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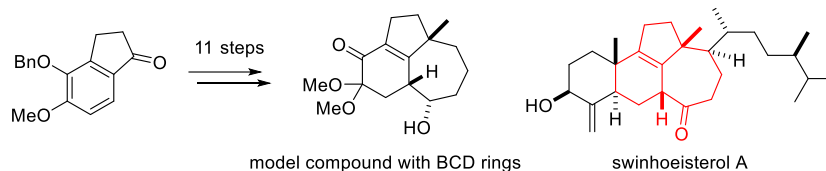
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### Synthetic studies toward swinhoeisterol A, a novel steroid with an unusual carbon skeleton

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## Synthetic studies toward swinhoeisterol A, a novel steroid with an unusual carbon skeleton

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### ABSTRACT

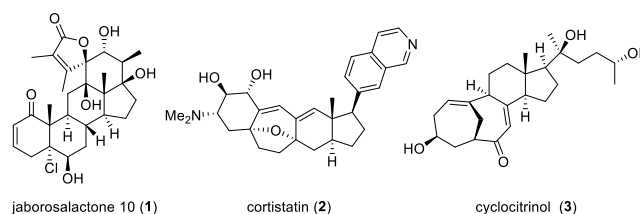
Swinhoeisterol A is a novel steroid with unusual 6/6/5/7 tetracyclic skeleton. The model compound with BCD rings is constructed by Friedel–Crafts acylation and an oxidative dearomatization as key steps.

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Steroids and steroid derivatives, such as testosterone<sup>1</sup> and cortisol,<sup>2</sup> are used as medicines for hormonal and anti-inflammatory drugs, respectively. These steroidal drugs are industrially semi-synthesized from compounds that contain a tetracyclic skeleton, for example, Marker degradation of diosgenin. In small-scale synthesis, steroids are prepared from Wieland–Miescher ketone<sup>3</sup> or by polyene cyclization<sup>4</sup> and Diels–Alder reaction.<sup>5</sup> Synthetic methods for generating the normal steroids are well developed.

Recently, novel steroids such as jaborosalactone 10 (**1**),<sup>6</sup> cortistatin (**2**),<sup>7</sup> and cyclocitrinol (**3**)<sup>8</sup> having unusual carbon skeletons were isolated (Figure 1). Some members of this family have interesting biological activities: jaborosalactone 10 (**1**), quinone reductase induction promoting action; cortistatin (**2**), anti-proliferative activity; and cyclocitrinol (**3**), cAMP production promoting action. Therefore, they have attracted the attention of synthetic organic chemists and natural product chemists. However, the existing synthetic methods for generating normal steroids are not applicable to steroids with novel structures.

The chemistry of benzene provides powerful tools in the synthesis of polycyclic compounds, because it is useful for ring construction as exemplified in Friedel–Crafts reactions, utilization of benzylic cations, S<sub>N</sub>Ar reactions and so on, even if the synthetic targets lack benzene rings. The chemistry of benzene has been used in many total synthesis,<sup>9</sup> but its application for the synthesis of non-aromatic steroids and related compound are limited.

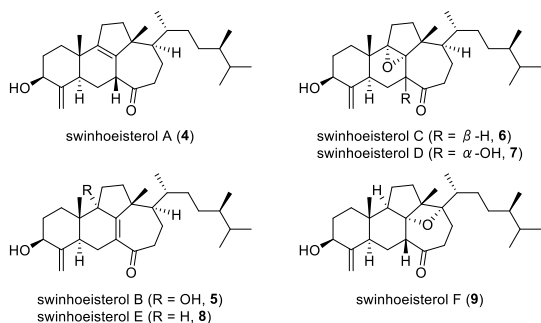


**Figure 1.** Structures of novel steroids with unusual carbon skeletons.

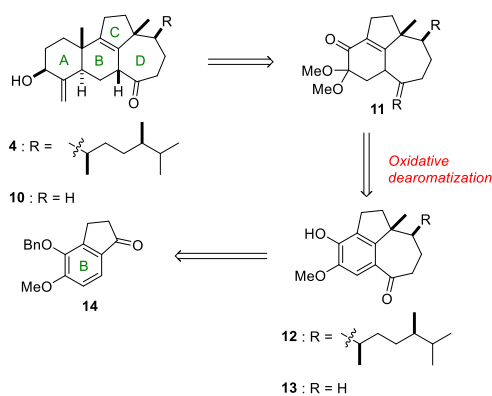
Swinhoeisterols A (**4**) and B (**5**)<sup>10</sup> were isolated from the South China Sea in 2014 (Figure 2). They are novel sterols which possess a 6/6/5/7 ring skeleton. The carbon framework is supposed to result from the rearrangement of normal a 6/6/6/5 steroidal structure. In 2018, swinhoeisterols C–F (**6–9**)<sup>11</sup> were isolated too. Swinhoeisterol A (**4**) shows a remarkable inhibitory activity against h(p300), a histone acetyltransferase associated with the manifestation cancer (IC<sub>50</sub> = 2.9 μM). We initiated a synthetic study of swinhoeisterol A (**4**) due to our interest in its challenging structure and biological activity. In this context, we envisioned the use of benzene's chemistry for the synthesis of novel steroids with unusual carbon skeletons, taking swinhoeisterol A (**4**) as an example. Herein, we report the establishment of a synthetic strategy for constructing the BCD ring skeleton in model compound **10**, and the assembly of other tricyclic compounds using our approach.

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The synthetic strategy for the ABCD rings of swinhoeisterol A is described in Scheme 1. Model compound **10** would be synthesized from  $\alpha$ ,  $\alpha$ -dimethoxy enone **11** with the installation of the A ring at a late stage. The access to the 6/5/7 tricyclic system of **11** is limited so far. Here,  $\alpha$ ,  $\alpha$ -dimethoxy enone **11** might be obtained by oxidative dearomatization of tricyclic compound **13**, which in turn would be constructed from indanone **14** through a Friedel–Crafts reaction.

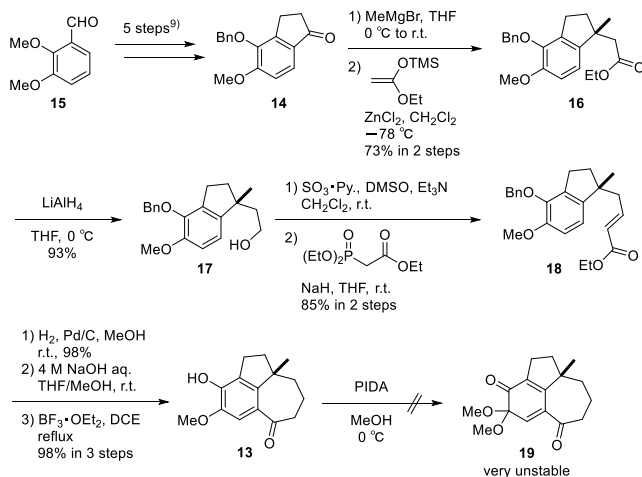


**Figure 2.** Structures of swinhoeisterols A-F (**4-9**).



**Scheme 1.** Synthetic strategy.

Our studies began with a 5-step synthesis of indanone **14** from commercially available 2,3-dimethoxybenzaldehyde (**15**), according to known procedures (Scheme 2).<sup>12</sup> Methylation and substitution of the resultant benzylic tertiary alcohol with ketene silyl acetal afforded ester **16**.<sup>13</sup> Redox steps on ester **16** followed by Horner–Wadsworth–Emmons reaction gave unsaturated ester **18**, which was transformed into tricyclic compound **13** in a 3-step sequence which included Friedel–Crafts reaction. Oxidative dearomatization did not give desired compound **19** but a complex mixture.

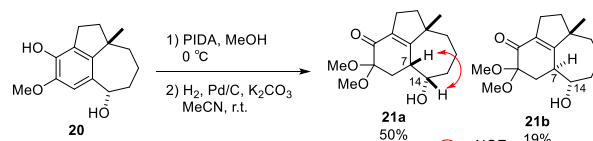


**Scheme 2.** Synthesis of tricyclic compound.

We supposed that the reaction failed because the desired compound **19** is so electronically deficient that side reactions might occur, such as Diels–Alder reaction and conjugate addition. Therefore, we decided to reduce the carbonyl group (Table 1). In entry 1, NaBH<sub>4</sub> provided a 1:1 diastereomeric products. In entry 2, the diastereoselectivity was 3:1 in the case of DIBAL. L-selectride, a bulky hydride reagent, did not reduce ketone **13** (entry 3). Alternatively, a borane reduction using 2-Me-CBS-oxazaborolidine<sup>14</sup> gave the alcohol **20** in a good diastereomeric ratio (entry 4). The (*R*)- or (*S*)-CBS catalyst could hardly resolve optical isomers. Alcohol **20** was dearomatized with phenyliodine(III) diacetate (PIDA) in MeOH (Scheme 3). Finally, regioselective hydrogenation of resultant *o*-quinone monoacetal gave the model compound **21a** with BCD rings stereoselectivity. The relative configurations of 6/5/7-ring systems of **21a** and **21b** were determined by NOE correlations of **21a** and the corresponding diketone.<sup>15</sup>

**Table 1.** Reduction of the carbonyl group in **13**.

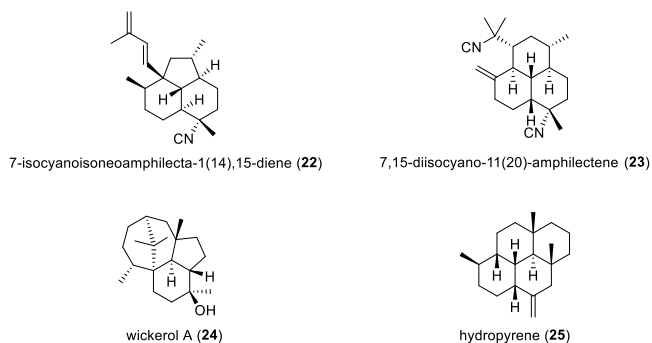
entry	conditions	results
1	NaBH <sub>4</sub> , MeOH, 0 °C	quant., <i>d.r.</i> = 1/1
2	DIBAL, CH <sub>2</sub> Cl <sub>2</sub> , -78 °C	quant., <i>d.r.</i> = 3/1
3	L-selectride, THF, -78 to 0 °C	N. R.
4	<i>rac</i> -2-Me-CBS, BH <sub>3</sub> •SMe <sub>2</sub> , -30 °C	94%, <i>d.r.</i> = 16/1



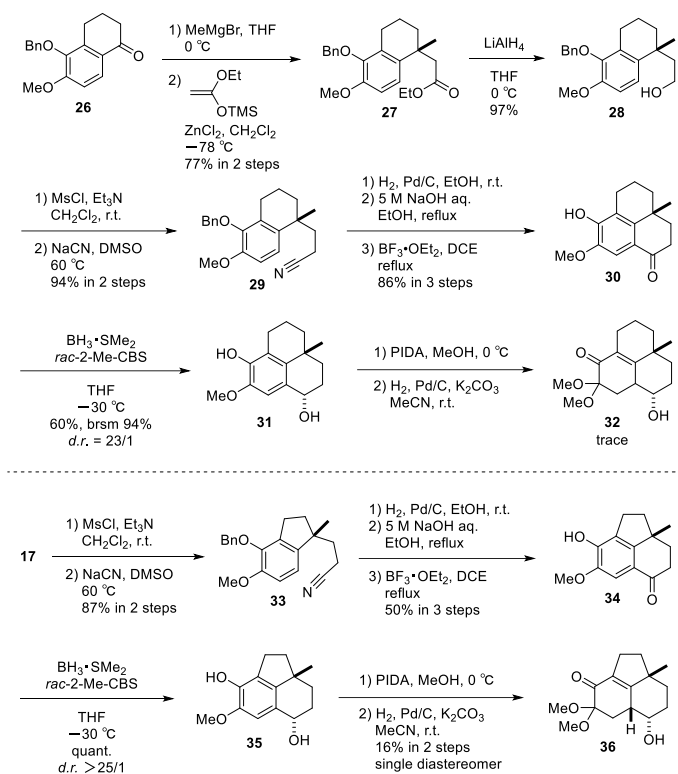
**Scheme 3.** Construction of the model compound with the BCD rings.

The analogous tricyclic skeletons of **21a** and **21b** prepared by this strategy are included in the natural compounds such as amphilectane-class diterpenes **22** and **23**,<sup>16,17</sup> wickerol A (**24**)<sup>18</sup>, and hydropyrene (**25**)<sup>19</sup> in Figure 3. We investigated the applicability of the above strategy for the synthesis of other polycyclic compounds, 6/6/6- and 6/5/6-ring systems. Known tetralone **26** was converted to ester **27**,<sup>20</sup> which was reduced to alcohol **28**. S<sub>N</sub>2 reaction with NaCN of the corresponding mesylate provided homologated nitrile **29**. After removal of the benzyl group, hydrolysis and Friedel–Crafts acylation gave the desired 6/6/6-compound **30**. Oxidative dearomatization of **30** failed as with compound **13**. Thus, 6/6/6-compound **30** was reduced by borane and CBS catalyst with good diastereoselectivity. However, oxidative dearomatization gave only a trace amount of the desired compound.<sup>21</sup>

Intermediate **17** was converted into nitrile **33** by S<sub>N</sub>2 reaction. The same 3-step transformation as in the preparation of **30** afforded 6/5/6-compound **34** in a moderate yield. Reduction, dearomatization, and hydrogenation afforded the desired compound **36** as a single diastereomer in 16% yield. These results indicated that the yields of oxidative dearomatizations of 6/5/7-, 6/6/6-, and 6/5/6-tricyclic systems were much influenced by the ring systems.<sup>22</sup>



**Figure 3.** Structures of amphilectane-class diterpenes **22** and **23**, wickerol A (**24**), and hydropyrene (**25**).



**Scheme 4.** Synthesis of 6/6/6 and 6/5/6 system compounds.

In conclusion, we have developed access to a tricyclic compound with BCD rings of swinhoeisterol A and a similar 6/5/6-tricyclic system. Friedel–Crafts acylation and an oxidative dearomatization are the key steps of our synthetic strategy. Further synthetic study is ongoing in our laboratory.

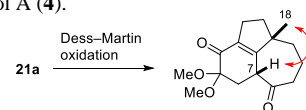
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- The stereochemistry of **32** was not determined.
- The corresponding *o*-quinone monoacetals of **31** and **35** were unstable under concentrated conditions and quickly decomposed.

## Supplementary Material

Supplementary data (<sup>1</sup>H and <sup>13</sup>C spectra) associated with this article can be found, in the online version, at doi:XXX.

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