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Asymmetric synthesis of 3-substituted pyrrolidones via α-alkylation of a chiral non-racemic γ-lactam

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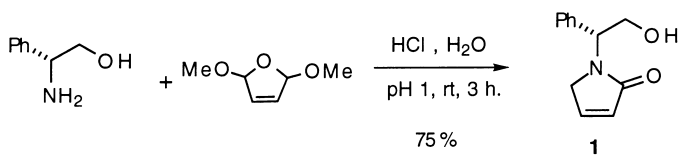
Abstract

3-Alkyl pyrrolidones **9** were synthesized in good yield and high diastereoselectivity by α-alkylation of the new chiral non-racemic lactam **8** derived from (*R*)-(−)-phenylglycinol. After debenzylation and introduction of an electron-withdrawing group, 3-methylpyrrolidone **10** is easily hydrolyzed in a basic medium to produce γ-aminobutyric acid (GABA) analogue **13**.

1. Introduction

Numerous biological compounds possess a pyrrolidine ring as the main structure or as a structural subunit.[1,2] Enantiomerically pure pyrrolidines and pyrrolidinones can also be used as chiral auxiliaries,[3] synthetic intermediates[4] or chiral ligands[5] in synthesis. Likewise, pyrrolidones are useful precursors of γ-aminobutyric acid (GABA) analogues.[6] In all cases, the heterocycle is substituted in various positions with precise configurations. There is a clear interest in developing a method for the construction of differently substituted pyrrolidines with control of the diastereoselectivity.

In this respect, we reported three years ago the one-step preparation of the lactam **1**[7] from (*R*)-(−)-phenylglycinol and dimethoxydihydrofuran and envisaged its use as a new chiral starting material (Scheme 1).



Scheme 1.

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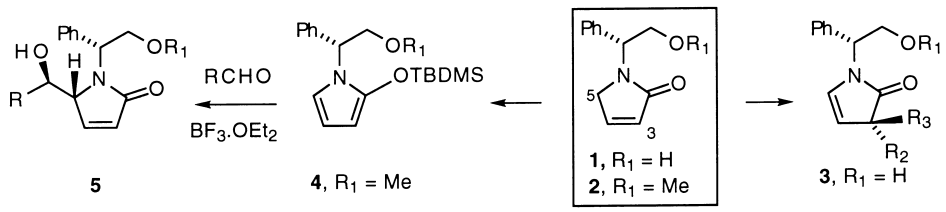
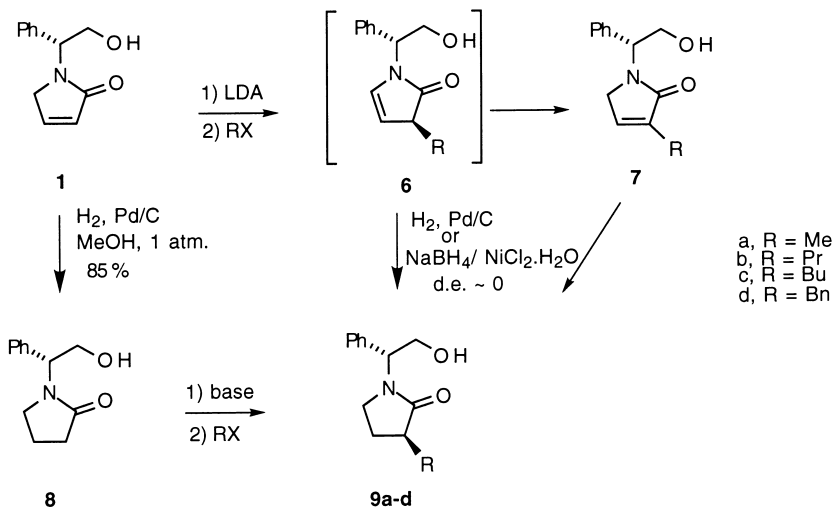
Indeed the lactam **1** was easily di-alkylated α to the carbonyl group[7] in high yield and high diastereomeric excess (Scheme 2). Furthermore, 5-substituted pyrrolidones **5** were obtained with complete *threo* selectivity through the condensation[8] of a chiral silyloxypyrrole **4** (derived from **1**) with achiral aldehydes (Scheme 2). This methodology was applied in the synthesis of an aza-muricatacin. [9]



Scheme 2.

Diastereoselective alkylations at C-3 of a pyrrolidine ring have already been reported, mainly starting from pyroglutamic acid.[10] Indeed, methods for the preparation of enantiomerically pure pyrrolidines and γ-lactams substituted exclusively at the C-3 position are rare.[11–13] The bicyclic lactam methodology developed by Meyers et al.[12] gave moderate diastereoselectivity for mono-substitution. Nevertheless, a new method using alkylation of *N*-dialkylaminolactams has been recently reported by Enders[13] to give good results.

With this objective, we first envisaged the reduction of α-monosubstituted α,β-unsaturated γ-lactams **7** synthesized by alkylation of the lactam **1** or preferably the *in situ* reduction of the supposed intermediate **6** (Scheme 3). However, under all the experimental conditions investigated, pyrrolidone **9** was obtained in an almost equimolar mixture of diastereomers. Thus, on the observation of the recently reported alkylation of an analogous δ-lactam,[14] we decided to transform **1** into the saturated γ-lactam **8** before carrying out the alkylation study (Scheme 3).



Scheme 3.

2. Results and discussion

After reduction of lactam **1** under catalytic hydrogenation conditions, the alkylation of **8** was investigated (Table 1). Following our previous studies with the α,β-unsaturated lactam **1**, LDA was first studied

Table 1

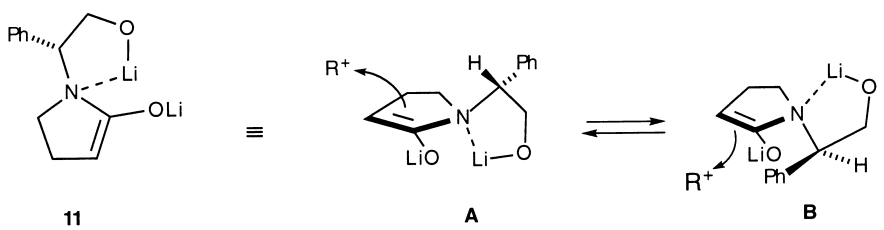
RX	base	**9** (yield%)[a)]	d.e. %
MeI	*sec*-BuLi	**9a** (87)	80[b)]
PrBr	LDA	**9b** (23)	-
PrBr	*sec*-BuLi	**9b** (52)	90[b)]
nBuI	*sec*-BuLi	**9c** (60)	81[c)]
BnBr	LDA	**9d** (29)	-
BnBr	*sec*-BuLi	**9d** (83)	87[c)]

a) isolated yield, b) determined by GC-MS analyses on the crude silylated reaction mixture
c) determined by ^{1}H and ^{13}C NMR analyses.

as the base but was not found to be the best reagent for deprotonation of **8**. The yields remained low in the presence of a cosolvent (HMPA) or a salt (LiBr). As observed in the δ-lactam series,[14] the best results were obtained using *sec*-butyllithium. Upon deprotonation with two equivalents of base in THF at −78°C for 20 min, the intermediate enolate was trapped with different alkyl halides. Lactams **9a–d** were obtained in good yields and diastereomeric purities (Table 1). The diastereoselectivities were determined by GC–MS or ^{1}H and ^{13}C NMR analyses on the crude reaction mixtures.

The major diastereomer resulted from a preferential attack of the electrophile on the *si* face of the enolate, as had been observed previously in the di-alkylation of **1**.[7] This was proved after determination of the absolute configuration of compound **9a** by chemical correlation (*vide infra*).

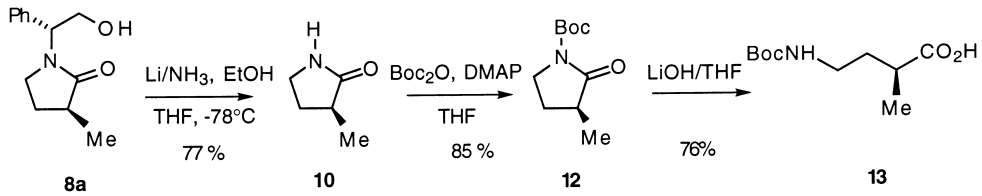
While the diastereoselectivity of this alkylation process was of the same order as that reported by Enders,[13] it remained lower than that observed in the δ-lactam or the acyclic amide series for the same chiral auxiliary and very similar experimental conditions.[14] This difference could not be explained. The origin of the diastereoselectivity has been examined using models depicted in Scheme 4. Due to a high pyramidalization of the nitrogen in amide enolate,[15,12a] the N-lone pair becomes a very good electron donor allowing chelation of the lithium ion. This chelation process had been previously invoked to explain alkylation results with amide enolates.[13,14b,16] Two diastereomeric chelated enolates A and B can be proposed (Scheme 4). On account of the stereoelectronic effect,[17] one can expect a preferred attack of the electrophile *anti* to the nitrogen lone pair. In each case, A and B, the phenyl group lies on this preferred face of the enolate, but is more remote from the double bond in A than in B. This could explain the observed majority *si* attack of the electrophile. Thus, both steric and stereoelectronic effects can explain the formation of **9** as the major compound.



Scheme 4.

The transformation of alkylated lactams **9** to 2-substituted GABA analogues was exemplified by the synthesis of (2*S*)-2-methyl-4-(*tert*-butyloxycarbonylamino)butyric acid **13** (Scheme 5). This transformation was achieved by debenzylation of lactam **9a** using lithium in liquid ammonia, followed by hydrolysis

of the resultant lactam **10** in a strongly acidic medium at reflux.[13,18] We preferred the introduction of an electron-withdrawing group on the nitrogen atom in order to facilitate the amide bond cleavage in basic media[19] in order to access the GABA analogues under milder conditions. Thus formation of the *N*-Boc derivative **12** was followed by hydrolysis with lithium hydroxide in THF using Grieco's conditions[20] to produce the GABA analogue **13** in 76% yield (Scheme 5). Furthermore, these transformations permitted the assignment of the absolute configuration of alkylated lactam **9a** to be 3*S* by comparison of specific rotations of lactam **10** and amino acid **13** with those reported in the literature. Another conceivable avantage of the presence of the *N*-Boc group might be the opening of the lactam by nucleophiles[21] (alcoholate, amine, Grignard reagent, organolithium compound, aminoester) to provide aminoamides, aminoesters, aminoketones, etc.



Scheme 5.

In conclusion, we have shown a new synthetic application of a γ-lactam derived from (*R*)-phenylglycinol. Using the chiral α,β-unsaturated lactam **1**, new asymmetric routes towards 5, 4,5- and 3,5-substituted pyrrolidones are under investigation and will soon be published.

3. Experimental

All the starting materials were commercially available and purified following standard techniques. (*R*)-(−)-Phenylglycinol was prepared according to the literature procedure.[22] THF was freshly distilled from sodium–benzophenone ketyl and methanol from magnesium iodine. *sec*-BuLi (1.6 M in hexane) was purchased from Aldrich. Product purification was performed by flash chromatography on silica gel (Merck art. 9305).

Optical rotations were measured at room temperature on a Perkin–Elmer 241 polarimeter. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300, AC-250 or AC-200 instrument using Me_4Si as internal standard. Mass spectra were recorded on an AEI MS-9 (CI; isobutane) or AEI MS-50 (EI) instrument. Elemental analyses were performed by the Microanalysis Laboratory at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette).

*3.1. 1-(2-Hydroxy-1-phenylethyl)-1,5-dihydropyrrol-2-one **1***

To a solution of 2,5-dimethoxy-2,5-dihydrofuran (4.44 ml, 36.5 mmol) and (*R*)-(−)-phenylglycinol (5.0 g, 36.5 mmol) in water (150 ml) was added a conc. solution of HCl (4.5 ml). The mixture was stirred at room temperature for 3 h then neutralized with solid $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent distilled off. The residual red oil was purified by flash chromatography (CH_2Cl_2:MeOH=96:4) to give the α,β-unsaturated-γ-lactam **1** as a red solid. Yield: 75% (5.13 g); mp: 103°C (heptane–AcOEt); $[\alpha]_D$ −21 (c=1.0, CH_2Cl_2); IR (film): ν (cm^{-1}) 3400 (OH st), 1653 (C=O st), 797, 725 (HC=CH cis); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.25–7.30 (5H, m), 7.00 (1H, d, 5.9 Hz), 6.10 (1H, d, 5.9 Hz), 5.25 (1H, dd, 5.1, 7.7 Hz), 4.65 (1H, sl),

4.00–4.15 (3H, d+m, 20.5 Hz), 3.80 (1H, d, 20.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 172.2, 143.8, 137.7, 128.5, 127.5, 127.2, 127.1, 62.5, 57.7, 50.9; MS (EI): m/z 203 (M^+), 185 (M^+-H_2O), 172 (M^+-CH_2OH), 144 (172−CO), 104 (Ph-CH=CH_2), 91 ($PhCH_2$); anal. calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89; found: C, 70.52; H, 6.39; N, 6.92.

*3.2. 1-(2-Hydroxy-1-phenylethyl)-pyrrolidin-2-one **8***

A solution of **1** (4.42 g, 0.021 mmol) in dry methanol (25 mL) and 10% Pd–C (0.1 g) were stirred at room temperature for 1 h under a hydrogen atmosphere (1 atm). The mixture was filtered and concentrated *in vacuo*. After purification by flash chromatography (CH_2Cl_2:MeOH=96:4), pyrrolidin-2-one **8** was isolated as a colourless oil. Yield: 85% (3.79 g); $[\alpha]_D$ −54 (c=3.4, CH_2Cl_2); IR (film): ν (cm^{-1}) 3400 (OH st), 1662 (C=O st); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.30 (5H, m), 5.18 (1H, dd, 6.0, 7.7 Hz), 4.40 (1H, bs), 4.05 (2H, m), 3.45 (1H, dd, 8.5, 14 Hz), 3.16 (1H, m), 2.44 (2H, m), 1.98 (2H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 176.3, 136.8, 128.5, 127.6, 127.3, 61.4, 57.7, 44.4, 31.4, 17.8; MS (CI): m/z 206 (MH^+); anal. calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.38; N, 6.82; found: C, 70.42; H, 7.35; N, 6.78.

*3.3. General procedure for the alkylation of **8***

To a solution of lactam **8** (1 equiv.) in THF, *sec*-BuLi (1.6 M in hexane, 2.5 equiv.) was slowly added at −78°C under a nitrogen atmosphere. The mixture was stirred for 20 min and alkyl halide (2 equiv.) was added dropwise. After stirring at −78°C or 0°C (depending on the electrophile), the mixture was hydrolyzed by addition of saturated NH_4Cl solution and extracted several times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by flash chromatography.

*3.4. 1-(2-Hydroxy-1-phenylethyl)-3-methyl-pyrrolidin-2-one **9a***

From lactam **8** (699 mg; 3.41 mmol) and methyl iodide; stirred for 1 h at −78°C; chromatography using CH_2Cl_2:MeOH (95:5); yield: 87% (652 mg); d.e.: 80%; amorphous solid; $[\alpha]_D$ −34 (c=1.0, CH_2Cl_2); IR (film): ν (cm^{-1}) 3400 (OH st), 1669 (C=O st); ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.20–7.40 (5H, m), 4.92 (1H, dd, 4.5, 8.6 Hz), 4.15 (1H, m), 4.05 (1H, m), 3.50 (1H, m), 3.29 (1H, ddd, 7.4, 8.8, 9.6 Hz), 3.1 (1H, ddd, 2.9, 8.8, 9.6 Hz), 2.61 (1H, m), 2.24 (1H, m), 1.63 (1H, m), 1.25 (3H, d, 7.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 178.4, 137.1, 128.4, 127.4, 127.1, 61.4, 57.5, 42.2, 37.0, 27.1, 15.9; MS (CI): m/z 220 (MH^+); anal. calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39; found: C, 71.01; H, 8.05; N, 6.28.

*3.5. 1-(2-Hydroxy-1-phenylethyl)-3-propylpyrrolidin-2-one **9b***

From lactam **8** (329 mg, 1.60 mmol) and propyl bromide; stirred for 1 h at −78°C and 2 h at 0°C; chromatography using CH_2Cl_2:MeOH (98:2); yield: 52% (207 mg); d.e.: 90%; pale yellow oil; $[\alpha]_D$ −20 (c=1.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.30 (5H, m), 5.18 (1H, t, 6.8 Hz), 4.3 (1H, bs), 4.10 (2H, d, 6.3 Hz), 3.35 (1H, ddd, 8.1, 9.1, 9.0 Hz), 3.1 (1H, ddd, 3.0, 9.1, 9.1 Hz), 2.50 (1H, m), 2.15 (1H, m), 1.85 (1H, m), 1.60 (1H, m), 1.30 (3H, m), 1.0 (3H, t, 7 Hz); ^{13}C NMR (75.3 MHz, $CDCl_3$): δ (ppm) 178.3, 137.1, 128.6, 127.7, 127.3, 61.93, 58.23, 43.0, 42.3, 33.2, 25.0, 20.2, 13.9; MS (CI): m/z 248 (MH^+); anal. calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66; found: C, 72.77; H, 8.77; N, 5.36.

3.6. 1-(2-Hydroxy-1-phenylethyl)-3-butylpyrrolidin-2-one **9c**

From lactam **8** (566 mg, 2.76 mmol) and butyl iodide; stirred for 1.5 h at −78°C and 1.5 h at 0°C; chromatography using CH_2Cl_2:MeOH (96.5:3.5); yield: 60%; d.e.: 81% (432 mg); yellow oil; $[\alpha]_D$ −11.5 (c=1.0, CH_2Cl_2); IR (film): ν (cm^{-1}) 3400 (OH st), 1662.5 (C=O st); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.20–7.40 (5H, m), 5.15 (1H, t, 6.4 Hz), 4.2 (1H, bs), 4.10 (2H, d, 6.2 Hz), 3.38 (1H, ddd, 3.5, 9.0, 9.5 Hz), 3.1 (1H, dd, 7.8, 9.6 Hz), 2.50 (1H, m), 2.19 (1H, m), 1.85 (1H, m), 1.60 (1H, m), 1.35 (5H, m), 0.9 (3H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 177.9, 137.1, 128.4, 127.4, 127.1, 61.4, 57.4, 42.4, 42.1, 30.6, 29.0, 24.8, 22.4, 13.7; MS (CI): m/z 262 (MH^+); anal. calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36; found: C, 73.59; H, 8.68; N, 5.58.

3.7. 1-(2-Hydroxy-1-phenylethyl)-3-benzylpyrrolidin-2-one **9d**

From lactam **8** (210 mg, 1.02 mmol) and benzyl bromide; stirred for 1 h at −78°C; chromatography using AcOEt:heptane (7:3); yield: 83%; d.e.: 87% (256 mg); colourless oil; $[\alpha]_D$ +33 (c=1.5, CH_2Cl_2); IR (film): ν (cm^{-1}) 3400 (OH st), 1662.5 (C=O st); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.25 (10H, m), 5.14 (1H, t, 6.7 Hz), 4.17 (1H, bs), 4.07 (2H, d, 7.0 Hz), 3.28 (1H, dd, 7.9, 9.2 Hz), 3.19 (1H, dd, 3.9, 13.5 Hz), 2.95 (1H, dt, 3.1, 9.2 Hz), 2.84 (1H, ddt, 3.9, 8.9, 9.2 Hz), 2.7 (1H, dd, 9.2, 13.5 Hz), 2.10 (1H, m), 1.66 (1H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm) 177.3, 139.2, 136.9, 129.1, 129.8, 128.4, 127.8, 127.4, 126.3, 62.1, 58.6, 44.2, 43.1, 36.8, 24.3; MS (CI): m/z 296 (MH^+); anal. calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.16; N, 4.74; found: C, 77.41; H, 7.38; N, 4.61.

3.8. (3S)-3-Methylpyrrolidin-2-one **10**

In a two-necked flask fitted with a dry-ice condenser, were placed lactam **9a** (234 mg, 1.07 mmol, d.e.=80%) anhydrous THF (10 ml) and anhydrous EtOH (0.6 mL, 10.7 mmol). The mixture was chilled to −78°C under a nitrogen atmosphere. Ammonia (40 ml) was condensed, then small pieces of lithium were added until the dark blue coloration persisted for more than 5 min. The mixture was stirred at −78°C for 30 min, then the cooling bath was removed to allow evaporation of NH_3. The solution was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2:MeOH=96:4) to give lactam **10** as a yellow oil, yield: 77% (81 mg); this compound exhibited analytical data identical to those reported in the literature.[13]

3.9. (4S)-4-Methyl-5-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester **12**

To a solution of pyrrolidinone **10** (103 mg, 1.04 mmol) in anhydrous THF (2 ml) were added DMAP (116 mg, 1.04 mmol) and $(Boc)_2O$ (375 mg, 2.6 mmol). The mixture was stirred at room temperature for 4 h. The solvent was distilled off and the residue dissolved in CH_2Cl_2. The solution was filtered through a small amount of silica gel 60. After the evaporation of the solvent, the product **12** was obtained with satisfactory purity. Yield: 85% (176 mg); yellow oil; IR (film): ν (cm^{-1}) 1785, 1754 (C=O Boc st), 1712 (C=O amide st): ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm)=3.78 (1H, ddd, 2.5, 8.7, 10.8 Hz), 3.61 (1H, m), 2.57 (1H, m), 2.25 (1H, m), 1.67 (1H, m), 1.60 (9H, s), 1.22 (3H, d, 7.1 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ (ppm)=176.2, 145.0, 82.1, 44.0, 39.1, 27.6, 26.0, 15.0.

3.10. (2S)-4-tert-Butoxycarbonylamino-2-methyl-butyric acid **13**

To a solution of lactam **12** (68 mg, 0.34 mmol) in THF:H_2O (2:1, 1 ml) was added $LiOH \cdot H_2O$ (42 mg, 1 mmol). The mixture was stirred at room temperature for 1 h then acidified to pH 1–2 with 0.5 N HCl solution. After extraction with Et_2O, the combined organic layers were dried over $MgSO_4$ then concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2:MeOH=96:4). The *N*-Boc-amino acid **13** was obtained in 76% yield (56 mg); e.e.: 80%; colourless oil; $[\alpha]_D$ +11 (c=1.0, CH_2Cl_2); [lit.[23] for the (2*R*)-enantiomer with 100% e.e: $[\alpha]_D$ −14 (c=0.31, CH_2Cl_2)]; anal. calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45; found: C, 55.87; H, 8.42; N, 5.66. All spectroscopic data are identical to those reported in the literature[23] for the 2*R* enantiomer.

Acknowledgements

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