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A novel approach to the synthesis of 11,11-dimethyl-bisbenzopyran-5-ones

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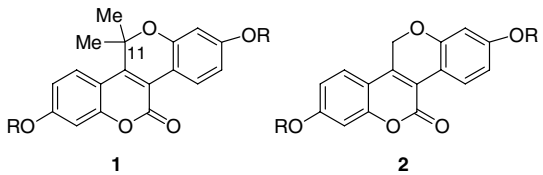
Abstract—A facile route for the synthesis of 11,11-dimethyl-bisbenzopyran-5-ones ring system is described. The key step, the late stage oxidation of the allylic methylene group was achieved by benzyl(triethyl)ammonium permanganate in CH_2Cl_2.

1. Introduction

Recently, we have disclosed a series of potent selective estrogen receptor modulators (SERMs) with bisbenzopyran system (**A**) mimicking steroid scaffold.[1] This novel class of compounds has demonstrated excellent in vitro and in vivo biological profiles for potential treatment of postmenopausal syndrome and hormone-dependent tumors such as breast and endometrial cancers. During development of this series of compounds, we observed that bisbenzopyran system (**A**) was found to be unstable in the air. At room temperature, these compounds turn into complex unidentifiable mixtures after a few days. We discovered that after staying in methanol for extended time, the methylene group in bisbenzopyran **A** was substituted with a methoxy group to yield **C**. We reasoned that the formation of oxonium **B** is the major mechanism for the instability of bisbenzopyran **A**, and decided to introduce *gem*-dimethyls to the methylene group to block the oxidation process (Scheme 1). Herein, we wish to report the chemistry we developed for the synthesis of the key intermediate, *gem*-dimethyl lactones **1**.



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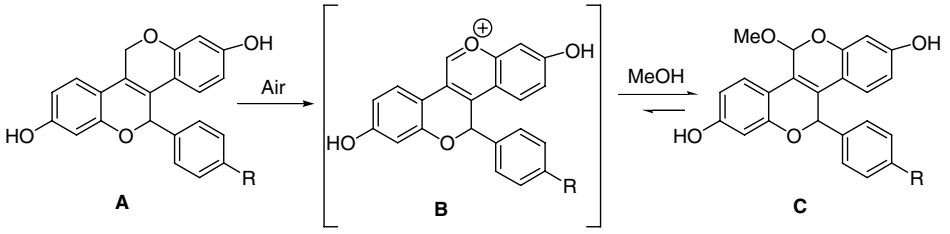
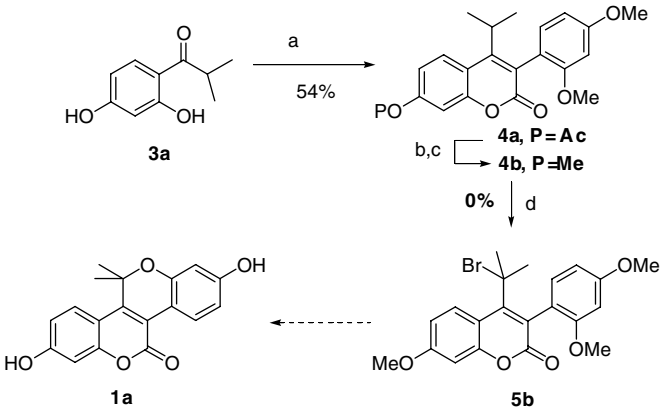
2. Results and discussion

Analogous to our earlier synthesis of lactones **2**,[2a] we first attempted the sequence illustrated in Scheme 2. Although the Perkin reaction of 2,4-dihydroxyphenylisoproanone **3a** and 2,4-dimethoxyphenylacetic acid delivered coumarin **4a** in moderate yield and the conversion of **4a** to **4b** proceeded in reasonable yield,[3] all attempts to introduce halogens using our previously reported anionic method (Br or Cl) to the allylic methine were unsuccessful.[2a,c]

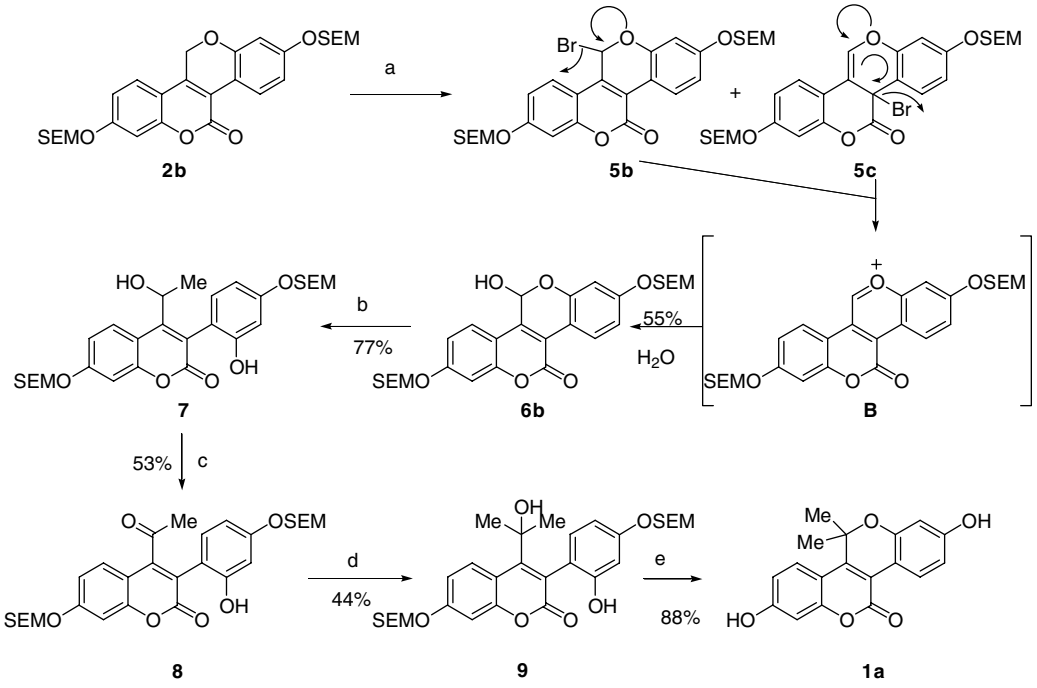
Since lactones **2** can be prepared in large scale, we decided to explore possible ways to directly introduce *gem*-dimethyl groups to methylene in **2**. Scheme 3 describes our first successful synthesis of lactone **1**. We discovered that bisbenzopyran lactone **2b** gave mixture of bromination products **5b** and **5c** in the 2:3 ratio when treated with LiHMDS, followed by reaction with NBS. When the mixture was stirred for extended time (>8 h) in saturated solution of $NaHCO_3$, hemiacetal **6b** was obtained as the major product in 55% yield over two steps. This indicates that both **5b** and **5c** were converted to **6b** during hydrolysis. We reasoned that this conversion proceeds through the oxonium intermediate **B** so that the overall yield of **6b** is higher than that from full conversion of **5b**. To our delight, **6b** reacts with MeMgBr efficiently and gave secondary alcohol **7** in high yield, which was converted to tertiary alcohol **9** in two steps by oxidation with Dess–Martin periodine to yield compound **8**, followed by addition of MeMgBr. The cyclization and global deprotection was achieved in one pot using 1 N HCl in 1:1 THF/ACN as solvent



Scheme 1. Proposed mechanisms of the instability of bisbenzopyran **A**.



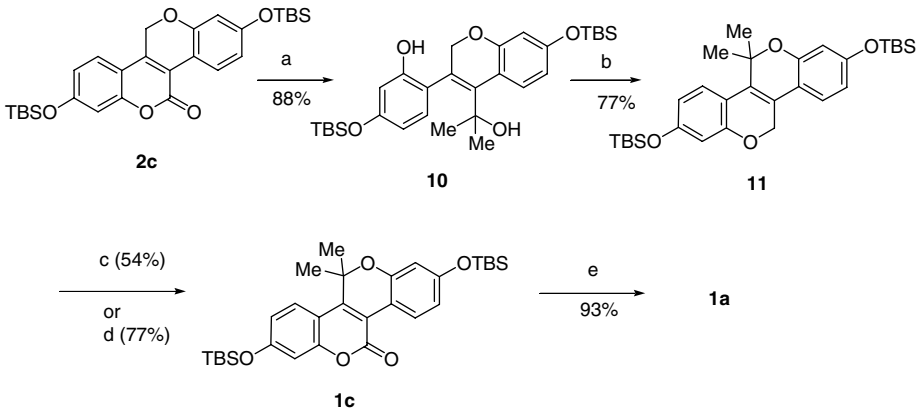
Scheme 2. Reagents and conditions: (a) Et_3N, Ac_2O/reflux, 2,4-dimethoxyphenylacetic acid, 36 h; (b) K_2CO_3, MeOH, rt, 7 h; (c) MeI, K_2CO_3, acetone, reflux, 12 h; (d) LiHMDS, THF, −30 °C, NBS, −30 °C to rt, 12 h.



Scheme 3. Reagents and conditions: (a) LiHMDS/THF/−32 °C→NBS/THF/−78 °C, 30 min-workup by satd aq $NaHCO_3$; (b) MeMgBr/THF/0 °C, 30 min; (c) Dess–Martin periodine (1.5 equiv)/CH_2Cl_2, 1 h; (d) MeMgBr (4 equiv)/THF/−10 °C, 12 h; (e) TFA/CH_3CN/THF (1:1:1), 0 °C, 3 h.

system to yield the final product 11,11-dimethylbenzopyran lactone **1a**.

Although the above conversion provided us with a reasonable access to *gem*-dimethyl lactones **1**, it is lengthy for large scale synthesis and the overall yield is moderate (~16%). To develop a second-generation synthesis for these critical intermediates, we took advantage of the symmetric nature of bisbenzopyran core in lactones **2** to introduce the *gem*-dimethyl groups first, followed



Scheme 4. Reagents and conditions: (a) MeMgBr (excess)/THF/−10 °C, 7 h; (b) TFA/toluene/0 °C, 30 min; (c) PCC (5 equiv), CrO_3 (5 equiv), 3,4-dimethylpyrazole (10 equiv), CH_2Cl_2, −20 °C; 6 h; (d) benzyl(triethyl)ammonium permanganate (9 equiv), CH_2Cl_2, 0 °C, 3 h.

by the oxidation of the methylene to re-introduce the lactone function group. Thus, the key intermediate **11** was prepared by addition of MeMgBr (10 equiv) to **2c** to yield tertiary alcohol **10**, followed by cyclization under acidic conditions. We screened many allylic oxidation conditions to re-introduce the lactone group.[4] Jones reagent, MnO_2, and RuO_4 failed to produce any desired compound. Oxidation via selenium dioxide, PCC, and KO_2 also proved unsuccessful. A protocol originally developed by Paquette using a mixture of PCC (5 equiv), chromium trioxide (5 equiv), and 3,5-dimethylpyrazole (10 equiv) proved to be successful and yielded 11,11-dimethylbisbenzopyran lactone **1c** in moderate yield. To our delight, when we carried out the reaction with benzyl(triethyl)ammonium permanganate as oxidant, the yield was improved to 77%. Finally, the deprotection of TBS group was achieved by tetrabutylammonium fluoride in high yield.[4] The overall yield to **1a** is 48% (Scheme 4). This synthetic sequence was employed in the synthesis of several lactones **1** with various protecting groups of the phenol hydroxyl groups, including in multi gram scale.

In conclusion, we have developed a novel, convenient, and practical method for the synthesis of 11,11-dimethylbisbenzopyran system (**1**). This procedure has been successfully used for the synthesis of SERM analogs.

3. Experimental procedures for Scheme 4

3.1. Synthesis of tertiary alcohol 10

To a solution of **2c** (2.55 g, 5 mmol) in 50 mL THF at −20 °C was added methyl magnesium bromide in ethyl ether (3.0 M, 5 mL). The reaction mixture was warmed to −10 °C and was stirred for 7 h at −10 °C. The reaction mixture was then quenched with aqueous saturated solution of ammonium chloride (200 mL) and extracted with ethyl acetate (300 mL). The organic layer was separated and the aqueous layer was extracted again with 100 mL of ethyl acetate. The combined organic layers were filtered through a pad of $MgSO_4$ (anhydrous) and concentrated at reduced pressure. The crude residue was purified by flash column chromatography on silica gel using 20% ethyl acetate in hexane as gradient solvent to yield **10** (2.3 g, 4.3 mmol, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41 (d, $J = 9$ Hz, 1H), 6.25 (d, $J = 9$ Hz, 1H), 6.21 (m, 4H), 4.15 (Abq, $J = 14$ Hz, 2H), 1.28 (s, 3H), 1.21 (s, 3H), 0.8 (s, 18H), 0.02 (s, 6H), 0.01 (s, 6H). *m/z*: 543 (M+1).

3.2. Synthesis of bisbenzopyran 11

To the solution of **10** (2.3 g, 4.3 mmol) in toluene (100 mL) at 0 °C was added 0.4 mL of TFA and was stirred for 30 min. The reaction mixture was diluted with ethyl acetate (250 mL) and 5% aqueous solution of sodium bicarbonate (350 mL). After stirring vigorously for 1 h, the organic layer was separated. The aqueous layer was extracted with ethyl acetate (150 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the organic layer was concentrated in vacuum to yield crude **11** as a dark viscous oil. This crude oil was purified by flash column chromatography using 20% ethyl acetate in hexane as mobile phase to yield **11** (1.73 g, 3.3 mmol, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.1 (d, $J = 9$ Hz, 1H), 6.8 (d, $J = 9$ Hz, 1H), 6.4 (m, 4H), 4.9 (s, 2H), 1.7 (s, 6H), 0.97 (s, 18H), 0.2 (s, 6H), 0.18 (s, 6H). *m/z*: 525 (M+1).

3.3. Synthesis of 11,11-dimethylbisbenzopyran 1c using PCC

In a 50 mL round bottom flask, 4 Å molecular sieve (125 mg) was flame-dried under high vacuum and cooled to rt under nitrogen. The flask was charged with pyridium chlorochromate (216 mg, 1.0 mmol), chromium trioxide (100 mg, 1.0 mmol), 3,5-dimethylpyrazole (192.3 mg, 2.0 mmol), and dichloromethane (2 mL). The reaction mixture was cooled to −20 °C and stirred for 30 min. Bisbenzopyran **11** (105 mg, 0.2 mmol) in 1 mL of dichloromethane was added slowly to the above reaction mixture at −20 °C. After stirring for 6 h at −20 °C, the reaction mixture was diluted with 100 mL of CH_2Cl_2 and filtered through a pad of silica gel (10 g). The silica gel was washed by 50 mL of dichloromethane and ethyl acetate (1:1). The combined organic layer was evaporated and purified by flash column chro-

matography using 20% ethyl acetate in hexane as mobile phase to yield **1c** as a yellow oil (59 mg, 0.109 mmol, 54%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.1 (d, $J = 9$ Hz, 1H), 7.4 (d, $J = 9$ Hz, 1H), 6.6 (d, $J = 1$ Hz, 1H), 6.56 (dd, $J = 1$, 9 Hz, 1H), 6.33 (dd, $J = 1$, 9 Hz, 1H), 6.28 (d, $J = 1$ Hz, 1H) 1.65 (s, 6H), 0.77 (s, 18H), 0.25 (s, 6H), 0.2 (s, 6H). *m*/*z*: 539 (M+1).

3.4. Synthesis of 11,11-dimethylbisbenzopyran 1c using benzyl(triethyl) ammonium permanganate

To a solution of **11** (330 mg, 0.62 mmol) in 10 mL of dichloromethane at 0 °C was added 11.2 mL of freshly prepared stock solution of benzyl(triethyl)ammonium permanganate (0.5 M in CH_2Cl_2, 5.6 mmol). After stirring for 3 h, the reaction mixture was diluted with 50 mL of CH_2Cl_2 and filtered through a pad of silica gel (10 g). The silica gel was washed with 50 mL of dichloromethane and ethyl acetate (1:1). The combined organic layers were dried with $MgSO_4$ and the solvents were evaporated. Flash column chromatography using 20% ethyl acetate in hexane as mobile phase yielded **1c** as a yellow oil (257 mg, 0.477 mmol, 77%). ^{1}H NMR and MS are identical to the product described in the last section.

3.5. Synthesis of 11,11-dimethylbisbenzopyran 1a

A solution of **1c** (118 mg, 0.21 mmol) in anhydrous THF was cooled to 0 °C. To this solution, TBAF (1 M in THF, 0.8 mL, 0.8 mmol) was added. After stirring for 3 h at 0 °C, the reaction mixture was diluted with 50 mL of aqueous saturated solution of NH_4Cl and 50 mL of ethyl acetate. After stirring vigorously for 1 h, the organic layer was separated. The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the organic layer was concentrated in vacuum to yield crude **1a** as a dark yellow solid. This crude oil was purified by short flash column chromatography using 50% ethyl acetate in hexane as mobile phase to yield **1a** as yellow solid (63 mg, 0.20 mmol, 93%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 10.6 (s, 1H), 9.8 (s, 1H), 8.23 (d, $J = 9$ Hz, 1H), 7.6 (d, $J = 9$ Hz, 1H), 6.85 (dd, $J = 9$ Hz), 6.75 (d, $J = 1$ Hz, 1H), 6.5 (dd, $J = 1$, 9 Hz, 1H), 6.38 (d, $J = 1$ Hz, 1H) 1.55 (s, 6H); *m*/*z*: 311 (M+H), 333 (M+Na).

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