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

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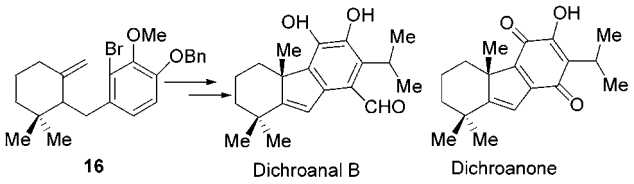
ABSTRACT



A simple synthesis of the 4*a*-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 4*a*-methyl tetra- (or -hexa)hydrofluorene skeleton were isolated from *Salvia dichroantha*. They were designated dichroanals 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 4*a*-methyltetrahydrofluorene diterpenoids (±)-dichroanal B (**2**) and (±)-dichroanone (**3**) employing a common hexahydrofluorenone 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 4*a*-methylhydrofluorene. These include acid-catalyzed cyclization of substituted benzyl cyclohexanols,[6] inter- and intramolecular (3 + 2) cycloaddition,[7] and the cyclization

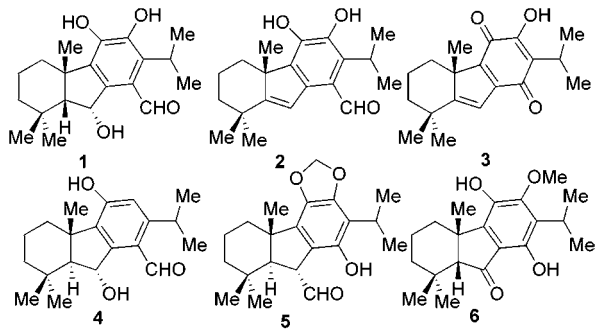


Figure 1. Natural 4*a*-methylhydrofluorene diterpenoids.

(1) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493−497.
(2) Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419−6422.
(3) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *40*, 871−873.
(4) Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742−745.
(5) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911−1921.

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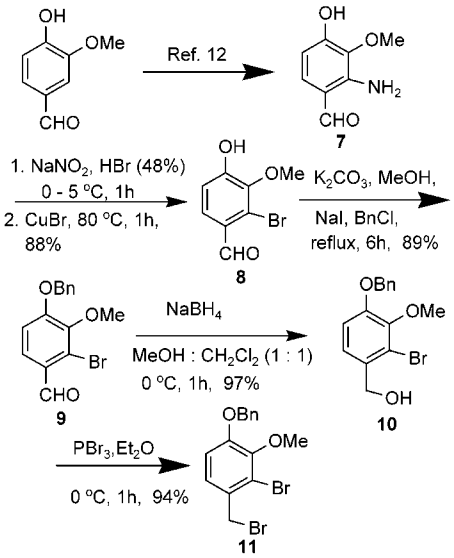
of an arylpalladium,[8] arylradical,[9] or aryllithium[10] tethered to methylene cyclohexane. Very recently, an efficient method for constituting this skeleton by intramolecular Friedel−Crafts cyclization of 1,3-bis-exocyclic diene has been reported.[11] We selected the strategy based on palladium-catalyzed reductive cyclization[8] of a substituted 2-(2-bromobenzyl) methylene cyclohexane, which appeared to be the most attractive.

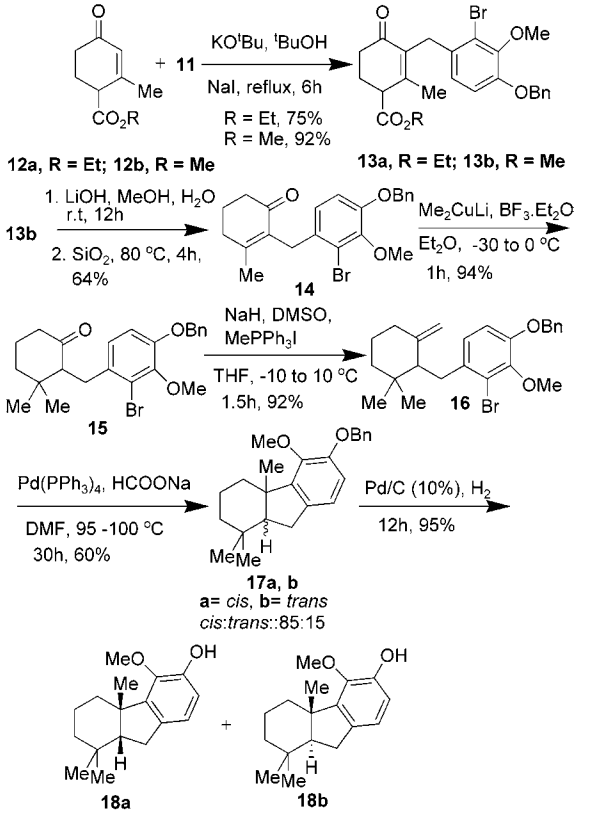
The synthesis began with the preparation of the appropriate benzyl bromide **11** from vanillin using a standard sequence of reactions that proceeded through the known[12] aldehyde **7** (Scheme 1). We sought to prepare the (*o*-bromobenzyl)-

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 route[13] 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 CH_2Cl_2 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 rearrangement[16] of the acetate **19** furnished

(6) (a) Ghatak, U. R.; Chakravarty, J. *Tetrahedron Lett*. **1966**, *7*, 2449−2458. (b) Ghatak, U. R.; Chakravarty, J.; Banerjee, A. K. *Tetrahedron* **1968**, *24*, 1577−1593. (c) Ghatak, U. R.; Chakravarty, J.; Dasgupta, R.; Chakraborti, P. C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2438−2445. (d) Chakravarty, J.; Dasgupta, R.; Ray, J. K.; Ghatak, U. R. *Proc. Indian Acad. Sci*. **1977**, *86A*, 317−325. (e) Chakarborti, P. C.; Ghosh, S.; Kanjilal, P. R.; Satyanarayana, G. O. S. V.; Ghatak, U. R. *Indian J. Chem*. **1979**, *18B*, 183−185.

(7) Angle, S. R.; Arnaiz, D. O. *J. Org. Chem*. **1992**, *57*, 5937−5947.

(8) Mukhopadhyaya, J. K.; Pal, S.; Ghatak, U. R. *Synth. Commun*. **1995**, *25*, 1641−1657.

(9) (a) Ishibashi, H.; Kobayashi, T.; Nakashima, S.; Tamura, O. *J. Org. Chem*. **2000**, *65*, 9022−9027. (b) Ishibashi, H.; Kobayashi, T.; Takamasu, D. *Synlett* **1999**, 1286−1288.

(10) Bailey, W. F.; Daskapan, T.; Rampalli, S. *J. Org. Chem*. **2003**, *68*, 1334−1338.

(11) Lomberget, T.; Bentz, E.; Bouyssi, D.; Blame, G. *Org. Lett*. **2003**, *5*, 2055−2057.

(12) Burger, A. P. N.; Brandt, E. V.; Roux, D. G. *Phytochemistry* **1983**, *22*, 2813−2817.

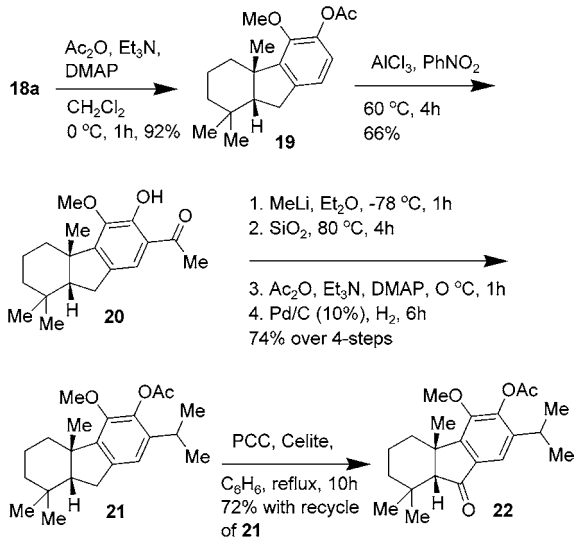
(13) Pal, S.; Mukhopadhyaya, J. K.; Ghatak, U. R. *J. Org. Chem*. **1994**, *59*, 2687−2694.

(14) Begbie, A. L.; Golding, B. T. *J. Chem. Soc., Perkin Trans. 1* **1972**, 602−605.

(15) Link, J. T. *Org. React*. **2002**, *60*, 157−534.

(16) (a) Gammill, R. B. *Tetrahedron Lett*. **1985**, *26*, 1385−1388. (b) Blatt, A. H. *Org. React*. **1942**, *1*, 342−369.

Scheme 3. Synthesis of Hexahydrofluorenone **22**

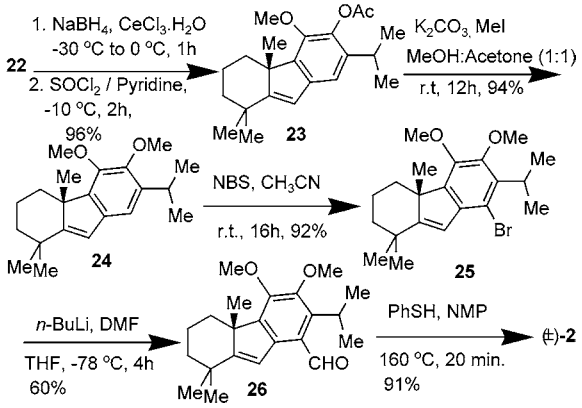


the 2-acetylphenol **20**. This, after condensation with MeLi, dehydration with silica gel, and acetylation afforded the acetate **21** in good yield after hydrogenation. Benzylic oxidation of **21** with PCC−Celite in benzene at reflux[17] provided the ketone **22** (mp 78 °C).

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 reported[1] for dichroanal A.

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

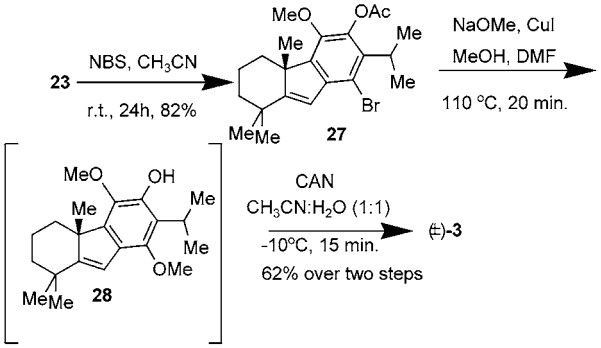
Scheme 4. Synthesis of Dichroanal B (**2**)



22 under controlled conditions[19] afforded the crude alcohol, which was directly subjected to dehydration with $SOCl_2$/pyridine.[20] Subsequent hydrolysis of the acetate **23** and methylation of the resulting phenol yielded the tetrahydrofluorene **24**. Introduction of the aldehyde group in **24** was realized by bromination followed by formylation,[21] and the resulting dimethyl ether **26** was smoothly converted[22] to (±)-**2**. The synthetic product exhibited spectral data identical to those reported[1] 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 CuI[23] 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 4*a*-methyltetrahydrofluorene diterpenoids (±)-dichronal 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: ^{1}H and ^{13}C 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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(17) (a) Ghosh, A. K.; Mukhopadhyay, C.; Ghatak, U. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 327−332. (b) Rathore, R.; Saxena, N.; Chandrasekaran, S. *Synth. Commun.* **1986**, *16*, 1493−1498.
(18) (a) Ghosh, S.; Ghatak, U. R. *J. Org. Chem.* **1981**, *46*, 1486−1490. (b) Parham, W. E.; Czuba, L. J. *J. Org. Chem.* **1969**, *34*, 1899−1904.
(19) (a) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226−2227. (b) Boutin, R. H.; Rapoport, H. *J. Org. Chem*, **1986**, *51*, 5320−5327.
(20) Allen, W. S.; Bernstein, S. *J. Am. Chem. Soc.* **1955**, *77*, 1028−1032.
(21) Maddaford, S. P.; Charlton, J. L. *J. Org. Chem.* **1993**, *58*, 4132−4138.
(22) Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1997**, *38*, 8749−8752.
(23) Sishido, K.; Goto, K.; Miyoshi, S.; Takaishi, Y.; Shibuya, M. *J. Org. Chem.* **1994**, *59*, 406−414.
(24) Horiguchi, Y.; Toeda, A.; Tomoda, K.; Suzuki, H.; Sano, T. *Chem. Pharm. Bull.* **1998**, *46*, 1356−1363.