Stereoselective Synthesis of (1*R*,2*S*,3*R*)-Camphordiamine

Carl A. Busacca,* Scot Campbell, Yong Dong, Danja Grossbach, Mike Ridges, Lana Smith, and Earl Spinelli

Departments of Chemical Development and Analytical Sciences, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877-0368

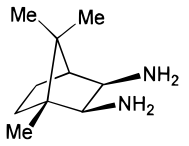
cbusacca@rdg.boehringer-ingelheim.com

Received February 15, 2000

Introduction

Chiral diamines[1a] form the backbone of a large number of ligands for asymmetric catalysis including those used for epoxidations,[1b] aldol condensations,[2] Diels−Alder cyclizations,[3] nucleophilic additions to carbonyls,[4] dihydroxylations of alkenes,[5] conjugate additions,[6] protonations,[7] cyclopropanations,[8] and aziridinations.[9] Diamines are also found in a number of natural products[10] and human pharmaceuticals.[11] Several diamine−metal complexes have important chemotherapeutic roles[12] as well. A structurally unique chiral diamine for ligand construction would be *exo*-camphordiamine **1** (as shown in Figure 1) due to the large degree of steric crowding enforced by the bridging 7-*gem*-dimethyl group.

Several syntheses of isomeric camphordiamines have been reported,[13−14] yet in no case was the stereochemistry of the various products ever determined. The first true stereoselective synthesis of *exo*-camphordiamine with full characterization is the subject of this paper.



(*exo*)-Camphordiamine 1

Figure 1.

Results and Discussion

Several investigators have developed diamine syntheses from 1,2-diketones[15] via reduction of the intermediate bisimines. Notable among these was the chirality transfer methodology of Nantz[15b] in which (*S*,*S*)-1,2-diphenylethylenediamine was condensed with diketones and then reduced with $NaBH_3CN$ to afford intermediate diamines with good diastereomeric excess. We reasoned that the camphor skeleton should enforce reduction from the α-face,[16] however, and that a chiral diamine might not be necessary. We thus condensed (*R*)-camphorquinone **2** with *meso*-1,2-diphenylethylenediamine **3**. Of the two possible diastereomeric bisimines **4** and **5**, only one could be isolated. This was tentatively assigned as species **4**, yet it also proved to be unstable on storage. Under the reaction conditions, **5** is not stable, leading to large amounts of benzaldehyde, **7**, and benzaldehyde condensation products **8** and **9**. We propose that **5** undergoes a facile electrocyclic ring opening[17] to **6**, which is then readily hydrolyzed on workup and chromatography, as shown in Scheme 1.

Condensation of (*R*)-diketone **2** with (*S*,*S*)-1,2-diphenylethylenediamine **10**, however, led cleanly to bisimine **11** with none of the instabilities associated with the adducts **4** and **5**. Formation of diastereomer **13** also proceeded in fair yield using the (*R*,*R*)-diamine **12**. With **11** and **13** in hand, we next examined reduction of these two species with $NaBH_4$/MeOH. The only components in addition to unreacted starting bisimines observed after 4 h at ambient temperature were diamines **14** and **15**, respectively (Scheme 2). Initial NMR analyses of **14** and **15** quickly established the exo stereochemistry at C3 for both compounds. This was accomplished by simple observation of H4: this proton exists in both compounds as a simple doublet with $J = 7.23$ Hz, showing that there is no coupling to H3 due to orthogonality; only coupling to H5β is seen. Careful NMR analysis using NOESY experiments revealed that both **14** and **15** possess the desired exo stereochemistry at C2 as well. Key NOESY cross-peaks observed with **14** included H2−H3 and H3−H12, while for **15** cross-peaks for H2−H3 and H2−H11 were readily seen. These results thus confirmed that reduction of the camphor bisimines takes place exclu-

(1) For an outstanding review, see: (a) Le Gall, T.; Mioskowski, C.; Lucet, D. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*(19), 2580−2627. (b) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189−214.

(2) (a) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247. (b) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990.

(3) (a) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027. (b) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938.

(4) (a) Knochel, P.; Berger, S.; Langer, C.; Lutz, C.; Mobley, T. A.; Reddy, C. K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1496. (b) Jiang, Y.; Gong. L.; Feng, X.; Hu, W.; Li, Z.; Mi, A. *Tetrahedron* **1997**, *53*, 14327.

(5) (a) Sharpless, K. B.; Kolb, H. C.; VanNieuwenhze, M. S. *Chem. Rev.* **1994**, *94*, 2483. (b) Corey, E. J.; Jardine, P. D.; Vigil, S.; Yuen, P.-W.; Connel, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.

(6) (a) Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114. (b) Rossiter, B. E.; Eguchi, M.; Hernandez, A. E.; Vickers, D.; Medich, J.; Marr, J.; Heinis, D. *Tetrahedron Lett.* **1991**, *32*, 3973.

(7) (a) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1995**, *117*, 891. (b) Koga, K.; Yasukata, T. *Tetrahedron*: *Asymmetry* **1993**, *4*, 35.

(8) Kobayashi, S.; Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N. *Tetrahedron* **1995**, *51*, 12013.

(9) Jacobsen, E. J.; Li, Z.; Conser, K. R. *J. Am. Chem. Soc.* **1993**, *115*, 5326.

(10) (a) Clardy, J.; Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Katz, B.; Steiner, J. R. *J. Am. Chem. Soc.* **1993**, *115*, 6452. (b) Rinehart, K. L. Jr.; Gardiner, R. A.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639.

(11) Cheney, B. V.; Szmuszkovicz, J.; Lahti, R. A.; Zichi, D. A. *J. Med. Chem.* **1985**, *28*, 1853.

(12) (a) Reedijk, J. *Chem. Commun.* **1996**, 801. (b) Rosenberg, B.; VanCamp, L.; Trosko, J. E.; Mansour, V. H. *Nature* **1969**, *222*, 385.

(13) Duden. *Chem. Ber.* **1905**, *II*, 176.

(14) (a) Rupe, H.; Bohny, P. *Helv. Chim. Acta* **1936**, *19*, 1305−1323. (b) Dornow, A.; Fust, K. J.; Jordan, H. D. *Chem. Ber.* **1957**, *90*, 2124−2137.

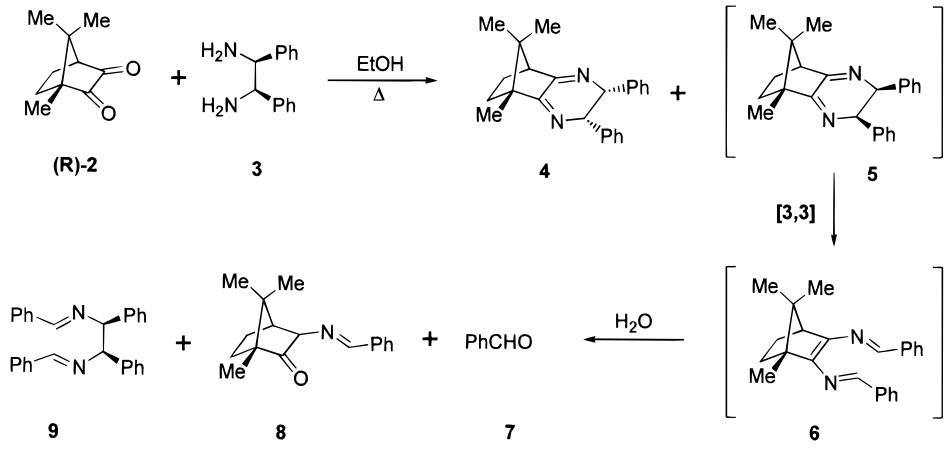
(15) (a) Corey, E. J.; Pikul, S. White, J. D.; Jeffrey, S. C. *Org. Synth.* **1993**, *71*, 22. (b) Nantz, M. H.; Lee, D. A.; Bender, D. M.; Roohi, A. H. *J. Org. Chem.* **1992**, *57*, 6653.

(16) Periasamy, M.; Devasagayaraj, A.; Stayanarayana, N.; Narayana, C. *Synth. Commun.* **1989**, *19*, 565−573.

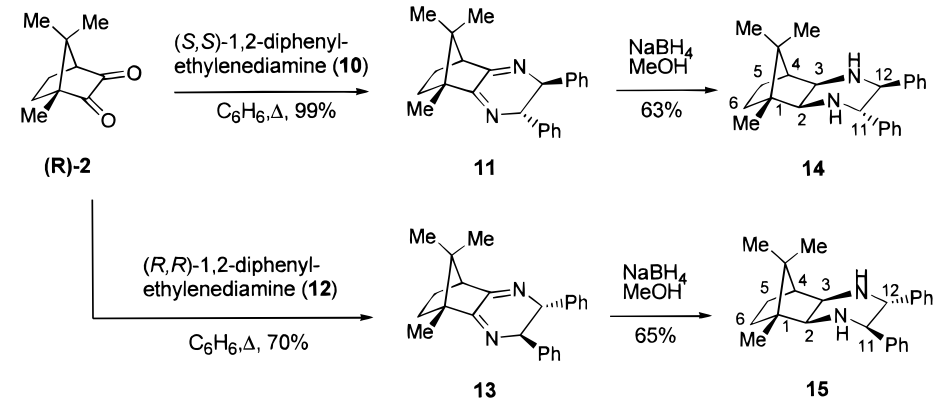
(17) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: Essex, 1976; pp 100−106.

10.1021/jo0002137 CCC: $19.00 © 2000 American Chemical Society
Published on Web 06/13/2000

Scheme 1



Scheme 2



sively from the α-face, as expected, irrespective of the diamine stereochemistry.

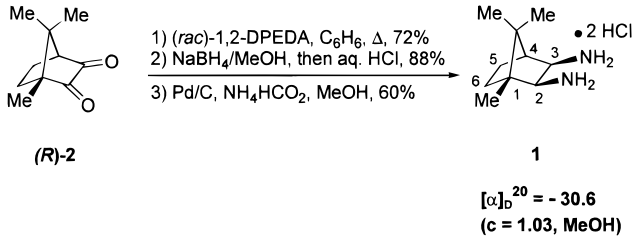
The original protocol[15b] for removal of the auxiliary was a three-step procedure consisting of (1) biscarbamate formation, (2) Li(0)/NH_3 double debenzylation, and (3) HBr/HOAc cleavage of the biscarbamate. Rather than adopting this strategy, we examined transfer hydrogenolysis. While hydrogenolysis using Pd/C in the presence of cyclohexene or formic acid donors were sluggish, use of ammonium formate on the dihydrochlorides of **14** and **15** led to rapid production of (*R*)-camphordiamine dihydrochloride (**1**) and bibenzyl. The compound thus obtained is a stable, nonhygroscopic salt. It is critical to isolate the product as the hydrochloride salt using a nonaqueous workup, as we have shown conclusively that the free base diamine is not stable to standard extractive isolation.

With this route established, we next carried out the synthesis of (*R*)-camphordiamine dihydrochloride **1** using *rac*-1, 2-diphenylethylenediamine.[15a] As shown in Scheme 3, (*R*)-camphordiamine dihydrochloride **1** was produced in 38% overall yield for the three-step process. An X-ray crystal structure obtained for a derivative[18] confirmed the stereochemical findings made via NMR NOESY analysis.

Conclusion

In summary, a convenient stereoselective synthesis of (*R*)-camphordiamine dihydrochloride from (*R*)-camphorquinone and *rac*-1,2-diphenylethylenediamine has been achieved. The sequence is operationally simple, is readily scaled, and furnishes the optically pure title compound as a stable, nonhygroscopic, crystalline salt. The use of (*R*)-camphordiamine and its derivatives in asymmetric catalysis is presently under active investigation.

Scheme 3



Experimental Section

Diamines 14 and 15. A 2 L flask was charged with 12.7 g of *rac*-1,2-diphenylethylenediamine (60.0 mmol, 1 equiv), 9.94 g of (*R*)-camphorquinone (60.0 mmol, 1 equiv), and 1.3 L of benzene. The mixture was heated at reflux using a Dean−Stark trap for 12 h, and then the volatiles were removed in vacuo. The residue was chromatographed on silica gel eluting with 5:1 Hex/EtOAc to give 14.8 g (72%) of bisimines **11** and **13**. A 14.8 g portion of bisimines **11** and **13** (43 mmol, 1 equiv) was dissolved in 500 mL of MeOH and cooled to 5 °C under N_2. To this mixture was then added 8.1 g of $NaBH_4$ (215 mmol, 5 equiv) at once. (Caution: gas evolution). After the mixture was stirred for 1 h at ambient temperature, the reaction was quenched by the addition of 500 mL of 1 N HCl. MeOH was then removed in vacuo, and the resulting suspension was extracted with EtOAc

(18) Full details are found in the Supporting Information.

and the aqueous phase saved. The EtOAc was dried ($MgSO_4$), and the volatiles were removed in vacuo to give 5.0 g of a yellow oil. This oil was dissolved in 150 mL of MeOH, cooled to 5 °C, and reduced with 2.7 g of $NaBH_4$ as described above. The combined aqueous phases from both runs were concentrated under high vacuum, the resultant solids recrystallized from H_2O and filtered, and the solids dried at ambient temperature to give 18.0 g of diamine dihydrochlorides **14** + **15** (88%) as trihydrate salts. Data for **14**: colorless solid; mp 282 °C dec; $[\alpha]^{20}_D = -70.3$ (*c* 0.495, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 7.40 (m, 10H), 5.00 (d, J = 11.2 Hz, 1H), 4.76 (d, J = 11.0 Hz, 1H), 3.92 (d, J = 8.6 Hz, 1H), 3.84 (d, J = 8.6 Hz, 1H), 2.16 (br s, 1H), 1.92 (m, 1H), 1.76 (t, J = 11.7 Hz, 1H), 1.40 (s, 3H), 1.33 (m, 2H), 1.04 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ 131.78 (s), 131.70 (s), 130.66 (d), 130.31 (d), 129.60 (d), 129.43 (d), 128.80 (d), 128.35 (d), 62.16 (d), 59.70 (d), 59.62 (d), 59.29 (d), 49.62 (s), 47.94 (d), 47.73 (s), 34.33 (t), 26.14 (t), 21.02 (q), 20.37 (q), 10.45 (q). Anal. Calcd for $C_{24}H_{32}N_2Cl_2 \cdot 3H_2O$: C, 60.88; H, 8.09; N, 5.92; Cl, 14.98. Found: C, 61.00; H, 7.70; N, 5.83; Cl, 15.27. Data for **15**: colorless solid; mp 290 °C dec; $[\alpha]^{20}_D = +93.4$ (*c* 0.198, MeOH); ^{1}H NMR (400 MHz, D_2O) δ 7.37 (m, 5H), 7.22 (m, 5H), 4.65 (d, J = 9.5 Hz, 1H), 4.14 (d, J = 9.5 Hz, 1H), 3.56 (d, J = 7.8 Hz, 1H), 3.41 (d, J = 7.8 Hz, 1H), 1.86 (m, 1H), 1.55 (m, 1H), 1.51 (s, 3H), 1.20−0.90 (m, 3H), 0.87 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, D_2O) δ: 139.27 (s), 133.39 (s), 130.13 (d), 129.38 (d), 129.07 (d), 128.92 (d), 128.43 (d), 127.62 (d), 67.54 (d), 63.21 (d), 62.17 (d), 56.46 (d), 48.35 (s), 48.29 (d), 46.91 (s), 34.30 (t), 25.67 (t), 21.21 (q), 20.74 (q), 9.96 (q). Anal. Calcd for $C_{24}H_{31}N_2Cl_1 \cdot 0.5H_2O$: C, 74.89; H, 8.17; N, 7.28; Cl, 9.21. Found: C, 74.51; H, 8.08; N, 7.12; Cl, 9.23.

(1*R*,2*S*,3*R*)-Camphordiamine Dihydrochloride 1. A flask was charged with 5.00 g of **14** + **15** trihydrate (11.9 mmol, 1 equiv), 3.75 g of NH_4HCO_2 (59.8 mmol, 5 equiv), and 250 mL of MeOH. As N_2 was bubbled beneath the surface, 2.0 g of 10% Pd/C (dry) was cautiously added. The resulting mixture was heated to reflux under N_2 (warning: gas evolution), and after 45 min, the mixture was cooled and filtered through a Celite pad, washing with MeOH. The volatiles were then removed *in vacuo*, and the residual solid was washed well with EtOAc and dried at ambient temperature to give 2.4 g of crude **1** (this material can be used without further purification). Recrystallization from H_2O provided a colorless solid that was slurried with MeCN, filtered, and dried to constant weight under high vacuum at ambient temperature to give 1.72 g (60%) of **1** as a colorless solid: mp >300 °C; $[\alpha]^{20}_D = -30.6$ (*c* 1.03, MeOH); ^{1}H NMR (500.13 MHz, DMSO) δ 6.01 (br s, 6H, 2xNH_3+), 3.04 (d, J = 8.3 Hz, 1H, H3), 2.96 (d, J = 8.3 Hz, 1H, H2), 1.89 (d, J = 4.4 Hz, 1H, H4), 1.67 (m, 1H, H5β), 1.47 (m, 1H, H6β), 1.13 (m, 1H, H6α), 1.09 (m, 1H, H5α), 0.97 (s, 3H, H9), 0.89 (s, 3H, H10), 0.75 (s, 3H, H8); ^{13}C NMR (125.77 MHz, DMSO) δ 60.05 (C2), 55.59 (C3), 49.19 (C4), 48.15 (C1), 46.61 (C7), 34.97 (C6), 25.93 (C5), 21.26 (C8), 21.17 (C9), 11.70 (C10); HRMS calcd for $C_{10}H_{21}N_2^+$ m/z 169.1705, found m/z 169.1705.

Supporting Information Available: Synthesis and full characterization of two derivatives of the title compound as well as X-ray crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0002137