ORGANIC LETTERS

2001
Vol. 3, No. 9
1359−1362

The First Total Synthesis of (±)-Linderol A, a Tricyclic Hexahydrodibenzofuran Constituent of *Lindera umbellata* Bark, with Potent Inhibitory Activity on Melanin Biosynthesis of Cultured B-16 Melanoma Cells

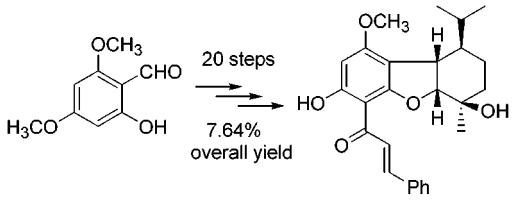
Masayuki Yamashita, Nobukazu Ohta, Ikuo Kawasaki, and Shunsaku Ohta*

Kyoto Pharmaceutical University, Misasagi-Nakauchicho 5, Yamashinaku, Kyoto 607-8414, Japan

sohta@mb.kyoto-phu.ac.jp

Received February 20, 2001

ABSTRACT



The first total synthesis of (±)-linderol A, a hexahydrodibenzofuran isolated from *Lindera umbellata* bark, with potent inhibitory activity on melanin biosynthesis of cultured B-16 melanoma cells was achieved via a 20-step of reaction in 7.64% overall yield starting from 4,6-dimethoxysalicylaldehyde.

In 1995, Sashida et al. reported isolation of linderol A (**1**), (5a*R**,6*R**,9*R**,9a*S**)-4-cinnamoyl-3,6-dihydroxy-1-methoxy-6-methyl-9-(1-methylethyl)-5a,6,7,8,9,9a-hexahydrodibenzofuran, from the fresh bark of *Lindera umbellata* (Lauraceae) (Figure 1).[1,2] They also reported the potent inhibitory activity of **1** on melanin biosynthesis of cultured B-16 melanoma cells without causing any cytotoxicity in the cultured cells or skin irritation in guinea pigs.[1]

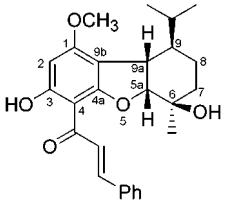
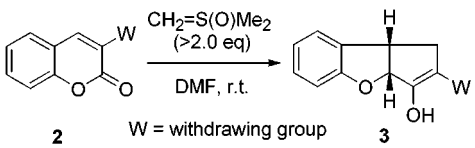


Figure 1. Structure of the natural product **1**.

We reported in 1995 an interesting rearrangement of the coumarin derivatives **2**, which had an electron-withdrawing group at the 3-position, to the tricyclic 2-substituted cyclopenta[*b*]benzofuran-3-ol derivatives **3** by treatment with a small excess over 2 equiv of dimethylsulfoxonium methylide (Scheme 1).[3]

We planned the total synthesis of **1** by applying this

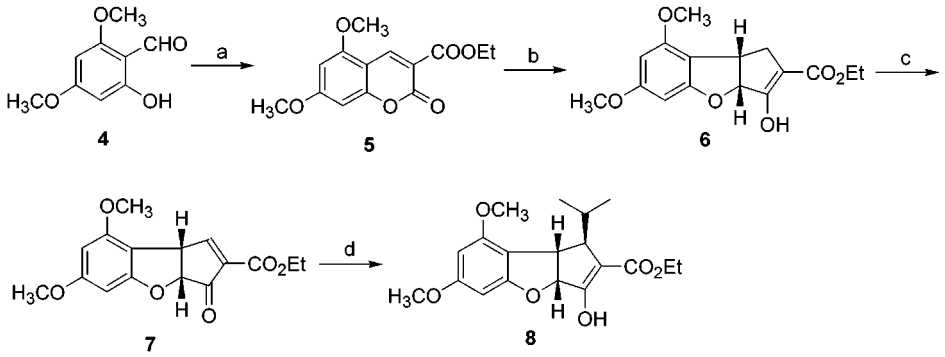
Scheme 1



2 W = withdrawing group **3**

10.1021/ol0157398 CCC: $20.00
Published on Web 04/06/2001

Scheme 2[a]



[a] (a) Ethyl malonate, piperidine, acetic acid, EtOH, reflux, 97.0%; (b) $Me_3S(O)I$, 60% NaH, DMF, rt, 78.8%; (c) i. PhSeCl, 60% NaH, THF, 0 °C to rt; ii. $NaIO_4$, THF−H_2O, rt, 78.9%; (d) *i*-PrMgBr, CuI, $BF_3{\cdot}Et_2O$, Et_2O−CH_2Cl_2, −78 °C, 65.5%.

rearrangement to an appropriately substituted coumarin followed by a one-carbon ring expansion of the cyclopentane portion of **3**. In this Letter, we describe the first total synthesis of (±)-**1** according to this strategy.

The starting material, 4,6-dimethoxysalicylaldehyde **4**,[4] was converted to the coumarin **5** by Knoevenagel reaction in 97.0% yield, and the product **5** was treated with 2.2 equiv of dimethylsulfoxonium methylide according to the previously reported procedure[3] to afford the rearranged cyclopenta[*b*]benzofuran derivative **6** in 78.8% yield.[5] The benzofuran **6** was converted to the α,β-unsaturated ketoester **7** according to the well-known phenylselenenylation−oxidation methodology.[6] The next step is introduction of an isopropyl group to **7**. We predicted that an appropriate organometallic reagent (RM) would attack almost exclusively from the less hindered side (convex face) of the 5,5-rings and the adduct would bring about the desired stereochemistry (Figure 2).

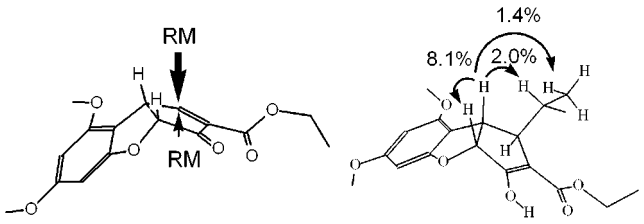


Figure 2. β-Face attack of RM to **7** (left) and observed NOEs for **8** (right).

In fact, the isopropyl group was regio- and stereoselectively introduced by treatment of **7** with isopropylmagnesium bromide in the presence of CuI and BF_3 etherate to afford the desired enolester **8** as a single product (Scheme 2). The stereochemistry of the introduced isopropyl group of **8** was confirmed on the basis of NOE data as shown in Figure 2.

After decarboxylation of **8** by heating in acetic acid, a one-carbon ring enlargement of the cyclopentanone ring in the resultant **9** was carried out by treatment with ethyl diazoacetate in the presence of BF_3 etherate to afford successfully the cyclohexane **10** in 85.8% yield.[7] Attempts of decarboxylation after acidic or alkaline hydrolysis of **10** resulted in a complex mixture or complete recovery of **10**, respectively; therefore, it was considered that alkaline hydrolysis of the ethoxycarbonyl group in **10** should be carried out after protection of the enol. Thus, the enol **10** was converted to the corresponding MOM ether **11** (84.0%), alkaline hydrolysis of which followed by acidification and refluxing in xylene gave the ketone **12** in 72.2% yield from **11**. Wittig olefination of ketone **12** (97.2%) with methylenetriphenylphosphorane followed by *cis*-1,2-dihydroxylation with a catalytic amount of microencapsulated OsO_4 in the presence of *N*-methylmorpholine *N*-oxide afforded the diol **14** as a single isomer in quantitative yield.[8,9] It was expected that OsO_4 oxidation would occur at the less hindered side (convex face) of **13** (Figure 3).

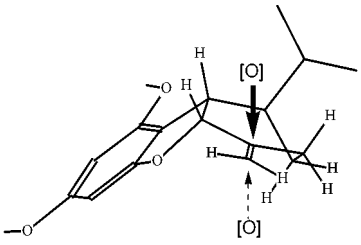


Figure 3. β-Face attack of OsO_4 to **13**.

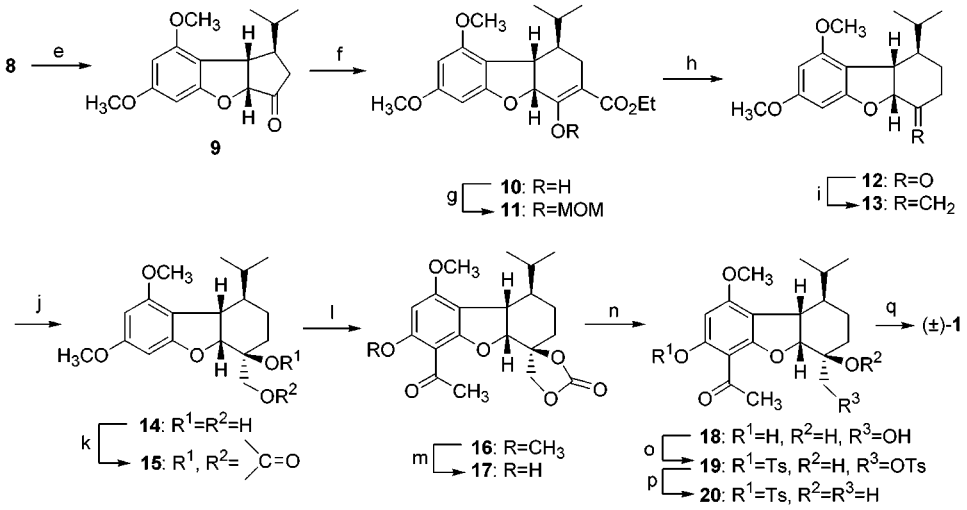
The desired stereochemistry of the tertiary alcohol portion was confirmed on the basis of NOE data of the corresponding

(1) Mimaki, Y.; Kameyama, A.; Sashida, Y.; Miyata, Y.; Fujii, A. *Chem. Pharm. Bull*. **1995**, *43*, 893.

(2) Recently, Professor Sashida (Tokyo University of Pharmacy and Life Science) proposed to us the name linderol A for compound **1**, which was treated as a no name natural product in the report (ref 1). In this Letter, we will use the name of linderol A.

(3) Yamashita, M.; Okuyama, K.; Kawasaki, I.; Ohta, S. *Tetrahedron Lett*. **1995**, *36*, 5603.

Scheme 3[a]



[a] (e) AcOH, 100 °C, 98.2%; (f) $N_2CHCOOEt$, $BF_3{\cdot}Et_2O$, Et_2O, 0 °C, 85.8%; (g) 60% NaH, MOMCl, THF, rt, 84.0%; (h) i. NaOH−H_2O, rt; ii. *c*-HCl, 0 °C; iii. xylene, reflux, 72.2%; (i) CH_3PPh_3Br, *n*-BuLi, THF, 0 °C, 97.2%; (j) MC OsO_4, NMO, rt, 100%; (k) CDI, Et_3N, DMAP, CH_2Cl_2, rt, 97.2%; (l) Ac_2O, $Sc(OTf)_3$, nitromethane, 50 °C, 75.9%; (m) BBr_3, CH_2Cl_2, 0 °C, 100%; (n) 1 N NaOH−dioxane, rt, 85.9%; (o) TsCl, Et_3N, DMAP, rt, THF, 84.2%; (p) $NaBH_3CN$, HMPA, 120 °C, 84.3%; (q) *t*-BuOK, *t*-BuOH, benzaldehyde, rt, then KOH aq−MeOH, rt, 86.7%.

cyclic carbonate **15**, that is, NOEs were not observed between 5a-H and -CH_2- of cyclic carbonate and 9a-H and -CH_2- of cyclic carbonate, respectively.[10,11]

Next, Friedel−Crafts reaction of **15** was carried out by treatment with acetic anhydride in the presence of a catalytic amount of $Sc(OTf)_3$ to give regioselectively the desired 4-acetyl compound **16** as the sole product in 75.9% yield.[12] The position of the introduced acetyl group was confirmed on the basis of the HMBC spectrum as shown in Figure 4.

Selective demethylation, assisted by the adjacent acetyl group, of the 3-methoxy group of **16** by treatment with BBr_3 afforded the phenol **17** in quantitative yield,[13] and then alkaline hydrolysis of the cyclic carbonate function in **17** gave the diol **18** in 85.9% yield. The ditosylate **19** was prepared in the usual manner, and its $NaBH_3CN$ reduction converted selectively only the alkyl tosylate function to the α-methyl group in 84.3% yield. Finally, treatment of **20** with benzaldehyde in the presence of *tert*-BuOK followed by alkaline hydrolysis gave crystalline (±)-**1** in 86.7% yield (Scheme 3). The spectral data of synthetic (±)-**1** were identical with those of an authentic sample[1] in all respects.[14]

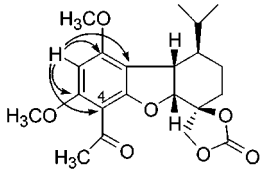
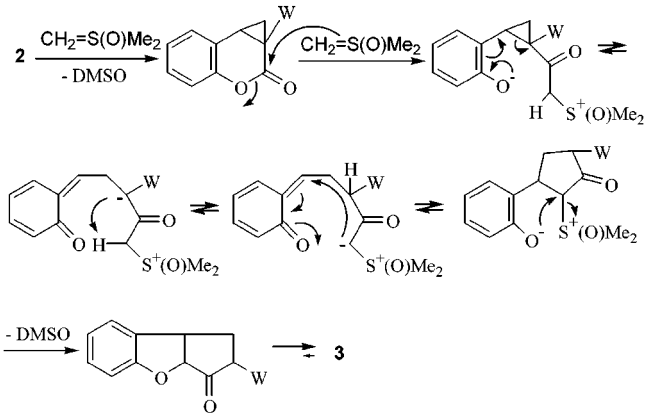


Figure 4. Selected HMBC correlation of **16**.

(4) Tsukayama, M.; Horie, T.; Fujimoto, K.; Nakayama, M. *Chem. Pharm. Bull.* **1986**, *34*, 2369.

(5) A plausible mechanism for the rearrangement is illustrated as follows.



(6) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

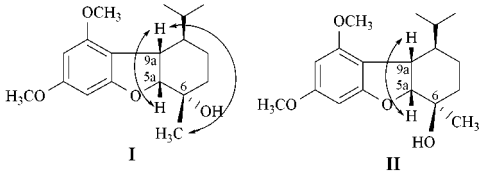
(7) Ghosh, A. K.; Biswas, S.; Venkastewaran, R. V. *J. Chem. Soc., Chem. Commun.* **1988**, 1421.

(8) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094.

(9) Unfortunately, epoxidation of **13** with MCPBA afforded a complex mixture.

(10) The numbering for the natural product **1** in ref 1 is conveniently used for the 6,5,6-ring systems appearing in this paper (see Figure 1).

(11) The stereochemistry of **15** was further supported by the following NOE data of diastereomers **I** and **II**, which were prepared from **12**/MeMgBr/THF/0 °C and **14**-monotosylate/$NaBH_3CN$/HMPA/120 °C, respectively.



(12) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545.

(13) Scäfer, W.; Franck, B. *Chem. Ber.* **1966**, *99*, 160.

(14) Satisfactory analytical and spectroscopic data have been obtained for all new compounds reported herein.

In conclusion, the first total synthesis of (±)-linderol A, a melanin biosynthesis inhibitory active natural product **1**, was achieved in 20 steps in 7.64% overall yield from 4,6-dimethoxysalicylaldehyde **4**.

Acknowledgment. The authors thank Professor Yutaka Sashida (Tokyo University of Pharmacy and Life Science) for providing the spectral data of linderol A. The authors are also grateful to Professor Tetsuaki Tanaka (Osaka University) for his useful advice. This research was financially supported in part by the Frontier Research Program of the Ministry of Education, Science, Sports and Culture of Japan.

Supporting Information Available: Characterization data for compounds **1** and **4**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0157398