Asymmetric reduction of a carbon–nitrogen double bond: enantioselective synthesis of 4,5-dihydro-3*H*-2,3-benzodiazepines

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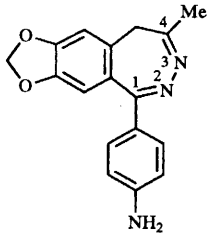
A highly specific enantioselective reduction, elaborated for the reduction of the 3,4-carbon–nitrogen double bond of 4-methyl-7,8-methylenedioxy-1-(4-nitrophenyl)-4,5-dihydro-3*H*-2,3-benzodiazepine **4** made possible the synthesis of the enantiomers of the potent non-competitive AMPA/kainate antagonists **2a**, **b**. NMR Investigations of the reducing complex show that there is no formation of an 1,3,2-oxazaborolidine ring as may have been presumed on the basis of literature data.

Compound **1** (GYKI 52 466) is a prototype of selective non-competitive AMPA/kainate antagonists.[1] Several years ago a synthetic project was started in our institute to study



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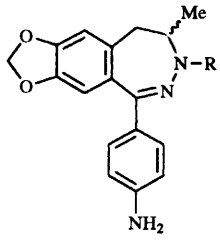


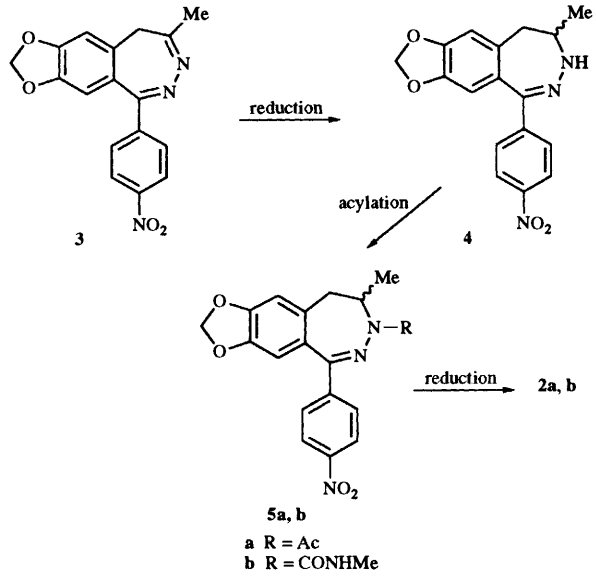
2
a R = Ac
b R = CONHMe

the structure–activity relationship. As a result of these investigations, new derivatives have been found which have significantly greater biological activity than the 'parent' compound.[2] The most effective molecules **2a** and **2b** are 3-*N*-acyl-3,4-dihydro derivatives of **1** having a chirality centre at C-4.

It is well-known that for many chiral molecules the biological effect is associated with one of the enantiomers, while the other enantiomer is much less active or inactive and, in addition, the toxicological, pharmacokinetical behaviour and metabolism of the enantiomers may be different. For this reason in modern drug development pure enantiomers are required. Two strategies were considered for the preparation of the pure enantiomers of **2a**, **b**: resolution and asymmetric synthesis with the application of a chiral auxiliary.

Because preliminary resolution experiments on compounds **2** and their chiral precursors were unsuccessful, an enantioselective synthesis of nitro compound **4** was attempted since it is the first chiral molecule in the synthetic route[3] and therefore a key intermediate (Scheme 1). It was also evident, that a suitable enantioselective reduction of **3** as the key step in the synthesis, should also show regio- and chemo-selectivity with respect to other functionalities in the molecule.

To date the enantioselective reduction of carbon–nitrogen double bonds has been realized by asymmetric homogeneous catalytic hydrogenation,[4] hydrosilylation,[5] and also by treatment with chirally modified sodium borohydride[6] and lithium aluminium hydride.[7] The pioneering work of Itsuno and Corey, suggests that borane complexes of chiral 1,3,2-oxazaborolidines[8] and chiral oxaborolanes[9] can also be used. From our earlier work it was apparent that the 3,4 double bond of **3** and of other similar 2,3-benzodiazepines can be reduced

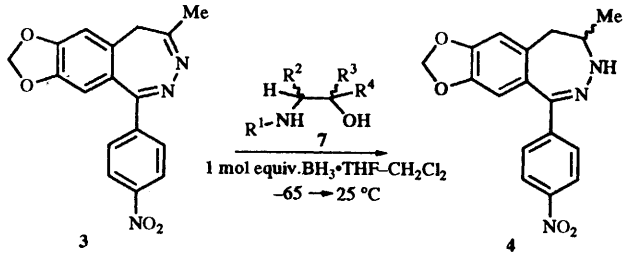


Scheme 1

selectively with sodium borohydride under acidic conditions or with borane, whilst the other carbon–nitrogen double bond and, in this case, the nitro group or other substituents in the molecule, remain unchanged.

First we examined the reduction of 2,3-benzodiazepine **3** with sodium borohydride, modified by chiral amino acids. According to the methods reported in the literature[6a–e] the reduction of **3** was attempted with an excess of 3 equiv. of chiral triacyloxysodium borohydride (prepared from *N*-acetyl- and *N*-benzyloxycarbonyl-L-proline and sodium borohydride in 3 : 1 molar ratio). Unfortunately, no formation of **4** could be detected in these reactions. However, when boron trifluoride–diethyl ether was added, or the starting compound **3** was applied as the hydrochloride salt, a *ca.* 50% chemical conversion could be achieved at room temperature with a reaction time of 7–10 days. The chromatographically isolated **4** had low enantiomeric purity (30–35% ee). A different method[6g] using an equilibrated system of L-proline and sodium borohydride in 1 : 1 molar ratio, also did not give **4** as reduction product, even with the addition of boron trifluoride–diethyl ether. When the hydrochloride salt of **3** was applied, similar results were obtained as with the previous reducing agent. We assume that in these reductions borane is formed when there is hydrochloride present and that the weak asymmetric induction is due to the presence of the chiral component. This was supported by an experiment where

Table 1 Enantioselective reduction of **3** by using a complex from borane and amino alcohol at 25 °C in methylene chloride

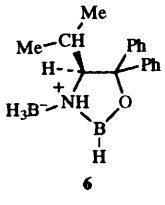


2-Amino alcohol	Precursor of 7	R^1	R^2	R^3	R^4	$[\alpha]_D^{25}$ [a] (*c*, 1.0, $CHCl_3$)	Enantiomeric ratio [b] (+):(−) [% ee]
(−)-**7a** [c]		H	Me	Ph	H	+46	— [d]
(−)-**7b** [c]		Me	Me	Ph	H	0	
(+)-**7c**	L-Valine	H	Pr^i	H	H	— [e]	
(−)-**7d**	L-Valine	H	Pr^i	Ph	Ph	−106	15:85 [70]
(+)-**7d**	D-Valine	H	Pr^i	Ph	Ph	+111	85:15 [70]
(−)-**7e**	L-Leucine	H	Bu^i	Ph	Ph	−142	7:93 [86]
(+)-**7e**	D-Leucine	H	Bu^i	Ph	Ph	+140	93:7 [86]
(−)-**7f**	L-Isoleucine	H	Bu^s	Ph	Ph	−101	— [d]
(+)-**7g**	D-α-Phenylglycine	H	Ph	Ph	Ph	+42	— [d]
(−)-**7h**	D-Phenylalanine	H	CH_2Ph	Ph	Ph	−107	— [d]
(+)-**7i** [c,f]	L-Proline		$-(CH_2)_3-$	Ph	Ph	+3	— [d]
(+)-**7i**	L-Proline		$-(CH_2)_3-$	Ph	Ph	−38	— [d]

[a] Optical rotation of raw product {optical rotation of pure enantiomers: $[\alpha]_D^{25}$ (+) or (−) 155 (*c* 1.0, $CHCl_3$)}. [b] The ratio was determined by chiral HPLC analysis and/or NMR shift reagent technique (see Experimental section). [c] Less than 50% chemical conversion in 7 days. [d] Not measured. [e] No reduction was observed. [f] The complex was prepared from toluene (mp 129–131 °C).

3 was reduced with a complex prepared from equivalent amounts of L-proline, sodium borohydride and trifluoroacetic acid. When the latter method was applied to the hydrochloride of **3** a full chemical conversion could be achieved with a more reasonable reaction time of 48 h and with 40% ee. Variation of the amino acid component did not significantly affect the degree of the optical induction.

Our attention then turned to chiral derivatives of borane, and it seemed promising to try complex **6** (Itsuno reagent) which is



6

prepared from (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol [(*S*)-(−)-AMDPB] (−)-**7d** and 2 mol equiv. borane, and which was used successfully for the asymmetric reduction of *N*-substituted ketimines,[8c–e] ketoxime ethers,[8a] and from which very good % ee values have been obtained. The preparation of reagent **6** is usually achieved by treating the chiral amino alcohol with 2 mol equiv. of borane–tetrahydrofuran complex at −78 °C followed by warming to 0 °C and equilibration over several hours. Generally the substrate is added to this solution of the preformed reagent. Corey *et al.*[8b] have also isolated compound **6** as colourless crystals. The excess solvent and borane were evaporated and the residue was sublimed twice under reduced pressure at high temperature. The formation of the 1,3,2-oxazaborolidine ring was proved using EIMS and IR, ^1H and ^{11}B NMR spectroscopic methods.

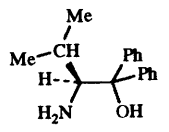
When the Itsuno reagent in methylene chloride was used for the reduction of **3**, the reaction was complete after several minutes, however only racemic **4** was formed in quantitative yield without any optical induction. However, we have observed a surprisingly high optical induction in our reduction step when the reducing complex was prepared from (*S*)-(−)-AMDPB and borane with a 1:1 stoichiometry and applied in at least equimolar amount. Although (−)-**4** was isolated in this reaction with an enantiomeric purity of 70% ee, to reach full chemical conversion at room temperature a reaction time of almost 7 days was needed.

We have investigated the influence of several 2-amino alcohols on the optical induction. The chiral 2-amino alcohols were obtained from the appropriate amino acids according to literature procedures.[8a,10–12] The results are summarized in Table 1. By changing the structure of the amino alcohol, the most significant optical induction was obtained with (*S*)-(−)- or (*R*)-(+)-2-amino-4-methyl-1,1-diphenylpentan-1-ol (−)- or (+)-**7e** (prepared from L- and D-leucine). The 86% ee observed in these transformations could be raised to 98% ee by recrystallization of the enantiomers of **4** giving an overall yield of *ca.* 70%. It can be seen from Table 1 that the presence of the geminal diphenyl group and the primary amino group adjacent to the chiral centre of the inducing agent are essential for achieving optical induction, while the bulkiness of the R^2 group only modifies it.

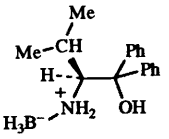
Experiments were carried out to speed up the reduction of **3** by using equimolar amounts of (*S*)-(−)-AMDPB and borane–tetrahydrofuran complex. We have found that at the boiling point of methylene chloride, the optical induction did not change significantly compared with the same reaction at room temperature. However, the reaction time could be reduced to 3 days. A further elevation of the reaction temperature was possible with the use of 1,2-dichloroethane as solvent and a full chemical conversion could be achieved within 24 hours at 60 °C, without deterioration of the good optical induction. Carrying out the reaction in boiling 1,2-dichloroethane (83 °C) the time of full conversion could be further shortened to 3 h, but only at a significant expense of the enantioselectivity.

In addition to the amino alcohols **7** several chiral diols **8** were tried as inducing agents in the reduction process. The reducing

Table 2 Comparison of the NMR signals of (*S*)-(−)-AMDPB **7d** and its borane complex **9**



7d

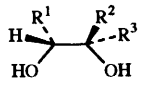


9

H or B	δ (*J*/Hz) AMDPB **7d**	Complex **9**[a]
CH_3	0.95 d, 0.90 d	1.26 d, 0.93 d
NCH	3.90 d ($J_{NCH.CH}$ 2.2)	3.80 d ($J_{NCH.NHa}$ 10.3)
CH	1.76 sp-d[b]	2.13 sp
NH_2	1.90 br	a: 3.60 br, b: 4.00 br
OH	4.50 br	2.99 s
B	—	−17.9 q ($J_{B.H}$ 102)

[a] (*S*)-(−)-AMDPB was treated with equivalent amount of borane–methyl sulfide complex at −70 °C in CD_2Cl_2 then the complex was equilibrated at 4 °C for 20 h. The spectra were recorded at 25 °C. [b] sp = septet.

complexes were prepared according to literature procedures.[9a,b] In these reductions only poor chemical conversion (< 50% after 10 days) and very weak optical induction could be observed (optical rotation of the raw products varied between 0–47).



8

a R^1 = Ph, R^2 = R^3 = H
b R^1 = R^2 = R^3 = Ph
c R^1 = R^2 = CMe_2OMe, R^3 = H

In addition to our results with the 2-amino alcohols we wanted to elucidate the structure of the reducing complex in our experiments. Our results with **6** were disappointing, but modification of the stoichiometry gave useful results. The main problems to be answered were, whether an 1,3,2-oxazaborolidine ring was formed as it was shown in the literature[8b] and if not, what happened to the borane molecule, which might be responsible for the reduction of the carbon–nitrogen double bond. We have not attempted the isolation of the reducing complex but rather investigated its structure after equilibration in solution by NMR techniques. Thus, the ^1H NMR spectra of (*S*)-(−)AMDPB was compared with that of the complex and a ^{11}B NMR spectra of the latter was also recorded. The data are summarized in Table 2. Complex formation is clearly demonstrated by the ^1H NMR chemical shift change of the amino alcohol signals because of the presence of borane. Furthermore, the quartet observed in the ^{11}B NMR spectra excludes the presence of the 1,3,2-oxazaboralidine ring in the reducing agent. Therefore, we infer the structure of the reducing species as complex **9**. This structure is proved by the good correlation of the measured ^{11}B chemical shift with published data on similar compounds with an N–B dative bond.[13] On the other hand, there is further proof of the participation of the nitrogen atom in the coordination, namely, that the two protons of the NH_2 group have different chemical shifts in the spectrum since their interconversion *via* nitrogen inversion is blocked. The complex can be characterized as predominantly a single conformation by the large (0.4 ppm) chemical shift difference between the protons on the NH_2 group, and by the *J* 10.3 Hz coupling constant between the NCH proton and the more shielded amine proton.

Summarizing, we have found that a complex formed from equivalent amounts of optically active 2-substituted 1,1-diphenyl-2-amino alcohols and borane (applied in tetrahydrofuran solution or as the methyl sulfide complex) reduced 2,3-benzodiazepine **3** with high enantio, regio- and chemoselectivity. The complex does not contain a 1,3,2-oxazaborolidine structure as would have been suggested on the basis of similar reactions published in the literature. The high purity of the enantiomers of compound **4** made it possible to synthesize the enantiomers of the biologically significant benzodiazepines **2a** and **2b** by two additional simple chemical transformations (see Experimental section).

Experimental

Melting points were determined on a Boetius hot-stage microscope and are uncorrected. The ^1H NMR spectra were recorded with a Bruker AC 250 instrument (250 MHz) in deuteriochloroform with tetramethylsilane as internal standard at *T* 298 K. The structure of the reducing complex was investigated by ^1H and ^{11}B NMR experiments using a Bruker AC 400 spectrometer in deuteriodichloromethane. ^{11}B NMR spectra were referenced to external BF_3•Et_2O. *J* Values are given in Hz. Mass spectra were recorded on a Finnigan MAT 8430 instrument under the following operating conditions: electron energy, 70 eV; resolution, 1250; source temperature, 250 °C; evaporation temperatures, 150–200 °C. Optical rotations were measured on a LEP OPTON polarimeter at 25 °C, and are given in units of 10^{-1} deg cm^2 g^{-1}. The enantiomeric purity was determined either by the ^1H NMR shift reagent [Eu(hfc)$_3$] techniques or by chiral HPLC analyses or by both. In the ^1H NMR spectra the doublet signal of 2′,6′-H was shifted to lower field and doubled on addition of the shift reagent. The chiral HPLC analyses were performed on a LKB HPLC system with a variable wavelength UV detector and integrator at 230 nm using Chiralcel OJ (mobile phase: hexane–isopropyl alcohol 35:65) for enantiomers of **4a**, **4b** and **5a**, **5b**. Chiralcel OF was used for enantiomers of **2a** and **2b** (mobile phase: hexane–isopropyl alcohol 1:1 + 0.1 v/v % diethylamine). The NMR-shift technique and the chiral HPLC methods generally gave identical results.

The starting material **3** was prepared according to a literature procedure.[3] 2-Amino alcohols **7** were prepared analogously to literature procedures.[8a,9] The borane–tetrahydrofuran complex was prepared by treatment of sodium borohydride with boron trifluoride–diethyl ether in dry diglyme and borane dissolved in dry tetrahydrofuran at −40 °C and stored in a refrigerator. Borane concentration was determined before each application. The borane–methyl sulfide complex was purchased from Aldrich.

(−)-4-Methyl-7,8-methylenedioxy-1-(4-nitrophenyl)-4,5-dihydro-3*H*-2,3-benzodiazepine (−)-4

Method A. A 1.8 mol dm^{-3} solution of borane–tetrahydrofuran complex in THF (9.5 cm^3, 17 mmol) was added dropwise to a stirred solution of (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol[8a,9] (−)-**7d** (4.75 g, 18.6 mmol) in dry methylene chloride (50 cm^3) at −70 °C during 20 min under nitrogen. The resulting solution was gradually warmed to 0 °C and left to stand in a refrigerator overnight (+4 °C). To this mixture a solution of **3** (5.0 g, 15.5 mmol) in dry methylene chloride (100 cm^3) was added dropwise at room temperature during *ca.* 1 h. The solution was left to stand at room temperature until the reduction was complete (7 days). The reaction mixture was then treated with 10% aq. Na_2CO_3 (50 cm^3). The organic layer was separated, washed with water (2 × 50 cm^3), dried (Na_2SO_4) and evaporated to give a yellow crystalline solid which was suspended in EtOH (50 cm^3) and

filtered, to yield after drying the crude product (4.47 g, 89%); $[\alpha]_D$ −106.1 (*c* 1.0, $CHCl_3$); enantiomeric ratio: (+):(−) = 15:85. The crude product (4.3 g) was recrystallized from ethyl acetate (54 cm^3) to yield (−)-**4** (2.87 g, 57%) as orange needles, mp 171–172 °C; $[\alpha]_D$ −155.6 (*c* 1.0, $CHCl_3$); ee >98%; δ_H 1.28 (3 H, d, 4-Me), 2.68 (1 H, dd, 5-H), 2.88 (1 H, dd, 5-H'), 4.09 (1 H, m, 4-H), 5.67 (1 H, s, NH), 5.98 (2 H, s, OCH_2O), 6.50 (1 H, s, 9-H), 6.73 (1 H, s, 6-H), 7.68 (2 H, dm, 2',6'-H) and 8.20 (2 H, dm, 3',5'-H); *m/z* 325 (M^+, 75%), 310 (39), 283 (39), 282 (100), 237 (44), 236 (28), 76 (32) and 42 (20).

Method B. The same procedure as in method A was used except that the solvent was 1,2-dichloroethane instead of methylene chloride and the reaction mixture was stirred at 60 °C. The reduction was complete after 24 h. The isolated crude product {4.2 g, 83%; $[\alpha]_D$ −106.6 (*c* 1.0, $CHCl_3$)} was recrystallized from ethyl acetate (50 cm^3) to give (−)-**4** (2.79 g, 55%), mp 171–173 °C; $[\alpha]_D$ −153.8 (*c* 1.0, $CHCl_3$); ee >98%.

Method C. The reducing complex was prepared from (*S*)-(−)-2-amino-4-methyl-1,1-diphenylpentan-1-ol [8a] (−)-**7e** (5.0 g, 18.6 mmol) using the same procedure as A. The crude product {4.25 g, 84%; $[\alpha]_D$ −142.1 (*c* 1.0, $CHCl_3$); enantiomeric ratio: (+):(−) = 7:93} was recrystallized from ethyl acetate (64 cm^3) to give (−)-**4** (3.40 g, 68%), mp 171–173 °C; $[\alpha]_D$ −154.9 (*c* 1.0, $CHCl_3$); ee >98%.

Method D. The same procedure as in method C was followed except that borane–methyl sulfide complex (1.6 cm^3, 17 mmol) was used to prepare the reducing complex in 1,2-dichloroethane and the reaction mixture was stirred at 60 °C. The reduction was complete after 3 h and the isolated crude product {4.08 g, 81%; $[\alpha]_D$ −141.5 (*c* 1.0, $CHCl_3$)} was recrystallized from ethyl acetate (61 cm^3) to give (−)-**4** (3.26 g, 65%); $[\alpha]_D$ −153.0 (*c* 1.0, $CHCl_3$); ee >98%.

(+)-4-Methyl-7,8-methylenedioxy-1-(4-nitrophenyl)-4,5-dihydro-3*H*-2,3-benzodiazepine (+)-4

The reducing complex was prepared from (*R*)-(+)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (+)-**7d** (4.75 g, 18.6 mmol) and borane–tetrahydrofuran complex (1.8 mol dm^{-3}; 9.5 cm^3, 17 mmol) in 1,2-dichloroethane using the same procedure as method A. To this mixture a solution of **3** (5.0 g, 15.5 mmol) in 1,2-dichloroethane was added at room temperature and the reaction mixture was stirred at 60 °C during 24 h. Work-up yielded a crude product {4.27 g, 85%; $[\alpha]_D$ +111.3 (*c* 1.0, $CHCl_3$); enantiomeric ratio: (+):(−) = 85:15} which was recrystallized from ethyl acetate (52 cm^3) to give (+)-**4** (2.84 g, 56%), mp 171–173 °C; $[\alpha]_D$ +155.1 (*c* 1.0, $CHCl_3$); ee >98%.

(−)-3-Acetyl-4-methyl-7,8-methylenedioxy-1-(4-nitrophenyl)-4,5-dihydro-3*H*-2,3-benzodiazepine (−)-5a

A suspension of (−)-**4** (2.34 g, 7.2 mmol) in acetic anhydride (11.7 cm^3) was stirred at room temperature for 2 h. After 15 min the solids had dissolved. When the reaction was complete, water (60 cm^3) was added dropwise to the solution which was cooled with ice–water and then the product was separated. After stirring overnight the crystalline precipitate was collected, washed with water (4 × 5 cm^3) and dried to yield (−)-**5a** (2.5 g, 95%) as pale yellow crystals, mp 173–177 °C; $[\alpha]_D$ −54.9 (*c* 1.0, $CHCl_3$); ee >98%; δ_H 1.06 (3 H, d, *J* 6.6, 4-Me), 2.33 (3 H, s, MeCO), 2.79 (1 H, dd, *J* 6 and 15, 5-H), 3.04 (1 H, dd, *J* 2 and 15, 5-H'), 6.02 (2 H, m, OCH_2O), 6.48 (1 H, s, 9-H), 6.76 (1 H, s, 6-H), 7.74 (2 H, m, 2',6'-H) and 8.25 (2 H, m, 3',5'-H); *m/z* 367 (M^+, 86%), 352 (32), 310 (66), 283 (46), 282 (100), 237 (28), 236 (25) and 43 (38).

(+)-3-Acetyl-4-methyl-7,8-methylenedioxy-1-(4-nitrophenyl)-4,5-dihydro-3*H*-2,3-benzodiazepine (+)-5a

The title compound was prepared from (+)-**4** by the previous method, 93% yield; mp 173–177 °C; $[\alpha]_D$ +49.6 (*c* 1.0, $CHCl_3$); ee >98%.

(+)-3-Acetyl-1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3*H*-2,3-benzodiazepine (+)-2a

98% Hydrazine hydrate (1.2 cm^3, 24.8 mmol) was added to a stirred suspension of (−)-**5a** (2.6 g, 7.08 mmol) and Raney-Ni (W-2) (0.5 g) in methanol (52 cm^3). The reaction mixture was stirred at room temperature for 1 h. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure. The oily residue solidified when water (50 cm^3) was added and the precipitate was filtered and dried to yield crude (+)-**2a** (2.17 g, 91%). The crude product was recrystallized from 50% aq. ethanol (14 cm^3) to give (+)-**2a** as a white powder (1.92 g, 81%), mp 168–170 °C; $[\alpha]_D$ +344.5 (*c* 1.0, MeOH); ee >98%; δ_H 1.31 (3 H, d, 4-Me), 2.02 (3 H, s, MeCO), 2.63 (1 H, dd, 5-H), 2.70 (1 H, dd, 5-H'), 4.02 (2 H, s, NH_2), 5.23 (1 H, m, 4-H), 5.98 (2 H, dd, OCH_2O), 6.58 (1 H, s, 9-H), 6.68 (2 H, dm, 2',6'-H), 6.77 (1 H, s, 6-H) and 7.51 (2 H, m, 3',5'-H); *m/z* 337 (M^+, 100%), 292 (24), 280 (52), 279 (20), 252 (78), 233 (44), 160 (21) and 43 (21).

(−)-3-Acetyl-1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3*H*-2,3-benzodiazepine (−)-2a

Prepared from (+)-**5a** as described for (+)-**2a**. Yield 78%, mp 167–170 °C (from 50% aq. ethanol); $[\alpha]_D$ −325.8 (*c* 1.0, MeOH); ee >98%.

(−)-4-Methyl-3-methylcarbamoyl-7,8-methylenedioxy-1-(4-nitrophenyl)-4,5-dihydro-3*H*-2,3-benzodiazepine (−)-5b

Methyl isocyanate (2.18 cm^3, 37 mmol) was added to a solution of (−)-**4** (4.0 g, 12.3 mmol) in dry methylene chloride (80 cm^3). The reaction mixture was left to stand at room temperature for 3 days. The solution was evaporated under reduced pressure and the oily residue solidified with water (60 cm^3). The precipitate was filtered and dried to yield (−)-**5b** (4.49 g, 96%) as a yellow powder; $[\alpha]_D$ −315.3 (*c* 1.0, $CHCl_3$); ee >98%; δ_H 0.95 (3 H, d, *J* 6.6, 4-Me), 2.88 (1 H, dd, *J* 6.3 and 14.6, 5-H), 3.12 (1 H, dd, *J* 1.9 and 14.6, 5-H'), 2.91 (3 H, d, *J* 5, CH_3NHCO), 5.49 (1 H, m, 4-H), 5.99 (2 H, m, OCH_2O), 6.44 (1 H, s, 9-H), 6.53 (1 H, q, NH), 6.71 (1 H, s, 6-H), 7.61 (2 H, m, 2',6'-H) and 8.24 (2 H, m, 3',5'-H); *m/z* 382 (M^+, 22%), 310 (26), 283 (40), 282 (100), 237 (25), 236 (23), 178 (14) and 58 (36).

(+)-4-Methyl-3-methylcarbamoyl-7,8-methylenedioxy-1-(4-nitrophenyl)-4,5-dihydro-3*H*-2,3-benzodiazepine (+)-5b

Prepared from (+)-**4** according to the previous method. Yield 95%; $[\alpha]_D$ +304.1 (*c* 1.0, $CHCl_3$); ee >98%.

(+)-1-(4-Aminophenyl)-4-methyl-3-methylcarbamoyl-7,8-methylenedioxy-4,5-dihydro-3*H*-2,3-benzodiazepine (+)-2b

Prepared from (−)-**5b** (2.42 g, 6.33 mmol) as described for (+)-**2a**. The work-up procedure yielded the product as a pale yellow powder (2.06 g, 95%); $[\alpha]_D$ +363.4 (*c* 1.0, $CHCl_3$); ee >98%; δ_H 1.13 (3 H, d, 4-Me), 2.67 (1 H, dd, 5-H), 2.84 (1 H, dd, 5-H'), 2.85 (3 H, d, CH_3NHCO), 3.93 (2 H, s, NH_2), 5.19 (1 H, m, 4-H), 5.95 (1 H, q, CH_3NHCO), 5.97 (2 H, dd, OCH_2O), 6.57 (1 H, s, 9-H), 6.67 (2 H, dm, 2',6'-H), 6.70 (1 H, s, 6-H) and 7.40 (2 H, dm, 3',5'-H); *m/z* 352 (M^+, 53%), 294 (9), 293 (8), 280 (52), 253 (42), 252 (100), 194 (5) and 160 (18).

(−)-1-(4-Aminophenyl)-4-methyl-3-methylcarbamoyl-7,8-methylenedioxy-4,5-dihydro-3*H*-2,3-benzodiazepine (−)-2b

It was prepared from (+)-**5b** analogously to the previous method. Yield 96%; $[\alpha]_D$ −365.9 (*c* 1.0, $CHCl_3$); ee >98%.

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Paper 4/07241C
Received 28*th November* 1994
Accepted 30*th January* 1995