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Stereoselective synthesis of (−)-6,7-dehydroferruginyl methyl ether

Yonghong Gan,[a] Anpai Li,[a] Xinfu Pan,[a,*] Albert S. C. Chan [b] and Teng-Kuei Yang [c]

[a]*Department of Chemistry, National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, People's Republic of China*

[b]*Union Laboratory of Asymmetry Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong*

[c]*Department of Chemistry, National Chung-Hsing University, Taichang, Taiwan*

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Abstract

A stereoselective synthetic route to (−)-6,7-dehydroferruginyl methyl ether was developed from (*S*)-(−)-α-cyclocitral.

1. Introduction

Most diterpenoids exhibit significant bioactivities, such as antibacterial,[1,2] antidermatophytic,[2,3] antioxidant,[4] etc. (−)-6,7-Dehydroferruginol **2**, a diterpenoid with the abietane skeleton, was separated from *Juniperus communis lin, wood* by Bredenberg.[5] Barton et al.[6] concluded that the A/B ring junction in the diterpenoids is *trans* and this was confirmed by King et al.[7] The synthetic route followed by King et al. is not stereospecific and the key intermediate **1** was obtained in low yield by a laborious process. In order to study further the relationship between the structure and bioactivities, it is desirable to develop a stereoselective synthetic route whereby the *trans*-isomer could be obtained predominantly. In connection with our synthetic studies on the naturally occurring diterpenes,[8,9] and based on our knowledge, no stereoselective synthetic work has been reported on the title compound. Here, we report a highly stereoselective synthetic route to (−)-6,7-dehydroferruginyl methyl ether **3**.

* Corresponding author. E-mail: panxf@lzu.edu.cn

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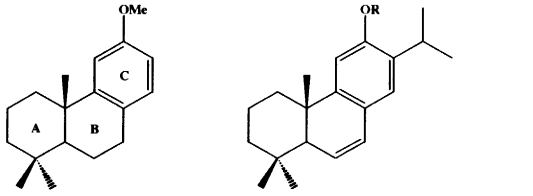
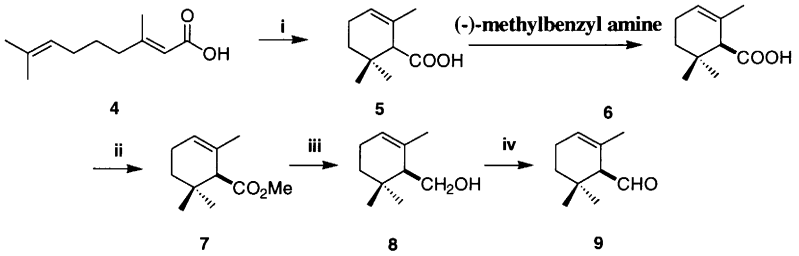


1

2 R = H (-)-6,7-dehydroferruginol
3 R = Me (-)-6,7-dehydroferruginyl methyl ether

2. Results and discussion

As shown in Schemes 1 and 2, our synthetic strategy is AC→ABC. Compared with Matsumoto's work,[10] we used readily available *p*-anisic acid as the C ring starting material. (*S*)-(−)-α-Cyclocitral **9** ($[\alpha]^{25}_{D}$ −708, *c* 0.03, $CHCl_3$; lit.[11] $[\alpha]^{25}_{D}$ −743, *c* 0.05, $CHCl_3$), which was prepared from geranic acid via five steps, was used as the A ring starting material (Scheme 1).

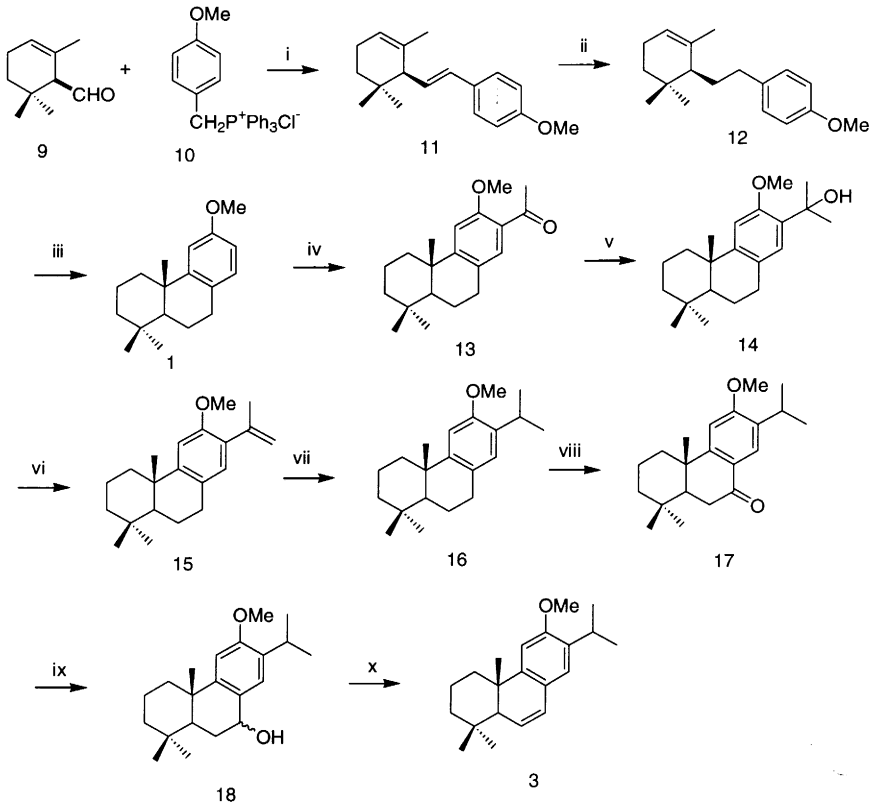


4 5 6 7 8 9

Scheme 1. Reagents and conditions: (i) 85% H_3PO_4, toluene; (ii) K_2CO_3/MeI; (iii) $LiAlH_4$; (iv) PCC, CH_2Cl_2

As shown in Scheme 2, condensation of **9** with **10** in the presence of *n*-BuLi/hexane afforded the desired stryene derivative **11** in 60% yield. The ^{1}H NMR of **11** reveals a *trans* disubstituted double bond (the vicinal coupling constant of vinyl protons is J=15 Hz). Selective hydrogenation of **11** over 10% Pd/C gave the phenethyl derivative **12**. In order to get a better yield and stereoselectivity in the intracyclization step, several conditions had been tested; we found $BF_3 \cdot Et_2O$ in CH_2Cl_2 to be the best condition, which gives the *trans*-isomer **1** in over 90% yield (d.e. >95%, determined by ^{1}H NMR). Compound **1** was acetylated by acetyl chloride and anhydrous $AlCl_3$ in CH_2Cl_2 to give the compound **13** in 90% yield. Compound **13** was then reacted with CH_3Li to give the alcohol **14** in high yield. Alcohol **14** was dehydrated with *p*-TosOH/benzene to give the styrene derivative **15**, then hydrogenation of **15** afforded (+)-ferruginyl methyl ether **16**, quantitatively. Oxidation of **16** by CrO_3/HOAc gave (+)-sugiyl methyl ether **17** in 85% yield. After reduction and dehydration, the title compound, (−)-6,7-dehydroferruginyl methyl ether **3**, was successfully obtained. To determine the stereochemistry of **3**, we introduced the stereogenic center from (*S*)-(−)-α-cyclocitral. According to the literature,[12] when the A/B ring is a *cis* junction, the δ value of the C4-α-methyl group will appear at about 0.4 ppm, if the A/B ring is a *trans* junction, the δ value of the C4-α-methyl group will appear at about 0.9–1.0 ppm. From the ^{1}H NMR of **3**, we did not find any signal at 0.4 ppm, so the *trans*-isomer was obtained in high stereoselectivity (d.e. >95% determined by NMR). Based on the above analysis, the compound **3** was assigned as (−)-6,7-dehydroferruginyl methyl ether.

In conclusion, we developed a route to (−)-6,7-dehydroferruginyl methyl ether via 15 steps with high overall yield and stereoselectivity.



Scheme 2. Reagents and conditions: (i) *n*-BuLi, *n*-hexane (60%); (ii) 10% Pd/C, ethanol (98%); (iii) $BF_3 \cdot Et_2O$, CH_2Cl_2 (85%); (iv) acetyl choride, anhydrous $AlCl_3$ (90%); (v) CH_3Li (95%); (vi) *p*-Tos, benzene (90%); (vii) 5% Pd/C (95%); (viii) CrO_3/HOAc (85%); (ix) $NaBH_4$/ethanol (95%); (x) *p*-Tos, benzene (90%)

3. Experimental

3.1. General

The ^1H NMR and ^{13}C NMR data were recorded in $CDCl_3$ solution with Bruker AM-80 or AM-400 MHz spectrometers. The chemical shifts are reported in ppm relative to TMS or $CDCl_3$. Optical rotations were determined on a JASCO J-20C polarimeter with a 0.2 dm tube. Mass spectra were recorded on a ZAB-HS mass spectrometer (EI). Microanalyses were performed on a MOD-1106 elemental analyser. Chiral analysis was performed on a Varian Dynamax SD-300 using Chiralcel column CDMPC (150×4.6 mm D) with hexane/isopropyl alcohol as eluant. Column chromatographs were generally performed on silica gel (200–300 mesh) eluting with petroleum ether:EtOAc (100:1→20:1 v/v) and TLC inspections on silica gel GF_{254} plates with petroleum ether:EtOAc (20:1 v/v) if not noted specifically below.

3.2. (±)-α-Cyclogeranic acid **5**

At 100°C, 85% H_3PO_4 (0.01 mmol) was added to geranic acid **4** (16 g, 0.1 mmol) in toluene (30 ml). The reaction mixture was stirred for 2 h at this temperature, then reaction was quenched with saturated $NaHCO_3$, extracted with ethyl ether, the combined organic layer was washed with brine and then dried with Na_2SO_4. After evaporation of the solvent under reduced pressure, the precipitate was recrystallized

from *n*-hexane to give the pure compound **5** (14 g, 90%). ^{1}H NMR (80 MHz) δ 0.90 (s, 3H), 0.96 (s, 3H), 1.60 (s, 3H), 1.8–2.5 (m, 5H), 5.6 (brs, 1H), 11.0 (s, 1H). MS (EI): 168, 153, 81 and 77. (Found: C, 71.29; H, 9.50. $C_{10}H_{16}O_2$ requires: C, 71.39; H, 9.59%).

3.3. (S)-(−)-Cyclogeranic acid **6**

Compound (±)-**5** (16.0 g) in ether (50 mL) was added to (−)-α-methylbenzylamine (9.0 g). The precipitate was recrystallized from *n*-hexane to give the (−)-salt. M.p. 110°C (needle). The solution of the (−)-salt in methanol was acidified with 5% HCl and extracted with ether. The combined organic layer was washed with brine, then dried with Na_2SO_4. Evaporation of the solvent under reduced pressure, followed by recrystallization from *n*-hexane gave the pure compound **6**. M.p. 101–102°C (as large prisms) ($[\alpha]_D^{25}$ −300 (*c* 0.5, ethanol), lit.[11] ($[\alpha]_D^{25}$ −319 ethanol); e.e. >90% compared with Charles et al.[11]). Other spectra data were the same as those of **5**.

3.4. (S)-Methyl-α-cyclogeranate **7**

To (*S*)-(−)-cyclogeranic acid (5.0 g, 30 mmol) in acetone (30 mL) was added anhydrous K_2CO_3 (5.0 g, 36 mmol) and 3 mL MeI (6.0 g, 36 mmol), and the mixture was stirred at room temperature for 3 h. The usual ether work-up gave the compound **7** as a colorless oil (5.0 g, 90%). ^{1}H NMR δ 0.90 (s, 3H), 0.96 (s, 3H), 1.60 (s, 3H), 1.8–2.5 (m, 5H), 3.1 (s, 3H), 5.6 (brs, 1H). MS (EI): 168, 153, 81 and 77. (Found: C, 71.29; H, 9.50. $C_{10}H_{16}O_2$ requires: C, 71.39; H, 9.59%). This compound was used for the next step without further identification.

3.5. (S)-2,6,6-Trimethyl-1-cyclohexenemethanol **8**

At −10°C, to a suspension of $LiAH_4$ (600 mg, 16 mmol) in anhydrous ethyl ether (30 mL), compound **7** (4.5 g, 25 mmol) in anhydrous ether (10 mL) was added dropwise. The mixture was stirred at this temperature for 1 h. Then the reaction was quenched with ice-water, extracted with ether, and the combined organic layer washed with brine and dried with Na_2SO_4. Evaporation of the solvent under reduced pressure gave the alcohol **8** (4.5 g, 90%), which was used for the next step immediately without further identification.

3.6. (S)-(−)-Cyclocitral **9**

The alcohol **8** (4.0 g, 23 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) containing 0.3 g 4 Å m.s. and anhydrous NaOAc (1.5 g). PCC (5.0 g, 26 mmol) in 30 mL anhydrous CH_2Cl_2 was added to the above solution portionwise at −10°C. The solution was stirred at this temperature for 1 h, then the salt was removed by passing through a short column of Al_2O_3. Purification by column chromatography gave the pure compound **9** (3.0 g, 75%) ($[\alpha]_D^{25}$ −708 (*c* 0.03, $CHCl_3$), lit.[11] ($[\alpha]_D^{25}$ −743 (*c* 0.05, $CHCl_3$); e.e. >90% by HPLC, lit.[11]); ^{1}H NMR δ 0.92 (s, 3H), 0.98 (s, 3H), 1.60 (s, 3H), 1.8–2.5 (m, 5H), 5.7 (brs, 1H), 9.2 (s, 1H). MS (EI): 152, 123, 137, 81 and 77.

3.7. 3-(4-Methoxystyryl)-2,4,4-trimethyl-1-cyclohexene **11**

A solution of *n*-butyllithium in hexane (1.6 N, 4 mL) was added to a suspension of (4-methoxybenzyl)triphenylphosphonium chloride (3.2 g, 7.55 mmol) in dry hexane (20 mL), under

an atmosphere of Ar, and stirred at room temperature for 1 h. Then a solution of **9** (700 mg, 4.6 mmol) in dry hexane (10 mL) was added over 10 min. The solution was stirred for 4 h to complete the reaction. Then the mixture was poured into diluted HCl, extracted with ether, and the combined organic layer was washed with brine and dried with Na_2SO_4. The crude product was purified by column chromatography to give the desired compound **11** (700 mg, 60%) ($[\alpha]_D^{25}$ −302 (*c* 0.25, $CHCl_3$); e.e. >90% by HPLC[10]); ^{1}H NMR (80 MHz) δ 0.94 and 1.00 (s, each 3H), 1.63 (bs, 3H), 3.83 (s, 3H), 5.50 (brs, 1H), 6.00 (1H, dd, *J*=8, 15 Hz), 6.40 (1H, d, *J*=15 Hz), 6.88 (2H, d, *J*=8.9 Hz), 7.34 (2H, d, *J*=8.9 Hz). MS (EI): 256, 200, 185, 121 and 91. (Found: C, 89.40; H, 9.40. $C_{18}H_{24}O$ requires: C, 84.32; H, 9.44%).

*3.8. 3-(4-Methoxyphenylethyl)-2,4,4-trimethyl-1-cyclohexene **12***

A suspension of **11** (500 mg) and 10% Pd/C (250 mg) in anhydrous ethanol (10 mL) was stirred at room temperature in an atmosphere of hydrogen. The reaction was monitored by TLC; when the reaction was completed, the mixture was filtered. The filtrate was evaporated in vacuo to yield the desired compound **12** (480 mg, 95%) as a colorless oil ($[\alpha]_D^{25}$ −132 (*c* 0.08, $CHCl_3$); e.e. >92%[10]); ^{1}H NMR δ 0.91 and 1.00 (s, each 3H), 1.70 (bs, 3H), 3.80 (s, 3H), 5.34 (brs, 1H), 6.84 (2H, d, *J*=8.6 Hz), 7.13 (2H, d, *J*=8.6 Hz). MS (EI): 258, 243, 121. (Found: C, 83.55; H, 10.10. $C_{18}H_{26}O$ requires: C, 83.67; H, 10.14%).

*3.9. 12-Methoxy-podocarpane-8,11,13-triene **1** (intramolecular cyclization of **12**)*

To a solution of **12** (300 mg, 1.2 mmol) in CH_2Cl_2 (15 mL) was added $BF_3 \cdot Et_2O$ (0.6 mL) dropwise. The mixture was left to stand overnight. Then 30 mL of ether was added and the solution was neutralized with saturated $NaHCO_3$. The mixture was extracted with ether and the combined organic layer was washed successively with saturated $NaHCO_3$ and brine, then dried with Na_2SO_4. Column chromatography purification gave the pure *trans* compound **1** (260 mg, 85%) (no *cis* compound was detected by ^{1}H NMR) ($[\alpha]_D^{25}$ −32 (*c* 0.10, $CHCl_3$); d.e. >95% determined by ^{1}H NMR); ^{1}H NMR δ 0.99 (s, 6H), 1.24 (s, 3H), 1.32–2.37 (m, 11H), 3.82 (s, 3H), 6.70 (1H, dd, *J*=8.0, 2.0 Hz), 6.85 (1H, d, *J*=2.0 Hz), 6.93 (1H, d, *J*=8.0 Hz). MS (EI): 258, 243, 187, 161, 121, 91. (Found: C, 83.57; H, 10.09. $C_{18}H_{26}O$ requires: C, 83.67; H, 10.14%).

*3.10. 13-Acetyl-12-methoxy-podocarpane-8,11,13-triene **13***

At −10°C, to a solution of **1** (300 mg, 1.2 mmol) in CH_2CL_2 (15 mL), anhydrous $AlCl_3$ (350 mg) was added portionwise, then acetyl chloride (0.2 mL) was added dropwise to keep the reaction temperature below −5°C. After stirring overnight, the mixture was poured into ice-water and extracted with CH_2Cl_2. The combined organic layer was successively washed with saturated $NaHCO_3$ and brine, then dried with Na_2SO_4. After column chromatography purification, the compound **13** was obtained as a yellowish oil (310 mg, 95%; d.e. >95% determined by ^{1}H NMR); ^{1}H NMR δ 0.91 (s, 3H), 0.95 (s, 3H), 1.21 (s, 3H), 1.32–2.37 (m, 11H), 2.58 (s, 3H), 3.87 (s, 3H), 6.83 (s, 1H), 7.44 (s, 1H). MS (EI): 300, 285, 256, 203, 163, 91. (Found: C, 79.73; H, 9.15. $C_{20}H_{28}O_2$ requires: C, 79.96; H, 9.39%).

*3.11. Alcohol **14***

To a solution of **13** (300 mg, 1.1 mmol) in anhydrous THF (5 mL), CH_3Li (1.3 N, 1.5 mL) was added at 0°C and the solution stirred for 4 h, then poured into ice-water and extracted with ether. The combined organic layer was washed with brine and dried with Na_2SO_4. The solvent was removed under

reduced pressure to give the alcohol **14** (310 mg, 95%), which was used for the next step without further identification.

3.12. 13-(1′-Methenylethyl)-12-methoxy-podocarpane-8,11,13-triene **15**

To a solution of **14** (500 mg, 1.6 mmol) in benzene was added cat. *p*-TosOH, and the solution was refluxed for 0.5 h. After cooling, saturated $NaHCO_3$ was added to the solution and the mixture was extracted with ether. The combined organic layer was washed with brine and dried with Na_2SO_4. Purification by column chromatography gave the styrene derivative **15** (450 mg, 90%) ($[\alpha]_D^{25}$ +52 (*c* 0.04, $CHCl_3$); d.e. >95% determined by ^1H NMR); ^1H NMR δ 0.92 (s, 3H), 0.94 (s, 3H), 1.21 (s, 3H), 1.71 (s, 3H), 1.32–2.37 (m, 11H), 3.8 (s, 3H), 5.05 (s, 1H), 5.10 (s, 1H), 6.75 (s, 1H), 6.85 (s, 1H). MS (EI): 298, 285, 163, 91. (Found: C, 79.73; H, 9.15. $C_{18}H_{26}O_5$ requires: C, 79.96; H, 9.39%).

3.13. (+)-Ferruginyl methyl ether **16**

A suspension of **15** (300 mg) and 5% Pd/C (150 mg) in ethanol (10 mL) was stirred at room temperature in an atmosphere of hydrogen. The reaction was monitored by TLC, and when the reaction was completed, the mixture was filtered. The filtrate was evaporated in vacuo to yield the desired compound **16** as a colorless heavy oil (280 mg, 95%) ($[\alpha]_D^{25}$ +45 (*c* 0.07, CH_2Cl_2); d.e. >95% determined by ^1H NMR); ^1H NMR δ 0.83 and 0.85 (s, each 3H), 1.14 (d, 6H, *J*=7.5 Hz), 1.17 (s, 3H), 1.10–3.00 (m, 11H), 3.25 (sept, 1H, *J*=7.5 Hz), 3.70 (s, 3H), 6.75 (s, 1H), 6.69 (s, 1H). MS (EI): 300, 176, 163, 133, 69. (Found: C, 83.75; H, 10.52. $C_{21}H_{32}O$ requires: C, 83.94; H, 10.73%).

3.14. (+)-Sugiyl methyl ether **17**

To a solution of **16** (300 mg, 1 mmol) in acetic acid (5 mL) was added CrO_3 (1 mmol) in acetic acid (5 mL) at room temperature, and the mixture was stirred for 0.5 h, then water was added to quench the reaction. After extraction with ether, the combined organic layer was washed with saturated $NaHCO_3$ and brine. Column chromatography purification gave the compound **17** (280 mg, 90%) as white needle crystals. M.p. 130–132°C ($[\alpha]_D^{25}$ +27 (*c* 0.9, MeOH), lit.[13] ($[\alpha]_D^{25}$ +32 (*c* 0.1, MeOH); d.e. >95%); ^1H NMR δ 0.93 and 1.00 (s, each 3H), 1.23 (d, 3H, *J*=7.0 Hz), 1.27 (d, 3H, *J*=7.0 Hz), 1.28 (s, 3H), 1.29–2.71 (m, 9H), 3.25 (sept, 1H, *J*=7.0 Hz), 3.88 (s, 3H), 6.75 (s, 1H), 7.89 (s, 1H). MS (EI): 300, 285, 189, 163, 69. (Found: C, 80.10; H, 9.52. $C_{21}H_{30}O_2$ requires: C, 80.21; H, 9.62%) .

3.15. Alcohol **18**

To a solution of **17** (200 mg, 0.67 mmol) in methanol (10 mL) was added $NaBH_4$ (30 mg), and the reaction mixture was stirred for 1 h. Then water was added, the mixture was extracted with ether, and the combined organic layer was washed with brine and then dried with Na_2SO_4. Evaporation of the solvent gave the alcohol **18** (200 mg, 95%). The compound **18** was used for the next step without further identification.

3.16. (−)-6,7-Dehydroferruginyl methyl ether **3**

To a solution of **18** (100 mg, 0.4 mmol) in benzene was added cat. *p*-Tos, and the solution was refluxed for 0.5 h. After completion of the reaction, ether (100 mL) was added and the organic layer was washed

with saturated $NaHCO_3$ and brine, and dried with Na_2SO_4. The crude product was purified by column chromatography to give the (−)-6,7-dehydroferruginyl methyl ether **3** (480 mg, 90%) ($[\alpha]_D^{25}$ −45 (*c* 0.05, $CHCl_3$); d.e. >90% determined by ^1H NMR); ^1H NMR δ 1.02 (s, 3H), 1.09 (s, 3H), 1.10 (s, 3H), 1.24 (d, 3H, *J*=7.0 Hz), 1.30 (d, 3H, *J*=7.0 Hz), 1.32–2.24 (m, 7H), 3.31 (sept, 1H, *J*=7.0 Hz), 3.88 (s, 3H), 5.93 (dd, 1H, *J*=3.0, 9.5 Hz), 6.55 (dd, 1H, *J*=9.5 Hz), 6.75 (s, 1H), 6.96 (s, 1H). ^{13}C NMR δ 19.0, 20.1, 22.5, 22.9, 26.4, 32.6, 32.8, 36.1, 37.9, 41.1, 51.1, 55.5, 104.7, 124.3, 125.8, 127.4, 133.8, 146.9, 156.4. MS (EI): 298, 283, 216, 173. (Found: C, 84.45; H, 10.05. $C_{21}H_{30}O$ requires: C, 84.51; H, 10.13%).

Acknowledgements

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