Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1977–1982

TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiomerically pure 4-substituted pyrrolidin-3-ols via asymmetric 1,3-dipolar cycloaddition

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Received 14 August 2001; accepted 20 August 2001

Abstract—Asymmetric 1,3-dipolar cycloadditions of chiral azomethine ylides to 3-benzyloxy-substituted alkenoylcamphorsultams are described. *trans*-3,4-Disubstituted pyrrolidines containing a protected hydroxyl group at C(4) of the pyrrolidine ring are obtained in high diastereomeric ratios. Such compounds can serve as chiral building blocks for the syntheses of enantiopure bioactive pyrrolidines. This is exemplified by a short synthetic route to a known glycosidase inhibitor, (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol and its enantiomer.

1. Introduction

Asymmetric 1,3-dipolar cycloadditions are among the most efficient reactions for the construction of enantiopure five-membered ring heterocycles.[1–3] The chirality of the products of these reactions can be introduced through enantioselective catalysis, e.g. by the use of either chiral Lewis acids[4] or enantiopure organic catalysts.[5] Alternatively, chiral auxiliaries can be used.[1,2]

Using the latter approach, we have recently studied the reactions of chiral ylides with chiral dipolarophiles in an attempt to improve the diastereoselectivity in reactions of azomethine ylides with dipolarophiles, which are attached to chiral auxiliaries.[3b,3c] Chiral non-racemic azomethine ylides show significantly higher diastereoselectivity than achiral ones when reacting with some α,β-unsaturated cycloalkenoic derivatives attached to chiral auxiliaries.[3c,6] In reactions with acyclic alkenoic substrates, however, the effect of using non-racemic ylides is small.[3b] The enantiomers of 1-phenylethylamine, which are comparatively inexpensive starting materials for the preparation of the ylide precursors, can, however, be used with some advantage in place of achiral benzylamine.

The reaction of an unstabilised azomethine ylide with a dipolarophile, such as an α,β-unsaturated acyl compound, is controlled by interaction of the HOMO of the azomethine ylide with the LUMO of the dipolarophile.[7] A dipolarophile containing a vinyl ether group (e.g. compounds **3** or **4**, Scheme 1) has a higher LUMO energy than the analogous cinnamoyl derivative, because of the electron donating nature of the ether oxygen. Thus, when the reaction is controlled by interactions between HOMO (azomethine ylide) and LUMO (dipolarophile), and when a dipolarophile containing an electron-rich vinyl ether is used, lower reactivity should result. We have recently shown that compound **3** can serve as a dipolarophile in a reaction with a sulphur-containing 1,3-dipolar compound,[3d] and that the resulting cycloadduct can serve as the starting material in the synthesis of a pheromone of the pine sawfly.[8]

A 1,3-dipolar cycloaddition reaction of a 3-benzyloxypropenoyl derivative, e.g. **3** or **4**, with an azomethine ylide (derived from either of the precursors **1** or **2**) would result in a pyrrolidine cycloadduct containing an ether group at the 4-position of the heterocyclic ring formed. Substituted pyrrolidines of this type should be useful intermediates for further manipulation into enantiopure alkaloids and bioactive substances. For example, racemic and non-racemic derivatives of such pyrrolidines have been prepared and found to have an inhibitory effect on certain enzymes[9–11] as well as on the glial GABA uptake systems.[12] These pyrrolidines have also been used as building blocks for further syntheses of compounds with antibacterial activity.[13,14]

We now present some doubly diastereoselective 1,3-dipolar cycloadditions of the chiral azomethine ylide precursor **1** and its enantiomer **2** to the β-benzyloxy-substituted α,β-unsaturated compound **3** and its enantiomer **4**. The diastereoselectivity of these reactions as a function of the solvent polarity is also discussed.

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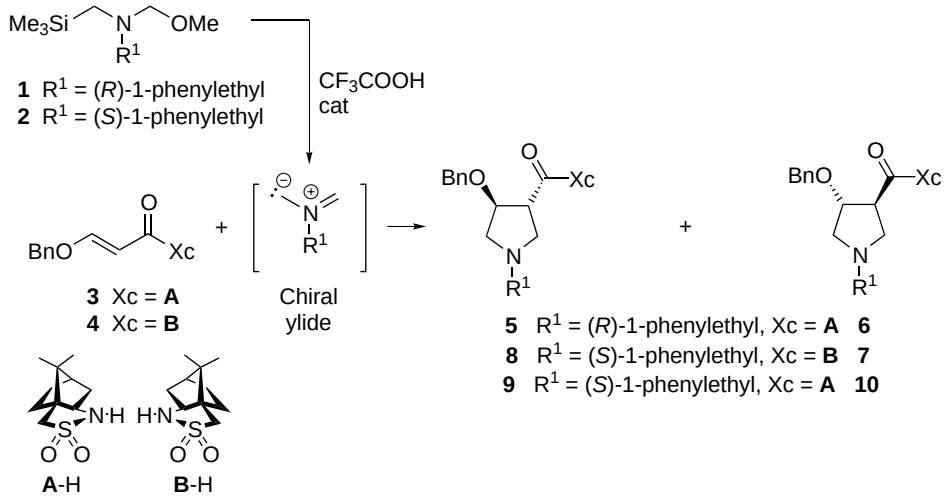
0957-4166/01/$ - see front matter
PII: S0957-4166(01)00367-6



Scheme 1.

Finally, a short synthesis of a known glycosidase inhibitor, (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol[15] **15**, and its enantiomer **14** is provided.

2. Results and discussion

2.1. Diastereoselectivity and solvent effects

The two enantiomers **3** and **4** (Scheme 1) of the dipolarophile were prepared from 3-benzyloxypropenoyl chloride and the appropriate enantiomer of camphorsultam (**A**-H and **B**-H) as described.[3d,8] When the ylide precursor **1** (or **2**) was treated with a catalytic amount of trifluoroacetic acid (TFA) in the presence of the dipolarophile **3** (or **4**) in CH_2Cl_2, the major cycloadduct **5** (or **7**) was formed along with the minor diastereomer **6** (or **8**) in an 83:17 diastereomeric ratio and a 94% combined isolated yield (Scheme 1).[†] The two products were separated by column chromatography to give the pure individual diastereoisomers each having d.r. of >200:1.

When the 1,3-dipolar cycloaddition reactions were performed in non-polar solvents such as CCl_4 and heptane, considerably lower diastereoselectivity (d.r. of 61:39 and 63:37, respectively) was observed. However, when more polar solvents were used, (e.g. CH_3CN or DMF), higher diastereoselectivity (d.r. of up to 88:12) was obtained. The same relationship has been observed in Diels–Alder reactions with another camphorsultam derived dienophile.[16] However, a reverse solvent effect was observed in a similar 1,3-dipolar cycloaddition of a nitrile oxide to a camphorsultam derived acrylate.[17] The results of the reactions of the dipolarophile **3** with either of the ylide precursors **1** or **2** are presented in Table 1.

A linear relationship was approached (Fig. 1), when the logarithm of the diastereomeric ratio (log d.r.) was plotted as a function of the empirical solvent polarity parameter, $E_T(30)$,[18] of the solvent used.

Table 1. Diastereomeric ratio (d.r.) as a function of the $E_T(30)$ value of the solvent in the 1,3-dipolar cycloaddition reaction of the dipolarophile **3** with either of the ylide precursors **1** and **2**

Entry[a,b]	Solvent	$E_T(30)$ [kcal mol^{-1}][c]	D.r.[d] **5**:**6** (**9**:**10**)
1	Heptane[e]	31.1	63:37 (65:35)
2	Cyclohexane[e]	30.9	64:36 (62:38)
3	CCl_4[e]	32.4	61:39 (50:50)
4	1,4-Dioxane	36.0	79:21 (61:39)
5	Toluene	33.9	70:30 (52:48)
6	Diethyl ether[e]	34.5	70:30 (54:46)
7	$CHCl_3$	39.1	74:26 (69:31)
8	EtOAc	38.1	78:22 (58:42)
9	THF	37.4	75:25 (58:42)
10	CH_2Cl_2	40.7	83:17 (71:29)
11	Acetone	42.2	85:15 (73:27)
12	CH_3CN	45.6	88:12 (75:25)
13	DMF	43.2	87:13 (71:29)
14	DMSO	45.1	86:14 (76:24)

[a] Compounds **1** or **2** (50–75 μmol) was added to a solution of **3** (25 μmol) in the solvent specified (0.5 mL). Trifluoroacetic acid (TFA, 2 μL) was then added at ambient temperature. After stirring for 1 h the reaction was quenched by the addition of Na_2CO_3 (aq. satd 3 mL) and the mixture was diluted with EtOAc (5 mL). Diastereomeric ratios were measured on the crude products.

[b] The reactions were performed on a small scale and, therefore, not completed by means of conversion. Approximately 10–50% conversion was achieved in all cases. However, complete conversions and more efficient reactions could be achieved, if the reactions were performed on a large scale, following the details in Section 4.

[c] Ref. 18.

[d] Determined by GC analyses.

[e] Low solubility of **3**.

[†] As expected, we observed a lower reactivity with the 3-benzyloxypropenoyl compound **3** (or **4**) than with the corresponding cinnamoyl compound. In order to obtain a reasonable yield of the minor diastereomer **6** (or **8**) for further manipulation, we performed the reaction on a large scale in CH_2Cl_2 even though better diastereoselectivity could be obtained in more polar solvents, as will be presented below.

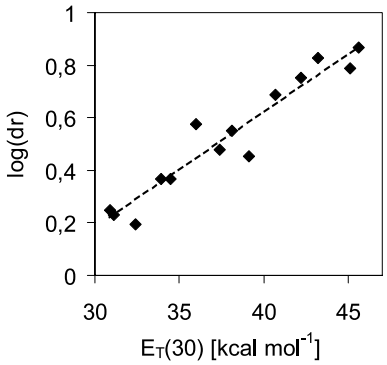


Figure 1. Log (d.r.) as a function of the $E_T(30)$ value of the solvent in the reaction of **1** with **3**.

Thus, solvents with great structural differences but with roughly the same polarity gave nearly the same diastereoselectivity (e.g. cyclohexane versus heptane). In a series of structurally similar solvents, the diastereoselectivity increased with the polarity of the solvent (e.g. entries 3, 7 and 10, Table 1).

2.2. Preparation of an enantiomerically pure glycosidase inhibitor

The chiral sultam auxiliaries Xc, constituting parts of the cycloadducts **5**, **6** and **7**, were removed reductively on reaction with $LiAlH_4$, leaving the individual enantiomers **11** and **13** and the diastereomer **12**, respectively, in approximately 90% yield along with a near quantitative recovery of the camphorsultam (Scheme 2).

Reductive cleavage of the benzyl and the 1-phenylethyl groups of **11**–**13** using 10% Pd/C under an atmosphere of hydrogen furnished the pyrrolidinediol **14** and its enantiomer **15** (Scheme 2). The latter is a known[15] inhibitor of glycosidase. The absolute configuration of **15** was verified by comparing the $[\alpha]_D$ value of its hydrochloride with that of an authentic sample.[15,‡]

2.3. Cycloaddition reaction pathway

When not chelated or complexed with Lewis acids, *N*-enoyl sultams are proposed to react with dipolar compounds in a conformation where the carbonyl oxygen and the sulfone moiety are *trans*-located in relation to the C–N amide bond (Fig. 2).[19,20] Reagents such as nitrile oxides then attack the *re–re* face, probably due to unfavourable interactions between the incoming dipole and the axially oriented O_α sulfone oxygen (see Fig. 2).[21] Thus, in our experiments and in the major pathway, the azomethine ylide probably reacts on the *re–re* face of compound **3** in the conformation shown in Fig. 2. The location of the partially charged sultam oxygens (O_α and O_β) in relation to the π-bond has been proposed to account for the facial selectivity in camphorsultam-derived acrylates.[17,20] Dipole–dipole interactions caused by a more polar solvent might, therefore, have a great impact on the stabilisation of the transition state.

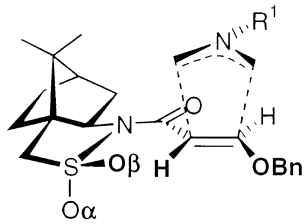
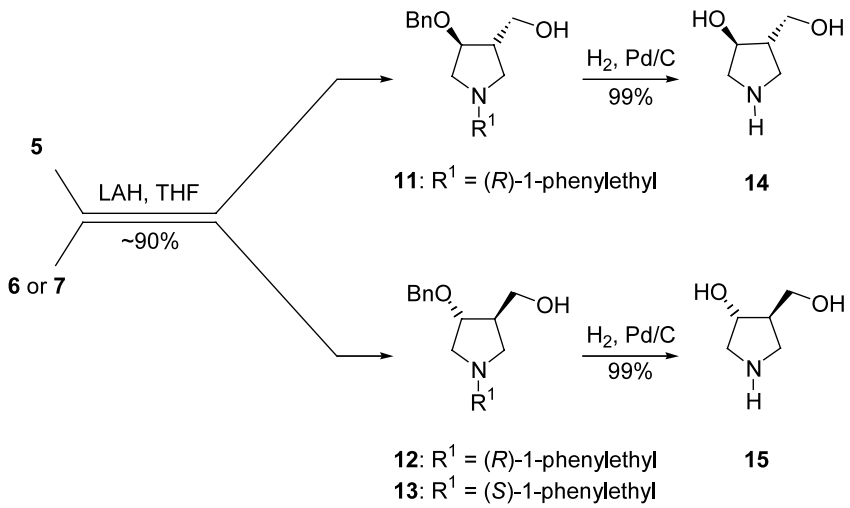


Figure 2.

3. Conclusion

In summary, the electron-rich dipolarophiles **3** or **4** containing a vinyl ether group were accepted as reac-



Scheme 2.

‡ An independently prepared sample of the *N*-Fmoc-4-trityloxymethyl derivative of (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol **15** (supplied by Dr Y. Ishikawa) was deprotected through treatment with 20% Et_3N/MeOH, followed by treatment with 1 M HCl/MeOH. This furnished **15**·HCl.[15]

tion partners in the 1,3-dipolar cycloaddition with the chiral azomethine ylide derived from the precursor **1** or **2**, respectively. Provided that the appropriate solvent was used, the major diastereomeric cycloadducts **5** or **7**, respectively, were obtained in high diastereoselectivity along with the minor diastereomers **6** or **8**, respectively. When highly polar solvents, such as DMF, DMSO and CH_3CN, were used, the cycloadducts were obtained with a diastereoselectivity of up to 88:12 d.r. Using these adducts as starting materials, we prepared an enantiomerically pure glycosidase inhibitor, (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol **15**, as well as its enantiomer **14**, in a two-step synthetic sequence in 87% overall yield.

4. Experimental

4.1. General

All chemicals and solvents were used as received unless otherwise stated. THF (K, benzophenone), toluene (CaH_2), CH_2Cl_2 (CaH_2), acetone (CaH_2) and diethyl ether ($LiAlH_4$) were distilled under argon from the drying agents indicated. ^1H and ^{13}C NMR spectra were recorded with a Bruker DMX 250 (250 MHz ^1H and 62.9 MHz ^{13}C) instrument. Preparative liquid chromatography was performed on straight phase silica gel (Merck 60, 230–400 mesh, 0.040–0.063 mm) using an increasing concentration of distilled ethyl acetate in distilled cyclohexane as eluent. GC analyses were carried out using a capillary column EC-5, 30 m, 0.32 mm i.d., $d_f = 0.25$ μm, carrier gas N_2. The elemental analyses (C, H and N) were performed by Mikro Kemi AB, SE-752 28 Uppsala, Sweden. Boiling points were uncorrected and were given as air bath temperatures (bath temp./mbar) in a bulb to bulb (Büchi GKR-51) apparatus. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter in a 10 cm cell. Mass spectra were recorded on a Saturn 2000 instrument, operating in the EI or CI (acetonitrile as chemical ionisation gas) mode, coupled to a Varian 3800 GC instrument. Compounds **1** and **2** were prepared using the procedure reported by Hosomi and Sakurai et al.[22] The work up was completed following an alternative method.[23] Compound **3** and its enantiomer **4** were obtained as previously described.[3d]

4.2. 1,3-Dipolar cycloadditions

4.2.1. *N*-[[(3*S*,4*R*)-4-Benzyloxy-1-(1(*S*)-phenylethyl)-pyrrolidin-3-yl]carbonyl]-(2′*S*)-bornane-10,2-sultam 7. Over a period of 0.5 h, (*S*)-*N*-(1-phenylethyl)-*N*-(methoxymethyl)-*N*-(trimethylsilyl)methylamine 2 (2.6 g, 10.3 mmol) was added under argon to a stirred solution of (*E*)-3-benzyloxypropenoyl-(2′*S*)-bornane-10,2-sultam[3d] **4** (2.9 g, 7.7 mmol) in a 5 mM TFA/CH_2Cl_2 solution (40 mL) at rt. After stirring the mixture for an additional 0.5 h, the reaction was quenched by addition of Na_2CO_3 (200 mL aq. satd), followed by extraction with EtOAc (200+100 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated at 150°C/1 mbar. GC analysis of the crude reaction mixture indicated a diastereomeric ratio of 83:17 of the two diastereomers **7** and **8**. The residue was purified by column chromatography (silica gel, EtOAc/cyclohexane 5→80% as eluent) to give the individual pure diastereomers **7** (3.05 g, 5.8 mmol, 75%) and **8** (0.71 g, 1.4 mmol, 18%; see below), each diastereomer in >99% d.e. (GC), as semi-crystalline compounds. Major isomer **7**: $[\alpha]_D^{25}$ +62.7 (*c* 0.56, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.92 (s, 3H), 1.05 (s, 3H), 1.31 (d, 3H, $J=6.5$ Hz), 1.31–1.42 (m, 2H), 1.79–1.91 (m, 3H), 2.02–2.07 (m, 2H), 2.60–2.74 (m, 2H), 2.80–2.87 (m, 1H), 3.09 (t, 1H, $J=9.1$ Hz), 3.28 (q, 1H, $J=6.5$ Hz), 3.41 (d, 1H, $J=14.0$ Hz), 3.47 (d, 1H, $J=14.0$ Hz), 3.62–3.71 (m, 1H), 3.88 (t, 1H, $J=6.2$ Hz), 4.36 (d, 1H, $J=11.5$ Hz), 4.53 (d, 1H, $J=11.5$ Hz), 4.57–4.62 (m, 1H), 7.16–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 19.7, 20.5, 22.4, 26.3, 32.5, 38.2, 44.3, 47.6, 48.3, 50.8, 52.8, 56.2, 58.5, 64.3, 64.9, 71.2, 78.9, 126.8, 127.0, 127.4, 127.8, 128.2, 138.0, 144.6, 172.2; MS (EI): *m*/*z* (%) 523 (27) [M^++H], 507 (25), 416 (14), 202 (8), 174 (100), 105 (87), 91 (70). Anal. calcd for $C_{30}H_{38}N_2O_4S$: C, 68.9; H, 7.3; N, 5.4. Found: C, 68.9; H, 7.4; N, 5.3%.

4.2.2. *N*-[[(3*R*,4*S*)-4-Benzyloxy-1-(1(*S*)-phenylethyl)-pyrrolidin-3-yl]carbonyl]-(2′*S*)-bornane-10,2-sultam 8. Minor diastereomer from sultam **4** and ylide precursor **2**: $[\alpha]_D^{25}$ +14.7 (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.98 (s, 3H), 1.19 (s, 3H), 1.29–1.44 (m, 2H), 1.37 (d, 3H, $J=6.5$ Hz), 1.81–2.09 (m, 5H), 2.51 (t, 1H, $J=8.3$ Hz), 2.68–2.75 (m, 2H), 3.22–3.43 (m, 2H), 3.44 (d, 1H, $J=13.8$ Hz), 3.55 (d, 1H, $J=13.8$ Hz), 3.77–3.93 (m, 2H), 4.26–4.32 (m, 1H), 4.34 (d, 1H, $J=11.7$ Hz), 4.55 (d, 1H, $J=11.7$ Hz), 7.18–7.36 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 19.8, 21.0, 23.0, 26.4, 32.9, 38.6, 44.7, 47.7, 48.3, 51.1, 53.2, 56.3, 58.9, 65.1, 65.3, 71.0, 82.5, 126.9, 127.1, 127.5, 127.7, 128.3 (2C), 137.8, 144.8, 173.5; MS (EI): *m*/*z* (%) 523 (2) [M^++H], 507 (22), 416 (8), 202 (10), 174 (100), 105 (73), 91 (72). Anal. calcd for $C_{30}H_{38}N_2O_4S$: C, 68.9; H, 7.3; N, 5.4. Found: C, 68.7; H, 7.4; N, 5.3%.

4.2.3. *N*-[[(3*R*,4*S*)-4-Benzyloxy-1-(1(*R*)-phenylethyl)-pyrrolidin-3-yl]carbonyl]-(2′*R*)-bornane-10,2-sultam 5. Major diastereomer from sultam **3** and ylide precursor **1**: $[\alpha]_D^{25}$ −61.0 (*c* 0.37, $CHCl_3$). All other data for **5** were identical to those of the enantiomer described under Section 4.2.1.

4.2.4. *N*-[[(3*S*,4*R*)-4-Benzyloxy-1-(1(*R*)-phenylethyl)-pyrrolidin-3-yl]carbonyl]-(2′*R*)-bornane-10,2-sultam 6. Minor diastereomer from sultam **3** and ylide precursor **1**. $[\alpha]_D^{25}$ −13.0 (*c* 0.45, $CHCl_3$). All other data for **6** were identical to those of the enantiomer described in Section 4.2.2.

4.3. Reductive cleavage of the enoyl camphorsultams

4.3.1. (3*R*,4*R*)-[4-(Benzyloxy)-1-[(*S*)-1-phenylethyl]-pyrrolidin-3-yl]methanol 13. Compound **7** (2.93 g, 5.6 mmol), dissolved in dry THF (40 mL), was added under argon to a stirred solution of $LiAlH_4$ (0.64 g, 16.9 mmol) in THF (25 mL) at 0°C. After 0.5 h at rt,

the reaction was quenched by the addition of H_2O (5 mL). The mixture was diluted with EtOAc (150 mL) and extracted with 1 M HCl solution (7×40 mL). The organic phase was dried over $MgSO_4$ and concentrated to give recovered (+)-camphorsultam (1.09 g, 5.06 mmol, 90%) in >99% purity as judged by GC analysis. The aqueous phases were combined, basified with NaOH (6 M) and extracted with EtOAc (3×80 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/cyclohexane 10–100% as eluent) to give 1.52 g (4.9 mmol, 88%) of **13** as a colourless oil in purity >99% (GC); bp 215°C/0.8 mbar; $[\alpha]_D^{25}$+6.2 (*c* 0.70, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.39 (d, 3H, J=6.6 Hz), 2.28–2.36 (m, 2H), 2.72 (dd, 1H, J=6.8, 9.0 Hz), 2.90 (dd, 1H, J=2.6, 9.1 Hz), 2.97 (dd, 1H, J=6.7, 10.2 Hz), 3.26 (q, 1H, J=6.6 Hz), 3.65 (dd, 1H, J=4.1, 10.2 Hz), 3.70 (s, 1H, br), 3.78 (dd, 1H, J=4.2, 10.2 Hz), 3.95–4.03 (m, 1H), 4.43 (s, 2H), 7.20–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 22.7, 46.0, 54.9, 59.8, 65.2, 66.1, 71.2, 81.0, 127.0, 127.1, 127.6 (2C), 128.4 (2C), 138.1, 144.3; MS (EI): *m*/*z* (%) 312 (5) [M$^+$+H], 296 (80), 205 (20), 134 (100), 105 (92), 91 (85). Anal. calcd for $C_{20}H_{25}NO_2$: C, 77.1; H, 8.1; N, 4.5. Found: C, 76.9; H, 8.4; N, 4.6%.

4.3.2. (3*R*,4*R*)-[4-(Benzyloxy)-1-[(*R*)-1-phenylethyl]-pyrrolidin-3-yl]methanol 12. Using a procedure analogous to that described in Section 4.3.1, compound **6** (4.2.4) gave the title compound as a colourless oil of >99% purity (GC); bp 210°C/0.8 mbar; $[\alpha]_D^{25}$ +53.0 (*c* 0.44, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.38 (d, 3H, J=6.6 Hz), 2.20–2.29 (m, 1H), 2.37–2.49 (m, 2H), 2.66 (dd, 1H, J=6.8, 9.3 Hz), 3.25 (q, 1H, J=6.6 Hz), 3.36 (dd, 1H, J=6.6, 9.9 Hz), 3.58–3.70 (m, 2H), 3.60 (s, br, 1H), 4.07–4.13 (m, 1H), 4.49 (s, 2H), 7.21–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 22.6, 45.7, 55.5, 59.1, 65.4, 66.2, 71.3, 81.2, 126.9, 127.2, 127.7 (2C), 128.4, 128.5, 138.1, 144.5; MS (EI): *m*/*z* (%) 312 (4) [M$^+$+H], 296 (62), 205 (25), 134 (100), 105 (87), 91 (75). Anal. calcd for $C_{20}H_{25}NO_2$: C, 77.1; H, 8.1; N, 4.5. Found: C, 76.7; H, 8.3; N, 4.6%.

4.3.3. (3*S*,4*S*)-[4-(Benzyloxy)-1-[(*R*)-1-phenylethyl]-pyrrolidin-3-yl]methanol 11. Using a procedure analogous to that described in Section 4.3.1, compound **5** (4.2.3) gave the title compound as a colourless oil of >99% purity (GC). $[\alpha]_D^{25}$ −6.1 (*c* 0.43, MeOH). All other data for **11** were identical to those for the enantiomer described in Section 4.3.1.

4.4. Reductive removal of benzyl groups

4.4.1. (3*R*,4*R*)-4-(Hydroxymethyl)pyrrolidin-3-ol[15] 15. Pd/C (10%, 150 mg) was added to a solution of **13** (1.49 g, 4.77 mmol) in MeOH (10 mL). The reaction was stirred at rt under hydrogen for 2 weeks. The Pd/C was removed by filtration and rinsed with MeOH. The filtrate was concentrated to give **15** (555 mg, 4.74 mmol, 99%) as a colourless oil of >99% purity (GC); bp 150°C/1 mbar; $[\alpha]_D^{25}$ +47.2 (*c* 1.1, MeOH, free base); MS (CI): *m*/*z* (%) 118 (100) [M$^+$+H], 100 (7), 82 (3). The free base was transformed to the corresponding hydrochloride through treatment with concentrated hydrochloric acid (aq.); $[\alpha]_D^{25}$ +19.0 (*c* 1.0, MeOH, hydrochloride); ^{1}H NMR (hydrochloride, D_2O): δ 2.44–2.53 (m, 1H), 3.17 (dd, 1H, J=5.8, 12.3 Hz), 3.27 (dd, 1H, J=2.7, 12.7 Hz), 3.44 (dd, 1H, J=5.0, 12.7 Hz), 3.55–3.67 (m, 3H), 4.39–4.44 (m, 1H); ^{13}C NMR (hydrochloride, D_2O): δ 46.5, 47.8, 52.0, 60.8, 71.8. This compound was in all respects identical to an authentic sample of **15**·HCl prepared from an independently prepared sample of *N*-FMOC protected (3*R*,4*R*)-4-(trityloxymethyl)pyrrolidin-3-ol[15] by treatment with Et_3N/MeOH, followed by acid treatment (1 M HCl/MeOH).

4.4.2. (3*S*,4*S*)-4-(Hydroxymethyl)pyrrolidin-3-ol 14. Using a procedure analogous to that described in Section 4.4.1, Compound **11** gave the title compound. $[\alpha]_D^{25}$ −49.0 (*c* 0.48, MeOH, free base). $[\alpha]_D^{25}$ −18.7 (*c* 1.2, MeOH, hydrochloride). All other data for **14** were identical to those of the enantiomer described in Section 4.4.1.

Acknowledgements

We are grateful to Dr. Yoshitaka Ichikawa for a gift of a sample of the *N*-FMOC protected (3*R*,4*R*)-4-(trityloxymethyl)pyrrolidin-3-ol. This work was supported by the Swedish Natural Science Research Council (NFR) and the Mid Sweden University.

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