Synthetic Studies on ET 743. Asymmetric, Stereocontrolled Construction of the Tetrahydroisoquinoline Core via Radical Cyclization on a Glyoxalimine

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Supporting Information

Experimental Details

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NMR Spectra

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Experimental Procedures

General Procedures. 1H and 13C NMR spectra were obtained using Varian 300 MHz or 400 MHz spectrometers, at room temperature unless otherwise stated. The chemical shifts are given in parts per million (ppm) relative to TMS at δ 0.00 ppm or to residual CHCl3 δ 7.24 ppm for proton spectra and relative to CDCl3 at δ 77.0 ppm for carbon spectra. Samples in toluene-d8 are referenced to residual PhCH3 at δ 2.09 ppm for proton spectra and relative to C1 of toluene-d8 at δ 137.86 ppm for carbon spectra. IR spectra were recorded on a Perkin-Elmer 1600 FTIR as thin films from CH2Cl2 on NaCl plates. Mass spectra were obtained using a Fisons VG Autospec spectrometer. Flash column chromatography was performed with silica gel grade 60 (230-400 mesh). Unless otherwise noted materials were obtained from commercially available sources and used without further purification. All reactions were performed under argon atmosphere.
5-bromo-3,4-dihydroxy-2-methylbenzaldehyde (5). Borchardt’s catechol\(^\text{1}\) 4 (15.20 g, 0.10 mol) was dissolved in AcOH (50 mL) and CH\(_2\)Cl\(_2\) (50 mL) at 0°C, to which was subsequently added NaOAc (8.60 g, 0.105 mol). Bromine (5.2 mL, 0.101 mol) was added drop-wise, and upon complete addition, the reaction mixture was allowed to warm to rt and stirred a total of 10 h. The mixture was poured slowly into vigorously stirring water (1L) and stirred for 1 h. Filtration provided a brown solid that was dried under vacuum (70°C, 0.5 mmHg) to provide the brominated product 5 (12.90 g). The aqueous filtrate was further extracted with Et\(_2\)O (x2), and the combined organic fractions washed with brine, dried over Na\(_2\)SO\(_4\) and filtered. Concentration and drying as above provided additional bromide 5 (8.33 g), for a total combined yield of 92%. Both crops provided satisfactory \(^1\)H NMR spectra and were used without further purification.

\(^1\)H NMR (300 MHz, Acetone-\(d_6\)) \(\delta\) 10.06 (s, 1H), 9.00, (s, 1H), 8.27 (s, 1H), 7.57 (s, 1H), 2.54 (s, 3H).

7-bromo-4-methylbenzo[d][1,3]dioxole-5-carbaldehyde (6). Catechol 5 (10.00 g, 43.29 mmol) was dissolved in dry CH\(_3\)CN (200 mL) in a sealable flask, to which Cs\(_2\)CO\(_3\) (21.40 g, 64.94 mmol) was added. The mixture was stirred at rt for 15 min, and then BrCH\(_2\)Cl (4.40 mL, 64.94 mmol) was added. The flask was sealed and immersed in a 110°C oil bath for 24 h. The reaction was cooled to rt and concentrated to provide a brown solid. This solid was suspended in EtOAc and passed through a short plug of silica gel to remove brown insoluble material. The filtrate was adsorbed onto silica gel and thoroughly dried before being purified by flash chromatography (5:1
hexanes:EtOAc) to produce the methylenedioxy derivative 6 (7.28 g, 69%) as of an off-white solid.
Rf 0.49 (5:1 Hexanes:EtOAc, UV, does not stain with PMA); M.p. 109-110°C (EtOAc/Hexanes) IR (thin film) 1674, 1590, 1423, 1402, 1253, 1058, 935 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.98 (s, 1H), 7.52 (s, 1H), 6.17 (s, 2H), 2.51 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 190.1, 149.5, 147.5, 132.5, 130.7, 120.2, 102.2, 98.0, 11.4.

HRMS(FAB+) m/z calcd. for C\(_9\)H\(_7\)BrO\(_3\) (M)\(^+\) 241.9579; m/z found 241.9576.

7-bromo-4-methylbenzo[d][1,3]dioxol-5-ol (7). To an ice cold solution of 6 (7.28 g, 30.0 mmol) in CHCl\(_3\) (200 mL) in a round bottom flask equipped with a reflux condenser was added mCPBA (12.9 g, 75.0 mmol). The mixture was stirred vigorously and brought to reflux for 3.5 h, and then cooled to rt. The yellow solution was diluted with CH\(_2\)Cl\(_2\) and then washed with a 5% solution of NaHCO\(_3\) (x4), brine, and then dried over MgSO\(_4\) and filtered. Evaporation of the solvent produced the formate intermediate as a highly crystalline yellow solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.23 (s, 1H), 6.70 (s, 1H), 6.04 (s, 2H), 2.00 (s, 3H). This solid was dissolved in MeOH (200 mL) and CH\(_2\)Cl\(_2\) (20 mL) with vigorous stirring and then cooled to 0°C. 4M HCl (50 mL) was added and the mixture allowed to warm to rt over 1.5 h. The clear yellow solution was diluted with brine and recovered with CH\(_2\)Cl\(_2\) (x4). The combined organic fractions were washed with brine and then dried over MgSO\(_4\) and filtered. Flash chromatography (8:1 hexanes:EtOAc) provided 7 (5.03 g, 73%) as an off-white solid.
Rf 0.43 (5:1 Hexanes:EtOAc, UV, PMA); M.p. 135-136°C (EtOAc/Hexanes) IR (thin film) 3216, 1428, 1397, 1192, 1090, 1031, 939, 834 cm\(^{-1}\).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.39 (s, 1H), 5.97 (s, 2H), 4.47 (s, 1H), 2.06 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.6, 147.0, 139.4, 109.6, 107.1, 101.3, 96.5, 8.6.

HRMS(FAB+) m/z calcd. For C\(_8\)H\(_7\)BrO\(_3\) (M)\(^+\) 229.9579; m/z found 229.9575.
(R)-tert-butyl 4-((S)-(6-allyloxy)-4-bromo-7-methylbenzo[d][1,3]dioxol-5-yl)(hydroxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (9).

Phenol 7 (3.00 g, 13.0 mmol) was added in one portion to a stirring solution of titanium(IV) isopropanoxide (3.90 mL, 14.3 mmol) in dry toluene (120 mL). The resulting red solution was distilled to half volume three times under an argon atmosphere in order to remove the resulting isopropanol, with the volume restored each time with fresh dry toluene. This red solution was cooled to 0°C and immersed in a sonicator filled with ice water. With vigorous sonication of the titanium phenolate solution under argon, a solution of R-Garner’s aldehyde\(^2\) (3.87 g, 16.9 mmol) in toluene (20 mL) was added drop-wise over 30 min. The reaction mixture was sonicated for 6 h while maintaining the temperature at 0-5°C. The reaction was then allowed to warm to rt overnight (16 h) with stirring. The reaction was poured into a vigorously stirring aqueous solution of DL-tartaric acid and stirred for 1 h, and then extracted with diethyl ether (x4). The combined ether extracts were washed with brine and dried over Na\(_2\)SO\(_4\), filtered and concentrated to provide an orange oil. Purification by flash chromatography (5:1 hexanes:EtOAc) provided the diol 8 (4.78 g) of a pale yellow foam that was carried on to the next step.

By TLC the product has a virtually identical Rf as R-Garner’s aldehyde, but the product stains strongly with KMnO\(_4\) and is UV active. R-Garner’s aldehyde is not UV active and stains very weakly with KMnO\(_4\).

Rf = 0.47 (3:1 hexanes:EtOAc, UV, KMnO\(_4\)); Rf = 0.19 (5:1 hexanes:EtOAc, UV, KMnO\(_4\))

HRMS(FAB+) \(m/z\) calcd. for C\(_{19}\)H\(_{26}\)O\(_7\)N\(_1\)Br (M\(^+\)) 459.0893; \(m/z\) found 459.0901.

The diol 8 (4.78 g, 10.39 mmol) was suspended in DMF (30 mL), to which was added Cs\(_2\)CO\(_3\) (6.77 g, 20.78 mmol) with stirring. Allyl bromide (2.70 mL, 31.17 mmol) was added drop-wise and the reaction stirred for 2 h before being diluted with Et\(_2\)O and H\(_2\)O. This mixture was extracted with Et\(_2\)O (x4), and the combined organic fractions washed with brine (x2), and then dried over MgSO\(_4\), filtered and concentrated. Flash chromatography (5:1 hexanes:EtOAc)
provided the allyl protected alcohol 9 (4.22 g, 65% for two steps) as an oil that solidified to an off-white solid on standing.

Rf 0.17 (5:1 Hexanes:EtOAc, UV, KMnO₄); M.p. 103-104°C (EtOAc/Hexanes)  
[α]₀²⁵ D -25.4 (c 1.0, CH₂Cl₂)

IR (thin film) 3458, 2977, 2934, 2880, 1694, 1386, 1365, 1099 cm⁻¹.

¹H NMR (300 MHz, toluene-d₈, 348K) δ 5.89 (dddd, J = 17.1, 10.8, 5.4, 5.4 Hz, 1H), 5.33 (m, 2H), 5.26 (dq, J = 17.4, 1.5 Hz, 1H), 5.26 (d, J = 1.8 Hz, 1H), 5.04 (dq, J = 10.5, 1.5 Hz, 1H), 4.51-4.57 (m, 1H), 4.48 (dd, J = 9.3, 1.2 Hz, 1H), 4.26-4.33 (m, 2H), 3.75 (dd, J = 9.0, 5.7 Hz, 1H), 1.98 (s, 3H), 1.79 (s, 3H), 1.47 (s, 3H), 1.26 (s, 9H).

¹³C NMR (75 MHz, toluene-d₈, 348K) δ 153.2, 153.0, 146.7, 143.1, 134.4, 127.1, 117.4, 113.5, 101.5, 100.3, 95.2, 79.7, 75.7, 73.3, 65.5, 61.7, 28.7 (3C), 27.7, 24.5, 10.0.

HRMS(FAB+) m/z calcd. For C₂₂H₃₀BrNO₇ (M)⁺ 499.1206; found 499.1193.

C₂₂H₃₀BrNO₇ requires C, 52.81; H, 6.04; N, 2.80. Found: C, 53.11; H, 5.71; N, 2.94.

![Chemical structure](image)

(4S,5R)-4-(6-(allyloxy)-4-bromo-7-methylbenzo[d][1,3]dioxol-5-yl)-2,2-dimethyl-1,3-dioxan-5-amine (11). To a stirred solution of benzylic alcohol 9 (2.00 g, 4.00 mmol) in methanol (60 mL) was added TsOH•H₂O (76 mg, 0.40 mmol) at 0°C. The stirred solution was allowed to warm to rt over 5 h, and then diluted with brine and extracted to CH₂Cl₂ (x3). The combined organic fractions were washed with brine and then dried over MgSO₄, filtered and concentrated. The resulting foam was dissolved in DMF (20 mL) at rt, to which was added TsOH•H₂O (38 mg, 0.20 mmol), followed by 2,2-dimethoxypropane (4.90 mL, 40.00 mmol). The resulting solution was stirred overnight (12 h) and then quenched with NaHCO₃ (sat.) and extracted to Et₂O (x3). The combined organic fractions were washed with brine and then dried over MgSO₄, filtered and concentrated. Flash chromatography (5:1 hexanes:EtOAc) provided 10 (1.67 g, 84% over 2 steps) as a pale yellow oil that was carried on to the next step.

Rf = 0.29 (5:1 Hexanes:EtOAc, UV, PMA).
HRMS(FAB) calcd. for C_{22}H_{36}O_{7}NBr (M)^+ 499.1206; found 499.1190.

The N-Boc protected acetonide 10 (1.67 g, 3.34 mmol) was dissolved in CH_{2}Cl_{2} (30 mL), to which was added 2,6-lutidine (0.78 mL, 6.68 mmol). This solution was cooled to −78°C and TBSOTf (0.85 mL, 3.76 mmol) was added drop-wise. The reaction was allowed to warm to rt over 3 h and then quenched with dry MeOH (2.0 mL) and stirred for 15 min. After concentration, the resulting oil was re-suspended in MeOH (25 mL) and KF•2H_{2}O (650 mg, 6.68 mmol) was added with stirring. After 1 h of stirring, the solution was diluted with brine and then extracted with CH_{2}Cl_{2} (x3). The combined organic fractions were washed with brine and then dried over MgSO_{4}, filtered and concentrated. Flash chromatography (1:1 Hexanes:EtOAc with 0.1% Et_{3}N) provided the amine 11 (1.02 g, 76 %) of a clear, colorless oil that solidified on standing.

Rf 0.09 (streaks) (5:1 EtOAc:Hexanes, UV, KMnO_{4}, ninhydrin); M.p. 99-100°C (EtOAc/Hexanes)

[α]_{D}^{25} -1.4 (c 1.0, CH_{2}Cl_{2})

IR (thin film) 2990, 1459, 1419, 1102 cm\(^{-1}\).

^{1}H NMR (300 MHz, CDCl_{3}) \(\delta\) 6.02–6.17 (m, 1H), 5.99 (s, 2H), 5.43 (dq, \(J\) = 12.3, 1.5 Hz, 1H), 5.27 (br d, \(J\) = 7.8 Hz, 1H), 5.01 (d, \(J\) = 7.2 Hz, 1H), 4.40-4.80 (br s, 1H), 4.19 (dd, \(J\) = 9.3, 4.5 Hz, 1H), 3.98 (dd, \(J\) = 8.1, 3.6 Hz, 1H), 3.82 (br s, 1H), 3.57 (dd, \(J\) = 8.4, 7.5 Hz, 1H), 2.11 (s, 3H), 1.57 (s, 3H), 1.45(s, 3H), 1.89 (br s, 1H).

The extremely broad allyl methylene peaks (4.40-4.80 and 3.82 ppm) are due to an allyl rotamer that was more clearly resolved with increased temperature (85°C) in toluene-d8 (see SI-2). The \(^{13}C\) NMR at rt in CDCl_{3} gave very broad and weak signals but a clean and sharp spectrum was obtained at 85°C, also in toluene-d8:

\(^{13}C\) NMR (75 MHz, toluene-d8, 348K) \(\delta\) 154.0, 147.1, 143.4, 135.0, 124.5, 116.8, 114.1, 102.0, 101.6, 99.8, 77.6, 76.0, 68.0, 48.3, 29.5, 20.0, 9.7.

HRMS(FAB+) \(m/z\) calcd. For C_{17}H_{23}BrNO_{5} (M+H)^+ 400.0760; found 400.0746.
(4R,5aR,9aS)-ethyl 10-(allyloxy)-8,8,11-trimethyl-5,5a,6,9a-tetrahydro-4H-[1,3]dioxino[5,4-c][1,3]dioxol[4,5-h]isoquinoline-4-carboxylate:

(1,3-cis-tetrahydroisoquinoline) (3). Amine 11 (1.0 g, 2.50 mmol) was dissolved in dry toluene (4.0 mL), to which was added powdered 4Å molecular sieves (600 mg) and ethyl glyoxalate (50% solution in toluene, 700 μL, ~3.5 mmol). This mixture was stirred at rt for 1 h and then filtered through celite, rinsing with dry CH2Cl2, into a 500 mL 3-neck round bottom flask. The solution was concentrated and dried under high vacuum to provide 12 as a clear, colorless oil [Rf 0.74 (streaks) (Hex:EtOAc 1:1, UV, KMnO4)] which was used immediately in the radical closure.

In the 3-neck RBF equipped with a cold finger, condenser and inlet septum, the glyoxalimine 12 was dissolved in dry, degassed (freeze/pump/thaw x3) benzene (200 mL) and immersed in an oil bath set to 90°C under argon atmosphere. A solution of Bu3SnH (1.33 mL, 5.0 mmol) and AIBN (recrystallized from MeOH) (495 mg, 3.0 mmol) in degassed benzene (20 mL) was added to the solution drop-wise using a syringe pump over 5.5 h. The reaction mixture was stirred for 1 h following complete addition, then cooled and concentrated. A 1H NMR spectrum was acquired of the crude oil, that was subsequently purified by flash chromatography (1:1 hexanes:EtOAc) using silica gel containing 10% powdered KF. The tetrahydroisoquinoline 3 (591 mg, 58% over 2 steps) was obtained as a white solid.

Recrystallization from CH2Cl2/hex produced X-ray quality crystals that provided the relative stereochemistry at C1.

Rf = 0.21 (1:1 Hexanes:EtOAc, faint UV, KMnO4, PMA); M.p. 140-141°C (CH2Cl2/Hexanes). 
[α]D25 = -129.1 (c 1.0, CH2Cl2)

IR (thin film) 2990, 1736, 1193, 1103, 1030 cm⁻¹.

1H NMR (300 MHz, CDCl3) δ 6.04 (dddd, J = 17.2, 10.5, 5.1, 5.1 Hz, 1H), 5.91 (d, J = 1.4 Hz, 1H), 5.85 (d, J = 1.4 Hz, 1H), 5.40 (dq, J = 17.2, 1.8 Hz, 1H), 5.22 (dq, J = 10.5, 1.5 Hz, 1H), 4.89 (dd, J = 9.8, 0.8 Hz, 1H), 4.82 (br s, 1H), 4.37 (1/2ABq, J = 12.3 Hz, further split as dt, J = 5.1, 1.8 Hz, 1H), 4.30 (1/2ABq, J = 12.3 Hz, further split as dt, J = 5.1, 1.8 Hz, 1H), 4.21 (dq, J = 7.2, 2.7 Hz, 2H), 3.96 (dd, J = 10.8, 4.8 Hz, 1H), 3.81 (app t, J = 10.8 Hz, 1H), 2.87 (m, 1H), 2.13 (s, 3H), 1.66 (br s, 1H), 1.60 (s, 3H), 1.47 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H).

13C NMR (100 MHz, CDCl3) δ 171.4, 150.6, 145.7, 139.4, 134.2, 121.1, 115.9, 114.2, 112.0, 101.2, 99.7, 73.3, 69.9, 64.4, 61.5, 57.7, 53.9, 29.6, 19.0, 13.9, 9.2.

HRMS(FAB+) m/z calcd. For C21H28NO7 (M+H)⁺ 406.1866; found 406.1852.
Toluene-\textit{d8}, 348K
Toluene-d8, 298K

T = 308K

T = 318K

T = 328K

T = 338K

T = 348K
3
CDCl₃, 295K