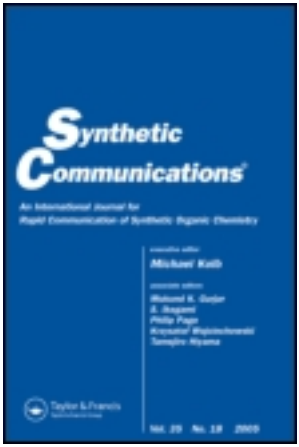

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Bicyclo[3.2.1]octanes via McMurry Couplings

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BICYCLO[3.2.1]OCTANES VIA MCMURRY COUPLINGS

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Abstract: A novel approach to the synthesis of bicyclo[3.2.1]octane systems is described. The key step involves the McMurry coupling of ketoaldehyde **7** which leads to the bridgehead dihydroxybicyclo[3.2.1]octane **8**.

The bicyclo[3.2.1]octane system is present in many naturally occurring biologically active compounds.[1] It has also served as a useful building block for the synthesis of a wide variety of natural and unnatural compounds.[2] The synthesis of 2-hydroxybicyclo[3.2.1]octane has received a great deal of attention over the years. A variety of approaches to the system have been outlined and successfully applied to the total synthesis of many natural products.[3] None the less, a general methodology for the synthesis of bridgehead dihydroxybicyclo-[3.2.1]octanes has never been realized.

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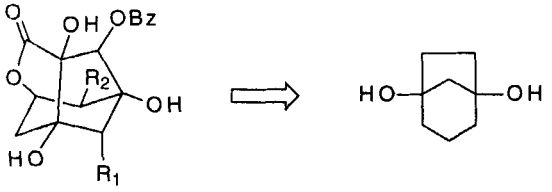
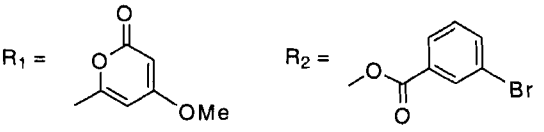
Scheme 1

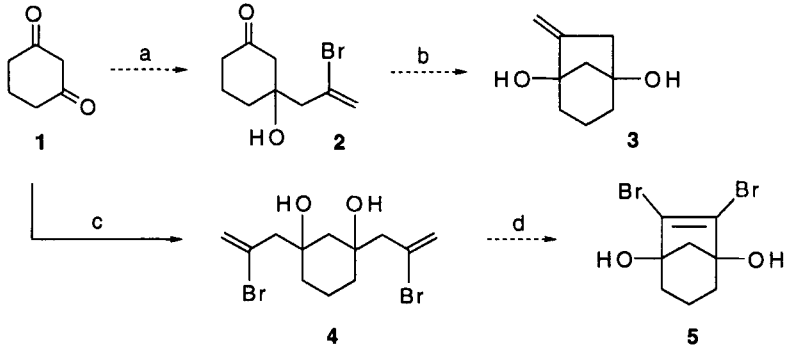


Enterocin



Enterocin is an antibiotic with static activity against gram-positive and gram-negative bacteria (scheme 1).[4] It was first isolated from Japanese soil samples containing *Streptomyces candidus* var. *enterostaticus* and *S. viridochromogenes* var. M-127. Initially, we planned a synthesis of enterocin which involved the preparation of the bridgehead dihydroxy bicyclo[3.2.1]octane **3** *via* a radical cyclization of bromoketone **2** (scheme 2). 3-Halohomoallyl alcohols can be prepared efficiently *via* zinc[5], tin[6] or indium[7]-promoted 2-haloallylation of carbonyl compounds with 2,3-dihalopropene. To the best of our knowledge, these methodologies have never been applied to the alkylation of 1,3-diones. This prompted us to rigorously examine the reaction of 1,3-cyclohexadione and 2,3-dibromopropene in the presence of zinc, tin and indium. Surprisingly, no reaction was observed with zinc and indium, while tin provided the dialkylated product **4** along with unreacted starting material. This lack of reactivity may in part be due the formation of the enol tautomer of 1,3-cyclohexadione which would reduce the electrophilic nature of the carbonyl groups. The ^{13}C NMR spectra of **4** shows 7 lines, indicating that it has a *cis* configuration.[8] Unfortunately, numerous attempts

Scheme 2



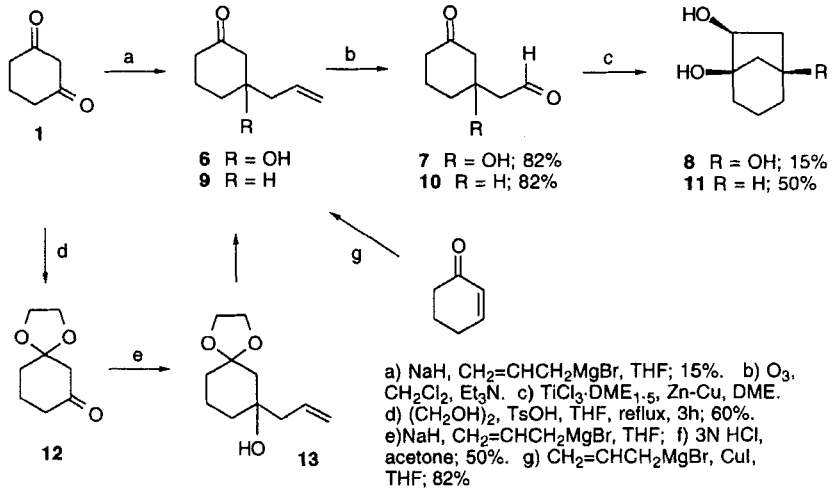
a) Sn or Zn or In, 2,3-dibromopropene, aq. solution. b) SmI_2, THF.
c) Sn, HBr, H_2O, ether, 10% d) metathesis

at the metathesis of **4** to diol **5** with $(Cy_3P)_2Cl_2Ru{=}CHPh$ or $Mo(CHCMe_2Ph)(N(2,6\text{-}(i\text{-}Pr)_2C_6H_3))(OCMe(CF_3)_2)_2$[9] failed.

Previously, the synthesis of the bridgehead hydroxy bicyclo[3.2.1]octane has been achieved *via* free radical cyclization[10], intramolecular enolate alkylation[11], reductive cyclization[12], Barbier reaction[13], photoreductive cyclization[14], C-H insertion reaction[15] and allylsilane annulation[16]. Nicolaou and coworkers have successfully applied the McMurry coupling reaction to the construction of the Taxol skeleton.[17] Encouraged by these results, we envisioned using this cyclization in our synthesis of the bridgehead hydroxy bicyclo[3.2.1]octane.

To this end, ketoalcohol **6** was prepared by addition of excess allylmagnesium bromide to the sodium enolate of cyclohexa-1,3-dione in 15% yield (Scheme 2).[18] This yield was enhanced to 31% when cyclohexa-1,3-dione was protected as its monoketal prior to alkylation. Alkene **6** was subsequently oxidized to aldehyde **7** in 82% yield. The Ti^0-mediated McMurry coupling reaction[19] occured when a DME solution of ketoaldehyde **7** was added by syringe pump to a

Scheme 3



DME solution of $TiCl_3 \cdot (DME)_{1.5}$ (11 equivalents) and Zn-Cu couple (26 equivalents) at 70 °C. Triol **8** was isolated in 15% yield. The rather low yield in this reaction reflects the inherent difficulty of forming such a highly functionalized and strained ring system. Alternatively, ketone **9** was prepared *via* conjugate addition of allyl Grignard to cyclohexenone in the presence of copper iodide Ozonolysis of **9** followed by a McMurry coupling under similar conditions provided **11** in 50% yield.

In summary, a bridgehead dihydroxybicyclo[3.2.1]octane (**8**) was synthesized by a relatively simple route. The key step involves a Ti°-mediated McMurry cyclization in the presence of Zn-Cu couple. This notes the first time a McMurry coupling was employed in the construction of the bicyclo[3.2.1]octane system. This procedure should make **8** readily available as an important intermediate for organic synthesis.

Experimental Section

1,3-di(2-bromoprop-2-enyl)cyclohexane-1,3-diol (4). To a solution of tin powder (120 mg, 1.0 mmol) and 2,3-dibromopropene (300 mg, 1.5 mmol) in Et_2O-H_2O (1:1, 2 mL) was added 2 drops of HBr (48% H_2O solution) and 1,3-cyclohexanedione (71 mg, 0.63 mmol) at 25°C. The reaction mixture was stirred at 25°C for 25 h. The resulting solution was diluted with Et_2O (30 mL), washed with H_2O (10 mL). The ether solution was dried over $MgSO_4$ and concentrated *in vacuo* to give the oil product. The crude product was purified by flash column chromatography (silica gel) with 15% EtOAc-hexane (R_f = 0.54 in 30% EtOAc-hexane) to give the diol **4** as a colorless oil (22 mg, 10% yield) and recovered 1,3-cyclopentadione (40 mg, 56% recovered). IR (neat): 3354, 2938, 1722, 1622, 1416, 1344, 1294, 1158, 992, 892 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.63 (d, J = 8.8 Hz, 4 H), 3.50 (br.s, 2 OH), 2.62 (s, 4 H), 1.17-2.09 (m, 8 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 127.23 (two C of C), 121.66 (two C of CH_2), 72.74 (two C of C), 54.25 (two C of CH_2), 44.57 (two C of CH_2), 36.64 (two C of CH_2), 16.87 (two C of CH_2); MS (m/z, relative intensity): 357 (M^++4, 6), 355 (M^++2, 14), 353 (M^+, 6), 235 (34), 233 (33), 217 (100), 215 (99), 135 (26), 113 (70), 85 (33); exact mass calculated for $C_{12}H_{19}O_2Br_2$ (M^++1): 352.9751; found 352.9773.

3-hydroxy-3-prop-2-enylcyclohexan-1-one (6). Method A: To a mixture of NaH (288 mg, 12 mmol) in THF (30 mL) was added 1,3-cyclohexanedione (1.12 g, 10 mmol) and stirred for 30 min at 25 °C. To this mixture was added a solution of allylmagnesium bromide in THF (1.1 N, 13.6 mL, 15 mmol). The reaction mixture was stirred at 60°C for 1 h. The reaction was quenched by addition of H_2O (2 mL) at 0 °C. The solution was extraction with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude

product **6**. The residue was purified by flash column chromatography with 10% EtOAc/hexane (R_f = 0.59 in 30% EtOAc/hexane) to give alcohol **6** as a colorless oil (231 mg, 15% yield). IR (neat): 3418, 2950, 1704, 1698, 1422, 1230, 1118, 972, 918 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.68-5.95 (m, 1 H), 5.07-5.20 (m, 2 H), 1.62-2.55 (m, 11 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 210.37 (C), 132.22 (CH), 120.10 (CH_2), 75.23 (C), 53.00 (CH_2), 47.00 (CH_2), 40.72 (CH_2), 35.47 (CH_2), 20.99 (CH_2); MS (m/z, relative intensity): 154 (M^+, 1), 136 (3), 113 (100), 85 (58), 55 (12); exact mass calculated for $C_9H_{14}O_2$ (M^+): 154.0994; found 154.0996.

Method B: To a solution of magnesium powder (1.6 g, 65.8 mmol) and ketal **12**[20] (3.5 g, 22.4 mmol) in dry THF (20 mL) was added a solution of allyl bromide (5.43 g, 44.9 mmol) in THF (20 mL) over a period of 15 min at 60°C. The reaction mixture was stirred at 60°C for 1 h. The reaction was quenched by addition of H_2O (2 mL) at 0 °C. The solution was extracted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product **13**. To a solution of this crude **13** in acetone (150 mL) was added HCl (0.5 mL, 3N in H_2O). The solution was stirred for 30 min at 25 °C and extracted with ethyl acetate (500 mL), washed with aqueous saturated $NaHCO_3$ solution (50 mL) and H_2O (50 mL), concentrated *in vacuo* to give the crude product **6**. The residue was purified by flash column chromatography with 10% EtOAc/hexane (R_f = 0.59 in 30% EtOAc/hexane) to give alcohol **6** as a colorless oil (1.6 g, 46% yield).

2-(1-hydroxy-3-oxocyclohexyl)ethanal (7). A stream of ozone was bubbled through a solution of alcohol **6** (1.5 g, 9.7 mmol) in CH_2Cl_2 (40 mL) at -78 °C until the solution turned into pale blue color. Triethylamine (5 mL) was added slowly and warmed up to room temperature over 1 h. The solution was

diluted with ethyl acetate (500 mL), washed with brine, dried over anhydrous magnesium sulfate, concentrated *in vacuo* and the residue was purified by flash column chromatography with 2% MeOH-CH_2Cl_2 (R_f = 0.58 in 10% MeOH-CH_2Cl_2) to give aldehyde **7** (1.24 g, 82% yield). IR (neat): 3416, 2954, 1712, 1416, 1352, 1318, 1234, 1126, 1062, 952 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 9.82 (t, J = 1.2 Hz, 1 H), 3.45 (s, 1 H), 2.72 (br.s, 2 H), 1.42-2.67 (m, 8 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 209.88 (C), 202.03 (CH), 74.37 (C), 54.28 (CH_2), 53.02 (CH_2), 40.42 (CH_2), 35.62 (CH_2), 20.55 (CH_2); MS (m/z, relative intensity): 156 (M^+, 8), 138 (57), 128 (28), 113 (65), 110 (100), 95 (39), 82 (65), 71 (55); exact mass calculated for $C_8H_{12}O_3$ (M^+): 156.0786; found 156.0779.

Bicyclo[3.2.1]octane-1,5,6-triol (8). A solution of $TiCl_3$·$DME_{1.5}$ (2.6 g, 9 mmol) and Zn-Cu (1.67 g, 27.1 mmol) in dry DME (25 mL) was heated to reflux for 5 h. To this solution was slowly added a solution of aldehyde **7** (140 mg, 0.90 mmol) in DME (25 mL) over 40 h. The solution was stirred for further 3 h and filtered through celite 545, washed with H_2O (50 mL), extracted with 10% isopropanol-EtOAc (5x150 mL). The organic solution was dried over $MgSO_4$, concentrated *in vacuo* to give the crude product. The residue was purified by flash column chromatography with 15% MeOH-CH_2Cl_2 (R_f = 0.23 in 15% MeOH-CH_2Cl_2) to give the triol **8** as a colorless oil (22 mg, 15% yield). IR (neat): 3390, 2946, 1652, 1338, 1264, 1104, 1056 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz): δ 4.11 (dd, J = 5.8, 2.2 Hz, 1 H), 3.92 (br.s, 3 OH), 1.03-2.22 (m, 10 H); ^{13}C NMR (acetone-d_6, 50 MHz): δ 80.65 (C), 78.62 (CH), 75.92 (C), 52.81 (CH_2), 46.66 (CH_2), 40.69 (CH_2), 34.94 (CH_2), 20.27 (CH_2); MS (m/z, relative intensity): 140 (M^+-18, 6), 113 (100), 97 (59), 84 (38); exact mass calculated for $C_8H_{14}O_3$ (M^+): 158.0943; found 158.0940.

2-(3-oxocyclohexyl)ethanal (10). Starting from ketone **9**[21] as described for the preparation of **7**, the crude product after purification by flash column chromatography with 40% EtOAc-hexane (R_f = 0.25 in 50% EtOAc-hexane) gave aldehyde **10** (85% yield). IR (neat): 2954, 1720, 1712, 1416, 1352, 1318, 1234, 1126 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 9.67 (s, 1 H), 1.12-2.56 (m, 11 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 210.02, 200.83, 49.98, 47.53, 40.96, 33.45, 30.83, 24.77.

Bicyclo[3.2.1]octane-1,7-diol (11). Starting from aldehyde **10** as described for the preparation of **8**, the crude product after purification by flash column chromatography with 70% EtOAc-hexane (R_f = 0.29 in 80% EtOAc-hexane) gave the diol **11** as a colorless oil (50% yield). IR (neat): 3390, 2932, 1258, 1110, 1054, 908 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 3.67 (dd, J = 10.4, 4.2 Hz, 1 H), 0.77-2.61 (m, 13 H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 78.09 (C), 73.65 (CH), 41.95 (CH_2), 38.83 (CH_2), 36.85 (CH_2), 32.49 (CH), 29.87 (CH_2), 19.05 (CH_2); MS (m/z, relative intensity): 142 (M^+, 3), 109 (22), 94 (100), 83 (41), 71 (58), 57 (66); exact mass calculated for $C_8H_{14}O_2$ (M^+): 142.0994; found 142.0996.

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