The First Total Syntheses of the Sesquiterpenes (±)-1,10;7,10-Bisepoxy-1,10-seco-calamanene and (±)-6,7;7,10-Bisepoxy-6,7-seco-calamanene

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Abstract: First total syntheses of the tricyclic sesquiterpenes mentioned in the title containing a benzo-fused 2,8-dioxabicyclo[3.2.1]octane framework, confirming the structures of the natural products, are described.

Key words: natural products, sesquiterpenes, total synthesis, intramolecular acetalisation, dioxabicyclo[3.2.1]octanes

The essential oils derived from plants belonging to the genus *Hedychium* are a rich source of a variety of mono- and sesquiterpenes. In continuation of their phytochemical investigations[1] on the genus *Hedychium*, Weyerstahl et al. reported[2] the isolation of a number of sesquiterpenes from the essential oil obtained by hydrodistillation of the rhizomes of the yellow flowering plant *Hedychium gardnerianum* Roscoe, collected from Mungpoo (Darjeeling, India) at an altitude of 1200 m. The essential oil was found to contain about 30% of sesquiterpenes, mainly cadinane derivatives. In addition to several known sesquiterpenes, they have reported the isolation of two new tricyclic compounds 1,10;7,10-bisepoxy-1,10-seco-calamanene (**1**) and 6,7;7,10-bisepoxy-6,7-seco-calamanene (**2**) as an inseparable mixture.[2] The structures of the compounds **1** and **2** were established based on the analysis of ^{1}H NMR and ^{13}C NMR spectra of a 3:1 mixture of the compounds **1** and **2** (Figure 1)

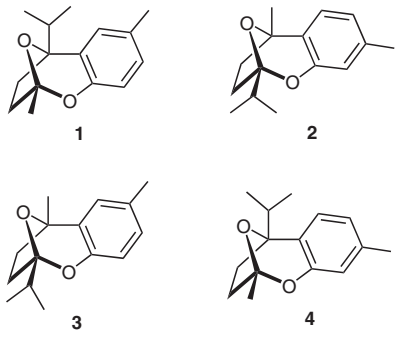
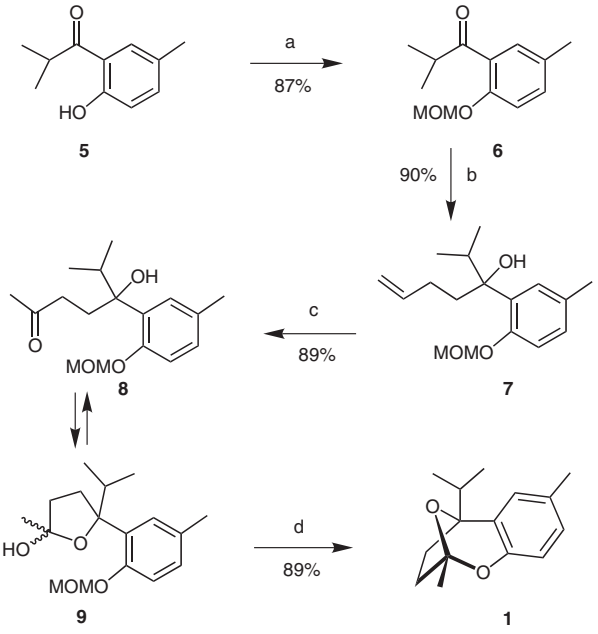


Figure 1

The presence of an interesting benzo-fused dioxabicyclo[3.2.1]octane framework present in the compounds **1** and **2** coupled with the fact that the structures were assigned on the basis of the spectral data of a mixture of **1** and **2** prompted us to investigate the synthesis of these compounds to confirm their structures. Since alternate regiostructures **3** and **4** were also possible, a general methodology was investigated for the synthesis of the compounds **1**–**4**. In continuation of our interest in the synthesis of tricyclic sesquiterpenes containing benzo-fused oxabicyclo[3.2.1]octanes,[3] herein we report the first total syntheses of the sesquiterpenes **1** and **2**.



Scheme 1 *Reagents and conditions*: (a) NaH, MOMCl, THF, 0 °C to r.t., 1.5 h; (b) CH_2=$CH(CH_2)_2MgBr$, THF, 0 °C to r.t.,))), 1 h; (c) $PdCl_2$ (0.5 equiv), CuCl (5 equiv), DMF–H_2O (4:1), O_2, r.t., 3 h; (d) 3 N HCl, THF, r.t., 2 h.

To begin with, the synthesis of compound **1** was addressed starting from the isobutyrophenone **5** obtained from *p*-cresol (Scheme 1). It was contemplated that introduction of a 3-oxobutyl side chain followed by an intramolecular acetalisation would lead to compound **1**, and 3-butenyl group was identified as the masked 3-oxobutyl group. Accordingly, the phenolic hydroxy group was protected as its methoxymethyl (MOM) ether by employing sodium hydride and methoxymethyl chloride to furnish the keto ether **6** in 87% yield. Grignard reaction of the keto ether **6** with but-3-enylmagnesium bromide in THF furnished the tertiary alcohol **7** in 90% yield. A Wacker oxidation[4] was opted for the conversion of the vinyl group to an acetyl group in **7**. Thus, reaction of the hydroxyole-

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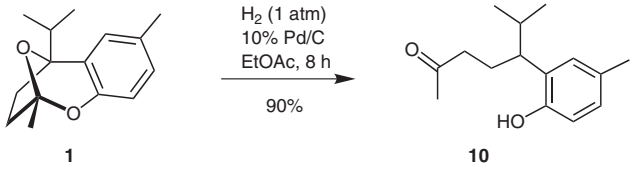
fin **7** with palladium chloride, copper(I) chloride in a mixture of dimethylformamide (DMF) and water in an oxygen atmosphere (balloon) for three hours furnished the hydroxy ketone **8** (in 89% yield),[5] which was found to be in equilibrium with an epimeric mixture of the hemiacetal **9**. Finally, hydrolysis of the MOM ether with 3 N aqueous hydrochloric acid in THF transformed the mixture of **8** and **9** into the tricyclic compound **1** (in 89% yield), which exhibited ^{1}H NMR and ^{13}C NMR spectral data[5] identical to those reported in the literature.[2]

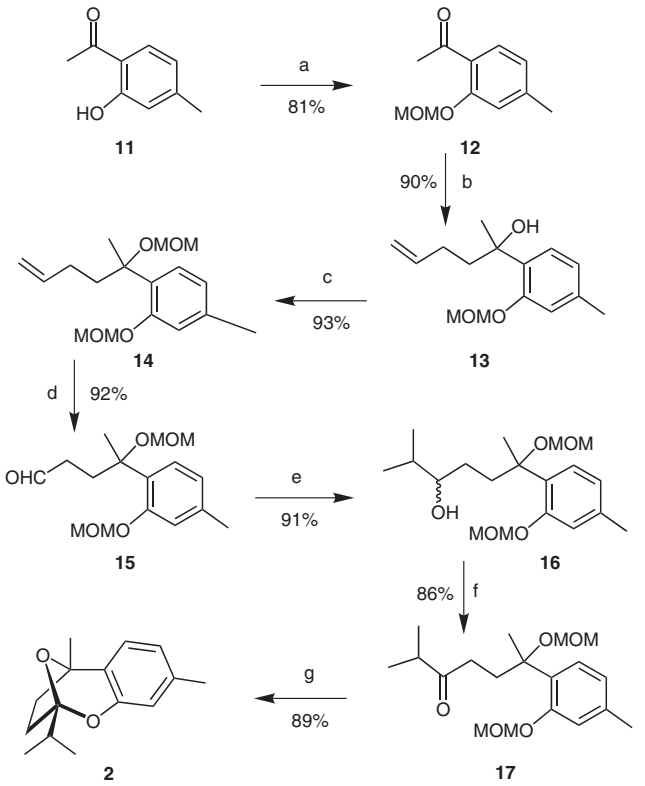


Scheme 2

After successfully accomplishing a four-step efficient synthesis of the tricyclic sesquiterpene **1**, it was readily identified that hydrogenolytic cleavage of the benzylic oxygen in **1** would lead to litseachromolaevane A (**10**), a sesquiterpene recently reported[6,7] from an anti-HIV fraction of the leaves and twigs of *Litsea verticillata* Hance (Scheme 2). Accordingly, hydrogenation of the tricyclic sesquiterpene **1** in ethyl acetate at one atmospheric pressure of hydrogen using 10% palladium over carbon as the catalyst furnished compound **10** in 90% yield, which exhibited ^{1}H NMR and ^{13}C NMR spectral data identical to those reported for the natural product in the literature.[6]

Next, the synthesis of compound **2** was investigated starting from 2-hydroxy-4-methylacetophenone (**11**), see Scheme 3. Protection of the phenolic hydroxy group with sodium hydride and methoxymethyl chloride transformed **11** into the MOM ether **12**.[8] Grignard reaction of the keto ether **12** with but-3-enylmagnesium bromide in THF furnished the tertiary alcohol **13** in 90% yield. Treatment of the tertiary alcohol **13** with methoxymethyl chloride and ethyldiisopropylamine in methylene chloride furnished the bis-MOM ether **14**.[5] Ozonolysis of the olefin in **14** followed by reductive workup with dimethyl sulfide generated the aldehyde **15**. Grignard reaction of the aldehyde **15** with isopropylmagnesium bromide furnished a 1:1 epimeric mixture of the secondary alcohol **16**, which on oxidation with pyridinium dichromate (PDC) in dichloromethane furnished the ketone **17**.[5] Finally, hydrolysis of the MOM ethers with 3 N aqueous hydrochloric acid in THF transformed the ketone **17** into the compound **2**, which exhibited ^{13}C NMR spectral data identical to those reported for the natural product in the literature.[2,9]

In conclusion, we have developed short and efficient syntheses of the tricyclic sesquiterpenes (±)-1,10;7,10-bisepoxy-1,10-seco-calamanene (**1**) and (±)-6,7;7,10-bisepoxy-6,7-seco-calamanene (**2**) confirming the structures of the natural products.



Scheme 3 *Reagents and conditions*: (a) NaH, MOMCl, THF, 0 °C to r.t., 1.5 h; (b) CH_2=$CH(CH_2)_2MgBr$, THF, 1 h; (c) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, r.t., 12 h; (d) O_3/O_2, MeOH–CH_2Cl_2 (1:5), cat. $NaHCO_3$, –70 °C; Me_2S, r.t., 3 h; (e) *i*-PrMgBr, Et_2O, 0 °C to r.t., 0.75 h; (f) PDC, CH_2Cl_2, r.t., 3 h; (g) 3 N HCl, THF, r.t., 1.5 h.

Acknowledgment

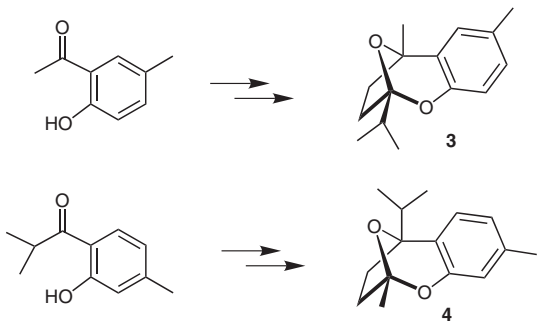
We thank the Council of Scientific and Industrial Research, New Delhi for the award of a research fellowship to G.R.

References and Notes

(1) Weyerstahl, P.; Schweiger, R.; Schwope, I.; Hashem, Md. A. *Liebigs Ann.* **1995**, 1389; and references cited therein.
(2) Weyerstahl, P.; Marschall, H.; Thefeld, K.; Subba, G. C. *Flavour Fragr. J.* **1998**, *13*, 377.
(3) Srikrishna, A.; Rao, M. S. *Synlett* **2004**, 374.
(4) Tsuji, T. *Organic Synthesis with Palladium Compounds*; Springer: New York, **1980**, 6–12.
(5) Yields refer to isolated and chromatographically pure compounds. All the compounds exhibited spectral data (IR, ^{1}H NMR, ^{13}C NMR, and HRMS) consistent with their structures.
Selected Spectral Data
Alcohol **7**: IR (neat): ν_{max} = 3531, 1639, 810 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12 (1 H, s), 7.00–6.90 (2 H, m), 5.82–5.72 (1 H, m), 5.15 (2 H, br s), 4.90 (1 H, d, *J* = 15.9 Hz), 4.86 (1 H, d, *J* = 9.0 Hz), 3.45 (3 H, s), 3.11 (1 H, br s), 2.29 (3 H, s), 2.30–1.95 (3 H, m), 1.81 (1 H, td, *J* = 12.9 and 4.2 Hz), 1.70–1.60 (1 H, m), 0.96 (3 H, d, *J* = 6.6 Hz), 0.72 (3 H, d, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4 (C), 139.4 (CH), 132.7 (C), 130.5 (C), 129.0 (CH), 128.1 (CH), 114.3 (CH), 114.1 (CH_2), 94.5 (CH_2), 79.8 (C), 56.0 (CH_3), 36.6 (CH_2), 36.2 (CH), 28.9 (CH_2), 20.9 (CH_3), 17.7 (CH_3), 16.8 (CH_3). HRMS: *m/z* calcd for $C_{17}H_{26}O_3Na$ [M +

Na]: 301.1780; found: 301.1776.
Compound **1**: IR (neat): ν_{max} = 1492, 1262, 1199, 814 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.86 (1 H, d, *J* = 8.1 Hz), 6.83 (1 H, s), 6.58 (1 H, d, *J* = 8.1 Hz), 2.50–2.14 (3 H, m), 2.25 (3 H, s), 2.10–1.90 (2 H, m), 1.65 (3 H, s), 1.14 (3 H, d, *J* = 6.6 Hz), 1.03 (3 H, d, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1 (C), 128.6 (C), 128.5 (C), 128.4 (CH), 123.8 (CH), 116.1 (CH), 106.6 (C), 87.7 (C), 38.9 (CH_2), 38.1 (CH_2), 30.4 (CH), 24.3 (CH_3), 21.0 (CH_3), 18.6 (CH_3), 16.8 (CH_3). HRMS: *m/z* calcd for $C_{15}H_{20}O_2Na$ [M + Na]: 255.1361; found: 255.1359.
Bis-MOM ether **14**: IR (neat): ν_{max} = 1613, 1151, 1016, 923, 817 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (1 H, d, *J* = 8.0 Hz), 6.90 (1 H, s), 6.76 (1 H, d, *J* = 8.0 Hz), 5.73 (1 H, ddt, *J* = 16.8, 10.4, 6.4 Hz), 5.17 (2 H, s, OCH_2O), 4.90 (1 H, d, *J* = 16.8 Hz), 4.84 (1 H, d, *J* = 10.4 Hz), 4.75 and 4.70 (2 H, 2 × d, *J* = 7.2 Hz), 3.47 (3 H, s), 3.41 (3 H, s), 2.32 (3 H, s), 2.20–1.90 (3 H, m), 1.86–1.70 (1 H, m), 1.68 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3 (C), 139.1 (CH), 138.1 (C), 130.0 (C), 127.8 (CH), 122.0 (CH), 115.1 (CH), 113.8 (CH_2), 93.9 (CH_2), 91.6 (CH_2), 80.3 (C), 56.0 (CH_3), 55.4 (CH_3), 39.1 (CH_2), 28.7 (CH_2), 24.7 (CH_3), 21.2 (CH_3). HRMS: *m/z* calcd for $C_{17}H_{26}O_4Na$ [M + Na]: 317.1729; found: 317.1717.
Ketone **17**: IR (neat): ν_{max} = 1711, 1613, 1150, 1015, 923, 817 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (1 H, d, *J* = 7.9 Hz), 6.89 (1 H, s), 6.75 (1 H, d, *J* = 7.9 Hz), 5.15 (2 H, s), 4.73 and 4.71 (2 H, 2 × d, *J* = 7.2 Hz), 3.45 (3 H, s), 3.39 (3 H, s), 2.50–2.35 (3 H, m), 2.30 (3 H, s), 2.15–2.07 (2 H, m), 1.66 (3 H, s), 1.00 (3 H, d, *J* = 6.9 Hz), 0.95 (3 H, d, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.3 (C), 154.0 (C), 138.2 (C), 129.8 (C), 127.5 (CH), 121.9 (CH), 115.2 (CH), 94.0 (CH_2), 91.4 (CH_2), 79.8 (C), 56.0 (CH_3), 55.4 (CH_3), 40.8 (CH), 35.6 (CH_2), 33.3 (CH_2), 24.7 (CH_3), 21.2 (CH_3), 18.3 (CH_3), 18.2 (CH_3). HRMS: *m/z* calcd for $C_{19}H_{30}O_5Na$ [M + Na]: 361.1991; found: 361.1990.
Compound **2**: IR (neat): ν_{max} = 1624, 1303, 1160, 907, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.89 (1 H, d, *J* = 7.9 Hz), 6.59 (1 H, d, *J* = 7.9 Hz), 6.56 (1 H, s), 2.26 (3 H, s), 2.20–2.08 (4 H, m), 1.90–1.83 (1 H, m), 1.69 (3 H, s), 1.09 (3 H, d, *J* = 6.7 Hz), 1.08 (3 H, d, *J* = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5 (C), 138.2 (C), 126.5 (C), 122.6 (CH), 120.4 (CH), 116.4 (CH), 111.0 (C), 82.6 (C), 42.8 (CH_2), 34.9 (CH_2), 34.8 (CH), 21.8 (CH_3), 21.2 (CH_3), 17.0 (CH_3), 16.8 (CH_3). HRMS: *m/z* calcd for $C_{15}H_{20}O_2Na$ [M + Na]: 255.1361; found: 255.1364.
Compound **3**: IR (neat): ν_{max} = 1237, 911, 815 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.92 (1 H, d, *J* = 7.8 Hz), 6.84 (1 H, s), 6.63 (1 H, d, *J* = 7.8 Hz), 2.24 (3 H, s), 2.22–2.05 (4 H, m), 1.95–1.83 (1 H, m), 1.69 (3 H, s), 1.09 (3 H, d, *J* = 6.9 Hz), 1.07 (3 H, d, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4 (C), 129.7 (C), 128.8 (CH), 128.7 (C), 123.4 (CH) 115.6 (CH), 111.1 (C), 82.7 (C), 42.7 (CH_2), 34.7 (CH), 34.6 (CH_2), 21.7 (CH_3), 20.7 (CH_3), 16.9 (CH_3), 16.7 (CH_3).
HRMS: *m/z* calcd for $C_{15}H_{20}O_2Na$ [M + Na]: 255.1361; found: 255.1360.
Compound **4**: IR (neat): ν_{max} = 1624, 1386, 1167, 1078 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.95 (1 H, d, *J* = 8.0 Hz), 6.63 (1 H, d, *J* = 8.0 Hz), 6.56 (1 H, s), 2.25 (3 H, s), 2.60–2.20 (4 H, m), 2.10–1.90 (1 H, m), 1.66 (3 H, s), 1.13 (3 H, d, *J* = 6.9 Hz), 1.03 (3 H, d, *J* = 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2 (C), 137.9 (C), 126.0 (C), 123.3 (CH), 120.5 (CH) 116.8 (CH), 106.9 (C), 87.8 (C), 38.9 (CH_2), 38.2 (CH_2), 30.6 (CH), 24.2 (CH_3), 21.1 (CH_3), 18.5 (CH_3), 16.8 (CH_3). HRMS: *m/z* calcd for $C_{15}H_{20}O_2Na$ [M + Na]: 255.1361; found: 255.1359.

(6) Cuong, N. M.; Soejarto, D. D.; Pezzuto, J. M.; Fong, H. H. S. *J. Nat. Prod.* **2003**, *66*, 609.
(7) Although litseachromolaevane A (**10**) was reported as a new compound in 2003, it is the same as sesquichamaenol reported earlier from *Chamaecyparis forrnosensis* Matsum. See: Ando, M.; Ibe, S.; Kagabu, S.; Nakagawa, T.; Asao, T.; Takase, K. *J. Chem. Soc., Chem. Commun.* **1970**, 1538.
(8) Nemoto, H.; Miyata, J.; Fukumoto, K. *Tetrahedron* **1996**, *52*, 10363.
(9) In the ^1H NMR spectrum of the synthetic sample **2**, it was found that signals due to four methyl groups and two aromatic protons were identical to those reported in the literature for the natural compound **2**. Since one of the aromatic resonances (δ = 6.59 ppm, d) did not match that reported (δ = 6.89 ppm, d) for **2** [reported in the literature[2] on the basis of the NMR spectrum of a 1:3 mixture (80% pure) of **2** and **1**, where the compound **2** is minor component], the ^1H NMR spectrum of a ca. 3:1 mixture of **1** and **2** was recorded and confirmed that the reported resonance at δ = 6.89 ppm is not due to **2**. To rule out the other possible regioisomers completely, synthesis of compounds **3** and **4** were also accomplished[5] starting from 2-hydroxy-5-methylacetophenones and 2-hydroxy-4-methylisobutyrophenones employing the same sequence of reactions as depicted in Schemes 1 and 3, respectively. The ^1H NMR and ^{13}C NMR spectra[5] of compounds **3** and **4** were found to be different from those reported in the literature[2] for the compound **2** (Scheme 4).



Scheme 4