Asymmetric synthesis of A-factor

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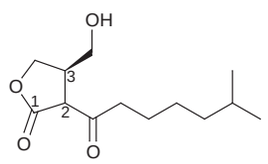
The synthesis of enantiopure A-factor ['autoregulatory factor'; (3*R*)-(−)-2-(6-methylheptanoyl)-3-hydroxymethylbutano-4-lactone] by the completely diastereoselective benzyloxymethylation of (4*R*)-3-(3-phenylpropanoyl)-4-isopropyloxazolidin-2-one is reported.

Introduction

The streptomycetes have a complex life cycle that includes the formation of multicellular mycelia, sporulation, and the production of an immense range of secondary metabolites usually produced at only specific periods during the organisms' life cycle. Understanding the control and regulation of prokaryotic cytodifferentiation[1] is necessary not only to maximise antibiotic production, but also to further understand how eukaryotic cytodifferentiation and cell communication evolved. A-factor **1** was first isolated by Khoklov from culture broth of



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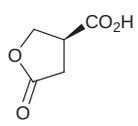

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Streptomyces griseus as a regulatory factor that induces antibiotic production and sporulation,[2,3] whose full stereostructure was revised by Mori in 1983 to (3*R*), with rapid epimerisation at C-2.[4] Mori reported a synthesis of enantiopure A-factor from enantiopure (*S*)-(−)-paraconic acid **2** in 15% yield,[5–7] which was obtained from *racemic* paraconic acid by repeated recrystallisation as its salt with enantiopure (*R*)-(1-phenylethyl)amine in 3% yield.[8] Mori later developed a synthesis of optically active paraconic acid based upon the mono-hydrolysis of 2-(acetoxymethyl)-3-phenylpropanoyl acetate using porcine pancreatic lipase in 62% ee.[9] An ingenious Johnson–Claisen rearrangement of a ketene acetal derived from a optically active allylic alcohol was used by Parsons to prepare optically active A-factor.[10] However, the unavailability of enantiopure substrate, coupled with partial racemisation of a later intermediate, resulted in the product A-factor possessing only 50% ee. We recently communicated[11] the asymmetric synthesis of enantiopure (*S*)-paraconic acid, based upon the completely diastereoselective benzyloxymethylation of the titanium enolate of (4*R*)-3-(3-phenylpropanoyl)-4-isopropyloxazolidin-2-one **3** to give **4** and we report here the full asymmetric synthesis of enantiopure A-factor.

Results and discussion

The preparation of (4*R*)-3-phenylpropanoyl-4-isopropyloxazolidin-2-one **3** was based upon literature procedures: valine was reduced to (2*R*)-2-amino-3-methylbutanol by borane generated by the dropwise addition of trimethylsilyl chloride to lithium borohydride.[12] Cyclisation with diethyl carbonate catalysed by base gave (4*R*)-4-isopropyloxazolidin-2-one.[13] Metalation with *n*-butyllithium and reaction with 3-phenylpropanoyl chloride gave **3** as a white crystalline solid.[14]

Evans has recently described the diastereoselective derivatisation of a series of 3-acylated oxazolidin-2-ones in which precomplexation of titanium(IV) chloride with the chiral auxiliary was followed by deprotonation with an amine base.[15] The enolate is held planar by complexation of titanium to the enolate oxyanion and oxazolidin-2-one carbonyl. Diastereofacially selective attack on the planar enolate–titanium complex is directed by the side chain on the oxazolidinone. In particular, Evans showed that (4*S*)-4-benzyl-3-propanoyloxazolidin-2-one could be hydroxymethylated or benzyloxymethylated with almost complete diastereoselectivity in high yield, and that (4*S*)-4-benzyl-3-(4-methoxycarbonylbutanoyl)oxazolidin-2-one could undergo a Michael reaction with propenonitrile with complete diastereoselectivity. We initially attempted to hydroxymethylate or benzyloxymethylate the nor analogues (4*S*)-4-benzyl-3-(3-methoxycarbonylpropanoyl)- and (4*S*)-benzyl-3-(3-ethoxycarbonylpropanoyl)-oxazolidin-2-one, but obtained complex product mixtures. We therefore investigated the use of phenyl groups as carboxylate synthons; Sharpless has converted phenyl groups to carboxylic acids using catalytic ruthenium tetroxide generated *in situ* from ruthenium(III) chloride and periodic acid in a biphasic solvent system (CCl_4–CH_3CN–H_2O).[16] The need to subsequently oxidise a phenyl group to a free acid restricted the choice of oxazolidin-2-one to those not containing aromatic side chains. Treatment of **3** at 0 °C with titanium(IV) chloride in dry dichloromethane gave the titanium complex as a yellow slurry, which upon addition of diisopropylethylamine yielded a deep blood-red solution of the titanium enolate. Whilst this enolate could be diastereoselectively hydroxymethylated with 1,3,5-trioxane in moderate yield (*ca.* 50%), quenching with benzyloxymethyl chloride gave (4*R*)-3-[(2*S*)-2-benzyloxymethyl-3-phenylpropanoyl]-4-isopropyloxazolidin-2-one **4** (Scheme 1) as a white crystalline solid in 94% yield, whose relative stereostructure was confirmed by X-ray analysis (Fig. 1). We could not detect by NMR analysis any evidence for the diastereoisomer in the crude product mixture.

Reaction of **4** with ruthenium tetroxide gave complex mixtures, presumably due to benzyl side chain oxidation. Martín[17] has shown that the Sharpless procedure proceeds smoothly in the presence of acetate functionality, so the benzyloxy group was hydrogenated to give **5** which was transformed into the acetate **6** in near quantitative overall yield, then the phenyl functionality was readily converted into the free carboxylic acid **7** with ruthenium tetroxide in 65% yield. Lithium hydroperoxide[18] removal of the chiral auxiliary and acetate followed by acidification gave (*S*)-(−)-paraconic acid **2** as a white solid in 40% yield with an optical rotation comparable to or above that reported.

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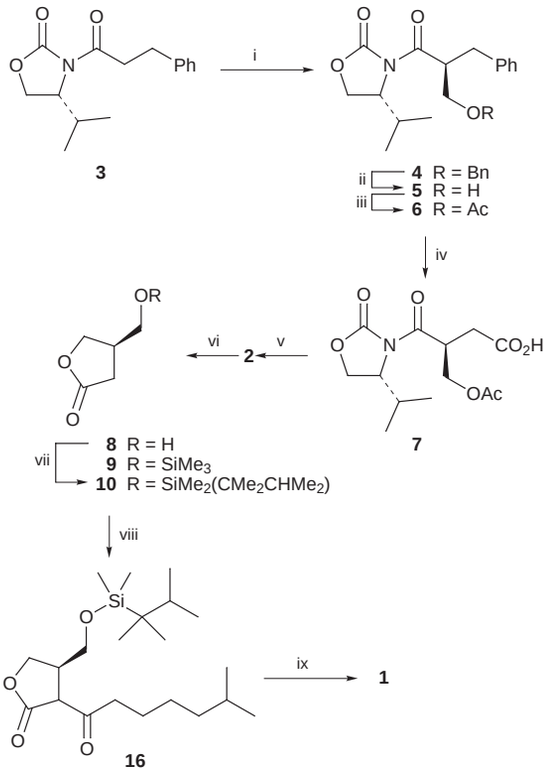
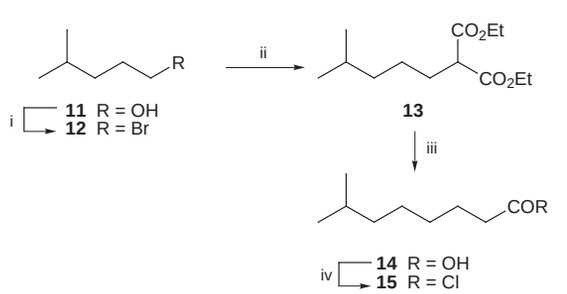


Scheme 1 *Reagents and conditions*: i, (a) $TiCl_4$, diisopropylethylamine; (b) $BnOCH_2Cl$; ii, H_2, Pd/C; iii, Ac_2O, pyridine; iv, $H_5IO_6/RuCl_3$; v, (a) LiOH, H_2O_2; (b) HCl (6 M); vi, $BH_3{\cdot}Me_2S$; vii, $(CMe_2CHMe_2)Me_2SiCl$, imidazole; viii, (a) $LiN(Me_3Si)_2$; (b) **15**; ix, Bu_4NF

Mori has converted enantiopure (*S*)-paraconic acid to A-factor *via* borane reduction of the carboxylic acid to the alcohol **8**, followed by protection as the trimethylsilyl ether **9**. However, the protection proceeded in relatively low yield; the protecting group is very labile, and the intermediate alcohol **8** has a tendency to epimerise.[6] We therefore decided to use the less labile (1,1,2-trimethylpropyl)dimethylsilyl (thexyldimethylsilyl) protecting group. Reduction of (*S*)-(−)-paraconic acid **2** using borane–dimethyl sulfide complex gave the desired alcohol **8** in 60% yield, which was purified by flash chromatography rather than distillation to avoid epimerisation.[6] Protection with (1,1,2-trimethylpropyl)dimethylsilyl chloride and imidazole to give **10** proceeded in much higher yield (87%) than that reported for trimethylsilyl protection (52%). The acyl group was prepared as follows: 4-methylpentanol **11** was converted to 1-bromo-4-methylpentane **12** using carbon tetrabromide and triphenylphosphine (Scheme 2).[19] Malonate extension gave



Scheme 2 *Reagents and conditions*: i, CBr_4, PPh_3; ii, diethyl malonate, NaH; iii, (a) NaOH; (b) HCl; iv, $SOCl_2$

diester **13**, which after hydrolysis and decarboxylation gave 6-methylheptanoic acid **14**,[20] which was reacted with thionyl chloride to give 6-methylheptanoyl chloride **15**[21] in 32% overall yield. Treatment of silyl ether **10** with lithium bis(trimethylsilyl)amide, then with 6-methylheptanoyl chloride **15**, gave silyl ether **16**. Cleavage of the silyl ether **16** with tetra-*n*-butylammonium fluoride gave A-factor **1** in 43% overall yield from the silyl ether **10**. Comparison of the observed optical rotation with that in the literature indicated that the A-factor produced was optically pure.

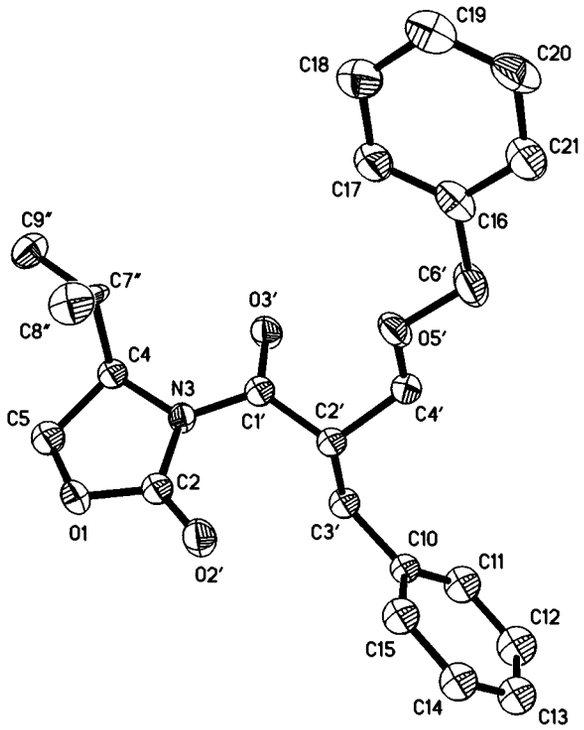


Fig. 1 Crystal structure of **4**

Experimental

Materials and general methods

Unless otherwise stated all chemicals were purchased from Aldrich Chemical Company Ltd, Lancaster Synthesis or Sigma Chemical Company Ltd. Benzyloxymethyl chloride was purchased from Tokyo Kasei Organic Chemicals through Fluorochem Ltd. Dry *N*,*N*-dimethylformamide was purchased from Aldrich. 'Hexanes' refers to the bp 40–60 °C distillation fraction of petroleum spirit. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Melting points were determined on a Koffler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 298 spectrophotometer as solutions in the specified solvent, neat as films between salt disks or as KBr disks. The following abbreviations were used: s = strong, m = medium, w = weak and br = broad. NMR spectra were recorded on a Bruker ARX-250 spectrometer in $CDCl_3$, proton spectra at 250 MHz (internal Me_4Si) and ^{13}C spectra at 62.9 MHz, with *J* values given in Hz. Carbon NMR spectra were proton decoupled, multiplicities being determined by performing DEPT experiments at 90 and 135°. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, sept = septet, m = multiplet and br = broad. Optical rotation measurements were carried out at room temperature (*ca.* 22 °C) using a Perkin-Elmer 141 polarimeter in the solvent specified; the values are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on a Kratos Concept H double focusing mass spectrometer using either electron impact (EI) at 70 eV and 170 °C, fast atom bombardment (FAB) at 6 kV using 3-nitrobenzyl alcohol (NBA) as the matrix and xenon gas, or chemical ionisation (CI).

(4*R*)-3-[(2*S*)-2-Benzyloxymethyl-3-phenylpropanoyl]-4-isopropyloxazolidin-2-one 4

To an ice-cooled solution of **3**[14] (4.0 g, 15.3 mmol) in dry dichloromethane (50 cm^3) under nitrogen was added titanium(IV) chloride (1.8 cm^3, 16.4 mmol). To the resulting yellow slurry after a 5 min delay diisopropylethylamine was added and the resulting blood-red solution stirred for 1 h at 0 °C. Benzyl chloromethyl ether (4.8 cm^3, 34.5 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature, then quenched by careful addition of saturated aqueous ammonium chloride (40 cm^3), stirred for 10 min and the organic layer separated. The aqueous layer was re-extracted with dichloromethane (2 × 30 cm^3) and the combined organic phases dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography [hexanes–diethyl ether (4:1)] furnished *the title compound* as a white solid (5.47 g, 94%), mp 72–74 °C; $[\alpha]_D$ −57.40 (*c* 1.22 in $CHCl_3$) (Found: C, 72.25; H, 7.2; N, 3.75. $C_{23}H_{27}NO_4$ requires C, 72.4; H, 7.1; N, 3.7%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3000–2890br m, 1780s, 1700s, 1390m, 1200m, 1150m, 900w; δ_H 7.30 (10 H, m, Ar-*H*), 4.55 (1 H, m, −C*H*CH_2Ph), 4.71 (2 H, d, *J* 4.7, −OCH_2Ph), 4.30 (1 H, m, −C*H*N), 4.05 (1 H, dd, *J* 3.0 and 9.0, −C*H*HOCO−), 3.95 (1 H, dd, *J* 8.5 and 8.9, −CH*H*OCO−), 3.78 (1 H, dd, *J* 7.5 and 9.1, −C*H*HOBn), 3.64 (1 H, dd, *J* 4.7 and 9.2, −CH*H*OBn), 2.96 (1 H, dd, *J* 8.1 and 13.4, −CHC*H*HPh), 2.83 (1 H, dd, *J* 7.3 and 13.4, −CHCH*H*Ph), 2.30 (1 H, d sept, *J* 4.1 and 6.9, −C*H*Me_2), 0.84 (3 H, d, *J* 7.0, −CH*Me*Me), 0.76 (3 H, d, *J* 7.0, −CHMe*Me*); δ_C 174.5 (s), 154.1 (s), 139.1 (s), 138.5 (s), 129.6 (d), 128.8 (d), 128.7 (d), 128.4 (d), 128.1 (d), 128.0 (d), 126.9 (d), 73.5 (t), 71.2 (t), 63.7 (t), 58.9 (d), 45.6 (d), 35.3 (t), 28.9 (d), 18.3 (q), 15.1 (q); *m*/*z* (EI) 381.194 06 ($C_{23}H_{27}NO_4$ requires 381.194 11), 381 (5.0%), 273 (14), 184 (24), 171 (13), 143 (38), 117 (12), 91 (100), 55 (9).

X-Ray crystal determination of 4

$C_{23}H_{27}NO_4$, M = 381.46, orthorhombic, space group $P2_12_12_1$, a = 6.272(5), b = 9.88(2), c = 33.845(5) Å, V = 2097(4) $Å^3$, T = 298 K (by least-squares refinement on diffractometer angles for 14 centred reflections in the range 4.8 < θ < 11.0°), Z = 4, D_c = 1.208 Mg m^{-3}, μ(Mo-Kα) = 0.082 mm^{-1}, colourless plate, crystal dimensions 0.48 × 0.18 × 0.07 mm.

Data were measured on a Siemens P4 diffractometer, graphite monochromated Mo-Kα radiation (λ = 0.7107 Å) using an ω scan technique. Three standard reflections monitored every 100 scans showed no significant variation in intensity, and the reflections were corrected for Lorentz and polarisation effects. 2135 data were measured (2.7 < θ < 22.5°), with 1932 independent reflections (merging R_{int} = 0.021) and 1128 having $F > 2\sigma(F)$ were regarded as observed. No corrections for absorption or crystal decay were required. The structure was solved by direct methods using the program SHELXTL-PC[22] and refined by full-matric least-squares on F^2 using the program SHELXL93.[23] Due to weak data and a low data-to-parameters ratio, carbon atoms C2, C2′, C3′, C4, C5 and C10 to C15 were refined with isotropic displacement parameters. All hydrogen atoms were included in calculated positions (C–H = 0.96 Å, U_{iso} = 0.08 $Å^2$) using a riding model. Full-matrix least-squares based on F^2 gave $R1$ = 0.0734, $wR2$ = 0.170 for all data, S = 1.041 for 169 parameters (R factors defined in ref. 23), weighting scheme $w = 1/[\sigma^2(F_o^2) + (0.0586P)^2 + 1.10P]$, where $P = [max(F_o^2, 0) + 2F_c^2]/3$ gave satisfactory analyses, maximum Δ/σ = 0.021. The final ΔF synthesis showed peaks of 0.41 and −0.20 e $Å^{-3}$. Displacement parameters are shown at the 30% probability level, H atoms are omitted for clarity. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/207.

(4*R*)-3-[(2*S*)-2-Hydroxymethyl-3-phenylpropanoyl]-4-isopropyloxazolidin-2-one 5

A mixture of **4** (9.4 g, 2.5 mmol) and palladium on carbon (2.0 g, 5% Pd/C) in ethyl acetate (100 cm^3) containing a catalytic amount of hydrochloric acid was stirred under an atmosphere of dihydrogen for 4 h at room temperature before being filtered through Celite and concentrated *in vacuo* to furnish *the title alcohol* as a white solid (7.15 g, 99%), mp 85–87 °C; $[\alpha]_D$ −118.7 (*c* 0.55 in $CHCl_3$) (Found: C, 65.8; H, 7.4; N, 5.0. $C_{16}H_{21}NO_4$ requires C, 66.0; H, 7.3; N, 4.8%); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3485m, 2950m, 1780s, 1690s, 1370m, 750 (m), 700 (m); δ_H 7.25 (5 H, m, Ar-*H*), 4.39 (2 H, m, -CH_2OH), 4.10 (2 H, m, −C*H*NCO− and −C*H*CH_2OH), 3.85 (2 H, m, −CH_2OCON−), 3.05 (1 H, dd, *J* 5.6 and 13.2, −C*H*HPh), 2.90 (1 H, dd, *J* 5.6 and 13.4, −CH*H*Ph), 2.55 (1 H, br s, −O*H*), 2.39 (1 H, m, −C*H*Me_2), 0.91 (3 H, d, *J* 7.2), 0.88 (3 H, d, *J* 7.2); δ_C 175.5 (s), 154.5 (s), 138.9 (s), 129.5 (d), 128.9 (d), 126.9 (d), 63.9 (t), 63.8 (2 C, d), 59.2 (d), 47.4 (d), 34.9 (t), 29.0 (d), 18.3 (q), 15.1 (q); *m*/*z* (EI) M^+ 291.147 06 ($C_{16}H_{21}NO_4$ requires 291.148 39), 291 (3.2%), 144 (96), 131 (61), 116 (24), 91 (100), 78 (12), 65 (11).

(4*R*)-3-[(2*S*)-2-Acetoxymethyl-3-phenylpropanoyl]-4-isopropyloxazolidin-2-one 6

To a stirred solution of **5** (4.7 g, 16.1 mmol) in dichloromethane (10 cm^3) was added pyridine (5.0 cm^3, 61.8 mmol) and acetic anhydride (5.0 cm^3, 53.0 mmol) and the mixture stirred at room temperature for 24 h before being quenched with hydrochloric acid (30 cm^3; 2 M) and the aqueous phase extracted with dichloromethane (3 × 30 cm^3). The combined organic phases were dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography [hexanes–diethyl ether (2:1)] yielded *the title compound* as a colourless oil (5.3 g, 99%); $[\alpha]_D$ −72.2 (*c* 1.09 in $CHCl_3$); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3000m, 1780s, 1740s, 1700s, 1380m, 1220m, 1100w, 1050w; δ_H 7.22 (5 H, m, Ar-*H*), 4.55 (1 H, m, −C*H*NCO−), 4.30 (3 H, m, −CH_2OAc −C*H*CH_2Ph), 4.10 (1 H, dd, *J* 2.8 and 9.1, −C*H*HOCO−), 4.00 (1 H, dd, *J* 2.8 and 8.7, −CH*H*OCO−), 2.97 (1 H, dd, *J* 5.6 and 13.4, −C*H*HPh), 2.79 (1 H, dd, *J* 5.9 and 13.4, −CH*H*Ph), 2.31 (1 H, m, −C*H*Me_2), 1.96 (3 H, s, −OAc), 0.88 (3 H, t, *J* 6.7), 0.85 (3 H, t, *J* 6.7); δ_C 173.7 (s), 170.8 (s), 154.0 (s), 138.1 (s), 129.5 (d), 128.9 (d), 127.1 (d), 64.9 (t), 63.8 (t), 59.0 (d), 44.4 (d), 35.4 (t), 29.4 (d), 18.2 (q), 15.1 (q); *m*/*z* (EI) M^+ 333.157 65, ($C_{18}H_{23}NO_5$ requires 333.159 07), 333 (0.3%) 273 (36), 169 (7), 144 (100), 131 (14), 117 (21), 91 (20).

(4*R*)-3-[(2*S*)-2-Acetoxymethyl-3-carboxypropanoyl]-4-isopropyloxazolidin-2-one 7

To a solution of **6** (5.2 g, 15.6 mmol) in water (50 cm^3), acetonitrile (30 cm^3) and carbon tetrachloride (30 cm^3) was added periodic acid (51.0 g, 224 mmol) followed by ruthenium(III) chloride trihydrate (0.125 g, 0.48 mmol) and the mixture stirred vigorously to ensure mixing of the phases for 6 h keeping the temperature below 40 °C. Diethyl ether (100 cm^3) was added carefully, the phases separated, and the aqueous phase re-extracted with a further portion of ether (2 × 75 cm^3). The combined organic phases were dried (sodium sulfate) and filtered through Celite before being concentrated *in vacuo*. Flash chromatography [diethyl ether–hexanes (2:1)] gave *the title acid* as a colourless oil (3.1 g, 65%); $[\alpha]_D$ −41.3 (*c* 1.21 in $CHCl_3$); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3200–2950m, 1780s, 1740s, 1710s, 1380m, 1210m; δ_H 10.60 (1 H, s, −CO_2H), 4.34 (4 H, m, −OCH_2-CHN− and −CH_2OAc), 4.08 (2 H, m, −C*H*CH_2CO_2H and −C*H*NCO−), 2.85 (1 H, dd, *J* 17.4 and 7.2, −C*H*HCO_2H), 2.42 (1 H, dd, *J* 17.4, 13.5, −CH*H*CO_2H), 2.15 (1 H, m, −C*H*Me_2), 1.90 (3 H, s, −OAc), 0.77 (3 H, t, *J* 6.7), 0.74 (3 H, d, *J* 6.7); δ_C 177.1 (s), 172.6 (s), 171.1 (2 C, 2 × s), 154.3 (s), 64.4 (t), 64.2 (t), 58.9 (d), 39.6 (d), 33.1 (t), 28.9 (d), 21.0 (q), 18.1 (q), 15.1 (q); *m*/*z* (EI) M^+ 301.116 15 ($C_{13}H_{19}NO_7$ requires 301.117 31), MH^+ 302 (0.7%), 301 (0.2), 258 (4), 241 (25), 196 (12), 173 (25), 131 (33), 113 (29), 86 (100), 69 (9), 55 (13).

(3*S*)-3-Carboxybutano-4-lactone [(*S*)-(−)-paraconic acid] 2

To a degassed solution of **7** (4.1 g, 13.6 mmol) in water (30 cm^3) and tetrahydrofuran (90 cm^3) under nitrogen was added hydrogen peroxide (100 vol; 10.0 cm^3, 89.1 mmol) followed after 5 min by lithium hydroxide (1.3 g, 5.4 mmol) and the reaction mixture stirred at room temperature for 48 h. Hydrochloric acid (50 cm^3, 6 M) was then added and stirring continued for a further 36 h. Tetrahydrofuran was removed *in vacuo* and the reaction mixture saturated with sodium chloride before being extracted with ethyl acetate (3 × 75 cm^3), the combined organic phases dried (sodium sulfate) and concentrated *in vacuo*. Flash chromatography [diethyl ether–hexanes (3:1)] gave (*S*)-paraconic acid **2** as a white solid (220 mg, 40%), mp 55–57 °C (lit.,[6] 57–58 °C); $[\alpha]_D$ −60.0 (*c* 2.1 in MeOH) [lit.,[6] −59.6 (*c* 0.614 in MeOH)]; $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3000br m, 1785m, 1710m; δ_H 9.40 (1 H, s, −CO_2H), 4.30 (2 H, m, −CH_2OCO−), 3.35 (1 H, m, −$CH$$CO_2$H), 2.74 (2 H, m, −CH$CH_2$CO−); δ_C 176.7 (s), 174.0 (s), 70.4 (t), 40.8 (d), 31.7 (t); *m*/*z* (EI) M^+ 130.026 61 ($C_5H_6O_4$ requires 130.026 94), 130 (4.6%), 113 (3), 102 (25), 100 (16), 86 (18), 71 (40), 55 (100).

(3*S*)-(−)-3-Hydroxymethylbutano-4-lactone 8

The method of Mori was used.[6] To a stirred ice-cooled solution of **2** (750 mg, 5.7 mmol) in dry tetrahydrofuran (10 cm^3) under nitrogen was added dropwise borane–dimethyl sulfide (0.9 cm^3, 9.5 mmol) and the mixture stirred for 2 h before the reaction was quenched with methanol (5 cm^3) and concentrated *in vacuo* below 30 °C. Flash chromatography [hexanes–ethyl acetate (1:2)] gave the title alcohol **8** as a colourless oil (400 mg, 60%); $[\alpha]_D$ −42.4 (*c* 6.8 in $CHCl_3$) [lit.,[6] −46.3 (*c* 1.224 in $CHCl_3$)]; ν_{max}(neat)/cm^{-1} 3400br m, 2900m, 1760s, 1190m; δ_H 4.44 (1 H, dd, *J* 9.4 and 1.5, −C*H*HOCO−), 4.24 (1 H, dd, *J* 9.4 and 4.0, −CH*H*OCO−), 3.68 (2 H, m, −CH_2OH), 2.78 (1 H, m, −C*H*CH_2OH), 2.64 (1 H, dd, *J* 17.6 and 8.8, −C*H*HCO−), 2.40 (1 H, dd, *J* 17.6 and 5.7, −CH*H*CO−); δ_C 178.6 (s), 72.2 (t), 63.3 (t), 37.4 (d), 31.3 (t); *m*/*z* (EI) M^+ 116.047 35 ($C_5H_8O_3$ requires 116.047 82), 116 (4.2%), 98 (8), 86 (10), 74 (54), 57 (100).

(3*R*)-(−)-3-[Dimethyl(1,1,2-trimethylpropyl)siloxymethyl]-butano-4-lactone 10

To a solution of alcohol **8** (310 mg, 2.7 mmol) in *N*,*N*-dimethylformamide (5 cm^3) was added imidazole (0.6 g, 8.8 mmol) followed after a 10 min delay by dimethyl(1,1,2-trimethylpropyl)silyl chloride (0.8 cm^3, 4.0 mmol) and the reaction mixture stirred at room temperature for 24 h before addition of dichloromethane (20 cm^3). The organic phase was washed with water (3 × 10 cm^3), dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography [hexanes–diethyl ether (12:1)] gave *the title compound* as a colourless oil (0.60 g, 87%); $[\alpha]_D$ −24.5 (*c* 0.92 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2980s, 1780s, 1460m, 1250m, 830m; δ_H 4.28 (1 H, dd, *J* 9.1 and 7.5, −C*H*HOCO−), 4.08 (1 H, dd, *J* 9.1 and 8.9, −CH*H*OCO−), 3.52 (2 H, m, −CH_2OSi), 2.64 (1 H, m, −C*H*CH_2OSi), 2.47 (1 H, dd, *J* 17.6 and 8.8, −C*H*HCOO−), 2.28 (1 H, dd, *J* 17.6 and 6.3, −C*H*HCOO−), 1.51 (1 H, sept, *J* 6.9, −C*H*Me_2), 0.75 (12 H, m, −CMe_2CHMe_2), 0.00 (6 H, s, −SiMe_2); δ_C 177.9 (s), 71.2 (t), 63.7 (t), 37.8 (d), 35.3 (d), 31.4 (t), 25.4 (s), 20.9 (2 C, q), 19.2 (2 C, q), −3.5 (2 C, q); *m*/*z* (FAB) MH^+ 259.172 95 ($C_{13}H_{26}O_3Si$ requires MH 259.174 63), 259 (5%), 173 (44), 159 (100), 137 (31).

1-Bromo-4-methylpentane 12

To an ice-cooled solution of 4-methylpentanol **11** (5.0 g, 49 mmol) and carbon tetrabromide (20.3 g, 61.2 mmol) in dichloromethane (50 cm^3) was added carefully in portions triphenylphosphine (19.2 g, 73.4 mmol) and, once the exothermic reaction was complete, the mixture stirred for 10 min. Light petroleum (bp 40–60 °C; 50 cm^3) was added, the precipitate removed by filtration, the filtrate concentrated *in vacuo* and the product distilled to give *the title bromide* **12** as a colourless liquid (6.75 g, 77%); bp 60–62 °C (10 mmHg); ν_{max}(neat)/cm^{-1} 2950m, 1470m, 1340m; δ_H 33.9 (2 H, t, *J* 6.9, −CH_2Br), 1.86 (2 H, m, −CH_2CH_2Br), 1.58 (1 H, sept, *J* 6.6, −C*H*Me_2), 1.31 (2 H, m, −CH_2CHMe_2), 0.90 (6 H, d, *J* 6.6, 2 × Me); δ_C 37.8 (t), 34.7 (t), 31.2 (t), 27.9 (d), 23.0 (2 C, q).

Diethyl (4-methylpentyl)malonate 13

To an ice-cooled suspension of sodium hydride (60% w/w dispersion in mineral oil; 1.5 g, 37.5 mmol) in dry *N*,*N*-dimethylformamide (30 cm^3) was added diethyl malonate (5.5 cm^3, 32.5 mmol), followed after a 15 min delay by bromide **12** (5.8 g, 32.4 mmol), and the reaction mixture stirred for 2 h at room temperature before being quenched with water (100 cm^3), extracted with dichloromethane (2 × 100 cm^3) and the combined organic phases dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography [hexanes–diethyl ether (12:1)] gave *the title compound* as a colourless oil (5.6 g, 70%); ν_{max}(neat)/cm^{-1} 2950m, 1750s, 1470s, 1370m; δ_H 4.20 (4 H, q, *J* 7.2, −OCH_2Me), 3.32 [1 H, t, *J* 7.5, −C*H*$(CO_2Et)_2$], 1.88 [2 H, q, *J* 7.8, −CH_2-CH$(CO_2Et)_2$], 1.54 (1 H, sept, *J* 6.6, −C*H*Me_2), 1.25 (10 H, m, −OCH_2CH_3 and −CH_2CH_2CH−), 0.85 (6 H, d, *J* 6.6, −CHMe_2); δ_C 169.9 (s), 61.6 (t), 52.4 (d), 38.8 (t), 29.3 (t), 25.5 (t), 28.0 (d), 22.8 (t), 14.4 (2 C, q); *m*/*z* (EI) M^+ 244.167 46 ($C_{13}H_{24}O_4$ requires 244.168 96).

6-Methylheptanoic acid 14

To a solution of **13** (5.8 g, 25 mmol) in water (60 cm^3) and tetrahydrofuran (30 cm^3) was added sodium hydroxide (10.0 g, 250 mmol) and the reaction mixture stirred for 48 h, when it was acidified (pH 1) with hydrochloric acid (6 M) and then heated at reflux for a further 36 h. The mixture was saturated with sodium chloride and extracted with ethyl acetate (3 × 75 cm^3), and the combined organic fractions dried (sodium sulfate) and concentrated *in vacuo*. Flash chromatography [hexanes–diethyl ether (9:1)] gave the title acid **14** (2.3 g, 71%); ν_{max}(neat)/cm^{-1} 3000br s, 1700s; δ_H 11.76 (1 H, br s, −CO_2H), 2.35 (2 H, t, *J* 7.5, −CH_2CO_2H), 1.63 (3 H, m, −CH_2C*H*Me_2 and −$CH_2CH_2CH_2$−), 1.22 (2 H, m, −CH_2CHMe_2), 0.90 (6 H, d, *J* 6.6, −CHMe_2); δ_C 181.0 (s), 38.6 (t), 34.8 (t), 28.1 (d), 22.9 (t), 22.8 (2 C, q).

6-Methylheptanoyl chloride 15

Thionyl chloride (1.0 cm^3, 14 mmol), acid **14** (0.70 g, 4.8 mmol) and a catalytical amount of *N*,*N*-dimethylformamide were combined and stirred at room temperature for 24 h, and the excess thionyl chloride removed *in vacuo*. Kugelrohr distillation furnished the title acid chloride as a colourless liquid (0.67 g, 85%); ν_{max}(neat)/cm^{-1} 2900s, 1800s, 1470w, 1370w; δ_H 2.89 (2 H, t, *J* 7.2, −CH_2COCl), 1.70 (2 H, quin, *J* 7.2, −CH_2CH_2COCl), 1.54 (1 H, sept, *J* 6.6, −C*H*Me_2), 1.35 (2 H, m), 1.20 (2 H, m), 0.87 (6 H, d, *J* 6.6, −CHMe_2); δ_C 173.9 (s), 47.1 (t), 38.3 (t), 27.8 (d), 26.2 (t), 25.3 (t), 22.5 (2 C, q).

(3*R*)-(−)-3-Hydroxymethyl-2-(6-methylheptanoyl)butano-4-lactone (A-Factor) 1

To a solution of protected alcohol **10** (460 mg, 1.8 mmol) in dry tetrahydrofuran (20 cm^3) under nitrogen at −78 °C was added lithium bis(trimethylsilyl)amide (1.0 M in THF; 4.4 cm^3, 4.4 mmol) followed after a 20 min delay by acid chloride **15** (450 mg, 2.8 mmol), and the mixture stirred for 3 h, the reaction mixture being allowed to warm to room temperature. The reaction mixture was quenched with sodium hydrogen carbonate (20 cm^3, saturated solution), extracted with diethyl ether (3 × 30 cm^3) and the combined organic fractions dried (magnesium sulfate) and concentrated *in vacuo*. Flash chromatography [hexanes–diethyl ether (13:1)] gave (3*R*)-3-[dimethyl(1,1,2-trimethylpropyl)siloxymethyl]-2-(6-methylheptanoyl)butano-4-lactone **16** as a colourless oil (310 mg, 45%); δ_H 4.30 (1 H, dd, *J* 9.1 and 8.8, −C*H*HOCO−), 4.03 (1 H, dd, *J* 8.8 and 6.6, −CH*H*OCO−), 3.53 (3 H, m, −CH_2OSi and −COC*H*CO−), 3.10 (1 H, m, −C*H*CH_2OSi), 2.87 (1 H, dt, *J* 17.6 and 7.5, −C*H*HCO−), 2.52 (1 H, dt, *J* 17.6, 7.2, −CH*H*CO), 1.51 (4 H,

m, −COCH$_2$CH_2CH_2−), 1.10 (4 H, m, −CH_2CHMe$_2$ and −CHMe$_2$), 0.77 (18 H, m), 0.00 (6 H, m, −SiMe_2); δ_C 203.5 (s), 173.2 (s), 69.9 (t), 62.3 (t), 55.3 (d), 43.3 (t), 39.9 (d), 39.3 (t), 34.8 (d), 28.5 (d), 27.4 (t), 25.8 (t), 25.4 (s), 23.2 (2 C, q), 20.9 (2 C, q), 19.1 (2 C, q), −3.3 (2 C, q).

Tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran; 5.0 cm^3, 5.0 mmol) and **16** (300 mg, 0.78 mmol) were combined and stirred at room temperature for 24 h. Ammonium chloride (10 cm^3; saturated solution) was added and the aqueous phase extracted with diethyl ether (3 × 10 cm^3). The combined organic phases were dried (sodium sulfate) and concentrated *in vacuo*. Flash chromatography [hexanes–diethyl ether (1:2)] gave A-factor as a colourless oil (81 mg, 43%); $[a]_D$ −16.3 (*c* 0.64 in $CHCl_3$) (lit.,[6] −13.1, *c* 1.18 in $CHCl_3$); $\nu_{max}(CH_2Cl_2)$/cm^{-1} 3400br m, 2950s, 1760s, 1380m, 1030w; δ_H 4.22 (1 H, m, −CHHOCO−), 3.94 (1 H, m, −CHHOCO−), 3.45 (3 H, m, −CH_2OH and COCHCO−), 2.98 (2 H, −CHCH$_2$OH), 2.72 (1 H, dt, *J* 17.9 and 7.2, −CHHCO−), 2.41 (1 H, dt, *J* 17.9, 7.5, −CHHCO−), 1.30 (3 H, m, −CH$_2$CH_2CO− and CHMe$_2$), 1.00 (4 H, m, −CH_2CH_2CHMe$_2$), 0.63 (6 H, d, *J* 6.6, −CHMe_2); δ_C 202.8 (s), 174.6 (s), 68.8 (t), 61.3 (t), 54.6 (d), 42.2 (t), 39.3 (d), 38.7 (t), 27.5 (d), 26.9 (t), 23.5 (t), 20.1 (2 C, q); *m*/*z* (EI) M^+ 242.151 83 ($C_{13}H_{22}O_4$ requires 242.153 18), 242 (3.2%) 211 (40), 158 (21), 143 (41), 127 (59), 109 (92), 85 (100), 69 (26), 57 (85).

Acknowledgements

The authors thank Dr Gerald Griffith for assistance with NMR spectroscopy and Dr Graham Eaton for Mass Spectroscopy.

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Paper 7/08638E
Received 1*st December* 1997
Accepted 10*th March* 1998