Synthesis of C_2-symmetric analogues of 4-(pyrrolidino)pyridine: new chiral nucleophilic catalysts

Alan C. Spivey,*[a] Adrian Maddaford,[a] Tomasz Fekner,†[a] Alison J. Redgrave[b] and Christopher S. Frampton‡[c]

[a] *Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, UK S3 7HF*
[b] *GlaxoWellcome Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*
[c] *Roche Discovery Welwyn, 40 Broadwater Road, Welwyn Garden City, Hertfordshire, UK AL7 3AY*

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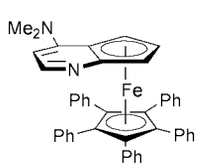
The syntheses of a series of enantiomerically pure C_2-symmetric 4-(pyrrolidino)pyridine (PPY) derivatives by S_NAr of 4-halo-/4-phenoxypyridines and by cyclocondensation from 4-aminopyridine are described. Preliminary results pertaining to their use as catalysts for acylative kinetic resolution of 1-phenylethanol are also presented. A single-crystal X-ray analysis of PPY **If** is reported.

Introduction

4-(Dimethylamino)pyridine (DMAP)[1,2] and 4-(pyrrolidino)-pyridine (PPY)[3] are potent nucleophilic catalysts for acyl transfer and related transformations.[3–7] In the last four years we[8–10] and others[11–24] have reported chirally modified derivatives of these structures as novel catalysts for enantioselective acyl transfer.[25] A number of such derivatives, notably Fu's planar-chiral DMAP **1**,[15–22] Fuji's chiral PPY **2**,[14] and our axially chiral DMAP **3**[8–10] offer practically useful levels of stereoselectivity in acylative kinetic resolutions (KRs)[26] or asymmetric desymmetrisations (ADs)[27] of alcohols. Prompted by a recent disclosure by Kotsuki[28] on the synthesis of (*S*)-prolinol-derived chiral PPY catalysts by pressure-promoted nucleophilic aromatic substitution (S_NAr) of 4-chloropyridine, we report here on the syntheses of a series of *trans*-2,5-disubstituted pyrrolidine-based C_2-symmetric PPY catalysts of general structure **I**, either by S_NAr of 4-halo-/4-phenoxy-pyridines or by cyclocondensation from 4-aminopyridine.



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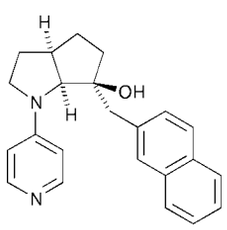

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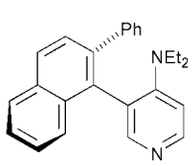

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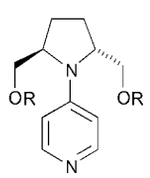

I

Preliminary results pertaining to the use of PPYs **I** as catalysts for KR of 1-phenylethanol are also described.

Our interest in *trans*-2,5-disubstituted pyrrolidine-based C_2-symmetric PPYs **I** as potential asymmetric acyl transfer catalysts arose from consideration of essentially two design tenets: the requirement for a DMAP derivative capable of exerting strict stereocontrol over the approach of a nucleophile (*e.g.* secondary alcohol) to the carbonyl of a derived acyl pyridinium salt, and the need to realise this without compromising the nucleophilicity, hence catalytic activity, of the pyridine nitrogen. These tenets constitute a dilemma as the introduction of stereogenic elements *ortho* to the pyridyl nitrogen, and thus proximal to the acyl pyridinium carbonyl group, strongly attenuate catalytic activity in acyl transfer processes.[5,11,29] However, Fuji *et al.* have shown that chiral PPY **2** can catalyse KR of certain *cis*-diol derivatives[14] and has proposed that ordering of the acyl pyridinium salt by face–face π–π interactions[30] between the 2-naphthyl substituent and the electron deficient acyl pyridinium ring§ is responsible for effective chirality transfer. Following molecular modelling studies, we envisaged that similar ordering influences, between the aryl ethers and the acyl pyridinium ring, might operate for C_2-symmetric PPYs **I**.[31] The decision to target structures with C_2 symmetry followed from the expectation that the presence of a C_2 axis of symmetry would serve to reduce the possible number of competing diastereomeric transition states available during acylative KR or AD processes.[32]

Results and discussion

Our first approach to the synthesis of C_2-symmetric chiral PPYs **I** involved an S_NAr reaction between *trans*-2,5-disubstituted pyrrolidines and pyridines containing a leaving group at the 4-position. Although the thermal reaction of 2,5-dimethylpyrroline (of unspecified stereochemistry) with 4-chloropyridine hydrochloride has been reported (21% yield, no experimental details provided),[3] highly substituted amines are known to be poorly nucleophilic and reluctant to participate in S_NAr reactions.[33] Using pyrrolidines **7** and **8** (>98%

† *Present address*: Department of Chemistry, The Ohio State University, 100 West 18th Ave., Columbus, OH 43210, USA.
‡ Author to whom correspondence regarding single-crystal X-ray analysis should be addressed.

§ As evidenced by ^{1}H NMR chemical shift and NOE data for the acylated and non-acylated forms of this catalyst.

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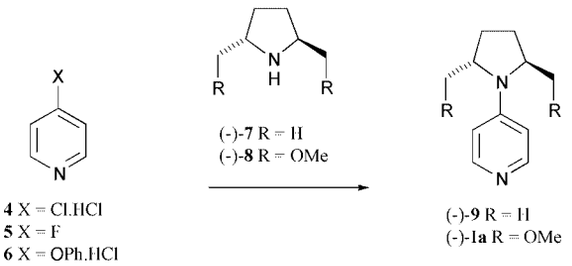
Table 1 S_NAr coupling between 4-substituted pyridines and *trans*-2,5-disubstituted pyrrolidines



4 X = Cl.HCl
5 X = F
6 X = OPh.HCl

(-)-**9** R = H
(-)-**1a** R = OMe

	% Yield (product)		
Pyrrolidine	Method A[a]	Method B[b]	Method C[c]
7	~50[d] (**9**)	~80[d] (**9**)	~90,[d] 50[e] (**9**)
8	—	0 (**Ia**)	<10[d] (**Ia**)

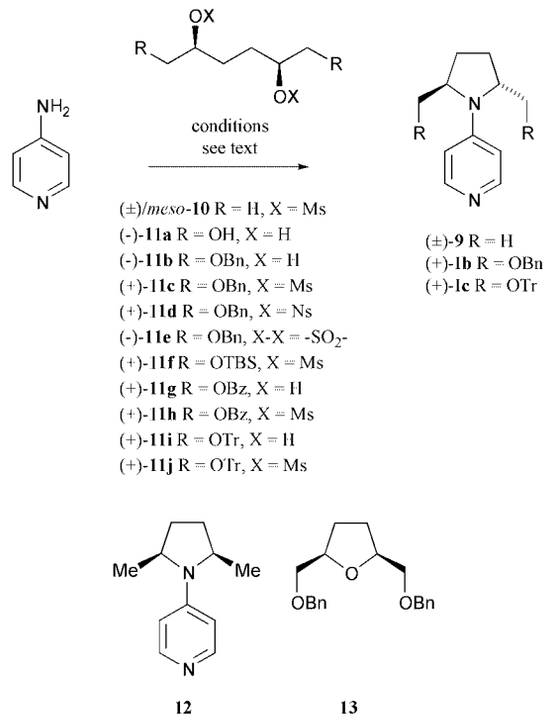
[a] Conditions: pyridine **4**–pyrrolidine **7**–K_2CO_3 (1:1.5:2), 110 °C, 15 h. [b] Conditions: pyridine **5**–pyrrolidine (**7**/**8**)–K_2CO_3 (1:1.7:1), DMF, 95 °C, 22 h. [c] Conditions: pyridine **6**–pyrrolidine (**7**/**8**) (1:1.3), 200 °C, 22 h. [d] By NMR integration. [e] Isolated by distillation.

ee[34,35] and >95% ee,[36] respectively), a series of exploratory thermal reactions was carried out (Table 1). The best procedure for the synthesis of chiral PPY **9** from pyrrolidine **7** involved heating 4-phenoxypyridine **6** at 200 °C in a bomb (~90% by ^{1}H NMR, 50% isolated following distillation). However, under identical conditions pyrrolidine **8** gave just traces of coupled product **Ia**, presumably because the alkoxy substituents inductively decrease its nucleophilicity relative to pyrrolidine **7**. An alternative route to the desired chiral PPYs **I** was therefore sought.

Thermal extrusion of SO_2 from pyridine-4-sulfonamides was briefly explored. Analogous extrusions of SO_2 from pyridine-4-sulfonyl chloride,[37] pyridine-4-sulfonohydrazides,[38] 4-(*N*-methylsulfonyl)-2,3,5,6-tetrachloropyridine,[39] *N*-alkyl-2,4-dinitrobenzenesulfonamides,[40] but not *N*,*N*-dialkylsulfonamides[41–43] are known. Disappointingly, SO_2 extrusion from 4-(pyrrolidinosulfonyl)pyridine[43] could not be induced under any of the conditions explored [(a) mesitylene ±TMSOTf (1 eq.), reflux; (b) DMSO, 150 °C; (c) ethylene glycol, reflux; (d) AcOH ±H_2O_2 (2 eq.), reflux].

We also explored Pd(0)-catalysed amination[44,45] of 4-bromopyridine as a number of unhindered secondary amines (*e.g.* morpholine,[46] dibutylamine,[47] diallylamine[48] and *N*-methylaniline[49]) have been successfully coupled to 4-halopyridines in this manner. We were able to readily reproduce Buchwald's[46] $Pd(OAc)_2$-catalysed coupling of morpholine with 4-bromopyridine to give 4-(*N*-morpholino)pyridine in 95% yield, but attempts to couple the more sterically demanding pyrrolidine **7** using these conditions failed.

Next we explored the construction of the chiral pyrrolidine around the exocyclic nitrogen of 4-aminopyridine. The synthesis of *N*-substituted 2,5-bis(alkoxymethyl)pyrrolidines (and isostructural borolanes[50] and phospholanes[51–53]) from enantiomerically pure 1,4-dimesylates,[54,55] 1,4-ditosylates,[55–57] 1,4-ditriflates,[55,58,59] and 1,4-cyclic sulfates[51] by cyclocondensation with primary amines is well known.[60] The feasibility of employing poorly nucleophilic 4-aminopyridine was first established by a cyclocondensation reaction between 2,5-bis-(methylsulfonyloxy)hexane **10** and the disodium salt of 4-aminopyridine[61] to give a ~1:1 mixture of PPYs (±)-**9** and **12** in 98% yield (Scheme 1).¶ For the synthesis of chiral PPYs



12 **13**

Scheme 1

I an efficient synthesis of enantiomerically pure tetrol **11a**[56,57,62] was required. We employed an established route from D-mannitol (5 steps, 42% overall yield)‖ in preference to one from hexa-1,5-diene involving isomer separation.[57] Selective protection of the primary hydroxy groups in tetrol **11a** with benzyl,[55,56,67] TBS,[68,69] TBDPS,[55] benzoyl,[66] and pivaloyl[66] groups has been reported previously. We initially opted to protect tetrol **11a** as the 1,6-dibenzyl ether *via* the bis(dibutylstannylene) acetal**[67] and to activate the 2,5-hydroxy groups as mesylates to give cyclocondensation precursor **11c**[67] (Scheme 1). Reaction of mesylate **11c** with the dianion of 4-aminopyridine under the conditions optimised for mesylate **10** gave the desired chiral PPY **Ib** in 40% yield, along with 52% of the *meso*-tetrahydrofuran derivative **13**. This transformation defied our attempts at optimisation. The corresponding nosyl derivative **11d** (nosyl = 4-nitrophenylsulfonyl) cyclocondensed to give exclusively tetrahydrofuran **13**

¶ A ratio of 5:2:1, NaH–4-aminopyridine–mesylate **10**, is required in this reaction. This appears to be due to the inability of NaH to form more than 50% of the disodium salt of 4-aminopyridine as judged by monitoring the evolution of H_2 during deprotonation in THF.

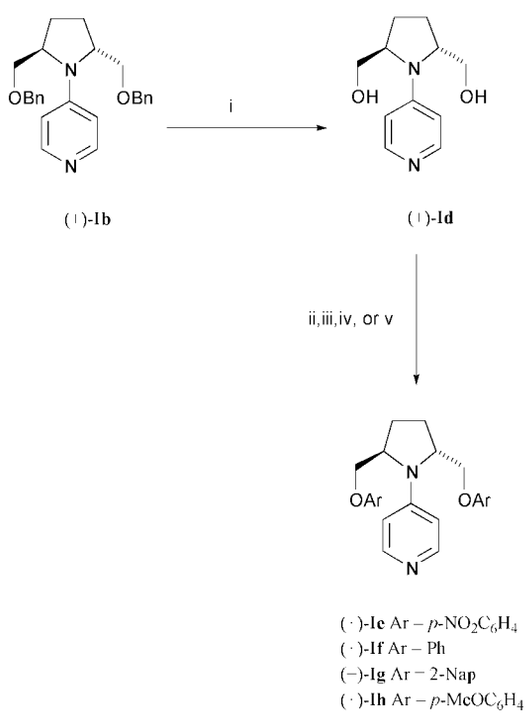
‖ Synthesis of tetrol **11a** from D-mannitol. 1) Formation of 1,2:5,6-bis(acetonide) using 2,2-dimethoxypropane–TsOH (60%).[63] 2) Conversion to the 3,4-thiocarbonate using thiophosgene–DMAP (87%).[64] 3) Corey–Winter type alk-3(4)-ene formation using $P(OEt)_3$ by a modification of the method of Haines (91%).[65] Complete hydrolysis of excess $P(OEt)_3$ following this reaction requires refluxing the crude reaction product with 6 M NaOH for 48 h (*cf.* prolonged stirring at rt). 4) Alkene hydrogenation using H_2 over Rh–Al_2O_3 by a modification of the methods of Marzi[56] and Kibayashi[66] (95%). The use of H_2 (1 atm) in THF[66] results in the formation of a number of unidentified by-products, particularly on a large scale. This can be circumvented by the use of H_2 (70 atm) in EtOH. The use of recrystallised alkene for this hydrogenation is also crucial as traces of phosphite, or phosphite-derived impurities, result in the formation of significant quantities of by-products. 5) Acetonide hydrolysis in refluxing 2 M HCl (~93%).[66]

** The duration of the reaction between the *in-situ* formed bis-(stannylene) acetal and BnBr–Bu_4NBr is critical to the ratio of 1,6-di-:1,2,6-tri-benzylated products obtained. Reaction times of 1–1.5 h (*cf.* Kibayashi, 1 h)[67] reproducibly give the desired 1,6-dibenzylated product **11b** in 50–60% yield [with 10–30% 1,2,6-tribenzylated product which can be readily recycled to tetrol **11a** by hydrogenation: 10% Pd–C, THF, H_2 (1 atm)] whereas longer periods (*cf.* Marzi, 24 h)[55] result in almost exclusive tribenzylation. An improved work-up for this reaction incorporates an extraction with 3 M NaOH to remove tin-containing by-products[70] thereby facilitating subsequent chromatography.

under analogous conditions. In contrast, cyclic sulfate **11e** gave the desired chiral PPY **Ib** in 52% yield, although the overall yield from tetrol **11a** was very similar to that *via* mesylate **11c**, a consequence of the slightly lower yield of cyclic sulfate formation.

Given the rather moderate efficiency of the mesylate and cyclic sulfate cyclocondensations, we explored alternative protecting group regimes. Although TBS ether **11f**[67] and benzoyl ester **11h**††[73] failed to give any cyclised products,‡‡ the trityl ether **11j** cyclocondensed to give chiral PPY **Ic** in 42% yield. Since this did not represent a significant improvement over the cyclocondensation using benzyl ether protected mesylate **11c**, we chose to concentrate our efforts towards the target aryl ether PPYs from benzyl ether **Ib**.

Benzyl ether hydrogenolysis of chiral PPY **Ib** with purification using an isolute-SCX ion-exchange cartridge afforded diol **Id** in 94% yield.§§ The synthesis of aryl ether derivatives **Ie**–**Ih** under Mitsunobu conditions was then explored (Scheme 2).[74]

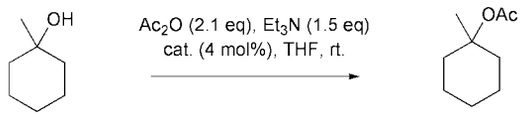


Scheme 2 *Reagents*: i, Pd–C, H_2; ii, *p*-$NO_2C_6H_4OH$, DEAD, PPh_3; iii, PhOH, ADDP, PBu_3; iv, 2-naphthol, ADDP, PBu_3; v, *p*-$MeOC_6H_4OH$, TMAD, PBu_3.

Ether **Ie** was prepared from diol **Id** and *p*-nitrophenol in 88% yield using standard DEAD–PPh_3-based Mitsunobu coupling conditions. Ethers **If** and **Ig** were prepared from phenol and 2-naphthol in 81 and 83% yields respectively, using Tsunoda's ADDP–PBu_3 REDOX system (ADDP = 1,1′-(azodicarbonyl)-dipiperidine).[75] Ether **Ih** was prepared from *p*-methoxyphenol in 83% yield using Tsunoda's TMAD–PBu_3 REDOX system (TMAD = *N*,*N*,*N*′,*N*′-tetramethylazocarboxamide).[14]

The structure of phenyl ether **If** was unequivocally determined by single-crystal X-ray analysis (Fig. 1). There are no intramolecular face–face π–π interactions between the phenyl groups and the pyridine ring in the crystal lattice. This may be due to the competition provided by intermolecular π–π interactions between interleaved phenyl groups (*i.e.* crystal packing forces), but intramolecular stacking prior to pyridinium salt formation was in any case not expected.[3]

Table 2 Catalysis of acylation of hindered alcohol, 1-methylcyclohexanol, with Ac_2O–Et_3N



Catalyst	Ratio of alcohol : acetate by GC	
	After 10 h	After 24 h
No catalyst	99 : 1	98 : 2
DMAP	10 : 90	2 : 98
PPY	7 : 93	1 : 99
(−)-**9**	7 : 93	2 : 98
(+)-**If**	34 : 66	24 : 76
(+)-**Ih**	90 : 10	80 : 20

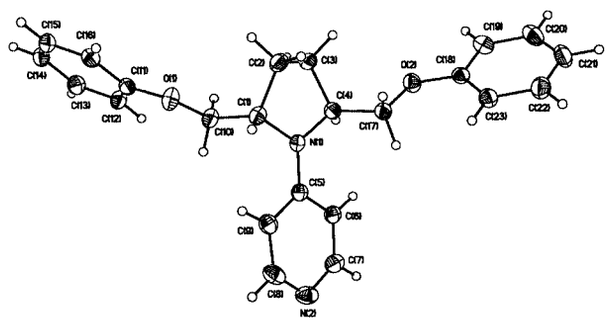


Fig. 1 X-Ray crystal structure of bis(phenyl ether) **If**.

Representative PPYs (−)-**9**, (+)-**If**, and (+)-**Ih** were shown to catalyse the acetylation of 1-methylcyclohexanol with Ac_2O under standard conditions (Table 2).[76] The catalytic activity of PPY (−)-**9** is comparable to that of DMAP but PPYs (+)-**If** and (+)-**Ih** show diminished activity. Since the rate-determining step for DMAP-catalysed acylation is the reaction of the alcohol with the acylpyridinium salt, the observed rate is a function of the concentration and reactivity of the acylpyridinium salt in solution.[76] It seems likely in these cases that the observed rate differences reflect primarily the respective acylpyridinium salt concentrations in solution, as PPYs (+)-**If** and (+)-**Ih** both displayed poor solubility under the test conditions.

PPYs (−)-**9**, (+)-**Ib**, (+)-**Ic** and (+)-**Ie**–**h** have also been subject to preliminary screening for their ability to effect KR of 1-phenylethanol with Ac_2O under standard conditions (Table 3). The selectivity factors obtained (s = 1.1–1.8)[77] are significantly lower than the accepted threshold of s = 7 required for a synthetically useful KR reaction.[26] Furthermore, given that the selectivities displayed by the aryl ether containing catalysts (+)-**Ie**–**h** are comparable to that of catalyst (−)-**9**, lacking aryl ether appendages, it is clear that the desired ordering interactions within the former either are not taking place or are ineffective for chirality transfer. Studies are ongoing using these and structurally related catalysts to address these issues and to delineate more efficient KR conditions.

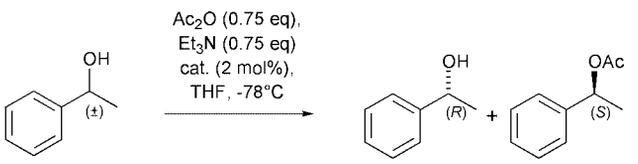
In summary, a series of novel chiral C_2-symmetric PPYs have been prepared and shown to catalyse the acylation of secondary alcohols. The efficient KR of secondary alcohols using these catalysts has not yet been achieved, however studies towards this goal are ongoing.

†† Mesylate **11h** was prepared using a variant of the method of Kibayashi[67] employing just catalytic quantities of tin.[71,72]

‡‡ Marzi has noted that the corresponding di-OTBDPS ditosylate fails to undergo thermal cyclisation with benzylamine and attributed this failure to steric effects.[55] However, in view of the successful cyclisation of the ditrityl derivative **11j** we believe that the failure of di-OTBS derivative **11f** to cyclise under our conditions is due to deprotection of these silyl groups during the reaction as **11f** is not recovered following work-up.

§§ These contain sulfonic acid-derivatised silica and are available from International Sorbent Technology Ltd., IST House, Duffryn Industrial Estate, Hengoed, Mid Glamorgan, UK CF82 7R3.

Table 3 KR of 1-phenylethanol using C_2-symmetric PPYs



Catalyst	*T*/min	*C*[a] (%)	(*R*)-Alcohol Ee_A (%)[b]	(*S*)-Acetate Ee_E (%)[b]	*s*
(−)-**9**	120	68.9	15.7[c]	6.6[c]	1.3
	328	75.5	21.7[c]	4.9[c]	1.3
(+)-**Ib**	120	45.8	18.0	14.5	1.8
	330	50.5	20.2	14.2	1.8
(+)-**Ic**	120	35.4	1.9	2.9	1.1
	330	40.8	3.0	2.4	1.1
(+)-**Ie**	120	9.5	1.8	16.7	1.4
	445	18.6	3.3	13.3	1.4
(+)-**If**	120	17.6	4.2	15.9	1.6
	520	45.4	8.3	14.3	1.3
(+)-**Ig**	120	15.8	3.2	17.0	1.5
	526	38.5	9.9	16.3	1.5
(+)-**Ih**	120	25.4	3.3	15.7	1.3
	510	31.0	6.8	16.8	1.5

[a] Conversion by (HPLC) mass balance. [b] By HPLC using a Chiralcel OD column. [c] (*S*)-Alcohol and (*R*)-acetate obtained as major enantiomers.

Experimental

General

All reactions were performed under anhydrous conditions and an inert atmosphere of nitrogen in flame-dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise indicated. Reagents were used as obtained from commercial sources or purified according to known procedures.[78] Flash chromatography was carried out using Merck Kieselgel 60 F_{254} (230–400 mesh) silica gel. Only distilled solvents were used as eluents. Thin layer chromatography (TLC) was performed on Merck DC-Alufolien or glass plates pre-coated with silica gel 60 F_{254} which were visualised either by quenching of ultraviolet fluorescence (λ_{max} = 254 nm) or by charring with 5% w/v phosphomolybdic acid in 95% EtOH, 10% w/v ammonium molybdate in 1 M H_2SO_4, or 10% $KMnO_4$ in 1 M H_2SO_4. Observed retention factors (R_f) are quoted to the nearest 0.05. All reaction solvents were distilled before use and stored over activated 4 Å molecular sieves, unless otherwise indicated. Anhydrous CH_2Cl_2 was obtained by refluxing over CaH_2. Anhydrous THF and Et_2O were obtained by distillation, immediately before use, from sodium–benzophenone ketyl under an inert atmosphere of nitrogen. Anhydrous DMF was obtained by distillation from CaH_2 under reduced pressure. Petrol refers to the fraction of light petroleum boiling between 40 and 60 °C. High resolution mass spectrometry (HRMS) measurements are valid to ±5 ppm. GC was performed on a Perkin-Elmer series 8600 instrument employing air/helium as carrier gas and using flame ionisation detection. HPLC was performed on a Hewlett-Packard series 1100 instrument using UV detection (monitoring at 211 ± 8 nm and referenced to 525 ± 50 nm). 4-Fluoropyridine **5** was prepared according to the method of Desai.[79] 4-(Pyrrolidinosulfonyl)pyridine[43] was prepared from 4-mercaptopyridine according to the method of Talik and Plazek.[41]

4-[(2*R*,5*R*)-2,5-Dimethylpyrrolidino]pyridine 9

An intimate mixture of 4-phenoxypyridine hydrochloride **6**[3] (1.4 g, 6.1 mmol) and (2*R*,5*R*)-2,5-dimethylpyrrolidine[34] (0.786 g, 7.94 mmol) was heated in a sealed tube at 200 °C for 24 h. The reaction was cooled, diluted with Et_2O (20 cm^3), and acidified with 1 M HCl (10 cm^3). The aqueous phase was washed with Et_2O (2 × 20 cm^3), basified with 10% NaOH (10 cm^3) and extracted with Et_2O (3 × 30 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting brown oil was purified by distillation (160 °C/0.3 mmHg) to give *pyridine* **9** as a clear yellow oil (0.537 g, 50%). R_f 0.40 (NH_3 saturated MeOH–CH_2Cl_2, 1:19); $[a]_D^{25}$ −119 (*c* 5.0 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1644, 1596, 1552, 1537, 1461, 1410, 1382, 1338, 1239, 1164; δ_H ($CDCl_3$) 1.20 (6H, d, *J* = 7.0 Hz, 2 × CH_3), 1.60–1.75 (2H, m, CH_2), 2.16–2.30 (2H, m, CH_2), 3.93–4.07 (2H, m, 2 × CH), 6.35 (2H, d, *J* = 6.5 Hz, 2 × CH), 8.12 (2H, d, *J* = 6.5 Hz, 2 × CH); δ_C ($CDCl_3$) 17.80 (2 × CH_3), 30.03 (2 × CH_2), 52.85 (2 × CH), 108.43 (2 × CH), 149.35 (2 × CH) and 149.84 (C_q); *m*/*z* (EI$^+$) (rel. intensity) 176 (M$^+$, 24%), 161 (100) and 78 (15). HRMS calcd. for $C_{11}H_{16}N_2$ (M$^+$) 176.1313, found 176.1311.

trans-3,4-Didehydro-3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-D-*threo*-hexitol[65,80]

A solution of 1,2:5,6-di-*O*-isopropylidene-3,4-*O*-thioxocarbonyl-D-mannitol[65] (52 g, 0.17 mol) and triethyl phosphite (265 cm^3) was heated at reflux for 17 h. The mixture was cooled to room temperature and 6 M NaOH (400 cm^3) added dropwise. After 2 days heating at reflux the reaction mixture was cooled and extracted with CH_2Cl_2 (3 × 300 cm^3). The combined organic extracts were washed with water (2 × 500 cm^3), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Recrystallisation from *n*-pentane gave the *title compound* as clear colourless needles (35.7 g, 91%). Mp 82–83 °C [lit.,[65] 80–82 °C (petrol)]; R_f 0.65 (EtOAc–petrol, 3:7); $[a]_D^{20}$ +68.6 (*c* 1.0 in $CHCl_3$) [lit.,[80] $[a]_D^{20}$ +58.8 (*c* 1.02 in $CHCl_3$)]; δ_H ($CDCl_3$) 1.39 (6H, s, 2 × CH_3), 1.43 (6H, s, 2 × CH_3), 3.6 (2H, t, *J* = 7.9 Hz, CH_2), 4.1 (2H, dd, *J* = 7.9, 6.3 Hz, CH_2), 4.45–4.57 (2H, m, 2 × CH), 5.76–5.84 (2H, m, CH); *m*/*z* (EI$^+$) (rel. intensity) 228 (M$^+$, 21%), 213 (79), 95 (67) and 72 (100).

3,4-Dideoxy-1,2:5,6-di-*O*-isopropylidene-D-*threo*-hexitol[56,66]

To a solution of *trans*-3,4-didehydro-3,4-dideoxy-1,2:5,6-di-*O*-isopropylidene-D-*threo*-hexitol (12.6 g, 55.3 mmol) in absolute EtOH (100 cm^3) was added 5% Rh–Al_2O_3 (0.32 g, 2.5% w/w). The mixture was stirred vigorously under hydrogen (1 atm) for 10 h. The mixture was then filtered through a Celite pad, concentrated *in vacuo*, and distilled to give the *title compound* as a clear colourless oil (12.1 g, 95%). R_f 0.60 (EtOAc–petrol, 3:7); $[a]_D^{20}$ +10.0 (*c* 2.0 in MeOH) [lit.,[66] $[a]_D^{23}$ +17.5 (*c* 5.78 in MeOH)]; δ_H ($CDCl_3$) 1.3 (6H, s, 2 × CH_3), 1.35 (6H, s, 2 × CH_3), 1.45–1.75 (4H, m, 2 × CH_2), 3.48–3.52 (2H, m, CH_2), 3.96–4.15 (4H, m, CH_2 + 2 × CH); *m*/*z* (CI$^+$) (rel. intensity) 231 (MH$^+$, 93%), 215 (100), 173 (80), 157 (84) and 72 (75).

(2*S*,5*S*)-1,6-Bis(benzyloxy)hexane-2,5-diol[56,67] 11b and (2*S*,5*S*)-1,2,6-tris(benzyloxy)hexan-5-ol

Tetrol **11a**[67] (21.8 g, 0.145 mol) was placed in a round bottomed flask (1 l) fitted with a Dean–Stark trap. Toluene (450 cm^3) and dibutyltin oxide (72 g, 0.29 mol) were added and the mixture was heated at reflux for 17 h. The reaction mixture was allowed to cool to room temperature and treated with tetrabutylammonium bromide (46.9 g, 0.145 mol) followed by benzyl bromide (73 cm^3, 0.61 mol). The mixture was heated to reflux for 75 min, cooled and poured into water (500 cm^3). After 2 h, the reaction mixture was filtered through a Celite pad. The organic phase was separated, washed with 3 M NaOH (500 cm^3), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with ethyl acetate–petrol (1:3) gave the following compounds.

Diol 11b.[67] (23.5 g, 49%) As a clear colourless oil. R_f 0.20 (EtOAc–petrol, 1:1); $[a]_D^{21}$ −10.0 (*c* 1.0 in MeOH) [lit.,[56] $[a]_D^{25}$

−5.9 (*c* 1.0 in MeOH)]; δ_H ($CDCl_3$) 1.55–1.65 (4H, m, 2 × CH_2), 3.35 (2H, dd, *J* = 9.4, 7.6 Hz, CH_2), 3.50 (2H, t, *J* = 7.0 Hz, CH_2), 3.77–3.91 (2H, m, 2 × CH), 4.54 (4H, s, 2 × CH_2), 7.26–7.39 ($10H_{arom}$, m); *m*/*z* (EI^+) (rel. intensity) 330 (M^+, 14%), 191 (53) and 91 (100).

(2*S*,5*S*)-1,2,6-Tris(benzyloxy)hexan-5-ol. (16.5 g, 27%) As a clear colourless oil. R_f 0.35 (EtOAc–petrol, 3:7); $[\alpha]_D^{21}$ −4.1 (*c* 2.4 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3005, 2913, 2855, 1450 and 1093; δ_H ($CDCl_3$) 1.45–1.85 (4H, m, 2 × CH_2), 3.30–3.85 (6H, m, 2 × CH_2 + 2 × CH), 4.55–4.75 (6H, m, 3 × CH_2), 7.26–7.39 ($15H_{arom}$, m); δ_C ($CDCl_3$) 27.81 (CH_2), 28.92 (CH_2), 70.22 (CH), 71.96 (CH_2), 72.09 (CH_2), 72.70 (2 × CH_2), 73.37 (CH_2), 77.74 (CH), 127.59 (CH), 127.70 (CH), 127.81 (CH), 127.91 (CH), 128.38 (CH), 128.44 (CH), 128.51 (CH), 138.09 (C_q), 138.36 (C_q) and 138.76 (C_q); *m*/*z* (CI^+) (rel. intensity) 421 (M^+, 52%), 191 (42) and 91 (100). HRMS calcd. for $C_{27}H_{33}O_4$ (M^+) 421.2379, found 421.2366.

Hydrogenolysis of (2*S*,5*S*)-1,2,6-tris(benzyloxy)hexan-5-ol to give (2*S*,5*S*)-hexane-1,2,5,6-tetrol[67] 11a

To a solution of (2*S*,5*S*)-1,2,6-tris(benzyloxy)hexan-5-ol (6.2 g, 15 mmol) in THF (25 cm^3) was added 10% Pd–C (0.6 g, 10% w/w). The mixture was stirred vigorously under hydrogen (1 atm) for 20 h, filtered through a Celite pad, and concentrated *in vacuo* to give *tetrol* **11a** (2.2 g, 99%) as a white amorphous solid. Mp 92–94 °C [lit.,[67] 92–94 °C (MeOH)]; $[\alpha]_D^{20}$ −17.8 (*c* 1.7 in MeOH) [lit.,[67] $[\alpha]_D^{26}$ −24.0 (*c* 1.69 in MeOH)]; δ_H (D_2O) 1.15–1.6 (4H, m, 2 × CH_2), 3.4–3.8 (6H, m, 2 × CH + 2 × CH_2); *m*/*z* (CI^+) (rel. intensity) 168 (MNH_4^+, 42%), 151 (MH^+, 100%) and 101 (42).

(2*S*,5*S*)-1,6-Bis(benzyloxy)-2,5-bis(methylsulfonyloxy)hexane[67] 11c

To a solution of diol **11b** (11 g, 0.033 mol) in CH_2Cl_2 (150 cm^3) was added Et_3N (18 cm^3, 0.13 mol). The mixture was cooled to 0 °C and methanesulfonyl chloride (7.7 cm^3, 0.099 mol) added dropwise. After 90 min the reaction mixture was washed with water (2 × 100 cm^3). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with CH_2Cl_2–EtOAc (4:1) gave *mesylate* **11c** as an amorphous white powder (16.0 g, 99%). R_f 0.25 (EtOAc–petrol, 3:7); $[\alpha]_D^{20}$ +8.5 (*c* 1.2 in $CHCl_3$); δ_H ($CDCl_3$) 1.76–1.83 (4H, m, 2 × CH_2), 3.02 (6H, s, 2 × CH_3), 3.42–3.67 (4H, m, 2 × CH_2), 4.51 (2H, d, *J* = 11.6 Hz, CH_2), 4.56 (2H, d, *J* = 11.6 Hz, CH_2), 4.86–4.97 (2H, m, 2 × CH), 7.25–7.48 ($10H_{arom}$, m); *m*/*z* (EI^+) (rel. intensity) 504 (MNH_4^+, 95%), 331 (58), 318 (76) and 91 (100).

(±)-4-(2,5-Dimethylpyrrolidino)pyridine (±)-9 and *meso*-4-(2,5-dimethylpyrrolidino)pyridine 12

Sodium hydride (60% dispersion in mineral oil, 0.53 g, 13 mmol) was washed with hexane (3 × 15 cm^3) and volatiles were removed *in vacuo*. A solution of 4-aminopyridine (0.50 g, 5.3 mmol) in THF (20 cm^3) was added and the mixture stirred for 3 h. After addition of a solution of 2,5-bis(methylsulfonyloxy)hexane [~1:1 (±)-:*meso*][35] (0.73 g, 2.7 mmol) in THF (10 cm^3), the reaction mixture was heated at reflux for 20 h. The reaction mixture was cooled to room temperature, carefully quenched with 1 M NH_4OH and extracted with CH_2Cl_2 (3 × 100 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with absolute ethanol gave a mixture of *pyridines* (±)-**9** and **12** (~1:1 by ^1H NMR) as a brown oil (0.46 g, 98%). R_f 0.40 (NH_3 saturated MeOH–CH_2Cl_2, 1:19); ν_{max}/cm^{-1} ($CHCl_3$) 1644, 1596, 1552, 1537, 1461, 1410, 1382, 1338, 1239, 1164; δ_H ($CDCl_3$) 1.10 (6H, d, *J* = 7.0 Hz, 2 × CH_3), 1.25 (6H, d, *J* = 7.0 Hz, 2 × CH_3), 1.6–1.8 (4H, m, 2 × CH_2), 2.0–2.25 (4H, m, 2 × CH_2), 3.75–3.90 (2H, m, 2 × CH), 3.93–4.05 (2H, m, 2 × CH), 6.34–6.43 (4H, m, 4 × CH), 8.07–8.21 (4H, m, 4 × CH); *m*/*z* (EI^+) (rel. intensity) 176 (M^+, 24%), 161 (100) and 78 (15). HRMS calcd. for $C_{11}H_{16}N_2$ (M^+) 176.1313, found 176.1311.

4-[(2*R*,5*R*)-2,5-Bis(benzyloxymethyl)pyrrolidino]pyridine Ib and *meso*-2,5-bis(benzyloxymethyl)oxolane 13. Method I

Sodium hydride (60% dispersion in mineral oil, 0.99 g, 25 mmol) was washed with hexane (3 × 10 cm^3) and the volatile components were removed *in vacuo*. A solution of 4-aminopyridine (1.16 g, 12.4 mmol) in THF (20 cm^3) was added and the mixture stirred for 3 h. Mesylate **11c** (3.0 g, 6.2 mmol) in THF (10 cm^3) was added and the mixture heated at reflux for 20 h. The reaction was cooled to room temperature, carefully quenched with 1 M NH_4OH (150 cm^3), and extracted with CH_2Cl_2 (2 × 300 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with petrol–EtOAc (2:1) and then EtOH gave the following compounds.

Pyridine Ib. As a pale yellow oil (0.96 g, 40%). R_f 0.40 (NH_3 saturated MeOH–CH_2Cl_2, 1:19); $[\alpha]_D^{17}$ +89 (*c* 1.6 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2930, 1592, 1503, 1454, 1377, 1093 and 1004; δ_H ($CDCl_3$) 1.97–2.19 (4H, m, 2 × CH_2), 3.22 (2H, dd, *J* = 9.5, 8.2 Hz, CH_2), 3.53 (2H, dd, *J* = 9.5, 3.1 Hz, CH_2), 3.92–4.04 (2H, m, 2 × CH), 4.47 (4H, s, 2 × CH_2), 6.35 (2H, d, *J* = 5.8 Hz, 2 × CH), 7.23–7.39 ($10H_{arom}$, m), 8.10 (2H, d, *J* = 5.8 Hz, 2 × CH); δ_C ($CDCl_3$) 26.75 (2 × CH_2), 57.24 (2 × CH), 68.17 (2 × CH_2), 73.32 (2 × CH_2), 108.64 (2 × CH), 127.68 (4 × CH), 127.83 (2 × CH), 128.47 (4 × CH), 137.96 (2 × C_q), 149.77 (2 × CH) and 150.00 (C_q); *m*/*z* (EI^+) (rel. intensity) 388 (M^+, 25%), 267 (100) and 91 (81). HRMS calcd. for $C_{25}H_{28}O_2N_2$ (M^+) 388.2151, found 388.2143.

Oxolane 13. As a pale yellow oil (1.00 g, 52%). R_f 0.20 (EtOAc–petrol, 1:9); ν_{max}/cm^{-1} ($CHCl_3$) 2864, 1719, 1703, 1600, 1493, 1149, 1231 and 1085; δ_H ($CDCl_3$) 1.63–1.78 (2H, m, CH_2), 1.87–2.01 (2H, m, CH_2), 3.42–3.56 (4H, m, 2 × CH_2), 4.07–4.20 (2H, m, 2 × CH), 4.50–4.63 (4H, m, 2 × CH_2), 7.25–7.38 ($10H_{arom}$, m); δ_C ($CDCl_3$) 27.99 (2 × CH_2), 72.88 (2 × CH_2), 73.36 (2 × CH_2), 78.68 (2 × CH), 127.58 (2 × CH), 127.72 (4 × CH), 128.37 (4 × CH) and 138.39 (2 × C_q); *m*/*z* (CI^+) (rel. intensity) 330 (MNH_4^+, 26%), 313 (MH^+, 10%), 221 (67) and 91 (100). HRMS calcd. for $C_{20}H_{25}O_3$ (M^+) 313.1804, found 313.1789.

(2*S*,5*S*)-1,6-Bis(benzyloxy)-2,5-bis(*p*-nitrophenylsulfonyloxy)-hexane 11d

To a solution of diol **11b** (0.45 g, 1.4 mmol) in CH_2Cl_2 (10 cm^3) was added Et_3N (0.76 cm^3, 5.5 mmol). The mixture was cooled to 0 °C and *p*-nitrobenzenesulfonyl chloride (0.91 g, 4.1 mmol) was added portionwise with stirring over 15 min. The mixture was stirred for 3 h at 0 °C and for 30 min at room temperature, diluted with CH_2Cl_2 (10 cm^3), and washed with 1 M HCl (20 cm^3) and water (20 cm^3). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with CH_2Cl_2–petrol (7:3) gave *nosylate* **11d** as an amorphous yellow powder (0.66 g, 69%). R_f 0.50 (EtOAc–petrol, 3:7); $[\alpha]_D^{19}$ +31.1 (*c* 2.2 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2868, 1532, 1349, 1182, 1099 and 912; δ_H ($CDCl_3$) 1.79–1.96 (4H, m, 2 × CH_2), 3.48 (4H, d, *J* = 7.0 Hz, 2 × CH_2), 4.17–4.38 (4H, m, 2 × CH_2), 4.87–5.03 (2H, m, 2 × CH), 7.03–7.12 ($4H_{arom}$, m), 7.21–7.32 ($6H_{arom}$, m), 7.92–8.03 ($4H_{arom}$, m) and 8.04–8.14 ($4H_{arom}$, m); δ_C ($CDCl_3$) 26.70 (2 × CH_2), 71.12 (2 × CH_2), 73.30 (2 × CH_2), 82.70 (2 × CH), 123.97 (4 × CH), 127.79 (4 × CH), 128.17 (2 × CH), 128.41 (4 × CH), 129.08 (4 × CH), 136.91 (2 × C_q), 142.59 (2 × C_q) and 150.34 (2 × C_q).

Found: C, 54.94; H, 4.67; N, 3.71. Calcd. for $C_{32}H_{32}N_2O_{12}S_2$: C, 54.85; H, 4.60; N, 3.71%.

(2*S*,5*S*)-1,6-Bis(benzyloxy)hexane-2,5-diyl cyclic sulfate 11e

To a solution of diol **11b** (0.23 g, 0.70 mmol) in CH_2Cl_2 (5 cm^3) was added Et_3N (0.39 cm^3, 2.8 mmol) and the mixture cooled to 0 °C. Thionyl chloride (0.25 g, 2.1 mmol) was added dropwise and the reaction mixture stirred for an additional 30 min. The mixture was diluted with Et_2O (10 cm^3) and the ethereal solution washed with brine (3 × 5 cm^3) and dried over $MgSO_4$. The organic phase was concentrated *in vacuo* and the residue dissolved in a mixture of CCl_4 (4 cm^3), MeCN (4 cm^3) and water (6 cm^3). To the reaction mixture was added $NaIO_4$ (0.3 g, 1.4 mmol), followed by $RuCl_3 \cdot xH_2O$ (1 mg) with stirring at 0 °C for 2 h. The mixture was then extracted with Et_2O (3 × 10 cm^3) and the combined extracts were washed with brine (5 cm^3), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with petrol–EtOAc (3:1) gave *cyclic sulfate* **11e** as a clear colourless oil (0.24 g, 87%). R_f 0.30 (EtOAc–petrol, 3:7); $[\alpha]_D^{20}$ −26.5 (*c* 9.0 in CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$) 1391, 1190, 1098, 964, 952 and 915; δ_H ($CDCl_3$) 1.98–2.08 (4H, m, 2 × CH_2), 3.54–3.72 (4H, m, 2 × CH_2), 4.58 (4H, s, 2 × CH_2), 4.72–4.84 (2H, m, 2 × CH), 7.25–7.40 (10H_{arom}, m); δ_C ($CDCl_3$) 29.04 (2 × CH_2), 70.93 (2 × CH_2), 73.94 (2 × CH_2), 82.75 (2 × CH), 127.78 (4 × CH), 127.97 (2 × CH), 128.54 (4 × CH) and 137.44 (2 × C_q); *m*/*z* (EI^+) (rel. intensity) 392 (M^+, 14%), 301 (67) and 91 (100). HRMS calcd. for $C_{20}H_{24}O_6S$ (M^+) 392.1294, found 392.1289.

4-[(2*R*,5*R*)-2,5-Bis(benzyloxymethyl)pyrrolidino]pyridine Ib. Method II

Sodium hydride (60% dispersion in mineral oil, 0.11 g, 2.7 mmol) was washed with hexane (3 × 5 cm^3) and the volatile components were removed *in vacuo*. A solution of 4-aminopyridine (0.10 g, 1.1 mmol) in THF (5 cm^3) was added and the mixture stirred for 3 h. A solution of cyclic sulfate **11e** (0.21 g, 0.54 mmol) in THF (5 cm^3) was added and the reaction was heated at reflux for 20 h. The reaction was cooled to room temperature, carefully quenched with 1 M NH_4OH (25 cm^3) and extracted with CH_2Cl_2 (2 × 25 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with petrol–EtOAc (2:1) and then ethanol gave *pyridine* **Ib** as a pale yellow oil (0.11 g, 52%). Spectroscopic data as above.

(2*S*,5*S*)-1,6-Bis(benzoyloxy)hexane-2,5-diol[67] 11g and (2*S*,5*S*)-1,2,6-tris(benzoyloxy)hexan-5-ol[67]

To a solution of tetrol **11a**[67] (0.20 g, 1.4 mmol) in *tert*-amyl alcohol (10 cm^3) was added dimethyltin dichloride (0.006 g, 0.03 mmol), K_2CO_3 (0.38 g, 2.7 mmol) and benzoyl chloride (0.38 cm^3, 3.3 mmol). The reaction mixture was stirred for 20 h and then concentrated *in vacuo*. The residue was diluted with water (25 cm^3) and extracted with CH_2Cl_2 (2 × 25 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography, eluting with petrol–EtOAc (2:1), gave the following compounds.

Diol 11g. (0.24 g, 49%) As an amorphous white powder. Mp 110–112 °C (CH_2Cl_2–petrol) [lit.,[67] 110.5–111.5 °C ($CHCl_3$–hexane)]; R_f 0.30 (EtOAc–petrol, 1:1); $[\alpha]_D^{18}$ +3.7 (*c* 2.7 in $CHCl_3$) [lit.,[67] $[\alpha]_D^{27}$ +2.5 (*c* 2.69 in $CHCl_3$)]; δ_H ($CDCl_3$) 1.65–1.90 (4H, m, 2 × CH_2), 3.30 (2H, br s, 2 × OH), 3.92–4.09 (2H, m, 2 × CH), 4.20–4.48 (4H, m, 2 × CH_2), 7.35–7.59 (6H_{arom}, m), 8.03 (4H_{arom}, m); *m*/*z* (CI^+) (rel. intensity) 359 (MH^+, 93%), 219 (100), 205 (71) and 105 (90).

(2*S*,5*S*)-1,2,6-Tris(benzoyloxy)hexan-5-ol. (0.037 g, 6%) As an amorphous white solid. $[\alpha]_D^{21}$ −9.9 (*c* 2.0 in $CHCl_3$) [lit.,[67] $[\alpha]_D^{29}$ −8.4 (*c* 2.04 in $CHCl_3$)]; δ_H ($CDCl_3$) 1.59–2.20 (4H, m, 2 × CH_2), 3.97–4.14 (1H, m, CH), 4.21–4.63 (4H, m, 2 × CH_2), 5.52–5.65 (1H, m, CH), 7.32–7.60 (9H_{arom}, m) and 7.92–8.08 (6H_{arom}, m); *m*/*z* (CI^+) (rel. intensity) 462 (M^+, 15%), 327 (10), 219 (37), 205 (32) and 105 (100).

(2*S*,5*S*)-1,6-Bis(benzoyloxy)-2,5-bis(methylsulfonyloxy)hexane[67] 11h

To a solution of diol **11g** (0.21 g, 0.59 mmol) in CH_2Cl_2 (5 cm^3) was added Et_3N (0.33 cm^3, 2.4 mmol). The mixture was cooled to 0 °C and methanesulfonyl chloride (0.14 cm^3, 1.8 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h. The mixture was then diluted with CH_2Cl_2 (5 cm^3) and washed sequentially with 1 M NaOH (10 cm^3) and 2 M HCl (10 cm^3). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with CH_2Cl_2–EtOAc (1:1) gave *mesylate* **11h** as an amorphous white powder (0.26 g, 86%). Mp 109–111 °C (CH_2Cl_2–petrol) [lit.,[67] 108–109 °C (CH_2Cl_2–hexane)]; $[\alpha]_D^{19}$ +15.4 (*c* 1.1 in $CHCl_3$) [lit.,[67] $[\alpha]_D^{28}$ +14.3 (*c* 1.13 in $CHCl_3$)]; δ_H ($CDCl_3$) 1.97–2.06 (4H, m, 2 × CH_2), 3.05 (6H, s, 2 × CH_3), 4.45 (2H, dd, *J* = 12.2, 6.6 Hz, CH_2), 4.55 (2H, dd, *J* = 12.5, 3.2 Hz, CH_2), 7.4–8.1 (10H_{arom}, m); *m*/*z* (CI^+) (rel. intensity) 359 (23, M^+), 223 (74) and 105 (100).

(2*S*,5*S*)-1,6-Bis(triphenylmethyloxy)hexane-2,5-diol 11i

To a solution of tetrol **11a**[67] (0.45 g, 3.0 mmol) in pyridine (20 cm^3) was added DMAP (0.04 g, 0.3 mmol) and trityl chloride (1.8 g, 6.5 mmol), and the mixture stirred for 24 h. The solution was concentrated *in vacuo*, dissolved in CH_2Cl_2 (30 cm^3), and washed with water (3 × 25 cm^3). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with EtOAc–petrol (1:2) gave *diol* **11i** as an amorphous white powder (1.29 g, 69%). R_f 0.70 (EtOAc–petrol, 1:1); mp 157–159 °C (EtOAc–petrol); $[\alpha]_D^{18}$ +4.0 (*c* 2.5 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3594, 3058, 1957, 1596, 1490, 1442, 1234, 1202 and 1008; δ_H ($CDCl_3$) 1.40–1.52 (4H, m, 2 × CH_2), 2.97–3.17 (4H, m, 2 × CH_2), 3.69–3.83 (2H, m, 2 × CH), 7.1–7.5 (30H_{arom}, m); δ_C ($CDCl_3$) 29.63 (2 × CH_2), 67.59 (2 × CH_2), 70.90 (2 × CH), 86.64 (2 × C_q), 127.10 (6 × CH), 127.87 (12 × CH), 128.65 (12 × CH) and 143.84 (6 × C_q). HRMS calcd. for $C_{44}H_{42}O_4$ 634.3083, found 634.3088.

(2*S*,5*S*)-1,6-Bis(triphenylmethyloxy)-2,5-bis(methylsulfonyloxy)-hexane 11j

To a solution of diol **11i** (0.43 g, 0.68 mmol) in CH_2Cl_2 (10 cm^3) was added Et_3N (0.38 cm^3, 2.7 mmol). The mixture was cooled to 0 °C and methanesulfonyl chloride (0.16 cm^3, 2.0 mmol) added dropwise. After 90 min at 0 °C, the reaction mixture was washed with water (2 × 10 cm^3). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with petrol–EtOAc (4:1) gave *mesylate* **11j** as an amorphous white powder (0.51 g, 94%). R_f 0.45 (EtOAc–petrol, 3:7); mp 149–151 °C (EtOAc–petrol); $[\alpha]_D^{21}$ +9.2 (*c* 2.2 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 3594, 3058, 1486, 1446, 1328 and 1008; δ_H ($CDCl_3$) 1.55–1.80 (4H, m, 2 × CH_2), 3.00 (6H, s, 2 × CH_3), 3.19 (2H, dd, *J* = 10.7, 6.6 Hz, CH_2), 3.35 (2H, dd, *J* = 10.7, 4.0 Hz, CH_2), 4.82–4.92 (2H, m, 2 × CH), 7.20–7.45 (30H_{arom}, m); δ_C ($CDCl_3$) 27.08 (2 × CH_2), 38.84 (2 × CH_3), 65.29 (2 × CH_2), 81.54 (2 × CH), 87.37 (2 × C_q), 127.40 (6 × CH), 128.11 (12 × CH), 128.67 (12 × CH) and 143.32 (6 × C_q). Found: C, 69.14; H, 6.04; S, 8.07. Calcd. for $C_{46}H_{46}O_8S_2$: C, 69.85; H, 5.86; S, 8.11%.

4-[(2*R*,5*R*)-2,5-Bis(triphenylmethyloxymethyl)pyrrolidino]-pyridine Ic

Sodium hydride (60% dispersion in mineral oil, 0.10 g, 2.5 mmol) was washed with hexane (3 × 5 cm^3) and the volatile

components were removed *in vacuo*. A solution of 4-aminopyridine (0.09 g, 1.0 mmol) in THF (7.5 cm^3) was added and the mixture stirred for 4 h. The mixture was brought to reflux and mesylate **11j** (0.4 g, 0.5 mmol) in THF (5 cm^3) added. After 17 h heating at reflux, the reaction mixture was cooled to room temperature, carefully quenched with sat. NH_4OH (25 cm^3) and extracted with CH_2Cl_2 (3 × 25 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography eluting with MeOH saturated with NH_3–CH_2Cl_2 (0.03:1) gave *pyridine* **Ic** as a clear colourless oil (0.15 g, 42%). R_f 0.65 (NH_3 saturated MeOH–CH_2Cl_2, 1:19); $[\alpha]_D^{17}$ +35 (*c* 1.7 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 2952, 2872, 1592, 1509, 1489, 1445, 1382, 1227 and 1073; δ_H ($CDCl_3$) 2.04–2.20 (4H, m, 2 × CH_2), 3.05 (2H, dd, J = 9.5, 7.9 Hz, CH_2), 3.21 (2H, dd, J = 9.5, 3.1 Hz, CH_2), 3.85–3.97 (2H, m, 2 × CH), 5.92 (2H, d, J = 6.4 Hz, 2 × CH), 7.15–7.45 (30H_{arom}, m), 7.92 (2H, d, J = 6.4 Hz, 2 × CH); δ_C ($CDCl_3$) 26.62 (2 × CH_2), 50.55 (2 × CH), 61.37 (2 × C_q), 86.96 (2 × CH_2), 108.52 (2 × CH), 127.11 (6 × CH), 127.85 (12 × CH), 128.59 (12 × CH), 143.92 (6 × C_q), 149.02 (2 × CH) and 150.20 (C_q); *m*/*z* (CI^-) (rel. intensity) 449 ($M^+ - C(C_6H_5)_3$, 30%), 259 (100) and 243 (35). Found: C, 85.41; H, 6.59; N, 3.78. Calcd. for $C_{49}H_{44}N_2O_2$: C, 84.94; H, 6.40; N, 4.04%.

4-[(2*R*,5*R*)-2,5-Bis(hydroxymethyl)pyrrolidino]pyridine Id

To a solution of pyridine **Ib** (1.0 g, 2.6 mmol) in a mixture of absolute EtOH (9 cm^3) and 1 M HCl (3 cm^3) was added 10% Pd–C (0.1 g, 10% w/w). The mixture was stirred vigorously under hydrogen (1 atm) for 4 h, filtered through a Celite pad, and concentrated *in vacuo*. The residue was dissolved in MeOH and loaded onto an SCX ion-exchange column (10 g). The column was washed with MeOH (3 × 25 cm^3) and the product eluted with MeOH saturated with NH_3 (25 cm^3). Evaporation and crystallisation from MeOH gave *pyridine* **Id** as clear colourless needles (0.45 g, 84%). Mp 197–198 °C (MeOH); R_f 0.05 (NH_3 saturated MeOH–CH_2Cl_2, 1:19); $[\alpha]_D^{17}$ +39 (*c* 1.3 in MeOH); ν_{max}/cm^{-1} (Nujol) 3326, 1600, 1533, 1374 and 1038; δ_H (CD_3OD) 2.03–2.25 (4H, m, 2 × CH_2), 3.33–3.41 (2H, m, CH_2), 3.62 (2H, dd, J = 11.0, 2.7 Hz, CH_2), 3.92–4.04 (2H, m, 2 × CH), 6.64 (2H, dd, J = 6.4, 1.4 Hz, 2 × CH) and 8.04 (2H, d, J = 6.4 Hz, 2 × CH); δ_C (CD_3OD) 27.03 (2 × CH_2), 60.68 (2 × CH), 60.99 (2 × CH_2), 110.20 (2 × CH), 149.57 (2 × CH) and 152.48 (C_q); *m*/*z* (EI^+) (rel. intensity) 208 (M^+, 12%), 177 (100). HRMS calcd. for $C_{11}H_{16}O_2N_2$ (M^+) 208.1212, found 208.1215.

4-[(2*R*,5*R*)-2,5-Bis(*p*-nitrophenoxymethyl)pyrrolidino]pyridine Ie

To a solution of pyridine **Id** (0.054 g, 0.26 mmol) in THF (4 cm^3) was added *p*-nitrophenol (0.15 g, 1.0 mmol) and triphenylphosphine (0.27 g, 1.0 mmol). The mixture was cooled to 0 °C and DEAD (0.16 cm^3, 1.0 mmol) added dropwise with vigorous stirring. After 2 h, the mixture warmed to room temperature, stirred for an additional 18 h, and concentrated *in vacuo*. The residue was dissolved in MeOH and loaded onto an SCX ion-exchange column (2 g). The column was washed with MeOH (20 cm^3) and the product eluted with MeOH saturated with NH_3 (25 cm^3). Evaporation and crystallisation from MeOH gave *pyridine* **Ie** as a pale yellow solid (0.11 g, 88%). Mp 86–88 °C (MeOH); R_f 0.45 (NH_3 saturated MeOH–CH_2Cl_2, 1:19); $[\alpha]_D^{16}$ +12.6 (*c* 1.4 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1588, 1515, 1466, 1373, 1340, 1255, 1211 and 1109; δ_H ($CDCl_3$) 2.14–2.47 (4H, m, 2 × CH_2), 3.86 (2H, dd, J = 9.2, 7.9 Hz, CH_2), 4.12 (2H, dd, J = 9.2, 2.7 Hz, CH_2), 4.33–4.45 (2H, m, 2 × CH), 6.59 (2H, d, J = 6.1 Hz, 2 × CH), 6.84–6.93 (4H_{arom}, m), 8.09–8.20 (2CH + 4H_{arom}, m); δ_C ($CDCl_3$) 26.75 (2 × CH_2), 56.67 (2 × CH), 66.52 (2 × CH_2), 108.94 (2 × CH), 114.47 (4 × CH), 125.97 (4 × CH), 141.89 (2 × C_q), 149.73 (C_q), 150.09 (2 × CH) and 163.29 (2 × C_q); *m*/*z* (EI^+) (rel. intensity) 450 (M^+, 7%), 298 (100) and 159 (14). HRMS calcd. for $C_{23}H_{22}O_6N_4$ (M^+) 450.1539, found 450.1528.

4-[(2*R*,5*R*)-2,5-Bis(phenoxymethyl)pyrrolidino]pyridine If

To a solution of pyridine **Id** (0.1 g, 0.5 mmol) in THF (10 cm^3) were added phenol (0.27 g, 2.9 mmol) and tributylphosphine (0.48 cm^3, 1.9 mmol). The mixture was cooled to 0 °C and a solution of ADDP[74] (0.49 g, 1.9 mmol) in THF (5 cm^3) was added dropwise with vigorous stirring. The reaction mixture was warmed to room temperature, stirred for 24 h, and diluted with petrol (10 cm^3). The reaction mixture was then filtered through a Celite pad and concentrated *in vacuo*. The residue was dissolved in MeOH and loaded onto an SCX ion-exchange column (2 g). The column was washed with MeOH (20 cm^3) and the product eluted with MeOH saturated with NH_3 (25 cm^3). Evaporation and further purification by flash chromatography eluting with MeOH saturated with NH_3–CH_2Cl_2–EtOAc (0.14:6:1) gave a white amorphous solid. Recrystallisation from MeOH gave *pyridine* **If** as white needles (0.14 g, 81%). Mp 163–164 °C (MeOH); R_f 0.45 (NH_3 saturated MeOH–CH_2Cl_2, 1:19); $[\alpha]_D^{17}$ +153 (*c* 1.4 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1596, 1499, 1470, 1377, 1239 and 1211; δ_H ($CDCl_3$) 2.14–2.40 (4H, m, 2 × CH_2), 3.71 (2H, t, J = 9.2 Hz, CH_2), 4.08 (2H, dd, J = 9.2, 2.7 Hz, CH_2), 4.26–4.38 (2H, m, 2 × CH), 6.57 (2H, dd, J = 5.2, 1.8 Hz, 2 × CH), 6.80–7.35 (10H_{arom}, m), 8.22 (2H, dd, J = 5.2, 1.8 Hz, 2 × CH); δ_C ($CDCl_3$) 26.70 (2 × CH_2), 56.97 (2 × CH), 65.68 (2 × CH_2), 108.89 (2 × CH), 114.51 (4 × CH), 121.24 (2 × CH), 129.61 (4 × CH), 149.89 (C_q), 150.27 (2 × CH) and 158.53 (C_q); *m*/*z* (EI^+) (rel. intensity) 360 (M^+, 11%), 253 (100). HRMS calcd. for $C_{23}H_{24}O_2N_2$ (M^+) 360.1838, found 360.1834.

4-[(2*R*,5*R*)-2,5-Bis(2-naphthyloxymethyl)pyrrolidino]pyridine Ig

To a solution of pyridine **Id** (0.512 g, 2.46 mmol) in THF (60 cm^3) were added 2-naphthol (2.13 g, 14.8 mmol) and tributylphosphine (2.5 cm^3, 9.8 mmol). The mixture was cooled to 0 °C and ADDP (2.5 g, 9.8 mmol) in THF (15 cm^3) added dropwise with vigorous stirring. The reaction was warmed to room temperature, stirred for 18 h and diluted with petrol (15 cm^3). The reaction mixture was then filtered through a Celite pad and concentrated *in vacuo*. The residue was triturated with MeOH (30 cm^3) to give *pyridine* **Ig** as an amorphous solid (380 mg, 34%). The mother liquor was concentrated *in vacuo* and loaded onto an SCX ion-exchange column (10 g). The column was washed with MeOH (3 × 20 cm^3) and the product eluted with MeOH saturated with NH_3 (50 cm^3). Evaporation and further purification by flash chromatography eluting with MeOH saturated with NH_3–CH_2Cl_2–EtOAc (0.1:5:1) gave an additional amount of *pyridine* **Ig** as an amorphous white solid (560 mg, 49%; total yield 0.94 g, 83%). Mp >225 °C (MeOH); R_f 0.75 (NH_3 saturated MeOH–CH_2Cl_2, 1:19); $[\alpha]_D^{17}$ +207 (*c* 1.6 $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1596, 1508, 1467, 1388 and 1226; δ_H ($CDCl_3$) 2.20–2.48 (4H, m, 2 × CH_2), 3.88 (2H, t, J = 8.5 Hz, CH_2), 4.23 (2H, m, CH_2), 4.37–4.47 (2H, m, 2 × CH), 6.65 (2H, d, J = 6.4 Hz, 2 × CH), 7.05–7.80 (14H_{arom}, m), 8.26 (2H, d, J = 6.4 Hz, 2 × CH); δ_C ($CDCl_3$) 26.78 (2 × CH_2), 56.99 (2 × CH), 65.81 (2 × CH_2), 106.77 (2 × CH), 108.94 (2 × CH), 118.65 (2 × CH), 123.92 (2 × CH), 126.59 (2 × CH), 126.77 (2 × CH), 127.69 (2 × CH), 129.14 (2 × C_q), 129.60 (2 × CH), 134.44 (2 × C_q), 149.94 (C_q), 150.34 (2 × CH) and 156.46 (2 × C_q); *m*/*z* (EI^+) (rel. intensity) 460 (M^+, 11%), 303 (100) and 159 (22). HRMS calcd. for $C_{31}H_{28}O_2N_2$ (M^+) 460.2151, found 460.2147.

4-[(2*R*,5*R*)-2,5-Bis(*p*-methoxyphenoxymethyl)pyrrolidino]-pyridine Ih

To a solution of pyridine **Id** (0.21 g, 1.0 mmol) in THF (10 cm^3) was added *p*-methoxyphenol (0.74 g, 6.0 mmol) and

tributylphosphine (1.0 cm^3, 4.0 mmol). The mixture was cooled to 0 °C and TMAD[75] (0.69 g, 4.0 mmol) in THF (5 cm^3) added dropwise with vigorous stirring. The reaction was warmed to room temperature, stirred for 18 h and diluted with petrol (5 cm^3). The reaction mixture was then filtered through a Celite pad and concentrated *in vacuo*. The residue was triturated with MeOH (30 cm^3) to give *pyridine* **Ih** as a white amorphous solid (270 mg, 65%). The mother liquor was concentrated *in vacuo* and loaded onto an SCX ion-exchange column (2 g). The column was washed with MeOH (25 cm^3) and the product eluted with MeOH saturated with NH_3 (25 cm^3). Evaporation and further purification by flash chromatography eluting with MeOH saturated with NH_3–CH_2Cl_2–EtOAc (0.1 : 5 : 1) gave an additional amount of *pyridine* **Ig** as a white amorphous solid (80 mg, 19%). Recrystallisation of the combined product batches from MeOH gave white needles (total yield 0.34 g, 82%). Mp 193 °C (MeOH); R_f 0.40 (NH_3 saturated MeOH–CH_2Cl_2, 1 : 19); $[\alpha]_D^{16}$ +134 (*c* 1.6 in $CHCl_3$); ν_{max}/cm^{-1} ($CHCl_3$) 1592, 1503, 1466, 1377, 1235 and 1036; δ_H ($CDCl_3$) 2.15–2.35 (4H, m, 2 × CH_2), 3.67 (2H, t, J = 8.9 Hz, CH_2), 3.77 (6H, s, 2 × CH_3), 4.04 (2H, dd, J = 8.9, 2.7 Hz, CH_2), 4.22–4.34 (2H, m, 2 × CH), 6.54 (2H, d, J = 5.8 Hz, 2 × CH), 6.75–6.9 (8H_{arom}, m), 8.24 (2H, d, J = 5.8 Hz, 2 × CH); δ_C ($CDCl_3$) 26.63 (2 × CH_2), 55.75 (2 × CH_3), 56.97 (2 × CH), 66.44 (2 × CH_2), 108.82 (2 × CH), 114.71 (4 × CH), 115.44 (4 × CH), 149.90 (C_q), 150.17 (2 × CH), 152.64 (2 × C_q) and 154.15 (2 × C_q); *m*/*z* (EI^+) (rel. intensity) 420 (M^+, 8%) and 283 (100). HRMS calcd. for $C_{25}H_{28}O_4N_2$ (M^+) 420.2049, found 420.2063.

A representative procedure for rate experiment using 1-methylcyclohexanol. The experiment employing DMAP

(Table 2, entry 2) To 1-methylcyclohexanol (0.23 g, 2.0 mmol) in Et_3N (0.42 cm^3, 3.0 mmol) was added DMAP (10 mg, 0.08 mmol). During vigorous stirring Ac_2O (0.40 cm^3, 4.2 mmol) was added. After 10 h, 1 μL of the reaction mixture was removed and diluted with CH_2Cl_2 (24 μL). After 24 h, a further 1 μL of the reaction mixture was removed and diluted with CH_2Cl_2 (24 μL). The extent of reaction was determined for both aliquots by analytical GC (DB1701 ISM capillary column, 30 m × 1.5 μm , 60 °C, 3 psi): R_t (acetate) 2.4 min; R_t (alcohol) 6.1 min.

A representative procedure for catalytic KR of 1-phenylethanol. The experiment employing catalyst (+)-If

(Table 3, entry 5) To a solution of diphenyl ether catalyst (+)-**If** (7.2 mg, 0.02 mmol) and 1-phenylethanol (0.12 cm^3, 1.0 mmol) in THF (2 cm^3) was added Et_3N (0.10 cm^3, 0.75 mmol) and the reaction cooled to −78 °C. Ac_2O (0.71 cm^3, 0.75 mmol) was then added with vigorous stirring. After 120 min, ~1 cm^3 of the reaction mixture was rapidly removed *via* syringe and added to MeOH (2 cm^3). After 10 min, the solvent removed *in vacuo* and the crude material passed through a short plug of silica to remove the catalyst. After 520 min, MeOH (2 cm^3) was added to the reaction mixture and warmed to room temperature. After 15 min, the solvent was removed *in vacuo* and the crude material passed through a short plug of silica. The ees of both the alcohol and the acetate were determined for both aliquots by analytical chiral HPLC (Chiralcel OD column, 0.46 × 25 cm, 0 °C, hexanes–propan-2-ol, 99 : 1, 1 cm^3 min^{-1}): R_t [(*R*)-acetate] 7.4 min; R_t [(*S*)-acetate] 8.4 min; R_t [(*R*)-alcohol] 31 min; R_t [(S)-alcohol] 49 min.[10]

Crystal data for If ¶¶

$C_{23}H_{24}O_2N_2$, M 360.44, orthorhombic, space group $P2_12_12_1$, a = 5.3697(3), b = 16.3416(14), c = 21.7265(18) Å, U = 1906.5(3) $Å^3$, Z = 4, D_c = 1.256 g cm^{-1}, μ = 0.080 mm^{-1} (Mo-Kα, λ = 0.71073 Å), F(000) = 768, T = 123(1) K. Bruker AXS SMART CCD area-detector diffractometer, crystal size, plate, 0.20 × 0.20 × 0.05 mm, θ_{max} 26.35°, 19928 reflections measured, 3905 unique, 100% complete (R_{int} = 0.0285). Structure solution by direct methods, full-matrix least-squares refinement on F^2 with weighting $w^{-1} = \sigma^2(F_o^2) + (0.0590P)^2$, where $P = (F_o^2 + 2F_c^2)/3$, anisotropic displacement parameters, riding hydrogen atoms with U_{iso} free, no absorption correction, absolute structure not determined. Final $Rw = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]^{1/2}\}$ = 0.0806 for all data, conventional R = 0.0298 on F values of 3531 reflections with $I > 2\sigma(I)$, S = 1.002 for all data and 268 parameters. Final difference map between +0.15 and −0.16 e $Å^{-3}$. Programs: Bruker AXS, SMART, SAINT and SADABS control and integration software,[81] SHELXTL structure solution and refinement.[82]

¶¶ CCDC reference number 207/477. See http://www.rsc.org/suppdata/p1/b0/b004704j/ for crystallographic files in .cif format.

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References

1 L. M. Litvinenko and A. I. Kirichenko, *Dokl. Chem.* (*Engl. Transl.*), 1967, 763; L. M. Litvinenko and A. I. Kirichenko, *Dokl. Akad. Nauk SSSR Ser. Khim.*, 1967, **176**, 97.
2 W. Steglich and G. Höfle, *Angew. Chem.*, *Int. Ed. Engl.*, 1969, **8**, 981.
3 A. Hassner, L. R. Krepski and V. Alexanian, *Tetrahedron*, 1978, **34**, 2069.
4 G. Höfle, W. Steglich and H. Vorbruggen, *Angew. Chem.*, *Int. Ed. Engl.*, 1978, **17**, 569.
5 F. V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129.
6 A. Hassner, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, New York, 1995, vol. 3, pp. 2022–2024.
7 U. Ragnarsson and L. Grehn, *Acc. Chem. Res.*, 1998, **31**, 494.
8 A. C. Spivey, T. Fekner and H. Adams, *Tetrahedron Lett.*, 1998, **39**, 8919.
9 A. C. Spivey, T. Fekner, S. E. Spey and H. Adams, *J. Org. Chem.*, 1999, **64**, 9430.
10 A. C. Spivey, T. Fekner and S. E. Spey, *J. Org. Chem.*, 2000, **65**, 3154.
11 E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1996, **118**, 1809.
12 E. Vedejs and X. Chen, *US Pat.* No. 5646287, 1997 (July 8th).
13 E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1997, **119**, 2584.
14 K. Fuji, T. Kawabata, M. Nagato and K. Tasasu, *J. Am. Chem. Soc.*, 1997, **119**, 3169.
15 J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1996, **61**, 7230.
16 J. C. Ruble, H. A. Latham and G. C. Fu, *J. Am. Chem. Soc.*, 1997, **119**, 1492.
17 J. C. Ruble, J. Tweddell and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 2794.
18 J. Liang, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 3154.
19 C. E. Garrett and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 7479; erratum, C. E. Garrett and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 10276.
20 J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 11532.
21 B. L. Hodous, J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 2637.
22 B. Tao, J. C. Ruble, D. A. Hoic and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 5091; erratum, B. Tao, J. C. Ruble, D. A. Hoic and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 10452.
23 Y. Ie and G. C. Fu, *Chem. Commun.*, 2000, 119.
24 S. J. Taylor and J. P. Morken, *Science*, 1998, **280**, 267.
25 P. Somfai, *Angew. Chem.*, *Int. Ed. Engl.*, 1997, **36**, 2731.
26 H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249.
27 W. C. Willis, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 1765.
28 H. Kotsuki, H. Sakai and T. Shinohara, *Synlett*, 2000, 116.
29 A. C. Spivey, A. Maddaford, D. Leese and A. J. Redgrave, manuscript in preparation.
30 F. Cozzi, F. Ponzini, R. Annunziata, M. Cinquini and J. S. Siegel, *Angew. Chem.*, *Int. Ed. Engl.*, 1995, **34**, 1019, and references therein.
31 Computer program: CS Chem3D Pro, version 4.0; Cambridge Soft Corp., US, 1997.
32 J. K. Whitesell, *Chem. Rev.*, 1989, **89**, 1581.
33 H. Vorbruggen, *Adv. Heterocycl. Chem.*, 1990, **49**, 117.

34 R. P. Short, R. M. Kennedy and S. Masamune, *J. Org. Chem.*, 1989, **54**, 1755.
35 M. E. Zwaagstra, A. Meetsma and B. L. Feringa, *Tetrahedron: Asymmetry*, 1993, **4**, 2163.
36 Y. Yamamoto, J. Hoshino, Y. Fujimoto, J. Ohamoto and S. Sawada, *Synthesis*, 1993, 298.
37 H. Kwart and R. W. Body, *J. Org. Chem.*, 1965, **30**, 1188, and references therein.
38 A. M. Comrie and J. B. Stenlake, *J. Chem. Soc.*, 1958, 3514.
39 E. Ager, B. Iddon and H. Suschitsky, *J. Chem. Soc.* (*C*), 1970, 1530.
40 T. Fukuyama, M. Cheung, C.-K. Jow, Y. Hidai and T. Kan, *Tetrahedron Lett.*, 1997, **38**, 5831.
41 Z. Talik and E. Plazek, *Acta Pol. Pharm.*, 1955, **12**, 5.
42 J. Angulo and A. M. Municio, *An. R. Soc. Esp. Fis. Quim.*, *Ser. B*, 1959, **55B**, 527.
43 F. Marsais, A. Cronnier, F. Trecourt and G. Queguiner, *J. Org. Chem.*, 1987, **52**, 1133.
44 J. F. Hartwig, *Angew. Chem.*, *Int. Ed.*, 1998, **37**, 2147.
45 B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125.
46 S. Wagaw and S. L. Buchwald, *J. Org. Chem.*, 1996, **61**, 7240.
47 J.-F. Marcoux, S. Wagaw and S. L. Buchwald, *J. Org. Chem.*, 1997, **62**, 1568.
48 S. Jaime-Figueroa, Y. Liu, J. M. Muchowski and D. G. Putman, *Tetrahedron Lett.*, 1998, **39**, 1313.
49 J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1158.
50 S. Masamune, T. Sato, B. Kim and T. A. Wollmann, *J. Am. Chem. Soc.*, 1986, **108**, 8279, and references therein.
51 M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem. Soc.*, 1993, **115**, 10125.
52 E. Vedejs, O. Daugulis and S. T. Diver, *J. Org. Chem.*, 1996, **61**, 430.
53 W. Li, Z. Zhang, D. Xiao and X. Zhang, *J. Org. Chem.*, 2000, **65**, 3489.
54 D. Enders and J. Wiedemann, *Synthesis*, 1996, 1443.
55 M. Marzi, P. Minetti and D. Misiti, *Tetrahedron*, 1992, **48**, 10127.
56 M. Marzi and D. Misiti, *Tetrahedron Lett.*, 1989, **30**, 6075.
57 H. Takahata, S. Takakashi, S.-I. Kouno and T. Momose, *J. Org. Chem.*, 1998, **63**, 2224.
58 T. K. M. Shing, *Tetrahedron*, 1988, **44**, 7261.
59 A. Defoin, A. Brouillard-Poichet and J. Streith, *Helv. Chim. Acta*, 1991, **74**, 103.
60 M. Pichon and B. Figadere, *Tetrahedron: Asymmetry*, 1996, **7**, 927.
61 H. Jitao, *J. Appl. Polym. Sci.*, 1995, **56**, 1805.
62 C. C. Deane and T. D. Inch, *J. Chem. Soc.*, *Chem. Commun.*, 1969, 813.
63 R. W. Kierstead, A. Faraone, F. Mennona, J. Mullin, R. W. Guthrie, H. Crowley, B. Simko and L. C. Blaber, *J. Med. Chem.*, 1983, **26**, 1561.
64 E. J. Corey and P. B. Hopkins, *Tetrahedron Lett.*, 1982, **23**, 1979.
65 A. H. Haines, *Carbohydr. Res.*, 1965, 214.
66 N. Machinaga and C. Kibayashi, *J. Org. Chem.*, 1992, **57**, 5178.
67 N. Machinaga and C. Kibayashi, *Synthesis*, 1992, 989.
68 N. Machinaga and C. Kibayashi, *J. Org. Chem.*, 1991, **56**, 1386.
69 N. Machinaga and C. Kibayashi, *Tetrahedron Lett.*, 1990, **31**, 3637.
70 P. Renaud, E. Lacote and L. Quaranta, *Tetrahedron Lett.*, 1998, **39**, 2123.
71 Y. Matsumura, T. Maki and F. Iwasaki, *Tetrahedron Lett.*, 1998, **39**, 5601.
72 Y. Matsumura, F. Iwasaki, T. Maki, W. Nakashima and O. Onomura, *Org. Lett.*, 1999, **1**, 969.
73 D. L. Hughes, *Org. Prep. Proced. Int.*, 1996, **28**, 127.
74 T. Tsunoda, Y. Yamamiya and S. Ito, *Tetrahedron Lett.*, 1993, **34**, 1639.
75 T. Tsunoda, Y. Yamamiya, Y. Kawamura and S. Ito, *Tetrahedron Lett.*, 1995, **36**, 2529.
76 W. Steglich, H. Vorbruggen and G. Höfle, *Angew. Chem.*, *Int. Ed. Engl.*, 1978, **17**, 569.
77 The selectivity, s = (rate constant of fast-reacting enantiomer)/(rate constant of slow-reacting enantiomer).
78 D. D. Perrin and W. C. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edn., Pergamon Press, Oxford, 1988.
79 P. B. Desai, *J. Chem. Soc.*, *Perkin Trans. 1*, 1973, 1865.
80 M. E. Maier and S. Reuter, *Liebigs Ann./Recl.*, 1997, **10**, 2043.
81 Bruker AXS (1997). SMART, SAINT and SADABS area detector control and integration software. Bruker AXS Inc., Madison, WI53179, USA.
82 G. M. Sheldrick, SHELXTL Version 5, Bruker AXS Inc., Madison, WI53179, USA, 1997.