Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 9, pp. 2551-2562, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00328-X

Chiral Carboxylic Acid Ligands Derived from Camphoric Acid

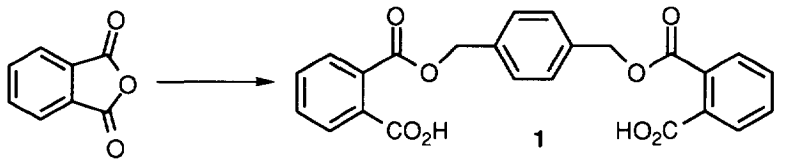
Mark G. Moloney*¶, Diana R. Paul¶, Russell M. Thompson†, and Emma Wright¶

¶ The Dyson Perrins Laboratory, University of Oxford, South Parks Rd, Oxford, OX1 3QY, U.K.
Email : mark.moloney@dpl.ox.ac.uk
† Associated Octel Company, Ellesmere Port, South Wirral, L65 4HF, U.K.

Abstract: Versatile and convenient preparations of chiral carboxylic acid ligands, derived from camphoric acid, are described, either by esterification of camphoric dichloride or by a regioselective opening of the corresponding anhydride by a variety of alcohols or diols.

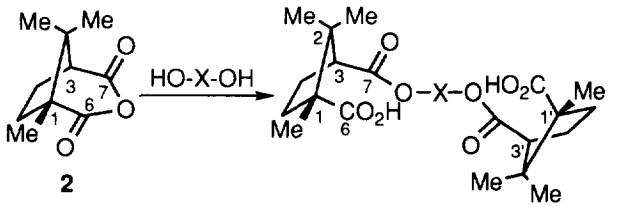
As part of a programme involving the study of the synthesis, characterisation and reactions of high oxidation state main group metal co-ordination complexes, in particular of lead(IV), we required a range of chiral ligands. Although guiding principles for the construction of ligands have been delineated for a variety of metal cations[1] including high oxidation state transition metal cations,[2,3] those for high oxidation state Group IV and V metals cations have not. The challenge for ligand design for this type of highly oxidising metal species lies in the identification of suitable electron donors which are also resistant to the oxidising potential of the metal cation, and which are organic soluble (the ready hydrolysis of, for example, lead tetraacetate enforces the use of non-aqueous solvents). We chose carboxylic acids as suitable ligands because of their well established[4] co-ordination with, and stability to, the Pb(IV) species, and have set about the design and construction of suitable compounds. Although the importance of simple carboxylic acids, both achiral[5] and chiral,[6,7] as ligands for a wide range of metal cations is well documented and of considerable current interest, methods for the preparation of chiral chelating carboxylates which are organic soluble are less so. Podal carboxylates for uranyl ion chelation in organic solvents, however, have recently been reported.[8]

We describe here a versatile and convenient preparation of both chiral monocarboxylic and C_2-symmetric[9] dicarboxylic acid ligands based upon a regioselective ring opening of camphoric anhydride, in which the nature and length of a spacer arm between the donor atoms of the ligand can be readily modified, or an alternative approach based upon the elaboration of camphoric acid dichloride. Camphor-based chiral auxiliaries in particular have received widespread application,[10,11] offering the advantages of chirality, inexpense and organic solubility, and recently have found use as ligands for a variety of metal complexes.[12] In a model study, the reaction of molten phthalic anhydride with 1,4-benzenedimethanol gave the diacid **1** in 31% yield, which could be easily purified by extraction into base followed by acidification and re-extraction into an organic solvent. This method, a modification of one which has been previously reported for the preparation of monoesters of phthalic anhydride,[13] provides a simple and convenient preparation of the diacid **1** which would allow preparation on a gram scale (Scheme 1).



Scheme 1

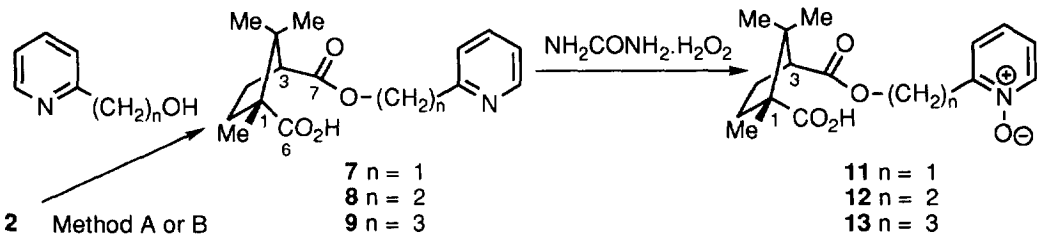
This ring opening reaction was then applied to enantiopure camphoric anhydride **2**, readily prepared from (1*R*,3*S*)-camphoric acid and refluxing thionyl chloride in 70% yield.[14] Fusion of a range of diols gave the corresponding diacids **3-6** in variable yields (15-65%) which were not optimised (Scheme 2), resulting from a highly regioselective ring opening at the least hindered C-7 carbonyl of the anhydride. Except for diacid **4**, for which a 3:1 inseparable mixture of isomers was obtained, only minor quantities of the other regioisomers (resulting from anhydride opening at C-6) were observed (<5-10%) in these reactions. The compounds, obtained as either hygroscopic oils or solids which were all highly soluble in organic solvents, could be readily purified using the base-acid extraction sequence outlined above. In the case of diester **3**, the regiochemistry of the anhydride opening was shown using HMBC spectroscopy,[15] in which the benzylic protons showed a correlation to carbonyl C-7, and the methine proton at C-3 a correlation with carbon C-2 as well as both of the geminal methyl substituents and C-7. This regioselectivity is consistent with the known opening of unsymmetrical anhydrides at the least hindered position, despite a possibly crowded angle of approach.[16,17] Although in some cases the yields were not high, the simplicity of the method enabled the convenient synthesis of chiral C_2-symmetric dicarboxylic ligands with varying spacing chain lengths.



	X	Yield(%)
3	-H_2C-C$_6H_4$-CH_2-	65
4	-CH_2CH_2-	15
5	-$(CH_2)_3$-	20
6	-$(CH_2)_4$-	40

Scheme 2

Ring opening of camphoric anhydride, using the conditions established above, with 2-hydroxyalkylpyridines gave the expected esters **7-9** (Scheme 3) in yields of up to 50% (Method A) again with a highly regioselective ring opening at C-7 (this was confirmed by HMBC or HQMC long range coupling analysis of **7** and **12** respectively). However, these yields were substantially improved (Method B) when the anhydride was opened with the corresponding alkoxide generated using sodium hydride as the base, although the regioselectivity in these cases was sometimes lower. Anhydride opening under these conditions with the relatively more hindered tosylamine derived from (1*R*,2*S*)-norephedrine[18] gave the corresponding product **10** in 36% yield. The pyridines **7-9** could be easily oxidised to the corresponding *N*-oxides **11-13** in yields of 53, 78 and 48% respectively by treatment with urea hydrogenperoxide.

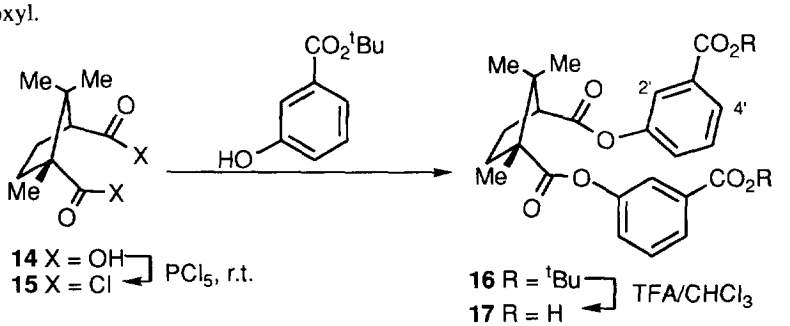


Compound	Yield(%)[a,b]	
	Method A	Method B
7	18:3	50:23
8	20	31
9	50	60:9
10	-	36

[a]Ratio of C-7 to C-6 ester; [b]Method A = anhydride **2**, alcohol, fusion at 100°C; Method B = alcohol/NaH then anhydride **2**, reflux

Scheme 3

The camphoric acid dichloride **15**, prepared from camphoric acid **14** and phosphorus pentachloride,[19] also proved to be a useful template for ligand construction, permitting the simultaneous manipulation of both carboxyl functionalities of the camphoric acid. Thus, treatment of **15** with *t*-butyl *m*-hydroxybenzoate (prepared from *m*-hydroxybenzoic acid and *N,N'*-dimethylformamide di-*t*-butyl acetal[20] in 56% yield) gave the diester **16** in 39% yield, and which could be readily purified by column chromatography. Deprotection with TFA/$CHCl_3$ to the corresponding diacid **17** occurred in quantitative yield. The corresponding *o*-derivative, however, could not be prepared under these conditions, presumably due to the additional steric hindrance at the phenolic hydroxyl.



Scheme 4

This methodology demonstrates that camphoric acid is a useful template for the preparation of enantiopure carboxylic acids, and the application of these compounds to main group organometallic chemistry is under active investigation in our laboratories.[21]

Experimental

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian Gemini (200MHz), Bruker AM-200 (200MHz), Bruker AM-500 (500MHz) and Bruker AMX-500 (500MHz) spectrometers.

Heteronuclear multiple bond correlation (HMBC) experiments were recorded on a Bruker AMX-500 (500MHz) spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Gemini and Bruker AM-200 (50.3MHz) and Bruker AM-500 (125.8MHz) spectrometers. Infra-red spectra were recorded using a Perkin-Elmer 1750 FT-IR spectrometer. Low resolution mass spectra were recorded on VG Micromass ZAB1F, VG Masslab 20-250 and VG BIO-Q spectrometers using ammonia desorption chemical ionisation (DCI), chemical ionisation (CI) or negative electrospray (ES^-) techniques. Gas chromatography mass spectra (GCMS) were recorded on a VG Trio-1 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, at the temperature stated. Microanalyses were performed by the microanalytical service of the Dyson Perrins Laboratory. Melting points were recorded on a Stuart Scientific SMP1 melting point device and are uncorrected. Short path distillations were performed using a horizontal Kugelrohr apparatus at 0.3mmHg.

1,1'-(Benzene-1,4-dimethyl)diphthalate **1**

Phthalic anhydride (1.00g, 6.75mmol) and benzene-1,4-dimethanol (0.47g, 3.37mmol) were heated together at 150°C[13] until a solid was obtained which was recrystallised from EtOAc to give the title compound **1** as a white solid (0.45g, 31%): m.p. 160-162°C (from EtOAc); ν_{max} (Nujol/cm^{-1}) 1714 (s), 1686 (s), 1600 (m), 1580 (m), 1490 (m), 1289 (s), and 1129 (s); δ_H (200MHz, $CDCl_3$) 5.30 (4H, s, 2x$C\underline{H}_2$), 7.44 (4H, s, benzenedimethyl-Ar$\underline{H}$), 7.55-7.67 (6H, m, Ar$\underline{H}$) and 7.76-7.80 (2H, m, Ar$\underline{H}$); δ_C (125.8 MHz, $CDCl_3$) 68.25 ($\underline{C}H_2$), 129.51, 129.64, 130.23, 132.15, 132.45 (Ar$\underline{C}$H), 133.46, 133.92, 137.22 (Ar$\underline{C}$), 169.69 (ester $\underline{C}$=O) and 170.47 (acid $\underline{C}$=O); *m/z* (Electrospray, ES^-) 435 (MH^+, 7%), 434 (30, M) and 433 (100, M-H).

(1R, 3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic anhydride **2** [22]

To a solution of (1*R*, 3*S*)-1,2,2-trimethylcyclopentane-1,3-dicarboxylic acid (10.00g, 49.94mmol) in CCl_4 (60ml) and DMF (1ml) at 40-50°C was added thionyl chloride (7.29ml, 99.88mmol) dropwise. The resulting solution was heated at reflux for 3 h. The cooled solution was poured onto ice (250ml) and left to stand overnight. The organic layer was then separated, washed with water (100ml) and the solvent was removed *in vacuo*. The resulting greenish solid was recrystallised from ethanol to give the title compound **2** as white needles (5.98g, 66%): m.p. 224-225°C (from EtOH), lit.[23] 222-223°C (from acetone); R_f 0.31 (DCM); $[\alpha]_D^{22}$ -0.90 (c=5.13 in $CHCl_3$) lit.[23] $[\alpha]_D^{22}$ -3.76 (c=0.60, benzene); ν_{max} (Nujol/cm^{-1}) 1804 (s), 1761 (s), 1180 (m), 1151 (w), 1129 (m), 1110 (w), 1042 (s), 982 (s) and 943 (m); δ_H (200MHz, $CDCl_3$) 1.01, 1.10, 1.28 (3x3H, 3xs, 3x$C\underline{H}_3$) 1.89-2.38 (4H, m, 2xC(4)H and 2xC(5)H) and 2.85 (1H, d, J = 6.5Hz, C(3)H); δ_C (50.3MHz, $CDCl_3$) 13.95, 20.02, 20.61 (3x$\underline{C}H_3$), 24.32 (C(4)), 33.36 (C(5)), 43.62 (C(2)), 53.76 (C(1)), 54.27 (C(3)) and 170.38, 173.04 (2x$\underline{C}$O); *m/z* (CI, NH_3, GCMS) 200 (MNH_4^+,100%), 183 (MH^+, 11), 172 (8), 155 (15), 138 (18), 137 (6) and 109 (10).

3,3'-(Benzene-1,4-dimethyl)di[(1R, 3S)-1,2,2-trimethylcyclopentane-1,3-dicarboxylate] **3**

Anhydride **2** (5.98g, 32.30mmol) and benzene-1,4-dimethanol (1.51g, 10.93mmol) were heated together at 150°C for 24 h.[13] The resulting solid was dissolved in EtOAc (50ml) and extracted with $NaHCO_3$ (sat. aq.) (3x50ml) and 3M NaOH (50ml). The combined aqueous layers were acidified (conc. HCl) and re-extracted with DCM (2x100ml). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give the title compound **3** as its monohydrate as a pale yellow foam (3.56g, 65%): m.p. 52-54°C; R_f 0.46 (EtOAc); (Found: C, 64.34; H, 7.70%. $C_{28}H_{38}O_8.H_2O$ requires C, 64.59; H, 7.74%.); $[\alpha]_D^{22}$ +10.9 (c=5.02, $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 3400-2800 (m, br), 1728 (s), 1699 (s), 1460 (w), 1379 (w), 1168 (s) and 1119 (m); δ_H

(500MHz, $CDCl_3$) 0.82, 1.24, 1.25 (3x6H, 3xs, 6x$C\underline{H}_3$), 1.49-1.54 (2H, m, 2xC(5)H), 1.80-1.88 (2H, m, 2xC(4)H), 2.17-2.26 (2H, m, 2xC(4)H), 2.50-2.57 (2H, m, 2xC(5)H), 2.85 (2H, t, J = 9.4Hz, 2xC(3)H), 5.10 (2H, d, J = 12.4Hz, 2xC(8)H), 5.16 (2H, d, J = 12.4Hz, 2xC(8)H) and 7.36 (4H, s, Ar$\underline{H}$); δ_C (125.8MHz, $CDCl_3$) 21.15, 21.56 (4x$\underline{C}H_3$), 22.57 (2xC(4)), 22.73 (2x$\underline{C}H_3$), 32.23 (2xC(5)), 46.82 (2xC(2)), 52.79 (2xC(3)), 56.15 (2xC(1)), 65.85 (2xC(8)), 128.50 (4xC(10)), 136.06 (2xC(9)), 173.60 (2xC(7)) and 181.99 (2xC(6)); *m/z* (DCI, NH_3) 503 (MH^+,5%), 320 (55), 303 (12), 200 (14), 183 (10), 155 (16), 138 (56) and 120 (100).

3,3'-(Ethylene-1,2-dioxy)di[(1R, 3S)-1,2,2-trimethylcyclopentane-1,3-dicarboxylate] **4**

Anhydride **2** (1.47g, 8.08mmol) and ethane-1,2-diol (0.17g, 2.69mmol) were heated together at 180°C for 24 h. The resulting brown solid was dissolved in EtOAc (30ml) and washed with 3M NaOH (3x15ml). The combined aqueous layers were acidified (conc. HCl) and re-extracted with DCM (3x50ml). The organic layers were then dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resulting brown oil was purified by silica chromatography (1:3 EtOAc:petrol, gradient to EtOAc). Those fractions which gave a yellow stain with bromocresol purple were combined to give the product **4** (3:1 mixture of regioisomers) as a hygroscopic white foam (0.17g, 15%): $[\alpha]_D^{22}$ +22.9 (c=1.19, $CHCl_3$); ν_{max} ($CDCl_3$/cm^{-1}) 3075 (br), 1731 (s), 1698 (s), 1460 (w), 1284 (m) and 1167 (m); δ_H (500MHz, $CDCl_3$) 0.84-0.95 (6H, m, 2x$C\underline{H}_3$), 1.05-1.42 (12H, m, 4x$C\underline{H}_3$), 1.50-1.57 (2H, m, 2xC(5)H), 1.80-1.90 (2H, m, 2xC(4)H), 2.15-2.26 (2H, m, 2xC(4)H), 2.52-2.59 (2H, m, 2xC(5)H), 2.79-3.00 (2H, m, 2xC(3)H), 4.22-4.38 (4H, m, 4xC(8)H); δ_C (50.3MHz, $CDCl_3$) 21.08, 21.43 (4x$\underline{C}H_3$), 22.30 (2xC(4)), 22.58 (2x$\underline{C}H_3$), 32.00 (2xC(5)), 46.71 (2xC(2)), 52.64 (2xC(3)), 56.06 (2xC(1)), 62.24 (2xC(8)), 174.05 (2xC(7)) and 182.64 (2xC(6)); *m/z* (Electrospray, ES^-) 425 ($M\text{-}H^-$); *m/z* (DCI, NH_3) 444 (MNH_4^+, 6%), 427 (MH^+, 4,), 262 (8), 245 (99), 227 (100), 201 (28), 183 (19), 181 (13), 155 (11), 137 (17), 136 (30) and 109 (49); Exact mass 449.2159. $C_{22}H_{34}O_8Na$ requires 449.2151.

3,3'-(Propylene-1,3-dioxy)di[(1R, 3S)-1,2,2-trimethylcyclopentane-1,3-dicarboxylate] **5**

Anhydride **2** (1.50g, 8.23mmol) and propane-1,3-diol (0.27g, 3.58mmol) were heated at 175°C for 24 h. The resulting brown solid was dissolved in EtOAc (30ml) and washed with $NaHCO_3$ (sat. aq.) (3x50ml). The aqueous layer was acidified (conc. HCl) and re-extracted into DCM (2x100ml). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo* to give a brown oil which was purified by silica chromatography (1:1 EtOAc:petrol, gradient to 3:1 EtOAc:petrol) to give the title compound **5** as a white hygroscopic foam (0.32g, 20%): R_f 0.26 (1:1 EtOAc:petrol); $[\alpha]_D^{22}$ +44.1 (c=0.98, $CHCl_3$); ν_{max} ($CDCl_3$/cm^{-1}) 3000 (br), 1728 (s), 1698 (s), 1173 (m) and 1126 (w); δ_H (500MHz, $CDCl_3$) 0.86 (6H, s, 2x$C\underline{H}_3$), 1.23-1.30 (12H, m, 4x$C\underline{H}_3$), 1.50-1.55 (2H, m, 2xC(5)H), 1.79-1.87 (2H, m, 2xC(4)H), 1.99-2.05 (2H, m, 2xC(9)H), 2.18-2.25 (2H, m, 2xC(4)H), 2.52-2.59 (2H, m, 2xC(5)H), 2.82 (2H, t, J = 9.4Hz, 2xC(3)H) and 4.15-4.25 (4H, m, 4xC(8)H); δ_C (50.3MHz, $CDCl_3$) 21.16, 21.44 (4x$\underline{C}H_3$), 22.34 (2xC(4)), 22.67 (2x$\underline{C}H_3$), 27.87 (C(9)), 32.03 (2xC(5)), 46.67 (2xC(2)), 52.73 (2xC(3)), 56.10 (2xC(1)), 60.94 (2xC(8)), 174.24 (2xC(7)) and 182.74 (2xC(6)); *m/z* (Electrospray, ES^-) 439 ($M\text{-}H^-$); *m/z* (DCI, NH_3) 458 (MNH_4^+,4%), 441 (MH^+, 2), 276 (4), 259 (60), 241 (100), 225 (6), 213 (4), 200 (20), 183 (7), 155 (8), 136 (12) and 109 (35); Exact mass 463.2286. $C_{23}H_{36}O_8Na$ requires 463.2307.

3,3'-(Butylene-1,4-dioxy)di[(1R, 3S)-1,2,2-trimethylcyclopentane-1,3-dicarboxylate] **6**

Anhydride **2** (1.67g, 9.14mmol) and butane-1,4-diol (0.28g, 3.05mmol) were heated together at 170°C for 10 h. The resulting brown solid was dissolved in EtOAc (30ml) and washed with $NaHCO_3$ (sat. aq.) (3x50ml). The combined aqueous layers were acidified (conc. HCl) and re-extracted with DCM (3x50ml) which was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The resulting brown oil was purified by silica chromatography (1:1 EtOAc:petrol, gradient to EtOAc). Those fractions which gave a yellow stain with bromocresol purple were combined to give the product **6** as a hygroscopic white foam (0.55g, 40%): $[\alpha]_D^{22}$ +28.9 (c=0.97, $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 2900 (br), 1726 (m), 1699 (s), 1284 (w), 1175 (m) and 1125 (w); δ_H (200MHz, $CDCl_3$) 0.84 (6H, s, 2xC$\underline{H}_3$), 1.24 (6H, s, 2xC$\underline{H}_3$), 1.25 (6H, s, 2xC$\underline{H}_3$), 1.45-1.55 (2H, m, 2xC(5)H), 1.72-1.90 (6H, m, 2xC(4)H and 4xC(9)H), 2.05-2.34 (2H, m, 2xC(4)H), 2.50-2.60 (2H, m, 2xC(5)H), 2.75-2.84 (2H, t, J = 9.0Hz, 2xC(3)H), 4.11 (4H, br, s, 4xC(8)H) and 10.86 (2H, br, s, 2xO$\underline{H}$); δ_C (50.3MHz, $CDCl_3$) 21.24, 21.54 (4xC$\underline{H}_3$), 22.42 (2xC(4)), 22.74 (2xC$\underline{H}_3$), 25.47 (2xC(9)), 32.12 (2xC(5)), 46.68 (2xC(2)), 52.76 (2xC(3)), 56.10 (2xC(1)), 63.91 (2xC(8)), 173.95 (2xC(7)) and 182.36 (2xC(6)); *m/z* (Electrospray, ES$^-$) 453 (M-H$^-$); *m/z* (DCI, NH_3) 455 (MH$^+$, 2%), 273 (38), 255 (48), 200 (53), 183 (30), 182 (15), 155 (36) and 109 (100); Exact mass 477.2465. $C_{24}H_{38}O_8Na$ requires 477.2464.

(1R,3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid mono-3-(2-methylpyridine)ester **7**

Method A: Anhydride **2** (0.500g, 2.75mmol) was stirred in excess pyridine carbinol (1.5ml) at 100°C for 18 h. The reaction mixture was then dissolved in diethyl ether (25ml) and washed repeatedly with NH_4Cl (sat. aq. solution). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The off-white solid obtained was recrystallised slowly from EtOAc (20ml) and petrol (150ml), giving two distinct crystal types. Separation by crystal picking gave the title compound **7** as short, square, off-white coloured crystals in 18% yield: m.p. 131°C; R_f 0.49 (40:5-DCM:MeOH); $[\alpha]_D^{22}$ +17.4 (c=0.50, $CHCl_3$); Analysis calc'd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81; found: C, 65.87; H, 7.24; N, 4.51; ν_{max} ($CHCl_3$/cm^{-1}) 3200-2400 (br), 2973 (s), 1732 (s), 1690 (s), 1597 (m), 1459 (m), 1439 (m), 1281 (m), 1230 (m), 1168 (s); δ_H (200 MHz, $CDCl_3$) 0.88, 1.27, 1.31 (3x3H, 3xs, 3xC$\underline{H}_3$), 1.48-1.61 (1H, m, C(5)H), 1.78-1.98 (1H, m, C(4)H), 2.16-2.35 (1H, m, C(4)H), 2.50-2.66 (1H, m, C(5)H), 2.94 (1H, t, J=9.5 Hz, C(3)H), 5.27 (2H, s, C(8)H_2), 7.27 (1H, t, J=6.0 Hz, C(12)H), 7.40 (1H, d, J=8.0 Hz, C(10)H), 7.74 (1H, td, J=7.5, 1.5 Hz, C(11)H), 8.63 (1H, d, J=5.0 Hz, C(13)H); δ_C (125.8 MHz, $CDCl_3$) 21.69 (C$\underline{H}_3$), 22.08 (C$\underline{H}_3$), 23.07 (C(4)), 23.21 (C$\underline{H}_3$), 32.72 (C(5)), 47.28 (C(2)), 53.21 (C(3)), 56.57 (C(1)), 67.21 (C(8)), 122.61 (C(10)), 123.43 (C(12)), 137.44 (C(11)), 149.67 (C(13)), 156.09 (C(9)), 174.01 (C(7)), 181.27 (C(6)); *m/z* (Electrospray) 294 (2%), 293 (18), 292 (MH$^+$, 100).

The minor product (1*R*,3*S*)-1,2,2-trimethylcyclopentane-1,3-dicarboxylic acid mono-1-(2-methylpyridine)ester was obtained as long, colourless, needle crystals in 3% yield: m.p. 133°C; R_f 0.49 (40:5-DCM:MeOH); $[\alpha]_D^{22}$ +44.0 (c=0.50, $CHCl_3$); Analysis calc'd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81; found: C, 66.28; H, 7.38; N, 4.56; ν_{max} ($CHCl_3$/cm^{-1}) 3600-2800 (br), 2973 (m), 1725 (s) , 1704 (s) , 1599 (m), 1459 (m), 1439 (m), 1152 (s), 1114 (s); δ_H (200 MHz, $CDCl_3$) 0.87, 1.29 and 1.33 (3x3H, 3xs, 3xC$\underline{H}_3$), 1.52-1.66 (1H, m, C(5)H), 1.77-1.97 (1H, m, C(4)H), 2.11-2.30 (1H, m, C(4)H), 2.58-2.74 (1H, m, C(5)H), 2.87 (1H, t, J=9.5 Hz, C(3)H), 5.18-5.34 (2H, dd, J=18.0, 13.5 Hz, C(8)H_2), 7.23-7.29 (1H, m, C(12)H), 7.39 (1H, d, J=7.5Hz, C(10)H), 7.74 (1H, td, J=7.5, 1.5 Hz, C(11)H), 8.62 (1H, d, J=5.0 Hz, C(13)H); δ_C (125.8 MHz, $CDCl_3$) 21.16 (C$\underline{H}_3$), 21.67 (C$\underline{H}_3$), 22.46 (C(4)), 22.81 (C$\underline{H}_3$), 32.56 (C(5)), 46.94 (C(2)), 52.76 (C(3)),

56.33 (C(1)), 66.55 (C(8)), 121.98 (C(10)), 122.98 (C(12)), 137.10 (C(11)), 149.09 (C(13)), 155.74 (C(9)), 175.19 (C(6)), 178.71 (C(7)); *m/z* (Electrospray) 314 (MNa^+, 4%), 294 (2), 293 (19), 292 ([MH^+], 100).

Method B: NaH (0.024g, 0.98mmol, 1.2 equiv) was washed with petrol (3 x 25ml) and then set to stir at 0°C in THF (30ml), forming a grey suspension. Pyridine carbinol (0.089g, 0.82mmol, 1.0 equiv) in THF (5ml) was then added dropwise and stirred for 1 h at 0°C. (1*R*,3*S*)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid anhydride (0.163g, 0.90mmol, 1.1 equiv) was added portionwise to the stirring mixture, and the vessel allowed to warm to room temperature. The reaction was then refluxed at 90°C overnight. The reaction mixture was concentrated *in vacuo*, redissolved in DCM (50ml) and filtered through Celite®, washing with DCM (3 x 50ml). The reaction mixture was again concentrated *in vacuo* and purified by column chromatography (eluting DCM gradient 80:5-DCM:MeOH) to give the mixture of regioisomers in 73% yield (50% major regioisomer) **7** which could be separated by crystal picking as above.

(1R,3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid mono-3-(2-ethylpyridine)ester **8**.
Method A: Anhydride **2** (0.500g, 2.75mmol) was stirred in excess 2-(2-hydroxyethyl)pyridine (2ml) at 100°C for 4 h. The reaction mixture was then partitioned between EtOAc (25ml) and $NaHCO_3$ (25ml). The aqueous layer was then washed EtOAc (3 x 20ml), acidified to pH6 with conc HCl, and then re-extracted into EtOAc (3 x 25ml). The combined organic extractions were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the title compound **8** as a white solid in 15-20% yield: m.p. 134-135°C; R_f 0.46 (40:5-DCM:MeOH); $[\alpha]_D^{22}$ +15.5 (c=1.00, $CHCl_3$); Analysis calc'd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59; found: C, 66.68; H, 7.79; N, 4.45; ν_{max} (Nujol/cm^{-1}) 3600-3200 (br), 1727 (s), 1602 (m), 1573 (w), 1346 (m), 1310 (m), 1270 (s), 1211 (m), 1173 (s), 1128 (m), 1104 (m), 1067 (m), 1021 (m), 1008 (m), 875 (w), 809 (w), 736 (w), 723 (w); δ_H (200 MHz, $CDCl_3$) 0.80, 1.18 and 1.24 (3x3H, 3xs, 3x$C\underline{H}_3$), 1.45-1.60 (1H, m, C(5)H), 1.73-1.89 (1H, m, C(4)H), 2.09-2.28 (1H, m, C(4)H), 2.46-2.62 (1H, m, C(5)H), 2.79 (1H, t, *J*=9.0 Hz, C(3)H), 3.18 (t, *J*=7.0 Hz, 2H, C(8)H_2), 4.36-4.60 (2H, m, C(9)H_2), 7.18-7.28 (2H, m, C(11)H and C(13)H), 7.68 (1H, td, *J*=7.5, 1.5 Hz, C(12)H), 8.60 (1H, d, *J*=5.0 Hz, C(14)H; δ_C (125.8 MHz, $CDCl_3$) 21.27 ($\underline{C}H_3$), 21.60 ($\underline{C}H_3$), 22.40 (C(4)), 22.73 ($\underline{C}H_3$), 32.35 (C(5)), 36.95 (C(9)), 46.59 (C(2)), 52.81 (C(3)), 56.12 (C(1)), 63.50 (C(8)), 121.94 (C(11)), 123.60 (C(13)), 136.95 (C(12)), 149.00 (C(14)), 157.58 (C(10)), 173.87 (C(7)), 180.10 (C(6)); *m/z* (Electrospray) 328 (MNa^+, 4%), 307 (20), 306 (MH^+, 100).

Method B: NaH (0.024g, 0.98mmol, 1.2 equiv) was washed with petrol (3 x 25ml) and then set to stir at 0°C in THF (30ml), forming a grey suspension. 2-(2-Hydroxyethyl)pyridine (0.100g, 0.81mmol, 1.0 equiv) in THF (5ml) was then added dropwise and stirred for 1 h at 0°C. Anhydride **2** (0.163g, 0.90mmol, 1.1 equiv) was added portionwise to the stirring mixture, and the vessel allowed to warm to room temperature. The reaction was then refluxed at 90°C overnight. The reaction mixture was concentrated *in vacuo*, redissolved in DCM (50ml) and filtered through Celite®, washing with DCM (3 x 50ml). The reaction mixture was again concentrated *in vacuo* and purified by column chromatography (eluting DCM gradient 80:5-DCM:MeOH) to give the product **8** in 26% yield (data as above).

(1R,3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid mono-3-(2-propylpyridine)ester **9**.
Method A: Anhydride **2** (0.250g, 1.37mmol) was stirred in excess pyridine propanol (1ml) at 100°C for 18 h. The reaction mixture was then dissolved in diethyl ether (20ml) and washed repeatedly with NH_4Cl (sat. aq.

solution) until all excess alcohol had disappeared. The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a brown oil. Purification by column chromatography (eluting 80:5-DCM:MeOH) gave the title compound **9** as a clear oil, which solidified over 3 days, in 50% yield: m.p. 63-65°C; R_f 0.49 (40:5-DCM:MeOH); $[\alpha]_D^{22}$ +22.0 (c=2.84, $CHCl_3$); Analysis calc'd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39; found: C, 67.36; H, 7.54; N, 4.24; ν_{max} ($CHCl_3$/cm^{-1}) 3400-2200 s (br), 2969 (s), 2881 (s), 1723 (s), 1696 (s), 1601 (m), 1573 (m), 1477 (s), 1460 (m), 1438 (m), 1392 (m), 1378 (m), 1318 (m), 1265 (s), 1235 (s), 1225 (s), 1216 (m), 1206 (s), 1175 (s), 1014 (m); δ_H (200 MHz, $CDCl_3$) 0.85, 1.23 and 1.28 (3x3H, 3xs, 3x$C\underline{H}_3$), 1.49-1.51 (1H, m, C(5)H), 1.65-1.90 (1H, m, C(4)H), 2.00-2.30 (3H, m, C(4)H and C(9)H), 2.45-2.70 (1H, m, C(5)H), 2.78 (1H, t, *J*=10.0 Hz, C(3)H), 2.89 (2H, t, *J*=7.0 Hz, C(8)H_2), 4.10 (2H, t, *J*=5.2 Hz, C(10)H), 7.10-7.20 (2H, m, C(12)H and C(14)H), 7.60-7.70 (1H, m, C(13)H), 8.58 (1H, d, *J*=4.0 Hz, C(15)H); δ_C (50.3 MHz, $CDCl_3$) 21.36 ($\underline{C}H_3$), 21.69 ($\underline{C}H_3$), 22.45 (C(4)), 22.96 ($\underline{C}H_3$), 28.66 (C(9)), 32.39 (C(5)), 33.84 (C(10)), 46.51 (C(2)), 52.82 (C(3)), 56.15 (C(1)), 63.67 (C(8)), 121.71 (C(12)), 123.29 (C(14)), 137.53 (C(13)), 148.28 (C(15)), 160.17 (C(11)), 174.11 (C(7)), 179.69 (C(6)); *m/z* (Electrospray) 342 (MNa^+, 2%), 322 (2), 321 (10), 320 (MH^+, 100).

Method B: NaH (0.024g, 0.98mmol, 1.2 equiv) was washed with petrol (3 x 25ml) and then set to stir at 0°C in THF (30ml), forming a grey suspension. Pyridine propanol (0.111g, 0.81mmol, 1.0 equiv) in THF (5ml) was then added dropwise and stirred for 1 h at 0°C. (1*R*,3*S*)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid anhydride (0.163g, 0.90mmol, 1.1 equiv) was added portionwise to the stirring mixture, and the vessel allowed to warm to room temperature. The reaction was then refluxed at 90°C overnight. The reaction mixture was concentrated *in vacuo*, redissolved in DCM (50ml) and filtered through Celite®, washing with DCM (3 x 50ml). The reaction mixture was again concentrated *in vacuo* and purified by column chromatography (eluting DCM gradient 80:5-DCM:MeOH) to give the mixture of regioisomers in 69% yield (60% major regioisomer isolated, data as above).

(1R,2S)-Norephedrine N-p-toluene sulphonate[18]

p-Toluenesulphonyl chloride (0.662g, 3.47mmol, 1.1 equiv) was added portionwise to a stirring solution of (1R,2S)-norephedrine (0.500g, 3.31mmol, 1.0 equiv) and triethylamine (0.435g, 4.299mmol, 1.3 equiv) in DCM (20ml) at room temperature until there was no further change by t.l.c. (40:5-DCM:MeOH). The reaction mixture was then concentrated *in vacuo* and purified by column chromatography (eluting DCM gradient 40:5-DCM:MeOH) to give the title product as a colourless oil, which solidified over a number of days, in 91% yield: m.p. 85-86°C; R_f 0.60 (40:5-DCM:MeOH); $[\alpha]_D^{21}$ -16.0 (c=0.89, $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 3615 (w), 3379 (m), 3066 (w), 3029 (m), 3015 (m), 2986 (m), 1495 (m), 1453 (m), 1411 (m), 1384 (m), 1393 (s), 1161 (s), 1093 (s), 968 (m), 815 (m); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (3H, d, *J*=6.5 Hz, CHC$\underline{H}_3$), 2.39 (3H, s, (C_6H_4)C$\underline{H}_3$), 3.50-3.61 (1H, m, C$\underline{H}$CH$_3$), 3.85 (1H, d, *J*=4.5 Hz, CHO$\underline{H}$), 4.84 (1H, m, C$\underline{H}$OH), 5.82 (1H, d, *J*=8.5 Hz, N$\underline{H}$), 7.20-7.36 (7H, m, 7 x Ar$\underline{H}$), 7.80 (2H, d, *J*=8.0 Hz, 2 x *o*- ($C_6\underline{H}_4$)CH$_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 13.97 (CH$\underline{C}$H$_3$), 21.40 ((C_6H_4)$\underline{C}$H$_3$), 55.23 ($\underline{C}$HCH$_3$), 75.84 ($\underline{C}$HOH), 126.33, 127.26, 127.62, 128.44 and 130.02 (5 x $\underline{C}$H).

(1R,3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid mono-3-((1R,2S)-norephedrine N-p-toluene sulphonate)ester **10**

NaH (0.047g, 1.97mmol, 1.2 equiv) was washed with petrol (3 x 15ml). THF (50ml) was added and the reaction mixture stirred at 0°C to form a grey suspension. (1R,2S)-Norephedrine N-*p*-toluene sulphonate (0.500g, 1.64mmol, 1.0 equiv) in THF(10ml) was added dropwise and the reaction stirred at 0°C for 1 h. Anhydride **2** (0.328g, 1.80mmol, 1.1 equiv) was added portionwise, the reaction allowed to warm to room temperature, and then refluxed at 90°C overnight. The reaction mixture was concentrated to dryness and then redissolved in DCM (25ml) and filtered through Celite®, washing with DCM (3 x 50ml). The combined organic washings were then concentrated *in vacuo* and purified by column chromatography (eluting DCM gradient 160:5-DCM:MeOH) to give the title compound **10** as a white foam in 24-36% yield: R_f 0.41 (40:5-DCM:MeOH); $[\alpha]_D^{21}$ -6.1 (c=0.18, $CHCl_3$); ν_{max} ($CHCl_3$/cm^{-1}) 3377 (w), 3020 (s), 2979 (s), 1729 (s), 1690 (s), 1599 (w), 1496 (w), 1458 (m), 1415 (m), 1381 (s), 1341 (s), 1289 (s), 1163 (s), 1093 (s), 909 (s), 815 (m), 670 (s); ^{1}H NMR (200 MHz, $CDCl_3$) 0.73 (3H, s, C$\underline{H}_3$), 1.01 (3H, d, *J*=7.0 Hz, C$\underline{H}_3$), 1.24 and 1.26 (6H, 2 x s, 2 x C$\underline{H}_3$), 1.45-1.59 (1H, m, C(5)H), 1.80-1.91 (1H, m, C(4)H), 2.12-2.37 (1H, m, C(4)H), 2.39-2.56 (4H, m, C(5)H and ArC$\underline{H}_3$), 2.81 (1H, t, *J*=9.0 Hz, C(3)H), 3.71-3.81 (1H, m, C(12)H), 4.63 (1H, d, *J*=9.0 Hz, N$\underline{H}$), 5.62 (1H, d, *J*=4.0 Hz, C(11)H), 7.18-7.39 (7H, m, 7 x Ar$\underline{H}$), 7.71 (2H, d, *J*=8.5 Hz, 2 x *o*-(C$_6\underline{H}_4$)SO_2); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.87 (C$\underline{H}_3$), 20.95, 21.15 and 21.45 (3 x C$\underline{H}_3$), 22.54 (C(4)), 22.72 (C$\underline{H}_3$), 32.04 (C(5)), 46.71 (C(2)), 52.71 and 52.91 (C(3) and C(12)), 56.21 (C(1)), 77.74 (C(11)), 126.72, 127.17, 127.32, 128.56 and 129.93 (5 x C$\underline{H}$), 135.29, 136.20, 138.12 and 143.63 (4 x *ipso*-C), 173.48 (C(7)), 182.11 (C(6)); *m/z* (Electrospray, ES$^-$) 488 (5%), 487 (M$^-$, 26), 486 (M-H$^-$, 100).

(1R,3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid mono-3-(2-methylpyridine-N-oxide)ester. **11**

A solution of urea hydrogen peroxide (Aldrich) (0.110g, 1.14mmol, 3.3 equiv) and phthalic anhydride (0.060g, 0.38mmol, 1.1 equiv) in DCM (5ml) was stirred at room temperature for 15 min. Ester **7** (0.100g, 0.34mmol, 1.0 equiv) was then added and the reaction mixture stirred for 4 h at room temperature, until no further change was observed by t.l.c. (40:5-DCM:MeOH). The reaction mixture was then filtered, and concentrated *in vacuo*. Purification by column chromatography (eluting DCM gradient 40:5-DCM:MeOH) gave the title compound **11** as a white solid in 53% yield: m.p. 153-155°C; R_f 0.34 (40:5-DCM:MeOH); $[\alpha]_D^{22}$ +10.9 (c=0.11, $CHCl_3$); Analysis calc'd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.89; N, 4.56; found: C, 62.63; H, 6.19; N, 4.29; ν_{max} ($CHCl_3$/cm^{-1}) 3600-2800 (br), 2972 (m), 1738 (s), 1698 (s), 1600 (m), 1442 (m), 1163 (s), 931 (m); δ_H (200 MHz, $CDCl_3$) 0.86, 1.26 and 1.33 (3x3H, 3xs, 3xC$\underline{H}_3$), 1.47-1.60 (1H, m, C(5)H), 1.78-1.98 (1H, m, C(4)H), 2.14-2.49 (1H, m, C(4)H), 2.52-2.65 (1H, m, C(5)H), 2.95 (1H, t, *J*=9.5 Hz, C(3)H), 5.32-5.49 (2H, dd, *J*=19.0, 15.5 Hz, C(8)H_2), 7.28-7.51 (3H, m, C(10)H, C(11)H and C(12)H), 8.46 (1H, d, *J*=6.0 Hz, C(13)H); δ_C (125.8 MHz, $CDCl_3$) 21.69 (C$\underline{H}_3$), 22.04 (C$\underline{H}_3$), 23.09 (C(4)), 23.37 (C$\underline{H}_3$), 32.85 (C(5)), 47.28 (C(2)), 53.35 (C(3)), 56.49 (C(1)), 60.96 (C(8)), 125.02, 125.34 and 126.66 (C(10), C(11) and C(12)), 140.10 (C(13)), 147.29 (C(9)), 173.66 (C(7)), 179.60 (C(6)); *m/z* (CI(NH_3)) 308 (MH$^+$, 3%), 293 (5), 292 (52), 201 (3), 200 (36), 110 (100).

(1R,3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid mono-3-(2-ethylpyridine-N-oxide)ester **12**.

A solution of urea hydrogen peroxide (0.252g, 2.68mmol, 3.3 equiv) and phthalic anhydride (0.132g, 0.89mmol, 1.1 equiv) in DCM (5ml) was stirred at room temperature for 15 min. Ester **8** (0.248g, 0.81mmol,

1.0 equiv) was then added and the reaction mixture stirred for 12 h at room temperature, until no further change was observed by t.l.c. (40:5-DCM:MeOH). The reaction mixture was then filtered, and concentrated *in vacuo*. Purification by column chromatography (eluting 80:5-DCM:MeOH) gave the title compound **12** as a white solid in 70% yield: m.p. 149-150°C; R_f 0.36 (40:5-DCM:MeOH); $[\alpha]_D^{21}$ +16.6 (c=0.50, $CHCl_3$); Analysis calc'd for $C_{17}H_{23}NO_5$: C, 63.51; H, 7.21; N, 4.36; found: C, 63.31; H, 7.41; N, 4.23; ν_{max} ($CHCl_3$/cm^{-1}) 2969 (s), 2248 (w), 1727 (s), 1698 (s), 1491 (m), 1443 (s), 1378 (m), 1171 (s); δ_H (200 MHz, $CDCl_3$) 0.75, 1.14 and 1.18 (3x3H, 3xs, 3x$C\underline{H}_3$), 1.39-1.50 (1H, m, C(5)H), 1.69-1.80 (1H, m, C(4)H), 2.06-2.20 (1H, m, C(4)H), 2.40-2.56 (1H, m, C(5)H), 2.73 (1H, t, *J*=9.5 Hz, C(3)H), 3.30 (2H, t, *J*=6.5 Hz, C(8)H_2), 4.50 (2H, t, *J*=6.0 Hz, C(9)H_2), 7.22-7.34 (3H, m, C(11)H, C(12)H and C(13)H), 8.46 (1H, d, *J*=6.0 Hz, C(14)H); δ_C (125.8 MHz, $CDCl_3$) 21.75 ($\underline{C}H_3$), 22.06 ($\underline{C}H_3$), 22.94 (C(4)), 23.25 ($\underline{C}H_3$), 31.10 (C(9)), 32.79 (C(5)), 46.98 (C(2)), 53.28 (C(3)), 56.51 (C(1)), 60.72 (C(8)), 124.83 (C(11)), 127.10 and 127.74 (C(12) and C(13), 140.54 (C(14)), 149.30 (C(10)), 174.21 (C(7)), 180.06 (C(6)); *m/z* (CI(NH_3)) 323 (4%), 322 (MH^+, 37), 306 (100), 200 (3), 140 (7), 122 (51), 106 (28).

(1R,3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid mono-3-(2-propylpyridine-N-oxide)ester **13**.
A solution of urea hydrogen peroxide (0.243g, 2.58mmol, 3.3 equiv) and phthalic anhydride (0.128g, 0.86mmol, 1.1 equiv) in DCM (5ml) was stirred at room temperature for 15 min. Ester **9** (0.250g, 0.78mmol, 1.0 equiv) was then added and the reaction mixture stirred for 12 h at room temperature, or until no further change was observed by t.l.c. (40:5-DCM:MeOH). The reaction mixture was then filtered, and concentrated *in vacuo*. Purification by column chromatography (eluting 80:5-DCM:MeOH) gave the title compound **13** as a white solid in 48% yield: m.p. 107-110°C; R_f 0.55 (40:5-DCM:MeOH); $[\alpha]_D^{22}$ +4.8 (c=0.11, $CHCl_3$); Analysis calc'd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18; found: C, 64.72; H, 7.69; N, 4.19; ν_{max} ($CHCl_3$/cm^{-1}) 3400-2800 (br), 2968 (s), 2258 (m), 1725 (s), 1695 (s), 1493 (m), 1446 (m), 1175 (s); δ_H (200 MHz, $CDCl_3$) 0.87, 1.24 and 1.33 (3x3H, 3xs, 3x$C\underline{H}_3$), 1.44-1.57 (1H, m, C(5)H), 1.71-1.91 (1H, m, C(4)H), 2.04-2.30 (3H, m, C(4)H and C(9)H), 2.47-2.63 (1H, m, C(5)H), 2.82 (1H, t, *J*=9.5 Hz, C(3)H), 3.03-3.10 (2H, m, C(8)H), 4.06-4.33 (2H, m, C(10)H_2), 7.19-7.33 (3H, m, C(12)H, C(13)H and C(14)H), 8.49 (1H, d, *J*=6.0 Hz, C(15)H); δ_C (125.8 MHz, $CDCl_3$) 21.34 ($\underline{C}H_3$), 21.70 ($\underline{C}H_3$), 22.51 (C(4)), 23.02 ($\underline{C}H_3$), 25.46 (C(9)), 27.87 (C(10)), 32.43 (C(5)), 46.58 (C(2)), 52.95 (C(3)), 56.21 (C(1)), 63.56 (C(8)), 123.90, 125.80 and 127.53 (C(12), C(13) and C(14)), 140.23 (C(15)), 151.68 (C(11)), 174.11 (C(7)), 179.39 (C(6)); *m/z* 336 (CI(NH_3)) (MH^+, 2%), 321 (3), 320 (15), 200 (3), 154 (4), 120 (58), 93 (100).

(1R, 3S)-1,2,2-Trimethylcyclopentane-1,3-dicarbonyl chloride **15**[19]
To a suspension of PCl_5 (10.40g, 49.94mmol) in petrol at 0°C was added (1*R*, 3*S*)-1,2,2-trimethylcyclopentane-1,3-dicarboxylic acid **14** (5.00g, 24.97mmol) in portions. The solution was allowed to stir at 0°C for 1 h and then warmed to room temperature and allowed to stir overnight. Any remaining solid PCl_5 was filtered off and the solvent was removed *in vacuo* to give the crude product as a pale yellow oil. This was purified by short path distillation at 75°C (lit.[19] 90°C at 0.5mmHg) to give the title compound **15** as a colourless oil (5.13g, 87%): $[\alpha]_D^{22}$ +35.7 (c=0.97, $CHCl_3$), lit.[19] $[\alpha]_D^{25}$ +14.0 (c=4, benzene); ν_{max} (Film/cm^{-1}) 2980 (m), 1790 (s), 1459 (m), 1398 (m) and 802 (s); δ_H (200MHz, $CDCl_3$) 1.06, 1.37, 1.45 (3x3H, 3xs, 3x$C\underline{H}_3$), 1.63-1.76 (1H, m, C(5)H), 1.94-2.29 (2H, m, 2xC(4)H), 2.49-2.65 (1H, m, C(5)H) and 3.29 (1H, t, *J* = 9.5Hz, C(3)H); δ_C (50.3MHz, $CDCl_3$) 20.42, 21.74, 22.62 (3x$\underline{C}H_3$), 23.63 (C(4)), 33.43 (C(5)), 47.57 (C(2)), 64.67 (C(3)), 65.56 (C(1)) and 174.71, 177.08 (2x$\underline{C}$OCl).

t-Butyl 3-hydroxybenzoate

3-Hydroxybenzoic acid (0.40g, 2.90mmol) was suspended in dry benzene (50ml) and the mixture heated to reflux. *N,N'*-Dimethylformamide di-*t*-butyl acetal (2.36g, 11.58mmol) was added dropwise over 20 min and the mixture was heated at reflux for a further 30 min. The cooled solution was washed with water (50ml), $NaHCO_3$ (sat. aq.) (2x50ml) and brine (50ml). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was then purified by silica chromatography (3:1 DCM:petrol, gradient to 1:9 EtOAc:DCM) to give the title compound as a colourless oil which solidified to a white solid under high vacuum (0.31g, 56%): m.p. 97-99°C; R_f 0.60 (1:1 EtOAc:petrol); ν_{max} ($CHCl_3$/cm^{-1}) 3413 (w, br), 1709 (m), 1601 (w), 1592 (w), 1453 (w), 1370 (w), 1304 (s), 1167 (s) and 1108 (m); δ_H (200MHz, $CDCl_3$) 1.60 (9H, s, ^{t}BuH), 6.79 (1H, s, br, OH), 7.04-7.10 (1H, m, ArH), 7.25-7.33 (1H, m, ArH) and 7.53-7.65 (2H, m, ArH); δ_C (50.3MHz, $CDCl_3$) 28.12 (CH_3), 81.60 ($C(CH_3)_3$), 116.23, 119.87, 121.59, 129.49 (ArCH), 133.06, 155.95 (ArC) and 166.16 (CO_2^{t}Bu); *m/z* (CI, NH_3, GCMS) 212 (MNH_4^+, 58%), 195 (MH^+, 75), 156 (89), 138 (40) and 121 (100).

(1R, 3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid di(t-butyl 3-hydroxybenzoate)ester **16**

(1*R*, 3*S*)-1,2,2-Trimethylcyclopentane-1,3-dicarbonyl chloride **15** (0.53g, 3.86mmol), *t*-butyl 3-hydroxybenzoate (1.50g, 7.71mmol), triethylamine (0.78g, 7.71mmol) and DMAP (0.09g, 0.77mmol) were heated at reflux in toluene (50ml) for 35 h. After this time, the solvent was removed *in vacuo* and the resulting residue dissolved in Et_2O (50ml). The organic layer was washed with 2M HCl (50ml) and 2M NaOH (50ml), dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield the title compound **9** as a yellow oil (0.84g, 39%): ν_{max} ($CHCl_3$/cm^{-1}) 1751 (s), 1712 (s), 1370 (m) and 1303 (s); δ_H (500MHz, $CDCl_3$) 1.16, 1.48, 1.54 (3x3H, 3xs, 3xCH_3), 1.61 (18H, s, 2x^{t}BuH), 1.71-1.77 (1H, m, C(5)H), 2.01-2.09 (1H, m, C(4)H), 2.33-2.42 (1H, m, C(4)H), 2.74-2.80 (1H, m, C(5)H), 3.16 (1H, t, J = 9.4Hz, C(3)H), 7.25-7.29 (2H, m, 2xC(6')H), 7.45 (2H, t, J = 7.9Hz, 2xC(5')H), 7.68 (1H, t, J = 2.0Hz, 1xC(2')H_A or 1xC(2')H_B), 7.70 (1H, t, J = 2.0Hz, 1xC(2')H_A or 1xC(2')H_B) and 7.88 (2H, dq, J_d = 7.8Hz, J_q = 1.4Hz, 2xC(4')H); *m/z* (CI, NH_3, Probe) 570 (MNH_4^+, 53%), 514 (7), 458 (24), 359 (44), 331 (16), 303 (39), 275 (18), 137 (83) and 109 (100).

(1R, 3S)-1,2,2-Trimethylcyclopentane-1,3-dicarboxylic acid di(3-hydroxybenzoic acid)ester **17**

Ester **16** (0.84g, 1.52mmol) was dissolved in $CHCl_3$ (5ml) and TFA (5ml) and stirred at room temperature overnight (or until t.l.c. analysis showed that there was no remaining ester). Removal of the solvent *in vacuo* gave the title compound **17** as a white solid (0.67g, quantitative): m.p. 230-232°C; (Found: C, 64.45; H, 5.36%. $C_{24}H_{24}O_8$ requires C, 65.45; H, 5.49%.); $[\alpha]_D^{22}$ +28.6 (c=1.01, MeOH); ν_{max} (Nujol/cm^{-1}) 3436 (m, br), 1757 (s), 1687 (s), 1590 (m) and 1302 (s); δ_H (500MHz, CD_3OD) 1.15, 1.50, 1.55 (3x3H, 3xs, 3xCH_3), 1.72-1.77 (1H, m, C(5)H), 2.01-2.15 (1H, m, C(4)H), 2.29-2.37 (1H, m, C(4)H), 2.70-2.77 (1H, m, C(5)H), 3.26-3.30 (1H, m, C(3)H), 7.33-7.37 (2H, m, 2xC(6')H), 7.51-7.55 (2H, m, 2xC(5')H), 7.70-7.73 (2H, m, 2xC(2')H) and 7.92 (2H, d, J = 7.7Hz, 2xC(4')H); δ_C (125.8MHz, CD_3OD) 22.05, 22.17, 23.72 (3xCH_3), 33.79 (C(5)), 54.16 (C(3)), 57.94 (C(1)), 123.89, 127.31, 127.39, 128.25, 130.75 (ArCH) and 152.34 (ArC); *m/z* (DCI, NH_3) 458 (6%, MNH_4^+), 414 (5), 320 (5), 303 (16), 294 (20), 259 (11), 200 (29), 139 (38), 138 (53), 137 (62), 121 (64) and 109 (100).

Acknowledgements

We thank the LINK Asymmetric Synthesis Programme (DTI, EPSRC and the Associated Octel Company) for funding of a studentship (E.W.) and EPSRC and the Associated Octel Company for a CASE award (D.R.P.), and Dr T. Claridge for the HMBC and HQMC experiments.

References

1. Hancock, R.D. and Martell, A.E., *Chem. Rev.*, 1989, **89**, 1875-1914.
2. Collins, T.J., *Acc. Chem. Res.*, 1994, **27**, 279-285.
3. Yang, H., Khan, M.A. and Nicholas, K.M., *Organometallics*, 1993, **12**, 3485-3494.
4. Rubottom, G.M. in *Oxidation in Organic Chemistry* (ed. Trahanovsky, W.H.) Ch1 (Academic, London, 1982).
5. Allred, G.D. and Liebeskind, L.S., *J.Am. Chem. Soc.*, 1996, **118**, 2748-2749.
6. Doyle, M.P., Protopopova, M.N., Brandes, B.D., Davies, H.M.L., Huby, N.J.S. and Whitesell, J.K., *Synlett.*, 1993, 151-153.
7. Ross, G.H.P. and McKervey, M.A., *Syn. Commun.*, 1992, **22**, 1751-1756.
8. Franczyk, T.S., Czerwinski, K.R. and Raymond, K.N., *J. Am. Chem. Soc.*, 1992, **114**, 8138-8146.
9. Whitesell, J., *Chem. Rev.*, 1989, **89**, 1581-1590.
10. Oppolzer, W., *Tetrahedron*, 1987, **43**, 1969-2004.
11. Sewald, N. and Wendisch, V., *Tetrahedron:Asymmetry*, 1996, **7**, 1269-1272.
12. Love, B.E. and Ren, J., *Synth. Commun.*, 1995, **25**, 73-86 and references therein.
13. Kenyon, J., *Org. Synth. Coll. Vol. 1*, 1941, 418.
14. The preparation of dicarboxylic acid dichorides have been reported under these conditions,[22] but camphoric acid gave the corresponding anhydride exclusively. We found, however, that the dichloride could be prepared from camphoric acid and PCl_5 at room temperature.
15. Summers, M.F., Marzilli, L.G., and Bax, A., *J. Am. Chem. Soc.*, 1986, **108**, 4285-4294.
16. Bone, W.A., Sudborough, J.J. and Sprankling, C.H., *J. Chem Soc.*, 1904, **85**, 534.
17. McMaster, L. and Ahmann, F.F., *J. Am. Chem. Soc.*, 1928, **50**, 145.
18. Xiang, Y., Olivier, E. and Ouimet, N., *Tetrahedron Lett.*, 1992, **33**, 457-460.
19. Toy, M.S., *J. Polym. Sci.*, 1967, **5**, 2481.
20. Widmer, U., *Synthesis*, 1983, 135.
21. Moloney, M.G., Thompson, R.M. and Wright, E., *Main Group Metal Chem.*, 1996, **19**, 133-137.
22. Maurer, F., Brandes, W. and Reinecke, P., D.E. 32 27 220 A1 (*Chem. Abstr.* 1984, **100**, 191432h).
23. Bell, K.H., *Aust. J. Chem.*, 1981, **34**, 665.

(*Received in UK* 10 *June* 1996)