Total Synthesis of (±)-Spirobenzofuran

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Abstract: Spirobenzofuran, embracing a cyclopentane-spirofused benzofuran carbon framework, was efficiently assembled via semipinacol rearrangement with Me_3Al from 2,5-dimethoxy-4-methylacetophenone.

Key words: spirobenzofuran, semipinacol rearrangement, trimethylaluminium, total synthesis, sesquiterpenoid

An interesting sesquiterpenoid, spirobenzofuran, was isolated from the fungi *Acremonium sp. HKI 0230* by Gräfe and co-workers. It displayed moderate antimicrobial activity against Gram-positive bacteria such as Bacilus subtilis ATCC 6623.[1] Structurally, spirobenzofurans were related to lagopodins **2a**–**c**,[2] cuparene-1,4-quinone **3a**,[3] helicobasidins **3b**,**c**,[5] and cuparene-1,4-diol **4** (Figure 1).[4] These natural products are embedded with a cyclopentane ring containing two contiguous quaternary centers, and thus have become interesting synthetic targets since their isolation and identification.[6,7]

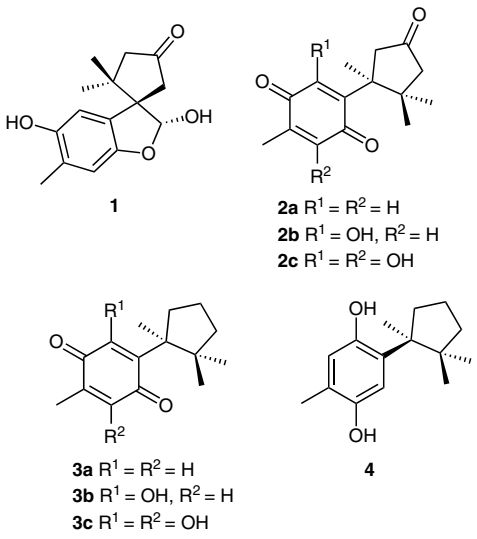
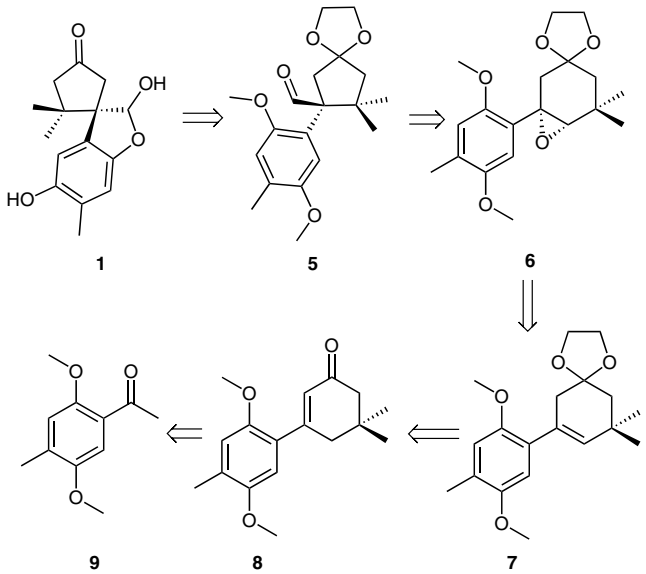


Figure 1

Among the completed total synthesis, several examples are impressing. In 2003, Mukherjee and co-workers reported the total synthesis of **3a** and **4** in 14 and 13 steps, respectively, from the known acetophenone **10**,[8] in which an intramolecular anionic cyclization strategy was developed to generate the vicinally substituted cyclopentanes (Scheme 2).[6d] In 2005, Srikrishna and coworkers accomplished the first racemic synthesis of spirobenzofuran **1** in 14 steps from **10**, featuring the key Ireland–Claisen rearrangement and ring-closing metathesis (RCM) reaction (Scheme 3).[7] Later, the Srikrishna group also accomplished the racemic synthesis of **2a**, **3a**, and **4** following the same synthetic strategy.[6a] Involved in the total synthesis of natural terpenoids,[9] we are also allured by the structure and bioactivity of this family of molecules, especially spirobenzofuran **1**. Herein, we would like to present our synthetic efforts on spirobenzofuran **1**.

The retrosynthetic analysis was depicted in Scheme 1. The aldehyde **5**, a key precursor towards our target molecule, could be obtained from compound **6** employing crucial semipinacol rearrangement. Compound **6** should be available from epoxidation of compound **7**, which could be produced from compound **8** through ketalization and simultaneous isomerization of the double bond. Compound **8** could be achieved from the acetophenone **9** through the combination of 1,4-addition and Robinson annulation.



Scheme 1 Retrosynthetic analysis of spirobenzofuran **1**

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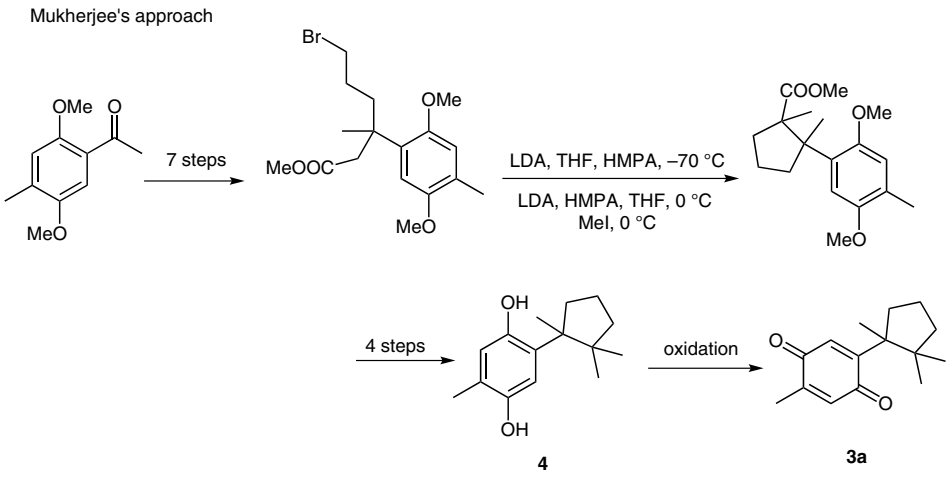
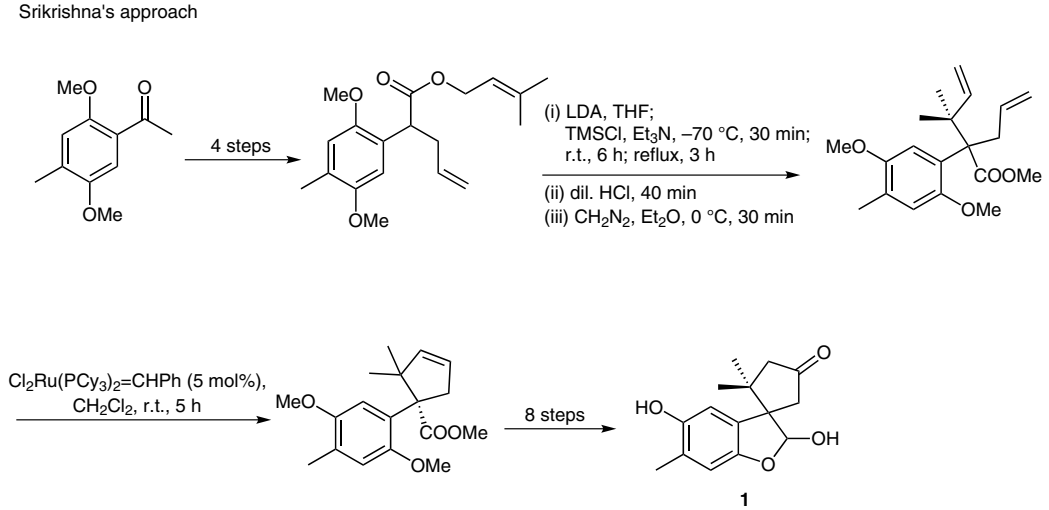


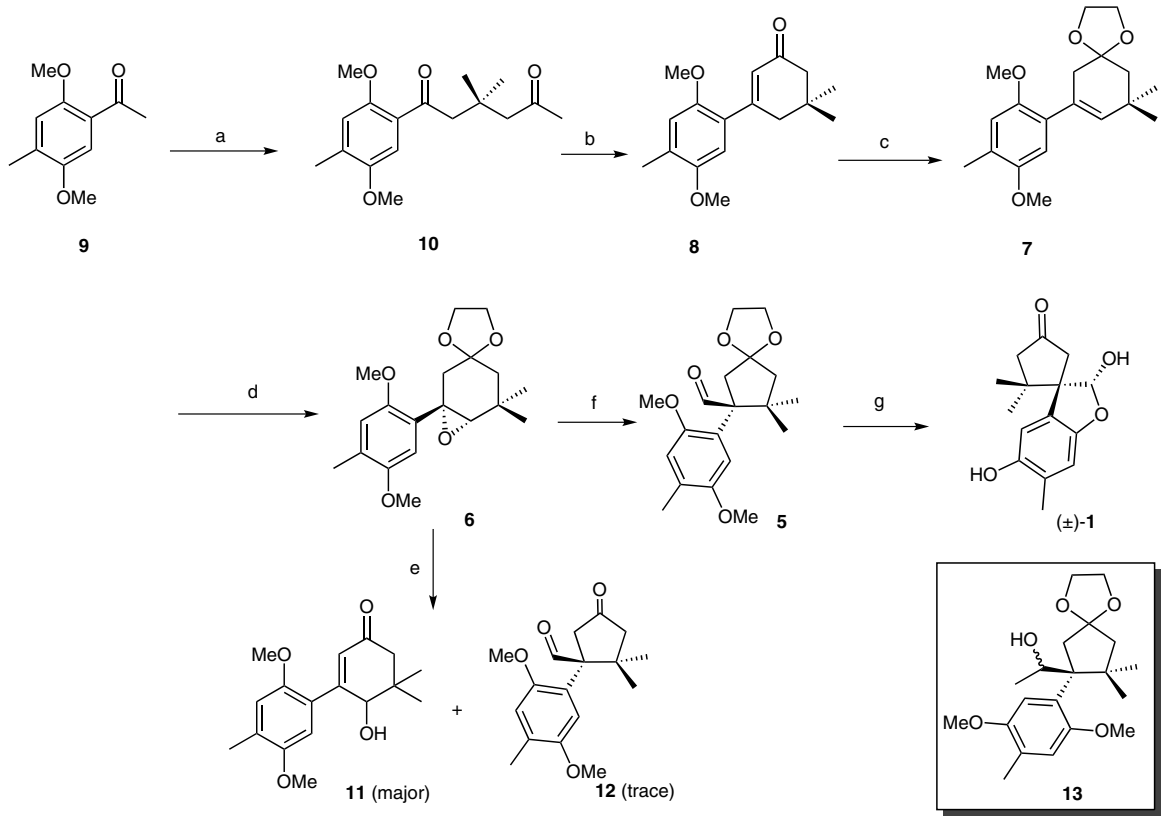
Scheme 2

Initially, compound **9** was first converted into the corresponding TBS enol ether, using Et_3N and TBSOTf in dichloromethane. Without quenching the reaction, the resultant enol ether was mixed with mesityl oxide in dichloromethane at –78 °C to give **10** in 58% yield.[10] It is notable that all trials to the direct Michael addition of compound **9** to mesityl oxide failed, which were catalyzed by different bases, such as KO*t*-Bu, KHMDS, NaHMDS, and LDA. The steric hindrance of mesityl oxide might account for the low reactivity under basic environment. Then intramolecular aldol condensation afforded **8** smoothly in 95% yield, by treating **10** with PTSA at 100 °C.[11] Subsequently, acid-catalyzed dioxolane formation, accompanied by isomerization of the double bond, gave rise to compound **7** in 50% yield (or 80% yield based on the recovery of the starting material **8**).[12] In the presence of MCPBA, compound **7** was transformed to the epoxy **6** in 66% yield.[13]

Then, to achieve the skeleton of spirobenzofuran, we turned our attention to the key semipinacol rearrangement. We envisioned that treating epoxide **6** with BBr_3 might lead to semipinacol rearrangement, demethylation and concomitant acetalation in one pot, resulting in the final natural product directly. However, to our disappointment, most of the epoxide **6**[14] was converted into the enone **11**, although trace of rearrangement product **12** was detected. Accordingly, the semipinacol rearrangement was systematically investigated under various conditions. In anhydrous dichloromethane, treating **6** with a variety of Lewis acids, such as $BF_3{\cdot}OEt_2$, $SnCl_4$, $AlCl_3$, $FeCl_3$, TBSOTf, TMSOTf, $LiClO_4$, $ZnCl_2$, LiI, $ZnBr_2$, $PdCl_2$, etc.,[15] led to decomposition of the substrate **6**. Moreover, the reaction with different protonic acids, that is, PTSA, CSA, TFA, and oxalic acid,[16] afforded no desired rearrangement product either. To minimize the formation of byproduct **11**, the reaction conditions keeping the ketal in **6** stable are obviously necessary. Therefore, the reactions with various acids in the presence of orthoester were attempted,[17] and the desired aldehyde **5** was formed but still in an unsatisfactory yield. Fortunately, when we treated **6** with Me_3Al, a very mild Lewis acid, compound **5**[18] was formed in 88% yield.[19] To the best of our knowledge, such



Scheme 3



Scheme 4 *Reagents and conditions*: (a) TBSOTf (1.2 equiv), Et_3N, CH_2Cl_2; 0 °C to r.t., 6 h; mesityl oxide, –78 °C, 58%; (b) PTSA, toluene, 100 °C, 5 h, 95% (c) PTSA, $HOCH_2CH_2OH$, benzene, Dean–Stark, reflux, 17.5 h, 80% (brsm); (d) MCPBA, $NaHCO_3$, CH_2Cl_2, –10 °C, 1.5 h, 66%; (e) BBr_3, CH_2Cl_2, –78 °C, 4 min, 86%; (f) Me_3Al, CH_2Cl_2, 0 °C to r.t., 4 h, 88%; (g) (i) CAN, MeCN, H_2O, –10 °C, 10 min; (ii) $Na_2S_2O_4$, THF, H_2O; 0 °C, 1.5 h; then HCl (1 N), 5 h, r.t., 84% over two steps.

a Me_3Al-promoted semipinacol rearrangement was seldom.[20] The mild nature of this transformation will surely make it potentially utilized in organic synthesis. It is interesting that compound **13**, resulting from Me_3Al addition to aldehyde **5**, was not detected in this step, probably due to the bulky environment adjacent to the aldehyde group.[21] Finally, after a routine oxidative demethylation–reduction–ketalization sequence,[22] we completed the total synthesis of *rac*-spiro-benzofuran **1** (Scheme 4).[23]

In summary, we have developed a concise synthesis of spirobenzofuran **1** with 21% overall yield in seven steps. The synthesis features a Me_3Al-promoted semipinacol rearrangement and paves the way towards other structurally related natural product.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **Analytical Data**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (s, 1 H), 6.67 (s, 1 H), 3.93–3.84 (m, 4 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 2.78 (s, 1 H), 2.37 (d, *J* = 15.2 Hz, A of AB, 1 H), 2.23 (d, *J* = 16.0 Hz, B of AB, 1 H), 2.20 (s, 3 H), 1.65 (d, *J* = 13.6 Hz, A′ of A′B′, 1 H), 1.42 (d, *J* = 13.6 Hz, B′ of A′B′ 1 H), 1.24 (s, 3 H), 1.15 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 150.1, 128.4, 126.6, 114.1, 109.5, 108.2, 68.2, 64.0, 63.9, 61.1, 56.1, 56.0, 41.2, 39.2, 32.0, 27.9, 26.2, 16.4. IR (thin film): 2955, 1506, 1296, 1093, 823 cm^{-1}.

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(18) **Synthesis of Aldehyde 5**
To a solution of compound **6** (200 mg, 0.59 mmol) in CH_2Cl_2 (10 mL) was added Me_3Al (0.59 mL, 1.18 mol, 2.0 M in toluene) dropwise at –10 °C under argon. The reaction was warmed to r.t. slowly and stirred for 4 h. Then it was quenched with sat. aq $NaHCO_3$ (2 mL) at 0 °C. Sat. aq sodium potassium tartrate (10 mL) was added, and the biphasic mixture was stirred overnight. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The residue was purified by flash chromatography (silica gel, PE–EtOAc = 10:1) to give compound **5** as a yellow solid (176 mg, 88%).^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.87 (s, 1 H), 6.92 (s, 1 H), 6.69 (s, 1 H), 3.93–3.88 (m, 4 H), 3.79 (s, 3 H), 3.67 (s, 3 H), 2.77 (d, *J* = 15.2 Hz, A of AB, 1 H), 2.31 (d, *J* = 15.2 Hz, B of AB, 1 H), 2.27 (d, *J* = 14.0 Hz, A′ of A′B′, 1 H), 2.20 (s, 3 H), 1.99 (d, *J* = 13.6 Hz, B′of A′B′, 1 H), 1.27 (s, 3 H), 0.83 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.8, 151.8, 150.7, 127.0, 125.8, 114.8, 114.8, 112.3, 64.3, 64.3, 63.3, 56.3, 55.9, 51.9, 44.2, 43.8, 27.0, 23.9, 16.2. IR (thin film): 2959, 1716, 1213, 858 cm^{-1}.

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(23) **Analytical Data**
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.66 (s, 1 H), 7.14 (d, *J* = 5.6 Hz, 1 H), 6.52 (s, 2 H), 5.79 (d, *J* = 5.6 Hz, 1 H), 2.83 (d, *J* = 18.8 Hz, A of AB, 1 H), 2.44 (d, *J* = 18.8 Hz, B of AB, 1 H), 2.34 (d, *J* = 18.4 Hz, A′ of A′B′, 1 H), 2.24 (d, *J* = 18.0 Hz, B′ of A′B′, 1 H), 2.07 (s, 3 H), 0.98 (s, 3 H), 0.85 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 216.2, 150.3, 148.9, 126.5, 123.8, 111.2, 111.0, 102.1, 59.2, 51.9, 42.7, 41.2, 24.6, 23.0, 16.3. IR (thin film): 3395, 1732, 1412, 1085, 923 cm^{-1}. HRMS (ES$^+$): *m/z* calcd for $C_{15}H_{18}O_4Na$ [M + Na]$^+$: 285.1103; found: 285.1101.

