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An efficient approach to chiral nonracemic *trans*- and *cis*-decalin scaffolds for drimane and labdane synthesis

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Abstract—Optically active *trans*- and *cis*-ring junction decalinic intermediates, which represent useful precursors for the synthesis of more complex natural targets, have been conveniently prepared starting from the β-ketoester **2** obtained by standard chemistry from β-ionone and dimethyl carbonate. The chiral auxiliary (−)-menthol, easily attached to **2** through DMAP-catalyzed transesterification, allowed a clean separation of the diastereomers obtained in the key electrocyclization step, which were further elaborated to chiral intermediates already taken to drimane and labdane sesquiterpenes.

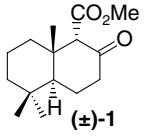
1. Introduction

A large number of naturally occurring compounds exhibiting diverse biological activities present as a common structural feature a 4,4,10-trimethyl substituted *trans*-decalin nucleus; representative examples are found particularly in the large families of drimane and labdane sesquiterpenes.[1]

Asymmetric syntheses of most of the members of these families are commonly based on starting chiral synthons derived by conversion of higher terpenes (e.g., sclareol, manool, abietic acid, communic acid, and larixol), or from simple terpenes [e.g., (−) and (+)-carvone or thujone] as well as from well-established synthetic chiral materials such as the Wieland–Miescher ketone.

Racemic β-ketoester **1**, which was first prepared in 1957 by Eschenmoser et al.[2] during their pioneering work on biogenetic-type cyclization of polyenes and later by White et al.[3] through an improved procedure, has often been exploited as the starting material for the synthesis of most of these products.

Not surprisingly, the preparation of both enantiomers of **1** and related compounds was attempted in different ways, including enzymatic resolution,[4–8] the use of enantiomerically pure 1,2-diols as chiral auxiliaries for acetal formation,[9–12] derivatization of the secondary alcohol obtained by sodium borohydride reduction via its (*R*)-naphthylethylcarbamate[13] or esterification of the primary alcohol with Boc-*L*-proline,[14] or by traditional salts formation with (−)-α-phenylethylamine or (−)-ephedrine of the C-2 methylene carboxylic acid.[15,16]



(±)-1

2. Results and discussion

As part of our continuous interest in the field,[17] we herein report our recent synthetic efforts to obtain chiral building blocks for the synthesis of this class of compounds.

In 1989 Isoe et al.[18] developed an efficient methodology for the preparation of racemic octalone **6** starting from the readily available β-ionone via the high-yield sequence depicted in Scheme 1. Thus, enolacetate **3** of the β-ketoester **2**, obtained by standard chemistry from β-ionone and dimethyl carbonate, was converted

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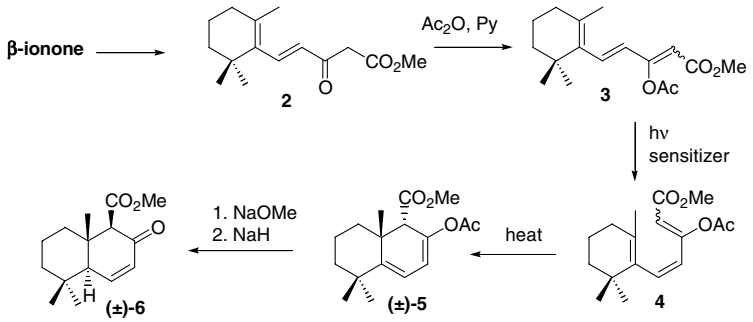


Scheme 1.

through irradiation with a high-pressure mercury lamp, in the presence of benzantrone as a sensitizer, into the corresponding *cis*-enolacetate **4**, which was then submitted to the featuring thermal electrocyclization to produce quantitatively the bicyclic derivative **5**. The latter could be subsequently converted to the interesting building block **6** through a careful choice of basic conditions to secure the desired relative stereochemistry in reproducible yields.

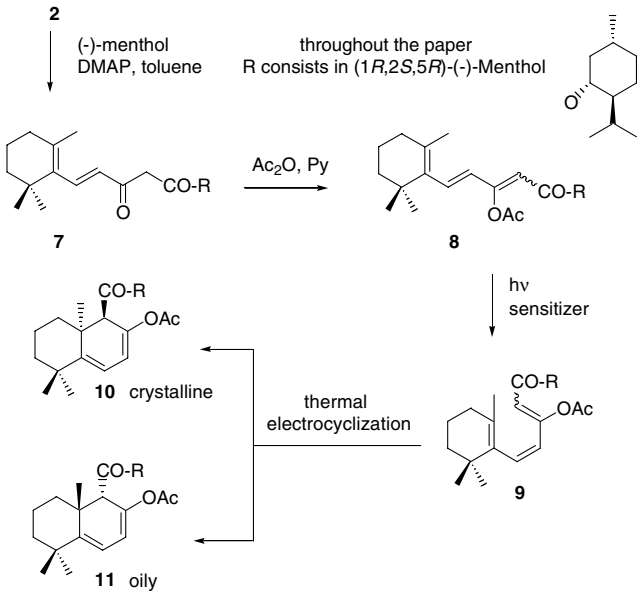
We were particularly intrigued by the possibility of performing this sequence in the presence of a chiral auxiliary in order to prepare bicyclo[4.4.0]decane (decalin) skeletons in enantiomerically pure form given that this route could open the way to *trans*-decalins (Scheme 4) as well as *cis*-decalins (Scheme 7).

To this end, we envisioned the use of the cheap commercially available (−)-menthol as the chiral auxiliary, which could be easily bound through DMAP-catalyzed transesterification of **2**.[19] We anticipated that the chiral auxiliary might act as an asymmetry inducer in the electrocyclization step or it might simply allow conventional separation of diastereomeric compounds **10** and **11** (Scheme 2). With this in mind, we submitted the (−)-menthyl ester derivative **7** to the synthetic sequence previously described by the Japanese group.[18] Thus, the formation of enolacetate **8** and its irradiation proceeded uneventfully to produce the menthyl *cis*-enolacetate ester **9**, which was submitted to thermal electrocyclization. This operation essentially generated the same amount of two compounds, which could be cleanly separated by simple crystallization, one being a white crystalline compound, the second one a yellow oil.

X-ray analysis (Fig. 1) allowed us to assign the stereostructure **10** to the crystalline derivative, the structure of the oily stereoisomer consequently being assigned as **11**.

In an attempt to obtain optically active *trans*-fused bicyclic compounds, following Isoe's directions, we first tried the removal of the enolacetate group by treating crystalline compound **10** with NaOMe (Scheme 3).

Unexpectedly, the basic treatment led to the formation of the rather unusual diosphenol **12**, whose identity was eventually confirmed by X-ray structure (Fig. 2).



Scheme 2.

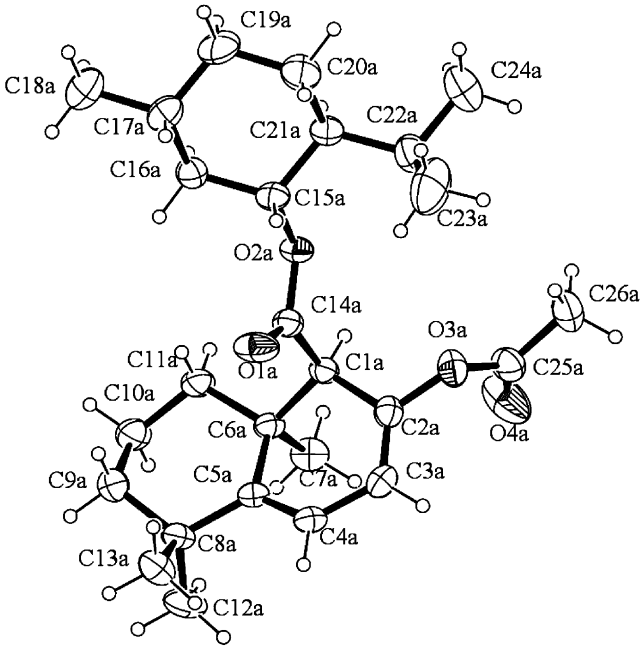
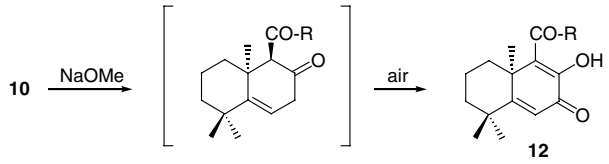


Figure 1. ORTEP view of compound **10** showing the thermal ellipsoids at 30% level of probability.



Scheme 3.

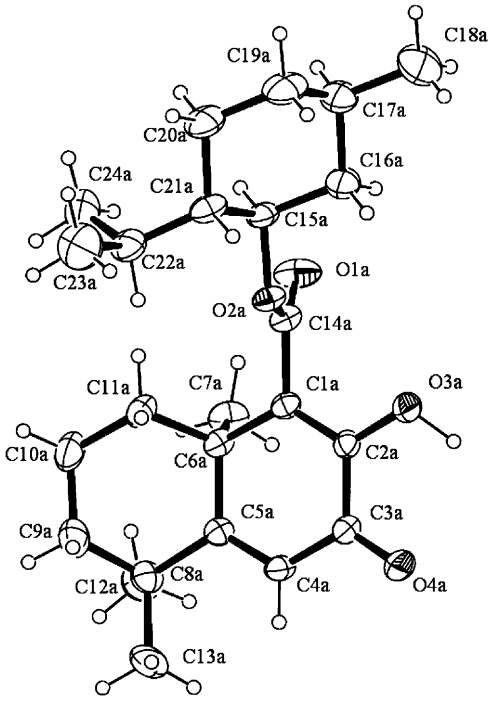
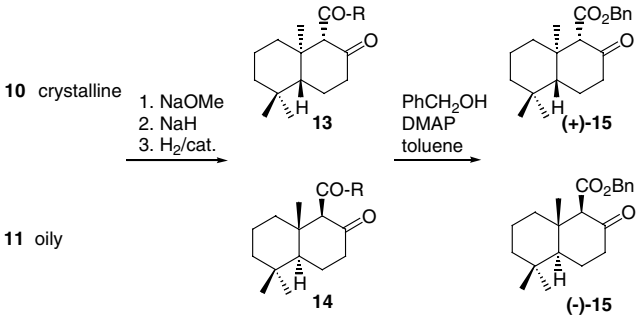


Figure 2. ORTEP view of compound **12** showing the thermal ellipsoids at 30% level of probability.

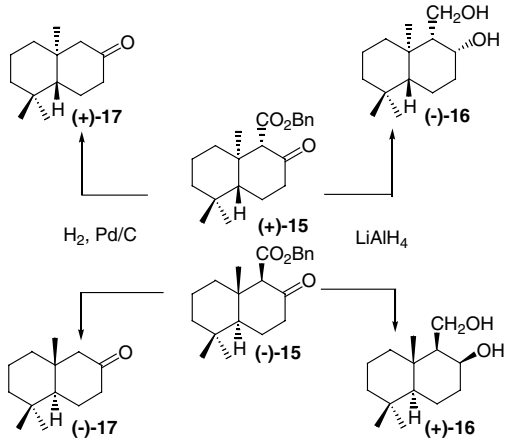
The formation of compound **12** can be accounted for by a spontaneous oxidation of the deacetoxylated intermediate, owing to the known[20] propensity to aerial oxidation of the active methylene groups in some deconjugated octalones. The undesired formation of diosphenol **12** was easily suppressed by working in an oxygen free atmosphere during the basic treatments. Thus, both the crystalline derivative **10** and the oily derivative **11** were converted into the corresponding conjugated ketones through sequential treatments under argon with sodium methoxide and sodium hydride and eventually submitted to catalytic reduction producing the expected β-ketoesters **13** and **14** in satisfactory overall yields (Scheme 4).

Having diastereomeric compounds **13** and **14** in hand, we tried unsuccessfully their conversion into the known enantiomers of **1** through direct transesterification by heating in methanol in the presence of a catalytic amount of DMAP, using the same protocol described for the preparation of **7**. However, removal of the chiral auxiliary was conveniently accomplished simply by substituting methanol with the higher boiling benzyl alcohol through a clean transesterification producing the benzyl esters (+)-**15** and (−)-**15**, respectively, featuring the additional advantage of an ester moiety cleavable by hydrogenolysis.



Scheme 4.

In order to gain further proof of the assigned structures of enantiomeric **15**, we decided to convert them into compounds already described in the literature as pure stereoisomers, but obtained by different routes (Scheme 5).



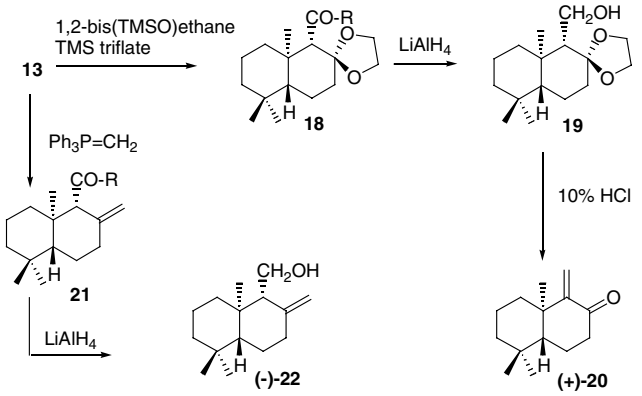
Scheme 5.

Thus, lithium aluminum hydride reduction of the β-keto-ester moiety cleanly converted (+)-**15** and (−)-**15** into enantiomeric diols (−)-**16** and (+)-**16**, useful synthetic intermediates for drimane sesquiterpenes and labdane diterpenes.[14] On the other hand, ketones (+)-**17** and (−)-**17**, known fragrance chemicals with distinct odor differences,[21,22] could be easily obtained by a one-pot hydrogenolysis/decarboxylation sequence of (+)-**15** and (−)-**15**, respectively.

The physical properties of the obtained *trans*-fused bicyclic compounds described in Scheme 5 perfectly agreed with the reported ones, thus confirming the assigned structure and stereochemistry.

Alternatively, a number of chemical manipulations were also performed on compounds still containing the chiral auxiliary (−)-menthol, using **13** as the starting model compound. In this way, we were able to prepare (−)-albicanol **22** as well as the C-1 *exo*-methylene compound

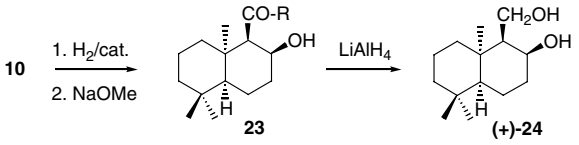
(+)-**20** (Scheme 6), which have been previously described, fully characterized and utilized as the key intermediates in the synthesis of several important compounds including the marine natural products zonarol[13] and copalol.[14]



Scheme 6.

Interestingly, along the route to (+)-**20** we needed to protect the carbonyl group of **13** as the corresponding 1,3-dioxolane, but this trivial operation cannot be achieved following usual directions (ethylene glycol in toluene in the presence of acid catalyst as well as the system triethyl orthoformate-ethylene glycol). However, a clean ketalization could be accomplished using less then usual conditions,[23] providing compound **18** in good yield. Reduction of the ester group with lithium aluminum hydride gave the corresponding primary alcohol **19**, which was easily taken to the target compound (+)-**20** by a two step transformation, that is, restoration of the C-2 keto group and acid promoted dehydration of the crude β-hydroxy carbonyl derivative.

Also starting from **13**, via Wittig olefination of the C-2 keto group and subsequent lithium aluminum hydride reduction of compound **21**, we obtained (−)-**22**, the unnatural antipode of albicanol.[24,25] Moreover, as anticipated, we demonstrated that the diastereomeric compounds **10** and **11**, obtained in the thermal electrocyclization step, could be conveniently used to access optically active *cis*-decalin systems (Scheme 7).



Scheme 7.

In fact, submitting the key intermediate **10** to catalytic reduction followed by sodium methoxide promoted *O*-deacetylation, we obtained hydroxy ester **23**, which on reduction with lithium aluminum hydride furnished the enantiomerically pure diol (+)-**24**. The structures of both new compounds have been confirmed by X-ray analysis (Figs. 3 and 4).

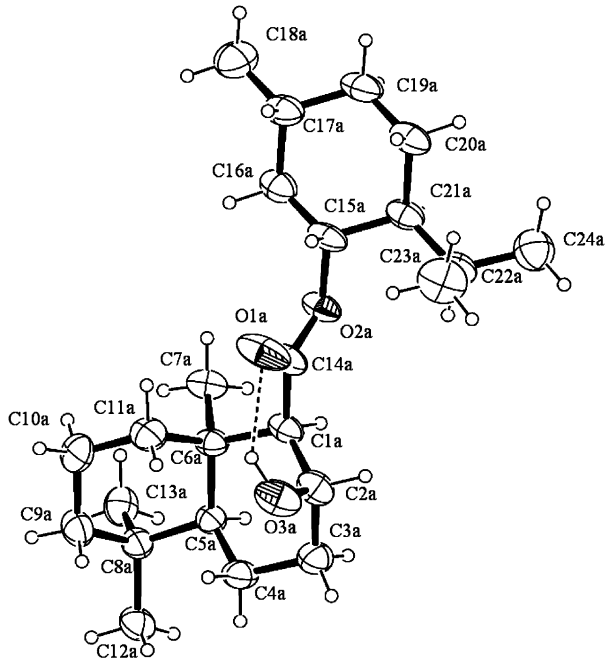


Figure 3. ORTEP view of compound **23** showing the thermal ellipsoids at 30% level of probability.

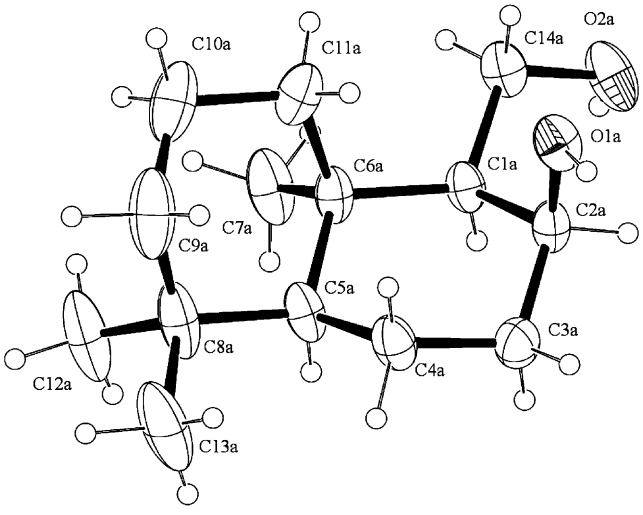


Figure 4. ORTEP view of compound (+)-**24** showing the thermal ellipsoids at 30% level of probability.

Assuming that the addition of hydrogen on compound **10** occurred stereoselectively *anti* to the ester group, enantiomer diol (−)-**24** is likely to derive from the oily diastereomer **11** as the starting chiron.

3. Conclusion

In summary, the original route developed by Isoe and co-workers[18] for the synthesis of racemic decalin intermediates, has been conveniently extended to the synthesis of both optically active *trans*- and *cis*-decalin synthons, which represent useful starting chiral materials for the synthesis of biologically active terpenes.

The racemic resolution has been achieved using as the chiral auxiliary the cheap (−)-menthol, which has been introduced and removed through DMAP-catalyzed transesterification, providing a facile entry to the optically active β-ketoesters **15**, which are valuable starting materials for the preparation of more complex natural targets.

4. Experimental

4.1. General

Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FT-IR Paragon 500 spectrometer. ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were taken on a Bruker AC spectrometer at 200 MHz and on a Varian Mercury Plus spectrometer at 400 MHz, for solutions in $CDCl_3$ unless otherwise noted. Chemical shifts are given in parts per million downfield from tetramethylsilane as the internal standard while coupling constants are given in hertz. Optical rotations were measured with a Perkin–Elmer 241 MC Polarimeter. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Petroleum ether refers to the fractions boiling in the range 40–60 °C and ether to diethyl ether. Merck silica gel (70–230 mesh) was used for column chromatography. All reactions were performed under an N_2 or Ar atmosphere. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

4.2. 3-Oxo-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)-pent-4-enoic acid (−)-menthyl ester, 7

A mixture of β-ketoester **2** (1.00 g, 4.00 mmol), (−)-menthol (1.26 g, 8.00 mmol), and 4-dimethylaminopyridine (50 mg, 0.40 mmol) in toluene (100 mL) was heated at reflux for 36 h and then evaporated in vacuo. The residue was chromatographed on silica gel (ether–petroleum ether 1:1) to give **7** (1.27 g, 85%) as an oil. $[\alpha]_D^{20} = -48.2$ (*c* 1.82, $CHCl_3$). IR (film) ν_{max}: 1740, 1640, 1580 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.72–1.12 (m, 18H); 1.20–2.15 (m, 15H); 3.59 (s, 2H); 4.73 (dt, J = 4.4, 10.8 Hz, 1H); 6.19 (d, J = 16.4 Hz, 1H); 7.37 (d, J = 16.4 Hz, 1H). Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.80; H, 10.05.

4.3. 3-Acetyloxy-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)-penta-2,4-dienoic acid (−)-menthyl ester, 8

A solution of **7** (1.00 g, 0.26 mmol) in dry pyridine (1 mL) was treated with acetic anhydride (1.5 mL, 0.16 mmol), stirred at rt for 8 h and then neutralized by careful addition of 10% HCl. The mixture was extracted with ether (2 × 25 mL), washed with saturated sodium bicarbonate solution, dried, and evaporated to give **8** (1.00 g, 93%) as oily mixture of C-2 stereoisomers (*E:Z* ratio = 2:3). IR (film) ν_{max}: 1760, 1720, 1450 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): 2(*E*) isomer δ: 0.73–1.12 (m, 18H); 1.30–2.20 (m, 15H); 2.22 (s, 3H); 4.69–4.75 (m, 1H); 5.52 (s, 1H); 5.92 (d, J = 16.2 Hz, 1H); 6.64 (d, J = 16.2 Hz, 1H); 2(*Z*) isomer δ: 0.73–1.22 (m, 18H); 1.30–2.20 (m, 15H); 2.27 (s, 3H); 4.69–4.75 (m, 1H); 5.63 (s, 1H); 6.62 (d, J = 16.2 Hz, 1H); 7.33–7.37 (d, J = 16.2 Hz, 1H). Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.81; H, 9.52.

4.4. 3-Acetyloxy-5-(2′,6′,6′-trimethylcyclohex-1′-enyl)-penta-2,4-dienoic acid (−)-menthyl ester, 9

A cooled (0 °C) solution of **8** (1.00 g, 2.40 mmol) in dry THF (50 mL) containing benzanthrone (160 mg, 0.07 mmol) was irradiated for 8 h with a 125 W, high-pressure, mercury-vapor lamp. Evaporation of the solvent followed by addition of hexane allowed removal of benzanthrone by filtration. The filtrate was evaporated and the residue purified by chromatography (ether–petroleum ether 1:9) to give oily **9** (0.97 g, 97%) as a C-2 diastereomixture. IR (film) ν_{max}: 1780, 1720, 1440 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.73–1.15 (m, 18H); 1.22–2.20 (m, 15H); 2.27 (s, 3H); 4.72 (dt, J = 4.4, 10.8 Hz, 1H); 5.63 (s, 1H); 6.62 (d, J = 16.2 Hz, 1H); 7.35 (d, J = 16.2 Hz, 1H). Anal. Calcd for $C_{26}H_{40}O_4$ requires C, 74.96; H, 9.68. Found: C, 74.85; H, 9.55.

4.5. (1*R*,8a*S*)- and (1*S*,8a*R*)-2-Acetyloxy-5,5,8a-trimethyl-1,5,6,7,8,8a-hexahydro-naphthalene-1-carboxylic acid (−)-menthyl ester, 10 and 11

Compound **9** (1.00 g, 2.45 mmol) was heated at 180 °C for 1.5 h, then the cooled oily residue was purified by chromatography (ether–petroleum ether 1:9) to give a semisolid mass (0.51 g, 50%), which was crystallized from EtOH 95% to give **10** (0.21 g) as white crystals. The filtrate was evaporated to give the oily **11** (0.25 g).

Compound **10**: Mp 89–90 °C. $[\alpha]_D^{20} = +395.0$ (*c* 1.00, $CHCl_3$). IR (film) ν_{max}: 1775, 1712, 1640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.70–1.08 (m, 12H); 1.14 (s, 6H); 1.21–1.82 (m, 13H); 1.92–195 (m, 2H); 2.09 (s, 3H); 2.85 (s, 1H); 4.62 (dt, J = 4.4, 10.8 Hz, 1H); 5.77 (s, 2H). Anal. Calcd for $C_{26}H_{40}O_4$ requires C, 74.96; H, 9.68. Found: C, 74.88; H, 9.60.

Compound **11**: $[\alpha]_D^{20} = -305.0$ (*c* 2.74, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.68–1.08 (m, 12H); 1.12–1.82 (m, 19H); 1.83–2.20 (m, 5H); 2.80 (s, 1H); 4.57 (dt, J = 4.0, 10.4 Hz, 1H); 5.75 (s, 2H). Anal. Calcd for $C_{26}H_{40}O_4$ requires C, 74.96; H, 9.68. Found: C, 74.78; H, 9.58.

4.6. (1*S*,4a*R*,8a*R*)-5,5,8a-Trimethyl-2-oxo-decahydro-naphthalene-1-carboxylic acid (−)-menthyl ester, 13, (1*R*,4a*S*,8a*S*)-5,5,8a-trimethyl-2-oxo-decahydro-naphthalene-1-carboxylic acid (−)-menthyl ester, 14 and (8a*S*)-2-Hydroxy-5,5,8a-trimethyl-3-oxo-3,5,6,7,8,8a-hexahydro-naphthalene-1-carboxylic acid (−)-menthyl ester, 12

A solution of **10** (1.00 g, 0.24 mmol) in MeOH (5 mL) containing NaOMe (0.22 g, 0.41 mmol) was stirred under argon for 4 h at 0 °C after which 10% phosphoric

acid was added until pH = 6. After evaporation of most of methanol, the residue was extracted with ether (3×25 mL), the extracts washed with saturated sodium bicarbonate solution, dried, and evaporated. The residue, dissolved in anhydrous benzene (10 mL), was added dropwise to a suspension of NaH (0.40 g, 16.40 mmol) in anhydrous benzene (10 mL) and heated at reflux for 1 h. To the cooled reaction mixture, 10% phosphoric acid was added until pH = 6, the organic layer was separated and the aqueous phase extracted with ether (2×30 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution, dried, and evaporated. The residue was dissolved in EtOH (25 mL) and the obtained solution shaken for 4 h at 20 psi in a Parr apparatus in the presence of 5% palladium on charcoal (100 mg). Filtration on Celite®, evaporation in vacuo, and crystallization from EtOH yielded **13** (0.66 g, 73%). Mp 154–155 °C (ethanol 95%). $[\alpha]_D^{20} = -11.9$ (*c* 0.92, $CHCl_3$). IR (KBr) ν_{max}: 1723, 1650 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.73–1.15 (m, 16H); 1.16–1.82 (m, 17H); 1.82–2.18 (m, 3H); 2.24–2.56 (m, 2H); 3.17 (s, 1H); 4.70 (dt, $J = 4.4$, 10.6 Hz, 1H). Anal. Calcd for $C_{24}H_{40}O_3$ requires C, 76.55; H, 10.71. Found: C, 76.30; H, 10.63.

When the first basic treatment (NaOMe) was performed in a nonoxygen-free atmosphere, compound **10** gave **12** in variable yield after purification by column chromatography (ether–petroleum ether 3:7). Mp 99–100 °C (EtOH 95%). $[\alpha]_D^{20} = -79.3$ (*c* 0.75, CH_3OH). IR (KBr) ν_{max}: 3380, 1715, 1650, 1260 cm^{-1}. ^1H NMR (200 MHz, acetone-d_6) δ: 0.74–1.81 (m, 30H); 1.81–2.24 (m, 3H); 4.89 (dt, $J = 4.4$, 10.8 Hz, 1H); 6.31 (s, 1H); 8.57 (s, 1H). Anal. Calcd for $C_{24}H_{36}O_4$ requires C, 74.19; H, 9.34. Found: C, 74.05; H, 9.28.

The same protocol described for the preparation of **13** from **10** allowed a clean conversion of **11**–**14**. Mp 101–102 °C (ethanol 95%). $[\alpha]_D^{20} = -58.8$ (*c* 0.83, $CHCl_3$). IR (KBr) ν_{max}: 1723, 1650 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.73–1.13 (m, 16H); 1.15–1.25 (m, 6H); 1.25–1.81 (m, 11H); 1.81–2.13 (m, 3H); 2.23–2.54 (m, 2H); 3.15 (s, 1H); 4.73 (dt, $J = 4.4$, 10.8 Hz, 1H). Anal. Calcd for $C_{24}H_{40}O_3$ requires C, 76.55; H, 10.71. Found: C, 76.41; H, 10.59.

4.7. (1*S*,4a*R*,8a*R*)- and (1*R*,4a*S*,8a*S*)-5,5,8a-Trimethyl-2-oxo-decahydro-naphthalene-1-carboxylic acid benzyl ester, (+)-15 and (−)-15

A mixture of **13** or **14** (0.50 g, 1.33 mmol), benzyl alcohol (0.28 mL, 2.65 mmol), and 4-dimethylaminopyridine (16 mg, 0.13 mmol) in toluene (40 mL) was heated at reflux for 36 h and then the solvent evaporated in vacuo and the residue chromatographed on silica gel (ether–petroleum ether 1:9) to give (+)-**15** or (−)-**15** (0.31 g, 72%), respectively.

Compound (−)-**15**: Mp 80–81 °C (ethanol 95%). $[\alpha]_D^{20} = -43.2$ (*c* 0.81, $CHCl_3$). Anal. Calcd for $C_{21}H_{28}O_3$ requires C, 76.79; H, 8.59. Found: C, 76.59; H, 8.51. Compound (+)-**15**: Mp 76–77 °C (ethanol 95%). $[\alpha]_D^{20} = +45.3$ (*c* 0.91, $CHCl_3$). Anal. Calcd for $C_{21}H_{28}O_3$ requires C, 76.79; H, 8.59. Found: C, 76.62; H, 8.53. The spectral data of (+)-**15** and (−)-**15** were identical: IR (film) ν_{max}: 1720, 1650, 1540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (s, 3H); 0.96 (s, 3H); 1.13–1.32 (m, 5H); 1.38–1.82 (m, 6H); 1.99–2.08 (m, 1H); 2.27–2.38 (m, 1H); 2.51 (dddd, $J = 1.6$, 5.2, 5.6, 14.6 Hz, 1H); 3.27 (s, 1H); 5.14 (s, 2H); 7.29–7.40 (m, 5H).

4.8. (1*R*,2*R*,4a*R*,8a*R*)- and (1*S*,2*S*,4a*S*,8a*S*)-1-Hydroxymethyl-2-hydroxy-5,5,8a-trimethyl-decahydronaphtalene, (−)-16 and (+)-16

A solution of (+)-**15** (0.34 g, 0.90 mmol) in anhydrous ether (10 mL) was added dropwise to a cooled (0 °C) suspension of lithium aluminum hydride (100 mg, 0.26 mmol) in anhydrous ether (25 mL). The reaction mixture was stirred at room temperature for 3 h, then quenched by careful addition of water, filtered, and the inorganic salts washed with ether. The filtrate was dried and evaporated to give a residue, which was chromatographed (ether–petroleum ether 6:4) to give (−)-**16** (0.15 g, 75%) as a white solid. Mp 132–134 °C (EtOAc–pentane) [lit.[14] mp 132–134 °C (EtOAc–hexane)]. $[\alpha]_D^{20} = -26.24$ (*c* 0.94, $CHCl_3$) {lit.[14] $[\alpha]_D^{24} = -25.5$ (*c* 0.94, $CHCl_3$)}. IR (KBr) ν_{max}: 3330, 1445, 1021 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (s, 3H); 1.04 (dd, $J = 3.6$, 12.4 Hz, 1H); 1.11–1.28 (m, 8H); 1.33–1.62 (m, 6H); 1.65–2.08 (m, 5H); 3.90 (dd, $J = 3.6$, 11.0 Hz, 1H); 4.06 (dd, $J = 7.6$, 11.0 Hz, 1H); 4.21–4.25 (m, 1H). Anal. Calcd for $C_{14}H_{26}O_2$ requires C, 74.29; H, 11.58. Found: C, 74.22; H, 11.50.

Similarly, (−)-**15** was converted to (+)-**16**, which showed spectral data identical to (−)-**16**. Mp 132–134 °C (EtOAc–pentane) [lit.[14] mp 132–134 °C (EtOAc–hexane)]. $[\alpha]_D^{20} = +26.8$ (*c* 0.94, $CHCl_3$) {lit.[14] $[\alpha]_D^{24} = +26.1$ (*c* 0.93, $CHCl_3$)}.

4.9. (4a*R*,8a*S*)- and (4a*S*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-5,5,8a-trimethyl-2(1*H*)-naphthalenone, (+)-17 and (−)-17

A suspension of (+)-**15** (0.36 g, 1.09 mmol) and 10% palladium on charcoal (100 mg) in EtOH (10 mL) was shaken for 2 h at 20 psi in a Parr apparatus, filtered on a pad of Celite® and the filtrate evaporated. The residue was purified by chromatography (EtOAc–petroleum ether 1:40) to give (+)-**17** (0.13 g, 72%) as white crystals. Mp 89–91 °C [lit.[21] mp 88–89 °C (hexane)]. $[\alpha]_D^{20} = +86.1$ (*c* 0.40, $CHCl_3$) {lit.[21] $[\alpha]_D^{20} = +84.9$ (*c* 1.07, $CHCl_3$)}. IR (KBr) ν_{max}: 1720 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.83 (s, 3H); 0.87 (s, 3H); 0.97 (s, 3H); 1.20–1.26 (m, 2H); 1.40–1.48 (m, 4H); 1.60–1.66 (m, 2H); 1.96–1.99 (m, 2H); 2.11–2.15 (m, 1H); 2.23–2.26 (m, 1H); 2.36–2.40 (m, 1H). Anal. Calcd for $C_{13}H_{22}O$ requires C, 80.35; H, 11.41. Found: C, 80.44; H, 11.60.

Similarly, (−)-**15** was converted to (−)-**17**, having spectral data identical to (+)-**17**. Mp 89–91 °C [lit.[21] mp 88–89 °C (hexane)]. $[\alpha]_D^{20} = -85.1$ (*c* 0.40, $CHCl_3$) {lit.[21] $[\alpha]_D^{20} = -84.0$ (*c* 1.30, $CHCl_3$)}. Anal. Calcd for $C_{13}H_{22}O$ requires C, 80.35; H, 11.41. Found: C, 80.38; H, 11.55.

4.10. (1′*S*,4′a*R*,8′a*R*)-5′,5′,8′a-Trimethyl-octahydrospiro{[1,3]dioxolane-2,2′-naphthalene}-1′-carboxylic acid (−)-menthyl ester, 18

To a cooled (−78 °C) solution of trimethylsilyl triflate (30 μL, 0.15 mmol) in anhydrous methylene chloride (1 mL) was added 1,2-bis(trimethylsilyloxy)ethane (0.42 mL, 1.7 mmol). A solution of the ketoester **13** (0.58 g, 1.55 mmol) in anhydrous methylene chloride (5 mL) was added and the mixture warmed to 0 °C. After the disappearance of the starting materials, the reaction was quenched with dry pyridine (0.35 mL), poured into saturated sodium bicarbonate solution (10 mL), and extracted with methylene chloride (2 × 20 mL). The extracts were washed with brine, dried, and evaporated to give an oily residue. Column chromatography on silica gel (ether–petroleum ether 0.6:9.4) gave **18** (0.59 g, 91%) as an oil. $[\alpha]_D^{20} = -62.7$ (*c* 0.88, $CHCl_3$). IR (film) ν_{max}: 1720, 1540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.70 (d, $J = 6.8$ Hz, 3H); 0.77–1.31 (m, 21H); 1.31–1.74 (m, 11H); 1.80–1.84 (m, 1H); 1.89–2.08 (m, 2H); 2.45 (s, 1H); 3.68–4.09 (m, 4H); 4.57 (dt, $J = 4.4$, 10.8 Hz, 1H). Anal. Calcd for $C_{26}H_{44}O_4$ requires C, 74.24; H, 10.54. Found: C, 74.10; H, 10.34.

4.11. (1′*R*,4′a*R*,8′a*R*)-5′,5′,8′a-Trimethyl-octahydrospiro{[1,3]dioxolane-2,2′-naphthalen}-1′-yl-methanol, 19

A solution of **18** (0.38 g, 0.90 mmol) in anhydrous ether (10 mL) was added dropwise to a cooled (0 °C) suspension of lithium aluminum hydride (100 mg, 0.26 mmol) in anhydrous ether (25 mL). The reaction mixture was stirred at room temperature for 3 h, then quenched by careful addition of water, filtered, and the inorganic salts washed with ether. The filtrate was dried and evaporated to give a residue, which was chromatographed on silica gel (ether–petroleum ether 6:4) to give **19** (0.19 g, 77%). Mp 117–118 °C (pentane). $[\alpha]_D^{20} = +7.9$ (*c* 0.83, $CHCl_3$). IR (KBr) ν_{max}: 3551, 1030 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.74–1.01 (m, 10H); 1.01–1.72 (m, 9H); 1.72–2.08 (m, 2H); 2.98 (br s, 1H); 3.58–3.62 (m, 1H); 3.76–4.19 (m, 5H). Anal. Calcd for $C_{16}H_{28}O_3$ requires C, 71.60; H, 10.52. Found: C, 71.38; H, 10.78.

4.12. (4a*R*,8a*R*)-1-Methylene-2-oxo-5,5,8a-trimethyl-decahydronaphtalene, (+)-20

A solution of **19** (0.40 g, 1.49 mmol) in acetone (10 mL) containing 10% HCl (4 mL) was stirred for 12 h at rt. Most of the solvent was removed in vacuo and the residue neutralized with saturated sodium bicarbonate solution (10 mL) and extracted with ether (2 × 20 mL). The extracts were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (ether–petroleum ether 1:1) to give (+)-**20** (0.23 g, 75%) as a white solid. Mp 55 °C (hexane) [lit.[12] mp 55–56 °C (pentane)]. $[\alpha]_D^{20} = +71.6$ (*c* 1.00, $CHCl_3$) {lit.[12] $[\alpha]_D^{20} = +71.9$ (*c* 0.69, $CHCl_3$)}. IR (KBr) ν_{max}: 1697, 1611, 1461, 1376 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.92 (s, 3H); 0.96 (s, 3H); 1.01 (s, 3H); 1.11–2.07 (m, 9H); 2.22–2.46 (m, 1H); 2.67 (ddd, $J = 1.9$, 5.5, 19.2 Hz, 1H); 5.01 (d, $J = 1.1$ Hz, 1H), 5.52 (d, $J = 1.1$ Hz, 1H). Anal. Calcd for $C_{14}H_{22}O$ requires C, 81.50; H, 10.75. Found: C, 81.27; H, 10.71.

4.13. (1*R*,4a*R*,8a*R*)-5,5,8a-Trimethyl-2-methylene-decahydro-naphthalene-1-carboxylic acid (−)-menthyl ester, 21

Sodium amide (0.25 g, 6.32 mmol) was added to a suspension of triphenylphosphonium bromide (2.40 g, 6.65 mmol) in toluene (25 mL) and the resultant mixture heated at reflux for 6 h. After being cooled at room temperature, the decanted yellow solution was added to a cooled (0 °C) solution of **13** (0.50 g, 1.33 mmol) in toluene (25 mL). The reaction mixture was stirred at rt for 2 h, the solvent evaporated and the residue chromatographed on silica gel (ether–petroleum ether 1:60) to give **21** (0.45 g, 90%). $[\alpha]_D^{20} = -41.1$ (*c* 0.79, $CHCl_3$). IR (film) ν_{max}: 1725, 1450, 1380 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.71–1.80 (m, 34H); 1.80–2.12 (m, 3H); 2.36–2.48 (m, 1H); 2.74 (s, 1H); 4.55–4.76 (m, 2H); 4.81 (d, $J = 1.2$ Hz, 1H). Anal. Calcd for $C_{25}H_{42}O_2$ requires C, 80.16; H, 11.30. Found: C, 79.93; H, 11.15.

4.14. (1*R*,4a*R*,8a*R*)-5,5,8a-Trimethyl-2-methylene-decahydro-naphthalen-1-yl-methanol, (−)-22

A solution of **21** (0.45 g, 1.20 mmol) in THF (30 mL) was added dropwise to a stirred slurry of lithium aluminum hydride (90 mg, 2.40 mmol) in THF (20 mL) and the reaction mixture stirred at rt for 6 h. Saturated aqueous ammonium chloride solution (5 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic phases were dried and evaporated. The residue was purified by column chromatography on silica gel (ether–petroleum ether 1.5:8.5) to give (−)-albicanol (−)-**22** (0.20 g, 75%) as a solid. Mp 69–70 °C [lit.[24] mp 69–70 °C (MeOH)]. $[\alpha]_D^{20} = -12.8$ (*c* 1.00, $CHCl_3$) {lit.[24] $[\alpha]_D^{20} = -14.0$ (*c* 1.00, $CHCl_3$) and lit.[25] $[\alpha]_D^{20} = -11.5$ (*c* 0.80, $CHCl_3$)}. IR (film) ν_{max}: 3450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.71 (s, 3H); 0.80 (s, 3H); 0.87 (s, 3H); 1.10–1.80 (m, 9H); 1.94–2.05 (m, 2H); 2.38–2.43 (m, 1H); 3.75 (dd, $J = 9.5$, 10.8 Hz, 1H); 3.83 (dd, $J = 3.8$, 10.8 Hz, 1H); 4.63 (d, $J = 1.4$ Hz, 1H); 4.93 (d, $J = 1.4$ Hz, 1H). Anal. Calcd for $C_{15}H_{26}O$ requires C, 81.02; H, 11.79. Found: C, 81.12; H, 11.82.

4.15. (1*R*,2*S*,4a*S*,8a*R*)-2-Hydroxy-5,5,8a-trimethyl-decahydro-naphthalene-1-carboxylic acid (−)-menthyl ester, 23

A suspension of **10** (1.33 g, 3.20 mmol) and 5% palladium on charcoal (100 mg) in EtOH (25 mL) was shaken for 4 h at 20 psi in a Parr apparatus, filtered on a pad of Celite® and the filtrate evaporated. The crude residue was dissolved in MeOH (5 mL) containing NaOMe (0.22 g, 0.41 mmol) and stirred for 4 h at 0 °C and then 10% phosphoric acid added until pH = 6. After evaporation of most of the methanol, the residue was extracted with ether (3 × 25 mL), the extracts washed with saturated sodium bicarbonate solution, dried, and evaporated to give **23** (0.99 g, 82%). Mp 130–131 °C

(acetone). $[\alpha]_D^{20} = -40.1$ (*c* 1.83, $CHCl_3$). IR (KBr) ν_{max}: 3518, 1704, 1450 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ: 0.75 (d, $J = 7.2$ Hz, 3H); 0.80–1.28 (m, 20H); 1.28–2.06 (m, 14H); 2.25–2.36 (m, 2H); 3.92–4.10 (m, 2H); 4.77 (dt, $J = 4.4$, 11.2 Hz, 1H). Anal. Calcd for $C_{24}H_{42}O_3$ requires C, 76.14; H, 11.18. Found: C, 75.92; H, 11.02.

4.16. (1*S*,2*S*,4a*S*,8a*R*)-2-Hydroxy-1-hydroxymethyl-5,5,8a-trimethyl-decahydronaphtalene, (+)-24

To a cooled (0 °C) suspension of lithium aluminum hydride (0.13 g, 3.30 mmol) in dry ether (20 mL) was added dropwise a solution of **23** (0.50 g, 1.32 mmol) in dry ether (25 mL). After the reaction was stirred at room temperature for 8 h, water was added, and the precipitate filtered through a pad of Celite®, after which the filtrate was concentrated in vacuo. Purification by silica gel column chromatography (ether–petroleum ether 6:4) gave the corresponding diol (+)-**24** (0.23 g, 77%) as white crystals. Mp 133–135 °C (EtOH). $[\alpha]_D^{20} = +15.3$ (*c* 0.74, MeOH). IR (KBr) ν_{max}: 3328, 1450, 1023 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6) δ: 0.88–1.10 (m, 5H); 1.10–1.26 (m, 7H); 1.26–1.87 (m, 8H); 2.02–2.17 (m, 1H); 2.91 (br s, 2H); 3.96–4.03 (m, 2H); 4.05–4.12 (m, 1H). Anal. Calcd for $C_{14}H_{26}O_2$ requires C, 74.29; H, 11.58. Found: C, 74.33; H, 11.60.

4.17. X-ray structure determinations

X-ray diffraction data for compound **10** were collected on a Nonius CAD-4 diffractometer and for compounds **12**, **23**, and (+)-**24** on a Nonius Kappa CCD diffractometer, at room temperature ($T = 295$ K), with graphite monochromated Mo Kα radiation ($\lambda = 0.7107$ Å). The structures were solved by direct methods (SIR97)[26] and refined (SHELXL-97)[27] by full matrix least squares with anisoptropic non-H and calculated H atoms except for O–H hydrogens, which were refined isotropically. ORTEP[28] views of the molecules are shown in Figures 1–4.

Crystal data: Compound **10**, $C_{26}H_{40}O_4$; monoclinic, space group $P2_1$, $a = 7.180(1)$, $b = 21.314(2)$, $c = 16.454(2)$ Å, $\beta = 90.33(1)°$, $V = 2518.0(5)$ Å^3, $Z = 4$, $D_c = 1.099$ g cm^{-3}. Intensity data collected with $\theta \leqslant 27.9°$; 6222 independent reflections measured; 3831 reflections observed [$I > 2\sigma(I)$]. Final *R* (observed reflections) = 0.055 and R_w (all reflections) = 0.148.

Compound **12**, $C_{24}H_{36}O_4$; orthorhombic, space group $P2_12_12_1$, $a = 11.7988(3)$, $b = 11.9152(1)$, $c = 32.4195(7)$ Å, $V = 4557.7(2)$ Å^3, $Z = 8$, $D_c = 1.132$ g cm^{-3}. Intensity data collected with $\theta = 27.5°$, 9750 independent reflections measured; 6875 reflections observed [$I > 2\sigma(I)$]. Final $R = 0.050$ (observed reflections), $R_w = 0.119$ (all reflections), $S = 1.031$. The asymmetric unit is built up by two independent molecules which, in the crystal, are linked in dimers by means of the following hydrogen bonds: O3A–H···O4B $(2 - x, 1/2 + y, 3/2 - z)$ [O3A···O4B = 2.779(2) Å]; O3B–H···O4A$(2 - x, y - 1/2, 3/2 - z)$ [O3B···O4A = 2.925(2) Å].

Compound **23**, $C_{24}H_{42}O_3$; orthorhombic, space group $P2_12_12_1$, $a = 8.6561(3)$, $b = 11.2047(3)$, $c = 47.8280(14)$ Å, $V = 4638.8(2)$ Å^3, $Z = 8$, $D_c = 1.084$ g cm^{-3}. Intensity data collected with $\theta = 23.5°$; 6600 independent reflections measured; 5365 reflections observed [$I > 2\sigma(I)$]. Final $R = 0.042$ (observed reflections) and $R_w = 0.110$ (all reflections). The molecules form an intramolecular hydrogen bond: O3–H···O1 [O3···O1 = 2.751(3) and 2.798(3) Å for the two independent molecules of the asymmetric unit].

Compound (+)-**24**, $C_{14}H_{26}O_2$; monoclinic, space group $P2_1$, $a = 8.4051(4)$, $b = 11.1196(2)$, $c = 15.3901(7)$ Å, $\beta = 103.070(2)°$, $V = 1401.1(1)$ Å^3, $Z = 4$, $D_c = 1.073$ g cm^{-3}. Intensity data collected with $\theta = 27.5°$, 6154 independent reflections measured; 5228 reflections observed [$I > 2\sigma(I)$]. Final $R = 0.045$ (observed reflections), $R_w = 0.115$ (all reflections). The asymmetric unit is built up by two independent molecules which, in the crystal, are linked by a network of hydrogen bonds: O2A–H···O2B(x, y, z) [O2A···O2B = 2.725(3) Å]; O1A–H···O1B$(x, y - 1, z)$ [O1A···O1B = 2.820(2) Å]; O1B–H···O2A$(-x, y + 1/2, z)$ [O1B···O2A = 2.740(3) Å]; O2B–H···O1A$(-x, y + 1/2, z)$ [O2B···O1A = 2.771(3) Å].

Complete crystallographic data (excluding structural factors) for the structures herein have been deposited at the Cambridge Crystallographic Data Centre and allocated deposition numbers CCDC 243501–243504. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk./conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033, e-mail: deposit@ccdc.cam.ac.uk].

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