Notes

Rapid Access to Enantiopure Bicyclic Diamines via *aza*-Diels−Alder Reaction of Iminoamides

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Introduction

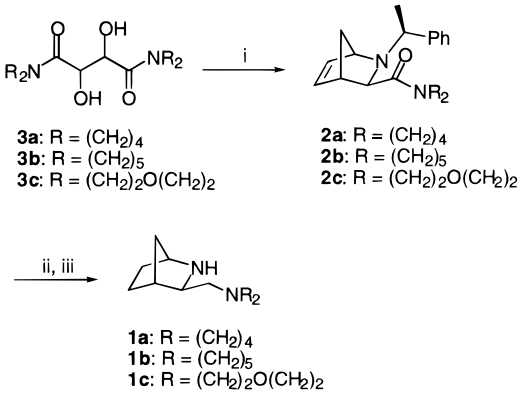
Enantiopure diamine ligands have been widely used over the last years.[1] Diamines have, for example, been used as lithium amide bases,[2] resolving agents,[3] and chiral ligands,[4] which clearly indicates considerable interest for structures of this kind. In our group bicyclic diamine ligands are currently being studied and applied in the rearrangement of *meso*-epoxides into chiral allylic alcohols.[5] We have earlier reported on the synthesis of these ligands using an *aza*-Diels−Alder reaction developed by Stella et al.[6] The resulting cycloaddition product was then modified into the desired ligand, and this reaction sequence has been successfully adopted for several other types of ligands by our group.[7] However, the synthesis of these diamines required six steps, and it was therefore of interest to find a new, shorter synthetic route to these ligands.

Results and Discussion

The synthesis of **1a**−**c** origins from bisamido tartrates and is outlined in Scheme 1.

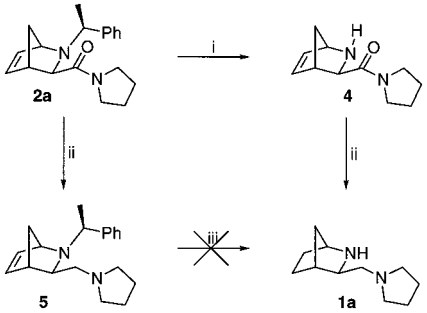
The first step in the synthesis of **1a**−**c** is an *aza*-Diels−Alder reaction involving the glyoxamide obtained from the oxidative cleavage of **3a**−**c** using periodic acid. The amidoaldehyde was treated with (*S*)-phenylethylamine in dry dichloromethane in the presence of molecular sieves 4 Å. To the resulting imine was added trifluoroacetic acid, boron trifluoride ethyl etherate, and cyclopentadiene at −78 °C, which led to the formation of **2a**−**c** as mixtures of diastereomers. This mixture was purified by flash chromatography and recrystallized to afford diastereomerically pure compounds **2a**−**c**.

Scheme 1[a]



[a] Reagents and conditions: (i) H_5IO_6, CH_2Cl_2 then (*S*)-phenylethylamine, then TFA, $BF_3{\cdot}Et_2O$, cyclopentadiene, −78 °C to rt. (ii) H_2 (1 atm), $Pd(OH)_2$/C, ethanol. (iii) $LiAlH_4$, THF.

Scheme 2[a]



[a] Reagents and conditions: (i) H_2 (1 atm), $Pd(OH)_2$/C, ethanol, overnight. (ii) $LiAlH_4$, THF. (iii) H_2 (1 atm), $Pd(OH)_2$/C, ethanol.

We found that the order of the last two reactions was important. Whereas amides **2a**−**c** were easily deprotected by hydrogenolysis at 1 atm of H_2, diamine **5** did not give any debenzylated product, even after prolonged reaction time of hydrogenation/hydrogenolysis at 1 atm of H_2 and $Pd(OH)_2$; see Scheme 2.

The last step, reduction of the amide to the corresponding amine, was performed using lithium aluminum hydride as reductant. The synthesis described in this paper gives enantiomerically pure **1a** in 38% overall yield in only three steps, whereas the original synthetic route gives **1a** in six steps. Furthermore, the methodology could be extended to produce azanorbornane derivatives with other N-substituents.[8]

(1) For a review of the chemistry of vicinal diamines see: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580.
(2) (a) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439. (b) de Sousa, S. E.; O'Brien, P.; Steffens, H. C. *Tetrahedron Lett.* **1999**, *40*, 8423.
(3) Clayden, J.; Lai, L. W. *Angew. Chem. Int. Ed.* **1999**, *38*, 2556.
(4) (a) Pénicaud, V.; Maillet, C.; Janvier, P.; Pipelier, M.; Bujoli, B. *Eur. J. Org. Chem.* **1999**, *1745*, 5. (b) Tommasino, M. L.; Thomazeau, C.; Touchard, F.; Lemaire, M. *Tetrahedron: Asymmetry* **1999**, *10*, 1813. (c) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186.
(5) (a) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760. (b) Södergren, M. J.; Bertilsson, S. K.; Andersson, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 6610.
(6) (a) Stella, L.; Abraham, H.; Feneau-Dupont, J.; Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2603. (b) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707.
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(8) (a) von Seebach, D.; Dörr, H.; Bastani, B.; Ehrig, V. *Angew. Chem.* **1969**, *81*, 1002. (b) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153. (c) Raczko, J.; Achmatowicz, M.; Jezewski, A.; Chapuis, C.; Urbanczyk-Lipkowska, Z.; Jurczak, J. *Helv. Chim. Acta* **1998**, *81*, 1264. (d) Frankland, P. F.; Ormerod, E. *J. Chem. Soc.* **1903**, *83*, 1343. (e) Frankland, P. F.; Twiss, D. F. *J. Chem. Soc.* **1910**, *97*, 154.

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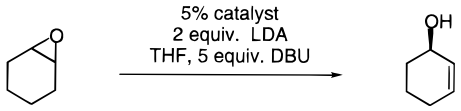
Scheme 3



Entry	Ligand	% yield (GC)[a]	% *ee*[a]
1	**1a**[b]	91	95
2	**1c**	67	72

[a] Experimental procedure as in ref 5. [b] Ligand as (-)-CSA salt.

To determine their absolute configuration, ligands **1a** and **c** were tested in the rearrangement of cyclohexeneoxide to the corresponding allylic alcohol as outlined in Scheme 3. The stereochemistry of the allylic alcohol was the same as obtained with ligands made from the *aza*-Diels–Alder of the ethylglyoxylate, implying that the stereochemistry of the aminoamido *aza*-Diels–Alder adduct **1a**–**c** is as indicated in the figures.

Conclusion

The new dienophile derived from bisamido tartrates has proven successful and results in a shorter and more efficient synthesis of chiral diamine ligands based on the *aza*-norbornyl skeleton. Further studies will be made to broaden the usefulness of this modification of the Diels–Alder reaction.

Experimental Section

General. For description of general experimental procedures see ref 5 and references therein. The diamides **3** were prepared using a literature procedure.[9]

(2*R*,3*R*)-2,3-Dihydroxy-1,4-dipyrrolidin-1-yl-butane-1,4-dione (3a). The diamide **3a** was synthesized using a literature procedure.[9] Purification by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol 90/10) gave **3a** (10.6 g, 85%) as a white solid. All spectroscopic and physical data were in accordance with those published.[9]

(2*R*,3*R*)-2,3-Dihydroxy-1,4-dipiperidin-1-yl-butane-1,4-dione (3b). The diamide **3b** was synthesized following a literature procedure, except that the reaction mixture was kept at 70 °C for 24 h.[9] Purification by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol 90/10) gave **3b** (866 mg, 60%) as a pale yellow solid: mp 58–59 °C; R_f 0.40 (ethyl acetate/methanol 90/10, silica gel); $[\alpha]^{25}_D = -5.0°$ (*c* 0.95, $CHCl_3$); IR (neat, cm^{-1}) 3392, 2937, 1631; ^1H NMR (200 MHz, $CDCl_3$) 1.64 (m, 12H), 3.52 (m, 8H); 4.32 (m, 2H), 4.61 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) 24.3, 25.4, 26.1, 44.0, 46.5, 69.9, 169.1; MS (EI) *m*/*z* (rel intensity) 285 ($M^+ + H$, 10%), 210 (12), 172 (49), 154 (23), 143 (30), 112 (100), 86 (26), 84 (44). Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.13; H, 8.51; N, 9.85. Found: C, 59.18; H, 8.58; N, 10.02.

(2*R*,3*R*)-2,3-Dihydroxy-1,4-dimorpholin-4-yl-butane-1,4-dione (3c). The diamide **3c** was synthesized following a literature procedure except that the reaction mixture was kept at 70 °C for 48 h.[9] Purification by flash chromatography (silica gel, ethyl acetate to ethyl acetate/methanol 90/10) gave **3c** (620 mg, 43%) as a white solid: mp 106–108 °C; R_f 0.10 (ethyl acetate/methanol 95/5, silica gel); $[\alpha]^{25}_D = +7.6°$ (*c* 1.06, $CHCl_3$); IR (neat, cm^{-1}) 3400, 1736, 1638; ^1H NMR (200 MHz, $CDCl_3$) 3.68 (m, 16H), 4.24 (m, 2H), 4.62 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) 43.1, 46.3, 66.6, 70.0, 169.8; MS (EI) *m*/*z* (rel intensity) 289 ($M^+ + H$, 45%), 70 (29), 83 (21), 88 (25), 114 (100), 145 (18), 174 (85), 202 (31), 271 (8). Anal. Calcd for $C_{12}H_{20}N_2O_6$: C, 49.99; H, 6.99; N, 9.72. Found: C, 49.89; H, 7.04; N, 9.68.

(9) Suzuki, M.; Kimura, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3559.

[(1*R*,3*R*,4*S*)-2-((*S*)-1-Phenylethyl)-2-azabicyclo[2.2.1]hept-5-en-3-yl]-pyrrolidin-1-yl-methanone (2a). In dry CH_2Cl_2 (40 mL) was dissolved **3a** (5.15 g, 20.1 mmol). Periodic acid (4.86 g, 21.3 mmol) was added portionwise during 1 h. The mixture was stirred for 1 h at room temperature and then poured onto molecular sieves (MS) 4 Å to remove any water. After about 10 min., the solid was filtrated off and the solvent was evaporated. To the crude glyoxylic acid pyrrolidide was added MS 4 Å, 100 mL of dry CH_2Cl_2, and (*S*)-phenylethylamine (5.27 mL, 40.7 mmol). After 1 h the reaction mixture was cooled to −78 °C, and in 10 min intervals TFA (3.4 mL, 44.4 mmol), boron trifluoride etherate (5.6 mL, 44.3 mmol), and cyclopentadiene (4.0 mL, 48.2 mmol) were added. The mixture was stirred overnight while warming to room temperature and then neutralized with $NaHCO_3$ (saturated aqueous), and the mixture was filtrated. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The crude **2a** was purified by flash chromatography (deactivated silica gel, pentane to ethyl acetate 90/10) to give **2a** (8.64 g, 72%) as a mixture of diastereomers in a 9:1 ratio. Recrystallization from hot *tert*-butyl methyl ether and washing of the crystals with 2,2,4-trimethylpentane provided 4.81 g (40%) of the major isomer **2a** as colorless crystals: mp 137 °C; R_f 0.55 (ethyl acetate, deactivated silica gel); $[\alpha]^{25}_D = +57.6°$ (*c* 0.97, $CHCl_3$); IR (neat, cm^{-1}) 1645; ^1H NMR (300 MHz, $CDCl_3$) 1.37 (m, 6H), 1.57 (m, 2H); 2.09 (m, 1H), 2.17 (s, 1H), 2.53 (m, 1H), 2.73 (br s, 1H), 2.94 (m, 1H), 3.03–3.20 (m, 3H), 4.28 (br s, 1H), 6.26 (m, 1H), 6.38 (m, 1H), 7.10–7.20 (m, 3H), 7.28–7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.3, 23.8, 25.9, 45.1, 45.4, 45.7, 48.6, 62.0, 62.8, 64.3, 126.8, 127.8, 127.9, 133.1, 136.6, 145.6, 172.1; MS (EI) *m*/*z* (rel intensity) 297 ($M^+ + H$, 100%), 231 (53), 230 (30), 105 (46), 94 (44). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.03; H, 8.11; N, 9.50.

[(1*R*,3*R*,4*S*)-2-((*S*)-1-Phenylethyl)-2-azabicyclo[2.2.1]hept-5-en-3-yl]-piperidin-1-yl-methanone (2b). Synthesized using the same procedure as for **2a** using **3b**. Purification by flash chromatography (deactivated silica gel, ethyl acetate) gave **2b** (1.35 g, 80%) as a mixture of diastereomers. Recrystallization from hot *tert*-butyl methyl ether hot filtration and washing of the crystals with 2,2,4-trimethylpentane provided 0.49 g (29%) of the major isomer as colorless crystals: mp 134–135 °C; R_f 0.5 (ethyl acetate, deactivated silica gel); $[\alpha]^{25}_D = +55.4°$ (*c* 0.99, $CHCl_3$); IR (neat, cm^{-1}) 1641; ^1H NMR (200 MHz, $CDCl_3$) 0.67 (m, 1H), 1.00–1.44 (m, 9H), 2.35 (m, 1H), 2.45 (s, 1H), 2.71 (m, 1H), 2.80–3.12 (m, 4H), 3.59 (m, 1H), 4.34 (m, 1H), 6.31 (m, 1H), 6.42 (m, 1H), 7.10–7.35 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) 23.2, 24.4, 25.3, 25.6, 43.1, 45.3, 45.9, 49.0, 61.6, 62.5, 64.6, 126.8, 128.0, 133.7, 136.2, 145.4, 171.5; MS (EI) *m*/*z* (rel intensity) 311 ($M^+ + H$, 89%), 245 (85), 159 (60), 131 (84), 105 (100), 94 (88). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 77.38; H, 8.44; N, 9.02. Found: C, 77.31; H, 8.41; N, 8.97.

Morpholin-4-yl-[(1*R*,3*R*,4*S*)-2-((*S*)-1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-en-3-yl]methanone (2c). Synthesized using the same procedure as for **2a**. Purification by flash chromatography (deactivated silica gel, ethyl acetate) gave **2c** (332 mg, 29%) as a mixture of diastereomers. Recrystallization from hot *tert*-butyl methyl ether and washing of the crystals with 2,2,4-trimethylpentane provided 0.16 g (14%) of the major isomer **2c** as colorless crystals: mp 155–156 °C; R_f 0.55 (ethyl acetate, deactivated silica gel); $[\alpha]^{25}_D = +61.7°$ (*c* 0.81, $CHCl_3$); IR (neat, cm^{-1}) 1646; ^1H NMR (200 MHz, $CDCl_3$) 1.39 (m, 4H), 2.38 (m, 2H); 2.70–3.49 (m, 10H), 4.34 (br s, 1H), 6.31 (m, 1H), 6.42 (m, 1H), 7.18–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.1, 42.1, 45.3, 48.9, 61.1, 62.4, 64.6, 66.0, 66.7, 127.1, 128.1, 132.3, 133.7, 136.2, 145.4, 172.0; MS (EI) *m*/*z* (rel intensity) 313 ($M^+ + H$, 100%), 247 (44), 159 (36) 131 (43), 105 (64), 94 (65). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.16; H, 7.67; N, 9.05.

(1*S*,3*R*,4*R*)-3-Pyrrolidin-1-ylmethyl-2-azabicyclo[2.2.1]-heptane (1a). To a 100-mL round-bottomed flask was added $Pd(OH)_2$ (1.0 g, 28 wt %), and the water content was removed in vacuo and by heating. Under an Ar flow were added ethanol (50 mL) and **2a** (3.52 g, 11.9 mmol), and the atmosphere was changed to H_2. The reaction mixture was stirred at room temperature overnight. Filtration through Celite and evaporation of the solvent gave deprotected amine (2.56 g), which was

used as is in the following reduction. To a suspension of lithium aluminum hydride (2.07 g, 54.5 mmol) in THF (80 mL) at 0 °C was added the deprotected amine (2.56 g, 13.2 mmol). The mixture was allowed to slowly reach room temperature and was then refluxed overnight. The reaction was cooled to 0 °C, diethyl ether (50 mL) was added, and the reaction quenched with water (2.1 mL), 2 M NaOH (aqueous) (2.1 mL), and water (6.3 mL). The mixture was filtered and evaporated to give pure **1a** (1.97 g, 92%). All spectroscopic and physical data were in accordance with those published.[5a]

(1*S*,3*R*,4*R*)-3-Piperidin-1-ylmethyl-2-azabicyclo[2.2.1]heptane (1b). Compound **1b** was synthesized using the same procedure as for **1a**. All spectroscopic and physical data were in accordance with those published.[5a]

(1*S*,3*R*,4*R*)-3-Morpholin-4-ylmethyl-2-azabicyclo[2.2.1]-heptane (1c). Compound **1c** was synthesized using the same procedure as for **1a**: $[\alpha]^{25}_{D} = -37.6°$ (*c* 0.33, $CHCl_3$); IR (neat, cm^{-1}) 3401; ^1H NMR (200 MHz, $CDCl_3$) 1.00−1.80 (m, 7H), 2.00−3.88 (m, 8H), 3.18 (br s, 1H), 3.54−3.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 28.7, 30.2, 31.7, 35.2, 39.9, 53.9, 55.8, 58.4, 62.2, 64.6, 66.9. Anal. Calcd for $C_{11}H_{20}N_2O$: C, 67.31; H, 10.27; N, 14.27. Found: C, 67.40; H, 10.21; N, 14.33.

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