Synthesis of Medium Sized Rings from the Cycloadducts of 3,5-Dibromo-2-pyrone *via* a Radical Mediated Fragmentation Reaction

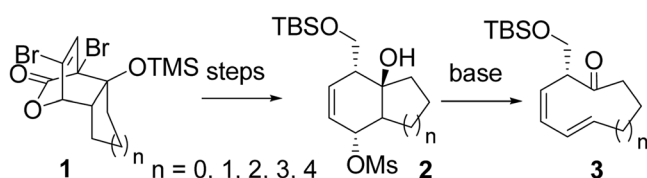**Jae-Hee Choi, In-Ji Shin, Eun-Sil Choi, and Cheon-Gyu Cho**[*]

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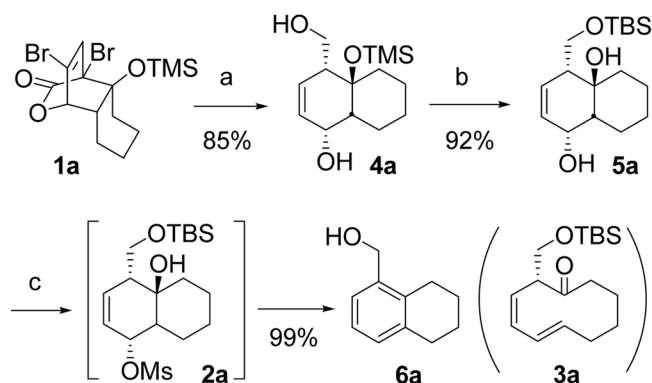*Received September 13, 2006*

Medium sized macrocycles, natural or unnatural, are important synthetic targets because of a wide spectrum of their intriguing biological activity.[1] Various synthetic strategies have been developed, most of which utilize ring closure of α,ω-bifunctional linear precursors.[2] Despite many examples in the literature, the formation of medium sized rings is not a trivial task, owing to the unfavourable entropic change associated with. Moreover, the requisite employment of high dilution conditions renders the preparative scale synthesis arduous. Also reported were various methods based on ring expansion including the Wharton/Grob fragmentation as alternatives.[3,4]

We have previously reported the synthesis of structurally novel tricyclolactones **1** from the Diels-Alder cycloadditions of 3,5-dibromo-2-pyrone[5] with cyclic enol ethers.[6] Envisioning the potency of mesylates **2**, readily accessible from **1**, for the ensuing the Wharton/Grob type fragmentation,[4] we decided to investigate the synthetic manipulation of **1** to medium sized rings **3** (Scheme 1).

The cycloadduct **1a** was first converted into triol **4a** upon

debrominations with 2 equiv of Bu$_3$SnH and reductive opening of the lactone bridge with excess LiAlH$_4$ (Scheme 2).[5] Deprotection of TMS followed by selective protection of the primary alcohol with TBS afforded **5a**. Subsequent mesylation of the secondary hydroxyl group of **5a** would set the stage for the Wharton/Grob fragmentation reaction. However, the attempted mesylation of **5a** furnished aromatized product **6a** in quantitative yield instead of the desired ketone **3a**. Evidently, the initially formed putative mesylate **2a** further underwent β-elimination and dehydration reaction. Running the mesylation reaction at lower temperatures produced similar results.

Triol **5a** was then hydrogenated into **7a** before the mesylation, envisioning the removal of the double bond may suppress the ensuing β-elimination reaction (Scheme 3). Treatment of **7a** with MsCl indeed provided mesylate **8a** in good yield. However, subjection of mesylate **8a** into the Wharton/Grob fragmentation conditions resulted in the formation of alkene **9a**, rather than the fragmentation product (Scheme 3).

During the investigation, Markó and coworkers reported an efficient radical fragmentation protocol for the Wharton/Grob type ring expansion reactions of bicyclic tertiary hydroxyl ketones, providing 9-, 10-, and 11-membered
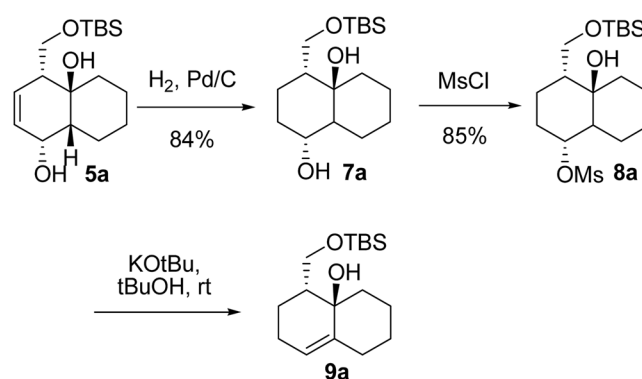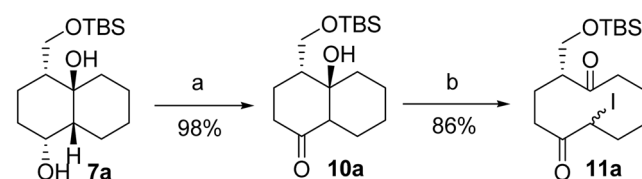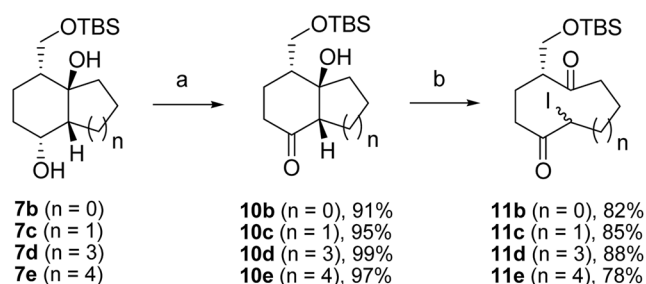
Scheme 1. Fragmentation reaction of **2**.

Scheme 2. Synthesis and fragmentation reaction of mesylate **2a**.
(a) (i) Bu$_3$SnH, AlBN, benzene, reflux, (ii) LiAlH$_4$, Et$_2$O, 0 °C; (b) (i) TBAF, THF, rt, (ii) TBSCl, imidazole, rt; (c) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C.

Scheme 3. Mesylation and fragmentation reaction of **7a**.

Scheme 4. Synthesis and fragmentation reaction of ketone **10a**. (a) Dess-Martin periodinane, CH$_2$Cl$_2$, rt; (b) HgO, I$_2$, CCl$_4$, rt, hv.

Scheme 5. Synthesis and fragmentation reactions of ketones **10b-10e**. (a) Dess-Martin periodinane, CH_2Cl_2, rt; (b) HgO, I_2, CCl_4, rt, hv.

diketo-macrocycles.[7] Triol **7a** was then oxidized to ketone **10a**, prior to the fragmentation reaction. Subjection of the resultant ketone **10a** into the Markó's conditions afforded the ring expansion product **11a** in 86% yield (Scheme 4).

The above protocol was equally effective for the fragmentation of other bicyclic system **10b-10e**, providing **11b-11e** in good yields (Scheme 5). Tributyltin hydride mediated deiodination reactions furnished 8-, 9-, 10-, 11-, 12-membered diketones in 80-85% yields.

In summary, the tricyclolactones **1** prepared from the Diels-Alder reactions of 3,5-dibromo-2-pyrone and cyclic silyl enol ethers were successfully converted into 8-, 9-, 10-, 11-, and 12-carbon medium sized macrocycles **11a-11e** in good overall yields with the Wharton/Grob fragmentation protocol developed by Markó and coworkers as key step.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz, with either TMS (δ = 0) or the signal for residual $CHCl_3$ in the $CDCl_3$ solvent (δ = 7.24) as internal standards. *J* values are reported in Hz. High resolution mass spectra were measured by using FAB method. Flash column chromatography was performed with 230-400 mesh grade silica-gel. All solvents used were purified according to standard procedures.

Preparation of 7a as Representative Procedure for 7b-7e: To a solution of **5a** (300 mg, 0.96 mmol) in dried THF (4.0 mL) was added 10 wt% Pd-C at rt. The mixture was degassed and subjected to a hydrogen atmosphere and agitated at rt for 8 h. The reaction mixture was then filtered through a plug of Celite, concentrated in vacuo, and purified by flash column chromatography (hexane/EtOAc = 10/1) to afford 253 mg of the product **7a** in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09 (bs, 1H), 3.76 (t, *J* = 9.9 Hz, 1H), 3.61 (dd, *J* = 9.9, 5.1 Hz, 1H), 2.13-2.08 (m, 1H), 1.85-1.68 (m, 5H), 1.60-1.51 (m, 6H), 1.44-1.33 (m, 1H), 1.23-1.18 (m, 1H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.5, 73.3, 65.6, 48.6, 44.9, 34.0, 28.4, 25.8, 25.8, 22.6, 20.2, 20.1, 17.9, −5.8; HRMS (M + Na^+) Calcd for $C_{17}H_{34}NaO_3Si$: 337.2175, found 337.2181.

Preparation of 10a as Representative Procedure for 10b-10e: To a round bottom flask were charged of **7a** (210 mg, 0.67 mmol) and anhydrous CH_2Cl_2 (4.0 mL). Dess-Martin periodinane (321 mg, 0.73 mmol) was slowly added

into the solution at rt. The reaction mixture was vigorously stirred for 30 min. After the reaction, the resulting solution was diluted with ether, successively washed with sat. $NaHCO_3$ (aq) and sat. $Na_2S_2O_3$ (aq). The organic solution was dried over Na_2SO_4 and purified by column chromatography (hexane/EtOAc = 5/1) to provide 204 mg of product **10a** in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (t, *J* = 10.3 Hz, 1H), 3.73 (dd, *J* = 10.3, 5.1 Hz, 1H), 2.48-2.47 (m, 1H), 2.38-2.33 (m, 3H), 2.05-2.01 (m, 1H), 1.83-1.60 (m, 4H), 1.55-1.44 (m, 2H), 1.43-1.16 (m, 3H), 0.92 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 75.9, 65.1, 56.1, 47.1, 40.0, 28.9, 25.8, 23.4, 21.7, 20.5, 19.8, 18.0, −5.8; HRMS (M + Na^+) Calcd for $C_{17}H_{32}NaO_3Si$: 335.2018, found 335.2012.

Preparation of 11a as Representative Procedure for 11b-11e: To a round bottom flask were charged **10a** (59 mg, 0.19 mmol) and anhydrous CCl_4 (3.0 mL). To the solution were added yellow HgO (123 mg, 0.57 mmol), I_2 (192 mg, 0.76 mmol) at rt. The reaction mixture was irradiated with 500W tungsten lamp with vigorous stirring for 2 h. After the reaction, the reaction mixture was filtered through a plug of Celite, diluted with CH_2Cl_2 and washed with sat. $Na_2S_2O_3$ (aq). The organic layer was died over Na_2SO_4, concentrated in vacuo, and purified by flash column chromatography (hexane/EtOAc = 30/1) to afford 71 mg of the product **11a** in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.43 (dd, *J* = 11.7, 3.3 Hz, 1H), 3.62-3.51 (m, 2H), 3.04-2.96 (m, 1H), 2.91-2.84 (m, 1H), 2.74-2.65 (m, 2H), 2.33-2.21 (m, 2H), 2.15-2.07 (m, 1H), 1.85-1.73 (m, 3H), 1.66-1.60 (m, 2H), 1.50-1.43 (m, 1H), 0.83 (s, 9H), 0.00 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.6, 206.8, 66.1, 52.2, 46.1, 35.1, 33.8, 32.1, 28.4, 25.8, 23.4, 21.4, 18.1, −5.7; HRMS (M + Na^+) Calcd for $C_{17}H_{31}INaO_3Si$: 461.0985, found 461. 0989.

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