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Short and simple synthesis of chelating bis-ethers and bis-amines in the bicyclo[3.3.1]nonane series

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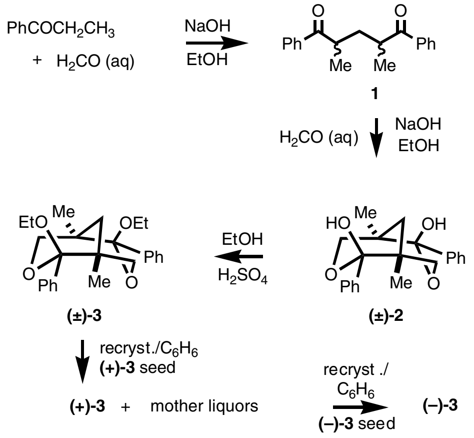
Abstract—A remarkably simple process for the synthesis of a series of rigid bicyclic diethers and diamines is described.

Some years ago Tilichenko et al.[1] described the coupling of propiophenone with 37% aqueous formaldehyde and ethanolic sodium hydroxide to give a 1:1 mixture of diastereomeric ketones **1**. When we carried out the reaction at 70 °C by slow addition (over 45 min) of formalin to a solution of propiophenone and base, a 95% yield of **1** was obtained readily and reproducibly on a 1 mol scale (which requires only a 1-L flask). Further reaction of **1** with formalin in ethanolic sodium hydroxide for 1 h at 50 °C gave after cooling, dilution with ethanol, and filtration of the precipitate essentially pure crystalline bicyclic bis-hemiketal **2** in 55% yield; mp 184–185 °C after recrystallization from C_6H_6 (see Scheme 1). Treatment of **2** with a catalytic amount of concd H_2SO_4 (ca. 2 mol %) in 2:1 EtOH–$CHCl_3$ at reflux gave upon cooling the crystalline ethyl ketal **3** (90% yield from the first two crops, additional after neutralization of H_2SO_4 and further concentration), mp 176–178 °C.[2] Upon slow recrystallization of **3** from benzene, large monoclinic crystals were obtained, which, when individually subjected to measurement of optical rotation, were found invariably to show $[\alpha]_D^{23}$ of either ca. +240 or −240 (in $CHCl_3$ solution). That these crystals were nearly enantiomerically pure was demonstrated by the fact that further recrystallization of either dextrorotatory **3** or levorotatory **3** raised the specific optical rotation only slightly.



Scheme 1. Efficient and simple preparation of the (+)- and (−)-enantiomers of bis-ketal **3**.

The ready availability of racemic **3** in quantity combined with the fact that this rigid molecule undergoes spontaneous resolution by simple crystallization, suggests that this system could be useful for enantioselective synthetic purposes. Crystals of **3** may be described as of the conglomerate type because the crystalline enantiomers are less soluble (and have a higher melting point) than those of the racemate.[3] Multigram quantities of the enantiomers of **3** were easily obtained by various recrystallization techniques. The simplest of these involved the induction of crystallization by seeding of a clear (particle-free), concentrated solution of the racemate in hot benzene with crystals of one of the pure enantiomers, arbitrarily chosen as dextro, although obviously either of the enantiomers could be used. After allowing the solution to cool very slowly to 23 °C, filtration of the crystals afforded (+)-**3** of ca. 90% enantiomeric purity. Recrystallization of this material from benzene afforded crystals of >98% enantiomeric purity; $[\alpha]_D^{23}$ +245 ($CHCl_3$), mp 206–208 °C.[4] The mother liquors were

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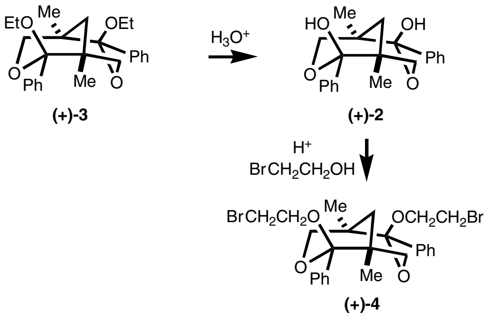
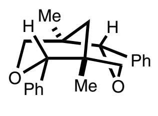
heated to form a clear, particle-free solution and seeded with crystals of (−)-**3**. In this way, enantiomerically pure (−)-**3** was obtained upon cooling and an additional recrystallization. There seems to be no obvious reason why this process should be limited with respect to scale.

The absolute configuration of (+)-**3** was established by X-ray crystallographic analysis of the corresponding bis-2-bromoethylketal, (+)-**4**. The synthesis of this derivative was carried out as follows. Hydrolysis of (+)-**3** using a 1:1:1 mixture acetone–THF–H_2O containing 0.001 vol of concd H_2SO_4 at reflux for 30 min afforded, after addition of Et_3N, concentration under reduced pressure and extractive isolation, 95% of (+)-**2**, $[\alpha]_D^{23}$ +225 ($CHCl_3$). Reaction of (+)-**2** with 2-bromoethanol and CH_3SO_3H in $CHCl_3$ solution provided (+)-**4** as colorless plates, mp 148–149 °C, $[\alpha]_D^{23}$ +170 ($CHCl_3$), the three-dimensional structure and absolute configuration of which followed from the X-ray data[5] (Scheme 2).



Scheme 2. Absolute configurations of (+)-**2**, (+)-**3**, and (+)-**4**.

Treatment of the bis-ethyl ketal (+)-**3** with triethylsilane and a catalytic amount of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 0 °C resulted in rapid reduction to the crystalline bicyclic ether (+)-**5**, $[\alpha]_D^{23}$ +190 ($CHCl_3$), mp 156–158 °C, obtained in >98% yield after sublimation at 140 °C and 20 mmHg. When (+)-**2** was treated with a catalytic amount of *p*-TsOH in CH_2Cl_2 at 23 °C or H_2SO_4 in HOAc at 60 °C for 15 min, it was transformed into the crystalline tricyclic triether **6**, (95%), $[\alpha]_D^{23}$ −175 ($CHCl_3$), the structure of which was confirmed by X-ray crystallographic analysis.[6]



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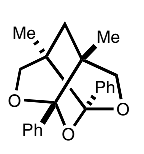

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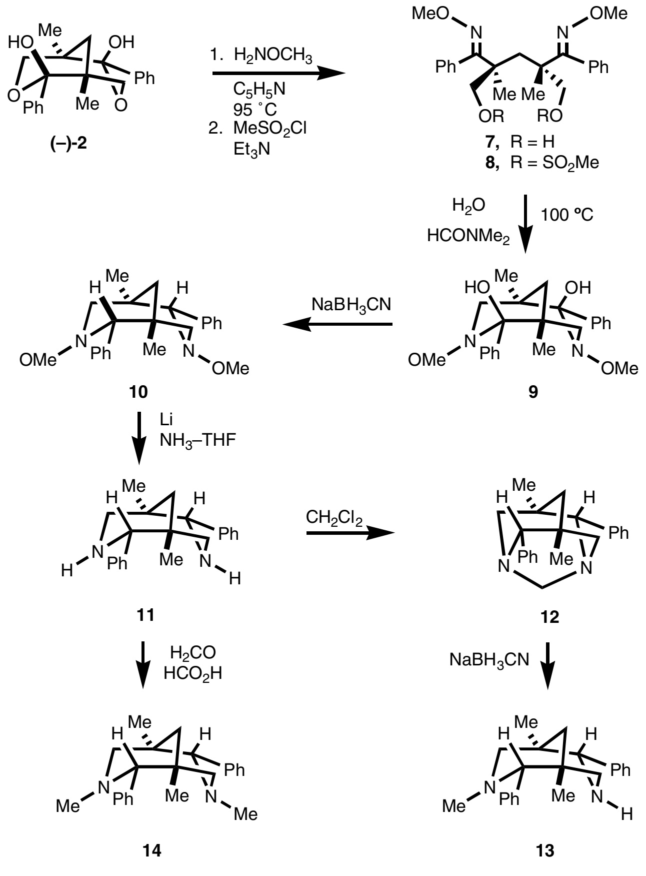
We have taken advantage of the ready availability of (+)- and (−)-**2** to synthesize diamine analogs of the diether **4**.

The chiral diethers and diamines in this series are promising bidentate C_2-symmetric chiral ligands. Bidentate coordination of a metal cation can generate a rigid diazaadamantane structure. Reaction of (−)-**2** (prepared from (−)-**3**) with 3 equiv of $MeONH_2{\cdot}HCl$ in pyridine at 95 °C for 10 h followed by extractive isolation and column chromatography on silica gel (30% EtOAc in hexane for elution) afforded the bis-*O*-methyloxime **7** (colorless oil, $[\alpha]_D^{23}$ −36.6 ($CHCl_3$)) in 90% yield, as outlined in Scheme 3. Reaction of **7** with 2.2 equiv of CH_3SO_2Cl and 2.5 equiv of Et_3N in CH_2Cl_2 at −30 °C for 4 h produced, after extractive isolation, the corresponding dimesylate (**8**) as a solid that was sufficiently pure to use directly in the next step. Upon heating the dimesylate **8** in dimethylformamide with 2 equiv of H_2O and 1 equiv of Et_3N at 100 °C for 12 h, concentration in vacuo, extractive isolation, and filtration through a column of basic alumina using CH_2Cl_2 as solvent, the bis-*N*-methyloxyamino-carbinol **9** was obtained in 70% yield; mp 196–197 °C, $[\alpha]_D^{23}$ −201 ($CHCl_3$). Reduction of **9** with 4 equiv of $NaBH_3CN$ in CH_3OH with gradual addition of 2 N-methanolic HCl at 0 °C for 4 h gave, after removal of methanol under reduced pressure and extractive isolation, the bis-*N*-methoxyamine **10** as a colorless solid, $[\alpha]_D^{23}$ −247 ($CHCl_3$), mp 205–207 °C (99% yield). Addition of a solution of **10** in THF to an excess of Li dissolved in liquid ammonia at reflux and further reaction at −33 °C for 20 min afforded, after quenching of excess Li with isoprene, evaporation of NH_3 and THF, extractive isolation, and column chromatography on silica gel (1:1 EtOAc–hexane for elution), the bicyclic diamine **11** (83%) as colorless needles, $[\alpha]_D^{23}$ −179 ($CHCl_3$). When the diamine **11** was stored in CH_2Cl_2 solution it was gradually transformed into the azaadamantane derivative **12**, mp 77–78 °C,



Scheme 3. Synthesis of chiral C_2-symmetric bis-amines.

$[\alpha]_D^{23}$ +117 ($CHCl_3$). The conversion **11**→**2** was also effected in >99% yield simply by reaction of **11** with 37% aqueous H_2CO. It is noteworthy that the levorotatory **11** gives rise to dextrorotatory **12**. Treatment of **12** with sodium cyanoborohydride followed by methanolic HCl provided the mono-*N*-methyl derivative **13** (>99%) as a thick oil. Bismethylation of **11** with formaldehyde-formic acid produced in >95% yield the diamine **14**.

The pK_a values were measured for the C_2-symmetric diamines **11** and **14** in 9:1 ethanol–H_2O and found to be 8.7 for **11** and 8.5 for **14**. We found the pK_a for sparteine to be 10.7 under the same conditions. The lower basicity (ca. 2 pK units) found for **11** and **14** relative to sparteine is probably due to a combination of the electron-withdrawing inductive effect of the α-phenyl substituent and the large degree of steric screening, which reduces solvation of the monoprotonated ammonium ion.

The remarkably easy access to the chiral bicyclic C_2-symmetric diethers and diamines described herein makes these compounds to be of unusual interest for further studies that are now in progress.

References and notes

1. (a) Tilichenko, M. N.; Astakhova, N. K. *Dokl. Akad. Nauk SSSR* **1950**, *74*, 951–953; (b) Tilichenko, M. N.; Kharchenko, V. G. *Zh. Obshch. Khim.* **1962**, *32*, 1192–1194; (c) Tilichenko, M. N. *Zh. Obshch. Khim.* **1965**, *35*, 440–444.
2. Satisfactory NMR and mass spectral data were obtained for all new compounds.
3. For a compilation of conglomerates and a general discussion, see: Jaques, J.; Collet, A.; Wilen, S. H. *Enantiomers Racemates, and Resolutions*; John Wiley and Sons: NY, 1981, p 43.
4. This mp was measured in a sealed tube. In an unsealed tube, compound sublimes without melting at 170 °C. All optical rotations were measured in $CHCl_3$ ($c = 1.0$–2.0). As expected from conglomerate formation, the mp of the chiral compound was considerably higher than that of the racemate.
5. X-ray data for compound **4**: $C_{25}H_{30}Br_2O_4$; M_r 554.31; plates, crystal size $0.40 \times 0.35 \times 0.10$; space group $P2_12_12_1$; $a = 8.3100(10)$, $b = 10.9260(10)$, $c = 25.694(3)$ Å; V (nm^3) 2332.9(4); $Z = 4$; $D_x = 1.578$; $F(000)$ 1128; Mo K_α radiation; 2θ 5–55°; 6238 measured reflections; 5355 reflections (independent). R_{int} 0.066; wR 0.0420; wR, F^2 (all data) 00705; S 0.7; Max. D/σ (e Å^3) 0.635; Max. D/ρ 0.003. An x-refinement (Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876) gave an x parameter of −0.009(11), indicating the correct absolute configuration. X-ray data have been submitted to the Cambridge Crystallographic Data Centre for compounds **4** and **6**.
6. X-ray data for compound **6**: $C_{21}H_{22}O_3$; M_r 322.39; plates, crystal size $0.65 \times 0.25 \times 0.07$ mm; space group $P2_1$; $a = 9.6680(10)$, $b = 8.3450(10)$; $c = 10.978(2)$ Å; V (nm^3) 852.3(2); $Z = 2$; $D_x = 1.256$; $F(000)$ 344; Mo K_α radiation; 2θ 6–60°; 9766 measured reflections; 4969 reflections (independent); R_{int} 0.062; wR, F^2 (all data) 0.1041; S 0.8; Max. D/σ (e Å^3) 0.168; D/ρ <0.001.