JOC*Note*

Concise Synthesis of 3,7-Dioxa-9-aza-bicyclo[3,3,1]-nonane

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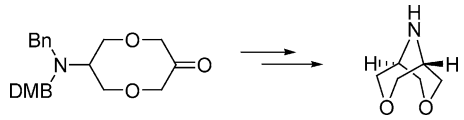
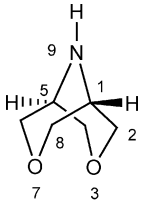


The basicity of an amine has a great impact on physicochemical properties and pharmacokinetics. To attenuate the basicity of morpholine, a bicyclic amine was designed and synthesized with the introduction of an additional β-oxygen. A transannular cyclization and reduction of a bridgehead α-chloro amine functionality produces the topographically unusual amine ($pK_a = 6.7$) in good yield.

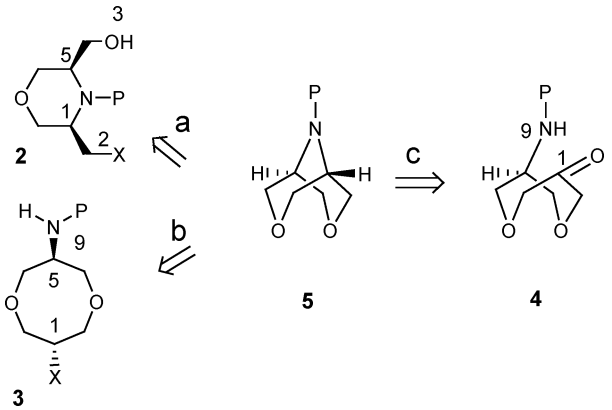
As part of a small molecule drug discovery program, we became interested in evaluating the incorporation of structurally diverse amines as a way to modulate pharmaceutical properties. The basicity of amines[1] has a great impact on physicochemical properties such as aqueous solubility and pharmacokinetics.[2] Among the amines considered, a symmetrical bicyclic amine[3] such as 3,7-dioxa-9-aza-bicyclo[3,3,1]-nonane **1** drew our attention in terms of both attenuated basicity due to the β-oxygen atoms[4] and the steric shielding around nitrogen. However, an extensive literature search revealed that the synthesis of this molecule had not been reported to date. Herein, we report the first synthesis of 3,7-dioxa-9-aza-bicyclo[3,3,1]-nonane **1**.



1

Retrosynthetically, we considered three approaches (Scheme 1). Path a involved formation of the 1,5-cis substituted morpholine derivative **2**, followed by ether bond formation between C2 and O3. However, all attempts to make the C2−O3 bond failed as a result of either the participation of the amino group or incompatibility of the amino protecting groups. Thus, we turned our attention to alternative routes (Scheme 1, paths b and c), which involved formation of an eight-membered ring followed by bicycle formation via transannular cyclization.[5] Although we expected that the proximity of the secondary amine to an electrophilic C1 site in **3** or **4** would allow formation of the desired [3,3,1] bicyclic system, we reasoned that it would be difficult to achieve the anti relationship necessary to make the C1−N9 bond by an S_N2-type displacement (path b). We therefore focused on path c, which involved formation of a bridgehead hemi-aminal followed by reduction.

SCHEME 1. Retrosynthetic Analysis



The synthesis commenced with differential protection of the amino group of amino diol **6** with 2,4-dimethoxybenzyl and benzyl groups (Scheme 2). The selection of the protecting groups was crucial to avoid neighboring group participation in the subsequent ether bond forming step. After investigation of suitable electrophiles for the eight-membered ring formation, the bis-allylic chloride was found to give the best yield of the bis-ether **8**. Oxidative cleavage[6] of the olefin **8**[7] revealed the latent keto group, and subsequent selective deprotection of the dimethoxybenzyl group in **9** under acidic conditions led to the spontaneous formation of the hemi-aminal **10**.

Several attempts were made to reduce the alcohol in **10** to the alkane; however, reaction conditions involving carbocation intermediates such as triethylsilane-TFA[8] were very sluggish, presumably because of the inability to form the bridgehead

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(2) Avdeef, A. *Curr. Top. Med. Chem.* **2001**, *1*, 277.

(3) Alder, R. W. *Tetrahedron* **1990**, *46*, 683.

(4) (a) Perrin, C. L.; Ohta, B. K.; Kuperman, J. *J. Am. Chem. Soc.* **2003**, *125*, 15008. (b) Baeten, A.; De Profit, F.; Geerlings, P. *Chem. Phys. Lett.* **1995**, *235*, 17. (c) Ponec, R.; Girones, X.; Carbo′-Dorca, R. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 564. (d) Graton, J.; Berthelot, M.; Laurence, C. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2130.

(5) (a) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129. (b) Dalgard, J. E.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2713. (c) Ader, T. A.; Champey, C. A.; Kuznetsova, L. V.; Li, T.; Lim, Y.-H.; Rucando, D.; Sieburth, S. M. *Org. Lett.* **2001**, *3*, 2165.

(6) O'Connor, P. D.; Mander, L. N.; McLachlan, M. M. W. *Org. Lett.* **2004**, *6*, 703.

(7) One-pot cleavage procedure using OsO_4−$NaIO_4$ destroyed the dimethoxybenzyl group with further complication on the substrate.

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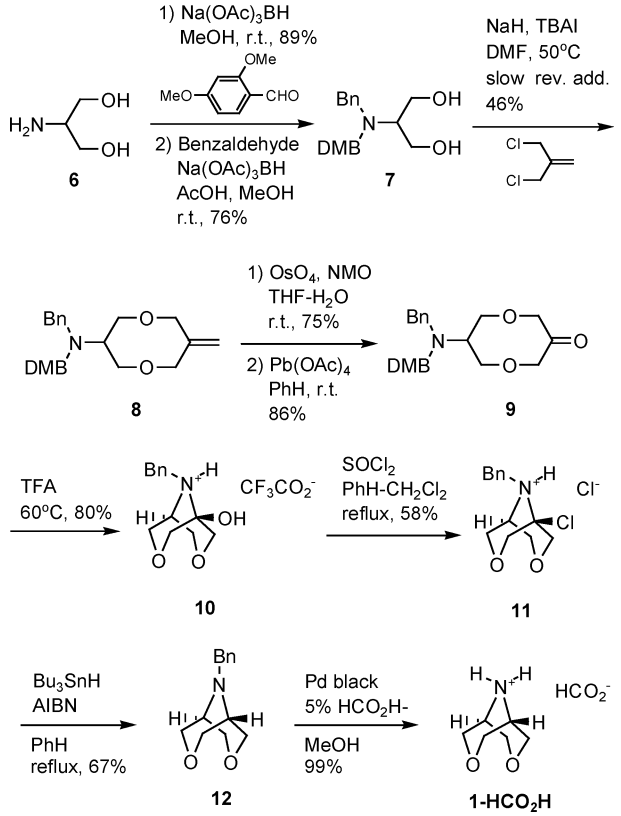
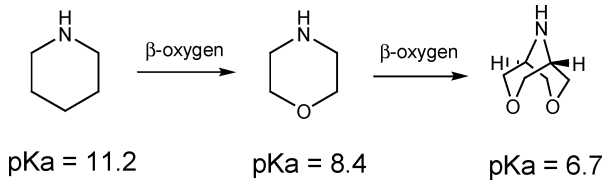
SCHEME 2[a]



[a] DMB = 2,4-dimethoxybenzyl.

SCHEME 3



iminium ion intermediate. Thus, reduction under radical conditions was investigated. The hydroxyl group was converted to chloride **11** using thionyl chloride at reflux,[9] and tributylstannane-mediated reduction[10] of chloride **11** smoothly provided the benzyl-protected amine **12**. The final deprotection was carried out under Pd black−HCO_2H conditions[11] to give **1** as a formic acid salt. The structure was confirmed by both NMR analysis and X-ray crystallography (Supporting Information).

The pK_a of **1** was determined to be 6.7 by standard titration. This attenuation in basicity of 1.7 pK_a units with respect to morpholine (pK_a = 8.4)[12] is consistent with an additive inductive effect of the second β-oxygen to the morpholine backbone in **1** (Scheme 3).

In summary, a synthesis of 3,7-dioxa-9-aza-bicyclo[3,3,1]-nonane involving transannular hemi-aminal formation and radical-mediated reduction of a bridgehead α-chloro amine as key steps has been described.

Experimental Section

2-[Benzyl-(2,4-dimethoxy-benzyl)-amino]-propane-1,3-diol (7). To a solution of **6** (3.0 g, 32.967 mmol) in MeOH (165 mL) was added 2,4-dimethoxybenzaldehyde (5.473 g, 32.967 mmol) at room temperature, and the mixture was stirred for 1 h. $Na(OAc)_3BH$ (9.785 g, 46.154 mmol) was added in one portion. The solution was stirred at room temperature for 5 h and treated with silica gel (27 g). The slurry was concentrated to powder and purified by flash chromatography (5%−15% MeOH (7 N NH_3)/DCM) to give 6.990 g (89%) of the amino diol: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J = 8.2 Hz, 1H), 6.45 (d, J = 2.4 Hz, 1H), 6.42 (dd, J = 2.4, 8.2 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.74 (s, 2H), 3.67 (dd, J = 4.8, 11.2 Hz, 2H), 3.53 (dd, J = 5.1, 11.2 Hz, 2H), 3.06 (br, 3H), 2.72 (quint, J = 2.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 158.6, 130.5, 120.0, 103.9, 98.7, 61.8, 58.7, 55.3, 55.3, 46.0; HRMS (ESI) calcd for $C_{12}H_{20}NO_4$ (M + H) 242.1387, found 242.1387.

To a solution of the amino diol (6.99 g, 29.247 mmol) in DCM was added benzaldehyde (3.41 g, 32.172 mmol) and acetic acid (1.7 mL, 29.247 mmol) at room temperature, and the mixture was stirred for 1 h. $Na(OAc)_3BH$ (8.681 g, 40.946 mmol) was added in one portion, and the solution was stirred at room temperature for 1 day. Additional portions of benzaldehyde (1.55 g, 14.624 mmol) and Na(OAc)BH (4.34 g, 20.473 mmol) were added, and the resulting mixture was stirred for another day. Solvent was removed in vacuo, and the residue was partitioned between ethyl acetate and 1 N NaOH. After the organic layer was separated, the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography (0−60% acetonitrile (containing 1% 7 N NH_3 in MeOH)/DCM) to give 7.262 g (76%) of **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 5H), 7.08 (d, J = 8.0 Hz, 1H), 6.43 (m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.77 (s, 2H), 3.75 (s, 2H), 3.73 (dd, J = 8.3, 11.1 Hz, 2H), 3.57 (dd, J = 5.5, 11.1 Hz, 2H), 2.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 158.8, 139.7, 132.0, 128.8, 128.2, 126.9, 119.2, 104.2, 98.8, 60.5, 59.8, 55.3, 55.3, 53.8, 48.8; HRMS (ESI) calcd for $C_{19}H_{26}NO_4$ (M + H) 332.1856, found 332.1858.

Benzyl-(2,4-dimethoxy-benzyl)-(7-methylene-[1,5]dioxocan-3-yl)-amine (8). To a solution of tetrabutylammonium iodide (279 mg, 0.757 mmol) and NaH (333 mg, 8.327 mmol) in DMF (65 mL) at 50 °C was slowly added a solution of **7** (1.253 g, 3.785 mmol) and 3-chloro-2-chloromethyl-1-propene (473 mg, 3.785 mmol) in THF (15 mL) by a syringe pump over 1 h. The solution was stirred for 1 hour and quenched with aqueous $NaHCO_3$. The mixture was partitioned between ethyl acetate and aqeous $NaHCO_3$. After the organic layer was separated, the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography (0−40% ethyl acetate/hexane) to give 664 mg (46%) of **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 2H), 7.25 (m, 3H), 7.17 (m, 1H), 6.43 (dd, J = 8.3, 2.5 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 5.12 (s, 2H), 4.13 (d, J = 12.9 Hz, 2H), 4.06 (d, J = 12.9 Hz, 2H), 3.88 (dd, J = 12.0, 6.8 Hz, 2H), 3.77 (s, 3H), 3.76 (dd, J = 12.0, 6.8 Hz, 2H), 3.75 (s, 3H), 3.72 (s, 2H), 3.62 (s, 2H), 2.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 158.6, 146.2, 140.7, 130.4, 128.3, 128.0, 126.5, 120.4, 118.5, 104.1, 98.2, 75.1, 68.5, 58.0, 55.3, 55.2, 54.8, 48.2; HRMS (ESI) calcd for $C_{23}H_{30}NO_4$ (M + H) 384.2169, found 384.2171.

7-[Benzyl-(2,4-dimethoxy-benzyl)-amino]-[1,5]dioxocan-3-one (9). To a solution of **8** (1.868 g, 4.877 mmol) in THF−H_2O (20 mL/5 mL) was added OsO_4 (2.5%, 1.2 mL, 0.0975 mmol) and NMO (628 mg, 5.365 mmol) at room temperature, and the mixture was stirred for 10 h. The solution was concentrated and filtered through a small pad of silica gel to give 1.52 g (75%) of the diol.

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(12) Hall, H. K. *J. Am. Chem. Soc.* **1957**, *79*, 5441.

To a solution of the diol (580 mg, 1.391 mmol) in benzene (7 mL) was added lead tetraacetate (739 mg, 1.669 mmol) at room temperature, and the mixture was stirred for 2 h (the reaction should be carefully monitored to avoid overoxidation). The mixture was filtered through a small pad of Celite, and the filtrate was concentrated and purified by flash chromatography (0−50% ethyl acetate/hexane) to give 460 mg of **9** (86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 4H), 7.21 (m, 2H), 6.45 (dd, J = 8.1, 2.5 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 4.16 (d, J = 16.2 Hz, 2H), 4.03 (d, J = 16.2 Hz, 2H), 3.96 (d, J = 6.6 Hz, 4H), 3.79 (s, 3H), 3.77 (s, 3H), 3.71 (s, 2H), 3.64 (s, 2H), 3.27 (dt, J = 12.9, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 159.9, 158.7, 140.1, 130.4, 128.3, 128.2, 126.8, 119.8, 104.2, 98.3, 78.2, 72.9, 57.9, 55.3, 55.2, 54.4, 48.0; HRMS (ESI) calcd for $C_{22}H_{28}NO_5$ (M + H) 386.1962, found 386.1963.

9-Benzyl-3,7-dioxa-9-aza-bicyclo[3,3,1]nonan-1-ol Trifluoroacetic Acid Salt (10). A solution of **9** (242 mg, 0.629 mmol) in trifluoroacetic acid (4.5 mL) was heated at 60 °C for 8 h and concentrated. The residue was purified by flash chromatography (0−50% acetonitrile/DCM) to give 117 mg of **10** (53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 4.10 (s, 2H), 4.02 (dd, J = 10.8, 2.4 Hz, 2H), 3.86 (d, J = 10.3 Hz, 2H), 3.75 (d, J = 11.4 Hz, 2H), 3.69 (d, J = 9.9 Hz, 2H), 2.71 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 128.5, 128.1, 127.0, 78.1, 71.4, 66.1, 53.8, 47.2; HRMS (ESI) calcd for $C_{13}H_{18}NO_3$ 236.1281, found 236.1282.

9-Benzyl-1-chloro-3,7-dioxa-9-aza-bicyclo[3,3,1]nonane Hydrochloric Acid Salt (11). To a solution of **10** (400 mg, 1.150 mmol) in benzene (6 mL)−DCM (2 mL) was added thionyl chloride (1.2 mL, 17.02 mmol), and the solution was refluxed for 6 h. After evaporation of the solvent, the residue was purified by flash chromatography (0−80% ethyl acetate/hexane) to give 250 mg of **11** (76%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 6.9 Hz, 2H), 7.33 (dd, J = 7.5, 7.5 Hz, 2H), 7.26 (t, J = 7.2 Hz, 1H), 4.25 (s, 2H), 4.12 (dd, J = 10.61, 5.31 Hz, 2H), 4.11 (d, J = 10.29 Hz, 2H), 4.03 (d, J = 10.29 Hz, 2H), 3.79 (d, J = 11.23 Hz, 2H), 2.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.5, 128.5, 127.3, 81.8, 72.4, 66.1, 54.6, 49.4; HRMS (ESI) calcd for $C_{13}H_{17}NO_2Cl$ (M + H) 254.0942, found 254.0944.

9-Benzyl-3,7-dioxa-9-aza-bicyclo[3,3,1]nonane (12). To a solution of **11** (150 mg, 0.523 mmol) in benzene (3 mL) was added tributyltin hydride (239 μL, 0.889 mmol) and AIBN (19 mg, 0.119 mmol), and the solution was refluxed for 24 h. After concentration, the residue was purified by HPLC (C-8 reverse phase column). The TFA salt of **12** was free-based by filtration through a small pad of silica gel using 50% ethyl acetate (containing 1% 7 N NH_3 in MeOH)/hexane to give 87 mg of **12** (76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.4 Hz, 2H), 7.32 (dd, J = 7.7, 7.1 Hz, 2H), 7.25 (dd, J = 7.4, 7.4 Hz, 1H), 4.17 (d, J = 12.6 Hz, 4H), 4.05 (s, 2H), 3.86 (d, J = 11.1 Hz, 4 H), 2.45 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.5, 128.4, 127.2, 67.2, 55.5, 52.5; HRMS (ESI) calcd for $C_{13}H_{18}NO_2$ (M + H) 220.1332, found 220.1333.

3,7-Dioxa-9-aza-bicyclo[3,3,1]nonane Formic Acid Salt (1-HCO_2H). To a solution of **12** (87 mg, 0.397 mmol) in 5% HCO_2H−MeOH (4 mL) was added Pd black (9 mg), and the mixture was stirred for 2 h. After filtration, the solution was concentrated to give 64 mg of **1** as a formic acid salt (99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 4.12 (dd, J = 12.0, 2.2 Hz, 4H), 4.07 (dd, J = 12.0, 2.2 Hz, 4H), 3.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 69.0, 49.2; HRMS (ESI) calcd for $C_6H_{12}NO_2$ (M + H) 130.0863, found 130.0859

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Supporting Information Available: Copies of ^{1}H NMR spectra for new compounds and crystallographic data for **1-HCO_2H** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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