Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4499–4507

TETRAHEDRON: *ASYMMETRY*

Stereoselective synthesis of highly oxygenated cyclohexanes through a [3+3] annulation approach†

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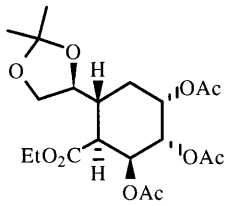
Received 31 August 2000; accepted 16 October 2000

Abstract

The synthesis of highly oxygenated cyclohexanes has been achieved through a Michael–Wittig protocol via a [3+3] annulation of the enal that is derived from 2,3-*O*-isopropylidene-(*R*)-glyceraldehyde. The γ-alkoxy enal system is responsible for the stereoselectivity.

1. Introduction

Highly functionalised cyclohexanes are useful intermediates for the synthesis of natural products. Oxygenated cyclohexane derivatives,[1,2] the pseudo sugars,[3,4] are fragments[5] of several bioactive natural products such as antibiotics, enzyme inhibitors, etc., which play a vital role in life processes. Because of the major significance of cyclohexane derivatives, several strategies have been devised[1,6] for their synthesis. In an attempt to develop simple methods for the synthesis of functionalised cyclohexane derivatives, which could be precursors to plant growth regulators[7] and others, we describe herein a stereoselective [3+3] annulation protocol for the synthesis of **1**–**3** by a Michael–Wittig reaction on the enal derived from 2,3-*O*-isopropylidene-(*R*)-glyceraldehyde.



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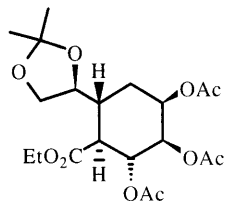

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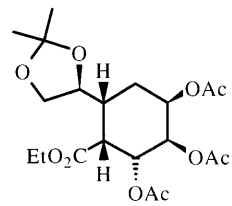

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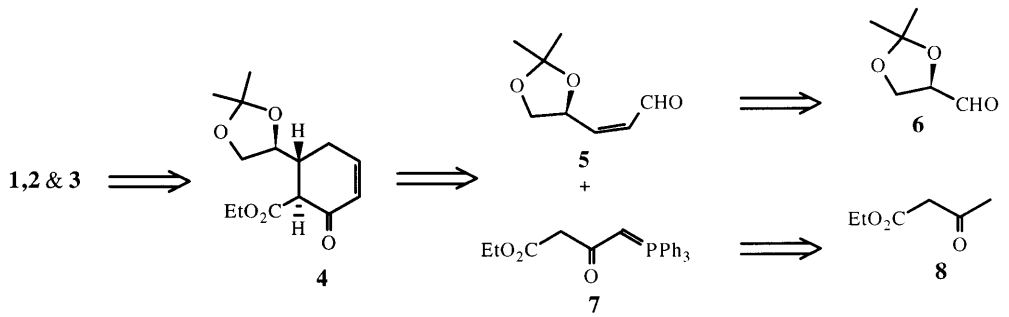
† IICT Communication No. 4610.

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00429-8

2. Results and discussion

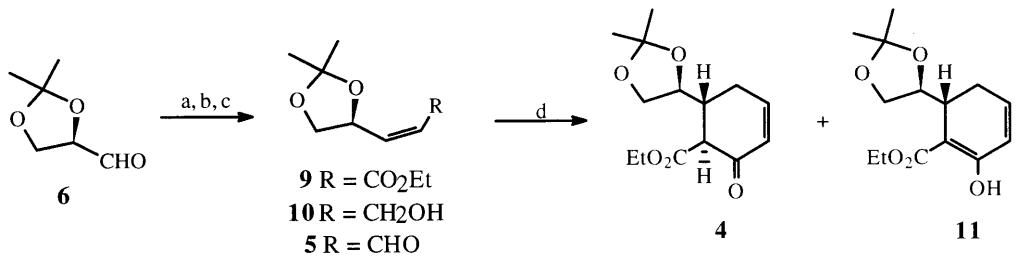
Michael addition[8] of nucleophiles to α,β-unsaturated carbonyl 'acceptors', especially those bearing a stereogenic oxygen substituted centre in the γ-position, to obtain enantiomerically pure products is a very useful tool in organic synthesis. From retrosynthetic analysis (Scheme 1) it was envisaged that a [3+3] annulation on a chiral acceptor, through an initial Michael addition followed by a Wittig reaction of the adduct, would result in the formation of cyclohexenone derivatives. Thus, in the present study, enal **5**, derived from 2,3-*O*-isopropylidene-(*R*)-glyceraldehyde **6**, and ethyl 3-oxo(triphenylphosphorylidene)butanoate **7**[9,10] are chosen as appropriate synthons for performing the Michael–Wittig reaction en route to the synthesis of **1**–**3** through the late stage intermediate **4**, wherein the chirality is induced from the γ-alkoxy stereocentre of enal **5**.



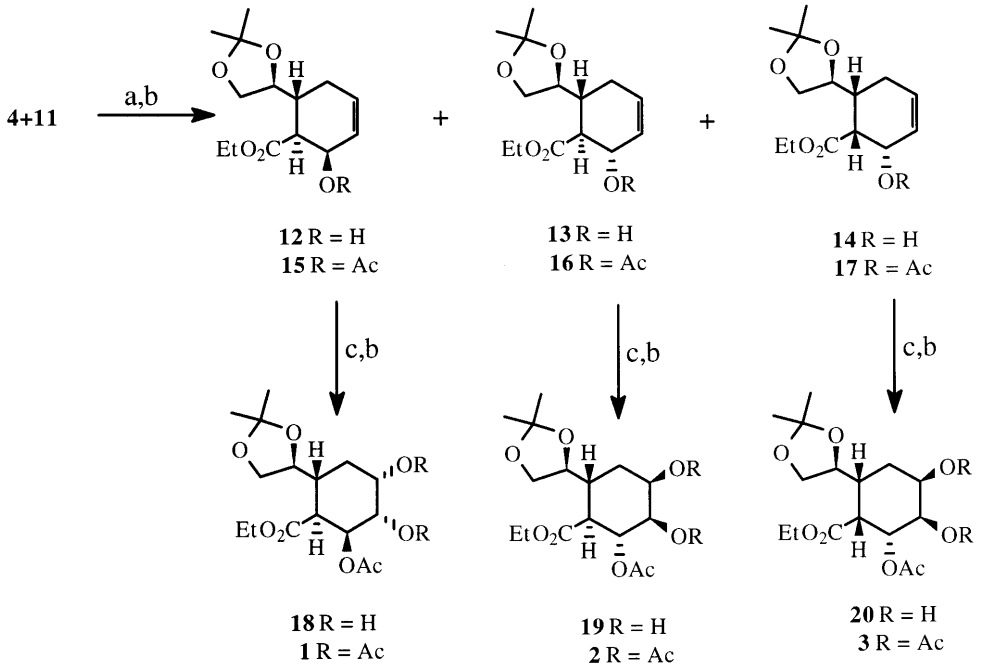
Scheme 1.

Accordingly, ester **9**, prepared from **6** (Scheme 2), was reduced with DIBAL-H to the corresponding alcohol **10**,[11] which on PDC oxidation gave enal **5** (72% yield). The crucial [3+3] annulation reaction of **5** with ylide **7** in the presence of NaH in THF containing two drops of water[9] at 50°C for 15 min resulted in the formation of **4** and **11** (68%) as a keto–enol mixture, as was evident from the ^{1}H NMR spectrum (Scheme 3).

The keto–enol mixture containing **4** and **11** was subjected to reduction with $CeCl_3$–$NaBH_4 \cdot 7H_2O$ in ethanol to afford a chromatographically (silica gel, 1:1 ethyl acetate:pet. ether) separable mixture of alcohols **12**, **13** and **14** in a 2:1:1.5 ratio, respectively. The formation of the



Scheme 2. Reagents: (a) $Ph_3P{=}CHCO_2Et$, MeOH, rt; (b) DIBAL-H, CH_2Cl_2; (c) PDC, CH_2Cl_2; (d) $Ph_3P{=}CHCOCH_2CO_2Et$, NaH, THF, two drops of water, 50°C



Scheme 3. Reagents: (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, EtOH; (b) Ac_2O, pyridine; (c) OsO_4, NMO, acetone:water (3:1)

isomer **14** could be attributed to the epimerisation at H-1 followed by reduction under the aforementioned reaction conditions. The carbinols **12**–**14**, independently on reaction with Ac_2O–pyridine, were converted into the corresponding acetates **15**, **16** and **17**, respectively. The structures of these compounds were unambiguously determined based on spectroscopic analysis.

Finally, stereoselective *cis*-hydroxylation of olefins in **15**–**17** was achieved by osmylation (OsO_4, NMO) to afford the diols **18**, **19** and **20** with complete diastereocontrol,[12,13] i.e. *anti* relative to the adjacent -OAc group. The diols **18**–**20** were converted under standard reaction conditions (Ac_2O, pyridine) to the triacetates **1**, **2** and **3**, whose structures were thoroughly established from spectroscopic analysis (Fig. 1).

The six-membered ring in **1** adopts a chair conformation ($^6C_3$) such that both the bulky substituents are equatorial. Couplings are consistent with the structure shown in Fig. 1. This is further supported by NOESY cross peaks H6–H4, H6–H5′b and H1–H4′. The five-membered ring exists in a twist conformation, consistent with the ^3J4′,5′a, ^3J4′,5′b and NOESY cross peaks methyl (A)-H5′a, methyl (A)-H4′ and methyl (B)-H5′b. NOESY cross peaks H6–H5′b and H1–H4′, as well as $J_{6,4}$ 2.9 Hz, imply a single conformation about C6–C4′ with a H6–C6–C4′–H4′ dihedral angle of about −110°.

For **2**, the six-membered ring is in $^6C_3$ chair conformation, with all the substituents in equatorial positions except for the C-4 acyl group. NOESY experiments also show diaxial disposition of protons H2–H6, H5ax–H3, H1–H5ax and H1–H3. The dihedral angle H6–C6–C5–H4′, as well as the five-membered ring conformation, is very similar to that of **1**.

For molecule **3** in the $^6C_3$ chair conformation, the five-membered ring is equatorial, while the -CO_2Et group adopts an axial position. The NOESY experiments show diaxial proximities of H2–H6 and H5a–H3. The five-membered ring adopts a conformation similar to that of **1** and **2**. NOE cross peaks H6–H5′b, H1–H4′ and H1–H5′a and $J_{6,4}$ 7.6 Hz are consistent with a dihedral angle H6–C6–C4′–H4′ of about −150°.

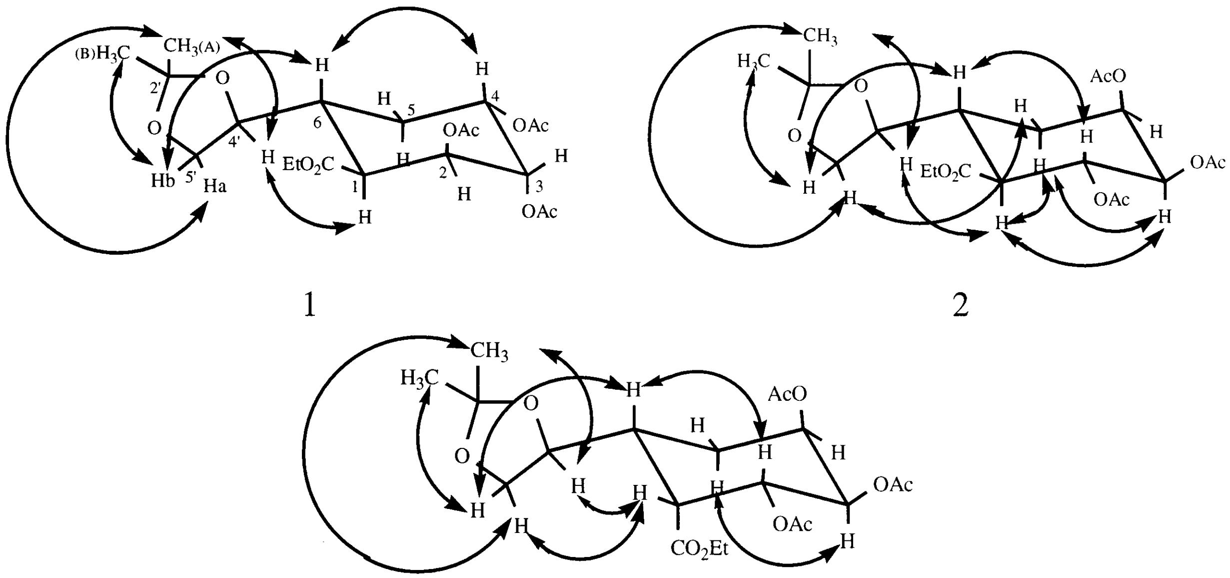


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Figure 1.

The configuration and conformational studies of the six-membered rings deduced in the present work are identical to those observed in our earlier work.[14] Interestingly the yields also follow the same pattern.

Taking advantage of the existing stereocentre of the three-carbon synthon, the enal, derived from 2,3-*O*-isopropylidene-(*R*)-glyceraldehyde, a Michael–Wittig protocol has been adopted for the construction of a homochiral cyclohexene system en route to the synthesis of highly functionalised cyclohexane derivatives. Since the two components of the [3+3] annulation viz. the enal and the phosphonium salt are simple and easily accessible starting materials, the present protocol should find wide use in the construction of carbocycles. Utilisation of the present strategy for the synthesis of related bioactive carbocycles is in progress.

3. Experimental

Solvents were dried over standard drying agents and freshly distilled prior to use. ^{1}H NMR (200 MHz, 500 MHz) and ^{13}C NMR (50 MHz, 125 MHz) spectra were recorded in deuteriochloroform solution with tetramethylsilane as an internal reference on Varian Gemini-200 MHz and INOVA-500 MHz spectrometers and J values are given in Hz. Optical rotations were measured with a Jasco DIP-370 instrument and $[\alpha]_D$ values are in units of 10^{-1} deg cm^2 g^{-1}. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40°C in vacuo. HRMS were recorded on a V G Autospec mass spectrometer at 5 or 7 K resolution using perfluoro kerosene as an internal reference.

3.1. 3-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-(Z)-propenal **5**

A solution of alcohol **10** (7.5 g, 47.4 mmol) in dry CH_2Cl_2 (80 mL) was treated with PDC (26.94 g, 71.5 mmol) and heated at reflux for 2 h. The reaction mixture was brought to room temperature, CH_2Cl_2 was removed under reduced pressure and the residue was filtered through a silica gel bed using ether as eluent. Evaporation of solvent gave the enal **5** (4.8 g) in 65% yield as a syrup, which was used as such for further reaction. $[\alpha]_D = -33.75$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.42, 1.45 (2s, 6H, CH_3), 3.75 (t, 1H, $J_{5'a,5'b}$ 10.5, $J_{4',5'b}$ 6.6 Hz, H-5′a), 4.25 (t, 1H, $J_{4',5'b}$ 9.9 Hz, H-5′b), 4.80 (m, 1H, H-4′), 6.35 (dd, 1H, $J_{2,3}$ 16.5, $J_{1,2}$ 5.5 Hz, H-2), 6.78 (dd, 1H, $J_{3,4'}$ 5.5 Hz, H-3), 9.60 (d, 1H, H-1).

3.2. Michael–Wittig reaction on **5**

A suspension of NaH (1.35 g, 58.9 mmol; 60% dispersion in mineral oil) was added to a stirred solution of the above enal **5** (4.6 g, 29.4 mmol) and ylide **7** (15.27 g, 32.4 mmol) in dry THF (70 mL) at 50°C under nitrogen followed by two drops of water and stirred for 15 min at the same temperature. The reaction mixture was brought to room temperature, acidified by adding a 5% aq. HCl solution (pH 6) and extracted with ether (3×50 mL). The combined ether layers were washed with water (50 mL) and brine (50 mL) and dried (Na_2SO_4). Evaporation of solvent under reduced pressure and purification of the residue by column chromatography (finer than 200 mesh, Si-gel, ethyl acetate:pet. ether, 1:5) gave a keto–enol mixture, *ethyl 6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-(1S,6R)-3-cyclohexene-1-carboxylate* ***4*** *and ethyl 6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-(1R,6R)-3-cyclohexene-1-carboxylate* ***11*** (5.4 g) in 68% yield as a syrup. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.54 (m, 9H, CH_3), 2.02–2.82 (m, 3H, H-5a,5b,6), 3.35 (d, 1H, $J_{1,6}$ 9.6 Hz, H-1 of keto form), 3.60–3.80 (m, 2H, H-4′a, 5′a), 3.95–4.32 (m, 3H, H-5′b, -OCH_2CH$_3$), 6.02–6.15 (m, 1H, H-3), 6.95–7.08 (m, 1H, H-4), 12.33 (s, 1H, OH of enolic form); EIMS (%): 253 (M^+−15; 55), 167 (38), 121 (83), 101 (73), 43 (100); EI-HRMS: calcd for $C_{13}H_{17}O_5$ (M^+−15): 253.107599, found: 253.108181.

3.3. Reduction of keto–enol mixture **4** and **11**

To a stirred solution of **4** and **11** (3 g, 11.2 mmol) and $CeCl_3 \cdot 7H_2O$ (4.5 g, 12.3 mmol) in ethanol (25 mL), sodium borohydride (0.82 g, 22.3 mmol) was added portionwise at 0°C. The reaction mixture was brought to room temperature and stirred for 1 h. Ethanol was removed under reduced pressure, the reaction mixture diluted with water (50 mL) and extracted with ether (3×50 mL). The combined ether layers were washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and the resulting residue was purified by column chromatography (finer than 200 mesh Si-gel, ethyl acetate:pet. ether 1:4) to give **12**, **13** and **14** in 2:1:1.5 ratio.

First eluted was *ethyl 6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxy-(1S,2R,6R)-3-cyclohexene-1-carboxylate* **12** (0.98 g) in 33.4% yield as a syrup. $[\alpha]_D = -152.0$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz,$CDCl_3$): δ 1.22–1.42 (m, 9H, CH_3), 2.20–2.32 (m, 3H, H-5a,5b,6), 2.84 (t, 1H, $J_{1,6}$ 4.2, $J_{1,2}$ 4.1 Hz, H-1), 3.60 (t, 1H, $J_{4',5'}$ 6.1, $J_{5a',5b'}$ 7.3 Hz, H-5′a), 4.08–4.30 (m, 3H, H-5′b, -OCH_2CH$_3$), 4.30–4.48 (m, 2H, H-2,4′), 5.69–5.89 (m, 2H, H-3,4); EIMS (%): 255 (M^+−15; 10), 195 (26), 121 (23), 101 (23), 79 (45), 43 (100).

Second eluted was e*thyl 6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxy-(1S,2S,6R)-3-cyclohexene-1-carboxylate* **13** (0.485 g) in 16.5% yield as a syrup. $[\alpha]_D = -4.8$ (*c* 1.5, $CHCl_3$); ^1H NMR (200 MHz,$CDCl_3$): δ 1.20–1.45 (m, 9H, CH_3), 2.00–2.20 (m, 3H, H-5a,5b,6), 2.42 (t, 1H, $J_{1,2}$ 8.9, $J_{1,6}$ 9.2 Hz, H-1), 3.56 (t, 1H, $J_{5a',5b'}$ 8.7, $J_{4',5b'}$ 7.6 Hz, H-5′a), 3.88 (t, 1H, $J_{4',6}$ 8.2 Hz, H-4), 3.92–4.18 (m, 1H, H-5′b), 4.20 (q, 2H, *J* 7.2 Hz, -OCH_2CH_3), 4.35–4.49 (m, 1H, H-2), 5.60–5.82 (m, 2H, H-3,4); EIMS (%): 255 (M^+-15; 12), 149 (38), 101 (86), 79 (32), 43 (100); EI-HRMS: calcd for $C_{13}H_{19}O_5$ (M^+-15): 255.123249, found: 255.122625.

Third eluted was e*thyl 6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-hydroxy-(1R,2S,6R)-3-cyclohexene-1-carboxylate* **14** (0.735 g) in 25% yield as a syrup. $[\alpha]_D = -148.2$ (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.22–1.41 (m, 9H, CH_3), 2.12–2.38 (m, 3H, H-5a,5b,6), 2.65 (dd, 1H, $J_{1,2}$ 5.2, $J_{1,6}$ 12.3 Hz, H-1), 3.66 (t, 1H, $J_{4',5'a}$ 8.6, $J_{5'a,5'b}$ 8.9 Hz, H-5′a), 3.98 (t, 1H, $J_{4',5'}$ 7.3, $J_{4',6}$ 10.9 Hz, H-4′), 4.22–4.35 (m, 4H, H-2,5′b, -O$CH_2$$CH_3$), 5.80–5.92 (m, 2H, H-3,4); EIMS (%): 255 (M^+-15; 8), 195 (18), 149 (35), 121 (25), 101 (78).

3.4. Ethyl 2-acetoxy-6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-(1S,2R,6R)-3-cyclohexene-1-carboxylate ***15***

A solution of alcohol **12** (0.9 g, 3.3 mmol) in pyridine (5 mL) containing DMAP (0.040 g, 0.3 mmol) was treated with acetic anhydride (0.34 mL, 3.6 mmol) at 0°C and stirred for 1 h at room temperature. The reaction mixture was diluted with a saturated aqueous $NaHCO_3$ solution (25 mL) and extracted with CH_2Cl_2 (2×25 mL). The combined CH_2Cl_2 layers were washed with an aq. saturated $CuSO_4$ solution (25 mL), water (25 mL), followed by brine (25 mL) and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and residue on purification by column chromatography (60–120 mesh, Si-gel, ethyl acetate:pet. ether 1:4) gave the acetate **15** quantitatively as a syrup. $[\alpha]_D = +27.0$ (*c* 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.25–1.40 (m, 9H, CH_3), 2.05 (s, 3H, -OAc), 2.05–2.45 (m, 3H, H-5a,5b,6), 2.95–3.05 (m, 1H, H-1), 3.65 (t, 1H, $J_{4',5'a}$ 7.4, $J_{5'a,5'b}$ 8.4 Hz, H-5′a), 3.86 (m, 4H, H-4′, 5′b, -O$CH_2$$CH_3$), 5.48–5.60 (m, 2H, H-3, 4), 5.91–6.02 (m, 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.25, 20.95, 25.72, 26.75, 29.64, 38.49, 43.57, 60.35, 67.83, 69.34, 77.68, 109.0, 123.77, 130.28, 169.88, 170.293; EIMS (%): 297 (M^+-15; 12), 195 (8), 121 (12), 101 (12), 79 (25), 72 (15), 43 (100); EI-HRMS: calcd for $C_{15}H_{21}O_6$ (M^+-15): 297.133814, found: 297.133015.

3.5. Ethyl 2-acetoxy-6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-(1S,2S,6R)-3-cyclohexene-1-carboxylate ***16***

A solution of alcohol **13** (0.5 g, 1.8 mmol) in pyridine (2 mL) was treated with acetic anhydride (0.2 mL, 2.0 mmol) at 0°C, worked up and purified as described for **15** to give acetate **16** in quantitative yield as a syrup. $[\alpha]_D = +148.8$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.20–1.45 (m, 9H, CH_3), 1.98–2.25 (m, 6H, H-5a,5b,6, -OAc), 2.58–2.70 (m, 1H, H-1), 3.62 (t, 1H, $J_{5'a,5'b}$ 8.6, $J_{4',5'a}$ 7.8 Hz, H-5′a), 3.93 (t, 1H, $J_{4',6}$ 8.6 Hz, H-4′), 4.00–4.25 (m, 3H, -O$CH_2$$CH_3$, H-5′b), 5.52–5.62 (m, 2H, H-3,4), 5.82–5.96 (m, 1H, H-2); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.16, 20.99, 24.68, 25.08, 26.25, 37.73, 49.32, 60.89, 66.80, 71.32, 75.94, 108.93, 125.22, 129.24, 170.20, 172.92; EIMS (%): 297 (M^+-15; 5), 237 (10), 149 (15), 121 (18), 101 (50), 43 (100); EI-HRMS: calcd for $C_{15}H_{21}O_6$ (M^+-15): 297.133814, found: 297.133690.

3.6. Ethyl 2-acetoxy-6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-(1R,2S,6R)-3-cyclohexene-1-carboxylate **17**

A solution of alcohol **14** (0.5 g, 1.8 mmol) in pyridine (2 mL) was treated with acetic anhydride (0.19 mL, 2.0 mmol) at 0°C, worked up and purified as described for **15** to give acetate **17** (0.46 g) in 93% yield as a syrup. $[\alpha]_D = -132.3$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25–1.48 (m, 9H, CH_3), 2.02–2.38 (m, 6H, -OAc, H-5a,5b,6), 2.82 (dd, 1H, $J_{1,2}$ 4.5, $J_{1,6}$ 11.3 Hz, H-1), 3.76 (dd, 1H, $J_{5'a,4'}$ 5.4, $J_{5'a,5'b}$ 9.0 Hz, H-5′a), 3.98–4.25 (m, 3H, H-5′b, -O$CH_2$$CH_3$), 4.45 (td, 1H, $J_{4',6}$ 5.4, $J_{4',5'}$ 6.7 Hz, H-4′), 5.58 (t, 1H, $J_{2,3}$ 5.4 Hz, H-2), 5.78–5.90 (m, 1H, H-3), 6.02–6.12 (m, 1H, H-4); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.01, 20.89, 23.49, 24.72, 26.02, 31.72, 45.91, 60.55, 66.55, 66.74, 75.40, 108.78, 122.76, 132.53, 170.13, 171.33; EIMS (%): 297 (M^+−15; 20), 195 (17), 149 (31), 121 (48), 101 (64), 435 (100); EI-HRMS: calcd for $C_{15}H_{21}O_6$ (M^+−15); 297.133814, found: 297.133470.

3.7. Ethyl 2-acetoxy-3,4-dihydroxy-6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-(1S,2S,3S,4S,6R)-cyclohexane-1-carboxylate **18**

To a stirred solution of compound **15** (0.85 g, 2.7 mmol) and NMO (0.35 g, 2.9 mmol, 50% aqueous solution) in acetone:water (3:1, 10 mL), OsO_4 (five drops, 0.04N solution in toluene) was added and stirred for 12 h at room temperature in darkness. Excess solid $NaHSO_3$ (100 mg) was added, stirred for 20 min, diluted with water (50 mL) and extracted in ethyl acetate (3×25 mL). The combined ethyl acetate layers were washed with brine (50 mL) and dried (Na_2SO_4). Evaporation of solvent under reduced pressure and purification of residue by column chromatography (60–120 mesh Si-gel, ethyl acetate:pet. ether 2:3) gave the diol **18** (0.68 g) in 88% yield as a syrup. $[\alpha]_D = -113.4$ (*c* 0.7, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.42 (m, 9H, CH_3), 1.80–2.40 (m, 6H, -OAc, H-5a,5b,6), 3.05 (t, 1H, $J_{1,6}$ 5.9 $J_{1,2}$ 4.2 Hz, H-1), 3.65 (t, 1H, $J_{5'a,5'b}$ 8.4, $J_{5'a,4'}$ 7.5 Hz, H-5′a), 3.82–3.86 (m, 1H, H-4), 4.00–4.28 (m, 4H, H-4′,5′b, -O$CH_2$$CH_3$), 4.32–4.44 (m, 1H, H-3), 5.05 (dd, 1H, $J_{2,3}$ 9.5 Hz, H-2); EIMS (%): 331 (M^+−15; 38), 228 (22), 183 (18), 165 (20), 101 (25), 43 (100).

3.8. Ethyl 2-acetoxy-3,4-dihydroxy-6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-(1S,2R,3R,4R,6R)-cyclohexane-1-carboxylate **19**

To a stirred solution of compound **16** (0.55 g, 1.7 mmol) and NMO (0.207 g, 1.7 mmol, 50% aqueous solution) in acetone:water (3:1, 10 mL), OsO_4 (five drops, 0.04N solution in toluene) was added, worked up and purified as described for **18** to give the diol **19** (0.52 g) in 88% yield as a syrup. $[\alpha]_D = -37.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20–1.41 (m, 9H, CH_3), 2.0–2.4 (m, 6H, -OAc, H-5a,5b,6), 2.5–2.65 (m, 1H, H-1), 3.49–3.69 (m, 1H, H-5′a), 3.86–4.28 (m, 6H, H-3,4,4′,5′b, -O$CH_2$$CH_3$), 5.28 (t, 1H, $J_{1,2}$ 10.7, $J_{2,3}$ 9.3, H-2); EIMS (%): 331 (M^+−15; 27), 271 (20), 165 (30), 91 (34), 108 (100), 43 (98).

3.9. Ethyl 2-acetoxy-3,4-dihydroxy-6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-(1R,2R,3R,4R,6R)-cyclohexane-1-carboxylate **20**

To a stirred solution of compound **17** (0.45 g, 1.44 mmol) and NMO (0.186 g, 1.58 mmol, 50% aqueous solution) in acetone:water (3:1, 10 mL), OsO_4 (five drops, 0.04N solution in

toluene) was added, worked up and purified as described for **18** to give the diol **20** (0.43 g) in 82% yield as a syrup. $[\alpha]_D = -8.8$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.20–1.46 (m, 9H, CH_3), 1.95–2.24 (m, 6H, H-5a,5b,6, -OAc), 2.92 (dd, 1H, $J_{1,2}$ 10.4, $J_{1,6}$ 2.8 Hz, H-1), 3.70 (dd, 1H, $J_{4',5'a}$, 7.6, $J_{5'a,5'b}$ 8.6 Hz, H-5′a), 3.85–4.24 (m, 6H, H-3,4,4′,5′b, -O$CH_2$$CH_3$), 5.39–5.43 (m, 1H, H-2); EIMS (%): 331 (M^+−15; 40), 228 (20), 183 (17), 165 (19), 165 (17), 137 (12), 101 (28), 72 (28), 43 (100).

3.10. Ethyl 6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,3,4-triacetoxy-(1S,2S,3S,4S,6R)-cyclohexane-1-carboxylate ***1***

Acetic anhydride (0.26 mL, 2.8 mmol) was added to a stirred solution of diol **18** (0.5 g, 1.44 mmol) in pyridine (3 mL) containing DMAP (0.017 g, 0.14 mmol), worked up and purified as described for **15** to gave **3** (0.52 g) in 85% yield. $[\alpha]_D = +6.6$ (*c* 0.45, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): 1.25 (t, 3H, *J* 7.2 Hz, O$CH_2$$CH_3$), 1.31 (s, 3H, $CH_{3(A)}$), 1.44 (s, 3H, $CH_{3(B)}$), 1.80–1.84 (m, 2H, H-5ax,5eq), 2.01, 2.07, 2.15 (3s, 9H, -OAc), 2.31 (ddt, 1H, $J_{4',6}$ 2.9, $J_{5a,6}$ 11.7, $J_{5e,6}$ 5.0, $J_{1,6}$ 11.5 Hz, H-6), 2.88 (dd, 1H, $J_{1,2}$ 2.9 Hz, H-1), 3.73 (dd, 1H, $J_{5'a,5'b}$ 8.5, $J_{4',5'a}$ 6.8 Hz, H-5′a), 4.00 (dd, 1H, $J_{4',5'b}$ 6.2 Hz, H-5′b), 4.11 (q, 2H, O$CH_2$$CH_3$), 4.20 (td, 1H, H-4′), 5.17 (ddd, 1H, $J_{4,5a}$ 11.2, $J_{4,5e}$ 5.9, $J_{3,4}$ 2.9 Hz, H-4), 5.24 (t, 1H, $J_{2,3}$ 4.2 Hz, H-3), 5.40 (t, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$): 14.24, 20.73, 20.74, 20.99, 25.52, 26.66, 27.19, 36.36, 46.13, 60.99, 67.71, 68.75, 69.48, 69.61, 76.79, 109.39, 169.92 (2C), 170.11, 170.18; FABMS (%): 453 (M+23; 5), 431 (M+1; 8), 415 (12), 373 (24), 313 (10), 221 (10), 207 (15), 147 (35), 123 (50), 109 (100); FAB-HRMS: calcd for (M^++1) $C_{20}H_{31}O_{10}$: 431.191723, found: 431.191376.

3.11. Ethyl 6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,3,4-triacetoxy-(1S,2R,3R,4R,6R)-cyclohexane-1-carboxylate ***2***

Acetic anhydride (0.217 mL, 2.31 mmol) was added to a stirred solution of diol **19** (0.4 g, 1.44 mmol) in pyridine (2.5 mL) containing DMAP (0.017 g, 0.14 mmol), worked up and purified as described for **15** to give **1** (0.58 g) in quantitative yield as a syrup. $[\alpha]_D = 40.3$ (*c* 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J* 7.1 Hz, -O$CH_2$$CH_3$), 1.30 (s, 3H, $CH_{3(A)}$), 1.39 (s, 3H, $CH_{3(B)}$), 1.66 (ddd, 1H, $J_{5a,6}$ 12.7, $J_{5a,5e}$ 15.1, $J_{4,5a}$ 2.3 Hz, H-5ax), 1.96 (dt, 1H, $J_{5e,6}$ 3.6, $J_{4,5e}$ 4.4 Hz, H-5eq), 1.99, 2.00, 2.14 (3s, 9H, OAc), 2.34 (tt, 1H, $J_{1,6}$ 11.7 Hz, H-6), 2.68 (t, 1H, $J_{1,2}$ 11.0 Hz, H-1), 3.60 (dd, 1H, $J_{4',5'a}$ 6.7, $J_{5'a,5'b}$ 8.2 Hz, H-5′a), 3.95 (dd, 1H, $J_{4',5'b}$ 6.2 Hz, H-5′b), 4.02 (dt, 1H, $J_{4',6}$ 3.2 Hz, H-4′), 4.17 (q, 2H, -O$CH_2$$CH_3$), 4.87 (dd, 1H, $J_{3,4}$ 3.0, $J_{2,3}$ 10.2 Hz, H-3), 5.48 (m, 1H, H-4), 5.51 (t, 1H, H-2); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.10, 20.59, 20.66, 21.06, 24.73, 25.94, 27.25, 35.57, 50.44, 61.21, 66.56, 68.29, 70.11, 72.94, 75.35, 109.25, 169.45, 170.09, 170.18, 171.38; FABMS (%): 431 (M+1; 28), 415 (37), 373 (100), 313 (28), 211 (25), 165 (35), 154 (32), 137 (59), 107 (38); FAB-HRMS: calcd for (M^++1) $C_{20}H_{31}O_{10}$: 431.191723, found: 431.191677.

3.12. Ethyl 6-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2,3,4-triacetoxy-(1R,2R,3R,4R,6R)-cyclohexane-1-carboxylate ***3***

Acetic anhydride (0.32 mL, 3.46 mmol) was added to a stirred solution of diol **20** (0.6 g, 1.73 mmol) in pyridine (5 mL) containing DMAP (0.021 g, 0.17 mmol), worked up and purified as described for **15** to give **16** (0.55 g) in 75% yield as a syrup. $[\alpha]_D = -10.8$ (*c* 0.50, $CHCl_3$); ^1H

NMR (500 MHz, $CDCl_3$): δ 1.27 (t, 3H, J 7.0 Hz, -OCH_2CH_3), 1.31 (s, 3H, $CH_{3(A)}$), 1.37 (s, 3H, $CH_{3(B)}$), 1.98, 2.01, 2.09 (3s, 9H, OAc), 2.02 (dt, 1H, $J_{5e,6}$ 3.0, $J_{5a,5e}$ 12.9, $J_{4,5e}$ 3.5 Hz, H-5eq), 2.17 (td, 1H, $J_{4a,6}$ 12.9, $J_{4,5a}$ 2.3 Hz, H-5ax), 2.23 (ddd, 1H, $J_{4',6}$ 7.6, $J_{1,6}$ 5.0 Hz, H-6), 3.11 (br. t, 1H, $J_{1,2}$ 5.9 Hz, H-1), 3.67 (dd, 1H, $J_{5'a,5'b}$ 8.2, $J_{4'5'a}$ 6.8 Hz, H-5′a), 3.83 (dd, 1H, $J_{4',5'b}$ 5.9 Hz, H-4), 4.05 (dd, 1H, H-5′b), 4.17 (m, 2H, -OCH_2CH_3), 5.26 (dd, 1H, $J_{2,3}$ 10.6 Hz, H-2), 5.57 (m, 1H, $J_{3,4}$ 3.5 Hz, H-4), 5.71 (dd, 1H, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): 13.96, 20.64, 20.81, 20.90, 23.31, 24.71, 25.97, 34.45, 43.84, 61.11, 66.65, 67.63, 68.43, 69.68, 75.41, 109.11, 169.02, 169.27, 170.06, 171.20; FABMS (%): 453 (M+23; 10), 431 (M+1; 8), 415 (M−15; 30), 373 (62), 165 (44), 147 (68), 109 (100); FAB-HRMS: calcd for (M^++1) $C_{20}H_{31}O_{10}$: 431.191723, found: 431.190130.

Acknowledgements

The authors T. Rajendra Prasad and M. H. V. Ramana Rao are thankful to CSIR, New Delhi, for the financial assistance.

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