Practical Synthesis of (*R,R*)- and (*S,S*)-Bis[2,6-bis(1-ethoxyethyl)phenyl] Diselenide

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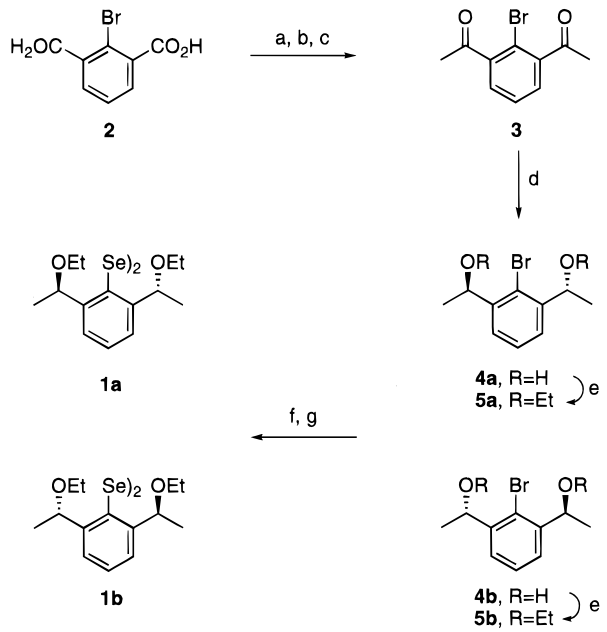
Received October 27, 1995

We recently reported the synthesis of a new chiral C_2 symmetrical organoselenium reagent, **1a**, and showed its usefulness in the asymmetric selenomethoxylation of olefins[1a] and in the preparation of enantiomerically enriched heterocycles *via* asymmetric ring closure reactions.[1b] However, in order for this new reagent to be more synthetically useful, a facile and economical access to both enantiomers was highly desirable. Although our original synthesis was highly enantioselective, it was, nevertheless, lengthy, and the chiral reagents involved were somewhat expensive. We now report a more practical enantioselective synthesis of (*R,R*)- and (*S,S*)-**1** featuring a dual asymmetric reduction of the diketone intermediate **3** (Scheme 1).

Our original synthesis involved the sequential conversion of each carboxylic acid in **2** to the desired chiral ethoxyethyl moiety. Clearly, it would be more efficient if we could convert both carboxylic acids simultaneously. However, attempts to prepare the diketone **3** by adding methyl organometallic reagents to activated acyl derivatives of the bromophthalic acid **2** turned out to be problematic. Loss of the bromine atom was a major side reaction, and the separation of **3** from the resultant complex mixture was difficult. We have now found that condensation of the diacyl chloride of **2** with the sodium salt of dimethyl malonate followed by hydrolysis and decarboxylation[2] afforded the desired diketone **3** in 75% yield after distillation. In our original synthesis, we achieved the stepwise enantioselective reduction of the two carbonyls *via* the oxazaborolidine-catalyzed borane reaction.[3] We thus attempted to use this reagent for the dual asymmetric reduction of **3** to give **4.** However, in our hands, this method gave irreproducible yields and enantioselectivities. We obtained more reproducible results including high enantioselectivities using commercially available (+)- or (−)-*B*-chlorodiisopinocampheylborane (DIP-chloride).[4] Thus treating **3** with 2.2 equiv of (+)-DIP-chloride in THF at −25 °C afforded the desired *R,R* diol **4a** in 81% yield and with an enantiomeric purity >99% (measured by chiral HPLC).[5] The *S,S* diol **4b** (>99% ee) was similarly obtained from (−)-DIP-chloride in 82% yield. It should be noted that both (+)- and (−)-DIP-chloride, even used in stoichiometric amounts, are less expensive than the α,α-diphenyl-2-pyrrolidinemethanol used in the oxazaborolidine-catalyzed borane reduction. Treatment of the diols **4a,b** with ethyl iodide and sodium hydride gave the diethyl ethers **5a,b** in 83% yield. As previously described, the diselenides **1a,b** were prepared by lithiation of **5a,b** with 2 equiv of *tert*-BuLi in THF at low temperature followed by the addition of elemental selenium. Air oxidation of the crude product in the presence of a catalytic amount of sodium hydroxide and crystallization from methanol afforded the desired diselenide **1a,b** in 70−76% yield with an enantiomeric purity >99%.

Scheme 1



Reaction conditions: (a) $SOCl_2$; (b) NaH, $CH_2(CO_2Me)_2$, THF; (c) H_2SO_4, CH_3CO_2H; (d) (+)-DIP-Chloride™, THF for **4a**, (-)-DIP-Chloride™, THF for **4b**; (e) NaH, EtI, THF-DMF; (f) *tert*-BuLi, THF, Se; (g) cat NaOH, air.

In summary we have developed a short and highly enantioselective synthesis of the C_2 symmetrical *R,R* and *S,S* diselenides **1**. This new synthetic route relies on the efficient and reproducible asymmetric reduction of the diketone **3** with (+)- or (−)-*B*-chlorodiisopinocampheylborane.

Experimental Section

2,6-Diacetylbromobenzene (3). The diacid **2**[6] (24.3 g, 0.0989 mol) was refluxed in 30 mL of thionyl chloride overnight. The reaction mixture was concentrated *in vacuo*, and the residue was kept under vacuum overnight to give the diacyl chloride derivative of **2** as an off-white solid (27.9 g) which was used as such for the next step. Dimethyl malonate (28.2 mL, 0.247 mol) was added dropwise to a 0 °C cooled suspension of sodium hydride (60% dispersion in mineral oil, 19.8 g, 0.495 mol) in THF (220 mL). The mixture was heated to reflux, and then a THF (130 mL) solution of the diacyl chloride (27.9 g, 0.0989 mol) was slowly added. After 15 h of reflux, the mixture was cooled and 10% sulfuric acid (200 mL) was slowly added. The THF was removed under vacuum, and the resultant mixture was extracted with ether (3×). The combined organic layers were concentrated under vacuum. The crude tetraester was then refluxed for 24 h in a mixture of water (44 mL), concentrated sulfuric acid (8.6 mL), and acetic acid (67 mL). The reaction mixture was diluted with water (100 mL) and extracted with EtOAc (2×). The combined organic layers were washed with brine, dried over K_2-

(1) (a) Déziel, R.; Goulet, S.; Grenier, L.; Bordeleau, J.; Bernier, J. *J. Org. Chem.* **1993**, *58*, 3619. (b) Déziel, R.; Malenfant, E. *J. Org. Chem.* **1995**, *60*, 4660.

(2) Protocol based on a similar transformation: McKinnon, D. M.; Wong, J. Y. *Can. J. Chem.* **1971**, *49*, 2018.

(3) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 4141 and references cited therein.

(4) Purchased from Aldrich Chemial Co. Inc. For a good review on this reagent see: Dhar, R. K. *Aldrichim. Acta* **1994**, *27*, 43.

(5) We also obtained some of the *R,S* (meso) isomer (6.5%) which was easily separated by column chromatography on silica gel.

(6) Prepared according to: Coulson, E. A. *J Chem. Soc.* **1937**, 1298.

0022-3263/96/1961-1875$12.00/0

CO_3 and $MgSO_4$, and concentrated under vacuum. After partial purification through a silica gel pad (hexane then EtOAc), the desired product was distilled (120 °C, 0.5 mmHg) to give pure **3** (17.9 g, 75% yield) as a colorless liquid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (m, 3 H), 2.62 (s, 6 H); IR (neat) 1750, 1720, 1600 cm^{-1}; HRMS m/z (M^+) calcd 241.9763, obsd 241.9786. Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76. Found: C, 49.71, H, 3.69.

2,6-Bis(1(*R*)-hydroxyethyl)bromobenzene (4a). To a solution of (+)-DIP-Cl (4.29 g, 13.4 mmol) in THF (20 mL), cooled at −25 °C, was slowly added a THF (6 mL) solution of **3** (1.50 g, 6.22 mmol). The resultant mixture was stirred at −25 °C overnight. Acetaldehyde (0.90 mL, 16 mmol) was added, and the mixture was allowed to warm to room temperature. After removal of the volatiles under vacuum, the residue was treated with 1 M sodium hydroxide (50 mL) and then extracted with EtOAc (2×). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated under vacuum. Purification by flash column chromatography on silica gel (15% EtOAc−hexane) gave pure *R*,*R* diol **4a** (1.22 g, 81% yield) as a white solid: mp 163−164 °C; $[\alpha]^{25}_D$ +119° (*c* 1.15, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, J = 7.6 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 1 H), 5.34−5.29 (m, 2 H), 2.03 (d, J = 3.5 Hz, 2 H), 1.48 (d, J = 6.4 Hz, 6 H); HRMS m/z (M^+) calcd 244.0095, obsd 244.0074. Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.35. Found: C, 48.79; H, 5.35. HPLC (Chiracel OD), 5% EtOH/hexane , 1 mL/min, λ = 205 nm, t_R for racemate *S*,*S* 15.52 min, *R*,*R* 26.02 min, no *S*,*S* detectable in diol **4a** (>99% ee).

2,6-Bis(1(*S*)-hydroxyethyl)bromobenzene (4b): prepared in 82% yield as described above using (−)-DIP-Cl: mp 162−164 °C; $[\alpha]^{25}_D$ −116° (*c* 1.20, MeOH); HRMS m/z (M^+), calcd 244.0099, obsd 244.0113. Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.35. Found: C, 48.64; H, 5.26. HPLC (see above conditions) >99% ee.

2,6-Bis(1(*S*)-ethoxyethyl)bromobenzene (5b). Sodium hydride (60% dispersion in mineral oil, 3.20 g, 80.0 mmol) was slowly added to a THF (50 mL) solution of the diol **4b** (6.54 g, 26.7 mmol) followed the addition of DMF (80 mL) and iodoethane (21 mL, 260 mmol). After stirring at room temperature for 48 h, water was added and the solution was extracted with ether (2×). The combined organic layers were successively washed with water, saturated sodium sulfite, and brine and then dried over magnesium sulfate. Concentration *in vacuo* and purification by flash column chromatography on silica gel (2% EtOAc−hexane and then 20% EtOAc−hexane) gave the desired diether **5b** (6.71 g, 83%) as a colorless oil: $[\alpha]^{25}_D$ −135° (*c* 3.31, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.35 (m, 3 H), 4.88 (q, J = 6.4 Hz, 2 H), 3.42−3.36 (m, 4 H), 1.41 (d, J = 6.4 Hz, 6 H), 1.21 (t, J = 7 Hz, 6 H); HRMS m/z (M^+) calcd 300.0725, obsd 300.0726. Anal. Calcd for $C_{14}H_{21}BrO_2$: C, 55.82; H, 7.03. Found: C, 55.63; H, 7.03.

2,6-Bis(1(*R*)-ethoxyethyl)bromobenzene (5a): prepared in 83% yield as described above: $[\alpha]^{25}_D$ +137° (*c* 2.15, MeOH).

Bis[2,6-bis(1(*R*)-ethoxyethyl)phenyl] Diselenide (1a). To a THF solution (100 mL) of **5a** (4.78 g, 15.8 mmol) at −78 °C was added a 1.7 M pentane solution of *tert*-BuLi (22 mL, 37 mmol) over 10 min. The reaction mixture was then stirred at 0 °C for 30 min, and selenium powder (1.33 g, 16.8 mmol) was added in two portions. The reaction mixture was kept at 0 °C for 15 min and then at room temperature for 30 min. HCl (1 N) was slowly added, the organic material was extracted with ether (2×), and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was dissolved in absolute EtOH (10 mL) and stirred vigorously in the presence of 50 mg of NaOH for 30 min. The orange solution was concentrated, and the resulting material was purified by silica gel flash chromatography to give a yellow solid (4.08 g). This solid was recrystallized from MeOH (25 mL) to give **1a** (3.60 g, 76%) as orange crystals: mp 96−97 °C; $[\alpha]^{25}_D$ −217° (*c* 1.29, MeOH); ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.42−7.36 (m, 6 H), 4.91 (q, J = 6.3 Hz, 4 H), 3.09−2.99 (m 8 H), 1.28 (d, J = 6.3 Hz, 12 H), 1.08 (t, J = 7.0 Hz, 12 H); HRMS m/z (M^+) calcd 602.1412, obsd 602.1359.

Bis[2,6-bis(1(*S*)-ethoxyethyl)phenyl] Diselenide (1b): prepared in 70% yield as described above: mp 95−96 °C; $[\alpha]^{25}_D$ +222° (*c* 1.25, MeOH); HRMS m/z (M^+) calcd 602.1412, obsd 602.1392. Anal. Calcd for $C_{28}H_{42}O_4Se_2$: C, 56.00; H, 7.05. Found: C, 55.87; H, 7.10.

Acknowledgment. We thank Dr. Neil Moss for his assistance in the preparation of this manuscript and Serge Valois, Nancy Shore, Colette Boucher, and Sylvain Bordeleau for HPLC and elementary analysis. We are also grateful to Dr. Paul C. Anderson for his support and encouragement for this work.

JO951919H