Total Synthesis and Absolute Stereostructure of (+)-Dysideapalaunic Acid

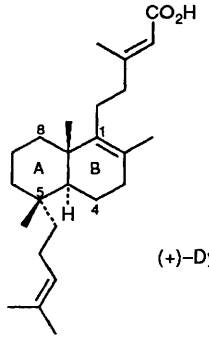
Hisahiro Hagiwara* and Hisashi Uda
Chemical Research Institute of Non-aqueous Solutions, Tohoku University, Katahira, 2-1-1, Aoba-ku, 980 Sendai, Japan

The total synthesis of (+)-dysideapalaunic acid, a sesterterpenic aldose reductase inhibitor, has been accomplished. Starting from optically active (8a*S*)-(+)-3,4,8,8a-tetrahydro-5,8a-dimethylnaphthalene-1,6(2*H*,7*H*)-dione, (5*S*)-(−)-3,4,4a,5,6,7,8,8a-octahydro-5,8a-dimethyl-5-(4-methylpent-3-enyl)naphthalen-1(2*H*)-one ethylene acetal has been synthesized in eight steps involving reductive allylation, deoxygenation, and a Wittig condensation. Transformation of this ethylene acetal *via* methylation at C-2, Grignard addition, and a Horner–Emmons reaction furnished the required (+)-acid in eight steps. Thus, the absolute stereochemistry of the (+)-acid has been established as (4a*S*,5*S*,8a*S*).

One of the major therapeutic needs in the treatment of diabetes is the prevention of its complications, since hyperglycaemia is now becoming controllable. The complications of diabetes, such as nephropathy, neuropathy, cataract, or retinopathy, are caused by intracellular accumulation of sorbitol in the glomerule, the peripheral nerve, the crystalline lens, or the retina, respectively.[1] As a result of hyperglycaemia, glucose is reduced by an aldose reductase in the sorbitol metabolic cycle. Since sorbitol is difficult to discharge from cells, the over-accumulation of sorbitol results in an osmotic imbalance, which damages cells. Hence, in both synthetic and natural product chemistry, aldose reductase inhibitors are being actively investigated.[2]

Utilizing their original assay of aldose reductase obtained from rat lenses, Nakagawa *et al.* investigated the marine sponge *Dysidea sp.* from the Palauan Sea and found some metabolites which inhibited the aldose reductase.[3] Among the active principles isolated was a structurally unprecedented sesterterpenic acid, dysideapalaunic acid **1**. Its structure and relative stereochemistry were determined by a combination of one- and two-dimensional NMR spectroscopy and mass spectroscopy, and it was shown to have both sacculatane and labdane units in the same molecule. However, the absolute stereostructure of compound **1** has not yet been assigned. Although the biological activity is modest (10^{-4} mol dm^{-3}),[3] the structure of compound **1** belongs to a new class of compounds, not only among other aldose reductase inhibitors but also among terpenoids.

Intrigued by the potentially useful biological activity mentioned above, along with our recent interest in the synthesis of biologically active sacculatane diterpenoids,[4,5] we disclose herein our synthesis of natural (+)-dysideapalaunic acid **1** which permits determination of the absolute stereochemistry.[6]

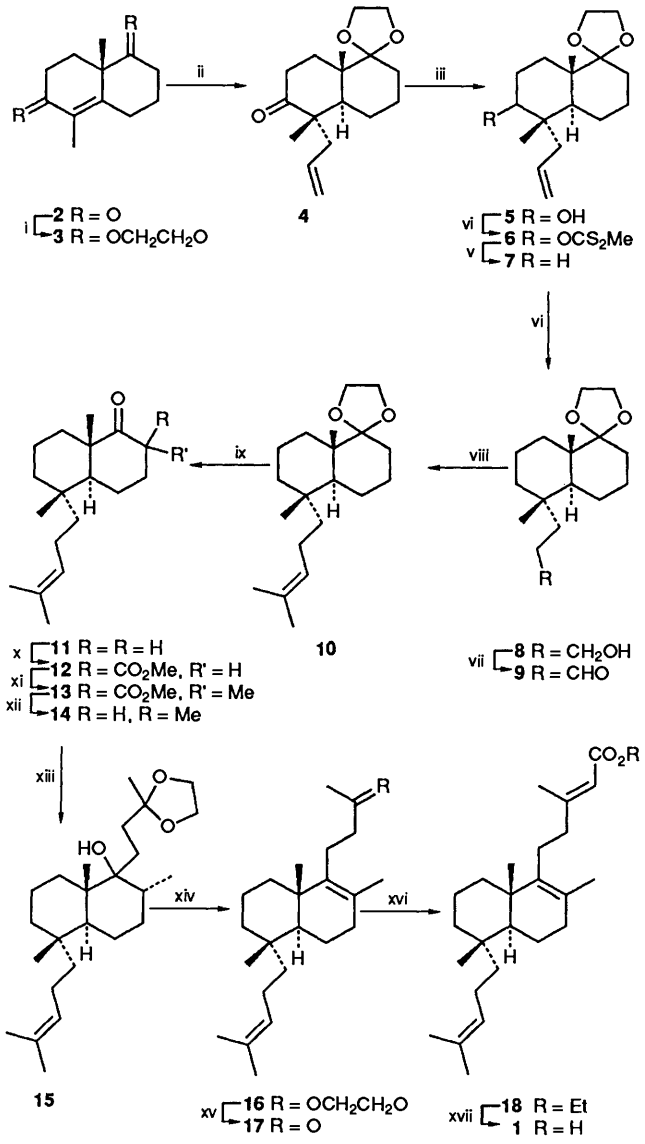


(+)-Dysideapalaunic acid **1**

Results

At the outset of synthesis, there was no preliminary information on the absolute stereochemistry of (+)-dysideapalaunic acid **1**. The synthesis started from the optically active Wieland–Miescher ketone analogue (8a*S*)-(+)-ene-dione **2** {80% optically pure; $[\alpha]_D$ +112° (*c* 1.31 in MeOH)[7]} which is available by an enantioselective aldol cyclization developed in our laboratory. The synthetic design starting from dione (+)-**2** is quite straightforward. The two remaining asymmetric centres, C-4a and -5, would be created in the desired configuration by application of well defined reductive alkylation of the enone moiety in liquid ammonia.[8] The functionality in ring A was elaborated first and manipulation of the side-chain in ring B was carried out, which would allow the total synthesis of the target compound (+)-**1** in natural enantiomeric form (Scheme 1).

Within this context, the saturated ketone group at C-1 of dione (+)-**2** was selectively protected by acetal exchange with the ethylene acetal of butan-2-one to give the acetal **3** in 89% yield after a recycle of recovered substrate **2**. Reductive alkylation of the enone moiety of compound **3** in liquid ammonia was accomplished by the use of 3-bromopropene as an alkylating reagent. Thus, treatment of the acetal **3** with lithium in liquid ammonia followed by 3-bromopropene afforded the allylated *trans*-decalone **4** in 70% yield as a single product. Assignment of the relative stereochemistry at C-4a and -5 in compound **4** followed from reductive alkylation of the analogous octalone derivatives,[8,9] and was confirmed by the final conversion of compound **4** into the natural product **1**. Attempts to introduce directly the 4-methylpent-3-enyl side-chain with 1-iodo-4-methylpent-3-ene failed, resulting in formation of the non-alkylated 1,4-reduction product of the acetal **3**. Reduction of the ketone at C-6 in the decalone **4** to a methylene group by the Wolff–Kishner reduction or modified procedures was unsuccessful, probably due to steric hindrance of the adjacent substituents at C-5. After a number of experiments, this problem was solved by the use of Barton's free-radical deoxygenation protocol,[10] which is known to be less susceptible to steric hindrance. Reduction of the decalone **4** with lithium aluminium hydride (LAH) gave the (6*S*)-alcohol **5** as a major isomer (6-H δ 3.45, $W_{\frac{1}{2}}$ 17 Hz). The isomeric mixture of alcohols **5** was transformed into the xanthate **6** by successive treatment with butyllithium, carbon disulphide, and iodomethane. Heating of the xanthate **6** with tributylstannane in the presence of a catalytic amount of azoisobutyronitrile (AIBN) in xylene provided the decalin **7** in 86% overall yield from the alcohol **5**.



Scheme 1 *Reagents and conditions*: i, butan-2-one ethylene acetal, $(CH_2OH)_2$, D-CSA, 45 °C; ii, Li, liq. NH_3, $CH_2{=}CHCH_2Br$, water (1 mol equiv.); iii, LAH Et_2O, −50 °C; iv, BuLi, THF, CS_2, MeI, room temperature; v, Bu_3SnH, AIBN, xylene, reflux; vi, BH_3–THF, THF, 0 °C; then NaOH, H_2O_2, 0 °C then room temperature; vii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −65 to −20 °C; viii, $Ph_3P{=}C(Me)_2$, Et_2O, 0 °C then room temperature; ix, PPTS, aq. acetone, reflux; x, NAH, $(MeO)_2CO$, THF, room temperature; xi, NaH, MeI, THF, room temperature; xii, LiCl, HMPA, 130 °C; xiii, 4-bromobutan-2-one ethylene acetal, Mg, THF, ultrasonic irradiation then reflux; xiv, $SOCl_2$, pyridine, 0 °C; xv, PTSA·H_2O, aq. acetone, reflux; xvi, NaH, $(EtO)_2P(=O)CH_2CO_2Et$, THF, reflux; xvii, 15% aq. NaOH, EtOH, reflux

The requisite 4-methylpent-3-enyl side-chain at C-5 in compound **1** was furnished in a straightforward manner. Hydroboration of the allylic double bond in the decalin **7** followed by hydrogen peroxide oxidation afforded the primary alcohol **8** in 58% yield. Swern oxidation[11] of the acetal **8** gave the aldehyde **9** in 77% yield. Wittig condensation of the aldehyde **9** with isopropylidene(triphenyl)phosphorane completed the elaboration of the side-chain at C-5, and gave the decalin **10** in 81% yield. Deprotection of the decalin **10** was achieved with pyridinium toluene-*p*-sulphonate (PPTS)[12] in acetone to give in quantitative yield the decalone **11**, the key intermediate for the synthesis of the diterpenoid sacculatane.[5]

In order to construct the remaining B-ring functionalities, the decalone **11** was transformed into the β-keto ester **12** by reaction of the enolate, generated with sodium hydride, with dimethyl carbonate in tetrahydrofuran (THF). The β-keto ester **12** reacted smoothly with sodium hydride and iodomethane to produce the methylated keto ester **13** in 77% yield. Attempts to monomethylate at C-2 of the decalone **11** by lithium diisopropylamide (LDA) and iodomethane afforded an inseparable mixture of mono- and di-methylated products. The methoxycarbonyl group of the keto ester **13** was removed by heating with lithium chloride in hexamethylphosphoric triamide (HMPA)[13] to yield the decalone **14** in 72% yield.

Elongation of the side-chain at C-1 of the decalone **14** was effected by addition of the Grignard reagent prepared from protected 4-bromobutan-2-one.[14] In the presence of 1,2-dibromoethane, initial addition of a small amount of neat 4-bromobutan-2-one ethylene acetal started the Grignard reaction and irradiation with ultrasound allowed complete generation of the Grignard reagent. Reaction of the decalone **14** with this Grignard reagent gave the adduct **15** in 90% yield. Dehydration of the adduct **15** with thionyl chloride in pyridine produced the desired *endo*-unsaturated acetal **16** in 86% yield without the exocyclic double-bond isomer. The unsaturated acetal **16** was deprotected with toluene-*p*-sulphonic acid (PTSA) monohydrate in aq. acetone to afford the ketone **17** in quantitative yield. The Horner–Emmons reaction of the ketone **17** in THF led to a single, (*E*)-unsaturated ester **18** (δ 2.18, olefinic methyl β to CO_2Et) quantitatively. Finally, hydrolysis of the unsaturated ester **18** in aq. sodium hydroxide culminated in the first total synthesis of (+)-dysideapalaunic acid **1**, in 67% yield. The spectral data (^1H NMR, IR and MS) were identical with those of the natural compound, as were optical rotational data, $[\alpha]_D$ +58° (*c* 0.33 in $CHCl_3$) (lit.,[15] +61° in $CHCl_3$). Some enantiomeric enrichment may occur during purification procedures. Since the starting (+)-ene-dione **2** has (8a*S*) absolute configuration,[7] the absolute stereochemistry of the (+)-acid **1** was unambiguously established as (4a*S*,5*S*,8a*S*) as depicted.

Experimental

IR spectra were recorded on a Jasco A-3 spectrophotometer for solutions in tetrachloromethane. ^1H NMR spectra were obtained for solutions in deuteriochloroform with JEOL FX-90Q (90 MHz) and PMX-60 (60 MHz) instruments, with tetramethylsilane as internal standard. *J*-Values are given in Hz. Mass spectra were run on a JEOL JMS-DX300 spectrometer with a JMA-3500 data system. Optical rotations $[\alpha]_D$ were determined on a JASCO DIP-4S polarimeter at 22 °C for solutions in methanol unless otherwise indicated. Medium-pressure liquid chromatography (MPLC) was carried out on a JASCO PRC-50 instrument with a silica gel packed column. Anhydrous sodium sulphate was used to dry organic extracts. Microanalyses were carried out in the microanalytical laboratory of this Institute. Ether refers to diethyl ether. THF was distilled from LAH before use.

(8aS)-(+)-3,4,8,8a-*Tetrahydro*-5,8a-*dimethylnaphthalene*-1,6-(2H,7H)-*dione* 1-(*Ethylene Acetal*) **3**.—A solution of the enone (+)-**2** (4.58 g, 15 mmol; $[\alpha]_D$ +112°; 80% optically pure) and D-camphorsulphonic acid (D-CSA) (403 mg, 1.7 mmol) in a mixture of the ethylene acetal of butan-2-one (5 cm^3) and ethylene glycol (3 cm^3) was heated at 40 °C for overnight under nitrogen. After cooling in an ice-bath, the resulting solution was poured into aq. sodium hydrogen carbonate, and the product was extracted with ether (50 cm^3 × 2). The combined extracts were washed with water. Evaporation of the solvent followed by column chromatography of the residue on silica gel provided the acetal **3** (3.065 g), along with a mixture of the acetal **3** and starting enone **2** (2.138 g) which was again treated with D-

camphorsulphonic acid (217 mg, 0.93 mmol) in the ethylene acetal of butan-2-one (5 cm^3) and ethylene glycol (3 cm^3) at 45 °C overnight. The same work-up procedure gave a further crop of the acetal **3** (1.95 g) and a mixture of the acetal **3** and the starting enone **2** (237 mg). The acetal **3** (5.015 g, combined yield 89%) exhibited $[\alpha]_D$ +88.8° (*c* 2.00); IR and ^1H NMR data were identical with those of an authentic sample.[7]

(4aS,5S,8aS)-(+)-3,4,4a,7,8,8a-*Hexahydro*-5,8a-*dimethyl*-5-(*prop*-2-*enyl*)*naphthalene*-1,6(2H,5H)-*dione* 1-(*Ethylene Acetal*) **4**.—To a solution of lithium (605 mg, 85 mmol) in liquid ammonia (~100 cm^3, distilled from sodium) was added a solution of the acetal **3** (5.02 g, 21 mmol) and water (0.38 cm^3, 21 mmol) in THF (30 cm^3) under nitrogen. The resulting solution was warmed under reflux of liquid ammonia for 50 min, and then a solution of 3-bromopropene (8.17 cm^3, 100 mmol) in THF (10 cm^3) was added. The reaction mixture was stored at room temperature overnight to ensure alkylation and to evaporate off the ammonia. After the addition of aq. ammonium chloride, extraction with ether followed by column chromatography in the usual manner afforded the *ketone* **4** (4.16 g, 70%) along with the recovered enone **3** (322 mg, 6%). The ketone **4** had $[\alpha]_D$ +19° (*c* 2.15); ν_{max}/cm^{-1} 3075, 2950, 1705, 1645, 1440, 1185, 1145, 1100, 1050 and 910; δ(60 MHz) 1.02 and 1.18 (each 3 H, s, 5- and 8a-Me), 1.0–2.8 (13 H, m), 3.88 (4 H, br s, OCH_2CH_2O) and 4.7–6.0 (3 H, m, olefinic H) (Found: C, 73.3; H, 9.4. $C_{17}H_{26}O_3$ requires C, 73.3; H, 9.4%).

(4aS,5S,6S,8aS)-(−)-2,4,4a,5,6,7,8,8a-*Octahydro*-6-*hydroxy*-5,8a-*dimethyl*-5-(*prop*-2-*enyl*)*naphthalen*-1(2H)-*one* 1-(*Ethylene Acetal*) **5**.—To a stirred slurry of LAH (701 mg, 18.4 mmol) in ahydrous ether (150 cm^3) at −45 °C was added dropwise a solution of the ketone **4** (10.23 g, 36.8 mmol) in ether (250 cm^3) during 30 min. The mixture was stirred for 1 h at that temperature and then at room temperature for 1.5 h. The reaction mixture was worked up as usual by careful addition of wet ether and then water to give the alcohol **5** (10.15 g, 100%); $[\alpha]_D$ −9.6° (*c* 2.21); ν_{max}/cm^{-1} 3625, 3400, 3080, 2950, 1640, 1450, 1385, 1180, 1110, 1040 and 910; δ(60 MHz) 0.85 and 1.08 (each 3 H, s, 5- and 8a-Me), 1.0–2.5 (14 H, m), 3.45 (1 H, br, $W_{\frac{1}{2}}$ 17 Hz, 6-H), 3.9 (4 H, br s, OCH_2CH_2O) and 4.77–6.2 (3 H, m, olefinic H).

O-[(1S,2S,4aS,8aS)-(−)-5-*Ethylenedioxydecahydro*-1,4a-*dimethyl*-1-(*prop*-2-*enyl*)*naphthalen*-2-*yl*] S-*Methyl Dithiocarbonate* **6**.—To a solution of the alcohol **5** (4.63 g, 16.5 mmol) in THF (40 cm^3) at 0 °C was added a solution of BuLi (1.57 mol dm^3 solution in hexane; 21 cm^3, 33 mmol) and then, after 30 min, carbon disulphide (2.3 cm^3, 49 mmol) was added under nitrogen. After addition of iodomethane (3 cm^3, 49 mmol), the mixture was stirred for 30 min at 0 °C. The reaction was quenched by the addition of aq. ammonium chloride. Extraction with ether afforded the *xanthate* **6** (9.1 g), which was used for the next reaction without further purification. A pure sample was obtained by MPLC and had $[\alpha]_D$ −18.6° (*c* 1.52); ν_{max}/cm^{-1} 3100, 2950, 1665, 1640, 1460, 1390, 1240, 1070 and 1050; δ(60 MHz) 1.0 and 1.1 (each 3 H, s, 1- and 4a-Me), 2.53 (3 H, s, SMe), 1.0–2.5 (13 H, m), 3.88 (4 H, br s, OCH_2CH_2O) and 4.42–6.13 (4 H, m, olefinic H and 2-H); *m*/*z* 370 (M^+, 2%), 263 (36), 201 (20), 99 (100) and 55 (21) (Found: C, 61.4; H, 8.4. $C_{19}H_{30}O_3S_2$ requires C, 61.6; H, 8.2%).

(4aS,5S,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-5,8a-*dimethyl*-5-(*prop*-2-*enyl*)*naphthalen*-1(2H)-*one Ethylene Acetal* **7**.—A solution of the xanthate **6** (9.1 g, crude), AIBN (501 mg, 3 mmol), and tributylstannane (13 cm^3, 49 mmol) in anhydrous xylene (230 cm^3) was heated at 150 °C under nitrogen. During heating, the solution changed colour from dark red through pale yellow to black. After being cooled to room temperature, the resulting solution was washed successively with water and brine. Evaporation of the xylene under reduced pressure, followed by column chromatography on silica gel, gave the *decalin* **7** (3.75 g, 86% in two steps), $[\alpha]_D$ −6.7° (*c* 0.53); ν_{max}/cm^{-1} 3100, 2950, 1640, 1460, 1385, 1190, 1140, 1150 and 910; δ(60 MHz) 0.83 and 1.07 (each 3 H, s, 5- and 8a-Me), 1.0–2.5 (15 H, m), 3.88 (4 H, br s, OCH_2CH_2O) and 4.67–6.17 (3 H, m, olefinic H); *m*/*z* 264 (M^+, 17%), 223 (33), 125 (20), 100 (28), 99 (100), 87 (23), 86 (25), 74 (33), 59 (47) and 45 (35) (Found: M^+, 264.209 03. $C_{17}H_{28}O_2$ requires M, 264.208 92).

(4aS,5S,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-5-(3-*hydroxypropyl*)-5,8a-*dimethylnaphthalen*-1(2H)-*one Ethylene Acetal* **8**.—To a solution of the decalin **7** (3.75 g, 14.2 mmol) in THF (30 cm^3) at 0 °C was added a solution of borane–THF complex (1 mol dm^{-3} in THF; 21 cm^3) under nitrogen. After being stirred for 20 min at 0 °C and for 20 min at room temperature, water (3 cm^3), aq. sodium hydroxide (3 mol dm^{-3}; 3 cm^3), and hydrogen peroxide (30%; 1 cm^3) were added successively to the mixture at 0 °C. After being stirred for 20 min at 0 °C and then for 20 min at room temperature, the resulting solution was poured into water. Extraction with ether, followed by column chromatography on silica gel [eluent hexane–ethyl acetate (1:1)], gave the *alcohol* **8** (2.34 g, 58%), $[\alpha]_D$ −1.1° (*c* 1.28); ν_{max}/cm^{-1} 3640, 3400, 2950, 1450, 1385, 1135 and 1060; δ(60 MHz) 0.83 and 1.07 (each 3 H, s, 5- and 8a-Me), 1.0–2.1 (18 H, m), 3.52 (2 H, t, *J* 6, CH_2OH) and 3.87 (4 H, br s, OCH_2CH_2O) (Found: C, 72.5; H, 11.0. $C_{17}H_{30}O_3$ requires C, 72.3; H, 10.7%).

3-[(1S,4aS,8aS)-5-*Ethylenedioxydecahydro*-1,4a-*dimethylnaphthalen*-1-*yl*]*propanol* **9**.—To a stirred solution of oxalyl dichloride (2.3 cm^3, 26 mmol) in anhydrous dichloromethane (10 cm^3) at −65 °C was added a solution of dimethyl sulphoxide (DMSO) (3.7 cm^3, 26 mmol) in dichloromethane (10 cm^3). After being stirred for 10 min, the mixture was treated at −65 °C with a solution of the alcohol **8** (2.45 g, 8.7 mmol) in dichloromethane (20 cm^3) and the mixture was stirred for 30 min until the temperature had risen to −43 °C. After the addition of triethylamine (11 cm^3, 78 mmol), the resulting slurry was stirred for a further 1 h and was then poured into water. Extraction with ether, followed by column chromatography on silica gel, afforded the *aldehyde* **9** (1.88 g, 77%); ν_{max}/cm^{-1} 2950, 2705, 1730, 1450, 1385 and 1135; δ(60 MHz) 0.87 and 1.1 (each 3 H, s, 1- and 4a-Me), 1.0–2.7 (17 H, m), 3.9 (4 H, br s, OCH_2CH_2O) and 9.68 (1 H, t, *J* 2, aldehydic H) (Found: M^+, 280.202 22. $C_{17}H_{28}O_3$ requires M, 280.203 72).

(4aS,5S,8aS)-(+)-3,4,4a,5,6,7,8,8a-*Octahydro*-5,8a-*dimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1(2H)-*one Ethylene Acetal* **10**.—To a stirred slurry of isopropyl(triphenyl)phosphonium iodide (717 mg, 2.1 mmol) in anhydrous ether (4 cm^3) at 0 °C was added dropwise a solution of BuLi (1.57 mol dm^{-3} in hexane; 1.1 cm^3, 1.73 mmol) and the resulting deep red solution was stirred for 30 min at room temperature under nitrogen. After addition, at 0 °C of a solution of the aldehyde **9** (195 mg, 0.7 mmol) in ether (7 cm^3) the resulting solution was stirred at room temperature for 3 h. The reaction was quenched by the addition of aq. ammonium chloride. Extraction with ether, followed by MPLC purification, gave the *decalin* **10** (162 mg, 76%), $[\alpha]_D$ +3.5° (*c* 0.48 in $CHCl_3$); ν_{max}/cm^{-1} 2950, 1450, 1385, 1135 and 1100; δ(60 MHz) 0.83 and 1.05 (each 3 H, s, 5- and 8a-Me), 1.6 and 1.67 (each 3 H, s, olefinic Me), 1.0–2.2 (17 H, m), 3.9 (4 H, br s, OCH_2CH_2O) and 5.08 (1 H, br t, olefinic H); *m*/*z* 306 (M^+, 30%), 162 (24), 109 (28), 99 (100), 86 (25), 69 (36) and 55 (28) (Found: M^+, 306.255 28. $C_{20}H_{34}O_2$ requires M, 306.255 78).

(4aS,5S,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-5,8a-*dimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1(2H)-*one* **11**.—A solution of the acetal **10** (938 mg, 3.1 mmol) and PPTS (118 mg) in acetone (10 cm^3)–water (2 cm^3) was heated under reflux for 4 h. The resulting solution was poured into brine and extracted with ether to give the *ketone* **11** (794 mg, 99%), $[\alpha]_D$ −8° (*c* 0.3); ν_{max}/cm^{-1} 2900, 1710, 1620, 1450, 1385 and 1100; δ(60 MHz) 0.92 and 1.18 (each 3 H, s, 5- and 8a-Me), 1.58 and 1.67 (each 3 H, s, olefinic Me), 1.0–3.0 (17 H, m) and 5.0 (1 H, br t, olefinic H); *m/z* 262 (M^+, 45%), 179 (39), 178 (57), 177 (41), 161 (35), 135 (38), 124 (60), 109 (72), 95 (51), 81 (55), 69 (100), 67 (37) and 55 (53) (Found: M^+, 262.228 91. $C_{18}H_{30}O$ requires M, 262.229 61).

(+)-*Methyl* (2ξ,4aS,5S,8aS)-*Decahydro*-5,8a-*dimethyl*-5-(4-*methylpent*-3-*enyl*)-1-*oxonaphthalene*-2-*carboxylate* **12**.—To a stirred slurry of sodium hydride (60%; 287 mg, washed with hexane 3 times; 6 mmol) in THF (2 cm^3) were added successively dimethyl carbonate (0.68 cm^3, 8 mmol) and solution of the ketone **11** (541 mg, 2 mmol) in THF (8 cm^3) under nitrogen. The resulting slurry was stirred at room temperature for 16 h and the reaction was then quenched at 0 °C by the addition of aq. ammonium chloride. Extraction with ether, followed by MPLC purification, afforded the *keto ester* **12** (573 mg, 87%); $[\alpha]_D$ +21° (*c* 1.3 in $CHCl_3$); ν_{max}/cm^{-1} 2925, 1750, 1715, 1655, 1610, 1440, 1365, 1320, 1240, 1030 and 910; δ(60 MHz) 0.85 and 0.92 (total 3 H, s) and 1.22 (3 H, s) (together 5- and 8a-Me), 1.6 and 1.68 (each 3 H, s, olefinic Me), 1.0–2.5 (16 H, m), 3.72 (3 H, s, CO_2Me) and 5.05 (1 H, br t, olefinic H); *m/z* 320 (M^+, 100%), 305 (27), 220 (46), 219 (24), 168 (88), 136 (27), 135 (26), 123 (25), 109 (27), 81 (24), 69 (60) and 55 (28) (Found: C, 75.2; H, 9.8. $C_{20}H_{32}O_3$ requires C, 75.0; H, 10.1%).

(+)-*Methyl* (2ξ,4aS,5S,8aS)-*Decahydro*-2,5,8a-*trimethyl*-5-(4-*methylpent*-3-*enyl*)-1-*oxonaphthalene*-2-*carboxylate* **13**.—To a stirred slurry of sodium hydride (60%; 102 mg, washed with hexane three times; 2.5 mmol) in THF (1 cm^3) at 0 °C was added a solution of the keto ester **12** (545 mg, 1.7 mmol) in THF (11 cm^3) under nitrogen. After being stirred for 50 min at room temperature, the mixture was treated with iodomethane (0.2 cm^3, 3.4 mmol) and was then stirred at room temperature overnight. The reaction was quenched by the addition of aq. ammonium chloride, and extractive work-up with ether, followed by MPLC purification, gave the *methylated product* **13** (435 mg, 77%); $[\alpha]_D$ +54° (*c* 1.6); ν_{max}/cm^{-1} 2950, 1740, 1715, 1610, 1480, 1390, 1250 and 1160; δ(60 MHz) 0.92, 1.1 and 1.3 (each 3 H, s, 2-, 5- and 8a-Me), 1.63 and 1.7 (each 3 H, s, olefinic Me), 1.0–2.2 (15 H, m), 3.72 (3 H, s, CO_2Me) and 5.08 (1 H, br t, olefinic H) (Found: C, 75.6; H, 10.5. $C_{21}H_{34}O_3$ requires C, 75.4; H, 10.3%).

(2ξ,4aS,5S,8aS)-(+)-3,4,4a,5,6,7,8,8a-*Octahydro*-2,5,8a-*trimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1(2H)-*one* **14**.—A solution of the keto ester **13** (436 mg, 1.3 mmol) and lithium chloride (277 mg, 6.5 mmol) in HMPA (10 cm^3) was heated at 130 °C for 2 h. After the addition of ice and water, the resulting solution was extracted with ether. Evaporation of the extract, followed by MPLC purification, gave the *ketone* **14** (260 mg, 72%); $[\alpha]_D$ +2.8° (*c* 1.7); ν_{max}/cm^{-1} 2950, 1710, 1620, 1455, 1385 and 910; δ(60 MHz) 0.92 and 1.15 (each 3 H, s, 5- and 8a-Me), 0.96 (3 H, d, *J* 5, 2-Me), 1.58 and 1.68 (each 3 H, s, olefinic Me), 1.0–3.0 (16 H, m) and 5.07 (1 H, br t, olefinic H); *m/z* 276 (M^+, 60%), 193 (39), 176 (24), 175 (23), 151 (27), 138 (76), 123 (40), 109 (86), 95 (63), 81 (74), 69 (100) and 55 (50) (Found: M^+, 276.245 49. $C_{19}H_{32}O$ requires M, 276.2453).

4-[(1ξ,2ξ,4aS,5S,8aS)-(+)-*Decahydro*-1-*hydroxy*-2,5,8a-*trimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1-*yl*]*butan*-2-*one Ethylene Acetal* **15**.—A slurry of magnesium powder (48.5 mg, 2 mmol) in THF (1 cm^3) was irradiated ultrasonically for 5 min. 1,2-Dibromoethane (5 mm^3) and then 4-bromobutan-2-one ethylene acetal[14] (100 mm^3, 0.77 mmol) were added dropwise to the above slurry. After the exothermic reaction had started, a solution of additional monobromide (160 mm^3, 1.23 mmol) in THF (2 cm^3) was added dropwise so as to maintain continuous reflux. After the exothermic reaction had subsided, the mixture was irradiated ultrasonically for 5 min to ensure completion of the reaction. A solution of the ketone **14** (137 mg, 0.5 mmol) in THF (2 cm^3) was added to the mixture at room temperature and the resulting solution was heated under reflux for 2 h. The reaction was quenched by the addition of aq. ammonium chloride. Extraction with ether, followed by MPLC purification, afforded the *alcohol* **15** (160 mg, 82%) along with its C-2 isomer (15 mg, 8%); $[\alpha]_D$ +39° (*c* 1.27); ν_{max}/cm^{-1} 3475, 2925, 1450, 1380 and 1060; δ(90 MHz) 0.82 and 1.26 (each 3 H, s, 5- and 8a-Me), 0.91 (3 H, d, *J* 4, 2-Me), 1.29 (3 H, s, acetal Me), 1.58 and 1.67 (each 3 H, olefinic Me), 1.0–2.5 (20 H, m), 3.96 (4 H, s, OCH_2CH_2O) and 5.06 (1 H, t, *J* 7.2, olefinic H); *m/z* 392 (M^+, 0.2%), 306 (33), 162 (27), 109 (33), 99 (100), 69 (43) and 55 (33) (Found: M^+, 392.329 17. $C_{25}H_{44}O_3$ requires M, 392.329 07).

4-[(4aS,5S,8aS)-(+)-3,4,4a,5,6,7,8,8a-*Octahydro*-2,5,8a-*trimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1-*yl*]*butan*-2-*one Ethylene Acetal* **16**.—To a stirred solution of the alcohol **15** (209 mg, 0.53 mmol) in pyridine (2 cm^3) at 0 °C was added thionyl chloride (0.2 cm^3, 2.7 mmol), and the resulting solution was stirred for 50 min at 0 °C. The addition of ice and extractive work-up with ether, followed by MPLC purication, gave the *olefin* **16** (171 mg, 86%); $[\alpha]_D$ +65° (*c* 0.48 in $CHCl_3$); ν_{max}/cm^{-1} 2950, 1620, 1460, 1380 and 1065; δ(60 MHz) 0.82 and 0.95 (each 3 H, s, 5- and 8a-Me), 1.32 (3 H, s, acetal Me), 1.57 and 1.67 (each 3 H, s, olefinic Me), 1.0–2.3 (22 H, m), 3.92 (4 H, s, OCH_2CH_2O) and 5.0 (1 H, br t, olefinic H); *m/z* 374 (M^+, 9%), 297 (14), 259 (12), 173 (16), 133 (16), 121 (21), 119 (25), 87 (100), 73 (26), 69 (39), 55 (18) and 43 (30) (Found: M^+, 374.3164. $C_{25}H_{42}O_2$ requires M, 374.3184).

4-[(4aS,5S,8aS)-(+)-3,4,4a,5,6,7,8,8a-*Octahydro*-2,5,8a-*trimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1-*yl*]*butan*-2-*one* **17**.—A solution of the acetal **16** (52.2 mg, 0.14 mmol) and PTSA monohydrate (6 mg) in acetone (1.5 cm^3)–water (0.15 cm^3) was heated under reflux for 1 h. Extractive work-up with ether, followed by MPLC purification, afforded the *ketone* **17** (40.0 mg, 87%); $[\alpha]_D$ +58° (*c* 0.5); ν_{max}/cm^{-1} 2950, 1720, 1620, 1455, 1380, 1360 and 1160; δ(60 MHz) 0.82 and 0.97 (each 3 H, 5- and 8a-Me), 1.53, 1.6 and 1.67 (each 3 H, s, olefinic Me), 2.1 (3 H, s, MeCO), 1.0–2.8 (19 H, m) and 5.05 (1 H, br t, olefinic H); *m/z* 330 (M^+, 33%), 259 (29), 257 (28), 231 (25), 230 (54), 177 (50), 175 (36), 173 (34), 149 (30), 146 (25), 135 (31), 133 (59), 121 (55), 119 (80), 109 (39), 93 (46), 83 (39), 81 (42), 69 (100), 55 (40) and 43 (55) (Found: M^+, 330.292 24. $C_{23}H_{38}O$ requires M, 330.292 24).

(+)-*Ethyl* (E)-(3-*Methyl*-5-[(4aS,5S,8aS)-3,4,4a,5,6,7,8,8a-*octahydro*-2,5,8a-*trimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1-*yl*]*pent*-2-*enoate* **18**.—To a stirred slurry of sodium hydride (60%; 81 mg, washed with hexane 3 times, 1.7 mmol) in THF (3 cm^3) at 0 °C was added 'triethyl phosphonoacetate' (ethyl diethoxyphosphonylacetate) (0.33 cm^3, 1.7 mmol). After the mixture had been stirred for 30 min at room temperature, a solution of the ketone **17** (96.8 mg, 0.29 mmol) in THF (3 cm^3) was added. The resulting solution was heated under reflux overnight, and the reaction was then quenched by the addition of aq. ammonium chloride. Extraction with ether, followed by

MPLC purification, gave the *ester* **18** (119 mg, 100%); $[\alpha]_D$ +55° (*c* in $CHCl_3$); ν_{max}/cm^{-1} 2950, 1720, 1650, 1390, 1230 and 1150; δ (90 MHz) 0.82 and 0.96 (5- and 8a-Me), 1.28 (3 H, t, *J* 7, OCH_2Me), 1.57 (2 × Me) and 1.67 (3 H, each s, olefinic Me), 2.18 (3 H, s, olefinic Me β to CO_2Et), 1.0–2.2 (19 H, m), 4.13 (2 H, q, *J*, OCH_2Me), 5.08 (1 H, br t, *J* 7, olefinic H) and 5.69 (1 H, br s, olefinic H α to CO_2Et); *m/z* 400 (M^+, 8%), 273 (63), 147 (24), 135 (25), 133 (57), 128 (100), 121 (30), 119 (51), 109 (34), 107 (32), 95 (42), 81 (31) and 69 (95) (Found: M^+, 400.3338. $C_{27}H_{44}O_2$ requires M, 400.33411).

(+)-*Dysideapalaunic Acid* **1**.—A solution of the ester **18** (22.6 mg, 0.056 mmol) in ethanol (2 cm^3) containing aq. sodium hydroxide (15%; 0.3 cm^3) was heated under reflux for 40 min under nitrogen. After the addition of ice and dil. hydrochloric acid, the resulting solution was extracted with ether. MPLC purification afforded (+)-dysideapalaunic acid **1** (14.1 mg, 67%); $[\alpha]_D$ +58° (*c* 0.33 in $CHCl_3$) (lit.,[15] +61° in $CHCl_3$); ν_{max} 2940, 1695, 1645 and 1255; δ(90 MHz) 0.87 and 0.95 (each 3 H, s, 5- and 8a-Me), 1.44, 1.6 and 1.71 (each 3 H, s, olefinic Me), 2.15 (3 H, s, olefinic Me β to CO_2H), 1.0–2.5 (20 H, m), 5.23 (1 H, t, *J* 7, olefinic H) and 5.89 (1 H, br s, olefinic H α to CO_2H); *m/z* (M^+, 8%), 273 (37), 189 (21), 161 (21), 147 (22), 135 (25), 133 (56), 121 (28), 119 (70), 109 (40), 107 (27), 95 (38), 81 (32), 69 (100) and 55 (26) (Found: M^+, 372.3023. Calc. for $C_{25}H_{40}O_2$: M, 372.3027).

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