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Synthesis of C_2 symmetric primary vicinal diamines. Double stereospecific Mitsunobu reaction on the heterocyclic diols derived from tartaric acid

Jacek Skarżewski * and Anil Gupta

Institute of Organic Chemistry, Biochemistry and Biotechnology, Technical University, 50–370 Wrocław, Poland

Abstract: Homochiral 1-alkyl-3,4-dihydroxypyrrolidines, (*S*,*S*)- and (*R*,*R*)-**5** were obtained by cyclization and reduction of both enantiomers of (+)- and (−)-tartaric acid, respectively. Also (*S*,*S*)-3,4-dihydroxytetrahydrofurane **6** was prepared from (+)-diethyl tartrate. All these heterocyclic *vic*-diols underwent twofold Mitsunobu reaction (Ph_3P/DEAD/HN_3) followed by catalytic hydrogenation forming stereospecifically the corresponding primary vicinal diamines (*R*,*R*)-, (*S*,*S*)-**2** and (*R*,*R*)-**3**. The absolute configuration of diamines **2**, **3** was established by the exciton-coupling CD spectra of their N,N′-diphthaloyl derivatives.
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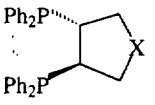
During the past decade remarkable achievements have been attained in the field of metal-catalyzed asymmetric synthesis.[1] Many successful catalysts are based on diamines used as chiral controllers.[2] Therefore, there is a continuing interest in the synthesis of new chiral vicinal diamines,[3] especially those with C_2 symmetry.[4] Particularly, primary amines with the relatively rigid, cyclic structure are highly desirable for their versatile further derivatization and use as chiral auxiliaries and ligands. However, there is rather limited list of the easily available derivatives of this type.[2] On the other hand, tartaric acid is regarded as the most successful single compound applied as a starting material for the synthesis of chiral ligands.[5] Phosphine-type heterocyclic ligands **1** with outstanding catalytic properties have been obtained from this precursor,[6,7] but its use for the preparation of the corresponding vicinal diamines is rather unexplored field.[8] We describe herein a synthetic route to homochiral *vic*-diamines (*R*,*R*)-, (*S*,*S*)-**2** and (*R*,*R*)-**3**, in which two stereogenic centers are derived from (+)- and (−)-tartaric acid.



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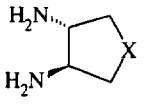
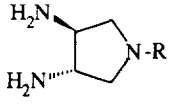


X = N-R (*R*,*R*)-**2**
X = O (*R*,*R*)-**3**

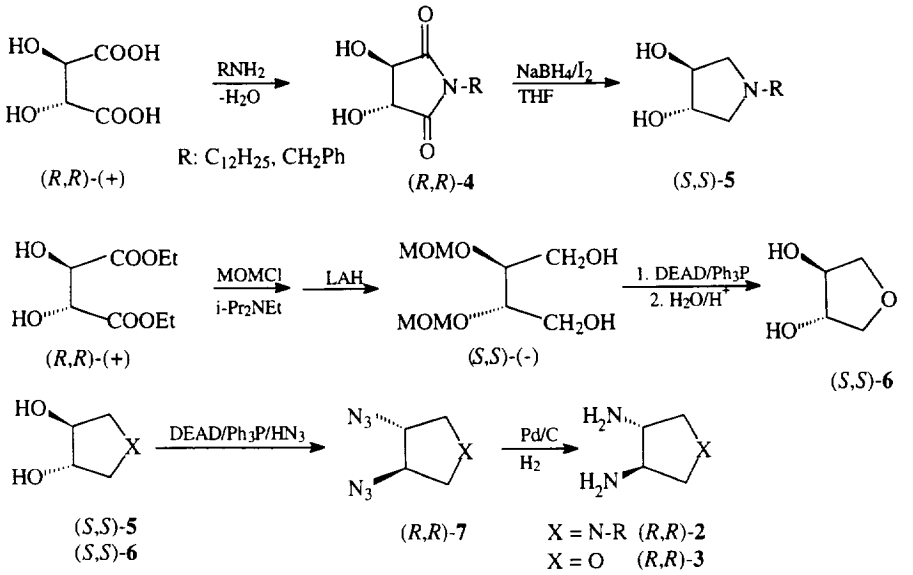


(*S*,*S*)-**2**

The outline of our synthesis is shown in Scheme 1. For clarity, the transformations of one enantiomer only are depicted there. Thus, starting from either enantiomer of tartaric acid we synthesized the corresponding homochiral N-substituted 3,4-dihydroxypyrrolidinediones **4**. In a view of our interest in lipophilic ligands which could bring together organic substrates and metal-ion catalyst (micellar and phase transfer catalysts),[9] N-dodecyl derivatives were included here. The products were easily reduced to the respective enantiopure 3,4-dihydroxypyrrolidines **5** using diborane generated in situ from sodium borohydride and iodine.[10] Another five-membered heterocyclic diol (*S*,*S*)-**6** was obtained from (*R*,*R*)-(+)-diethyl tartrate. After the OH groups were protected as the methoxymethyl ether functions, the resulting ester was reduced. Thus prepared (*S*,*S*)-(−)-threitol derivative was treated with triphenylphosphine and diethyl azodicarboxylate (DEAD) and gave the cyclized product in over 90%

* Corresponding author. Email: skarzewski@kchf.ch.pwr.wroc.pl

yield. After deprotection 3*S*,4*S*-tetrahydrofuranediol, (*S*,*S*)-**6** was obtained in excellent overall yield. It is noteworthy that the applied Mitsunobu reaction conditions[11] gave much higher yield than the acid-catalyzed cyclization of threitol used by Terfort.[7]



Scheme 1.

In order to obtain 3,4-diamino-1-dodecylpyrrolidine *via* the corresponding diazide, we transformed diol (*S*,*S*)-**5** into its mesyl diester. However, when the dimesylate was treated with sodium azide in DMF, HMPA or under the two-phase conditions with PTC, the reaction was sluggish and only up to 10% of the desired diazide could be isolated along with the elimination products. Thus, in spite of the various reaction conditions applied, no practically useful substitution could be achieved, so we turned to the Mitsunobu reaction[11] as a tool for the diazide synthesis.

Although the efficient and stereospecific conversion of secondary alcohols into azido-compounds by means of the Mitsunobu reaction is a well established procedure,[11] we could not find any literature report on this reaction being successfully carried out on the *vic*-diol. Nevertheless, we treated enantiomeric diols **5** (R: $C_{12}H_{25}$) with hydrazoic acid as the azide source followed by addition of triphenylphosphine and DEAD, in the same manner as reported for mono-alcohols by Loibner and Zbiral.[12] After the usual work-up the corresponding diazides were obtained in 80% yield. The azides were easily reduced catalytically (10% Pd/C, H_2 1 atm) to the respective diamines, (−)- and (+)-**2** (R: $C_{12}H_{25}$). The obtained products were homogeneous (GC, NMR) and optically active. The stereochemical outcome of the reaction was in agreement with the expected inversion at both stereogenic centers, thus (−)-**2** was obtained from (*S*,*S*)-(+)-**5** derived from natural (2*R*,3*R*)-(+)-tartaric acid. We established the absolute configuration of diamines by the exciton-coupling CD spectra of their diphthaloyl derivatives.[13] Thus, both (+)- and (−)-**2** (R: $C_{12}H_{25}$) were converted into their N,N′-diphthalimides. The derivative of diamine (−)-**2** shows strong negative Cotton effect $\Delta\epsilon(\lambda)$: −80(224 nm), +57(213 nm) (Figure 1, Θ, dotted line), as expected for the diphthaloyl derivative of (3*R*,4*R*)-diamino-1-dodecylpyrrolidine, (*R*,*R*)-**2**. Its enantiomer, the derivative of (+)-**2** derived from (2*S*,3*S*)-(−)-tartaric acid demonstrates positive Cotton effect $\Delta\epsilon(\lambda)$: +78(224 nm), −58(213 nm) (Figure 1, ⊕, solid line) as predicted for the diphthaloyl derivative of (*S*,*S*)-**2**.

When we applied the identical Mitsunobu reaction conditions to 1-benzyl-3,4-dihydroxypyrrolidines, only low yield of the diazides resulted. Moreover, the other azide sources used instead of azidoic acid, namely zinc diazide bis-pyridine complex[14] or diphenylphosphoryl

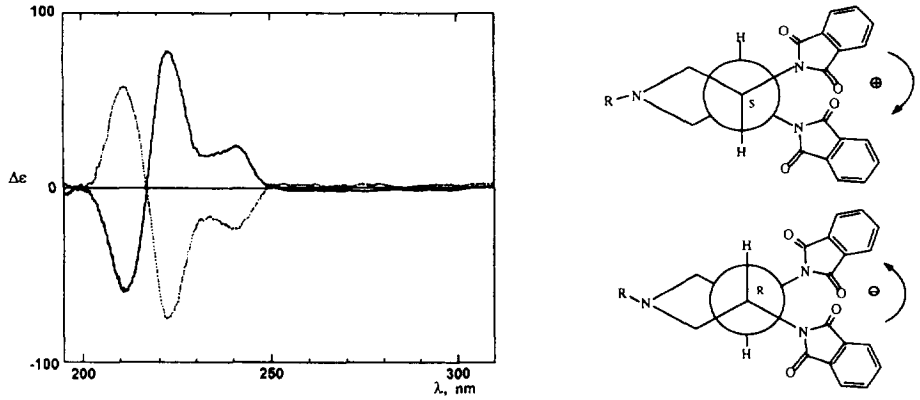


Figure 1. CD spectra and structures of N,N′-diphthaloyl derivatives of (3*R*,4*R*)-(−)-**2** (R: $C_{12}H_{25}$) (dotted line, Θ, negative Cotton effect) and (2*S*,3*S*)-(+)-**2** (R: $C_{12}H_{25}$) (solid line, ⊕, positive Cotton effect), $c=1.40\times10^{-4}$ in MeCN.

azide[15] also failed in this reaction. However, when the preformed betaine-type adduct of triphenylphosphine–DEAD–azidoic acid was treated with the substrate diol (the Mitsunobu reaction conditions with the reversed addition order),[16] an appropriate product was furnished in good yield.

Analogously, the reversed addition order was used in preparation of (3*R*,4*R*)-diaminotetrahydrofuran, (*R*,*R*)-**3** and also inversion of configuration at both centers resulted in this process, as confirmed by $\Delta\epsilon(\lambda)$: −83(225 nm), +50(213 nm) in the CD spectrum for the corresponding diphthaloyl derivative of **3**. It seems that the difference in Mitsunobu reaction conditions required for N-dodecyl and N-benzyl derivatives can be due to the difference in solubility of the respective intermediates formed when the normal addition order is applied.

Homochiral diamine (*S*,*S*)-**2** (R: $C_{12}H_{25}$) was transformed into the corresponding Schiff base and its Mn(III) complex was tested as a catalyst in the Jacobsen-type epoxidation,[17] but the results obtained were disappointing.[18] Further studies on the catalytic application of new C_2 symmetric primary vicinal diamines are underway.

In summary, the developed stereospecific double Mitsunobu substitution on the five membered heterocyclic *vic*-diols offers simple synthetic way to the corresponding homochiral *vic*-diamines of C_2 symmetry, prospective chiral auxiliaries and ligands.

Experimental

Melting points were determined using a Boetius hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. ^{1}H NMR spectra were measured on a Bruker CPX (300 MHz) spectrometer using TMS as an internal standard. Observed rotations at 578 nm were measured using an Optical Activity Ltd. Model AA-5 automatic polarimeter. CD spectra were recorded with a JASCO J 600 instrument. GC/MS spectra were determined on a Hewlett–Packard 5890 II gas chromatograph (25 m capillary column) with a Hewlett Packard mass spectrometer 5971 A operating on the electron impact mode (70 eV). Separations of products by chromatography were performed on silica gel 60 (230–400 mesh) purchased from Merck or florisil from Fluka. Thin layer chromatography analyses were performed using silica gel 60 precoated plates (Merck). When the identical spectra were obtained for the respective enantiomers, only one set of data was reported.

N-Substituted 3,4-dihydroxypyrrolidinediones **4**

The particular amine (0.2 mol) and tartaric acid (30.02 g, 0.2 mol) were azeotropically dehydrated with boiling xylene in a Dean–Stark apparatus. After cooling, the crystalline product was filtered off, washed with hexane (R: $C_{12}H_{25}$) or acetone (R: CH_2Ph) and recrystallized from the hexane–methanol mixture (4:1) or ethanol, respectively.

From natural (+)-tartaric acid: (3*R*,4*R*)-(+)-**4** (R: $C_{12}H_{25}$): yield 54%; m.p. 127–128°C; $[\alpha]_D$ +113 (c 1.0, MeOH).

From unnatural (−)-tartaric acid: (3*S*,4*S*)-(−)-**4** (R: $C_{12}H_{25}$): yield 65%; m.p. 128–129°C; $[\alpha]_D$ −113 (c 1.0, MeOH).

IR (KBr): 1704, 2852, 2920, 3392br; NMR ($CDCl_3$): 0.82 (t, 3H, J=5 Hz, -CH_3), 1.22 (s, 20H, -$(CH_2)_{10}$-,), 1.45–1.62 (m, 2H, -CH_2N=), 3.35–3.55 (m, 2H, 3-H, 4-H), 4.55 (s, 2H, -OH).

From natural (+)-tartaric acid: (3*R*,4*R*)-(+)-**4** (R: CH_2Ph): yield 70%; m.p. 196–197°C; lit.[6] m.p. 196–198°C; $[\alpha]_D$ +135 (c 1.0, MeOH).

From unnatural (−)-tartaric acid: (3*S*,4*S*)-(−)-**4** (R: CH_2Ph): yield 67%; m.p. 197–198°C; $[\alpha]_D$ −135 (c 1.0, MeOH); IR (KBr): 1710, 2882, 3020, 3286br; NMR (DMSO-d_6): 4.38 (d, 2H, 3-H, 4-H, J=4.8 Hz), 4.52, 4.56 (m, 2H, (m, 2H, PhCH_2-, diastereotopic, ^{2}J=12.5 Hz), 6.27 (d, 2H, -OH, J=5.4 Hz), 7.20–7.39 (m, 5H, ArH); MS, m/e (rel. abundance): 221 (M^+, 30%), 91 ($C_7H_7^+$, 100%).

N-Substituted 3,4-pyrrolidinediols **5**

Imide (10 mmol) in dry THF (30 ml) was added to the stirred slurry of $NaBH_4$ (2.05 g, 54 mmol) in THF (30 ml) in a three-necked flask equipped with a reflux condenser, a mechanical stirrer and a dropping funnel. Iodine (6.1 g, 24 mmol) in THF (60 ml) was added under N_2 atmosphere at 0°C for 2.5 h. The mixture was refluxed for 6 h, then cooled to 0°C and the excess of hydride was carefully decomposed with 3 N HCl (ca. 10 ml). After the gas evolution ceased, the mixture was neutralized with 3 N NaOH (26 ml). The organic layer was separated and the aqueous layer was extracted with ether (3×20 ml). The combined organic phase was washed with water, brine and dried over anh. Na_2SO_4. The solvent was evaporated, the crude product was dissolved in methanol (30 ml) and 12 N HCl (2.5 ml) was added. After the exothermic reaction, methanol was distilled off and again the mixture was diluted with methanol (30 ml), which was also removed. This methanol addition and evaporation was repeated until no borate ester was present in the distillate (no green flame, when burned). The residue was treated with a solution of KOH (0.5 g) in methanol (25 ml) and anh. K_2CO_3 (35 g) and finally, methanol was evaporated to dryness. Thus obtained solid material was extracted continuously with ether. The crude product left after the solvent removal was recrystallized from hexane (R: $C_{12}H_{25}$) or ethyl acetate (R: CH_2Ph) to give pure **5**.

From (3*R*,4*R*)-(+)-**4** (R: $C_{12}H_{25}$): (3*S*,4*S*)-(+)-**5** (R: $C_{12}H_{25}$); yield 62%; m.p. 70.5–71.5°C; $[\alpha]_D$ +15 (c 1.0, MeOH).

From (3*S*,4*S*)-(−)-**4** (R: $C_{12}H_{25}$): (3*R*,4*R*)-(−)-**5** (R: $C_{12}H_{25}$); yield 65%; m.p. 70–71.5°C; $[\alpha]_D$ −15 (c 1.0, MeOH).

IR (film): 2856, 2928, 3308br; NMR ($CDCl_3$): 0.83 (t, 3H, J=5 Hz, -CH_3), 1.22 (s, 18H, -$(CH_2)_9$-), 1.63 (bs, 2H, -CH_2CH_2N=), 2.42, 2.50 (m, AB system when decoupled from the signal at 1.6 ppm, 2H, -CH_2CH_2N=, diastereotopic, ^{2}J=11.7 Hz), 2.57 (dd, 2H, 2-H, 5-H, ^{2}J=10.2 Hz, ^{3}J=3.8 Hz), 2.97 (m, 2H, 2-H, 5-H, ^{2}J=10.2 Hz, ^{3}J=5.9 Hz), 4.12 (bs, 2H, 3-H, 4-H), 5.27 (s, 2H, -OH).

From (3*R*,4*R*)-(+)-**4** (R: CH_2Ph): (3*S*,4*S*)-(+)-**5** (R: CH_2Ph); yield 70%; m.p. 99–100°C; lit.[6] m.p. 100°C; $[\alpha]_D$ +32.5 (c 1.0, MeOH); lit. [6] $[\alpha]_D$ +32.4 (c 4.2, MeOH).

From (3*S*,4*S*)-(−)-**4** (R: CH_2Ph): (3*R*,4*R*)-(−)-**5** (R: CH_2Ph); yield 67%; m.p. 98–99°C; $[\alpha]_D$ −32.5 (c 1.0, MeOH); IR (KBr): 2808, 2930, 3018, 3437br; NMR ($CDCl_3$): 2.40 (dd, 2H, 2-H, 5-H, ^{2}J=10.2 Hz, ^{3}J=3.8 Hz), 2.87 (dd, 2H, 2-H, 5-H, ^{2}J=10.2 Hz, ^{3}J=4.0 Hz), 3.49–3.62 (m, 2H, PhCH_2-, diastereotopic, ^{2}J=12.6 Hz); 4.02 (t, 2H, 3-H, 4-H, J=4.3 Hz), 4.27 (s, 2H, -OH); 7.23 (s, 5H, ArH).

(S,S)-3,4-Tetrahydrofuranediol **6**

(+)-Diethyl tartrate dissolved in diisopropylethylamine was reacted with methoxymethyl chloride at room temperature for two days. The mixture diluted with ethyl acetate was washed with water, brine, dried over anh. K_2CO_3, and evaporated. Thus obtained product (98% pure by GC) was directly reduced with LAH in dry THF to give (*S,S*)-2,3-bis(methoxymethoxy)butane-1,4-diol, recrystallized

from the toluene–hexane mixture, m.p. 63°C; lit.[19] m.p. 62–63°C; $[\alpha]_D$ −5 (c 1.0, MeOH); lit.[19] $[\alpha]_D$ −7.7 (c 3.37, MeOH).

To a solution of (*S,S*)-2,3-bis(methoxymethoxy)butane-1,4-diol (1.2 g, 5.7 mmol) and triphenylphosphine (1.8 g, 6.8 mmol) in dry benzene (15 ml) DEAD (1.06 ml, 6.84 mmol) was added dropwise during 30 min. and the mixture was stirred for 24 h at room temperature. Then, the solvent was evaporated and the residue was treated with the hexane–ether mixture (1:1) and left in a refrigerator overnight. The crystalline precipitate was filtered off and the filtrate was purified on a chromatography column filled with silica gel. (*S,S*)-3,4-Bis(methoxymethoxy)tetrahydrofurane was obtained in 93% yield. Oil; GC purity over 98%; R_f 0.49 (t-BuOMe–hexane–$CHCl_3$, 4:4:1), $[\alpha]_D$ −25 (c 1.0, MeOH); IR (film): 1032, 1153, 2891, 2948; NMR ($CDCl_3$): 3.38 (s, 6H, -OCH_3), 3.81 (dd, 2H, 2-H, 5-H, ^2J=9.8 Hz, ^3J=2.4 Hz), 3.99 (dd, 2H, 2-H, 5-H, ^2J=9.8 Hz, ^3J=4.2 Hz), 4.22 (dd, 2H, 3-H, 4-H J=2 and 3.5 Hz), 4.60–4.67 (m, 2H, -O*C*H_2O-, diastereotopic, ^2J=12.6 Hz); MS, m/e (rel. abundance): 69 (100%), 57 (42%), 42 (54%), 29 (63%).

Both methoxymethyl protecting groups were deblocked by adding 12 N HCl (1.05 ml) to the above product (0.95 g) in methanol (3 ml) followed by evaporation of all volatile substances in vacuo at room temperature. Thus obtained oil was taken into chloroform, dried over anh. K_2CO_3, and the solvent removal furnished the known diol (*S,S*)-**6** of satisfactory purity (NMR) in 85% yield. IR (film): 978, 1085, 2879, 2945, 3325br; NMR ($CDCl_3$): 3.75 (br d, 2H, 2-H, 5-H, ^2J=10 Hz), 4.10 (dd, 2H, 2-H, 5-H, ^2J=10 Hz, ^3J=4 Hz), 4.19 (s, 2H -OH), 4.25 (m, 2H, 3-H, 4-H).

3,4-Diamino-1-dodecylpyrrolidines **2** *R:* $C_{12}H_{25}$

To a magnetically stirred solution of (3*S*,4*S*)-(+)-**5** (R: $C_{12}H_{25}$) (0.50 g, 1.84 mmol) and triphenylphosphine (1.26 g, 4.79 mmol) dissolved in dry benzene (12 ml), a solution of 1.8 M azidoic acid in benzene (2.7 ml, 4.8 mmol) was added dropwise, and then DEAD (0.96 g, 5.52 mmol) in dry benzene (8 ml) was added gradually at 20°C. The reaction mixture was stirred for 3 h at r.t., the solvent was evaporated (a bath at 40°C), the residue was treated with the hexane–ether mixture (1:1) and left in a refrigerator overnight. The crystalline precipitate was filtered off and the product was purified by chromatography on florisil using hexane–diisopropyl ether–chloroform (100:2.5:2.5) as an eluent. The proper fraction was evaporated (a bath at 40°C) giving pure diazide **7** X: $NC_{12}H_{25}$, 0.472 g, 80% yield. R_f 0.25 (hexane–*i*-Pr_2O–$CHCl_3$, 100:2.5:2.5); IR (film): 2100, 2856, 2932; NMR ($CDCl_3$): 0.86 (t, 3H, J=5 Hz, -CH_3), 1.25 (s, 18H, -$(CH_2)_9$-), 1.90 (bs, 2H, -C$H_2$$CH_2$N=), 2.32–2.50 (m, 2H, -$CH_2CH_2$N=), 2.63 (dd, 2H, 2-H, 5-H, ^2J=10 Hz, ^3J=4 Hz), 3.02 (dd, 2H, 2-H, 5-H, ^2J=10 Hz, ^3J=6 Hz), 3.92 (t, 2H, 3-H, 4-H J=5 Hz).

To a stirred solution of 3,4-diazido-1-dodecylpyrrolidine **7**, X: $NC_{12}H_{25}$ (0.40 g, 1.24 mmol) in ethyl alcohol (5 ml), Pd 10% on charcoal was added (40 mg) and the mixture was hydrogenated at the atmospheric pressure at r.t. for 6 h. The catalyst was filtered off and washed with ethyl alcohol. Alcohol was evaporated and the product dissolved in benzene was dried over KOH (powder). Subsequent evaporation gave the proper product as a semicrystalline material, 0.314 g, 94% yield. Analytical sample was obtained after chromatography on silica gel. R_f 0.30 (MeOH, aq. ammonia, 20:1 v/v).

From (3*S*,4*S*)-(+)-**5**: (3*R*,4*R*)-(−)-**2** (R: $C_{12}H_{25}$); $[\alpha]_D$ −14 (c 1.0, MeOH).

From (3*R*,4*R*)-(−)-**5**: (3*S*,4*S*)-(+)-**2** (R: $C_{12}H_{25}$) $[\alpha]_D$ +14 (c 1.0, MeOH).

IR (KBr): 1600, 2850, 2920, 3162br, 3290; NMR ($CDCl_3$): 0.86 (t, 3H, J=5 Hz, -CH_3), 1.21 (s, 18H, -$(CH_2)_9$-), 1.63 (bs, 2H, -C$H_2$$CH_2$N=), 1.95–2.47 (m, 8H, -$CH_2CH_2$N=, 3-H, 4-H, -$NH_2$), 2.80–3.07 (m, 4H, 2-H, 5-H).

Derivatives of **2** *R:* $C_{12}H_{25}$

Diacetamides

Diamine **2** (R: $C_{12}H_{25}$) (100 mg, 0.37 mmol), triethylamine (0.12 ml, 0.9 mmol) and 4-dimethylaminopyridine (2.3 mg, 5% mol) in methylene dichloride (2.5 ml) were treated with acetic anhydride (0.08 ml, 0.9 mmol) and left at r.t. for 24 h. The solution was washed with water, dried over

anh. Na_2SO_4. After evaporation, the product was recrystallized from the hexane–benzene mixture (3:1).

From (3*R*,4*R*)-(−)-**2** (R: $C_{12}H_{25}$): m.p. 189.5–190°C; $[\alpha]_D$ −17.5 (c 0.46, MeOH); Anal. for $C_{20}H_{39}N_3O_2$ (353.5) calcd. C 67.95, H 11.12, N 11.89, found C 68.08, H 11.30, N 12.10.

From (3*S*,4*S*)-(+)-**2** (R: $C_{12}H_{25}$): m.p. 191°C; $[\alpha]_D$ +17.5 (c 0.86, MeOH); Anal. for $C_{20}H_{39}N_3O_2$ (353.5) calcd. C 67.95, H 11.12, N 11.89, found C 68.12, H 11.43, N 11.95.

Schiff bases

Diamine **2** R: $C_{12}H_{25}$ (100 mg, 0.37 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (195 mg, 0.82 mmol) were refluxed in abs. ethanol for 1.5 h. Alcohol was evaporated and oily, yellow product was obtained after chromatography on florisil. R_f 0.61 (silica gel, hexane–*i*-Pr_2O–$CHCl_3$, 7:1.5:1.5).

From (3*R*,4*R*)-(−)-**2** (R: $C_{12}H_{25}$): 44% yield; $[\alpha]_D$ −260 (c 1.03, CCl_4).

From (3*S*,4*S*)-(+)-**2** (R: $C_{12}H_{25}$): 36% yield; $[\alpha]_D$ +259 (c 0.94, CCl_4).

IR (film): 1628, 2856, 2928, 3492; NMR ($CDCl_3$): 0.88 (t, 3H, J=5 Hz, -CH_3), 1.26 (s, 38H, -$C(CH_3)_3$, -$(CH_2)_{10}$-), 1.46 (s, 18H, -$C(CH_3)_3$), 2.45–2.75 (m, -CH_2N=), 3.07 (m, 4H, 2-H, 5-H), 4.02 (m, 2H, 3-H, 4-H), 7.10 (d, 2H, J=2.5 Hz, ArH), 7.45 (d, 2H, J=2.5 Hz, ArH), 8.35 (s, 2H, -N=CH-), 13.50 (br s, 2H, -OH).

Diphthalimides

Diamine **2** R: $C_{12}H_{25}$ (100 mg, 0.37 mmol) and N-(ethoxycarbonyl)phthalimide (179 mg, 0.80 mmol) dissolved in dry acetonitrile (2.5 ml) were left over anh. K_2CO_3 at r.t. for 24 h. After evaporation, the product was recrystallized twice from the hexane–benzene mixture (3:1).

M.p. 110–111°C; IR (KBr): 720, 1384, 1705, 2852, 2921; NMR ($CDCl_3$): 0.88 (t, 3H, J=6.5 Hz, -CH_3), 1.26 (s, 18H, -$(CH_2)_9$-), 1.57 (5 lines, 2H, -CH_2CH_2N=, J=7.2 Hz), 2.45–2.78 (m, -CH_2CH_2N=), 3.13 (t, 2H, 2-H, 5-H, J=7.7 Hz), 3.35 (t, 2H, 2-H, 5-H, J=7.5 Hz), 5.46 (t, 2H, 3-H, 4-H, J=6.2 Hz), 7.74 (m, 10H, ArH); UV (1 mm cell, 1.4×10^{-4} M, MeCN): λ_{max}=220 nm, $\epsilon=7.6\times10^4$.

3,4-Diamino-1-benzylpyrrolidines **2**, *R: CH_2Ph and (*R,R*)-3,4-diaminotetrahydrofuran* **3**

A solution of DEAD (1.98 g, 11.4 mmol) in dry benzene (10 ml) was added dropwise with stirring and external cooling (0–2°C) to a solution of triphenylphosphine (3.12 g, 11.9 mmol) in dry benzene (35 ml) under N_2. Then, a solution of 1.43 M azidoic acid in benzene (7.95 ml, 11.4 mmol) was added dropwise at 0°C. To this solution, **5** (R: CH_2Ph) (1.0 g, 5.2 mmol) was added in one portion and the reaction mixture was stirred for 3 h at r.t. The solvent was partially evaporated (a bath at 30°C) and product was isolated by filtration through a column with silica gel using hexane–diisopropyl ether–chloroform (100:2.5:2.5) as an eluent. The proper fraction was evaporated (a bath at 40°C) giving pure diazide **7** (X: NCH_2Ph), 0.910 g, 72% yield. R_f 0.36 (hexane–*i*-Pr_2O–$CHCl_3$, 4:1:1); IR (film): 2099, 2802, 2922; NMR ($CDCl_3$): 2.63 (dd, 2H, 2-H, 5-H, ^{2}J=10.5 Hz, ^{3}J=4.0 Hz), 3.00 (m, 2H, 2-H, 5-H, ^{2}J=10.5 Hz, ^{3}J=5.5 Hz), 3.68 (m, 2H, PhCH_2-, diastereotopic, ^{2}J=12.6 Hz), 3.89 (t, 2H, 3-H, 4-H J=5 Hz), 7.32 (s, 5H, ArH).

Analogously, the diol (*S,S*)-**6** dissolved in dry DMF (20 ml) was added to the preformed betaine giving the respective diazide **7** (X: O) in 54% yield. R_f 0.31 (hexane–*i*-Pr_2O–$CHCl_3$, 4:1:1); IR (film): 2102, 2878, 2954; NMR ($CDCl_3$): 2.82 (dd, 2H, 3-H, 4-H J=2.0 and 7.8 Hz), 4.01–4.11 (m, 4H, 2-H, 5-H).

Thus obtained diazides **7**, X: NCH_2Ph and X: O were hydrogenated as described above for **7**, X: $NC_{12}H_{25}$ during 1 and 3 h, respectively.

From (3*S*,4*S*)-(+)-**5**: (3*R*,4*R*)-(−)-**2** (R: CH_2Ph); yield 93%; $[\alpha]_D$ −15 (c 1.0, MeOH).

From (3*R*,4*R*)-(−)-**5**: (3*S*,4*S*)-(+)-**2**. (R: CH_2Ph); yield 90%;$[\alpha]_D$ +15 (c 1.0, MeOH).

R_f 0.37 (MeOH, aq. ammonia, 20:1 v/v); IR (film): 1602, 2794, 2912, 3027, 3349; NMR ($CDCl_3$): 1.63 (br s, 4H, -NH_2), 2.15–2.35 (m, 2H, 3-H, 4-H), 2.90 and 3.05 (two m, 2×2H, 2-H, 5-H), 3.57 and 3.63 (m, AB system, 2H, PhCH_2-, diastereotopic, ^{2}J=12.3 Hz), 7.29 (s, 5H, ArH); MS, m/e (rel.

abundance): 191 (M^+, 1.0%), 174 (M^+-NH_3, 25%), 149 (M^+-42, 35%), 91 ($C_7H_7^+$, 100%), 42 ($CH_2=N=CH_2^+$, 66%).

From (3*S*,4*S*)-**6**: (3*R*,4*R*)-(−)-**3**; yield 57%; R_f 0.31 (MeOH, aq. ammonia, 20:1 v/v); $[\alpha]_D$ −32 (c 0.63, MeOH); IR (film): 1603, 2870, 2933, 3027, 3350; NMR ($CDCl_3$): 1.44 (br s, 4H, -NH_2), 3.15–3.22 (m, 2H, 3-H, 4-H), 3.49 (m, 2H, 2-H, 5-H), 4.09 (dd, 2H, 2-H, 5-H, J=5.2 and 8.9 Hz); MS, m/e (rel. abundance): 102 (M^+, 0.34%), 60 (M^+-42, 79%), 43 (100%), 42 (34%), 30 (21%).

Diphthalimide

Diamine (3*R*,4*R*)-(−)-**3** was treated with N-(ethoxycarbonyl)phthalimide as described above for **2** R: $C_{12}H_{25}$ and the product was recrystallized from the hexane–benzene mixture (3:1). M.p. 228–229°C; IR (KBr): 719, 1386, 1707, 2889, 2939, 3057; NMR ($CDCl_3$): 4.23 (dd, 2H, 2-H, 5-H, ^{2}J=8.9 Hz, ^{3}J=7.9 Hz), 4.38 (t, 2H, 2-H, 5-H, ^{2}J=8.9 Hz, ^{3}J=8.8 Hz), 5.47 (t, 2H, 3-H, 4-H, J=7.9 and 8.8 Hz), 7.76 (m, 10H, ArH); UV (1 mm cell, 1.4×10^{-4} M, MeCN): $\lambda_{max.}$=220 nm, $\epsilon=8.0\times10^4$; Anal. for $C_{20}H_{14}N_2O_5$ (362.3) calcd. C 66.30, H 3.89, N 7.73, found C 66.44, H 3.96, N 7.85.

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