Homochiral C_3-Symmetric Triols and Triamines: Straightforward Syntheses, and Applications as Chiral Ligands

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Abstract: Homochiral C_3-symmetric triols and triamines of varying steric demands have been made using an efficient one- or two-step procedure. The triols' use as ligands in organometallic complexes is explored briefly, as is the use of the titanium complex of one triol for asymmetric induction.

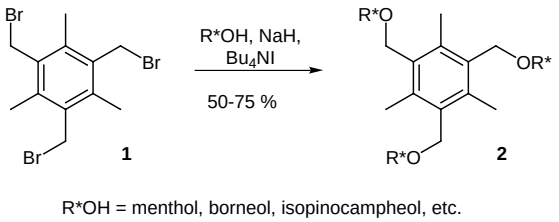
Key words: C_3-symmetric, homochiral, triols, triamines, asymmetric induction, chiral organometallic complexes, ligands, tin

Introduction

In recent years, chiral systems showing C_3 symmetry have created interest and found application in several areas, including molecular receptors,[1] ion channel mimics,[2] dendrimers,[3] organometallic ligands,[1] and chromatographic stationary phases.[4] An excellent review has illustrated the importance of C_3 symmetry in asymmetric catalysis and chiral recognition.[1] C_3-Symmetric tripodal ligands, which in octahedral organometallic complexes render the remaining three co-ordination sites identical, have a major contribution to make to asymmetric catalysis.

Chirality in C_3-symmetric systems may be caused by chiral centres in the starting materials, or by a twist in the molecular structure. Chiral starting materials permit synthesis in optically pure form, whereas resolution is necessary when achiral starting materials give a structurally twisted C_3-symmetric product. Homochiral C_3-symmetric ligands frequently form hydrogen-bonded or organometallic complexes with a twist axis, but as the twist chirality generally follows the point chirality (unless the chiral centre is remote from the twist element[5]), the complexes are generally homochiral with respect to both symmetry elements.[6]

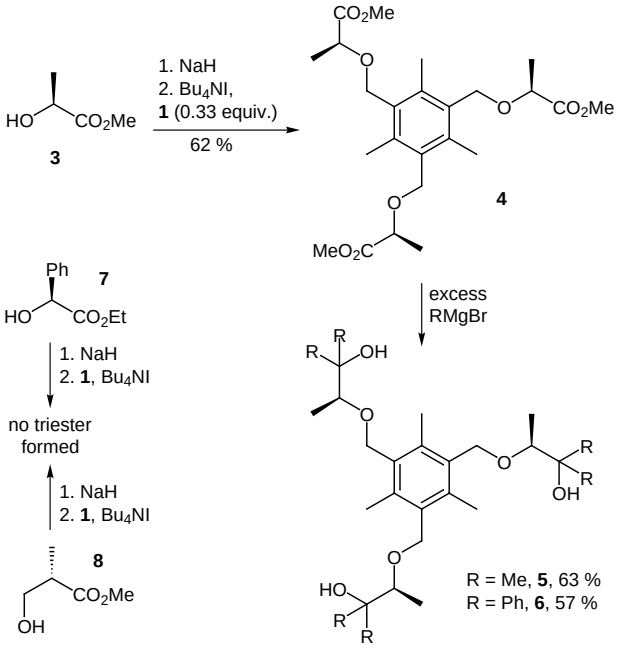
The homochiral C_3-symmetric ligands so far reported almost all consist of three chiral arms radiating from a central atom. By contrast, we were attracted by the extra rigidity of ligands in which the three chiral arms radiate from a ring, of which very few examples are known.[7–9] We earlier reported the development of an efficient one-step method (Scheme 1) for the preparation of homochiral C_3-symmetric triethers **2** consisting of three homochiral arms radiating from a central benzene ring.[10] An important feature of this synthetic method was the large increase in enantiomeric purity achieved by the synthesis. The cases studied showed no detectable diastereoselectivity between the *like* and *unlike* isomers. The minor enantiomer of the chiral starting material will therefore be incorporated for the most part into the *unlike* diastereomer of the C_3-symmetric product. Following purification, no trace of this minor diastereomer remains: the *like* isomers may therefore be assumed to have extremely high enantiomeric purity (e.g. *RRR*:*SSS* >13500:1 from starting material of *R*:*S* = 96:4), by analogy with our triethers **2**. We here report our extension of this synthesis to more highly functionalised species, including esters, amines and alcohols. We describe some metal-binding properties of these novel ligands, together with a preliminary exploration of their potential for asymmetric induction.



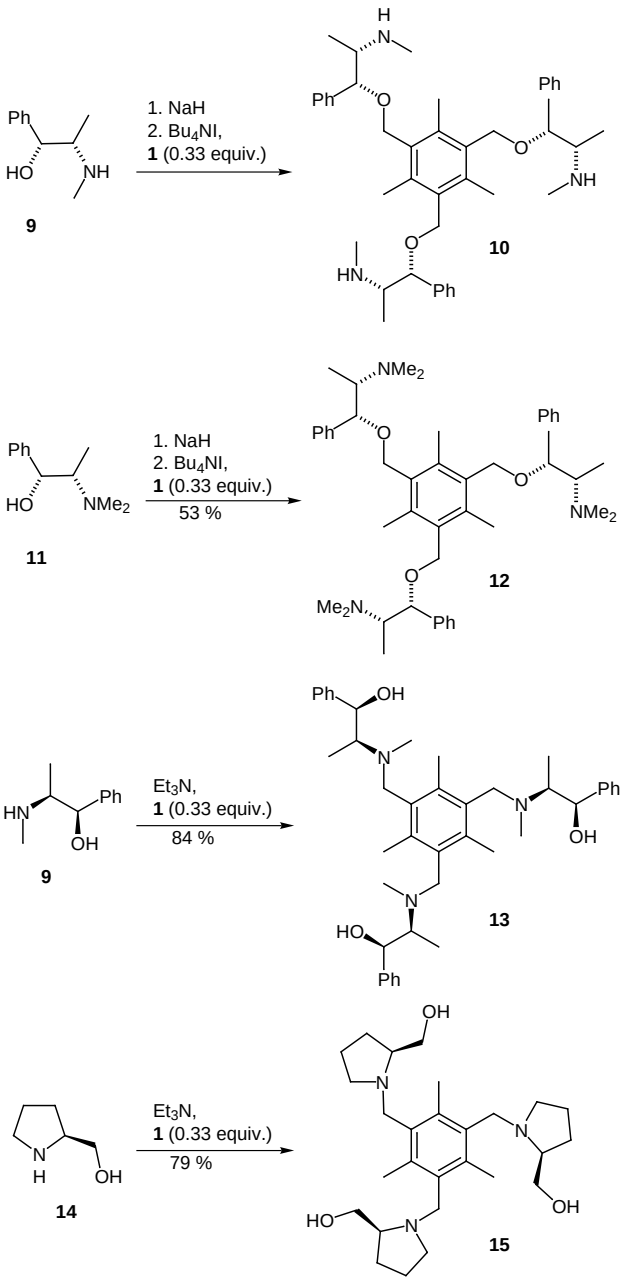
Scheme 1

Synthesis of C_3-Symmetric Triols and Triethers

The central ring in our new compounds is benzene, chosen for its conformational rigidity, its stability in many chemical environments, and the availability of various suitably functionalised derivatives. For this as for our earlier work, the C_3-symmetric starting material was 2,4,6-tris(bromomethyl)mesitylene (**1**), available commercially or by our modification of the method of Závada et al.[10,11] As shown in Scheme 2, treatment of methyl (*S*)-lactate (**3**) with one equivalent of sodium hydride followed by one third of an equivalent of 2,4,6-tris(bromomethyl)mesitylene (**1**) gave triester **4**. This was then converted by treatment with either methyl- or phenylmagnesium bromide to the triols **5** and **6** respectively. We attempted to vary the the steric demand of the ligand, and the length of the tether between the central ring and the donor groups, but unfortunately neither ethyl (*S*)-mandelate (**7**) nor methyl (*S*)-3-hydroxy-2-methylpropionate (**8**) gave good results in the coupling reactions. There is surprisingly little precedent for reaction of either alcoholate with a benzylic electrophile.[12]



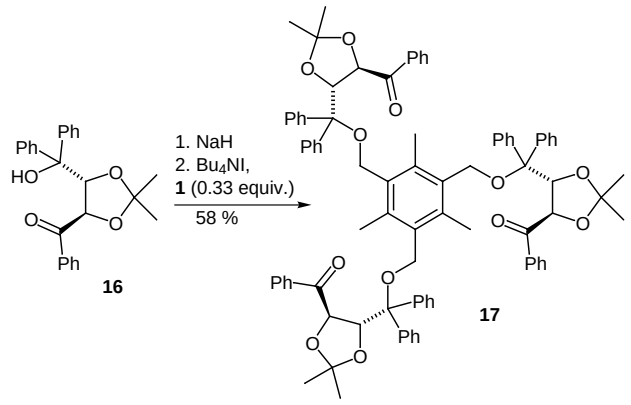
Scheme 2



Scheme 3

C_3-symmetric ligands having nitrogen/oxygen mixed donor sets have given interesting results in the past.[6a,7] We therefore treated (1*R*,2*S*)-ephedrine (**9**) and (1*R*,2*S*)-*N*-methylephedrine (**11**) separately with one equivalent of sodium hydride followed by one third of an equivalent of 2,4,6-tris(bromomethyl)mesitylene (**1**). The tertiary amine **12** was obtained in good yield, but contains no acidic donor group; the more interesting secondary amine **10** proved difficult to purify (Scheme 3). By carrying out the reaction between (1*R*,2*S*)-ephedrine (**9**) and 2,4,6-tris(bromomethyl)mesitylene (**1**) using triethylamine instead of sodium hydride, tertiary amine triol **13** was prepared, which proved amenable to purification. In the same way, (*S*)-pyrrolidine-2-methanol (**14**) was treated with triethylamine and 2,4,6-tris(bromomethyl)mesitylene (**1**) to give tertiary amine triol **15** (Scheme 3).

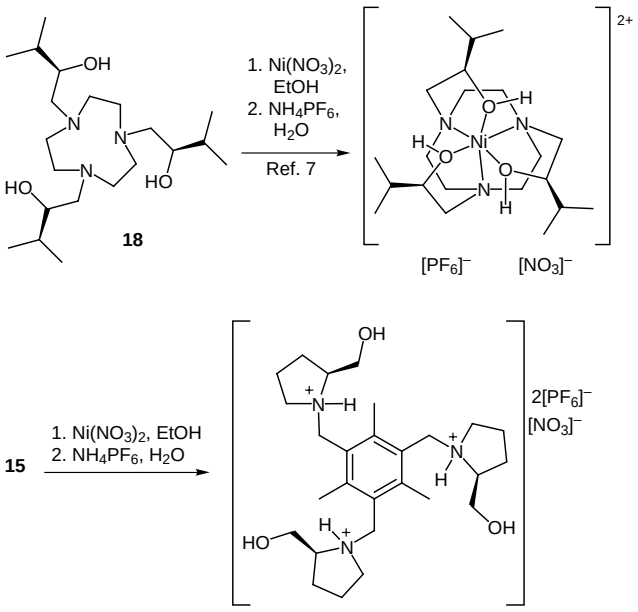
Both ^{1}H and ^{13}C NMR spectroscopy showed that compounds **4**, **5**, **10**, **12**, **13** and **15** are C_3-symmetric in solution. In the ^{1}H NMR spectrum, all showed clearly the diagnostic AB quartet centred at approximately $\delta = 4.5$, attributable as in our earlier work[10] to the diastereotopic benzylic protons. Triol **6** gave more complex spectra in both ^{1}H and ^{13}C NMR, indicative of lower symmetry in the molecule. This may be attributed to intramolecular hydrogen bonding or to π-stacking among the benzene rings; we are unable to define precisely why the symmetry is reduced in this somewhat crowded compound. The still more crowded triketone **17**, synthesised from tartrate-derived keto alcohol **16** and 2,4,6-tris(bromomethyl)mesityl-ene (**1**), proved to be C_3-symmetric in solution, so simple steric crowding is an insufficient explanation for the reduction in symmetry observed spectroscopically for triol **6**.



Complexation Reactions of Homochiral C_3-Symmetric Triols

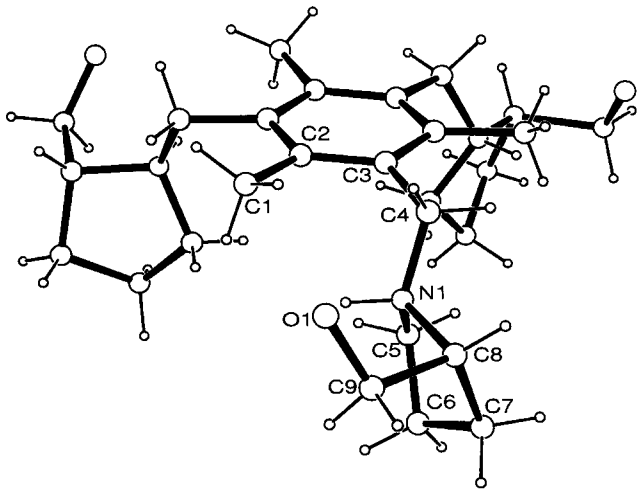
With homochiral C_3-symmetric triols in hand, we could now investigate their metal-binding properties. C_3-symmetric ligands are of interest in the context of both tetrahedral and, in particular, octahedral metal complexes, since the symmetry of the ligand is appropriate in each case to that of the complex. We therefore chose to investigate complexation of ligands **5**, **13** and **15** to tin, titanium, nickel and copper.

Our amino alcohol ligands **13** and **15** were investigated as potential ligands for the divalent metal ions Ni^{2+} and Cu^{2+} using the procedure of Peacock and co-workers for complexation of their C_3-symmetric amino alcohols **18** (Scheme 4).[7] One equivalent of our ligand (**13** or **15**) in ethanolic solution was added to an ethanolic solution of the hydrated metal nitrate. The ethanol was removed, and the resulting green solid was redissolved in water. An aqueous solution of ammonium hexafluorophosphate was added to induce crystallisation. In the case of ligand **15** this protocol resulted in the formation of colourless crystals. Their X-ray diffraction patterns at 296 and 123 K were consistent with the composition (**15**)•$3H^+(PF_6)_2(NO_3)$.[13] However, at both temperatures the finer structural details were obscured by disorder of the pyrrolidine rings and of one of the two independent PF_6^- anions.



Scheme 4

The crystals were cubic in form, so that exact C_3 symmetry was imposed by the space group on both independent hexafluorophosphate residues, on the nitrate anion, and on the tris-ammonium cation. This cation consequently but unexpectedly adopts a conformation (Figure) with all three radiating chains on the same face of the central aromatic ring. We have shown by molecular modelling (using an MM2 force field and molecular dynamics) that the lowest energy conformation for isolated ligands of this general type is one with two radiating chains above the face of the central ring and one below it; this is also the conformation we have previously observed for related species in the solid state.[10]

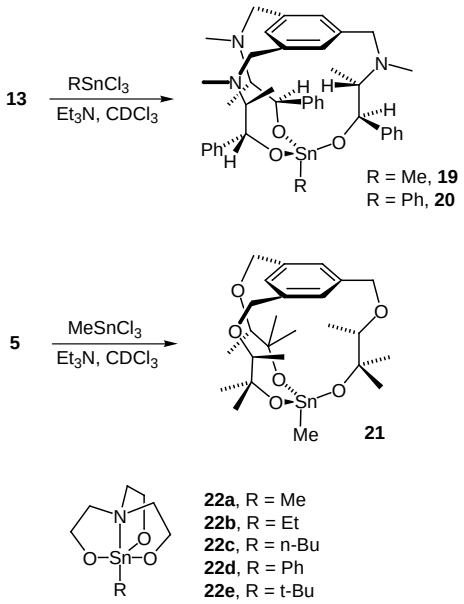


Structure of the (**15**)•$3H^+$ cation at 123 K as determined by X-ray crystallography. Atoms are shown as spheres of arbitrary size. Severe disorder affects particularly atoms C6−C9 and O1 and the positions of these atoms are subject to large systematic errors.

Figure

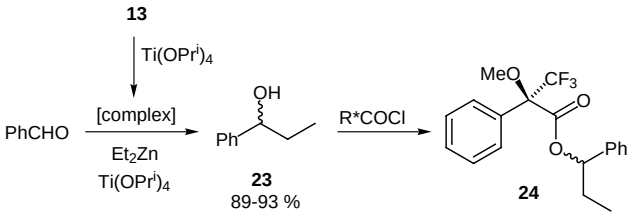
We therefore adopted a different strategy in screening our ligands for metal complexation. Triol ligands **5** and **13** were treated separately in anhydrous deuterochloroform with one equivalent of freshly prepared methyl- or phenyltin trichloride and three equivalents of anhydrous triethylamine. The supernatant liquid (above precipitated triethylammonium chloride) was analysed by ^1H, ^{13}C and ^{119}Sn NMR spectroscopy. These showed clearly that the trialkoxy tin complexes **19**−**21** had formed (Scheme 5). The formation of complex **21** was followed by ^1H NMR spectroscopy, and the presence of triethylamine shown to be essential to complexation. The ^{119}Sn chemical shift data are unequivocal: complexes **19** and **20** come into resonance at −268 and −391 ppm respectively, while complex **21** shows two signals, at −224 and −227 ppm (relative to $SnMe_4$). By constrast, the starting materials gave signals at −18 ppm ($MeSnCl_3$) and −61 ppm ($PhSnCl_3$). It is not unusual for alkyltin complexes of trihydroxy ligands to give more than one peak in the ^{119}Sn NMR spectrum. Stannatrane complexes **22a**−**d**, for example, are reported to give three peaks, attributed to a trimeric structure in which each tin atom is hexacoordinate and each occupies a different coordination sphere.[14] These trimeric structures decrease in stability with increasing steric bulk at the metal (**22a** is most stable, **22d** least stable as the trimer), and the *tert*-butyl compound **22e** is apparently monomeric. Our rather bulky complexes **19** and **20**, giving single peaks in the ^{119}Sn spectra, are apparently

monomeric, but we can obtain no direct proof of this owing to the air-sensitive nature of the materials. The ^1H and ^{13}C NMR spectra of the complexes were harder to interpret than the ^{119}Sn spectra, owing to considerable line broadening. This was greatly reduced by obtaining spectra of complex **19** at 90°C in toluene-d_8, enabling chemical shifts and splitting patterns to be elucidated (see experimental section). Similar temperature effects have been attributed in the past to alkyl chain flexing,[15] which explanation seems appropriate to our complexes also. Such flexing, occuring slowly at room temperature, may also account for the presence of two ^{119}Sn signals in the spectrum of complex **21**; alternatively, a dimeric structure involving two tin atoms in different coordination spheres cannot be ruled out.



Scheme 5

In order to investigate the potential of our new ligands for asymmetric induction, titanium complexes were made by treating ligands **5**, **13** and **15** with one equivalent of titanium tetraisopropoxide in toluene, followed after an hour by exposure to high vacuum. NMR analysis at this stage showed increased complexity and considerable line broadening in both ^1H and ^{13}C spectra, suggesting metal complexation but precluding detailed structural analysis. The presumed complex arising from ligand **13** and titanium tetraisopropoxide was treated with benzaldehyde at room temperature for half an hour, followed by diethylzinc at −10°C, then at 0°C for 48 h. Analysis of the resulting 1-phenylpropanol **23** via the Mosher's esters **24** revealed a racemic mixture; however, if an extra ten equivalents of Ti(Opr-*i*)$_4$ were added with the benzaldehyde and the reaction and analysis carried out as before (Scheme 6), the resulting alcohol showed a 10% enantiomeric excess in favour of the *R*-enantiomer.[16] We therefore deduce that the titanium complex of our triol is acting in a mechanistically similar manner to that described by Seebach et al. for TADDOLate titantium complexes.[17] This preliminary result, although showing low selectivity, demonstrates that our C_3-symmetric triols have potential for asymmetric induction in organic synthesis. We are pursuing this in several areas.



Scheme 6

Starting materials were used as supplied by the manufacturers without further purification unless indicated. 2,4,6-Tris(bromomethyl)mesitylene (**1**) was purchased from Aldrich, or made according to the procedure in our earlier paper.[10] THF was dried by distillation under N_2 from CaH_2 and $LiAlH_4$ using Ph_3CH as indicator. Other solvents were dried when necessary over molecular sieves (4Å). Petroleum ether used had bp 40−60°C. Reactions involving air-sensitive reagents were carried out under nitrogen in oven-dried glassware using standard Schlenk techniques. Melting point determinations were carried out using a Kofler hot-stage microscope and are uncorrected. IR spectra were obtained as KBr disks on an ATI Mattson Genesis series FTIR instrument. ^1H NMR spectra were obtained at 250 MHz in $CDCl_3$ and ^{13}C NMR spectra at 62.5 MHz in $CDCl_3$ on a Bruker AC 250 with a Tecmag data station. Chemical shifts are given in ppm relative to TMS or $CHCl_3$. Coupling constants in ^1H NMR spectra are given in Hz, and assignments in ^{13}C NMR spectra are made on the basis of DEPT-135 experiments. Mass spectra were obtained on either a Finnigan Masslab Navigator (low resolution) or a Jeol JMS 700 instrument (high resolution), running in CI, EI or FAB mode.

(*S*)-1,3,5-Tris(1-methoxycarbonylethoxymethylene)-2,4,6-trimethylbenzene (4)

NaH (360 mg, 7.5 mmol, 50% dispersion in oil) was added with cooling to a solution of methyl (*S*)-lactate (**3**; 782 mg, 7.5 mmol) in anhyd THF (20 mL), and the mixture was stirred for 30 min before the catalyst Bu_4NI (280 mg, 0.75 mmol) and 1,3,5-tris(bromomethyl)mesitylene (**1**; 1.00 g, 2.5 mmol) were added. The mixture was stirred at r.t. overnight, then filtered and the solvent removed under reduced pressure. The residue was separated by gravity chromatography using Et_2O/petroleum ether (1:1). to give the triester **4** as a low melting amorphous white solid (0.73 g, 62%); mp 69−71°C.

^1H NMR: δ = 4.72 (3 H, d, $J_{\alpha,\beta}$ = 10.4 Hz, 3 ArCH_αH$_\beta$), 4.43 (3 H, d, $J_{\beta,\alpha}$ = 10.4 Hz, 3 ArCH$_\alpha H_\beta$), 4.02 (3 H, q, *J* = 6.7 Hz, 3 CH), 3.75 (9 H, s, 3 CO_2CH_3), 2.40 (9 H, s, 3 ArCH_3), 1.37 (9 H, d, *J* = 6.7 Hz, 3 CH_3).

^{13}C NMR: δ = 173.9 (CO_2CH_3), 139.0 (C_{arom}), 132.1 (C_{arom}), 74.2 (CH), 67.0 (ArCH_2), 51.9 (CO_2CH_3), 18.9 (CHCH_3), 15.5 (ArCH_3).

IR: ν = 2987, 2955, 2913, 2895 (CH, alkyl), 1743 (C=O), 1449, 1372 (CH, alkyl), 1267, 1209, 1142 cm^{-1} (C−O, alkyl).

MS: *m/z* (%) = 468 (M^+, 12), 207 ($C_{12}H_{15}O_3$, 2), 191 ($C_{12}H_{15}O_2$, 6), 175 ($C_{12}H_{15}O$, 9), 157 (MH_3^{3+}, 100).

Anal. calcd for $C_{24}H_{36}O_9$: C, 61.5; H, 7.7. Found: C, 61.8; H, 7.5.

(*S*)-1,3,5-Tris(2-hydroxy-2-methylbut-3-oxymethylene)-2,4,6-trimethylbenzene (5)

Methylmagnesium bromide (4.3 mL, 3.0 M in Et_2O, 12.9 mmol) was added dropwise to a solution of the triester **4** (450 mg, 0.96 mmol) in anhyd Et_2O (30 mL). The mixture was heated to reflux for 4 h then allowed to cool and stirred at r.t. for 16 h. The mixture was cooled to 0°C and satd aq NH_4Cl solution (10 mL) was added dropwise. The resulting layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The organic phases were combined and washed with satd aq NaCl solution (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product could be purified either by recrystallising from Et_2O or by column chromatography (R_f 0.45, EtOAc/hexane, 3:2) to yield the triol **5** as white needles (281 mg, 63%); mp 130−132°C.

^{1}H NMR: δ = 4.72 (3 H, d, $J_{\alpha,\beta}$ = 10.1 Hz, ArCH_αH$_\beta$), 4.39 (3 H, d, $J_{\beta,\alpha}$ = 10.1 Hz, ArCH$_\alpha H_\beta$), 3.38 (3 H, q, J = 6.4 Hz, 3 CH), 2.44 (9 H, s, 3 ArCH_3), 1.24 (9 H, d, J = 6.4 Hz, 3 CH_3), 1.19 (9 H, s, 3 CH_3), 1.11 (9 H, s, 3 CH_3).

^{13}C NMR: δ = 138.3, 133.1 (C_{arom}), 82.3 (CH), 72.7 (COH), 66.0 ($ArCH_2$), 26.2 (CH_3), 23.6 (CH_3), 15.8 ($ArCH_3$), 13.8 (CH_3).

IR: ν = 3384 (OH), 2981, 2932, 2880 (CH, alkyl), 1459, 1383, 1367, 1331 (C−OH), 1171, 1097, 1073 cm^{-1} (C−O)

MS: *m*/*z* (%) = 492 (M^+ + Na, 10), 207 ($C_{12}H_{15}O_3$, 6), 191 ($C_{12}H_{15}O_2$, 9), 175 ($C_{12}H_{15}O$, 29), 157 (MH_3^{3+}, 100), 144 ($C_{11}H_{12}$, 55).

Anal. calcd for $C_{27}H_{48}O_6$: C, 69.2; H, 10.3. Found: C, 69.4; H, 10.2.

***(S)*-1,3,5-Tris(1,1-diphenyl-1-hydroxyprop-2-oxymethylene)-2,4,6-trimethylbenzene (6)**

Phenylmagnesium bromide (4.8 mL, 3.0 M in Et_2O, 14 mmol) was added dropwise to a solution of the triester **4** (500 mg, 1.07 mmol) in anhyd Et_2O (30 mL). The mixture was heated to reflux for 16 h, cooled to 0°C and satd aq NH_4Cl solution (10 mL) was added dropwise. The resulting layers were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with satd aq NaCl solution (20 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (R_f 0.4, EtOAc/hexane, 1:4) to yield the triol **6** as colourless needles (482 mg, 57%); mp 90−92°C.

^{1}H NMR: δ = 7.55−7.50 (6 H, m, ArH), 7.44−7.40 (6 H, m, ArH), 7.25−7.11 (18 H, m, ArH), 4.52−4.48 (6 H, m, 3 CH and ArCH_αH$_\beta$), 4.29−4.24 (3 H, m, ArCH$_\alpha H_\beta$), 1.85, 1.77, 1.76 (9 H, 3 x s, 3 ArCH_3), 1.12 (9 H, d, J = 5.8 Hz, 3 CH_3).

^{13}C NMR: δ = 146.9, 146.8, 144.2, 138.8, 138.7, 132.3, 132.3 (C_{arom}), 128.1, 128.0, 126.6, 125.9, 125.5 (CH_{arom}), 80.0 (COH), 78.6, 78.5, 78.3 (CH), 65.9 ($ArCH_2$), 15.0 ($ArCH_3$), 14.9 ($ArCH_3$), 13.5 (CH_3).

IR: ν = 3477 (OH), 3087, 3057, 3025 (CH, aromatic), 2977, 2932, 2909, 2897, 2784 (CH, alkyl), 1492, 1449 (CH, alkyl), 1373, 1316 (C−OH), 1172, 1093, 1041, 1032(C−O), 700 cm^{-1} (CH, aromatic).

MS: *m*/*z* (%) = 863 (M^+ + Na, 8), 368 (80), 272 (55), 157 (70), 133 (100).

HRMS (FAB): *m*/*z* calcd for $C_{57}H_{60}NaO_6$ (M^+ + Na): 863.4287. Found: 863.4279.

(1*R*,2*S*)-1,3,5-Tris(2-*N*-methylamino-1-phenylprop-1-oxymethylene)-2,4,6-trimethylbenzene (10)

NaH (360 mg, 7.5 mmol, 50% dispersion in oil) was added with cooling to a solution of (1*R*,2*S*)-(−)-ephedrine (**9**; 1.24 g, 7.5 mmol) in anhyd THF (20 mL) and the mixture stirred for 30 min. before the catalyst Bu_4NI (280 mg, 0.75 mmol) and the tribromide **1** (1.0 g, 2.5 mmol) were added. The mixture was stirred at r.t. overnight, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography eluting with CH_2Cl_2/MeOH/NH_3 (80:19:1) to yield the triamine **10**, which was identified by ^{1}H NMR, but could not be fully purified.

^{1}H NMR: δ = 7.40−7.25 (15 H, m, 3 C_6H_5), 4.43 (3 H, d, $J_{\alpha,\beta}$ = 10.4 Hz, ArCH_αH$_\beta$), 4.27 (3 H, d, partially obscured, ArCH$_\alpha H_\beta$), 4.26 (3 H, d, partially obscured, 3 OCH), 3.44−3.32 (3 H, m, 3 NH), 2.75−2.70 (3 H, m, 3 NCH), 2.29 (9 H, s, 3 ArCH_3), 2.21 (9 H, s, 3 NCH_3), 1.07 (9 H, d, J = 6.4 Hz, 3 CH_3).

(1*R*,2*S*)-1,3,5-Tris(2-N,*N*-Dimethylamino-1-phenylprop-1-oxymethylene)-2,4,6-trimethylbenzene (12)

NaH (0.36 g, 7.5 mmol, 50% dispersion in oil) was added with cooling to a solution of (1*R*,2*S*)-(−)-methylephedrine (**11**; 1.35 g, 7.5 mmol) in THF (20 mL), and the mixture stirred for 30 min before the catalyst Bu_4NI (0.28 g, 0.75 mmol) and the tribromide **1** (1.00 g, 2.5 mmol) were added. The mixture was heated to reflux overnight, filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography eluting with CH_2Cl_2/MeOH/NH_3 (90:9:1, R_f 0.7) to yield the triamine **12** as a viscous oil which slowly crystallised on standing (0.92 g, 53%); mp 100−102°C.

^{1}H NMR: δ = 7.38−7.25 (15 H, m, 3 C_6H_5), 4.75 (3 H, d, J = 6.4 Hz, OCH), 4.33 (3 H, d, $J_{\alpha,\beta}$ = 10.5 Hz, ArCH_αH$_\beta$), 4.24 (3 H, d, $J_{\beta,\alpha}$ = 10.5 Hz, ArCH$_\alpha H_\beta$), 2.81 (3 H, quin, J = 6.4 Hz, 3 NCH), 2.21 [18 H, s, 3 $N(CH_3)_2$], 2.15(9 H, s, 3 ArCH_3), 1.72 (9 H, d, J = 6.8 Hz, 3 CH_3).

^{13}C NMR: δ = 141.9, 138.4, 132.8 (C_{arom}), 128.2, 127.5 (CH_{arom}), 84.5 (OCH), 66.1 ($ArCH_2$), 64.5 (NCH), 41.2 [$N(CH_3)_2$], 15.8 ($ArCH_3$), 8.22 (CH_3).

IR: ν = 3083, 3064, 3030 (CH, aromatic), 2968, 2932, 2906, 2867, 2822 (CH, alkyl), 1493, 1472, 1454 (CH, alkyl), 1269, 1187, 1132 (C−O), 761, 746 cm^{-1} (CH, aromatic).

MS: *m*/*z* = 694 (MH^+, 100%), 516 ($MH^+ - C_{11}H_{16}NO$, 55), 354 ($MH^+ - C_{22}H_{32}N_2O$, 10), 338 ($MH^+ - C_{22}H_{32}N_2O_2$, 38), 176 ($MH^+ - C_{33}H_{48}N_3O_2$, 33), 160 ($MH^+ - C_{33}H_{48}N_3O_3$, 64).

HRMS (FAB): *m*/*z* calcd for $C_{45}H_{64}N_3O_3$ (M^++H): 694.4948. Found: 694.4955.

(1*R*,2*S*)-1,3,5-Tris[2-*N*-methylamino-1-phenylprop-1-oxymethylene]-2,4,6-trimethylbenzene (13)

(1*R*,2*S*)-(−)-Ephedrine (**9**; 1.24 g, 7.5 mmol) and Et_3N (0.76 g, 7.51 mmol) were added to a solution of the tribromide **1** (1.00 g, 2.50 mmol) in chlorobenzene (10 mL). The mixture was stirred at r.t. for 1 h. The resulting precipitate was removed by filtration and the solvent removed from the filtrate under reduced pressure at 100°C. The residue was purified by column chromatography eluting with CH_2Cl_2/MeOH/NH_3 (90:9:1, R_f 0.5) to give the triol **13** as white needles (1.36 g, 84%); mp 70−72°C.

^{1}H NMR: δ = 7.25−7.11 (15 H, m, 3 C_6H_5), 4.58 (3 H, d, J = 6.1 Hz, OCH), 3.91 (3 H, d, $J_{\alpha,\beta}$ = 13.1 Hz, ArCH_αH$_\beta$), 3.71 (3 H, d, $J_{\beta,\alpha}$ = 13.1 Hz, ArCH$_\alpha H_\beta$), 2.86 (3 H, dq, J = 6.2, 6.6 Hz, 3 NCH), 2.17 (9 H, s, 3 NCH_3), 2.05 (9 H, s, 3 ArCH_3), 1.12 (9 H, d, J = 7.0 Hz, 3 CH_3).

^{13}C NMR: δ = 142.9, 137.5, 133.2 (C_{arom}), 127.8, 126.7, 126.4 (CH_{arom}), 74.7 (OCH), 60.2 (CH_2), 53.7 (NCH), 36.9 (NCH_3), 16.3 ($ArCH_3$), 10.0 (CH_3).

IR: ν = 3420 (OH), 3027 (CH, aromatic), 2963, 2920, 2870 (CH, alkyl), 1451 (CH, alkyl), 1383, 1354, 1264 (C−O), 760, 710 cm^{-1} (CH, aromatic).

MS: *m*/*z* (%) = 651 (M^+, 100), 634 (M^+ − OH, 20), 487 ($M^+ - C_{10}H_{14}NO$, 49), 323 ($M^+ - C_{20}H_{28}N_2O_2$, 61), 155 (37).

HRMS (FAB): *m/z* calcd for $C_{42}H_{58}N_3O_3$ (M^+ + H): 652.4478. Found: 652.4479.

(*S*)-1,3,5-Tris(2-hydroxymethylenepyrrolidin-1-ylmethylene)-2,4,6-trimethylbenzene (15)

(*S*)-(+)-2-Pyrrolidinemethanol (**14**; 760 mg, 7.5 mmol) and Et_3N (0.76 g, 7.5 mmol) were added to a solution of the tribromide **1** (1.00 g, 2.5 mmol) in chlorobenzene (15 mL). The mixture was stirred at r.t. overnight. The resulting precipitate was removed by filtration and the solvent removed from the filtrate under reduced pressure at 100°C. The residue was purified by column chromatography eluting with CH_2Cl_2/MeOH/NH_3 (90:9:1, R_f 0.4) to give the triol **15** as a white amorphous solid (911 mg, 79%); mp 116−118°C.

^{1}H NMR: δ = 3.90 (3 H, d, $J_{\alpha,\beta}$ = 12.8 Hz, ArCH_αH$_\beta$), 3.71 (3 H, d, $J_{\beta,\alpha}$ = 12.8 Hz, ArCH$_\alpha H_\beta$), 3.23−3.09 (6 H, m, 3 CH_2OH), 2.93−2.87 (3 H, m, 3 NCH_αH$_\beta$), 2.76−2.73 (3 H, m, 3 NCH), 2.52−2.43 (3 H, m, partially obscured, 3 NCH$_\alpha H_\beta$), 2.47 (9 H, s, 3 ArCH_3), 1.98−1.89 (3 H, m, 3 CH_αH$_\beta$), 1.78−1.64 (3 H, m, partially obscured, 3 CH$_\alpha H_\beta$), 1.78−1.64 (6 H, m, partially obscured, 3 CH_2).

^{13}C NMR: δ = 137.6, 134.8 (C_{arom}), 65.6 (CH), 64.2 (CH_2OH), 55.9 (NCH_2), 54.1 (ArCH_2), 29.5 (CH_2), 24.9 (CH_2), 18.2 (ArCH_3).

IR: ν = 3350 (OH), 2948, 2868, 2784 (CH, alkyl), 1457 (CH, alkyl), 1357, 1343 cm^{-1}(COH).

MS: *m/z* (%) = 460 (MH^+, 100), 443 (MH^+ − OH, 27), 429 (MH^+ − CH_2OH, 33), 360 (MH^+ − $C_5H_{10}NO$, 33), 266 (30), 155 (41).

HRMS (FAB): *m/z* calcd for $C_{27}H_{46}N_3O_3$ (M^+ + H): 460.3540. Found: 460.3548.

2,2-Dimethyl-4-phenylcarbonyl-5-diphenylmethanol-1,3-dioxolane (16)

Phenylmagnesium bromide (27.1 mL, 3.0 M in Et_2O, 81.4 mmol) was added dropwise to a solution of dimethyl 2,3-*O*-isopropylidene-L-tartrate (15.0 g, 68.8 mmol) in anhyd Et_2O (100 mL). The mixture was heated to reflux for 5 h, then allowed to cool and stirred at r.t. overnight, cooled to 0°C and quenched carefully with satd aq NH_4Cl solution (200 mL). The resulting layers were separated and the aqueous layer was washed with Et_2O (3 × 100 mL). The organic phases were combined and washed with satd aq NaCl solution (100 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The remaining oil was distilled under reduced pressure to remove the some of the unreacted tartrate. The residue was purified by gravity column chromatography (Et_2O/petroleum ether, 3:7) to yield the crude keto alcohol **16** (R_f 0.5) which was then recrystallised from EtOAc/hexane; white needles (0.42 g, 2%); mp 180−182°C, and tetraphenyl TADDOL (R_f 0.45) as white cuboids (5.64 g, 18%). The remaining mixture of unreacted tartrate and 2,2-dimethyl-4-methoxycarbonyl-5-diphenylmethanol-1,3-dioxolane could not be adequately separated.

^{1}H NMR: δ = 7.79−6.92 (15 H, m, 3 C_6H_5), 5.85 (1 H, d, *J* = 6.4 Hz, CH), 5.14 (1 H, d, *J* = 6.4 Hz, CH), 3.29 (1 H, s, OH), 1.51 (3 H, s, CH_3), 1.42 (3 H, s, CH_3).

^{13}C NMR: δ = 196.9 (C=O), 145.3, 142.4, 135.5 (C_{arom}), 133.3, 129.1, 128.2, 128.1, 127.4, 127.2, 127.1, 125.8 (CH_{arom}), 112.2 [*C*$(CH_3)_2$]), 80.7(CH), 77.0 (C−OH), 76.2 (CH), 27.0 (CH_3), 26.1 (CH_3).

IR: ν = 3420 (OH), 2955, 2942, 2853 (CH, alkyl), 1685 (C=O), 1449, 1374 (COH), 1212, 1151, 1041 (C-O), 753, 690 cm^{-1} (CH, arom).

MS: *m/z* (%) = 412 (M^+ + Na, 8), 167 (100), 104 (80).

Anal. calcd for $C_{25}H_{24}O_4$: C, 77.3; H, 6.2. Found: C, 77.0; H, 6.0.

1,3,5-Tris[(2,2-dimethyl-4-phenylcarbonyl-1,3-dioxolan-5-yl)diphenylmethoxy]methylene-2,4,6-trimethylmesitylene (17)

NaH (25 mg, 0.52 mmol, 50% dispersion in oil) was added with cooling to a solution of the keto alcohol **16** (200 mg, 0.515 mmol) in anhyd THF (20 mL) and the mixture stirred for 30 min before the catalyst Bu_4NI (19 mg, 0.051 mmol) and the tribromide **1** (68 mg, 0.17 mmol) were added. The mixture was stirred at r.t. overnight, filtered and the solvent removed under vacuum. The crude product was purified by column chromatography (Et_2O/petroleum ether, 4:7, R_f 0.4) to yield the triketone **17** as white needles (132 mg, 58%).

^{1}H NMR: δ = 7.49−7.07 (45 H, m, 9 C_6H_5), 5.73 (3 H, s, 3 CH), 5.19 (3 H, s, 3 CH), 4.53 (3 H, d, *J* = 11.9 Hz, 3 ArCH_αH$_\beta$), 4.44 (3 H, d, *J* = 11.6 Hz, 3 ArCH$_\alpha H_\beta$), 2.20 (9 H, s, 3 ArCH_3), 1.41 (9 H, s, 3 CH_3), 1.01 (9 H, s, 3 CH_3).

MS: *m/z* = 1344 (M^+ + Na), 973 (M^+ − $C_{25}H_{23}O_3$), 371 ($C_{25}H_{23}O_3$), 469, 205.

HRMS (FAB): *m/z* calcd for $C_{42}H_{72}NaO_3$ (M^++Na): 1344.5959. Found: 1344.5846.

Phenyltin Trichloride

$SnCl_4$ (9.77 g, 37.5 mmol) was added under N_2 to $SnPh_4$ (5.34 g, 12.5 mmol). The mixture was heated at 180°C for 12 h and allowed to cool to r.t. before being exposed to air for 10 min. The resulting liquid was then distilled at 150°C/2 Torr via Kugelrohr to yield the product as a colourless liquid (2.12 g, 56%).

^{119}Sn NMR: δ = −61.4.

Methyltin Complex of Ephedrine-Derived Triol 19

To a 5 mL round bottom flask purged with N_2 and charged with the ephedrine-derived triol **13** (40 mg, 0.061 mmol) and Et_3N (19 mg, 0.19 mmol) in anhyd $CDCl_3$ (0.5 mL) was added slowly $MeSnCl_3$ (15 mg, 0.061 mmol). The mixture was left for 30 min during which time a colourless precipitate formed. The liquid phase of the mixture was transferred via syringe to an NMR tube for spectroscopic analysis.

^{119}Sn NMR: δ = −267.8.

Phenyltin Complex of Ephedrine-Derived Triol 20

To a 5 mL round bottom flask purged with N_2 and charged with the ephedrine-derived triol **13** (40 mg, 0.061 mmol) and Et_3N (19 mg, 0.19 mmol) in anhyd $CDCl_3$ (0.5 mL) was added slowly $PhSnCl_3$ (19 mg, 0.061 mmol). The mixture was left for 30 min during which time a colourless precipitate formed. The liquid phase of the mixture was transferred via syringe to an NMR tube for spectroscopic analysis.

^{119}Sn NMR: δ = −390.7.

Methyltin Complex of Lactate-Derived Triol (21)

To an NMR tube purged with N_2 and charged with the lactate-derived triol **5** (50 mg, 0.11 mmol) in anhyd $CDCl_3$ (0.5 mL) was added slowly $MeSnCl_3$ (26 mg, 0.11 mmol). The mixture was left for 30 min before ^{1}H and ^{119}Sn NMR analyses were carried out. Both spectra indicated that no reaction had occurred. On the addition of Et_3N (32 mg, 0.32 mmol) a colourless precipitate formed. This was removed by filtration and the filtrate was analysed by NMR.

^{119}Sn NMR: δ = −233.8, −227.0 (1:1).

1-Phenylpropan-1-ol (23) (no excess of titanium tetraisopropoxide)

Titanium tetraisopropoxide (87 mg, 0.31 mmol) was added under N_2 to a solution of the ephedrine-derived triol **13** (200 mg, 0.31 mmol) in anhyd toluene (5 mL). The mixture was left for 1 h at r.t. before being exposed to a high vacuum (1 Torr) for 30 min. Benzaldehyde (326 mg, 3.1 mmol) was then added to the mixture which

was then allowed to stand at r.t. for a further 30 min. The mixture was then cooled to −10°C before diethylzinc (9.2 mL, 1.0 M in toluene, 9.2 mmol) was added and the mixture left to stand at 0°C for 48 h. The reaction was quenched with satd aq NH_4Cl solution (2 mL) and acidified with dil HCl. The layers were separated and the organic phase washed with satd aq Na_2CO_3 solution. The two layers were again separated and the combined aqueous layers washed with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure to give **23** as a colourless oil (374 mg, 89%) which was recognised by its ^{1}H NMR spectrum.

^{1}H NMR: δ = 7.35 −7.20 (5 H, m, C_6H_5), 4.55 (1 H, t, *J* = 6.3 Hz, CH), 1.70 (2 H, dt, *J* = 6.4, 7.3 Hz, CH_2), 0.92 (3 H, t, *J* = 7.3 Hz, CH_3). [Lit.[18] δ = 7.36−7.24 (5 H, m), 4.57 (1 H, t, *J* = 6.6 Hz), 1.86−1.71 (2 H, m), 0.90 (3 H, t, *J* = 7.6 Hz).

1-Phenylpropan-1-ol (23) (with an excess of titanium tetraisopropoxide)

The experiment described directly above was repeated using the same quantities of reagents, and extra Ti(*i*-PrO)$_4$ (872 mg, 3.1 mmol) was added to the reaction mixture at the same time as the benzaldehyde. Once again 1-phenylpropan-1-ol (**23**) was obtained as a colourless oil (387 mg, 93%) which gave ^{1}H NMR data identical to the previous experiment.

(*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl Chloride

A mixture of *(R)*-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (100 mg, 0.43 mmol) and $SOCl_2$ (2 mL) was heated to relux for 4 h. The mixture was allowed to cool, and the excess of thionyl chloride was removed under reduced pressure. The resulting acid chloride was used without purification.

1-Phenylpropan-1-yl (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenyl Acetate (24)

(*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (28 mg, 0.11 mmol) was added under N_2 to a solution of each sample of 1-phenylpropan-1-ol (15 mg, 0.11 mmol) in anhyd CCl_4 (5 drops) and anhyd pyridine (5 drops). Each mixture was left to stand at r.t. for 12 h, then H_2O (1 mL) and Et_2O (10 mL) were added. The layers were separated, and the organic phase was washed with dil HCl (1 mL) and satd aq $NaHCO_3$ solution and dried ($MgSO_4$). The solvent was removed under reduced pressure from each sample to give the ester **24** as a colourless oil.

(*S*)-1-Phenylpropan-1-yl (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenyl Acetate (*S*,*R*-24)

^{1}H NMR: δ = 7.42−7.20 (10 H, m, 2 C_6H_5), 5.93 (1 H, dd, *J* = 6.0, 7.9 Hz, CH), 3.56 (3 H, s, OCH_3), 2.08−1.85 (2 H, m, CH_2), 0.85 (3 H, t, *J* = 7.4 Hz, CH_3) [Lit.[17] δ = 7.66−7.00 (10 H, m), 5.90 (1 H, dd, *J* = 6.1, 7.7 Hz), 3.54 (3 H, q, *J* = 1.2 Hz), 2.10−1.75 (2 H, m), 0.83 (3 H, t, *J* = 7.3 Hz).

^{19}F NMR: δ = −73.2 [Lit.[17] δ = −72.2].

(*R*)-1-Phenylpropan-1-yl (*R*)-(−)-α-Methoxy-α-(trifluromethyl)phenyl Acetate (*R*,*R*-24)

^{1}H NMR: δ = 7.42−7.20 (10 H, m, 2 C_6H_5), 5.84 (1 H, dd, *J* = 6.4, 7.6 Hz, CH), 3.43 (3 H, s, OCH_3), 2.08−1.85 (2 H, m, CH_2), 0.94 (3 H, t, *J* = 7.3 Hz, CH_3) [Lit.[17] δ = 7.66−7.00 (10 H, m), 5.82 (1 H, dd, *J* = 6.4, 7.6 Hz), 3.45 (3 H, q, *J* = 1.2 Hz), 2.10−1.75 (2 H, m), 0.93 (3 H, t, *J* = 7.3 Hz).

^{19}F NMR: δ = −72.9 [Lit.[17] δ = −71.9].

In the sample from the reaction with one equivalent of Ti(OPr-*i*)$_4$, the ratio of these signals was 1:1. In the sample from the reaction with an excess of Ti(OPr-*i*)$_4$, the ratio was 45:55 (*SR*:*RR*).

Formation of Crystals of 15•3H$^+$2PF$_6^-$ NO$_3^-$

The pyrrolidine-derived triol **15** (200 mg, 0.44 mmol) in absolute EtOH (2 mL) was added to a solution of $Ni(NO_3)_2$•$6H_2O$ (152 mg, 0.44 mmol) in EtOH (2 mL). The solvent was removed under vacuum and the green solid was redissolved in H_2O (5 mL). A solution of NH_4PF_6 (212 mg, 1.3 mmol) in H_2O (2 mL) was added to the mixture which was left to stand overnight, after which time colourless crystals had formed. X-ray crystallographic analysis of a crystal identified it as a mixture of the cation **15•3H**$^+$, one NO_3^- and two PF_6^- counter ions.

Crystal Data for 15•3H$^+$(PF$_6$)$_2$(NO$_3$)

$C_{27}H_{48}F_{12}N_4O_6P_2$, *M* = 814.63, cubic, space group *P* 2$_1$ 3 (No. 198), *Z* = 4. At 296 K *a* = 15.240(1) Å, *V* = 3540(1) Å^3 and at 123 K *a* = 15.090(1) Å, *V* = 3436(1) Å^3. Disorder of the pyrrolidine residues and of a PF_6^- resulted in poor refinements (R = 0.09 for 1102 reflections with $I > 2\sigma(I)$ at 296 K and R = 0.11 for 1220 reflections at 123 K) with physically unreasonable bond lengths and anisotropic displacement parameters for the C6−C9 and O1 atoms. Although this disorder precludes detailed discussion of the crystal and molecular structure the X-ray analyses, together with the its chemical history, establish the chemical composition of the sample and the cation conformation.

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