

Lewis Acid-Induced Intramolecular Friedel–Crafts Cyclization of 1,3-Bis-exocyclic Dienes. A New Route to 4a-Methyltetrahydrofluorenes

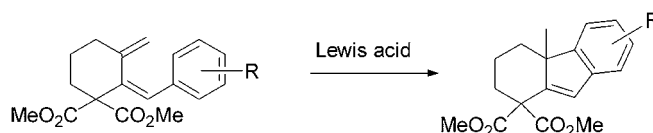
Thierry Lomberget, Emilie Bentz, Didier Bouyssi, and Geneviève Balme*

Laboratoire de Chimie Organique 1, associé au CNRS, Université Claude Bernard
Lyon 1, CPE, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne, France

balme@univ-lyon1.fr

Received March 11, 2003

ABSTRACT



An efficient new method for constructing the 4a-methyltetrahydrofluorene skeleton was achieved via Friedel–Crafts intramolecular cyclization of 1,3-bis-exocyclic dienes. This strategy offers a simple and promising method for accessing complex structures.

The 4a-methyltetra- (and hexa-)hydrofluorene skeleton is relatively uncommon in natural products. Recently, five compounds possessing this six-five-six fused-ring structure have been isolated: Standishinal from the stem bark of *Thuja standishii*,¹ Taiwaniaquinol A and B from *Taiwania cryptomerioides*² (an endemic tree), and Dichroanal A and B from the root of *Salvia dichroantha*³ collected in Turkey (Figure 1). These compounds were also accompanied by homologues, Taiwaniaquinone A–C and Dichroanone, possessing a quinone nucleus instead of the substituted aromatic nucleus. Little is known about the bioactivity of these compounds since they were only recently isolated. However, promising studies demonstrated aromatase inhibitory activities⁴ of Standishinal and significant antitumor promoting activity in a two-stage mouse skin carcinogenesis test using 7,12-dimethylbenz[*a*]anthracene and TPA.⁵

In the literature, several strategies have been reported for the preparation of 4a-methylhexahydrofluorenes. These

include the acid-catalyzed cyclization of substituted benzyl-cyclohexanols,⁶ inter- and intramolecular [3 + 2] cycloadditions,⁷ and the cyclization of an arylradical,⁸ aryllithium,⁹ or arylpalladium¹⁰ tethered to a methylene cyclohexane. By contrast, studies dealing with the synthesis of 4a-methyltetrahydrofluorenes are scarce. A report described an acetylation of 1-methylcyclohexene with substituted acyl halides in the

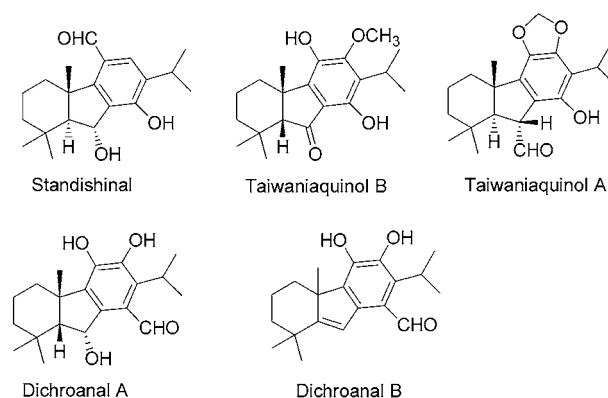


Figure 1. Natural 4a-methyltetrahydrofluorenes.

(1) Ohtsu, H.; Iwamoto, M.; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419–6422.

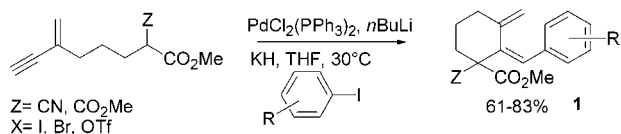
(2) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *40*, 871–873.

(3) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493–497.

(4) Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742–745.

presence of $\text{CF}_3\text{SO}_3\text{H}$, but this led to low yields and mixtures of products.¹¹ This structure could also be obtained by a palladium-catalyzed cyclization of 2-(2-bromobenzyl)-methylenecyclohexanes, but this reaction has a limitation, the requirement for a stoichiometric quantity of palladium.¹⁰ We previously reported a new approach to functionalized 1,3-bis exocyclic dienes **1** that was particularly efficient for forming six-membered rings (Scheme 1) and explored their

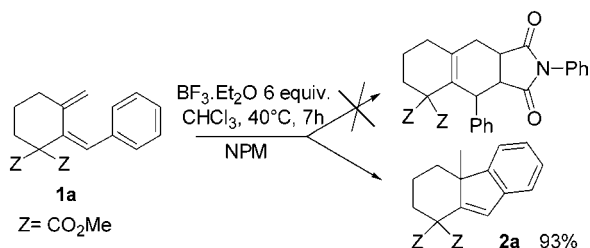
Scheme 1. Palladium-Catalyzed Synthesis of 1,3-Bis-exocyclic Dienes



synthetic potential.¹² In line with this, these exodienes were recently engaged in Diels–Alder reactions with very reactive dienophiles to reach synthetically useful carbocycles.¹³

However, with relatively unreactive dienophiles such as *N*-phenylmaleimide (NPM), these 1,3-bis exocyclic dienes failed to undergo the thermal Diels–Alder reaction. As many Diels–Alder reactions are known to be accelerated by Lewis acid catalysts,¹⁴ compound **1a** was reacted with NPM in CHCl_3 at 40 °C using an excess of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (6 equiv). Surprisingly, instead of the desired product, the tricyclic compound **2a** having the 4a-methyltetrahydrofluorene skeleton was obtained in 93% yield. This compound would result from an internal Friedel–Crafts alkylation (Scheme 2).¹⁵

Scheme 2. Lewis Acid-Catalyzed Cyclization of **1a**



The reaction of **1a** was then examined with various amounts of $\text{BF}_3\cdot\text{Et}_2\text{O}$ in order to determine the optimal

conditions (Table 1). We found the reaction to be highly sensitive to the amount that was used (entries 1–4). Indeed, to achieve a good conversion, the reaction has to be conducted in the presence of 6 equimolecular amounts of $\text{BF}_3\cdot\text{Et}_2\text{O}$. Complexation of the Lewis acid by the ester groups certainly explains the necessity to use a large excess of Lewis acid in that case.

Table 1. Lewis Acid Screening for Friedel–Crafts Cyclization of **1a**

entry	Lewis acid	equiv	conditions	yield (%)
1	$\text{BF}_3\cdot\text{Et}_2\text{O}$	1.5	CHCl_3 , 40°C, 30 h	a
2	$\text{BF}_3\cdot\text{Et}_2\text{O}$	3	CHCl_3 , 40°C, 6 h	b
3	$\text{BF}_3\cdot\text{Et}_2\text{O}$	4	CHCl_3 , 40°C, 4 h	b
4	$\text{BF}_3\cdot\text{Et}_2\text{O}$	6	CHCl_3 , 40°C, 7 h	93
5	TiCl_4	6	CHCl_3 , 40°C, 30 h	b
6	SnCl_4	6	CHCl_3 , 40°C, 6 h	92
7	ZnBr_2	6	Et_2O , reflux, 30 h	a
8	$\text{Sc}(\text{OTf})_3$	1	toluene, reflux, 6.5 h	85
9	$\text{Sc}(\text{OTf})_3$	0.2	toluene, reflux, 4 h	96
10	$\text{Sc}(\text{OTf})_3$	0.1	toluene, reflux, 24 h	85

^a Starting material was recovered. ^b Intense degradation of the reaction mixture.

A series of Lewis acidic metal reagents were also screened (entries 5–7). SnCl_4 showed the best activity leading to **2a** in high isolated yield. The mild Lewis acid ZnBr_2 was ineffective to promote the reaction, and TiCl_4 led to the formation of a complex mixture of products. Recently, the beneficial effect of rare earth metal Lewis acids such as scandium triflate in Friedel–Crafts reaction, in particular for acylation or alkylation reactions, has been reported.¹⁶ A 96% yield of **2a** was obtained when 20% of this acid was used (entry 9). Lowering the quantity to 10% gave also good results, but a prolonged heating time was necessary (entry 10).

For the mechanism of this $\text{Sc}(\text{OTf})_3$ -catalyzed Friedel–Crafts alkylation, the reaction should proceed via an intramolecular attack of the arene onto the exomethylene double bond of **1** electrophilically activated by the metal triflate to furnish intermediate **4** (Scheme 3, path a).

Another possible pathway should be the formation of alkyl cation **3** by the reaction of **1** with the metal triflate followed by attack of the arene (Scheme 3, path b). A subsequent loss of a proton leads to aromatization and regenerates the catalyst.

(5) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911–1921.

(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.; Chakravarti, P. J. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2439. (d) Chakravarty, J.; Dasgupta, R.; Ray, J. K.; Ghatak, U. R. *Proc. Indian Acad. Sci.* **1977**, *86A*, 317. (e) Chakravarti, P. J.; Ghosh, S.; Kanjilal, P. B.; Satyanarayana, G. O. S. V.; Ghatak, U. R. *Indian J. Chem.* **1979**, *18B*, 183.

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

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

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

(10) Mukhopadhyaya, J. K.; Pal, S.; Ghatak, U. R. *Synth. Comm.* **1995**, *25*, 1641–1657.

(11) Roussel, C.; Shaima, L.; Chemlal, A. *Bull. Soc. Chim. Fr.* **1988**, 688–693.

(12) Lomberget, T.; Bouyssi, D.; Balme, G. *Synlett* **2002**, 1439–1442.

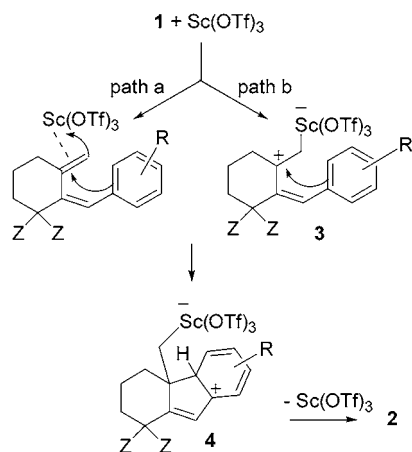
(13) Lomberget, T.; Bouyssi, D.; Balme, G. To be published.

(14) Caruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990; Vol. 8.

(15) For a related internal cyclization, see: Akita, H.; Naito, T.; Oishi, T. *Chem. Lett.* **1979**, 1365.

(16) (a) Kawada, A.; Mitamura, S.; Matsuo, J.-I.; Tsuchiya, T.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2325–2333. (b) Song, C. E.; Shim, W. H.; Roh, E. J.; Choi, J. H. *J. Chem. Soc., Chem. Commun.* **2000**, 1695–1696.

Scheme 3. Plausible Mechanism for Sc(OTf)₃-Catalyzed Alkylation Reaction



To study the influence of the aromatic ring substitution, we prepared several 1,3-bis exocyclic dienes from the corresponding aryl iodides (Scheme 1). These substrates were then submitted to our previously optimized conditions: BF₃·Et₂O (6 equiv)¹⁷ and Sc(OTf)₃ (0.2 equiv). As shown in Table 2, reaction of dienes with electron-activating groups on the aryl moiety afforded the corresponding 4a-methyltetrahydrofluorenes in very good yields (entries 2–5). The yields indicate the processes employing BF₃·Et₂O and Sc(OTf)₃ are equally effective. It is worth noting that the Friedel–Crafts reaction of compound **1c** is highly regioselective leading to the exclusive formation of isomer **2c** in good yield. Incorporation of an electron-withdrawing group on the aryl nucleus completely suppressed the Friedel–Crafts reaction, and the only isolated product resulted from migration of the exocyclic double bond¹⁸ (entries 6–8). However, although this reaction is limited to aromatic rings bearing an electron-donating group, it allows access to 4a-methyltetrahydrofluorene structures having the aromatic substitution pattern present in natural products (see Figure 1). Moreover, the presence of the geminal dicarboxylate makes this strategy appealing in accessing these naturally occurring compounds since this may allow for the introduction of the gemdimethyl moiety.¹⁹

In conclusion, this letter describes an unprecedented and very efficient method for constructing the 4a-methyltetrahydrofluorene skeleton via an intramolecular Friedel–Crafts reaction. Application of this methodology to the synthesis of natural products is in progress and will be reported in due course.

(17) Although SnCl₄ was found as effective as BF₃·Et₂O for this reaction, the latter remains more practical of use and was therefore preferred in the following studies.

(18) Failure of nonactivated aromatic rings to undergo cationic cyclization is well documented in the literature. See: Olah, G. A. *Friedel–Crafts Chemistry*; Wiley: New York, 1973.

(19) This strategy was previously reported by our group for the synthesis of (±)-Capnellene; see: Balme, G.; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403–414.

Table 2. Friedel–Crafts Cyclization of Compounds of Type **1** Mediated by BF₃·Et₂O or Sc(OTf)₃

entry	R	Lewis acid (time)	product	yield (%) ^a
1	H 1a	BF ₃ ·Et ₂ O (6h)		93
2	3,4,5-trimethoxy 1b	Sc(OTf) ₃ (4h)		96
3	3,4-methylenedioxy 1c	BF ₃ ·Et ₂ O (7h)		74
4	<i>o</i> -tolyl 1d	Sc(OTf) ₃ (6h)		97
5	1,2-dimethoxy,3-isopropyl-4-methyl 1e	BF ₃ ·Et ₂ O (6h)		69
6	<i>o</i> -Br 1f	Sc(OTf) ₃ (6h)		73
7	<i>p</i> -CO ₂ Me 1g	BF ₃ ·Et ₂ O (24h)		67
8	<i>m</i> -CF ₃ 1h	Sc(OTf) ₃ (8h)		60

^a Isolated yield.

Acknowledgment. T.L. thanks the Ministère de l'Éducation Nationale, de la Recherche et de la Technologie for a fellowship.

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>.

OL0344265