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Efficient Route to 4a-Methyltetrahydrofluorenes: A Total Synthesis of (±)-Dichroanal B via Intramolecular Heck Reaction

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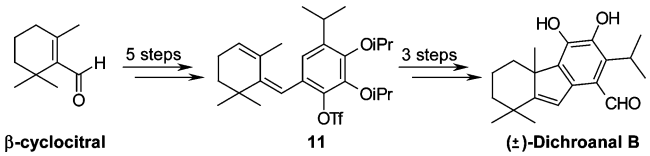

An efficient new route based on intramolecular Heck cyclization of the diene **11** was developed to prepare the 4a-methyltetrahydrofluorene diterpenoids and utilized for the total synthesis of (±)-dichroanal B with significantly improved overall yield.

During the past decade, several diterpenoids with the 4a-methyltetra-(or hexa-)hydrofluorene skeleton, such as taiwaniaquinols A (**1**) and B (**2**),[1] dichroanals A (**3**) and B (**4**),[2] standishinal (**5**),[3] and taiwaniaquinols C (**6**), D (**7**),[4] E (**8**), and F (**9**),[5] were isolated from *salvia dichroantha*, *thuja standishii*, *taiwania cryptomerioides*, and other related plants (Figure 1). Although little is known about their bioactivities, standishinal is known to demonstrate aromatase inhibitory activities,[6] and, therefore, this class of compounds may be promising candidates for the treatment of breast cancer.[7]

Several syntheses with different strategies have been reported for the construction of the 4a-methylhydrofluorenes,[8] and the first total synthesis of (±)-dichroanal B (**4**) was recently disclosed.[9] Its synthesis, however, requires multiple steps, and the overall yield is considerably low. We herein report a new strategy to construct the six-five-six ring system and an application of the methodology to the total synthesis of (±)-**4**, with a shorter synthetic route and much improved overall yield.

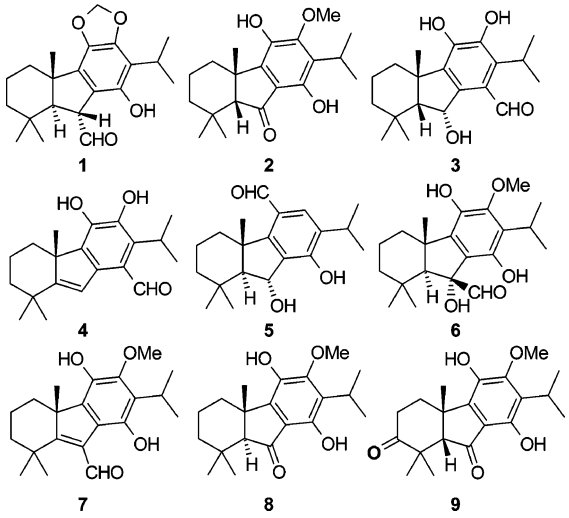

FIGURE 1. Natural products with a 4a-methylhydrofluorene skeleton.

In the report by Banerjee et al.,[9] (±)-**4** was prepared in a total of 27 steps with less than 5% overall yield via an intramolecular Heck reaction of the *exo*-olefin **10** (Scheme 1a). We sought to construct the 4a-methyltetrahydrofluorene skeleton using the diene **11**, which could be readily prepared from commercially available *β*-cyclocitral (Scheme 1b).

To confirm the synthetic feasibility of the intramolecular Heck cyclization,[10] a test reaction was carried out with the substrate diene **12** (Scheme 2). The Pd(0)-catalyzed reaction proceeded smoothly in acetonitrile at 60 °C. The obtained isomers, **13a**,**b**, underwent selective hydrogenation using Wilkinson's catalyst,[11] providing the desired 4a-methyltetrahydrofluorene **14**. While the result was satisfactory, a computational model suggested that substrate **12** is expected to have a planar half-chair conformation as the most stable form, in which the arylpalladium is distant from the olefin. To explain the reaction mechanism, the diene moiety should take a "boatlike" conformation with increased temperature to bring the arylpalladium species and the olefin in close contact (Figure 2).

The new methodology to prepare the 4a-methyltetrahydrofluorene skeleton was adopted for the total synthesis of (±)-**4**. The synthesis started with the preparation of the aryl bromide **18** in four steps from commercially available 2′,3′-dihydroxy-4′-methoxyacetophenone **15** (Scheme 3). A Grignard reaction

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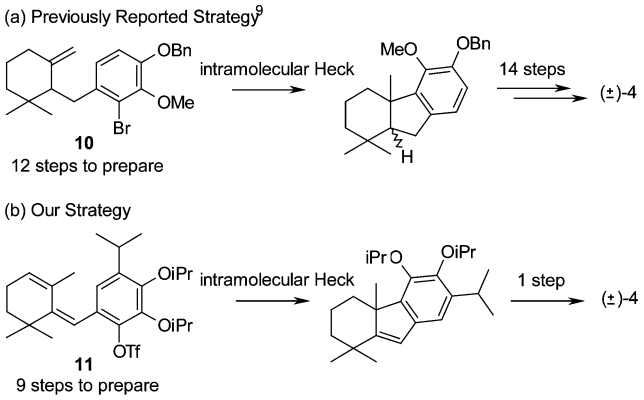
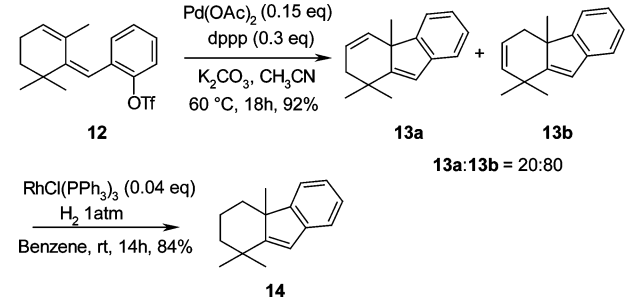
SCHEME 1



SCHEME 2



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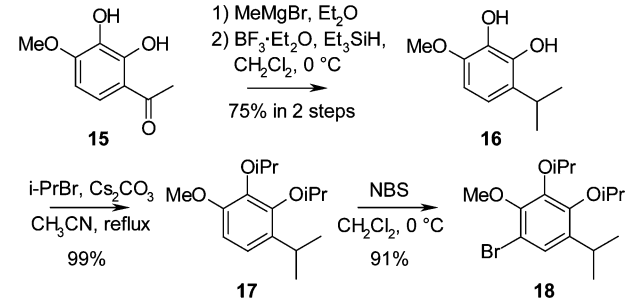

with MeMgBr, followed by reduction using $BF_3{\cdot}Et_2O/Et_3SiH$, afforded the isopropyl derivative **16**. The hydroxyl groups were protected as isopropyl ether, and the selective bromination of **17** using NBS provided the aryl bromide **18**. The diene substrate **11** was prepared as follows (Scheme 4). The reaction of *β*-cyclocitral with **18** using *n*-butyllithium afforded the alcohol **19**. Dehydration of the newly generated hydroxyl group using triflic anhydride in the presence of pyridine provided the pyridium salt **20**, which after elimination with DABCO, provided the diene **21** as a mixture of Z/E isomers. Configuration of the double bond in the major isomer of **21** was determined to be Z by NOE experiments. Demethylation of **21** using sodium hydride and dodecanthiol, an odorless sulfur reagent developed by our group,[12] afforded the phenol **22** in high yield, which was then converted to the triflate **11** with triflic anhydride.

The diene substrate **11** was utilized for the construction of the 4a-methyltetrahydrofluorene skeleton and the synthesis of (±)-dichroanal B (**4**) (Scheme 5). The key step, Heck cyclization

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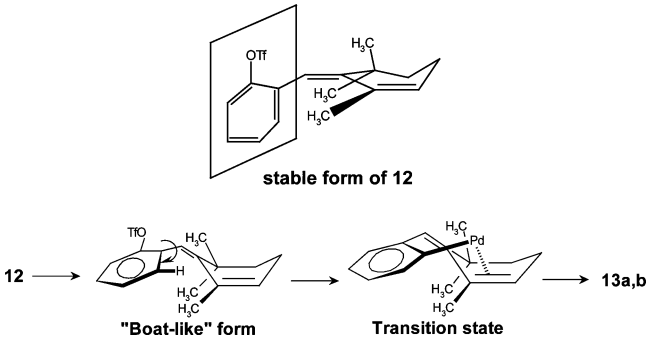
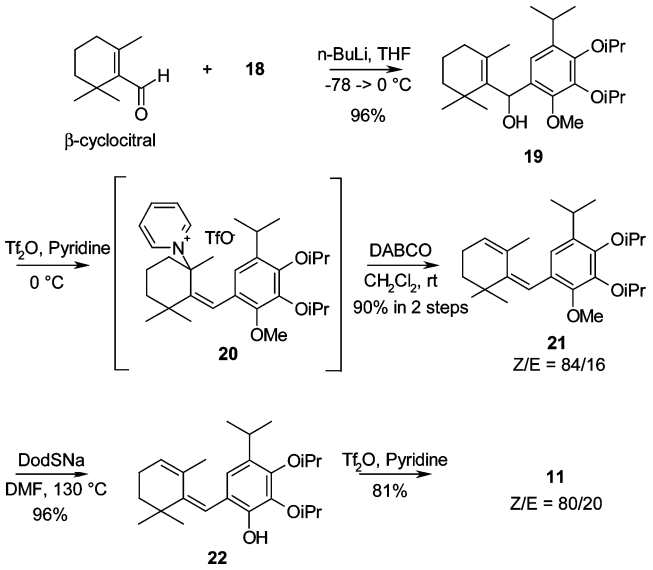
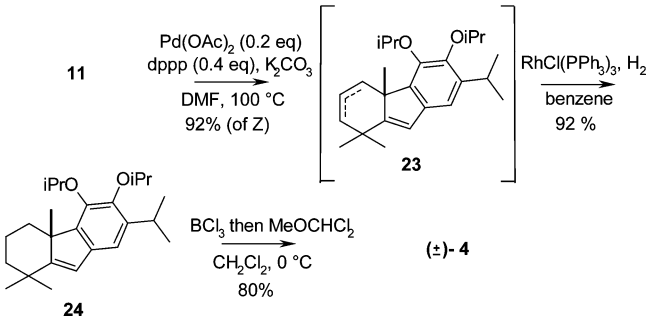


FIGURE 2. Proposed mechanism via a "boatlike" conformation.

SCHEME 4



SCHEME 5



of **11**, was accomplished with high yield (92% from the Z isomer) and provided **23** as an inseparable mixture of the double bond isomers, which were selectively hydrogenated using Wilkinson's calatyst to afford **24**. Finally, deprotection of the phenolic groups, followed by the formylation reaction, led to the formation of (±)-dichroanal B.

In conclusion, a new efficient method to prepare a 4a-methyltetrahydrofluorene system was developed via an intramolecular Heck cyclization of the novel diene **11**. The methodology was applied to the synthesis of (±)-dichroanal B and allowed to achieve a remarkably shorter synthesis (eight steps from *β*-cyclocitral) with an improved yield (36% from **18**), compared to the previously reported total synthesis.[9] This methodology also provides the opportunity for a convenient construction of

chiral 4a-methyltetrahydrofluorene. The asymmetric synthesis using related diene substrates is in progress.

Experimental Section

5,6-Diisopropoxy-7-isopropyl-1,1,4a-trimethyl-2,3,4,4a-tetrahydro-1*H*-fluorene (24). To a suspension of **11** (170 mg, 0.33 mmol, Z/E, 80/20), potassium carbonate (226 mg, 1.64 mmol), and 1,3-bis(diphenylphosphino)propane (54 mg, 0.13 mmol) in *N*,*N*-dimethylformamide (3.3 mL) was rapidly added palladium acetate (14.7 mg, 0.07 mmol). The mixture was stirred for 15 min at room temperature and 17 h at 100 °C. After the reaction mixture was quenched with water and extracted with ethyl acetate, the organic phase was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (hexane/diethyl ether, 95/5), providing **23** (83 mg, 92%) as a colorless oil along with unreacted (*E*)-**11** (25 mg). To a solution of the obtained mixture of **23** and (*E*)-**11** (26 mg of **23**, 0.07 mmol) in benzene (2 mL) was added $RhCl(PPh_3)_3$ (25 mg, 0.027 mmol) under a nitrogen atmosphere. The nitrogen was replaced with hydrogen, and the solution was stirred for 15 h. The reaction mixture was concentrated and purified by chromatography on silica gel (hexane/diethyl ether, 95/5), providing **24** (24 mg, 92%) as a colorless solid. Recrystallization from ethyl acetate gave an analytically pure product as colorless crystals: mp 86−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, J = 6.0 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.22 (s, 3H), 1.26 (s, 3H), 1.28 (d, J = 6.2 Hz, 3H), 1.29 (d, J = 6.2 Hz, 3H), 1.45 (s, 3H), 1.60 (m, 2H), 1.93 (m, 2H), 2.48 (m, 2H), 3.37 (sept, J = 7.0 Hz, 1H), 4.31 (sept, J = 6.2 Hz, 1H), 5.09 (sept, J = 6.2 Hz, 1H), 6.25 (s, 1H), 6.86 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 19.9, 21.6, 22.4, 22.4, 22.8, 23.0, 23.8, 24.8, 25.9, 26.5, 31.8, 35.6, 37.6, 42.7, 52.5, 70.9, 74.0, 112.0, 120.4, 138.4, 142.2, 143.7, 144.4,145.8, 163.8. IR ($CHCl_3$, cm^{-1}): 2966, 2932, 2361, 1421, 1111. HRMS $(M + H)^+$ calcd for $C_{25}H_{38}O_2$, 370.2872; found, 370.2869. Anal. Calcd for $C_{25}H_{38}O_2$: C, 81.03; H, 10.34. Found: C, 80.87; H, 10.52.

(±)-Dichroanal B (4). To a solution of **24** (30 mg, 0.081 mmol) in dichloromethane (1 mL) was slowly added 1 M boron trichloride solution in dichloromethane (400 μL, 0.405 mmol) at 0 °C. After stirring for 1 h, dichloromethyl methyl ether (11 μL, 1.12 mmol) was added. The reaction mixture was stirred for 3 h at 0 °C, quenched with water, and then extracted with ethyl acetate. The organic phase was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by short-column chromatography on silica gel (hexane/ethyl acetate, 1/1), providing (±)-**4** (20 mg, 80%) as an oil. ^{1}H NMR (400 MHz, C_5D_5N): δ 1.05−1.15 (m, 1H), 1.15−1.30 (m, 1H), 1.24 (s, 3H), 1.30 (s, 3H), 1.50−1.70 (m, 2H), 1.66 (d, J = 7.1 Hz, 6H), 1.73 (s, 3H), 1.94 (q, J = 13.7, 1H), 2.93 (dd, J = 1.3, 12.6 Hz, 1H), 4.47 (sept, J = 7.1 Hz, 1H), 5.05 (br s, 2H), 7.59 (s, 1H), 10.96 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 20.1, 20.7, 23.0, 23.1, 25.9, 27.4, 31.9, 36.2, 36.7, 43.4, 51.5, 120.9, 121.3, 139.5, 139.7, 141.3, 143.0, 150.8, 167.5, 192.2. IR ($CHCl_3$, cm^{-1}): 3524, 2964, 2934, 1670, 1589, 1458, 1275. HRMS $(M + H)^+$ calcd for $C_{20}H_{26}O_3$, 314.1882; found, 314.1879.

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Supporting Information Available: Experimental procedures and compound characterizations for **11**, **13a**,**b**, **14**, **16**−**22** and ^{1}H and ^{13}C NMR spectra for **4**, **11**, **13a**,**b**, **14**, **16**−**22**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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