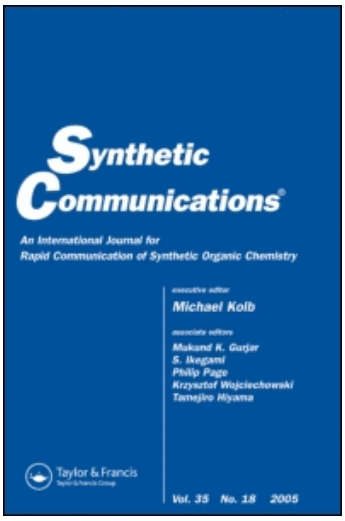

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Simple Synthesis of Enantiomerically Pure C_2-Symmetric Bisoxazolidines from Amino Alcohols and Formaldehyde

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SIMPLE SYNTHESIS OF ENANTIOMERICALLY PURE C_2-SYMMETRIC BISOXAZOLIDINES FROM AMINO ALCOHOLS AND FORMALDEHYDE

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Abstract: Treatment of chiral amino alcohols **1** with an excess of formaldehyde followed by reaction with NaOH at room temperature provides optically active C_2-symmetric *N,N'*-methylenebisoxazolidines **2** in high yield.

Oxazolidines have been known for several years and have received considerable attention in organic synthesis.[1,2] They can be used as carbon transfer agents[3] and serve as masked aldehydes in which the carbonyl moiety is protected in a cyclic array.[4] Enantiomerically pure oxazolidines are of high value for asymmetric synthesis due to their stability, ease of formation and cleavage and stereochemistry-directing properties.[5,6,7]

Structures, syntheses and reactions of oxazolidines have profoundly been discussed by Bergmann.[8] They are usually obtained by condensation of carbonyl compounds with amino alcohols in a 1:1 ratio. With complex ketones, this condensation reaction requires acceleration by traces of iodine[9] or sodium cyanide[10] as catalyst. Smooth condensations have been observed in reactions of ethylenimine with aliphatic aldehydes.[11] Attempts to reduce oxazoles and

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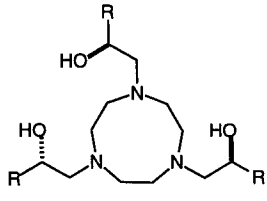
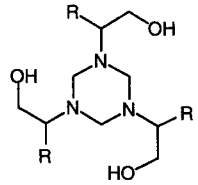
oxazolines to the corresponding oxazolidines have been unsuccessful.[12] Amino polyhydric alcohol, bearing one amino and two hydroxy groups, reacts with one equivalent of aldehyde to give the expected oxazolidine. With two equivalents, substituted 1-aza-3,7-dioxabicyclo[3.3.0]octanes are formed.[13]

Being interested in the application of cyclic triamines, such as chiral 1,4,7-triazacyclononanes (TACN) as ligands in asymmetric catalysis,[14] we decided to investigate the potential of the structurally related 1,3,5-triazacyclohexanes (TACs), having a central core of smaller size.



TACN



TAC

The existence of TACs of the type depicted above having hydroxyethyl-substituents (here: R = H) has been reported in the literature,[15] and spectroscopic data revealed the strong tendency of these compounds to depolymerize giving three molecules of simple oxazolidines. We now wondered if the use of chiral amino alcohols with appropriate substituents would lead to enantiomerically pure TACs with C_3-symmetry.

At first, we chose *(1S,2R)*-1-amino-2-indanol (**1a**) as starting material and reacted it in an aqueous solution with an excess of formaldehyde in the presence of NaOH following a literature protocol for the synthesis of simple TACs without hydroxyl-bearing substituents.[16] A smooth reaction occurred, but the product was not the desired TAC derivative, but *N,N'*-methylenebisoxazolidine **2a** which was isolated as the sole product in 87% yield. ^1H and ^{13}C NMR spectra indicated the high symmetry of **2a**, and its molecular structure was confirmed by X-ray structure analysis (Figure 1).

Using the same reaction conditions, various optically active *N,N'*-methylenebisoxazolidines were obtained in good yields and the most significant results are summarized in the Table.

N,N'-Methylenebisoxazolidines of type **2** are known compounds which have already been used in synthesis[18] and which can show interesting biological activities.[19]

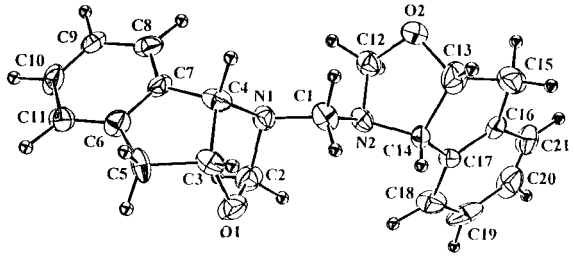


Figure 1. Molecular structure of **2a** in the solid state as determined by X-ray crystal structure analysis.[17]

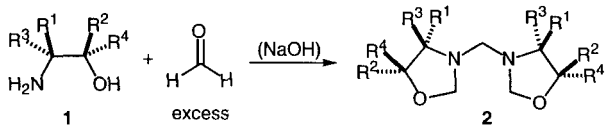


Table. Bis(oxazolidine)s **2** prepared from amino alcohols and formaldehyde

Entry	R^1	R^2	R^3	R^4	**1**	**2** (yields in %)
1			H H	H H	**1a**	**2a** (87)
2	H	H			**1b**	**2b** (89)
3	t-Bu	H	H	H	**1c**	**2c** (86)
4	i-Pr	H	H	H	**1d**	**2d** (84)
5	Bn	H	H	H	**1e**	**2e** (93)
6	H	H	Ph	H	**1f**	**2f** (56) **2f'** (29)
7	Me	Ph	H	H	**1g**	**2g** (86)

From the reaction of (*R*)-phenylglycinol (**1f**) and formaldehyde two products **2f** and **2f'** were obtained in 56% and 29% yields, respectively (entry 6). The molecular structure of **2f'** was determined by X-ray structure analysis, and it is shown in Figure 2. Apparently, condensation with three equivalents of formaldehyde led to a bicyclic bridged structure with three methylenes connecting two amino alcohols.

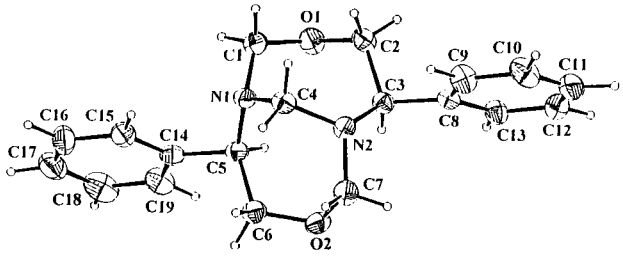


Figure 2. Molecular structure of **2f'** in the solid state as determined by X-ray crystal structure analysis.[17]

An unsubstituted 1,6-diaza-3,8-dioxabicyclo[4.4.1]undecane of type **2f'** has been obtained earlier as a byproduct from the condensation of monoethanolamine with formaldehyde, and its structure was deduced on the basis of its NMR spectra.[20]

L-Alaninol (**1h**) also reacted under the standard conditions but gave the corresponding product **2h** (R^1 = Me; R^2, R^3, R^4 = H) only with unsatisfactory purity. The structure of **2h** was inferred by mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy .

Attempts to optimize the reaction conditions revealed that shorter reaction times were possible (complete conversion of **2c** and **2d** after 3 h) and that NaOH was not essential for high product yield (for **2c**: 80% yield after 3 h).

In summary, we have not been able to obtain the desired C_3-symmetric TAC derivatives but the simple procedure for the synthesis of optically active C_2-symmetric *N,N'*-methylenebis-oxazolidines from amino alcohols and formaldehyde allows rapid access to compounds which could also be of interest as ligands in asymmetric catalysis.

Experimental

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR spectrometer (300 MHz, 75 MHz). Tetramethylsilane (δ = 0 ppm) was used as internal standard in ^{1}H NMR spectra. Mass spectra were recorded on a Varian MAT 212/Finnigan SSQ 7000 at an ionizing voltage of 70 eV. Infrared spectra were obtained with a Perkin-Elmer 1760 spetrometer. Elemental analyses were recorded on Heraus CHN-O-Rapid element analyzer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Merck silica gel 60F

sheets were used for analytical thin-layer chromatography. Column chromatography was performed on SiO_2 (230-400 mesh); gradients of EtOAc and *n*-hexane were used as eluents. **1a** and **1b** were obtained from Sepracor. **1g** is commercially available from Aldrich. Amino alcohols **1c-g** and **1h** were prepared from the corresponding amino acids using a literature protocol.[21]

General Procedure for the Synthesis of N,N'-Methylenebisoxazolidines **2**:

To a solution of formaldehyde in water (37%, 0.72 mL, 8.88 mmol) was added amino alcohol **1** (3 mmol) at room temperature (20 °C). The resulting solution was stirred for 5 min and then NaOH (144 mg, 4.8 mmol) was added. After stirring of the mixture for 12 h at room temperature, 10 mL of ether were added. The organic layer was separated, washed with H_2O (5 mL x 2), brine (5 mL x 2) and dried over Na_2SO_4. After filtration, the organic solvent was removed *in vacuo* and the product was purified by column chromatography (silica-gel) or by recrystallization from CH_2Cl_2/hexane, affording analytically pure *N,N'*-methylenebis-oxazolidines **2**.

(3a*S*,3'a*S*,8a*R*,8'a*R*)-3-(3-aza-1-oxacyclopentanindan-3-yl)methylindano-[1,2-*d*]oxazolidine (2a).

Yield: 438 mg (87%); mp > 220 °C; $[\alpha]^{20}_D = -22.0°$ (*c* = 1.0, $CHCl_3$); TLC [EtOAc/hexane (1:2)] R_f = 0.2; ^{1}H NMR ($CDCl_3$/TMS): δ 3.11-3.26 (m, 4 H), 3.64 (s, 2 H), 3.97 (d, 2 H, *J* = 6.5 Hz), 4.62 (d, 2 H, *J* = 6.5 Hz), 4.79 (m, 2 H), 5.20 (d, 2 H, *J* = 5.4 Hz), 7.17-7.25 (m, 6 H), 7.45-7.51 (m, 2 H); ^{13}C NMR ($CDCl_3$/TMS): δ 39.3 (x 2), 71.4 (x 2), 75.1, 76.6 (x 2), 84.3 (x 2), 124.7 (x 2), 125.7 (x 2), 127.1 (x 2), 128.3 (x 2), 140.8 (x 2), 142.3 (x 2); IR (cm^{-1}): 3016, 2923, 1459, 1344; MS *m/z* (%): 174 (38), 161 (49), 144 (100), 132 (94); Anal. calcd for $C_{21}H_{22}N_2O_2$: C, 75.42%; H, 6.63%; N, 8.37%. Found: C, 75.41%; H, 6.97%; N, 8.34%.

(3a*R*,3'a*R*,8a*S*,8'a*S*)-3-(3-aza-1-oxacyclopentanindan-3-yl)methylindano[1,2-*d*]oxazolidine (2b).

Yield: 445 mg (89%); mp > 220 °C; $[\alpha]^{20}_D = +29.8°$ (*c* = 0.6, $CHCl_3$); TLC [EtOAc/hexane (1:2)] R_f = 0.2; ^{1}H NMR ($CDCl_3$/TMS): δ 3.11-3.26 (m, 4 H), 3.67 (s, 2 H), 3.99 (d, 2 H, *J*

= 6.5 Hz), 4.64 (d, 2 H, J = 6.5 Hz), 4.79 (m, 2 H), 5.20 (d, 2 H, J = 5.4 Hz), 7.19-7.26 (m, 6 H), 7.46-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$/TMS): δ 39.4 (x 2), 71.5 (x 2), 75.1, 76.6 (x 2), 84.4 (x 2), 124.8 (x 2), 125.7 (x 2), 127.2 (x 2), 128.3 (x 2), 140.9 (x 2), 142.4 (x 2); IR (cm^{-1}): 3016, 2923, 1459, 1344; MS *m/z* (%):174 (100), 144 (16), 132 (11), 115 (18); Anal. calcd for $C_{21}H_{22}N_2O_2$: C, 75.42%; H, 6.63%; N, 8.37%. Found: C, 75.33%; H, 6.61%; N, 8.34%.

1,1-Bis[(*S*)-4-*tert*-butyloxazolidin-3-yl]methane (2c).

Yield: 347 mg (86%); mp 59-61 °C; $[\alpha]^{20}_D$ = +48.2° (c = 1.0, $CHCl_3$); TLC [EtOAc/hexane (2:8)] R_f = 0.2; ^{1}H NMR ($CDCl_3$/TMS): δ 0.88 (s, 18 H), 2.58 (dd, 2 H, J = 7.8, 7.8 Hz), 3.32 (s, 2 H), 3.47 (dd, 2 H, J = 8.4, 7.8 Hz), 3.91 (dd, 2 H, J = 8.4, 8.4 Hz), 4.03 (d, 2 H, J = 6.4 Hz), 4.88 (d, 2 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$/TMS): δ 26.2 (x 6), 34.2 (x 2), 66.2 (x 2), 70.2 (x 2), 78.3, 84.9 (x 2); IR (cm^{-1}): 2953, 1477, 1367, 1136; MS *m/z* (%): 240 (3), 225 (0.6), 182 (6), 142 (100); Anal. calcd for $C_{15}H_{30}N_2O_2$: C, 66.62%; H, 11.18%; N, 10.35%. Found: C, 66.53%; H, 11.19%; N, 10.11%.

1,1-Bis[(*S*)-4-isopropyloxazolidin-3-yl]methane (2d).

Yield: 305 mg (84%); oil; $[\alpha]^{20}_D$ = +50.5° (c = 1.0, $CHCl_3$); TLC [EtOAc/hexane (1:6)] R_f = 0.2; ^{1}H NMR ($CDCl_3$/TMS): δ 0.84 (d, 6 H, J = 6.7 Hz), 0.98 (d, 6 H, J = 6.7 Hz), 1.57 (m, 2 H), 1.52-1.64 (m, 2 H), 3.29 (s, 2 H), 3.38 (dd, 2 H, J = 8.4, 6.0 Hz), 3.92 (dd, 2 H, J = 8.4, 7.4 Hz), 4.15 (d, 2 H, J = 6.4 Hz), 4.73 (d, 2 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$/TMS): δ 18.7 (x 2), 20.1 (x 2), 31.6 (x 2), 68.0 (x 2), 68.1 (x 2), 76.7 (x 2), 84.4; IR (cm^{-1}): 2958, 1468, 1384, 1155; MS *m/z* (%): 128 (100), 113 (3), 100 (15), 72 (38); Anal. calcd for $C_{13}H_{26}N_2O_2$: C, 64.42%; H, 10.81%; N, 11.55%. Found: C, 64.41%; H, 10.91%; N, 11.71%.

1,1-Bis[(*S*)-4-phenylmethyloxazolidin-3-yl]methane (2e).

Yield: 473 mg (93%); oil; $[\alpha]^{20}_D$ = −8.7° (c = 1.6, $CHCl_3$); TLC [EtOAc/hexane (4:6)] R_f = 0.3; ^{1}H NMR ($CDCl_3$/TMS): δ 2.54 (dd, 2 H, J = 7.4, 7.4 Hz), 2.77 (dd, 2 H, J = 7.4, 7.4 Hz), 3.19-3.28 (m, 4 H), 3.38 (dd, 2 H, J = 8.0, 5.3 Hz), 3.81 (dd, 2 H, J = 8.0, 7.4 Hz),

4.32 (d, 2 H, J = 5.7 Hz), 4.37 (d, 2 H, J = 5.7 Hz), 7.14-7.29 (m, 10 H); ^{13}C NMR ($CDCl_3$/TMS): δ 39.9 (x 2), 62.9 (x 2), 69.3 (x 2), 76.6, 84.6 (x 2), 126.3 (x 2), 128.2 (x 4), 129.1 (x 4), 138.8 (x 2); IR (cm^{-1}): 3026, 2933, 1454, 1175; MS *m/z* (%): 338 (M^+, 1), 247 (4), 176 (100), 146 (4); Anal. calcd for $C_{21}H_{26}N_2O_2$: C, 74.52%; H, 7.74%; N, 8.27%. Found: C, 74.46%; H, 7.69%; N, 8.53%.

1,1-Bis[(*R*)-4-phenyloxazolidin-3-yl]methane (2f).

Yield: 262 mg (65%); mp 133-135 °C; $[\alpha]^{20}_D$ = −90.5° (*c* = 0.5, $CHCl_3$); TLC [EtOAc/hexane (3:7)] R_f = 0.2; ^{1}H NMR ($CDCl_3$/TMS): δ 3.42 (s, 2 H), 3.60 (dd, 2 H, J = 7.9, 7.9 Hz), 3.82 (dd, 2 H, J = 7.9, 7.1 Hz), 4.20 (dd, 2 H, J = 7.9, 7.1 Hz), 4.40 (d, 2 H, J = 4.1 Hz), 4.80 (d, 2 H, J = 4.1 Hz), 7.22-7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$/TMS): δ 65.1 (x 2), 71.6, 73.7 (x 2), 86.6 (x 2), 127.1 (x 4), 127.6 (x 2), 128.6 (x 4), 139.9 (x 2); IR (cm^{-1}): 3060, 2869, 1453, 1209; MS *m/z* (%): 310 (M^+, 4), 280 (38), 250 (10), 162 (100); HRMS calcd for $C_{21}H_{22}N_2O_2$: 310.1681, found 310.1681.

***(R,R)*-5,10-Diphenyl-1,6-diaza-3,8-dioxabicyclo[4.4.1]-undecane (2f´).**

Yield: 132 mg (29%); mp 189-190 °C; $[\alpha]^{20}_D$ = −154.4° (*c* = 0.6, $CHCl_3$); TLC [EtOAc/hexane (3:7)] R_f = 0.4; ^{1}H NMR ($CDCl_3$/TMS): δ 3.85 (d, 4 H, J = 6.7 Hz), 4.18 (s, 4 H), 4.60 (t, 2 H, J = 6.7 Hz), 4.82 (s, 2 H), 7.24 (tt, 2 H, J = 7.0, 2.0 Hz), 7.31 (t, 4 H, J = 7.0 Hz), 7.39 (dd, 4 H, J = 7.0, 2.0 Hz); ^{13}C NMR ($CDCl_3$/TMS): δ 65.7 (x 2), 71.0, 74.4 (x 2), 86.1 (x 2), 127.3 (x 4), 127.4 (x 2), 128.3 (x 4), 141.4 (x 2); IR (cm^{-1}): 3055, 2908, 1236, 1095; MS *m/z* (%): 310 (M^+, 9), 280 (38), 162 (81), 91 (100); Anal. calcd for $C_{19}H_{22}N_2O_2$: C, 73.52%; H, 7.14%; N, 9.02%. Found: C, 73.46%; H, 7.25%; N, 8.98%.

1,1-Bis[(*4S,5R*)-4-methyl-5-phenyloxazolidin-3-yl]methane (2g).

Yield: 440 mg (86%); mp 101-102 °C; $[\alpha]^{20}_D$ = −60.8° (*c* = 1.7, $CHCl_3$); TLC (EtOAc) R_f = 0.3; ^{1}H NMR ($CDCl_3$/TMS): δ 0.69 (d, 6 H, J = 6.7 Hz), 3.47 (quin, 2 H, J = 6.7 Hz), 3.62 (s, 2 H), 4.52 (d, 2 H, J = 4.7 Hz), 4.91 (d, 2 H, J = 4.7 Hz), 5.08 (d, 2 H, J = 6.7 Hz), 7.22-7.35 (m, 10 H); ^{13}C NMR ($CDCl_3$/TMS): δ 15.3 (x 2), 60.2 (x 2), 72.6, 80.2 (x 2), 85.2 (x 2), 126.4 (x 4), 127.2 (x 2), 128.0 (x 4), 139.6 (x 2); IR (cm^{-1}): 3031, 2877, 1353, 1189;

MS *m/z* (%): 338 (M^+, 0.1), 176 (68), 146 (30), 57 (100); Anal. calcd for $C_{21}H_{26}N_2O_2$: C, 74.52%; H, 7.74%; N, 8.27%. Found: C, 74.30%; H, 7.71%; N, 8.27%.

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