ORGANIC LETTERS

2005
Vol. 7, No. 9
1765−1768

Structures, Biological Activities, and Total Syntheses of 13-Hydroxy- and 13-Acetoxy-14-nordehydrocacalohastine, Novel Modified Furanoeremophilane-Type Sesquiterpenes from *Trichilia cuneata*

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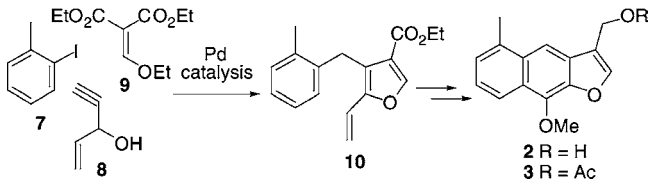
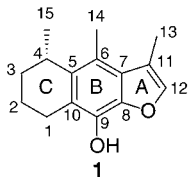
Received February 18, 2005

ABSTRACT



13-Hydroxy-14-nordehydrocacalohastine (2) and 13-acetoxy-14-nordehydrocacalohastine (3), two novel modified furanoeremophilane-type sesquiterpenes isolated from *Trichilia cuneata*, showed inhibitory activities for membrane lipid peroxidation in mitochondria and microsomes. The first, highly convergent total syntheses of new compounds 2 and 3 have also been achieved via a palladium-mediated three-component coupling reaction between 2-iodotoluene (7), 1-penten-4-yn-3-ol (8), and diethyl ethoxymethylenemalonate (9).

Cacalia decomposita A. Gray,[1] a compositae widely distributed in the northern part of Mexico, is a shrub popularly known as matarique and maturin.[2] Matarique is a medicinal plant complex of Mexico, the concoction of which is drunk for treating diabetes, kidney pain, and rheumatism, and it can also be applied as a wash or cataplasm to treat wounds and skin ulcers.[3] Recently, in vivo bioassay-directed fractionation of an extract from the roots of *C. decomposita* A. Gray revealed that a modified eremophilane cacalol (**1**) exhibits antihyperglycemic[4] and antimicrobial[5] activities. These stimulating findings prompted us to undertake studies on biologically active chemical constituents of *Trichilia cuneata*, one of shrubs composing the endemic medicinal plant complex in Mexico.[6] In this paper, we preliminarily report structures and biological activities of 13-hydroxy-14-nordehydrocacalohastine (**2**) and 13-acetoxy-14-nordehydrocacalohastine (**3**), two novel modified furanoeremophilane-type sesquiterpenes, and a known compound (**4**). We also report the first, highly convergent total syntheses of **2**



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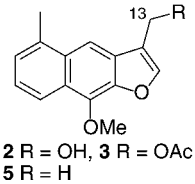
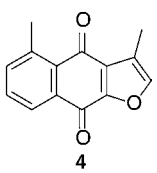


2 R = OH, **3** R = OAc
5 R = H



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(1) Synonyms for *Cacalia decomposita* A. Gray include *Psacalium decompositum* and *Odontorichum decompositum* (Gray) Rydb.

(2) Romo, J.; Joseph-Nathan, P. *Tetrahedron* **1964**, *20*, 2331.

(3) (a) Linares, E.; Bye, R. A. *J. Ethnopharmacol.* **1987**, *19*, 153. (b) Bye, R. A. *Econ. Bot.* **1986**, *40*, 103.

10.1021/ol050346k CCC: $30.25
Published on Web 03/30/2005

and **3** through a palladium-catalyzed three-component coupling reaction.

The methanol extract (10.9 g) of dried stem bark and leaves of *T. cuneata*, which showed inhibition for mitochondrial and microsomal lipid peroxidation and weak antibacterial activities, was partitioned between chloroform and water. Purification of the chloroform extract was repeated by column chromatography on silica gel. Further purification by recycling preparative GPC (gel permeation chromatography) provided two novel compounds **2** (3.7 mg, 0.034 wt % yield) and **3** (5.6 mg, 0.051 wt % yield) along with a known compound, maturinone (**4**).[7,8]

The molecular formula of compound **2** was established as $C_{15}H_{14}O_3$ by EI-HRMS [*m*/*z* 242.0942 (M^+) −0.1 mmu]. The IR spectrum of **2** suggested the presence of a hydroxy group (3363 cm^{-1}). The ^1H NMR spectrum of **2** in $CDCl_3$ exhibited signals due to five sp^2 methine protons at δ 8.21, 7.89, 7.69, 7.34, and 7.28, one benzenoid *exo*-methyl group at δ 2.75, and one methoxy group at δ 4.36 (Table 1). The

Table 1. ^1H (500 MHz) and ^{13}C (100 MHz) NMR and HMBC Spectral Data for Compound **2** in $CDCl_3$[a]

position	δ_C	δ_H	HMBC (H → C)
1	120.4	8.21 (d, 8.6)	C-3, 4, 5, 9
2	124.1	7.34 (dd, 8.6, 6.8)	C-3, 4
3	125.3	7.28 (br d, 6.8)	C-1, 5, 15
4	134.0		
5	130.8		
6	107.7	7.89 (s)	C-4, 5, 7, 8
7	120.5		
8	142.7		
9	138.9		
10	124.9		
11	129.8		
12	144.2	7.69 (s)	C-7, 8, 11
13	56.1	4.95 (2H, s)	C-7, 11, 12
15	20.3	2.75 (3H, s)	C-3, 4, 5
C9−OMe	60.9	4.36 (3H, s)	C-9

[a] Proton resonance multiplicities and coupling constants (*J* in hertz) are given in parentheses.

15 carbon signals observed in the ^{13}C NMR spectrum were characterized by a DEPT experiment, which suggested that **2** had seven sp^2 quaternary carbons, five sp^2 methines, one oxygenated methylene, one oxygenated methyl, and one methyl. Complete ^1H and ^{13}C chemical shift assignments were made from the H−H COSY, HMQC, and HMBC spectral data, and the resulting structure **2** was also supported by NOEs observed between the diagnostic protons as shown in Figure 1. Thus, the structure of **2** was assigned to a C13-hydroxylated derivative of 14-nordehydrocacalohastine (**5**).[7f,9]

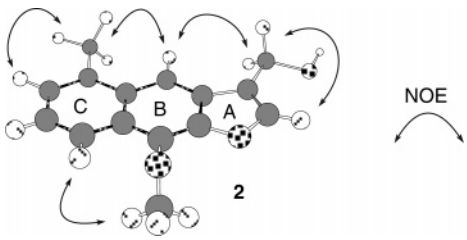

Figure 1. Diagnostic NOEs observed in NOESY spectrum of **2**.

The molecular formula of compound **3** was determined to be $C_{17}H_{16}O_4$ by EI-HRMS [*m*/*z* 284.1032 (M^+) +0.5 mmu], and the molecular weight was found to be 42 mu (C_2H_2O) more than that of **2**. The IR spectrum of **3** indicated the disappearance of a hydroxy band observed in **2** and the appearance of an ester carbonyl band (1734 cm^{-1}). In the ^{13}C DEPT spectrum of **3**, 15 signals were well resolved and corresponded closely to those of **2** except for one carbonyl carbon at δ 170.9 and one methyl at δ 20.9 (Table 2). The ^1H NMR spectrum of **3** in $CDCl_3$ was suggestive of one additional methyl group with its resonance at δ 2.12 (3H, s), and the downfield shift of the C13 methylene protons at δ 4.95 in **2** to δ 5.36 in **3** compared with that of **2**. From the above results, the structure of **3** was assigned to an acetyl derivative of the C13 hydroxy group in **2**.

In preliminary biological tests, antioxidative activities were evaluated for two new compounds, **2** and **3**, and maturinone (**4**)[10] thus isolated from *T. cuneata*. It was found that they were effective at preventing membrane lipid peroxidation. The NADH-dependent mitochondrial and NADPH-dependent microsomal lipid peroxidations were inhibited with IC_{50} values (μM) of 16.4 and 41.6 for **2**, 59.7 and 54.3 for **3**, and 71.7 and 74.4 for **4**, respectively.[11] These pharmacological properties imply that some of the effects of the endemic medicinal plant complex might be attributable to compounds **2**−**4** and that these natural products might be useful as lead compounds in the field of medicinal chemistry. Therefore, we planned total syntheses of the two new compounds **2**

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(7) Isolation: (a) Correa, J.; Romo, J. *Tetrahedron* **1966**, *22*, 685. (b) Naya, K.; Miyoshi, Y.; Mori, H.; Takai, K.; Nakanishi, M. *Chem. Lett.* **1976**, 73. (c) Joshi, K. C.; Singh, P.; Singh, G. *Indian J. Chem.* **1976**, *14B*, 637. (d) El-Emary, N. A.; Takemoto, T.; Kusano, G. *Planta Med.* **1980**, *38*, 161. (e) Torres, P.; Mancheno, B.; Chinchilla, R.; Asensi, M. C.; Grande, M. *Planta Med.* **1988**, *54*, 257. (f) Torres, P.; Chinchilla, R.; Asensi, M. C.; Grande, M. *Phytochemistry* **1989**, *28*, 3093. (g) Abdo, S.; de Bernardi, M.; Marinoni, G.; Mellerio, G.; Samaniego, S.; Vidari, G.; Finzi, P. V. *Phytochemistry* **1992**, *31*, 3937.

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(9) Synthesis: Hirai, Y.; Doe, M.; Kinoshita, T.; Morimoto, Y. *Chem. Lett.* **2004**, *33*, 136.

(10) There has been no report on biological activities of maturinone (**4**).

(11) (a) Haraguchi, H.; Ishikawa, H.; Kubo, I. *Planta Med.* **1997**, *63*, 213. (b) Haraguchi, H.; Ishikawa, H.; Mizutani, K.; Tamura, Y.; Kinoshita, T. *Bioorg. Med. Chem.* **1998**, *6*, 339.

Table 2. ^{1}H (500 MHz) and ^{13}C (100 MHz) NMR and HMBC Spectral Data for Compound **3** in $CDCl_3$[a]

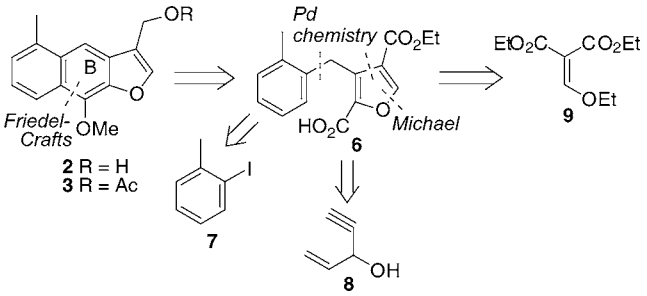
position	δ_C	δ_H	HMBC (H → C)
1	120.4	8.21 (d, 8.5)	C-5, 9, 10
2	124.2	7.35 (dd, 8.5, 6.8)	C-3, 4
3	125.4	7.29 (br d, 6.8)	C-5, 15
4	133.9		
5	130.9		
6	107.5	7.86 (s)	C-4, 7, 8, 9, 10
7	116.1		
8	142.5		
9	139.0		
10	124.9		
11	129.1		
12	146.0	7.76 (s)	C-7, 8, 11
13	56.6	5.36 (2H, s)	C-7, 11, 12, 1′[b]
15	20.4	2.76 (3H, s)	C-3, 4, 5
C9−OMe	60.9	4.36 (3H, s)	C-9
1′	170.9		
2′	20.9	2.12 (3H, s)	C-13, 1′

[a] Proton resonance multiplicities and coupling constants (J in hertz) are given in parentheses. [b] C1′ and C2′ denote the numbering of C13−OC(1′)OC(2′)H_3 in **3**.

and **3** in conjunction with confirmation of the structures elucidated by spectroscopic methods.

The retrosynthetic analysis of compounds **2** and **3** is depicted in Scheme 1. We devised a highly convergent route

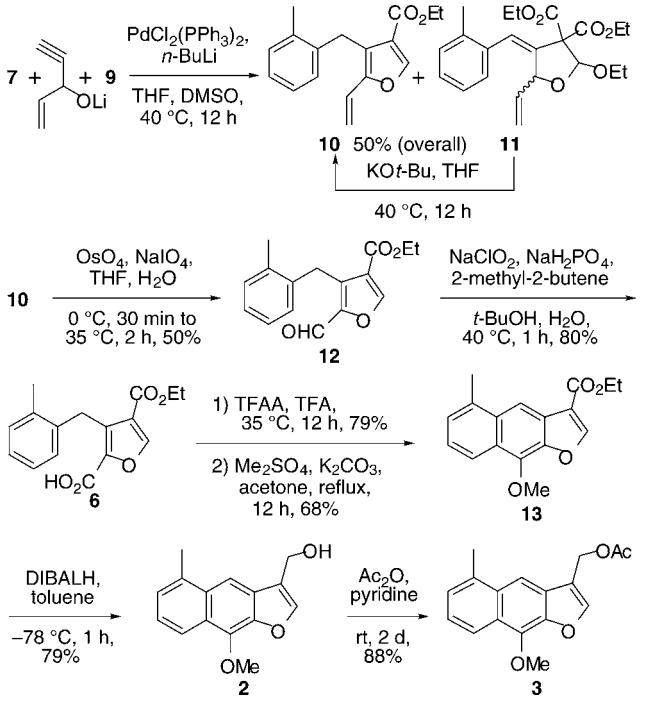
Scheme 1. Retrosynthetic Analysis of Novel Compounds **2** and **3**



based on the regioselective trisubstituted furan synthesis using a palladium-catalyzed three-component coupling reaction developed by Balme et al.[12] The naphthofuran A,B,C-ring framework could be constructed by an intramolecular Friedel−Crafts acylation of carboxylic acid **6**. It was envisaged that a key synthetic equivalent of the trisubstituted furan **6** could be formed by the palladium-mediated coupling reaction of three readily available components, 2-iodotoluene (**7**), 1-penten-4-yn-3-ol (**8**), and diethyl ethoxymethylenemalonate (**9**).

1-Penten-4-yn-3-ol (**8**) required for the three-component coupling was readily prepared in 80% overall yield by a 1,2-addition reaction of the lithium acetylide of trimethylsilylacetylene to acrolein followed by desilylation with potassium carbonate. The key three-component coupling reaction of the lithium alkoxide of alcohol **8** with commercially available 2-iodotoluene (**7**) and diethyl ethoxymethylenemalonate (**9**) was mediated in tetrahydrofuran and dimethyl sulfoxide by a palladium(0) catalyst prepared in situ from dichlorobis(triphenylphosphine)palladium(II) and *n*-butyllithium to afford the desired trisubstituted furan **10** together with the precursor **11**, which could be converted into **10** by potassium *tert*-butoxide[12] (Scheme 2). Lemieux−Johnson oxidation[13]

Scheme 2. Total Syntheses of Compounds **2** and **3**



of alkene **10** and subsequent sodium chlorite oxidation[14] of the resulting aldehyde **12** smoothly proceeded to provide carboxylic acid **6**. The central B ring was constructed by the intramolecular Friedel−Crafts acylation of carboxylic acid **6** with trifluoroacetic anhydride in trifluoroacetic acid[15] to yield a phenolic product, methylation of which furnished ester **13**. Finally, diisobutylaluminum hydride reduction of the ester **13** at −78 °C for 1 h gave alcohol **2**, acetylation of which produced acetate **3**. The spectral characteristics of synthetic **2** and **3** were consistent with those observed for the natural products 13-hydroxy-14-nordehydrocacalohastine (**2**) and 13-acetoxy-14-nordehydrocacalohastine (**3**), respectively.

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(14) Bal, B. S.; Childers Jr., W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

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In conclusion, we have determined the structures of 13-hydroxy-14-nordehydrocacalohastine (**2**) and 13-acetoxy-14-nordehydrocacalohastine (**3**), two novel modified furanoeremophilane-type sesquiterpenes isolated from *T. cuneata*, and accomplished the first, highly convergent total syntheses thereof through the palladium-catalyzed three-component coupling reaction. We have also found that the new compounds **2** and **3** and known maturinone (**4**) possess antioxidative activities. This highly convergent synthesis might be applicable for the combinatorial synthesis directed toward library construction of antioxidative agents that use natural products **2**−**4** as the lead compounds. Further studies on biologically active chemical constituents of *T. cuneata* are in progress and will be reported in due course.

Acknowledgment. We are grateful to the Mitsui Chemical Co. for supplying the methanol extract of *T. cuneata*. M.D. thanks Osaka City University for the OCU Grant for Graduate Course Students.

Supporting Information Available: Characterization data and NMR spectra for natural products **2**−**4** and experimental procedures for syntheses of **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050346K