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# Application of a Domino Friedel−Crafts Acylation/Alkylation Reaction to the Formal Syntheses of (±)-Taiwaniaquinol B and (±)-Dichroanone

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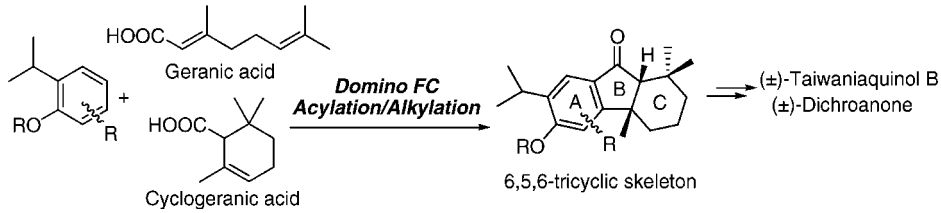
## ABSTRACT




**An efficient acid-promoted domino Friedel−Crafts (FC) acylation/alkylation reaction has been developed for the construction of the core 6,5,6-ABC tricyclic skeleton of taiwaniaquinoids. The formal total syntheses of diterpenoids (±)-taiwaniaquinol B and (±)-dichroanone based on this strategy have been achieved.**

The 4a-methyltetra- (and hexa-)hydrofluorene skeleton is relatively uncommon in natural products. During the past decade, several diterpenoids with this skeleton, such as taiwaniaquinols A (**1**), B (**2**), and D (**3**) and taiwaniaquinone D (**4**) and H (**5**) as well as some structurally related diterpenoids, such as dichroanone (**6**), dichroanal B (**7**), and standishinal (**8**), have been isolated from *Taiwania cryptomerioides*, *Salvia dichroantha*, *Thuja standishii*, and other related plants (Figure 1).[1] Preliminary studies revealed that taiwaniaquinone D (**3**) possesses antitumor activity and standishinal (**8**) shows promising antitumor and aromatase inhibitory potential.[2] As a result of these biologically significant activities and their intriguing structures, these diterpenoids have been attracting considerable attention of organic chemists, and several total syntheses have been demonstrated so far.[3] For example, the first total syntheses of dichroanone and (±)-dichroanal B were disclosed by Banerjee, in which a Pd(0)-catalyzed intramolecular reductive

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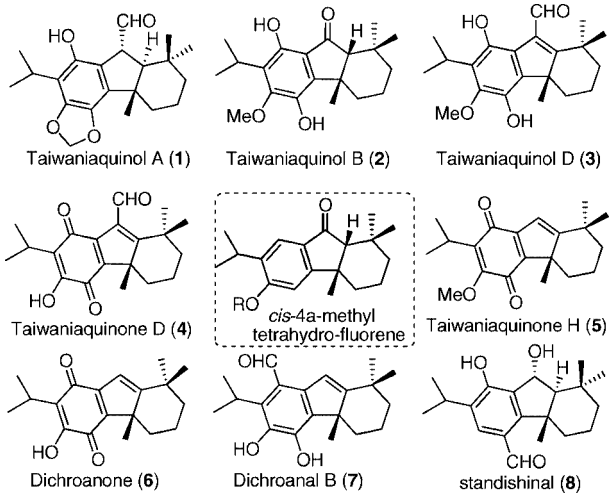


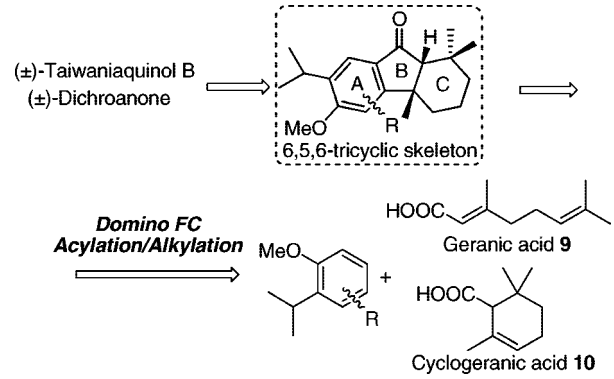

**Figure 1.** Representative diterpenoids with a 6,5,6 4a-methylhydrofluorene skeleton.

cyclization served as the key step.[3a]Fillion developed an interesting domino intramolecular acylation carbonyl α-*tert*-alkylation reaction in the first total synthesis of (±)-taiwaniaquinol B.[3b] Stoltz published a synthesis of (+)-dichroanone based on a novel asymmetric palladium-catalyzed alkylation.[3c] Trauner reported a concise and convergent synthetic approach toward the taiwaniaquinoid family that relies on Nazarov cyclization.[3d] Many approaches toward this type of diterpenoids have also been reported,[3e–g] while more recently, Chiu utilized an intramolecular acid-promoted sequential cationic cyclization for the synthesis of (±)-taiwaniaquinol B.[3h]

A structural feature common to all of these diterpenoids is the key *cis*-4a-methyltetrahydrofluorene (Figure 1) containing a substituted aromatic core and two all-carbon quaternary centers located at the $\beta$-positions of the carbonyl group. The establishment of this ring system represents a central synthetic challenge, and a number of synthetic efforts have emerged to address this problem.[4] In connection with our ongoing projects related to the use of intramolecular cyclization and Friedel−Crafts alkylation methodology in diterpenoid synthesis,[5] we describe herein a highly efficient route to the basic 6,5,6-tricyclic system of the above diterpenoids and its application to the syntheses of (±)-dichroanone and (±)-taiwaniaquinol B. As shown in Scheme 1, our retrosynthetic analysis on the basic 6,5,6-tricyclic skeleton was focused on the efficient establishment of ring B and C. We envisioned that both of ring B and C could be available through a acid promoted domino[6] Friedel−Crafts

(4) Several strategies have been reported for the preparation of 4a-methylhexahydrofluorenes: (a) Ghatak, U. R.; Chakravarty, J.; Banerjee, A. K. *Tetrahedron* **1968**, *24*, 1577. (b) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5937. (c) Ishibashi, H.; Kobayashi, T.; Nakashima, S.; Tamura, O. *J. Org. Chem.* **2000**, *65*, 9022. (d) Bailey, W. F.; Daskapan, T.; Rampalli, S. *J. Org. Chem.* **2003**, *68*, 1334. (e) Lomberget, T.; Bentz, E.; Bouyssi, D.; Balme, G. *Org. Lett.* **2003**, *5*, 2055. (f) Fillion, E.; Dumas, A. M.; Hogg, S. A. *J. Org. Chem.* **2006**, *71*, 9899. (g) Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23.

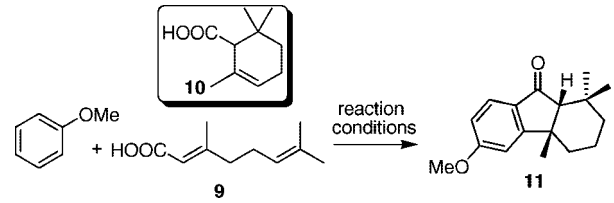
**Scheme 1.** Retrosynthetic Analysis




(FC) acylation/alkylation of the substituted methyl phenol ether derivative with geranic acid (**9**) or cyclogeranic acid (**10**).[7]

Model reactions were carried out first to confirm the synthetic feasibility of the domino Friedel−Crafts acylation/alkylation. We selected anisole as the substrate to react with geranic acid or cyclogeranic acid under various acidic conditions and all results were tabulated in Table 1. A small

**Table 1.** Optimization of the Domino Friedel−Crafts Acylation/Alkylation[a]




| entry | 9/10 | acidic medium | $T$ (°C)/time (h) | yield **11**[b] (%) |
|---|---|---|---|---|
| 1 | **9** | $BF_3-Et_2O$ | 0 to rt/12 | 0 |
| 2 | **9** | TMSOTf | 0/3 | trace |
| 3 | **9** | $H_2SO_4$, AcOH | 0/3 | 0 |
| 4 | **9** | PPA | rt/24 | <5 |
| 5 | **9** | $CH_3SO_3H/P_2O_5$ | rt/24 | 64 |
| 6 | **10** | $CH_3SO_3H/P_2O_5$ | rt/12 | 71 |
| 7 | **10** | $CH_3SO_3H/P_2O_5$ | 70/1.5 | 75 |

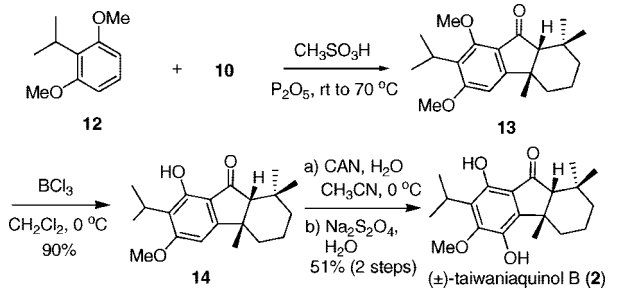
[a] Reaction conditions: 1 mmol portion of geranic acid **9**/**10** and 2 mmol of anisole were used. [b] Isolated yield.

amount of monocyclized Friedel−Crafts acylation product was observed with $BF_3{\cdot}Et_2O$[4e,f] and TMSOTf[3d] as Lewis acids, and anisole was completely recovered when subjected to concentrated $H_2SO_4$[8] in $Et_2O$ (entry 3). After an extensive survey, we discovered that the conditions using neat methanesulfonic acid ($CH_3SO_3H$) in the presence of $P_2O_5$[9] (20:1) exhibited the most promising result (entry 5). With reaction time reduced, the desired acid promoted domino Friedel−Crafts (FC) acylation/alkylation reaction proceeded smoothly to give the tricyclic product **11** in good yields either

at room temperature or at 70 °C (entries 6 and 7). The relative stereochemistry of ketone **11** was assigned as cis by the NOESY. This single step transformation afforded the thermodynamically more favorable tricyclic *cis*-indan, which could be generally used as a key intermediate in the synthesis of the above diterpenoids.

Initially, we selected (±)-taiwaniaquinol B possessing all the structural element of interest as an optimal target to test the synthetic utility of this domino Friedel−Crafts acylation/alkylation reaction. Starting from 1,3-dimethoxy-2-isopropylbenzene **12** and cyclogeranic acid **10** (Scheme 2), the key

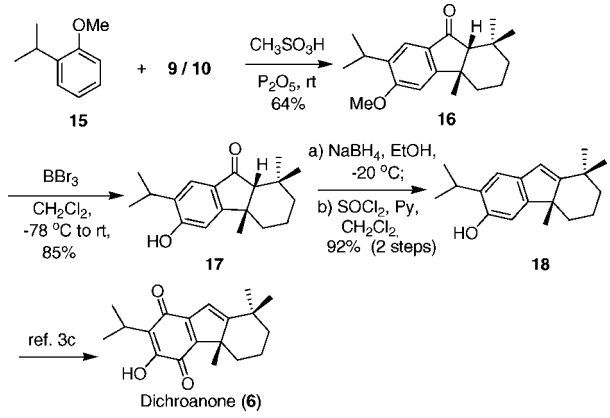
**Scheme 2**




domino reaction proceeded smoothly and afforded the desired tricyclic **13** as a single diastereomer in 70% yield which is the advanced tricyclic intermediate reported by Fillion[3b] in the synthesis of **2**. Then, the total synthesis of **2** was accomplished according to the reported sequence through selective demethylation, CAN oxidation, and the final sodium dithionite reduction.[3d]

The synthesis of (±)-dichroanone (**6**) was illustrated in Scheme 3. Reaction of isopropylanisole **15** and geranic

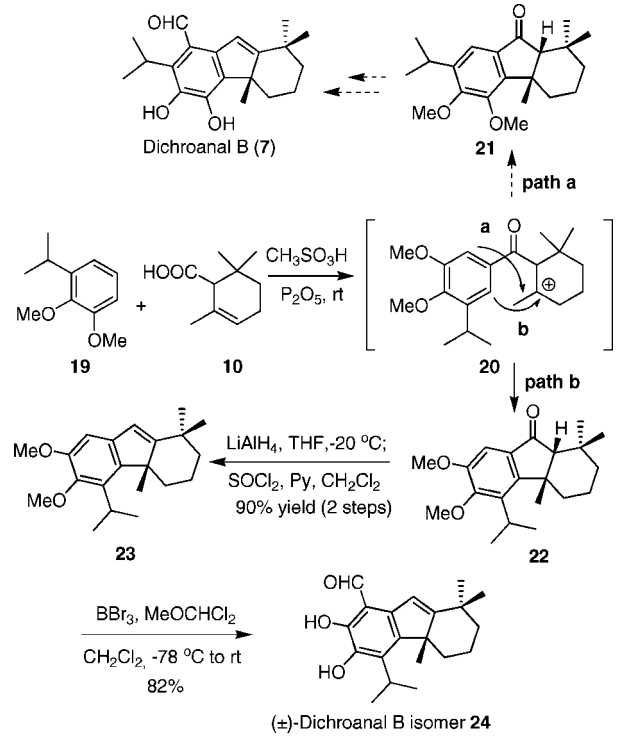
**Scheme 3**




acid **9** or cyclogeranic acid **10** in the neat $CH_3SO_3H$ in the presence of $P_2O_5$ produced a mixture of regioisomers in 70% and 72% combined yield, respectively. The major isomer **16** was obtained through **9** in 64% yield after chromatography. Deprotection of **16** with $BBr_3$ in $CH_2Cl_2$ at 0 °C provided **17**. After reduction[10] and dehydration,[11] ketone **17** was transformed to the key intermediate phenol **18** in 92% yield over two steps. Then phenol **18** was treated by Stoltz's approach[3c,12] to give (±)-dichroanone, and its spectral properties were in agreement with those previously reported.[1,3c]

The successful formal total synthesis of (±)-taiwaniaquinol B and (±)-dichroanone encouraged us to apply and further extend this strategy to the total synthesis of (±)-dichroanal B. However, instead of the key intermediate **21**, the major product we obtained using the domino Friedel−Crafts acylation/alkylation reaction was its corresponding regioisomer **22**. We reasoned that after the formation of cationic intermediate **20**, the cyclization underwent through path b due to the para-directing electronic effect of the −OMe group on the aromatic ring.

**Scheme 4**




After reduction and dehydration, the key intermediate **22** was tranformed to **23** in 90% yield over two steps. Finally,

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deprotection and formylation with $BBr_3/CH_3OCHCl_2$ in one pot,[13] a yellow solid was obtained in 82% yield. By careful analysis of its IR, NMR and HRMS data, the final product **23** was identified as the structural isomer of (±)-dichroanal B, which could be applied for the purpose of structure−activity relationship (SAR) studies (Scheme 4).

In summary, we have developed an efficient acid promoted domino Friedel−Crafts (FC) a cylation/alkylation reaction for the construction of the core 6,5,6-ABC tricyclic skeleton of diterpenoids. The formal total syntheses of diterpenoids (±)-taiwaniaquinol B and (±)-dichroanone have been achieved. Efforts directed toward the asymmetric synthesis of related natural products are underway.

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**Supporting Information Available:** Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The direct condensation of free carboxylic acids in $P_2O_5$-MsOH, see: (a) Eaton, P. E.; Carson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071. (b) Yonezawa, N.; Tokita, Y.; Hino, T.; Nakamura, H.; Katakai, R. *J. Org. Chem.* **1996**, *61*, 3551. (c) So, Y. H.; Heeschen, J. P. *J. Org. Chem.* **1997**, *62*, 3552. (d) Yonezawa, N.; Hino, T.; shimizu, M.; Matsuda, K.; Ikeda, T. *J. Org. Chem.* **1999**, *64*, 4179.

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(13) For deprotection of the phenolic groups with $BBr_3$ followed by the formylation reaction with $CH_3OCHCl_2$ promoted by $BBr_3$, see: Felix, A. M. *J. Org. Chem.* **1974***39*. 1427 and ref 3e.