

First Total Synthesis of the 4a-Methyltetrahydrofluorene Diterpenoids (±)-Dichroanal B and (±)-Dichroanone

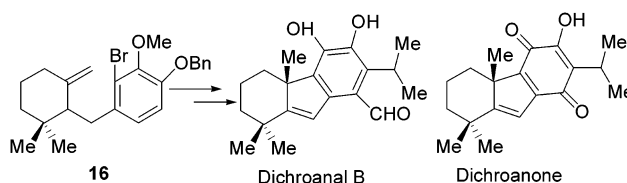
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ABSTRACT



A simple synthesis of the 4a-methyltetrahydrofluorene diterpenoids (±)-dichroanal B and (±)-dichroanone has been achieved through a common hexahydrofluorenone intermediate obtained via Pd(0)-catalyzed reductive cyclization of a substituted 2-(2-bromobenzyl) methylene cyclohexane.

Recently, three rearranged diterpenoids that possessed the uncommon 4a-methyl tetra- (or -hexa)hydrofluorene skeleton were isolated from *Salvia dichroantha*. They were designated dichroanal A (**1**) and B (**2**) and dichroanone (**3**) (Figure 1).¹ Several structurally related diterpenoids have also been isolated that include standishinal (**4**) from *Thuja standishii*² and taiwaniaquinols A (**5**) and B (**6**) from *Taiwania cryptomerioides*.³ Although not much is known about their bioactivities, preliminary studies on **4** indicated its promising tumor-inhibiting potential.^{4,5} No synthesis of this rare group of six-five-six tricyclic ring natural products has appeared so far.

We report herein the first total synthesis of two 4a-methyltetrahydrofluorene diterpenoids (±)-dichroanal B (**2**) and (±)-dichroanone (**3**) employing a common hexahydro-

fluorenone intermediate **22**, obtained by a simple and flexible convergent route suitable for the preparation of other members of this family.

There are several methods available for the preparation of 4a-methylhydrofluorene. These include acid-catalyzed cyclization of substituted benzyl cyclohexanols,⁶ inter- and intramolecular (3 + 2) cycloaddition,⁷ and the cyclization

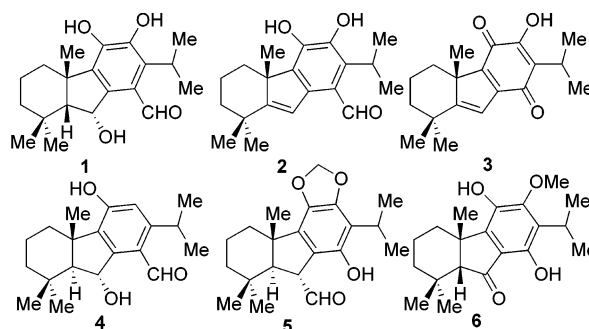


Figure 1. Natural 4a-methylhydrofluorene diterpenoids.

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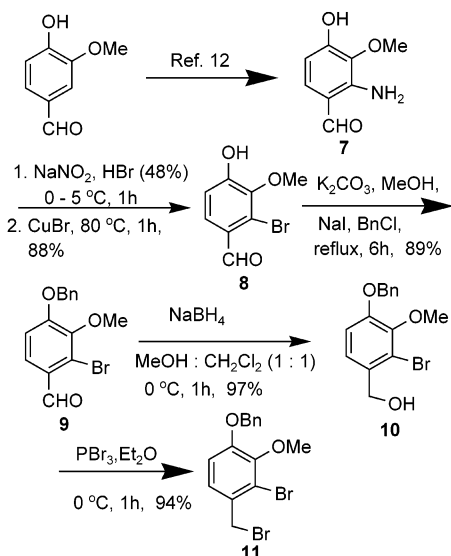
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of an arylpalladium,⁸ arylradical,⁹ or aryllithium¹⁰ tethered to methylene cyclohexane. Very recently, an efficient method for constituting this skeleton by intramolecular Friedel–Crafts cyclization of 1,3-bis-exocyclic diene has been reported.¹¹ We selected the strategy based on palladium-catalyzed reductive cyclization⁸ of a substituted 2-(2-bromobenzyl) methylene cyclohexane, which appeared to be the most attractive.

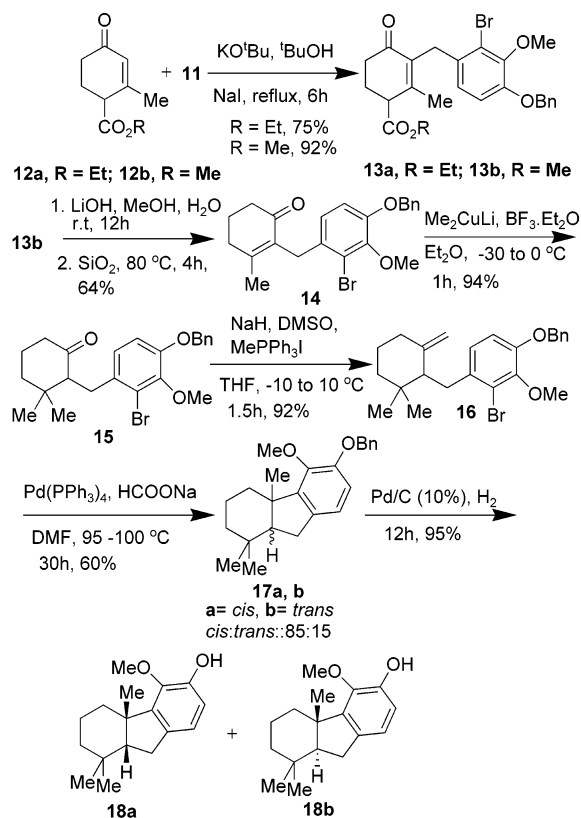
The synthesis began with the preparation of the appropriate benzyl bromide **11** from vanillin using a standard sequence of reactions that proceeded through the known¹² aldehyde **7** (Scheme 1). We sought to prepare the (*o*-bromobenzyl)-

Scheme 1. Synthesis of Aromatic Bromide **11**



cyclohexanone **15**, a key intermediate for the olefin **16** (Scheme 2), from the cyclohexenone **14** by an established route¹³ involving conjugate addition of a methyl group. While alkylation of Hagemann's ester **12a** gave the alkylated product^{6b,13} **13a** in 75% yield, its attempted hydrolytic decarboxylation under the usual condition^{6b,13} of refluxing with aqueous ethanolic KOH gave a complex mixture of products presumably due to oxidative side reactions involving

Scheme 2. Synthesis of Phenol **18a**



the heavily oxygenated aromatic ring. To our satisfaction, however, the alkylated methyl ester **13b**, obtained in 92% yield from the methyl ester analogue **12b**¹⁴ of Hagemann's ester, underwent smooth hydrolysis with aqueous methanolic LiOH, and the resulting crude acid on heating with a slurry of silica gel in CH₂Cl₂ produced the desired cyclohexenone **14** through decarboxylation. Wittig olefination of **15** proceeded uneventfully, producing the alkene **16** in good overall yield.

Conversion of the bicyclic intermediate to a tricyclic product was next accomplished via Pd(0)-catalyzed cyclization in the presence of a hydride donor.^{8,15} This gave an inseparable mixture of the epimeric hydrofluorenes **17a** and **17b** in a ratio of ca. 85:15 in 60% yield. A separation of the epimers could, however, be realized after deprotection of the *O*-benzyl ether mixture and recrystallization of the resulting product, which afforded the major epimer **18a** (mp 94 °C), assigned *cis* stereochemistry by analogy.⁸ The minor epimer **18b** could not be isolated in pure form.

With the tricyclic product **18a** in hand as a single epimer, our next task was to introduce an isopropyl group in the aromatic ring and to convert the benzylic methylene group to a ketone. This was best achieved via the sequence of reactions described in Scheme 3. Thus, acetylation of **18a** followed by Fries rearrangement¹⁶ of the acetate **19** furnished

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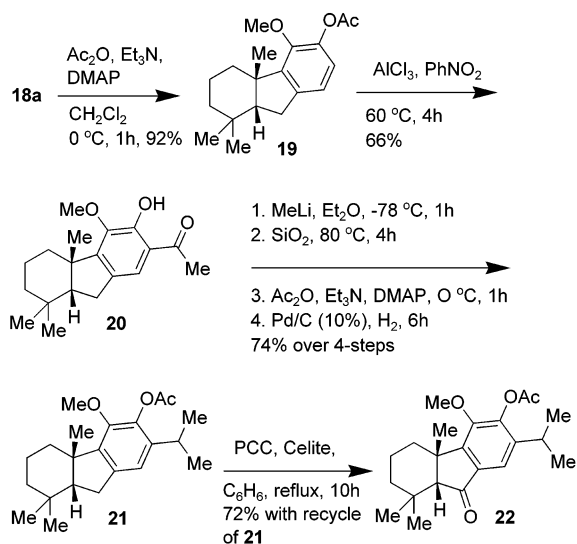
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Scheme 3. Synthesis of Hexahydrofluorenone 22

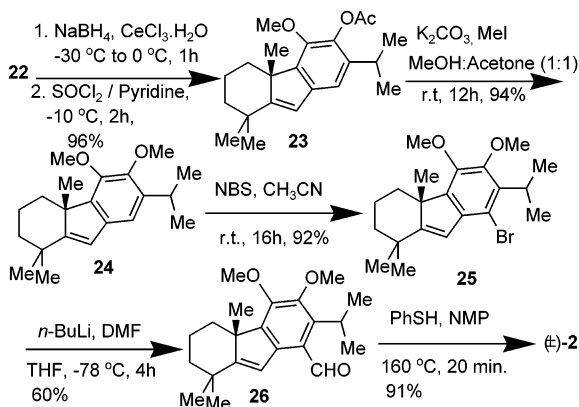


the 2-acetylphenol **20**. This, after condensation with MeLi, dehydration with silica gel, and acetylation afforded the acetate **21** in good yield after hydrogenation. Benzylic oxidation of **21** with PCC–Celite in benzene at reflux¹⁷ provided the ketone **22** (mp 78 °C).

Following the same sequence of reactions, the epimeric mixture of the cyclized products **17a** and **17b** (ca. 85:15) was conveniently converted to **22** without separation of the epimeric intermediates. The cis ring fusion for **22**, assumed on the basis of analogy,^{6b,18} received support from the NOESY spectrum also. Thus, the singlet for the ring juncture methine proton showed NOESY cross-peaks with two methyl singlets, as reported¹ for dichroanal A.

Finally, the ketone **22** was converted to the desired (±)-dichroanal B (**2**) as follows (Scheme 4). The reduction of

Scheme 4. Synthesis of Dichroanal B (2)

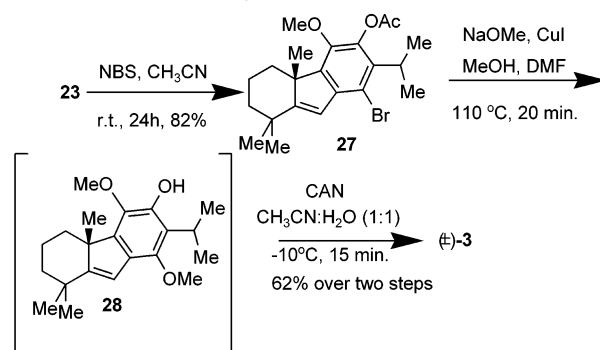


22 under controlled conditions¹⁹ afforded the crude alcohol, which was directly subjected to dehydration with SOCl₂/pyridine.²⁰ Subsequent hydrolysis of the acetate **23** and methylation of the resulting phenol yielded the tetrahydro-

fluorene **24**. Introduction of the aldehyde group in **24** was realized by bromination followed by formylation,²¹ and the resulting dimethyl ether **26** was smoothly converted²² to (±)-**2**. The synthetic product exhibited spectral data identical to those reported¹ for the natural material.

Only three reactions were required to complete the synthesis of (±)-dichroanone (**3**) from the intermediate tetrahydrofluorene acetate **23** (Scheme 5). This product was

Scheme 5. Synthesis of Dichroanone (3)



smoothly transformed to the bromo derivative **27**, which on heating with NaOMe in MeOH and DMF in the presence of CuI²³ produced the dimethoxy phenol intermediate **28**. On direct oxidation with CAN,²⁴ **28** afforded (±)-dichroanone (**3**) in good yield, identified by spectral comparison with the natural product.¹

In conclusion, the first synthesis of the 4a-methyltetrahydrofluorene diterpenoids (±)-dichroanal B and (±)-dichroanone has been realized through a simple and convergent route. Extension of this methodology to the other members of the group is in progress.

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Supporting Information Available: ¹H and ¹³C NMR spectra of compounds **2**, **3**, **16**, **18a**, **21–24**, **26**, and **27**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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