Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 605–618

TETRAHEDRON: *ASYMMETRY*

Synthesis of chiral non-racemic azetidines by lipase-catalysed acetylations and their transformation into amino alcohols: precursors of chiral catalysts

Giuseppe Guanti* and Renata Riva*

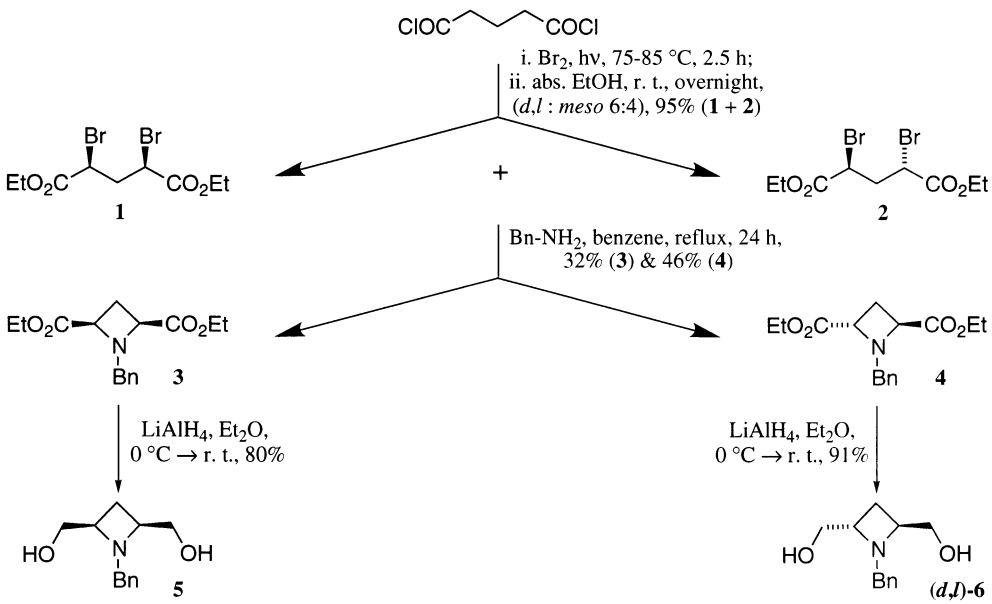
Dipartimento di Chimica e Chimica Industriale and CNR,
Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici,† via Dodecaneso 31, I-16146 Genoa, Italy

Received 8 January 2001; accepted 15 February 2001

Abstract—Azetidinic mono-acetate **7**, diol **6b** and di-acetate **10a** were prepared with high e.e. using PPL-catalysed acetylations. The absolute configurations of all new enantioenriched compounds were assigned by chemical correlation with known compounds. Mono-acetate **7** was then transformed into **30**, an amino alcohol of noteworthy potential interest since it represents an interesting precursor for chiral catalysts, such as **32**.

1. Introduction

The occurrence of the azetidine nucleus in natural products is uncommon; derivatives of this four-membered moiety have been isolated from some marine sponges,[1] the culture broth of *Streptomyces cacaoi*[2] and from the roots of barley.[3] The syntheses of some azetidine alkaloids,[4–9] of differently *N*-substituted aze-

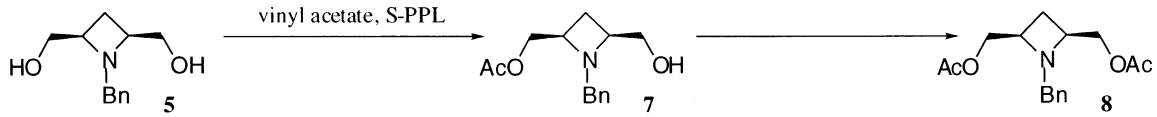


Scheme 1.

* Corresponding authors. E-mail: guanti@chimica.unige.it; riva@chimica.unige.it
† Associated to the National Institute of the CNR for the Chemistry of Biological Systems.

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00077-5

Table 1. Asymmetrisation of diol **5** using S-PPL



Entry	mg enz./mg **5**	Solvent	Time (min)	Conversion[a] (%)	**5**:**7**:**8**[b]	E.e.[c] (%)
1	2	VA[d]	600	57.6	3.2:78.3:18.5	98.2
2	2	VA	60	16.3	67.9:31.5:0.6	93.7
3	2	VA	360	49.6	11.4:77.9:10.7	96.2
4	2	VA	1440	67.3	0.1:65.2:34.7	99.5
5	2	VA	2880	75.1	0.0:49.8:50.2	>99.5
6	1	VA–*i*-Pr_2O 1:1	440	49.8	10.6:79.2:10.2	95.5
7	1	VA–*i*-Pr_2O 1:1	1390	55.7	5.1:78.4:16.5	98.0
8	1	VA–hexane	1400	44.1	26.2:59.4:14.4	94.6

[a] % of acetylated -OH groups versus initial -OH groups.
[b] Determined by GC–MS (SIM procedure); isolated yields of **5**, **7**, and **8** were in agreement with the gas chromatographic data.
[c] Determined by GLC using Cyclodex-B™ (J & W) column.
[d] VA, vinyl acetate.

tidine-2,4-dicarboxylic acids as precursors of rigid glutamate analogues[10] and of cyclic peptides derived from L-azetidine-2-carboxylic acid[11] have been reported. More recently, homochiral azetidines have been prepared and used as ligands[12–15] and catalysts[16–18] for asymmetric synthesis; however, the number of applications in this field appears limited.

We have been active in the design and synthesis of new chiral building blocks and in their utilisation as precursors of polyfunctionalised natural products.[19] Recently, we reported some preliminary results on the preparation of optically active azetidines, following a chemoenzymatic route.[20,‡]

Herein, we describe in more detail the preparation of azetidines **6b**, **7** and **10a** and establish their absolute configuration. The azetidinic mono-protected diol **7** was transformed into the amino alcohol **30**, which has previously been used as a precursor of the oxazaborolidine **32**, a homogeneous catalyst for the enantioselective reduction of ketones in the presence of borane.

2. Results and discussion

The synthesis of diols **5** and **6** was performed as summarised in Scheme 1, starting from commercially available glutaryl dichloride.

Since diol **5** is a *meso*-form, it can be desymmetrised and transformed into the mono-acetate **7**. Diol **6**, being a racemic compound with C_2 symmetry, can then be subjected to a double sequential kinetic resolution, to transform the faster reacting enantiomer into the corresponding di-acetate **10a**. The slower reacting enantiomer remained unreacted as diol **6b**.

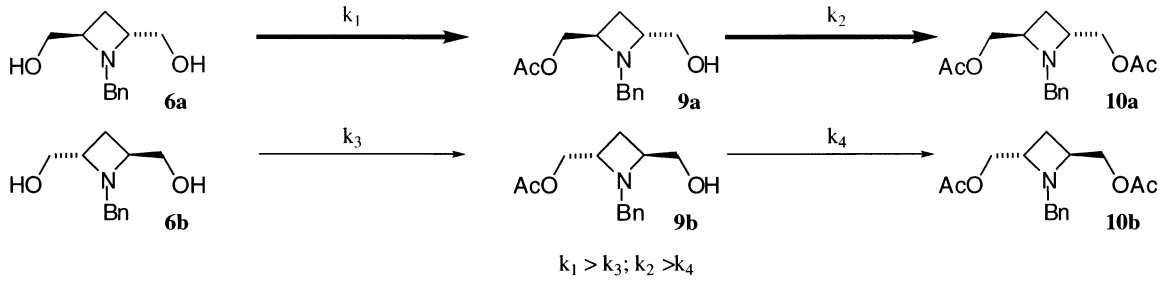
The enzymatic reactions were performed on both diols **5** and **6** using first the microbial lipase from *Pseudomonas cepacia* (from Amano), which has been successfully used on analogous pyrrolidine derivatives.[22] However, since the outcome of the reaction was rather modest, we abandoned this enzyme and turned our attention to the mammalian lipase from porcine pancreas (PPL), immobilised on Celite, following our previously reported optimised procedure.[23] Both diols appeared to be good substrates for this enzyme and a study on the factors affecting the reactivity was performed in order to define the protocol of choice for further synthetic applications. The reaction times, yields and e.e.s for enzymatic reactions with **5** and **6** are reported in Tables 1 and 2, respectively.

In the asymmetrisation of **5** (Table 1) the e.e. increased with conversion, a result of kinetic resolution of the minor enantiomer of **7** (entries 2–5). However, since higher conversions caused a marked decrease in the yield, we usually stopped the reaction at around 55% conversion; at this point the e.e. is at least 98%. The employment of di-*iso*-propyl ether as co-solvent with vinyl acetate as acyl donor proved to be a useful alternative set of reaction conditions (entries 6 and 7).

In the double kinetic resolution of **6** (Table 2), the best results were obtained when a solubilising co-solvent was added with vinyl acetate. Tetrahydrofuran was the best solvent, giving rapid reaction and easier work-up, although the presence of pyridine gave a higher enantiomeric ratio (E) value.[20] The optimised procedure required the reaction to be stopped at a moderate degree of conversion (entry 2). While acetate **10a** has a high e.e. of 98.5%, the moderate e.e. of the alcohol **6b** (85.6%) could be increased to up to 94.5% by a simple recrystallisation from acetone.

‡ Only after our preliminary data were published[20] was an enzymatic resolution of azetidines described.[21]

Table 2. Double sequential resolution of diol **6** using S-PPL



Entry	mg enz./mg **6**	Solvent	Time (min)	Conversion[a] (%)	**6**:**9**:**10**[b]	E.e.[c,d] (%) **6**, **9**, **10**
1	2.5	VA–THF 1:1	178	31.3	53.0:26.0:21.0	79.7, 82.2, 99.6
2	2.5	VA–THF 1:1	388	37.8	49.7:18.8:31.5	85.6,[e] 61.6, 98.5
3	2.5	VA–Me_2CO 1:1	451	26.7	65.5:10.7:23.8	43.0, 43.1, 98.7
4	2.5	VA–CH_3CN 1:1	451	26.9	62.0:11.8:26.2	45.0, 20.5, 97.3
5	2.5	VA–Py 1:1	451	26.5	60.0:21.3:18.7	61.3, 85.2, 99.4

[a] See Table 1, footnote a.
[b] See Table 1, footnote b.
[c] The major enantiomers were always **6b** and **10a**, while the prevailing mono-acetate was usually **9a**.
[d] Determination of e.e. for **9** and **10**: GLC, using Dmet.terBut.SBeta (persilylated β-cyclodextrin from MEGA); diol **6** was previously acetylated, then analysed like **10**.
[e] The e.e. can be increased by crystallisation: in this case the racemic diol precipitated out of solution while the almost optically pure enantiomer remained in the mother liquor.

The absolute configuration of **6**, **7**, **9** and **10** was established by chemical correlation with compounds of known absolute stereochemistry. One of the few commercially available azetidines in enantiomerically pure form is L-azetidine-2-carboxylic acid **16**. For this reason we transformed both **7** and **16** into a common derivative, alcohol **15**, using a non-racemising strategy, in order to compare the signs of their optical rotations (Scheme 2).

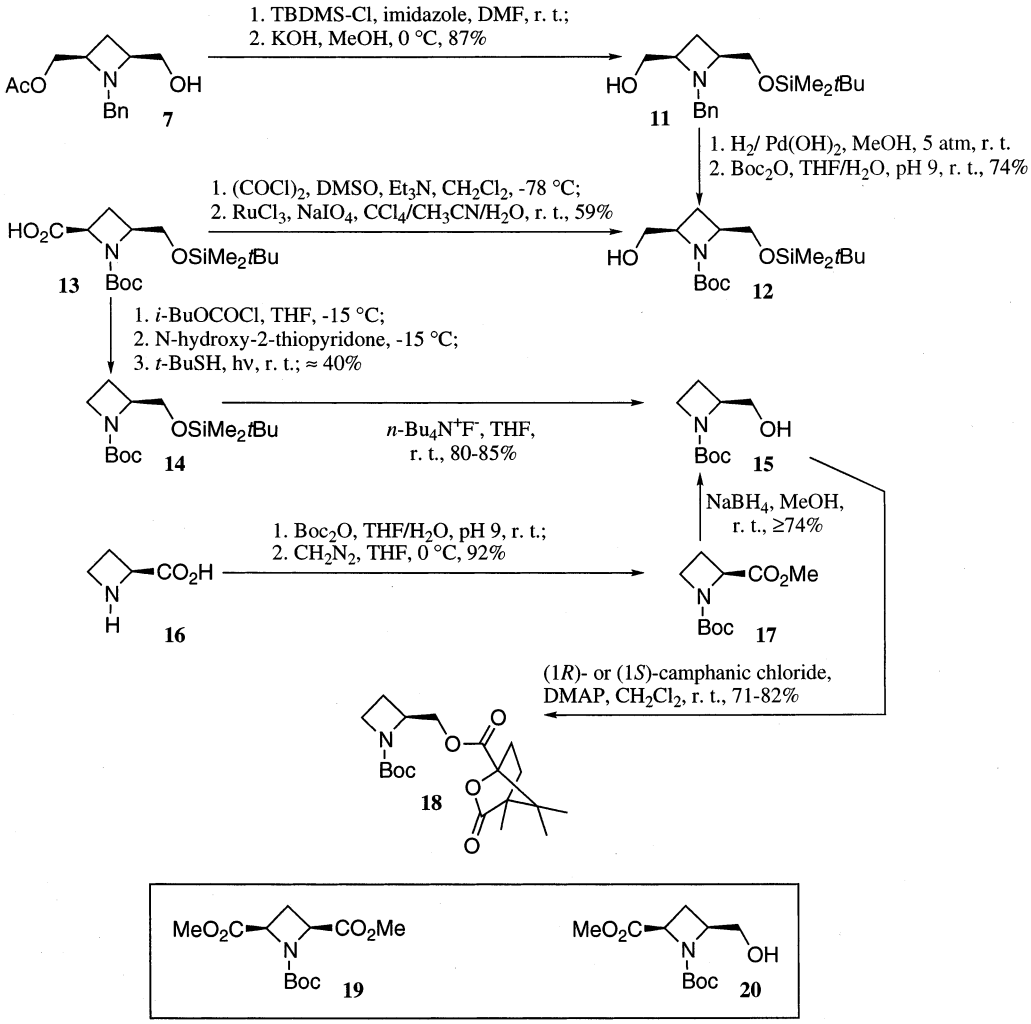
The chemical elaboration of **7** thus required a demolition process in order to eliminate one of the two hydroxymethyl groups. For this purpose we planned to oxidise the hydroxyl group of **7** to the corresponding carboxylic acid group for subsequent decarboxylation. However, in practice, these transformations proved to be more troublesome than expected and, after many unsuccessful attempts to oxidise **7**, we decided to change the nitrogen protection from benzyl to *t*-butoxycarbonyl. Moreover, during the conventional hydrogenolysis of **7**[10] simultaneous cleavage of the acetyl group occurred and, for this reason, we had to protect the hydroxyl function of **7** as a *tert*-butyldimethylsilyl ether before cleaving the benzyl protecting group. The absence of the benzyl chromophore made the reaction difficult to follow and the debenzylated derivative of **11** was volatile; however, we could not use the more suitable *tert*-butyldiphenylsilyl group since with this protecting group in place hydrogenolysis was very sluggish, probably due to steric reasons.

Finally, carbamate **12** was oxidised using Sharpless' methodology,[24,25] which has been successfully applied previously on a similar piperidinic compound.[25] However, the oxidation proceeded only in moderate and variable yield, in the range 31–48%. A better yield (59%) was obtained by performing the transformation in two steps: Swern oxidation of **12** to the corresponding aldehyde, and treatment with $RuCl_3$–$NaIO_4$ in CCl_4–CH_3CN–H_2O, maintaining the reaction pH at higher values of 6–7 than the usual pH of 4. The moderate yield is most likely due to double oxidation of both the unprotected and protected hydroxymethyl groups; actually, after treatment of the crude reaction mixture with diazomethane, we also isolated **19** and **20**. It is known from the literature[24] that methyl ethers can be oxidised to the corresponding methyl esters by Ru(VIII) but, in this case, since **20** was also identified, it is unclear if the TBDMS group was hydrolysed before or after oxidation of the methylene group.

The decarboxylation step was performed using Barton's protocol,[26,27] transforming **13** into the mixed anhydride and then into the *O*-acylthiohydroxamate, which, by treatment with *t*-BuSH/*hv*, gave **14**. This intermediate could not be purified completely because it was always contaminated by the disulfide arising from radical coupling of *t*-BuS$^{\bullet}$ and 2-Py-S$^{\bullet}$. Deprotection of the silyl ether with fluoride gave **15**, which was easily purified by silica chromatography.

The preparation of **15** from **16** was performed by transforming commercial L-azetidine-2-carboxylic acid into **17** by conventional reactions; the ester function was then chemoselectively reduced with $NaBH_4$ to give **15**.[28,29,§] The optical rotation of **15** obtained from both

[§] This compound is volatile and the yield of **15** cannot be determined very precisely since total solvent removal after chromatography also causes a loss of product.



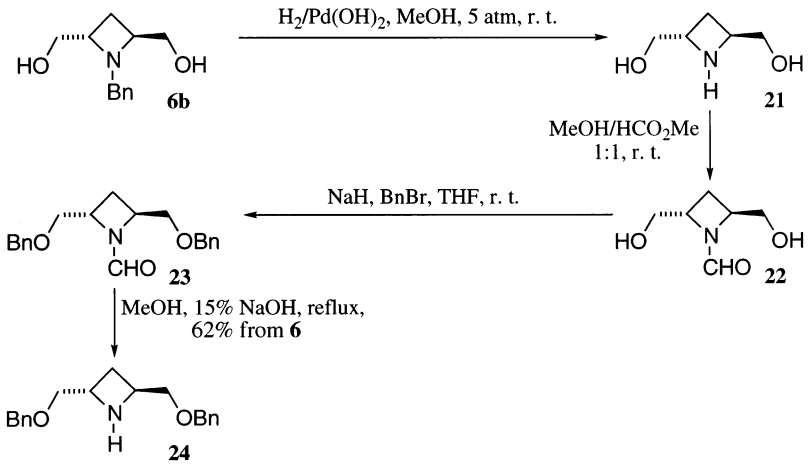
Scheme 2.

7 and from **16** had a negative sign, thus allowing assignment of (*S*)-configuration at C-(2) of **7**. Moreover, since the two substituents in **7** have a *cis*-relationship, the stereogenic centre bearing the acetoxymethyl group must be (*R*)-configured. Finally, we demonstrated that no racemisation occurred during both transformations of **7** and **16** into **15** by converting alcohol **15** into the corresponding diastereomeric camphanoates **18** and by checking their enantiomeric purity using ^{1}H NMR.

The absolute configuration of the *trans*-azetidines was determined by transforming **6b** into **24**, using a procedure developed by Yamamoto et al. on similar compounds.[12] The benzyl protecting group was removed and substituted with a formyl group to give **22**, which was *O*-benzylated to give **23**. Finally, base induced cleavage of the formyl group gave the known compound **24**. The whole sequence was performed without purification of intermediates, which were identified by GC–MS analysis of crude reaction products. The sign of the optical rotation of **24**, compared with the reported dibenzyl ether, confirmed the (2*S*,4*S*)-absolute stereochemistry shown in Scheme 3, which is identical to **6b**. The opposite absolute configuration of di-acetate **10a** was assigned by acetylation of **6b** and comparing the retention times by GLC analysis on a β-cyclodextrin based column. Finally, acetylation of the mono-acetate **9a**, which is present in small amounts, confirmed that the mono-acetate has usually the same absolute configuration as the di-acetate.[20]

These results are in agreement with our previously proposed model[30] for the enzymatic hydrolysis of esters or acetylations of alcohols catalysed by PPL: the pro-(*R*)-hydroxyl group of **5** was acylated and, analogously, in the double resolution, sequential acetylation of the two pro-(*R*)-hydroxyl groups was observed.

As a possible synthetic application of these azetidines we first chose an elaboration of *cis*-**7**, which, derived from an asymmetrisation, can be obtained in virtually



Scheme 3.

100% yield.[¶] The mono-protected diol **7** is characterised by the property of enantiodivergency[30] and thus both enantiomers of a given target can be obtained easily using an appropriate protection–deprotection strategy of the two oxygenated groups.

We envisaged in **7** a possible precursor for chiral non-racemic amino alcohols. These compounds are very important in asymmetric synthesis since they are useful precursors for chiral auxiliaries[31,32] and catalysts.[33–35] After a review of the literature, we aimed to prepare an amino alcohol which, in principle, could be used to prepare an oxazaborolidine, one of the most powerful families of homogeneous catalysts, first of all for the enantioselective reduction of prochiral carbonyl compounds.[34–37] At present, only two examples of oxazaborolidines bearing an azetidinic nucleus are known.[16,17] The homochiral amino alcohols were obtained by resolution of a racemic azetidine using an L-tyrosine derivative[16] or by formation of the azetidine ring using (*S*)-1-phenylethylamine as reagent.[17] Aziridinic oxazaborolidines, derived from both enantiomers of serine and threonine, are known.[38]

In our opinion, the preparation and use of amino alcohol **30** would be advantageous because the above-mentioned enantiodivergency means that both enantiomers can be prepared from a common intermediate. Additionally, this homochiral building block can be obtained easily in an almost enantiopure form with a simple chemoenzymatic procedure, avoiding tedious and expensive resolution procedures. Moreover, in our opinion, the presence of two stereogenic centres in the azetidinic moiety should induce better enantioselectivity, since the steric difference of the two faces of the amino alcohol would be enhanced (Scheme 4).

We then prepared an analogue of the threonine-derived amino alcohol studied by Zwanenburg et al., bearing an azetidine instead of an aziridine ring.[38] Mono-acetate **7** was mesylated and crude **25** was reduced by a one-pot procedure to give **26**. The formal substitution of Bn with Boc, necessary to ensure good results in the following oxidation step, was realised in this case in just one step, by hydrogenating **26** in the presence of both Pd–C and Boc_2O. It was not necessary to isolate the intermediate secondary amine and the hydrogenolysis could be carried out under atmospheric pressure giving a clean and direct conversion of **26** to **27**. The driving force for this unusual one-pot transformation is probably removal of the secondary amine, which reacted as soon as it formed. Since a high concentration of amine results in partial deactivation of the catalyst, rapid transformation into the carbamate lowers the overall amine concentration during the reaction, allowing **27** to form under very mild conditions.

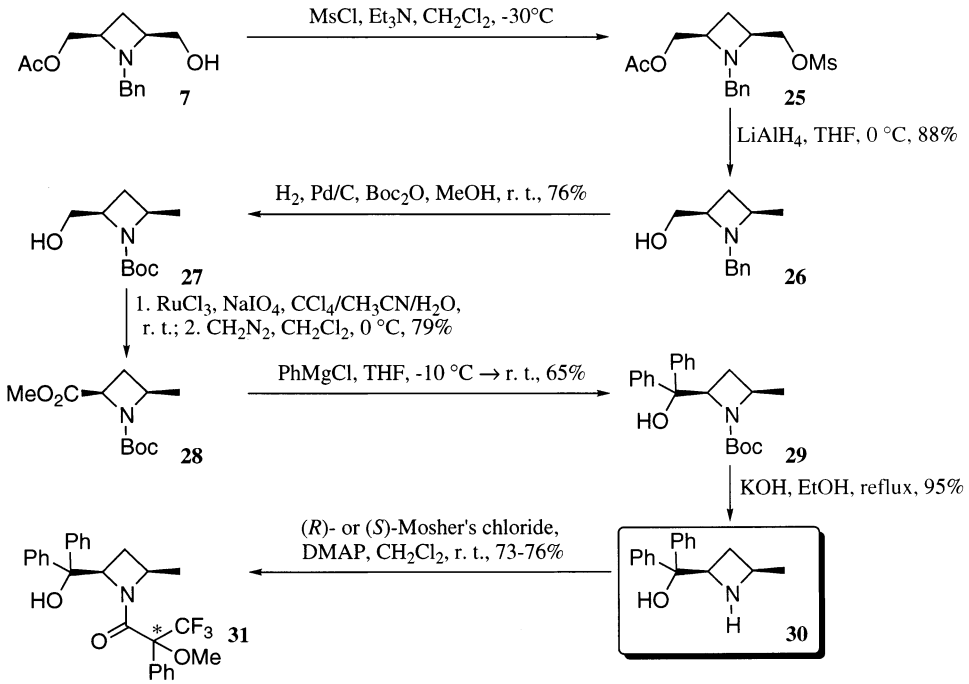
The Ru(VIII)-catalysed oxidation worked well in this case, probably since no alkoxymethylene groups are present as in **13**. Methyl ester **28** was then treated with an excess of PhMgCl in order to prepare tertiary alcohol **29**. In **29** two phenyl groups were introduced because the presence of the diphenylhydroxymethyl group, which does not introduce an additional stereogenic centre, appears to play an essential (although as yet unrationalised) role in determining the asymmetric induction in many reactions.[39]

Finally, the Boc group was hydrolysed in near quantitative yield by basic treatment. The e.e. of alcohol **30** was tested by transformation into the Mosher amide **31**, which was analysed by HPLC, thus demonstrating that no racemisation occurred during the transformation of **7** into **30**.[‖]

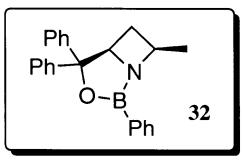
We then studied the transformation of **30** into oxazaborolidine **32** (Scheme 5). We chose the oxazaborolidine with a phenyl group bonded directly to boron after careful evaluation of the literature data. Stone[40] optimised the reduction of acetophenone using the

[¶] In this case, due to an incomplete substrate selectivity, the maximum obtained yields are around 80%, depending also on the degree of conversion.

[‖] Moreover, after crystallisation of **29** and/or **30**, the e.e., being 98%, can be increased up to 100%.



Scheme 4.



Scheme 5.

oxazaborolidine formed by condensation of phenylboronic acid and (*S*)-diphenyl prolinol[35] as catalyst in the presence of BH_3·1,4-oxathiane complex, working at 40°C. We employed a similar procedure for the preparation of **32** and then reduced acetophenone using BH_3·Me_2S. Our preliminary results showed good catalytic activity for (2*R*,4*R*)-**32** and we isolated (*S*)-1-phenylethanol in 83% yield. However, the e.e. was only a mediocre 53%. Optimisation of this procedure is currently under investigation in our laboratories since, in this case, other reaction conditions or oxazaborolidines bearing a different substituent at boron should give better results. The reduction of other prochiral ketones in the presence of borane should be investigated since acetophenone is possibly a poor substrate for testing the catalyst. The results of our further studies will be reported in due course.

3. Conclusions

In conclusion, we report here the synthesis and synthetic elaboration of uncommon optically active N-containing heterocycles to give a new class of 2-amino alcohols, exemplified structurally by **30**. To the best of our knowledge, the synthesis of **30** represents the first approach reported in the literature to a potentially useful oxazaborolidine through a chemoenzymatic route, although non-heterocyclic homochiral ligands for hydrogenation have already been prepared by biocatalytic methods.[41]

4. Experimental

4.1. General

NMR spectra were taken, unless otherwise indicated, in $CDCl_3$ at 200 MHz (^1H) and 50 MHz (^{13}C). Chemical shifts are reported in ppm (δ scale) from TMS and coupling constants are reported in hertz. Peak assignment in ^1H NMR spectra was also carried out with the aid of double-resonance experiments. In ABX systems, the proton A is considered downfield and B upfield. Peak assignment in ^{13}C spectra was made with the aid of DEPT experiments. GC–MS were carried out on an HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 170°C. Unless otherwise indicated, analyses were performed with a constant He flow of 0.9 mL/min, starting at 100°C for 2 min and then raising the temperature by 20°C/min until 260°C; the split ratio was about 100:1. Retention times are measured in minutes from injection. Enantiomeric excesses were determined by GLC analysis using an HRGC 5300 instrument from Carlo Erba equipped with: (a) Cyclodex-B™ (from J & W) column for compound **7**; (b) Dmet.terBut.SBeta (persilylated β-cyclodextrin, from Mega) for compounds **9** and **10**. Diastereomeric ratios were determined with an HP model 1090 liquid chromatograph equipped with a Hypersil column. Values of $[\alpha]_D$ were measured on a Jasco DIP 181 instrument, usually as $CHCl_3$ (contain-

ing 0.75% EtOH) solutions; concentrations of the samples are calculated in g/100 mL. IR spectra were measured with a Perkin–Elmer 881 instrument as $CHCl_3$ solutions. TLC analyses were carried out on silica gel plates, which were developed by these detection methods: (**A**) UV; (**B**) I_2; (**C**) dipping into a ninhydrin solution (900 mg in 300 mL *n*BuOH+9 mL AcOH) and warming; (**D**) dipping into a solution of $(NH_4)_4MoO_4{\cdot}4H_2O$ (21 g) and $Ce(SO_4)_2{\cdot}4H_2O$ (1 g) in H_2SO_4 (31 mL) and H_2O (469 mL) and warming. R_f values were measured after an elution of 7–9 cm. Chromatography was carried out on 220–400 mesh silica gel using the 'flash' methodology. Petroleum ether (40–60°C) is abbreviated as PE. In extractive work-up, aqueous solutions were always re-extracted thrice with the appropriate organic solvent. Organic extracts were dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen (or argon, where indicated) atmosphere. The purity of all compounds was established by TLC, ^{1}H NMR, and (when possible) GC–MS. PPL was purchased from Sigma and supported over Celite, as described in Ref. 23.

4.2. Diethyl (2*R**,4*S**)-2,4-dibromoglutarate 1 and diethyl (2*R**,4*R**)-2,4-dibromoglutarate 2

4.2.1. (2*R,4*S**)- and (2*S**,4*S**)-2,4-dibromoglutaryl dichloride**. Commercial glutaryl dichloride (50 mL, 0.39 mmol) was placed in a two-necked flask, equipped with a dropping funnel and an efficient reflux condenser, and warmed in an oil bath to 85°C. A 300 W sun lamp was positioned ca. 10 cm from the flask and turned on for the duration of the reaction. Neat bromine (48.9 mL, 0.95 mol) was then added very slowly through a dropping funnel over a period of 1.25 h, while maintaining the temperature at 85°C. Effluent from the reflux condenser was vented to a scrubber system capable of trapping bromine with 10% aqueous $Na_2S_2O_3$ and hydrogen bromide gas with soda lime. The dark mixture was kept at the same temperature for an additional 4.25 h and then cooled to rt.

4.2.2. Esterification. Absolute ethanol (200 mL) was placed in a 1 L flask equipped with a dropping funnel. The above prepared dichloride was transferred under nitrogen into the funnel and dropped over a period of 15 min into the flask, which was previously cooled in an ice bath. EtOH (3×25 mL) was used in order to transfer the dichloride quantitatively. The orange–brown solution was stirred at rt for 18 h. After cooling the solution to 0°C, solid $NaHCO_3$ was added cautiously until CO_2 evolution finished. Ice cold water and Et_2O were added and the mixture was transferred into a separatory funnel. After extraction with Et_2O, the combined organic layers were washed with 10% $Na_2S_2O_3$ solution and brine. Solvent removal gave a crude product, which was purified by distillation to give a pale yellow oil (138 g) having a gas chromatographic purity of around 93% and containing a 42:58 mixture of **1**:**2** in 95% overall yield. Bp = 117–118°C (5.5×10^{-2} torr).

4.2.3. Characterisation of 1. R_f 0.58 (CH_2Cl_2–PE 6:4, **B**). IR: ν_{max} 2983, 1737, 1374, 1265, 1094, 1014 (for both **1** and **2**). GC–MS: R_t 6.18; *m*/*z* 348 [M^+ (^{81}Br), 0.20]; 303 (12); 302 (51); 301 (27); 300 (100); 299 (13); 298 (51); 275 (14); 274 (14); 273 (28); 272 (25); 271 (14); 270 (12); 245 (18); 243 (11); 221 (22); 219 (24); 193 (50); 191 (48); 181 (20); 179 (19); 168 (75); 166 (82); 165 (57); 163 (61); 153 (11); 151 (12); 141 (15); 140 (40); 138 (39); 137 (18); 135 (22); 122 (22); 121 (10); 120 (24); 119 (11); 113 (18); 85 (27); 55 (17); 39 (14). ^{1}H NMR: 1.32 [6 H, t, C*H*$_3$CH$_2$O-, *J* = 7.1]; 2.63 [1 H, dt, -CHBrCH*H*CHBr-, *J* = 14.8, 7.3]; 2.87 [1 H, dt, -CHBrC*H*HCHBr-, *J* = 14.8, 7.3]; 4.26 [4 H, q, CH$_3$C*H*$_2$O-, *J* = 7.1]; 4.38 [2 H, t, >C*H*Br, *J* = 7.4].

4.2.4. Characterisation of 2. R_f 0.51 (CH_2Cl_2–PE 6:4, **B**). GC–MS: R_t 6.26; *m*/*z* 346 [M^+ (^{79}Br), 0.30]; 302 (53); 301 (27); 300 (100); 299 (14); 298 (51); 275 (13); 274 (13); 273 (28); 272 (24); 271 (14); 270 (11); 245 (19); 221 (20); 219 (20); 193 (45); 191 (42); 181 (19); 179 (19); 168 (68); 166 (78); 165 (57); 163 (56); 141 (13); 140 (37); 138 (37); 137 (17); 135 (21); 122 (22); 121 (11); 120 (21); 119 (11); 113 (16); 85 (28); 55 (20); 39 (16). ^{1}H NMR: 1.32 [6 H, t, C*H*$_3$CH$_2$O-, *J* = 7.2]; 2.66 [2 H, dd, -CHBrC*H*$_2$CHBr-, *J* = 7.8, 6.4]; 4.26 [4 H, q, CH$_3$C*H*$_2$O-, *J* = 7.2]; 4.51 [2 H, dd, >C*H*Br, *J* = 7.9, 6.5].

4.3. Diethyl (2*R**,4*S**)- and (2*R**,4*R**)-1-benzylazetidine-2,4-dicarboxylates 3 and 4

A 42:58 mixture of **1**:**2** (16.15 g, purity 93%, ≈43.41 mmol) was dissolved in benzene (160 mL) and treated with benzylamine (15.6 mL, 143.28 mmol). The solution was refluxed under N_2 for 24 h and the precipitation of benzylammonium bromide began after 10–15 min. The mixture was diluted with water until all the salts dissolved and extracted with Et_2O. The combined organic layers were washed with water and brine. Chromatography with PE–Et_2O 9:1→6:4 gave pure **3** (4.05 g, 32%) and **4** (5.82 g, 46%) as yellow oils.

4.3.1. Characterisation of 3. R_f 0.36 (PE–Et_2O 6:4, **B**). IR: ν_{max} 2980, 1731, 1443, 1370, 1202, 1180, 1027. GC–MS: R_t 7.70; *m*/*z* 292 (M^++1, 0.043); 219 (5.9); 218 (40); 191 (7.1); 174 (6.5); 117 (7.5); 92 (7.6); 91 (100); 65 (8.3). ^{1}H NMR: 1.18 [6 H, t, C*H*$_3$CH$_2$O-, *J* = 7.1]; 2.41 [2 H, centre of m, *H*$_3$]; 3.59 [2 H, t, *H*$_2$+*H*$_4$, *J* = 8.3]; 3.88 [2 H, s, -C*H*$_2$Ph]; 4.08 [4 H, centre of m, CH$_3$C*H*$_2$O-]; 7.29–7.33 [5 H, m, aromatics]. ^{13}C NMR: 14.09 [2 C, *C*H$_3$CH$_2$O-]; 24.69 [*C*$_3$]; 59.39 [2 C, *C*$_2$+*C*$_4$]; 60.19 [-*C*H$_2$Ph]; 60.71 [2 C, CH$_3$*C*H$_2$O-]; 127.42 [*C*H *para* of -CH$_2$Ph]; 128.16 and 129.88 [4 C, *C*H *ortho* and *meta* of -CH$_2$Ph]; 135.59 [*C ipso* of -CH$_2$Ph]; 171.58 [2 C, >*C*O].

4.3.2. Characterisation of 4. R_f 0.50 (PE–Et_2O 6:4, **A**, **B**). IR: ν_{max} 2979, 1726, 1446, 1372, 1344, 1181, 1025, 844. GC–MS: R_t 7.80; *m*/*z* 291 (M^+, 0.18); 218 (44); 191 (5.2); 117 (8.8); 92 (7.6); 91 (100); 86 (5.7); 65 (8.2). ^{1}H NMR: 1.20 [6 H, t, C*H*$_3$CH$_2$O-, *J* = 7.1]; 2.50 [2 H, t, *H*$_3$, *J* = 6.8]; 3.88 [2 H, s, -C*H*$_2$Ph]; 4.12 [4 H, q, CH$_3$C*H*$_2$O-, *J* = 7.1]; 4.20 [2 H, t, *H*$_2$+*H*$_4$, *J* = 6.7]; 7.21–

7.30 [5 H, m, aromatics]. ^{13}C NMR: 14.16 [2 C, CH_3CH_2O-]; 25.46 [C_3]; 55.74 [-CH_2Ph]; 60.61 [2 C, CH_3CH_2O-]; 61.77 [2 C, C_2+C_4]; 127.14 [*C*H *para* of -CH_2Ph]; 128.15 and 128.91 [4 C, *C*H *ortho* and *meta* of -CH_2Ph]; 137.12 [*C ipso* of -CH_2Ph]; 172.45 [2 C, >*C*O].

4.4. (2*R**,4*S**)- and (2*R**,4*R**)-1-benzylazetidine-2,4-dimethanols 5 and 6

A suspension of $LiAlH_4$ (3.37 g, 88.80 mmol) in dry Et_2O (50 mL) was cooled to 0°C. A solution of **3** or **4** (6.47 g, 22.21 mmol) in Et_2O (50 mL) was added using an addition funnel over a period of 15 min. The resulting slurry was stirred at 0°C for 1 h and then at rt for an additional 3 h. The reaction flask was cooled again to 0°C and aqueous NaOH (409 mg, 10.22 mmol in 13.3 mL of water, 738.9 mmol) was added very carefully. The resultant mixture was stirred until the aluminium salts became easily filtrable (preferably overnight). After Buchner filtration the solid was washed with warm acetone and, if necessary, the aluminates were extracted in a Soxhlet with Et_2O. The organic layer was dried with Na_2SO_4 and the solvent was evaporated.

4.4.1. Purification and characterisation of 5. Gradient-elution chromatography with Et_2O, then AcOEt and, finally, AcOEt:MeOH 9:1→7:3 gave a pale yellow solid (3.68 g, 80%), which can be crystallised from CH_2Cl_2–*i*-Pr_2O to give a white solid. Mp = 77.7–79.0°C (CH_2Cl_2–*i*-Pr_2O). R_f 0.40 (Me_2CO–MeOH 9:1, **A**, **B**). IR: ν_{max} 3432, 2919, 2869, 1452, 1399, 1330, 1157, 1089, 1011. GC–MS (in this case initial temperature was 80°C): R_t 7.68; *m*/*z* 207 (M^+, 0.17); 177 (6.3); 176 (51); 117 (3.7); 92 (7.5); 91 (100); 72 (3.5); 65 (7.6); 44 (2.2); 39 (2.9). Anal. calcd for $C_{12}H_{17}NO_2$ (207.27): C, 69.54; H, 8.27; N, 6.76. Found: C, 68.56; H, 8.11; N, 6.83%. ^{1}H NMR (DMSO-d_6): 1.72 [1 H, dt, H_3, J = 10.3, 8.1]; 2.12 [1 H, dt, H_3, J = 10.5, 7.5]; 3.10–3.31 [6 H, m, -CH_2OH+H_2+H_4]; 3.76 [2 H, s, -CH_2Ph]; 4.41 [2 H, broad s, -O*H*]; 7.33–7.46 [5 H, m, aromatics]. ^{13}C NMR (DMSO-d_6): 23.73 [C_3]; 61.21 [-*C*H$_2$Ph]; 63.18 [2 C, C_2+C_4]; 64.65 [2 C, -*C*H$_2$OH]; 126.87 [*C*H *para* of -CH_2Ph]; 127.97 and 129.09 [4 C, *C*H *ortho* and *meta* of -CH_2Ph]; 139.08 [*C ipso* of -CH_2Ph].

4.4.2. Purification and characterisation of 6. The crude product was crystallised directly from acetone to give a white solid (4.19 g, 91%). Mp = 129.1–129.5°C (Me_2CO). R_f 0.15 (Me_2CO–MeOH 9:1, **A**, **B**). IR: ν_{max} 3431, 2911, 2874, 1402, 1310, 1190, 1093, 1023. GC–MS (in this case initial temperature was 80°C): R_t 8.11; *m*/*z* 207 (M^+, 0.51); 177 (6.8); 176 (55); 117 (4.6); 92 (7.8); 91 (100); 72 (3.4); 65 (6.1). Anal. calcd for $C_{12}H_{17}NO_2$ (207.27): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.00; H, 8.12; N, 6.83%. ^{1}H NMR (DMSO-d_6): 2.04 [2 H, t, H_3 J = 6.3]; 3.50–3.67 [6 H, m, -CH_2OH+H_2+H_4]; 3.78 and 4.06 [2 H, AB syst., -CH_2Ph, J = 14.2]; 4.58 [2 H, broad t, -O*H*; J = 4.6]; 7.25–7.46 [5 H, m, aromatics]. ^{13}C NMR (DMSO-d_6): 23.94 [C_3]; 53.96 [-*C*H$_2$Ph]; 62.21 [2 C, C_2+C_4]; 62.96 [2 C, -*C*H$_2$OH]; 126.36 [*C*H *para* of -CH_2Ph]; 127.92 and 128.01 [4 C, *C*H *ortho* and *meta* of -CH_2Ph]; 140.72 [*C ipso* of -CH_2Ph].

4.5. General procedure for the enzymatic acetylations (both asymmetrisation and double sequential kinetic resolution)

Specific data, including quantity of enzyme, solvent, reaction time, conversion, yield, and product e.e., are reported in Tables 1 and 2; more data can be obtained from Ref. 20. All reactions were performed at 0°C, starting from 50 mg of **5** and 100 mg of **6**. The diol was dissolved in the appropriate solvent (VA as acylating agent and solvent, with or without added co-solvent), cooled to 0°C, and stirred for 15 min in the presence of powdered 3 Å molecular sieves (10 mg/50 mg of diol). Supported PPL was added and the mixture was stirred again for the desired time. The enzyme was filtered and washed with CH_2Cl_2 (*cis*-derivative) and acetone (*trans*-derivative). The solvent was removed in vacuo to give crude product, i.e. mixtures of **5**, **7**, **8** and **6b**, **9a**, **10a**, respectively. Both enzymatic reactions were also performed on a multigram scale and the results were reproducible.

Racemic **7**, **9**, **10**, necessary in order to set up the gas chromatographic analysis, were prepared by treating a solution of **5** or **6** in dry pyridine with a suitable amount of acetic anhydride. Standard extractive work-up with Et_2O gave the desired products.

4.5.1. Purification of *cis*-series products and determination of conversion. Chromatography was performed with AcOEt–PE 6:4→9:1, AcOEt, AcOEt–MeOH 9:1→7:3 or PE–Me_2CO 8:2→Me_2CO (100%) solvent mixtures. Conversion was measured by GC–MS analysis with SIM procedure (usual gas chromatographic conditions, but a split ratio of 50:1 and an initial temp. of 80°C). R_t 7.63 **5**, 8.24 **7**, 8.89 **8**.

4.5.2. Purification of *trans*-series products and determination of conversion. Chromatography was performed with PE–Me_2CO 1:1→0:100, and CH_2Cl_2–MeOH–NH_3 (50:50:2) as solvent mixtures. Conversion was measured by GC–MS analysis with SIM procedure (usual gas chromatographic conditions, but a split ratio of 50:1 and an initial temp. of 80°C). R_t 8.14 **6b**, 8.67 **9a**, 9.21 **10a**.

4.5.3. Characterisation of (2*S*,4*R*)-4-acetoxymethyl-1-benzylazetidine-2-methanol 7 (pale yellow oil). R_f 0.50 (PE–Me_2CO 6:4, **A**, **B**). $[\alpha]_D$ = +14.8 (*c* 2.13, $CHCl_3$, determined on a sample with 99.5% e.e.). IR: ν_{max} 3432, 2919, 2869, 1729, 1452, 1365, 1194, 1089, 1027. GC–MS: R_t 7.28; *m*/*z* 249 (M^+, 0.17); 219 (2.3); 218 (16); 177 (1.8); 176 (14); 159 (3.0); 158 (26); 92 (7.5); 91 (100); 65 (6.3); 43 (8.6). GLC [Cyclodex-B™ column; He flow 3.1 mL/min (at rt), split ratio 50:1, inj. temp. 240°C, det. temp. 250°C, oven temp. 150°C): R_t 69.17 (2*S*,4*R*-**7**), 70.56 (2*R*,4*S*-**7**), α 1.023, R_S 1.23. ^{1}H NMR: 1.92–2.10 [2 H, m, H_3]; 2.02 [3 H, s, CH_3CO-]; 3.12 and 3.18 [2 H, AB part of ABX syst., -CH_2OH, J_{AB} = 11.4; J_{AX} and J_{BX} = 3.2, 1.2]; 3.27–3.45 [2 H, m, H_2+H_4]; 3.62

and 3.78 [2 H, AB syst., -CH_2Ph, J=12.5]; 3.96 [2 H, d, -CH_2OAc, J=4.8]; 7.25–7.32 [5 H, m, aromatics]. ^{13}C NMR: 20.78 [-COCH$_3$]; 21.07 [C_3]; 60.04 [C_4]; 60.92 [-CH$_2$Ph]; 62.01 [-CH$_2$OH]; 62.90 [C_2]; 66.73 [-CH$_2$OAc]; 127.45 [CH *para* of -CH$_2$Ph]; 128.39 and 128.94 [4 C, CH *ortho* and *meta* of -CH$_2$Ph]; 137.88 [C *ipso* of -CH$_2$Ph]; 170.82 [>CO].

4.5.4. Characterisation of (2*R,4*S**)-2,4-bis(acetoxymethyl)-1-benzylazetidine 8 (pale yellow oil)**. R_f 0.72 (PE–Me$_2$CO 6:4, **A**, **B**). IR: ν_{max} 2998, 1729, 1365, 1194, 1027. GC–MS: R_t 7.92; m/z 291 (M$^+$, 0.42); 231 (2.9); 219 (2.0); 218 (14); 159 (5.0); 158 (40); 92 (7.6); 91 (100); 65 (6.0); 43 (18). ^{1}H NMR: 1.96 [6 H, s, CH_3CO-]; 1.69 [1 H, dt, H_3, J=10.6, 8.4]; 2.16 [1 H, dt, H_3, J=10.7, 7.7]; 3.31 [2 H, centre of m, H_2+H_4]; 3.71 [2 H, s, -CH_2Ph]; 3.85 and 3.96 [4 H, AB part of ABX syst., -CH_2OAc, J_{AB}=11.4, J_{AB} and J_{BX}=5.8, 4.8]; 7.23–7.33 [5 H, m, aromatics]. ^{13}C NMR: 20.76 [2 C, -COCH$_3$]; 23.68 [C_3]; 60.06 [2 C, C_2+C_4]; 61.44 [-CH$_2$Ph]; 67.40 [2 C, -CH$_2$OAc]; 127.13 [CH *para* of -CH$_2$Ph]; 128.14 and 129.09 [4 C, CH *ortho* and *meta* of -CH$_2$Ph]; 138.17 [C *ipso* of -CH$_2$Ph]; 170.72 [2 C, >CO].

4.5.5. Characterisation of (2*S*,4*S*)-benzylazetidine-2,4-dimethanol 6b. $[\alpha]_D$=−33.6 (*c* 1.47, Me$_2$CO, determined on a sample with 94.7% e.e). Spectroscopic data have already been reported after the preparation of racemic compound. GLC (Dmet.terBut.SBeta column): analyses performed after acetylation in the conditions described above for **9a**.

4.5.6. Characterisation of (2*R*,4*R*)-4-acetoxymethyl-1-benzylazetidine-2-methanol 9a. R_f 0.63 (AcOEt–MeOH 8:2, **A**, **B**). $[\alpha]_D$=+18.1 (*c* 2.28, CHCl$_3$, determined on a sample with 82.2% e.e.). IR: ν_{max} 3432, 2919, 2869, 1729, 1452, 1365, 1194, 1089, 1027. GC–MS: R_t 7.66; m/z 249 (M$^+$, 0.41), 218 (15), 177 (2.1); 176 (16), 159 (2.8); 158 (24); 117 (2.0); 92 (7.3), 91 (100), 65 (5.8), 43 (7.3). GLC [Dmet.terBut.SBeta column; He flow 1.1 mL/min (at rt), split ratio 70:1, inj. temp. 200°C, det. temp. 220°C, oven temp. 150°C→170°C, init. time 5 min, rate 2°C/min, final time 40 min): R_t 37.92 [(2*R*,4*R*)-**9a**], 39.39 [(2*S*,4*S*)-**9b**], α 1.040, R_S 2.56. ^{1}H NMR: 1.83 [1 H, centre of m, H_3]; 2.00 [3 H, s, CH_3CO-]; 2.41 [1 H, dt, H_3, J=11.0, 7.8]; 3.26 and 3.30 [2 H, AB part of ABX syst., -CH_2OH, J_{AB}=11.6, J_{AX} and J_{BX}=3.1, 1.9]; 3.67 and 3.91 [2 H, AB system, -CH_2Ph, J=13.7]; 3.67–3.91 [2 H, m, H_2+H_4]; 4.23 and 4.39 [2 H, AB part of ABX syst., -CH_2OAc, J_{AB}=12.0, J_{AX} and J_{BX}=6.4, 3.8]; 7.23–7.32 [5 H, m, aromatics]. ^{13}C NMR: 20.72 [-COCH$_3$]; 21.52 [C_3]; 53.71 [-CH$_2$Ph]; 58.42 [C_4]; 61.47 [-CH$_2$OH]; 63.72 [-CH$_2$OAc]; 64.04 [C_2]; 127.43 [CH *para* of -CH$_2$Ph]; 128.35 and 128.44 [4 C, CH *ortho* and *meta* of -CH$_2$Ph]; 136.98 [C *ipso* of -CH$_2$Ph]; 170.63 [>CO].

4.5.7. Characterisation of (2*R*,4*R*)-2,4-bis(acetoxymethyl)-1-benzylazetidine 10a. R_f 0.70 (PE–Et$_2$O 3:7, **A**, **B**). $[\alpha]_D$=+39.0 (*c* 2.56, CHCl$_3$, determined on a sample with 99.6% e.e.). IR: ν_{max} 2946, 1724, 1367, 1248, 1027. GC–MS: R_t 8.26; m/z 291 (M$^+$, 0.28); 218 (7.7); 159 (3.5); 158 (28); 92 (7.9); 91 (100); 65 (7.2); 43 (24); 41 (2.3); 39 (2.3). GLC [Dmet.terBut.SBeta column; the same conditions used for **9a**): R_t 47.30 [(2*R*,4*R*)-**10a**], 48.99 [(2*S*,4*S*)-**10b**], α 1.037, R_S 2.30. ^{1}H NMR: 1.99 [6 H, s, -CO$_2$CH_3]; 2.07 [2 H, t, H_3, J=6.7]; 3.73 and 3.89 [2 H, AB syst., -CH_2Ph, J=14.1]; 3.74–3.84 [2 H, m, H_2+H_4]; 4.10 and 4.12 [4 H, AB part of ABX syst., -CH_2OAc, J_{AB}=11.7, J_{AX} and J_{BX}=8.4, 1.7]; 7.18–7.34 [5 H, m, aromatics]. ^{13}C NMR: 20.77 [2 C, -COCH$_3$]; 23.60 [C_3]; 54.44 [-CH$_2$Ph]; 59.42 [2 C, C_2+C_4]; 65.59 [2 C, -CH$_2$OAc]; 126.75 [CH *para* of -CH$_2$Ph]; 127.87 and 128.16 [4 C, CH *ortho* and *meta* of -CH$_2$Ph]; 139.16 [C *ipso* of -CH$_2$Ph]; 170.78 [>CO].

4.6. (2*R*,4*S*)-1-Benzyl-4-{[(*t*-butyldimethyl)silyloxy]-methyl}azetidine-2-methanol 11

4.6.1. (2*R*,4*S*)-2-(Acetoxymethyl)-1-benzyl-4-{[(*t*-butyldimethyl)silyloxy]methyl}azetidine. Mono-acetate **7** (1.25 g, 5.01 mmol) was dissolved in dry DMF (7 mL) and treated with imidazole (854 mg, 12.54 mmol) and *t*-BuMe$_2$SiCl (97%, 937 mg, 6.03 mmol). After stirring for 4 h at rt, the solution was diluted with water and extracted with Et$_2$O. Solvent removal gave the crude product used directly in the saponification. R_f 0.46 (PE–Et$_2$O 7:3, **A**, **B**). GC–MS (in this case the initial temperature was 80°C): R_t 9.81; m/z 363 (M$^+$, 0.012); 306 (2.4); 290 (3.4); 219 (4.2); 218 (29); 159 (8.6); 158 (71); 156 (2.6); 92 (7.6); 91 (100); 89 (7.5); 75 (5.8); 73 (9.2); 65 (4.4); 59 (5.1); 57 (2.8); 43 (14); 41 (4.1).

4.6.2. Saponification reaction. The crude product obtained above was dissolved in absolute MeOH (7 mL) and cooled to 0°C. A 1 M solution of KOH in MeOH (7.5 mL, 7.50 mmol) was added and stirring was continued at the same temperature for 1 h. $NH_4H_2PO_4$ (5% solution in water, 2 mL) was added and the solution was concentrated under reduced pressure. Standard extraction with AcOEt was performed, followed by washing of the combined organic layers with brine. After solvent removal, chromatography with PE–AcOEt 3:7→AcOEt 100% gave pure **11** as a colourless oil (1.40 g, 88%). R_f 0.39 (PE–AcOEt 8:2, **A**, **B**). $[\alpha]_D$=−16.7 (*c* 2.11, CHCl$_3$). IR: ν_{max} 3440, 2954, 2927, 2858, 1194, 1125, 1076. GC–MS: R_t 8.39; m/z 321 (M$^+$, 0.065); 291 (2.7); 290 (11); 264 (3.0); 190 (3.2); 177 (13); 176 (100); 158 (3.7); 142 (2.9); 117 (4.3); 92 (7.4); 91 (93); 89 (2.6); 75 (6.0); 73 (8.3); 72 (3.1); 65 (5.2); 59 (4.8); 57 (3.0); 45 (2.1); 41 (4.0). ^{1}H NMR: 0.04 [6 H, s, (CH_3)$_2$*t*-BuSi-]; 0.90 [9 H, s, Me$_2$(CH_3)$_3$CSi-]; 1.99 [2 H, t, H_3, J=8.0]; 3.09 and 3.16 [2 H, AB part of ABX syst., -CH_2OH, J_{AB}=11.3, J_{AX} and J_{BX}=3.1, 1.4]; 3.18–3.32 [2 H, m, H_2+H_4]; 3.46 [2 H, d, -CH_2OSiMe$_2$*t*-Bu, J=5.0]; 3.61 and 3.83 [2 H, AB syst., -CH_2Ph, J=12.6]; 7.23–7.34 [5 H, m, aromatics]. ^{13}C NMR: −5.34 and −5.31 [2 C, (CH_3)$_2$*t*-BuSi-]; 18.38 [(CH$_3$)$_3$*C*-]; 20.76 [C_3]; 25.96 [3 C, (CH_3)$_3$C-]; 61.21 [-CH$_2$Ph]; 62.04 [-CH$_2$OH]; 62.72 and 63.02 [2 C, C_2+C_4]; 66.47 [-CH$_2$OSiMe$_2$*t*-Bu]; 127.25 [CH *para* of -CH$_2$Ph]; 128.28 and 128.99 [4 C, CH *ortho* and *meta* of -CH$_2$Ph]; 138.38 [C *ipso* of -CH$_2$Ph].

4.7. (2*R*,4*S*)-1-(*t*-Butoxycarbonyl)-4-{[(*t*-butyldimethyl)-silyloxy]methyl}azetidine-2-methanol 12

4.7.1. (2*R*,4*S*)-4-{[(*t*-Butyldimethyl)silyloxy]methyl}azetidine-2-methanol. A solution of **11** (499 mg, 1.55 mmol) was dissolved in MeOH (30 mL) and treated with $Pd(OH)_2$ over charcoal (20%, 250 mg). The mixture was hydrogenated for 24 h under 5 atm hydrogen pressure. The catalyst was filtered and the solvent evaporated to give a colourless oil which was used 'as is' in the next reaction. GC–MS: R_t 5.92; m/z 200 (M^+-31, 6.1); 174 (7.7); 158 (8.3); 157 (20); 156 (19); 127 (6.8); 116 (27); 101 (14); 100 (6.3); 87 (5.4); 86 (100); 82 (6.1); 75 (34); 73 (25); 69 (22); 68 (24); 60 (8.3); 59 (11); 45 (5.0); 41 (11).

4.7.2. Protection reaction. The crude amine obtained above was dissolved in a THF–H_2O mixture (8 mL, 1:1) and cooled to 0°C. Di-*tert*-butyl dicarbonate (500 μL, 2.18 mmol) was added, followed by $NaHCO_3$ (183 mg, 2.18 mmol) and aqueous NaOH (1N, 2 mL). The mixture was then stirred at rt for 24 h, the aqueous solution was saturated with NaCl and extracted with AcOEt. The combined organic layers were washed with brine and concentrated in vacuo. Chromatography with PE–AcOEt 8:2→65:35 gave pure **12** as a colourless oil (382 mg, 74%). R_f 0.50 (PE–AcOEt 7:3, **C**). $[\alpha]_D=-39.0$ (c 1.52, $CHCl_3$). IR: ν_{max} 3683, 3437, 2957, 2931, 2858, 1666, 1460, 1393, 1368, 1247, 1146. GC–MS: R_t 7.63; m/z 275 (M^+-57, 0.01); 220 (5.2); 219 (14); 218 (100); 200 (9.0); 160 (8.8); 158 (7.5); 157 (17); 156 (40); 142 (6.6); 127 (5.3); 116 (22); 115 (5.1); 101 (7.9); 100 (7.7); 89 (5.2); 86 (17); 82 (8.7); 75 (32); 73 (24); 68 (11); 59 (9.8); 58 (6.0); 57 (57); 55 (5.8); 41 (14). ^{1}H NMR (DMSO-d_6, temp. 110°C): 0.07 [6 H, s, $(CH_3)_2t$-BuSi-]; 0.91 [9 H, s, $Me_2(CH_3)_3CSi$-]; 1.40 [9 H, s, $-CO_2C(CH_3)_3$]; 1.99 [1 H, dt, H_3, $J=11.0$, 6.2]; 2.22 [1 H, dt, H_3, $J=11.0$, 8.4]; 3.44–3.63 [2 H, m, H_2+H_4]; 3.69 and 3.77 [2 H, AB part of ABX syst., $-CH_2OSiMe_2t$-Bu, $J_{AB}=10.6$, J_{AX} and $J_{BX}=5.7$, 3.2]; 3.97–4.11 [2 H, m, $-CH_2OH$]; 4.27 [1 H, t, -O*H*, $J=5.1$]. ^{13}C NMR: −5.51 and −5.42 [2 C, $(CH_3)_2t$-BuSi-]; 18.41 [$Me_2C(CH_3)_3Si$-]; 19.95 [C_3]; 25.90 [3 C, $Me_2C(CH_3)_3$-Si-]; 28.33 [3 C, $-CO_2C(CH_3)_3$]; 59.77 and 60.75 [2 C, C_2+C_4]; 63.34 and 65.66 [2 C, $-CH_2O$-]; 80.12 [$-CO_2C(CH_3)_3$]; 157.05 [$-CO_2t$-Bu].

4.8. (2*R*,4*S*)-1-(*t*-Butoxycarbonyl)-4-{[(*t*-butyldimethyl)-silyloxy]methyl}azetidine-2-carboxylic acid 13

4.8.1. (2*R*,4*S*) - 1 - (*t* - Butoxycarbonyl) - 4 - {[(*t* - butyldimethyl)silyloxy]methyl}azetidine-2-carbaldehyde. Dry DMSO (2.82 M in dry CH_2Cl_2, 1.34 mL, 3.76 mmol) was cooled to −78°C and treated with oxalyl chloride (2.41 M, in CH_2Cl_2, 976 μL, 2.35 mmol). After 10 min, a solution of **12** (312 mg, 94.1 μmol) in dry CH_2Cl_2 (5 mL) was added and stirring continued for 10 min. Finally, Et_3N (918 μL, 6.59 mmol) was added and the temperature was allowed to rise to −40°C. The reaction was quenched with water and extracted with Et_2O to give, after solvent removal, crude aldehyde, which was used directly in the next oxidation. R_f 0.46 (PE–AcOEt 8:2, **B**, **C**).

4.8.2. Second oxidation step. The crude aldehyde was dissolved in CCl_4–CH_3CN (6 mL, 1:1) and treated with a previously prepared solution of $NaIO_4$ (890 mg, 4.16 mmol) and $RuCl_3$ (13 mg, 62.7 μmol) in water (4.5 mL). The pH was maintained at 7 by adding solid $NaHCO_3$. The biphasic system was vigorously stirred at rt for 21 h. Since the reaction was incomplete, the pH was adjusted to 3.8 by adding 1 M H_2SO_4 and additional $RuCl_3$ (17 mg). After 1 h the reaction mixture was saturated with NaCl and extracted with AcOEt. The combined organic extracts were washed with 10% aq. Na_2SO_3 and brine. After evaporation, chromatography with PE–AcOEt 8:2→0:100 gave pure **13** as a viscous colourless oil (192 mg, 59%). R_f 0.41 (PE–AcOEt 1:1 with 1% AcOH, **C**). $[\alpha]_D=+9.3$ (c 0.92, $CHCl_3$). IR: ν_{max} 3420, 3004, 1696, 1603, 1390, 1369, 1144. GC–MS: **13** is not suitable for this analysis. ^{1}H NMR: 0.01 [6 H, s, $(CH_3)_2t$-BuSi-]; 0.92 [9 H, s, $Me_2C(CH_3)_3Si$-]; 1.46 [9 H, s, $-CO_2C(CH_3)_3$]; 1.35–1.75 [1 H, m, H_3]; 2.50 [2 H, broad s, H_3]; 3.56–4.40 [3 H, m, $-CH_2OSiMe_2t$-Bu+H_4]; 4.60 [1 H, broad t, H_2, $J=7.4$]. ^{13}C NMR: −5.50 and −5.43 [2 C, $(CH_3)_2t$-BuSi-]; 18.39 [$Me_2C(CH_3)_3Si$-]; 22.04 [C_3]; 25.95 [3 C, $Me_2C(CH_3)_3Si$-]; 28.25 [3 C, $-CO_2C(CH_3)_3$]; 57.88 and 61.22 [2 C, C_2+C_4]; 65.31 [$-CH_2O$-]; 81.20 [$-CO_2C(CH_3)_3$]; 156.85 [$-CO_2t$-Bu]; 173.57 [$-CO_2H$].

4.9. (*S*)-1-(*t*-Butoxycarbonyl)-2-{[(*t*-butyldimethyl)-silyloxy]methyl}azetidine 14

Acid **13** (144 mg, 417 μmol) was dissolved in dry THF (4 mL) and cooled to −15°C. To this solution *iso*-butyl chloroformate (54 μL, 417 μmol) and 4-methylmorpholine (46 μL, 417 μmol) were added and the mixture was stirred for 5 min. A solution of *N*-hydroxy-2-thiopyridone (63.6 mg, 500 μmol) and Et_3N (70 μL, 500 μmol) in THF (10 mL) was added, while the reaction flask was maintained in the dark. After 1 h *t*-BuSH (141 μL, 1.25 mmol) was added and the reaction was stirred at 15°C while irradiating with a 300 W sun lamp. After 1–2 min the solution, initially yellow, became colourless and, after an additional 10 min, was extracted with Et_2O. After evaporation, the crude reaction mixture was purified by chromatography with PE–Et_2O 100:0→85:15 to give 76.8 mg of product. ^{1}H NMR analysis revealed that this compound is a 65:35 (weight) mixture of **14** and *t*-butyl-(2-pyridyl)disulfide. Thus, the estimated yield is approx. 40%. R_f 0.28 (PE–Et_2O 9:1, **C**). GC–MS: R_t 6.41; m/z 228 (M^+-73, 2.0); 189 (15); 188 (100); 100 (10); 75 (44); 73 (24); 71 (7.6); 70 (6.3); 59 (8.7); 58 (7.6); 57 (50); 56 (27); 41 (16). ^{1}H NMR: 0.03 and 0.06 [6 H, 2 s, $(CH_3)_2t$-BuSi-]; 0.91 [9 H, s, $Me_2(CH_3)_3CSi$-]; 1.43 [9 H, s, $-CO_2C(CH_3)_3$]; 2.17 [2 H, q, H_3, $J=7.4$]; 3.65 and 3.92 [2 H, AB part of ABX syst., $-CH_2OSiMe_2t$-Bu, $J_{AB}=10.8$, J_{AX} and $J_{BX}=3.8$, 2.5]; 3.78 [2 H, t, H_4, $J=7.6$]; 4.21 [1 H, centre of m, H_2].

4.10. (*S*)-1-(*t*-Butoxycarbonyl)azetidine-2-methanol 15

4.10.1. From 14. A solution of **14** (74.7 mg, about 65% pure) in dry THF (1 mL) cooled to 0°C was treated with a 1 M solution of n-$Bn_4N^+F^-$ (331 μL, 331 μmol)

and, after 10 min, the solution was stirred at rt for an additional 15 min. Extraction with Et_2O and solvent removal under reduced pressure gave crude **15**, which was purified by chromatography using pentane–Et_2O 4:6→100:0 as eluent. Alcohol **15** was obtained in 80–85% yield (see text).

4.10.2. From 17. Ester **17** (41.5 mg, 193 μmol) was dissolved in MeOH (1 mL) and cooled to 0°C. $NaBH_4$ (21.9 mg, 5.78 μmol) was then added and the mixture was stirred at rt for 1 h. Quenching with saturated aqueous NH_4Cl, followed by extraction with Et_2O, gave crude alcohol, which was purified by chromatography with pentane–Et_2O 3:7→0:100 to give **15** as a colourless oil with an overall yield ≥74%. R_f 0.28 (PE–Et_2O 2:8, **C**). $[\alpha]_D = -20.3$ (*c* 0.72, $CHCl_3$). IR: ν_{max} 3393, 2923, 2893, 1660, 1393, 1368, 1152. GC–MS: R_t 4.22; *m*/*z* 187 (M^+, 0.40); 157 (8.7); 156 (28); 114 (17); 113 (5.7); 101 (6.7); 100 (45); 71 (11); 59 (7.2); 57 (100); 58 (5.6); 56 (90); 55 (6.0); 43 (10); 41 (25); 31 (6.3). ^1H NMR: 1.45 [9 H, s, -$CO_2C(CH_3)_3$]; 1.71–2.27 [2 H, m, H_3]; 3.72–3.94 [4 H, m, H_4+-CH_2OH]; 4.45 [1 H, centre of m, H_2]. ^{13}C NMR: 17.91 [C_3]; 28.32 [3 C, -$C(CH_3)_3$]; 46.65 [C_4]; 63.64 [C_2]; 66.76 [-CH_2OH]; 80.30 [-$C(CH_3)_3$]; 157.14 [-CO_2t-Bu].

4.11. Methyl (*S*)-1-(*t*-butoxycarbonyl)azetidine-2-carboxylate 17

4.11.1. (*S*)-1-(*t*-Butoxycarbonyl)azetidine-2-carboxylic acid. Commercial **16** (41 mg, 406 μmol) was *N*-protected following the same procedure described to prepare **12**. R_f 0.64 (*n*-PrOH–30% NH_3 8:2, **C**).

4.11.2. Esterification. The crude acid prepared above was dissolved in THF (5 mL) and treated with CH_2N_2 (1 M solution in Et_2O, 5 mL). After a few minutes the reaction was complete and the excess CH_2N_2 was quenched by reaction with AcOH (≈0.2 mL). After solvent removal, crude **17** was purified directly by chromatography, using PE–Et_2O 6:4→1:1 as eluent, to give a colourless oil (80 mg, 92%). R_f 0.25 (PE–Et_2O 6:4, **C**). $[\alpha]_D = -108.6$ (*c* 1.06, $CHCl_3$). IR: ν_{max} 2897, 1742, 1695, 1394, 1368, 1145. GC–MS: R_t 4.71; *m*/*z* 215 (M^+, 0.59); 160 (9.0); 159 (7.4); 156 (26); 142 (7.5); 114 (28); 100 (26); 59 (5.1); 57 (96); 56 (100); 55 (9.8); 41 (18). ^1H NMR: 1.43 [9 H, s, -$C(CH_3)_3$]; 2.09–2.25 [1 H, m, H_3]; 2.50 [1 H, centre of m, H_3]; 3.78 [3 H, s, -CO_2CH_3]; 3.83–4.10 [2 H, m, H_4]; 4.62 [1 H, dd, H_2, J=8.9, 5.4]. ^{13}C NMR: 20.23 [C_3]; 28.28 [3 C, -$C(CH_3)_3$]; 47.54 [C_4]; 52.07 [-OCH_3]; 60.46 [C_1]; 79.98 [-$C(CH_3)_3$]; 155.34 [-CO_2t-Bu]; 171.82 [-CO_2Me].

4.12. (*S*)-1-(*t*-Butoxycarbonyl)-2-[(+)- or (−)-(camphanoyloxy)methyl]azetidine 18

Alcohol **15** (6.0 mg, 32.04 μmol) was dissolved in dry CH_2Cl_2 (500 μL) and treated with 4-*N*,*N*-dimethylaminopyridine (23.5 mg, 192 μmol) and (1*S*)- or (1*R*)-camphanic chloride (20.8 mg, 96.12 μmol). After 1 h the solution was purified directly by preparative TLC, using PE–Et_2O 2:8 as eluent. Ester **18** was obtained in 71–82% yield. R_f 0.60 (PE–Et_2O 2:8, **A**, **C**) for **18** prepared from (2*S*)-**15** and (1*S*)-camphanic chloride and 0.54 (PE–Et_2O 2:8, **A**, **C**) for **18** prepared from (2*S*)-**15** and (1*R*)-camphanic chloride.

4.13. (2*S*,4*S*)-Azetidine-2,4-dimethanol 21

Diol **6b** (502 mg, 2.42 mmol) was dissolved in MeOH (50 mL) and treated with $Pd(OH)_2$–C (20%, 500 mg). The suspension was stirred at rt and hydrogenated at 5 atm for 29 h. The catalyst was filtered out and the solvent was removed from the filtrate in vacuo to give crude **21**. R_f 0.30 (Me_2CO–MeOH 7:3, **B**). GC–MS (inj. temp. 150°C, det. temp. 280°C, init. temp. 50°C, rate 20°C/min, final temp. 220°C, He constant flow 0.9 mL/min): R_t 5.87; *m*/*z* 117 (M^+, 4.0); 87 (7.4); 86 (100); 69 (45); 68 (24); 60 (6.1); 58 (21); 57 (7.8); 56 (8.2); 55 (5.6); 54 (5.4); 44 (10); 43 (9.4); 42 (20); 41 (56); 40 (5.0); 39 (8.9); 32 (11); 31 (20).

4.14. (2*S*,4*S*)-2,4-Bis(hydroxymethyl)azetidine-1-carbaldehyde 22

Crude **21** was suspended in MeOH–HCO_2Me (10 mL, 1:1 mixture) and stirred at rt for 63 h and at 80°C for 1.75 h. The solvent was removed in vacuo to give crude **22**. R_f 0.57 (Me_2CO–MeOH 7:3, **B**). GC–MS (inj. temp. 150°C, det. temp. 280°C, init. temp. 50°C, rate 20°C/min, final temp. 220°C, He constant flow 0.9 mL/min): R_t 8.29; *m*/*z* 127 (M^+–H_2O, 5.5); 115 (33); 114 (95); 109 (6.8); 100 (6.9); 96 (14); 88 (12); 86 (48); 84 (8.5); 82 (5.1); 71 (9.2); 70 (10); 69 (100); 68 (85); 67 (6.2); 60 (12); 58 (35); 57 (13); 56 (12); 54 (10); 46 (7.5); 44 (7.2); 43 (18); 42 (25); 41 (98); 40 (6.1); 39 (17); 31 (34).

4.15. (2*S*,4*S*)-2,4-Bis(benzyloxymethyl)azetidine-1-carbaldehyde 23

Crude **22** was dissolved in dry THF (20 mL) and cooled to 0°C. Benzyl bromide (749 μL, 6.30 mmol) and NaH (303 mg, 52% suspension in mineral oil) were added cautiously. After a few minutes the mixture was stirred at rt for 30 min and then heated under reflux for 3.25 h. After cooling to rt the reaction was diluted with water and extracted with Et_2O. The ethereal extract was evaporated under reduced pressure and crude **23** was used directly in the next reaction. R_f 0.41 (Et_2O, **A**, **B**). GC–MS (inj. temp. 150°C, det. temp. 280°C, init. temp. 50°C, rate 20°C/min, final temp. 220°C, He constant flow 0.9 mL/min): R_t 14.20; *m*/*z* 217 (M^+–117, 0.24); 128 (3.0); 126 (3.0); 113 (16); 111 (2.6); 100 (5.8); 98 (17); 96 (3.4); 92 (9.1); 91 (100); 72 (6.3); 71 (4.3); 70 (3.2); 68 (3.5); 65 (5.9).

4.16. (2*S*,4*S*)-2,4-Bis(benzyloxymethyl)azetidine 24

Crude **23** was dissolved in MeOH (25 mL) and treated with 15% aqueous NaOH (2 mL). The mixture was refluxed for 38 h wherein the biphasic system gradually became a homogeneous solution; 5% aqueous $NH_4H_2PO_4$ (3 mL) was added and the suspension was concentrated in vacuo. Extraction with AcOEt, followed by washing of the combined organic layers with brine and solvent removal, gave crude **24**. Chromatog-

raphy with AcOEt–PE–Et_3N 60:40:0→100:0:3 gave **24** as an oil (444 mg, 62% from **6b**). R_f 0.25 (PE–AcOEt–Et_3N 40:60:2, **A**, **B**). $[\alpha]_D = -6.5$ (*c* 1.83, $CHCl_3$). GC–MS (inj. temp. 150°C, det. temp. 280°C, init. temp. 50°C, rate 20°C/min, final temp. 220°C, He constant flow 0.9 mL/min): R_t 12.68, *m*/*z* 297 (M^++1, 0.015); 176 (11); 150 (18); 92 (7.8); 91 (100); 70 (26); 68 (3.3); 65 (5.8); 41 (2.1). ^1H and ^{13}C NMR data are in agreement with reported data.[12]

4.17. (2*R*,4*S*)-2-(Acetoxymethyl)-1-benzyl-4-(methanesulfonyloxy)methylazetidine 25

A solution of **7** (2.85 g, 11.4 mmol) in dry CH_2Cl_2 (50 mL) was cooled to −30°C and treated with Et_3N (1.91 mL, 13.7 mmol) and MsCl (973 μL, 12.6 mmol). After 3 h the mixture was diluted with aqueous saturated NH_4Cl solution (30 mL) and extracted with AcOEt. The combined organic layers were washed with brine and concentrated in vacuo. Mesylate **25** was used directly in the following reaction. R_f 0.36 (Et_2O–PE 8:2, **A**, **B**). GC–MS (in this case initial temperature was 80°C): R_t 10.65; *m*/*z* 268 (M^+−59, 0.90); 256 (2.7); 255 (6.1); 254 (42); 232 (2.8); 159 (5.8); 158 (49); 92 (7.7); 91 (100); 65 (5.6); 43 (6.1).

4.18. (2*R*,4*R*)-1-Benzyl-4-methylazetidine-2-methanol 26

The same procedure described for the reduction of diesters **3** and **4** was followed, but performing the reaction at 0°C. Chromatography with PE–Me_2CO 1:1→0:100 gave **26** directly as a colourless oil (88%). R_f 0.40 (PE–Me_2CO 6:4, **A**, **B**). $[\alpha]_D = -15.9$ (*c* 0.81, $CHCl_3$). IR: ν_{max} 3007, 2957, 2922, 2863, 1601, 1384, 1236, 1084. GC–MS (in this case the initial temperature was 80°C): R_t 6.22; *m*/*z* 191 (M^+, 0.87); 161 (7.8); 160 (64); 117 (11); 92 (8.2); 91 (100); 90 (2.1); 65 (7.3); 56 (6.2); 44 (2.4); 39 (2.0). ^1H NMR: 1.01 [3 H, d, -CH_3, J=6.0]; 1.74 [1 H, dt, H_3, J=10.4, 8.1]; 2.08 [1 H, dt, H_3, J=10.5, 7.5]; 3.10–3.28 [4 H, m, H_2+H_4+-CH_2OH]; 3.57 and 3.68 [2 H, AB syst., -CH_2Ph, J=12.5]; 7.19–7.38 [5 H, m, aromatics]. ^{13}C NMR: 21.64 [-CH_3]; 26.52 [C_3]; 58.49 [-CH_2Ph]; 60.79 and 61.53 [2 C, C_2+C_4]; 63.12 [-CH_2OH]; 127.18 [*C*H *para* of -CH_2Ph]; 128.22 and 129.02 [4 C, *C*H *ortho* and *meta* of -CH_2Ph]; 138.20 [*C ipso* of -CH_2Ph].

4.19. (2*R*,4*R*)-1-*t*-Butoxycarbonyl-4-methylazetidine-2-methanol 27

A suspension of **26** (1.55 g, 8.10 mmol) in MeOH (30 mL) was treated with di-*tert*-butyl dicarbonate (2.79 mL, 12.15 mmol) and Pd–C (10%, 500 mg). The mixture was hydrogenated at 1 atm for 30 h. The catalyst was filtered and the resulting solution concentrated. After dilution with water the slurry was extracted with Et_2O and the combined organic extracts were washed with brine. The solvent was then removed and the crude product was chromatographed with PE–Et_2O 6:4→1:9, Et_2O (100%) to give **27** as a colourless oil (1.24 g, 76%). R_f 0.33 (PE–Et_2O 1:1, **C**). $[\alpha]_D = -12.0$ (*c* 2.02, $CHCl_3$). IR: ν_{max} 3376, 2978, 2929, 1664, 1368, 1345, 1155, 1070, 1041. GC–MS: R_t 4.27; *m*/*z* 201 (M^+, 0.39); 171 (8.4); 170 (29); 128 (11); 115 (8.5); 114 (87); 70 (99); 59 (7.4); 58 (6.1); 57 (100); 43 (11); 42 (8.2); 41 (22); 39 (5.3); 31 (6.2). ^1H NMR: 1.34 [3 H, d, -CH_3, J=6.2]; 1.46 [9 H, s, -C(CH_3)$_3$]; 2.28 [1 H, dt, H_3, J=11.2, 8.2]; 2.31 [1 H, dt, H_3, J=11.3, 8.2]; 3.75 and 3.77 [2 H, AB part of ABX syst., -CH_2OH, J_{AB}=11.5, J_{AX} and J_{BX}=3.71, 3.69]; 4.09–4.34 [2 H, m, H_2+H_4]. ^{13}C NMR: 21.92 [>CH*C*H$_3$]; 26.25 [C_3]; 28.37 [3 C, -C(*C*H$_3$)$_3$]; 55.17 [C_4]; 60.66 [C_2]; 67.32 [-*C*H$_2$OH]; 80.19 [-*C*(CH$_3$)]; 157.75 [-*C*O$_2$*t*-Bu].

4.20. Methyl (2*R*,4*R*)-1-(*t*-butoxycarbonyl)-4-methylazetidine-2-carboxylate 28

4.20.1. (2*R*,4*R*)-1-(*t*-Butoxycarbonyl)-4-methylazetidine-2-carboxylic acid. A solution of **27** (1.24 g, 6.16 mmol) in CCl_4–CH_3CN–H_2O (21 mL, 2:2:3) was cooled to 0°C and treated with $NaIO_4$ (5.37 g, 25.1 mmol) and $RuCl_3$ (28 mg, 135 μmol). The resulting dark mixture was stirred at rt for 5 h and then diluted with 5% aqueous $NH_4H_2PO_4$. The resulting biphasic system was filtered over a Celite pad, the extraction was performed with AcOEt and the resulting combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ and brine, before the solvent was removed in vacuo. The crude acid was esterified directly without further purification. R_f 0.20 (PE–Et_2O 1:1 with 1% AcOH, **C**).

4.20.2. Esterification. The crude acid was treated with CH_2N_2, as described above for compound **17**. After solvent removal, direct chromatography with PE–Et_2O 7:3→4:6 gave **28** as a colourless oil (1.11 g, 79%). R_f 0.66 (PE–Et_2O 2:8, **C**). $[\alpha]_D = +70.2$ (*c* 1.72, $CHCl_3$). IR: ν_{max} 3682, 3439, 2979, 2930, 1702, 1382, 1281, 1155, 1076, 1049, 1010. GC–MS: R_t 4.70; *m*/*z* 229 (M^+, 2.2); 174 (8.8); 173 (7.0); 170 (45); 156 (15); 142 (6.4); 128 (22); 114 (76); 113 (14); 71 (5.1); 70 (100); 59 (8.7); 57 (78); 43 (5.3); 41 (14). ^1H NMR: 1.43 [9 H, s, -C(CH_3)$_3$]; 1.44 [3 H, d, CH_3CH-, J=6.1]; 1.83 [1 H, dt, H_3, J=11.3, 6.3]; 2.60 [1 H, ddd, H_3, J=11.3, 9.3, 8.1]; 3.77 [3 H, s, -CO$_2$CH_3]; 4.24 [1 H, centre of m, H_4]; 4.52 [1 H, dd, H_4, J=9.2, 6.3]. ^{13}C NMR: 21.43 [>CH*C*H$_3$]; 28.32 [4 C, C_3+-C(*C*H$_3$)$_3$]; 52.10 [-CO$_2$*C*H$_3$]; 56.14 and 57.28 [2 C, C_2+C_4]; 79.84 [-*C*(CH$_3$)]; 155.66 [-*C*O$_2$*t*-Bu]; 171.95 [-*C*O$_2$Me].

4.21. (2*R*,4*R*)-1-(*t*-Butoxycarbonyl)-α,α-diphenyl-4-methylazetidine-2-methanol 29

To a THF solution of PhMgCl (2 M, 7.26 mL, 14.52 mmol), cooled to 0°C, was added a solution of **28** (1.11 g, 4.84 mmol) in dry THF (20 mL) via an addition funnel over a 20 min period. The solution was allowed to warm to rt. Since it was difficult for the reaction to go to completion, additional PhMgBr solution was added periodically, after cooling the mixture to 0°C (i.e. a total of 24.25 mmol of Grignard reagent was used). After 8 h aqueous saturated NH_4Cl (20 mL) was added and the extraction was performed with AcOEt. The combined organic extracts were washed with 1N NaOH, in order to extract the traces of phenol always present, and then washed again with water until a neutral pH was reached. After one treatment with

brine, the solution was concentrated in vacuo and chromatographed with PE–Et_2O 8:2→65:25 to give **29** as a white solid (1.11 g, 65%), which was then recrystallised from *i*-Pr_2O–pentane. Mp = 125.1–125.7°C (*i*-Pr_2O–pentane). R_f 0.30 (PE–Et_2O 8:2, **A**, **C**). $[\alpha]_D$ = +261.5 (*c* 0.76, $CHCl_3$). IR: ν_{max} 3293, 2970, 2926, 1656, 1398, 1368, 1354, 1151. GC–MS: R_t 10.03; *m*/*z* 280 (M^+–73, 0.84); 184 (5.8); 183 (38); 171 (7.6); 170 (37); 115 (24); 114 (97); 105 (36); 77 (22); 71 (5.6); 70 (100); 57 (52); 43 (6.4); 41 (8.6). ^{1}H NMR: 0.46 [3 H, d, CH_3CH-, *J* = 6.3]; 1.46 [9 H, s, -C(CH_3)$_3$]; 1.73 [1 H, dt, H_3, *J* = 11.6, 6.5]; 2.57 [1 H, dt, H_3, *J* = 11.6, 8.6]; 4.04 [1 H, centre of m, H_2]; 4.99 [1 H, dd, H_4, *J* = 8.5, 7.0]; 6.64 [1 H, broad s, -O*H*]; 7.29–7.33 [10 H, m, aromatics]. ^{13}C NMR: 19.50 [>CHCH_3]; 27.74 [C_3]; 28.36 [3 C, -C(CH_3)$_3$]; 55.24 [C_4]; 66.57 [C_2]; 79.91 [-C(CH_3)]; 80.84 [Ph_2COH-]; 126.77, 126.98, 128.08, and 128.56 [8 C, *C ortho* and *meta* of Ph]; 126.92 and 127.21 [2 C, *C para* of Ph]; 143.82 and 144.75 [2 C, *C ipso* of -Ph]; 158.46 [>*C*O].

4.22. (2*R*,4*R*)-α,α-Diphenyl-4-methylazetidine-2-methanol 30

Compound **29** (587 mg, 16.61 mmol) was dissolved in a solution of KOH in absolute ethanol (4 M, 11 mL) and the resulting solution was stirred under reflux for 2.5 h. The solution was concentrated under reduced pressure, diluted with water and AcOEt and extracted with AcOEt–MeOH 9:1. The combined organic extracts were washed with brine and then with $NH_4H_2PO_4$ (1 mL, 5% aqueous solution). The solvent was removed under reduced pressure and crude **30** was purified by chromatography with AcOEt–Et_3N 100:0→98:2 to give a white solid (400 mg, 95%). Compound **30** was then crystallised from *i*-Pr_2O–PE. Mp = 97.7–98.2°C (*i*-Pr_2O–PE). R_f 0.37 (AcOEt with 2% of Et_3N, **A**, **C**). $[\alpha]_D$ = +23.5 (*c* 0.78, $CHCl_3$). IR: ν_{max} 3347, 2998, 2956, 1598, 1486, 1445, 1379, 1307, 1167, 1135, 1106, 1059. GC–MS: R_t 8.33; *m*/*z* 235 (M^+–H_2O, 0.097); 183 (2.0); 165 (2.2); 105 (10); 77 (10); 70 (100); 43 (5.8). ^{1}H NMR: 1.16 [3 H, d, -CH_3, *J* = 6.1]; 1.87 [1 H, dt, H_3, *J* = 11.0, 8.3]; 2.09 [1 H, dt, H_3, *J* = 11.1, 7.4]; 2.17 [1 H, s, -O*H*]; 3.85 [1 H, centre of m, H_2]; 4.65 [1 H, t, H_4, *J* = 7.8]; 5.12 [1 H, broad s, -N*H*]; 7.13–7.45 [10 H, m, aromatics]. ^{13}C NMR: 18.86 [>CHCH_3]; 26.88 [C_3]; 51.72 [C_4]; 60.51 [C_2]; 76.38 [Ph_2COH-]; 125.55, 125.86, 128.29 and 128.67 [8 C, *C ortho* and *meta* of Ph]; 127.44 and 127.82 [2 C, *C para* of Ph]; 141.31 and 142.49 [2 C, *C ipso* of -CH_2Ph].

4.23. (2*R*,4*R*)-α,α-Diphenyl-1-{(+)- or (−)-[(methoxy)-phenyl(trifluoromethyl)acetyl]}-4-methylazetidine-2-methanol 31

Neat **30** (5.2 mg, 20.53 μmol) was treated with NaOH (1N, 150 μL), THF (400 μL) and (1*R*)- or (1*S*)-Mosher's chloride. The mixture was stirred for 3 h at rt, then diluted with water and extracted with Et_2O. After chromatography on preparative TLC (PE–Et_2O 1:1), amide **31** was obtained (73–76%). R_f 0.39 (PE–Et_2O 1:1, **A**, **D**) for **31** prepared from (2*R*,4*R*)-**30** with (*R*)-Mosher's chloride and 0.53 (PE–Et_2O 1:1, **A**, **D**) for **31** prepared from (2*R*,4*R*)-**30** with (*S*)-Mosher's chloride. These compounds were analysed using HPLC [Hypersil column, flow 0.9 mL/min; hexane:Et_2O 85:15; detector: UV at 210 nm]. R_t 8.21 [**31** from reaction of (2*R*,4*R*)-**30** with (*R*)-Mosher's chloride] and 14.62 [**31** from reaction of (2*R*,4*R*)-**30** with (*S*)-Mosher's chloride].

4.24. (5*R*,7*R*)-7-Methyl-2,4,4-triphenyl-3-oxa-1-aza-2-borabicyclo[3.2.0]heptane 32

In a 50 mL flask, **30** (108 mg of 426 μmol) was dissolved in dry toluene (10 mL), which was then removed in vacuo. The resulting solid was dried at 0.9 mbar overnight and then dissolved in toluene (10 mL). The solution was treated with powdered 4 Å molecular sieves (22 mg), previously activated at 250°C for 1 day, and then with phenylboronic acid (57 mg, 468 μmol). After refluxing for 3.5 h through a trap filled with 4 Å molecular sieves (beads placed between the flask and the condenser), the solvent was removed and the crude oxazaborolidine was dried for 2 h at 0.9 mbar. The pale yellow solid was then dissolved in toluene to give a 0.21 M solution of **32**, which was stored under nitrogen and used directly in the following reduction.

4.25. Reduction of acetophenone to give (*S*)-1-phenylethanol in the presence of 32

A solution of **32** (0.21 M, 1 mL) was poured into a two-necked flask equipped with an addition funnel. Dry THF (2.5 mL) was added, followed by the addition of a solution of BH_3·Me_2S in THF (2 M, 1.07 mL, 2.14 mmol). The mixture was stirred for 12 min at 40°C, then acetophenone (249 μL, 2.14 mmol) in dry THF (2.5 mL) was added over a period of 40 min. TLC at the end of the addition showed that the reaction was complete. The crude mixture was diluted with Et_2O and extracted with aqueous H_2SO_4 (1 M). After washing the organic phase until neutral with 5% aqueous $NH_4H_2PO_4$ and brine, the solvent was removed. The crude product was purified by chromatography with PE–Et_2O 7:3→3:7 to give pure (*S*)-1-phenylethanol (217 mg, 83%). $[\alpha]_D$ = −22.2 (*c* 3.46, $CHCl_3$). E.e. 53%, determined by chiral GLC [Dmet.terBut.SBeta column].

Acknowledgements

The authors would like to thank the CNR, the MURST (COFIN) and the University of Genova for financial assistance, Amano for the generous gift of lipase from *Pseudomonas cepacia* and Miss Domenica Talia for her precious contribution to this project.

References

1. Kobayashi, J.; Cheng, J.; Ishibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135–1137.

2. Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490–7505 and references cited therein.
3. Nomoto, K.; Mino, Y.; Ishida, T.; Yoshioka, H.; Ota, N.; Inoue, M.; Takagi, S.; Takemoto, T. *J. Chem. Soc., Chem. Commun.* **1981**, 338–339 and references cited therein.
4. Takikawa, H.; Maeda, T.; Seki, M.; Koshino, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 97–111.
5. Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett.* **1997**, *38*, 3283–3284.
6. Knapp, S.; Dong, Y. *Tetrahedron Lett.* **1997**, *38*, 3813–3816.
7. Lin, G.-Q.; Liu, D.-G. *Heterocycles* **1998**, *47*, 337–348.
8. Liu, D.-G.; Lin, G.-Q. *Tetrahedron Lett.* **1999**, *40*, 337–340.
9. Hamada, Y.; Shioiri, T. *J. Org. Chem.* **1986**, *51*, 5489–5490.
10. Kozikowski, A. P.; Tückmantel, W.; Liao, Y.; Manev, H.; Ikonomovic, S.; Wroblewski, J. T. *J. Med. Chem.* **1993**, *36*, 2706–2708 and references cited therein.
11. Boni, R.; Verdini, A. S.; Deber, C. M.; Blout, E. R. *Biopolymers* **1978**, *17*, 2385–2399.
12. Hoshino, J.; Hiraoka, J.; Hata, Y.; Sawada, S.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 693–697.
13. Starmans, W. A. J.; Walgers, R. W. A.; Thijs, L.; de Gelder, R.; Smits, J. M. M.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 4991–5004.
14. Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 1673–1679.
15. Marinetti, A.; Hubert, P.; Genêt, J.-P. *Eur. J. Org. Chem.* **2000**, 1815–1820.
16. Rama Rao, A. V.; Gurjar, M. K.; Kaiwar, V. *Tetrahedron: Asymmetry* **1992**, *3*, 859–862.
17. Starmans, W. A. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 629–636.
18. Wilken, J.; Erny, S.; Wassmann, S.; Martens, J. *Tetrahedron: Asymmetry* **2000**, *11*, 2143–2148.
19. Banfi, L.; Guanti, G. *Eur. J. Org. Chem.* **1998**, 745–757 and references cited therein.
20. Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2921–2924.
21. Starmans, W. A. J.; Doppen, R. G.; Thijs, L.; Zwanenburg, B. *Tetrahedron: Asymmetry* **1998**, *9*, 429–435.
22. Sibi, M. P.; Lu, J. L. *Tetrahedron Lett.* **1994**, *35*, 4915–4918.
23. Banfi, L.; Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **1995**, *6*, 1345–1356.
24. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
25. Clinch, K.; Vasella, A.; Schauer, R. *Tetrahedron Lett.* **1987**, *28*, 6425–6428.
26. Barton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479–5486.
27. Knight, D. W. In *Encyclopaedia of Reagents in Organic Synthesis (EROS)*; Paquette, L. A., Ed.; J. Wiley: Chichester, UK, 1995; Vol. 4, pp. 2775–2778.
28. Baldwin, J. E.; Adlington, R. M.; Jones, R. H.; Schofield, C. J.; Zarocostas, C.; Greengrass, C. W. *Tetrahedron* **1986**, *42*, 4879–4888.
29. Zarocostas, C.; Greengrass, C. W. *J. Chem. Soc., Chem. Commun.* **1985**, *42*, 194–196.
30. Guanti, G.; Banfi, L.; Narisano, E. *J. Org. Chem.* **1992**, *57*, 1540–1554.
31. Studer, A. *Synthesis* **1996**, 793–815.
32. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835–875.
33. Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497–526.
34. Walbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475–1504.
35. Corey, E. J.; Helal, C. J. *Angw. Chem., Int. Ed. Engl.* **1998**, *37*, 1986–2012.
36. Singh, V. K. *Synthesis* **1992**, 605–617.
37. Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784.
38. Willems, J. G. H.; Dommerholt, F. J.; Hammink, J. B.; Vaarhorst, A. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 603–606.
39. Brown, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 519–522.
40. Stone, G. B. *Tetrahedron: Asymmetry* **1994**, *5*, 465–472.
41. Adger, B.; Berens, U.; Griffiths, M. J.; Kelly, M. J.; McCague, R.; Miller, J. A.; Palmer, C. F.; Roberts, S. M.; Selke, R.; Vitinius, U.; Ward, G. *J. Chem. Soc., Chem. Commun.* **1997**, 1713–1714.