 1261, 1215, 1187, 1120, 1088, 1030, 1009, 886 cm^{-1}. HRMS (FAB): calcd. for $C_{15}H_{26}O_2Na$ $[M + Na]^+$ 261.1830; found 261.1832.

11-epi-Kudtdiol (13): ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 0.70 (s, 3 H, 14-H), 0.77–0.99 (m, 3 H, 1β-H, 8a-H, 9a-H), 1.09 (q, *J* = 12.3 Hz, 1 H, 6β-H), 1.19–1.32 (m, 3 H, 1α-H, 2 2-H), 1.31 (s, 3 H, 13-H), 1.43–1.63 (m, 6 H, 6α-H, 7α-H, 8b-H, 9b-H, 2 OH), 1.76 (br. d, *J* = 12.3 Hz, 1 H, 5α-H), 1.99 (br. dt, *J* = 8.0, 11.8 Hz, 1 H, 3α-H), 2.31 (br. d, *J* = 12.6 Hz, 1 H, 3β-H), 3.77 (d, *J* = 9.0 Hz, 1 H, 12a-H), 4.04 (d, *J* = 9.0 Hz, 1 H, 12b-H), 4.40 (d, *J* = 1.1 Hz, 1 H, 15a-H), 4.70 (d, *J* = 1.1 Hz, 1 H, 15b-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 16.5 (CH_3, C-14), 22.0 (CH_2, C-8), 23.7 (CH_2, C-2), 24.7 (CH_2, C-6), 24.8 (CH_3, C-13), 36.2 (C, C-10), 37.1 (CH_2, C-3), 40.9 (CH, C-1)*, 42.0 (CH_2, C-9)*, 47.6 (CH, C-7), 49.7 (CH, C-5), 74.6 (CH_2, C-12), 83.9 (C, C-11), 105.6 (CH_2, C-15), 151.0 (C, C-4) ppm (signals denoted with an * are exchangeable).

Sharpless Asymmetric Epoxidation of 10: A mixture of powdered, activated 4 Å molecular sieves (120 mg) and dry CH_2Cl_2 (2 mL) was cooled to –20 °C. To this mixture was added titanium(IV) isopropoxide (12 μL) and then L-(–)-diethyl tartrate (8 μL) under an argon atmosphere with vigorous stirring. The resulting mixture was stirred for a further 15 min at –20 °C. At this point, a solution of **9** (80 mg) in dry CH_2Cl_2 (2 mL) was then added dropwise. After

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stirring for 15 min, *t*BuOOH (5.0–6.0 M in decane, 0.25 mL) was then added dropwise. The mixture was then kept at –20 °C for an additional 24 h. After this time, a 5 N solution of NaOH saturated with NaCl was added, and the mixture was kept at 0 °C for 1 h whilst stirring. Finally, the resulting mixture was filtered through Celite, the organic layer was removed and combined with three extractions of aqueous layer (CH_2Cl_2, 3 × 20 mL). The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield a crude product that was purified by column chromatography over silica gel (hexane/*tert*-butyl methyl ether, 80:20) to obtain a mixture of epimers **11** and **12** in a 6:1 ratio (52 mg, 61%). Reduction of that mixture with $LiEt_3BH$ (1 M in THF, 0.44 mL) by following the above method afforded **4** with a diastereomer excess of 70%. $[\alpha]_D$ = +65.8 (*c* = 1.0, $CHCl_3$) {ref.[16] $[\alpha]_D$ = +72.9 (*c* = 1.0, $CHCl_3$)}.

Preparation of β-Eudesmol (1) by the Reduction of the Mixture of Diols 4+13: Tosyl chloride (160 mg) and DMAP (3 mg) were added to a cold (0 °C) solution of the mixture of **4+13** (40 mg, 0.17 mmol) in dry pyridine (1.0 mL) under an argon atmosphere with vigorous stirring. The mixture was kept at room temperature for 28 h, and then poured into ice and extracted with *tert*-butyl methyl ether (3 × 10 mL). The organic layer was washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to yield a crude product (50 mg) that was dissolved in dry THF (2 mL). The solution was added dropwise to a cold (0 °C) suspension of $LiAlH_4$ (15 mg) in THF (1 mL) under an argon atmosphere with vigorous stirring. The mixture was heated at 65 °C for 15 h and then cooled to room temperature and diluted with *tert*-butyl methyl ether. At this point, a 10% NaOH solution (5 mL) was added to the mixture, and the resulting suspension was filtered through a layer of silica gel/anhydrous Na_2SO_4 (2:1). The filtrate was concentrated in vacuo to yield a crude product that was purified by column chromatography over silica gel (hexane/*tert*-butyl methyl ether, 90:10) to obtain β-eudesmol (**1**; 31 mg, 81%). $[\alpha]_D$ = +60.9 (*c* = 1.6, CH_3Cl_3) {ref.[16] $[\alpha]_D$ = +61.2 (*c* = 1.6, $CHCl_3$)}.

Preparation of α-Eudesmol (2) by the Isomerization of the C4,C15 Double Bond of 1: A suspension of dry $FeCl_3$ (0.034 g, 0.21 mmol, 1.05 equiv.) in dry THF (5 mL) was treated with bromine (0.011 mL, 0.21 mmol, 1.05 equiv.). After stirring at room temperature for 45 min, compound **1** (40 mg, 0.20 mmol, 1.0 equiv.) was added. The mixture was stirred at room temperature for 2.5 h, before it was diluted with *tert*-butyl methyl ether (10 mL) and water (15 mL). The layers were separated, and the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. To a solution of the crude product (35 mg) in dry and strictly deoxygenated benzene (2.5 mL) under an argon atmosphere and heated at 90 °C was added dropwise (20 mL h^{-1}) a solution of Bu_3SnH (165 μL, 0.64 mmol) and AIBN (5.5 mg, 0.03 mmol) in dry and strictly deoxygenated benzene (2 mL). After further stirring for 40 min, the solvent was evaporated in vacuo, and the crude product was dissolved in *tert*-butyl methyl ether (12.5 mL). A saturated aqueous KF solution (2 mL) was added, and the mixture was stirred for 2 h at room temperature and then filtered through a Celite column. The biphasic filtrate was extracted with *tert*-butyl methyl ether, and the combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography over silica gel (hexane/*tert*-butyl methyl ether, 90/10) to yield **2** (32 mg, 80%). $[\alpha]_D$ = +28.4 (*c* = 1.2, $CHCl_3$) {ref.[26] $[\alpha]_D$ = +28.5 (*c* = 1.2, $CHCl_3$)}.

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