Synthesis of 2,3,4,5-Tetrahydro-1,5-methano-1*H*-3-benzazepine via Oxidative Cleavage and Reductive Amination Strategies

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Abstract: Preparations of 2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine (**5**) from benzonorbornadiene (**1**) by oxidative cleavage and reductive amination sequences were investigated. Osmium-mediated dihydroxylation of **1** followed by NaIO$_4$ cleavage, reductive amination and debenzylation provides **5** in 64–73% yield overall in three operations. A tandem ozonolysis-reductive amination procedure gives **5** as the tosylate salt from benzonorbornadiene with no isolation of intermediates in 28% yield.

Key words: oxidation, ozonolysis, amination, reduction, bicyclic compounds

We recently required an efficient synthesis of **5** to support the preparation of pharmaceutically active intermediates. Originally **5** was prepared from benzonorbornadiene (**1**)[1] via hydration of the olefin and sequential oxidations [Al(O*t*-Bu)$_3$, SeO$_2$, and KO$_2$] which ultimately led to **4** (Scheme 1).[2] Diacid **4** was converted to the corresponding cyclic imide by dehydration, treatment with ammonium hydroxide and thermal dehydration. Finally, LiAlH$_4$ reduction provided **5** in 1.2% yield overall from **1**. Described herein are high yielding alternatives to the published synthesis of **5** from benzonorbornadiene.
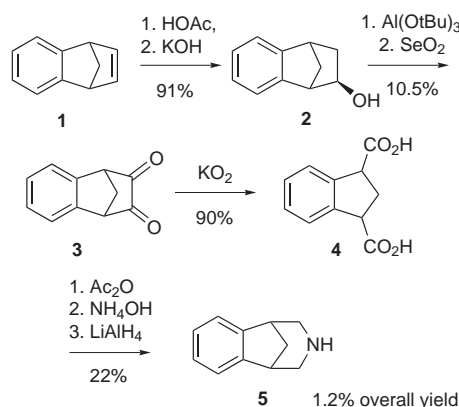
Scheme 1

Adopting Mazzocchi's strategy,[2] we focused on alternative oxidation protocols to cleave olefin **1** and gain access to the key precursor, dialdehyde **7**, which could be direct-ly converted to **8** using conventional reductive amination methods.[3] Osmium-catalyzed dihydroxylation of benzonorbornadiene (**1**) by the VanRheenan procedure was studied first.[4] Although successful, the conversion to diol **6** was extremely sluggish below 4–5 mol% OsO$_4$ catalyst load with *N*-methylmorpholine-*N*-oxide (NMO) in acetone–H$_2$O (8:1, 0.2 M).[5] The somewhat water soluble diol product, purified by traditional aqueous workup and chromatography, was an oily solid. After some experimentation we found that at higher concentration (0.5–1.5 M) and with rapid stirring, granular crystals precipitated directly from the reaction mixture leading to complete conversion within 60 hours.[6] Decanting or filtering the product and rinsing with fresh acetone afforded analytically pure **6** in 89% yield using 0.13–0.26 mol% catalyst loading (Scheme 2). We suspect that the increased dihydroxylation rate results from the direct crystallization of diol **6**.[7,8] Crystallization presumably liberates active osmium from catalytically less active species allowing osmium reentry into the catalytic cycle, thereby driving the reaction to completion.[9,10]
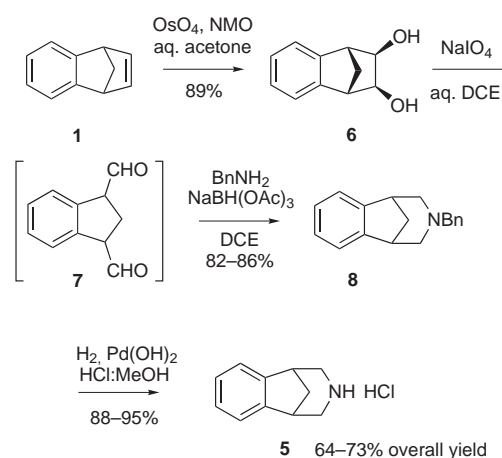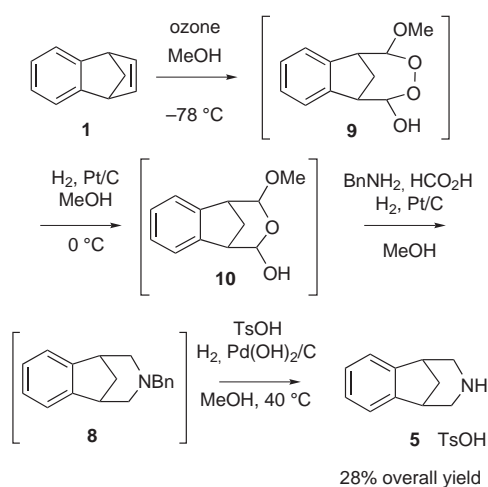

Scheme 2

Diol **6** was conveniently converted to **8** in a two-step procedure. Oxidative cleavage of **6** with NaIO$_4$ (1 equiv) gave dialdehyde **7** in aqueous dichloroethane. After washing with water to remove NaIO$_x$ salts, the extracts were combined with benzylamine (1.05 equiv) and added to NaBH(OAc)$_3$ (3.6 equiv).[11] Conversion to **8** occurs within hours. Aqueous workup and silica pad filtration of the extracts gave **8** in 82–85% yield. Hydrogenolysis of **8** (HCl

salt) removes the benzyl group[12] to provide target **5** in 97% yield, 64–73% for the overall sequence from **1**.

While this route was reliable, it required the use of osmium, which must be removed from the product. As an alternative we investigated ozonolysis for the oxidation of **1**.[13] A tandem process was realized by carrying out the ozonolysis of **1** and subsequent reductions in MeOH (Scheme 3). To form methoxyhydroperoxide glycal **9**, a stream of ozone was passed through a solution of **1** in MeOH at –78 °C. Once **9** had formed completely, it was reduced to **10** with 5% Pt/C under 40 PSI of H$_2$.[14] Benzylamine and HCOOH were added and hydrogenolysis was resumed to carry out the reductive amination to afford **8**.[15] Finally, the *N*-benzyl group was cleaved from **8** by hydrogenolysis with Pearlman's catalyst under acidic conditions (*p*-toluenesulfonic acid) and **5** was crystallized as the tosylate salt in 28% yield overall from **1**.

Scheme 3

Despite the lower yield by the ozonolysis approach relative to the osmium dihydroxylation route, the ozonolysis strategy avoids workups and chromatography: only a filtration is required between two of the steps. The single purification step at the end of the sequence is all that is required to isolate **5**. The process could be optimized further by improved cryogenic control during the hydrogenolysis steps.[16] Side products arise from both the reduction of the methoxyhydroperoxide (**9 → 10**) and the reductive amination (**10 → 8**), both steps of which are exothermic. Overall, we have demonstrated operationally simple and high yielding alternatives to the preparation of **5** from benzonorbornadiene (**1**).

All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by TLC or HPLC. HPLC analyses were performed using a YMC basic column (15 cm × 4.6 mm, 3 μm) and a mobile phase of (0.1% H$_3$PO$_4$, 10 mM SDS in H$_2$O)–MeCN (72:28). TLC was performed with EM separations technology silica gel F$_{254}$. Silica gel chromatography was carried

out with J. T. Baker 40 μm silica gel according to Still's procedure (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923). All glassware was flame-dried under dry nitrogen purge before use. ^{1}H NMR spectra were collected at 400 MHz with residual CHCl$_3$ as standard (7.26 ppm) and ^{13}C NMR were collected at 100 MHz. GC-MS and LC-MS data are reported with observed parent ions measured by TIC (total ion count).

Preparation of 1,4-Dihydro-1,4-methanonaphthalene [Benzonorbornadiene (1)];[17] Typical Procedure

1,2-Dibromobenzene (100 g, 429 mmol) and cyclopentadiene (28.4 g, 429 mmol) were stirred in toluene (510 mL) at 0 °C under N$_2$. To this solution was added *n*-BuLi (241 mL, 1.78 M in hexanes, 429 mmol) dropwise over 30 min during which the reaction solution became first yellow then cloudy white. After an additional 10 min at 0 °C the mixture was allowed to warm to r.t., stirred overnight, treated with H$_2$O (200 mL) and extracted with hexanes (3 × 150 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated to obtain yellow oil. The product was purified by chromatography on silica gel eluting with hexanes to provide **1** (54.3 g, 89%) as a colorless oil. Alternatively, the product could be distilled at 78–83 °C at 15 mmHg.

Preparation of 1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol (6); Typical Procedure

In a 2 L three-necked round-bottomed flask equipped with a N$_2$ flow adapter and mechanical stirrer was stirred **1** (79.5 g, 560 mmol) in acetone (800 mL) and H$_2$O (100 mL) with *N*-methyl morpholine *N*-oxide (67.5 g, 576 mmol). To this mixture was added osmium tetroxide (OsO$_4$, 15 mL of a 15 mol% *t*-BuOH solution, 1.48 mmol, 0.26mol%) and the mixture was stirred vigorously. After 60 h, the reaction was filtered, and the white product rinsed with acetone and air-dried (60.9 g). The mother liquor was partially concentrated to an oily solid which was triturated with acetone, filtered and rinsed with acetone to provide additional **6** (27.4 g, total 88.3 g, 89%); mp 176–177.5 °C; R$_f$ = 0.5 (TLC, 50% EtOAC–hexanes).

^{1}H NMR (400 MHz, CD$_3$OD): δ = 7.13 (m, 2 H), 7.03 (m, 2 H), 3.63 (d, *J* = 1.2 Hz, 2 H), 3.08 (s, 2 H), 2.20 (br d, *J* = 9.5 Hz, 1 H), 1.78 (ddd, *J* = 9.5, 3.3, 1.6 Hz, 1 H).

^{13}C NMR (100 MHz, CD$_3$OD): δ = 145.5, 126.3, 121.7, 71.0, 50.6, 42.5.

Anal. Calcd for C$_{11}$H$_{12}$O$_2$: C, 74.98; H, 7.05. Found: C, 75.02; H, 6.87.

Preparation of 1,2,3,4-Tetrahydro-1,4-methanonaphthalene-2,3-diol (6) with Seeding; Typical Procedure

In a 5 L three-necked round-bottomed flask equipped with a N$_2$ flow adapter and mechanical stirrer was placed benzonorbornadiene (**1**, 445 g, 3.13 mol) stirred in acetone (1.8 L) and H$_2$O (300 mL). *N*-Methyl morpholine *N*-oxide monohydrate (435.2 g, 3.22 mol) was added followed by OsO$_4$ (1 g, 3.9 mmol, 0.126mol%) and the mixture was vigorously stirred for 60 h (it was seeded after 12 h with authentic product: product could be seen as a white precipitate in the brown solution after 24 h). After 60 h, the reaction was filtered, and the white product rinsed with acetone and air-dried (355 g, 2.01 mol). The mother liquor was concentrated to an oily solid and acetone trituration, filtration and acetone rinse provided the desired product (48 g, 0.273 mol). A second concentration cycle provided additional product (87 g, 0.494 mol: total 490 g, 2.78 mol, 88.8%).

Alternative Preparation of 1,2,3,4-Tetrahydro-1,4-methano-naphthalene-2,3-diol (6); Typical Procedure

In a 1 L round-bottomed flask containing sodium chlorite (28.7 g, 80% purity from Aldrich, 254 mmol) dissolved in H$_2$O (200 mL) and *i*-PrOH (45 mL) was added K$_2$OsO$_4$·2H$_2$O (21.1 mg, 57.3 μmol, 0.045 mol%). The reaction flask was placed in a water bath at ap-

prox. 25 °C and a solution of **1** (18.1 g, 127 mmol) in *i*-PrOH (227 mL) was added dropwise over 20 min. The reaction is exothermic and the final temperature reached 32 °C. The reaction mixture was stirred for an additional 30 min and sodium sulfite was added in 3 portions (64.0 g, 508 mmol). The mixture was stirred for 1 h and the *i*-PrOH was distilled under reduced pressure followed by addition of H_2O (200 mL). The mixture was stirred for 15 min and the solids were filtered to yield ca. 25 g of a brown solid which triturated with 2:1 hexanes–MTBE (60 mL/30 mL) overnight to yield **6** (16.21 g, 72%).

Preparation of 3-Benzyl-2,3,4,5-tetrahydro-1,5-methano-1*H*-3-benzazepine (8); Typical Procedure

Diol **6** (40 g, 227.3 mmol) was stirred in H_2O (1050 mL) and 1,2-dichloroethane (DCE) (420 mL) in a 2 L round-bottomed flask under N_2 with cool water bath (ca 10 °C). To this $NaIO_4$ (51 g, 239 mmol) and Et_3BnNCl (50 mg) were added. The resulting mixture was stirred for 1 h (slight initial exotherm), then the layers were separated and the aqueous layer was extracted with dichloroethane (200 mL). The organic layer was washed with H_2O (4 × 200 mL, or until no reaction to KI–starch was observed in the aqueous wash) then dried through a cotton plug. To this solution of **7** was added benzylamine (25.5 g, 238.6 mmol) and the mixture was stirred for 2 min then immediately transferred over 10 min into a magnetically stirred dispersion of $NaBH(OAc)_3$ (154 g, 0.727 mmol) in dichloroethane (800 mL) at 0 °C under N_2 in a separate 2 L round-bottomed flask. The resulting orange mixture was allowed to warm to r.t. and stirred for 30–120 min. The reaction was quenched by addition of sat. aq Na_2CO_3 solution (ca 300 mL), carefully at first, and the mixture was stirred for 1 h (pH 9). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL). The organic layer was washed with sat. aq NaCl solution (200 mL), dried through a cotton plug and evaporated to a red oil. This oil was dissolved in a minimum of Et_2O and filtered through a silica pad (3 × 4 inch) eluting with 15% EtOAc–hexanes (+1% of 37% aq NH_4OH solution) to remove baseline red color. Concentration affords **8** (48.5 g, 195 mmol, 85.7%) as a light yellow oil; $R_f = 0.75$ (TLC, 10% EtOAc–hexanes).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.16 (m, 7 H), 6.89 (m, 2 H), 3.48 (m, 2 H), 3.08 (m, 2 H), 2.80 (d, $J = 9.5$ Hz, 2 H), 2.42 (d, $J = 9.5$ Hz, 2 H), 2.27 (m, 1 H), 1.67 (d, $J = 10.0$ Hz, 1 H).

MS (APCI): $m/z = 250.3$ [M + 1]⁺.

Preparation of 2,3,4,5-Tetrahydro-1,5-methano-1*H*-3-benzazepine (5); Typical Procedure

Benzylamine **8** (70.65 g, 284 mmol) was stirred in EtOAc (250 mL) and treated with 3 N HCl·ethyl acetate (1.03 equiv) slowly with cooling (ice bath). The resulting precipitate was filtered, rinsed with EtOAc and dried to give the HCl salt of **8** (80.6 g, 100%) as an off white solid. These solids were dissolved in MeOH (250 mL) in a Parr bottle. To this was added $Pd(OH)_2$ (7 g of 20% wt/C) and the mixture was shaken under 50–40 psi of H_2 for 24 h or until done by TLC. The reaction was filtered through a Celite pad and concentrated to an oily solid. This was azeotropically dried with MeOH (3 ×) then triturated with acetone and Et_2O to precipitate product. Filtration, concentration of the mother liquors and a second treatment provided **5** (48.95 g, 88%) as an off white solid. A sample was converted to the free base using CH_2Cl_2–aq Na_2CO_3 solution.

HCl Salt of 8

$R_f = 0.75$ (TLC, 10% EtOAc–hexanes).

^1H NMR (400 MHz, CD_3OD): δ = 7.46–7.40 (m, 5 H), 7.34–7.27 (m, 4 H), 4.27 (s, 2 H), 3.45 (br d, $J = 12.1$ Hz, 2 H), 3.38 (br s, 2 H), 3.28 (m, 2 H), 2.30 (m, 1 H), 2.05 (d, $J = 10.8$ Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 142.0, 131.7, 130.1, 129.0, 128.8, 128.7, 123.9, 60.6, 55.2, 41.5, 39.5.

MS (APCI): $m/z = 250.3$ [M + 1]⁺.

Anal. Calcd for $C_{18}H_{19}N \cdot HCl$: C, 75.64; H, 7.05; N, 4.90. Found: C, 75.36; H, 7.06; N, 4.78.

2,3,4,5-Tetrahydro-1,5-methano-1*H*-3-benzazepine (5)

$R_f = 0.2$ [TLC, 10% MeOH–CH_2Cl_2 (NH₃)].

^1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (m, 4 H), 2.97 (m, 4 H), 2.68 (d, $J = 12.5$ Hz, 2 H), 2.41 (m, 1 H), 1.95 (d, $J = 11.0$ Hz, 1 H).

MS (APCI): $m/z = 160.2$ [M + 1]⁺.

Preparation of 5 from 1 via Ozonolysis; Typical Procedure

A stream of ozone was bubbled through a solution of benzonorbornadiene, (**1**, 4.00 g, 28.1 mmol, 1.0 equiv) in MeOH (80 mL) at –78 °C. Once the solution developed a blue color (approx. 20 min), ozone generation was stopped then oxygen was bubbled through for 5 min to purge the blue color. The solution was further purged with N_2 for 20–40 min to deoxygenate the solution. This solution was transferred to a Parr bottle. To the cold solution was added of 5% Pt/C (55% wet, 0.20 g, 0.001 equiv, supplied by Johnson Matthey). The system was passivated with H_2, pressurized to 40 PSI of H_2, and gradually warmed to r.t. (ideally the reactor was maintained at 0 °C or colder). Once the methoxyhydroperoxide glycal **9** was reduced to **10** completely (no reaction to KI–starch was observed, H_2 uptake had ceased and HPLC showed consumption of **9** within 45–60 min), an additional amount of 5% Pt/C (0.798 g, 0.004 equiv) was added to the reaction mixture at 0 °C, followed by benzylamine (3.07 mL, 1.0 equiv) and 96% HCOOH (0.56 mL, 0.50 equiv). The system was repressurized to 50 PSI of H_2 and allowed to warm to r.t. Once compound **10** was consumed (within 4 h, monitored by HPLC), the reaction mixture was removed from the reactor and filtered through a pad of celite, washing with MeOH (20 mL). A pressure reactor was charged with the crude reaction mixture in MeOH (100 mL) and *p*-toluene sulfonic acid monohydrate (3.74 g) and 20% $Pd(OH)_2/C$ (0.986 g, 50% wet by weight). The reactor was pressurized to 50 PSI of H_2 after passivation and heated to 40 °C. After heating for 15 h the reactor was cooled to r.t. and the reaction mixture was filtered through celite (washing with MeOH). The filtrate was concentrated in vacuo and stripped from *i*-PrOH (20 mL). The residue was redissolved in *i*-PrOH (32 mL) and heated to 70 °C. To the hot solution was added hexane (16 mL) and the resulting solution was allowed to slowly cool with stirring. Crystals formed and were stirred at r.t. for 12 h. The white crystals were filtered and dried to give the tosylate salt of **5** (2.65 g, 28%); mp: 207–208 °C.

IR (KBr): 3438, 3021, 2958, 2822, 2758, 2719, 2683, 2611, 2424, 1925, 1606, 1497, 1473, 1428, 1339, 1302, 1259, 1228, 1219, 1176, 1160, 1137, 1122, 1087, 1078, 945, 914, 876, 847, 829, 818, 801, 710, 492 cm⁻¹.

^1H NMR (400 MHz, CD_3OD): δ = 7.69 (d, $J = 7.9$ Hz, 2 H), 7.43–7.32 (m, 4 H), 7.23 (d, $J = 7.9$ Hz, 2 H), 3.37 (d, $J = 11.2$ Hz, 4 H), 3.30 (br s, 2 H), 3.15 (d, $J = 12.4$ Hz, 2 H), 2.36 (s, 3 H), 2.40–2.35 (m, 1 H), 2.08 (d, $J = 11.2$ Hz, 1 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 140.8, 140.5, 139.1, 127.2, 127.2, 124.3, 122.3, 45.1, 39.7, 37.3, 18.7.

Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23; Found: C, 65.05; H, 6.48; N, 4.26.

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