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Synthesis and disproof of the structure proposed for the tetrahydrofuranol isolated from Michelia compressa var. lanyuensis (Magnoliaceae)

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Synthesis and disproof of the structure proposed for the tetrahydrofuranol isolated from *Michelia compressa* var. *lanyuensis* (Magnoliaceae)

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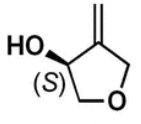
ABSTRACT

The previously proposed structure for a tetrahydrofuranol isolated from the leaves of *Michelia compressa* var. *lanyuensis* (Magnoliaceae) was synthesised in an enantiopure form using diethyl D-tartarate as the starting material. The synthetic sample showed spectroscopic data incompatible with those for the natural product and thus unequivocally disproved the previously assigned structure.



"Nat. **1**": $[\alpha]_D^{25}$ +1.48 (*c* 0.55, $CHCl_3$)

Synth.**1**: $[\alpha]_D^{26}$ –6.3 (*c* 0.25, $CHCl_3$)

(NMR for two samples were incompatible with each other)

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KEYWORDS
Michelia compressa var. *lanyuensis*; pressalanin A; Magnoliaceae; chiral pool; configuration

1. Introduction

In their study of a new taxon of *Michelia*, *Michelia compressa* var. *lanyuensis* S. Y. Lu (*Magnolia compressa* Maxim.), Chen and co-workers isolated and characterised several new compounds (Chen 2010; Cheng et al. 2010; Lo et al. 2010; Wang et al. 2010), one of which was assigned a tetrahydrofuranol structure (**1**) through extensive spectroscopic analyses (Chen 2010). Given the very simple molecular architecture of **1** and the seemingly very convincing line of reasoning, the conclusion about the deduced structure appeared impeccable. However, the absolute configuration of **1** remained unelucidated. To gain this final missing piece of structural information, the absolute configuration, a chiral pool-based synthesis was carried out.

2. Results and discussion

The synthesis of **1** was performed according to the route shown in Scheme 1. Following the literature (Somfai & Olsson 1993) the commercially available diethyl D-tartrate was

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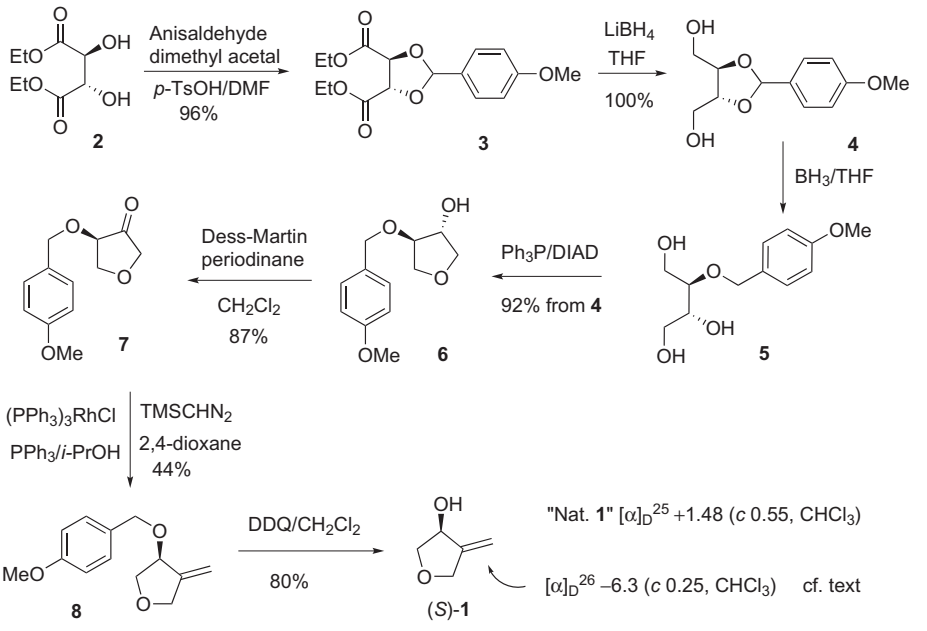

Scheme 1. Synthesis of (*S*)-**1**.

transformed into triol **5** via the three-step sequence: (1) protection with anisaldehyde dimethylacetal in the presence of *p*-TsOH to afford **3**, (2) reduction of the ester groups with $LiBH_4$ and (3) reductive cleavage of the acetal group in diol **4** with BH_3 to afford **5**.

The known triol (**5**) was then treated with Ph_3P/DIAD (diisopropyl azodicarboxylate) to provide tetrahydrofuranol **6** in 92% yield over two steps (from **4**). The free hydroxyl group in **6** was oxidised with Dess–Martin periodinane. Subsequent conversion of the cyclopentanone was achieved smoothly using the $(Ph_3P)_3RuCl/Ph_3P/TMSCHN_2/i$-PrOH/2,4-dioxane conditions, an effective protocol developed by Lebel and co-workers (Lebel et al. 2004) for conversion of ketones of low reactivity into alkenes. Finally, the PMB protecting group was cleaved with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) to provide the desired (*S*)-**1** in 80% yield.

In the previous study (Chen 2010), it was already concluded that natural **1** and a (racemic) synthetic **1** were identical by comparison of spectral data. Therefore, the only missing information for establishment of the absolute configuration for natural **1** appeared to be the optical rotation data for either (*R*)- or (*S*)-**1**. Thus, once the (*S*)-**1** was in hand, the optical rotation was measured.

The result was somewhat unexpected; the specific rotation turned out to be –6.3 (*c* 0.25, $CHCl_3$), seemingly substantially different from the corresponding data for natural **1** (+1.48 (*c* 0.55, $CHCl_3$)). Besides, contrary to what was claimed by the previous investigator, significant discrepancies existed between both the ^1H and ^{13}C NMR data for natural **1** and the synthetic samples (cf. Tables S1 & S2). Thus, it can be safely concluded that the planar structure previously assigned for the natural product must be incorrect.

3. Experimental

3.1. General

The NMR spectra were recorded on either an Agilent 500/54 NMR spectrometer (operating at 500 MHz for ^1H) or a Bruker Advance 400 (operating at 400 MHz for ^1H) NMR spectrometer.

IR spectra were measured on a Nicolet 380 Infrared spectrophotometer. ESI-MS data were recorded on a Shimadzu LCMS-2010EV mass spectrometer. EI-MS data were acquired on an Agilent Technologies 5973 N mass spectrometer. ESI-HRMS data were obtained with a Fisher Scientific LTQFT Ultra mass spectrometer. EI-HRMS data were collected on a Waters Micromass GCY Premier instrument. Optical rotations were measured on a Jasco P-1030 polarimeter. CH_2Cl_2 was dried with activated 4 Å MS (molecular sieves). Dry THF and 2,4-dioxane were obtained by distillation over Ph_2CO/Na under argon prior to use. Dry *i*-PrOH was commercially available and used as received. All chemicals were reagent grade and used as purchased. Column chromatography was performed on silica gel (300–400 mesh) under slightly positive pressure. PE = petroleum ether (b.p. 60–90 °C).

3.2. Synthesis

3.2.1. Synthesis of 4

A solution of ester **3** (324 mg, 1.0 mmol) in dry THF (2 mL) was added slowly to a suspension of powdered $LiBH_4$ (174 mg, 8.0 mmol) in dry THF (3 mL) stirred in an ice-water bath. After completion of the addition, stirring was continued in the ice-water bath for 10 min and at ambient temperature for 2 h. When TLC showed completion of the reduction, EtOH (4.7 mL, 80 mmol) was added slowly. The solids were filtered off with suction through a sintered glass funnel. The filtrate was concentrated on a rotary evaporator to give a sticky oil, which was purified by column chromatography (10:1 CH_2Cl_2/MeOH) on silica gel to afford the known diol **4** as a colourless oil (247 mg, 1.0 mmol, 100%): $[\alpha]_D^{25}$ −10.4 (*c* 1.90, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD): δ 7.42 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 5.90 (s, 1H), 4.10–4.06 (m, 1H), 4.04–4.01 (m, 1H), 3.79 (s, 3H), 3.76–3.72 (m, 4H); ^{13}C NMR (125 MHz, CD_3OD): δ 161.9, 131.1, 129.4, 114.5, 105.0, 80.6, 80.2, 63.5, 63.2, 55.7; FT-IR (film): ν_{max} 3259 (br), 2926, 2853, 1517, 1248, 1062, 808 cm^{-1}; ESI-MS *m/z* 241.3 ([M + H]$^+$).

3.2.2. Synthesis of 6

BH_3 (1.0 M, in THF, 1.8 mL, 1.8 mmol) was added slowly to a solution of diol **4** (120 mg, 0.5 mmol) in dry THF (0.2 mL) stirred in a −20 °C bath (ice-NaCl) under N_2 (balloon). After completion of the addition, the mixture was heated to reflux under argon (balloon) for 2 h (when TLC showed completion of the reduction). The heating bath was removed. To the mixture already cooled to ambient temperature, MeOH (1 mL) was added very slowly. The mixture was concentrated on a rotary evaporator. The residue was purified by column chromatography (20:1 EtOAc/MeOH) on silica gel to afford triol **5** as a colourless oil, from which the following data were collected: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.63 (d, J = 11.5 Hz, 1H), 4.51 (d, J = 11.5 Hz, 1H), 3.88–3.79 (m, 2H), 3.80 (s, 3H), 3.75–3.62 (m, 3H), 3.60–3.51 (m, 1H), 2.75 (br s, 3H); FT-IR (film) ν_{max} 3375 (br), 2939, 1612, 1586, 1513, 1425, 1250, 1032, 822 cm^{-1}; ESI-MS *m/z* 265.2 ([M + Na]$^+$). All the above-mentioned **5** was then directly dissolved in dry THF (4 mL). To this solution was added Ph_3P (158 mg, 0.6 mmol), followed by a solution of DIAD (122 mg, 0.6 mmol) in dry THF (2 mL). The mixture was stirred at ambient temperature for 12 h. When TLC showed completion of the reaction, the mixture was concentrated on a rotary evaporator. The residue was purified by column chromatography (1:1 EtOAc/PE) on silica gel to afford alcohol **6** as a colourless oil (88 mg, 0.4 mmol, 80% overall from **4**). Data for **6**: $[\alpha]_D^{27}$ −6.4 (*c* 0.46, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 4.51 (s, 2H), 4.32 (d, J = 4.1 Hz, 1H), 4.06 (dd, J = 10.1, 4.9 Hz, 1H), 3.972 (d, J = 5.9 Hz, 1H), 3.971 (dd, J = 10.0,

4.1 Hz, 1H), 3.81 (s, 3H), 3.78 (dd, J = 9.5, 1.7 Hz, 1H), 3.74 (d, J = 9.9 Hz, 1H), 1.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 129.8, 129.4, 113.9, 84.5, 75.5, 73.8, 71.5, 71.3, 55.3; FT-IR (film) ν_{max} 3413 (br), 2936, 2871, 1612, 1514, 1249, 1091 cm^{-1}; ESI-MS m/z 247.3 ([M + Na]$^+$); ESI-HRMS calcd for $C_{12}H_{20}O_4N$ ([M + NH_4]$^+$)242.1387, found 242.1385.

3.2.3. Synthesis of 7

A mixture of Dess–Martin periodinane (585 mg, 1.38 mmol), $NaHCO_3$ (773 mg, 9.2 mmol) and alcohol **6** (103 mg, 0.46 mmol) in dry CH_2Cl_2 (5 mL) was stirred at ambient temperature for 8 h. When TLC showed completion of the oxidation, solids were filtered off. The filtrate was concentrated on a rotary evaporator. The yellowish oily residue was purified by column chromatography (1:5 EOAc/PE) on silica gel to afford **7** as a colourless oil (89 mg, 0.4 mmol, 87%): $[\alpha]_D^{27}$ +19.7 (c 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.84 (d, J = 11.5 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 4.26 (dd, J = 9.5, 7.5 Hz, 1H), 4.03 (d, J = 17.0 Hz, 1H), 4.02 (t, J = 7.5 Hz, 1H), 3.96 (d, J = 17.5 Hz, 1H), 3.83 (dd, J = 9.5, 7.8 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.0, 159.6, 129.9, 128.9, 113.9, 75.7, 72.3, 70.8, 69.9, 55.2; FT-IR (film) ν_{max} 2933, 2870, 1771, 1612, 1514, 1249, 1110, 1033, 822 cm^{-1}; ESI-MS m/z 277.2 ([M + MeOH + Na]$^+$); ESI-HRMS calcd for $C_{12}H_{18}O_4N$ ([M + NH_4]$^+$) 240.1230, found 240.1229.

3.2.4. Synthesis of 8

To a mixture of $(Ph_3P)_3RhCl$ (8 mg, 0.0085 mmol) and Ph_3P (97 mg, 0.37 mmol) in dry 2,4-dioxane (1 mL) stirred in a 60 °C bath under argon (balloon) were added dry *i*-PrOH (0.39 mL), a solution of **7** (76 mg, 0.34 mmol) in dry 2,4-dioxane (1 mL) and Me_3SiCHN_2 (2.0 M, in *n*-hexane, 0.41 mL, 0.82 mmol). The yellow solution was stirred at 60 °C for 4 h (TLC showed full consumption of the starting **7**). Oxone (209 mg, 0.34 mmol) was added, followed by $NaHCO_3$ (29 mg, 0.34 mmol). The mixture was stirred at 60 °C for 2 h before being cooled to ambient temperature, diluted with Et_2O (50 mL), washed with aq. sat. $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:10 EtOAc/PE) on silica gel gave **8** as a yellowish oil (33 mg, 0.15 mmol, 44%). $[\alpha]_D^{25}$ –11.3 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 9.6 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 5.29 (dt, J = 3.7, 1.3 Hz, 1H), 5.20 (dd, J = 3.7, 2.2 Hz, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.48 (dt, J = 12.8, 3.0 Hz, 1H), 4.45 (d, J = 11.6 Hz, 1H), 4.30 (ddd, J = 4.4, 3.0, 1.5 Hz, 1H), 4.26 (dt, J = 13.0, 2.4 Hz, 1H), 3.92 (dd, J = 9.7, 3.1 Hz, 1H), 3.88 (dd, J = 9.7, 4.7 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.3, 147.2, 130.1, 129.4, 113.9, 109.3, 78.9, 73.4, 70.2, 70.0, 55.3; FT-IR (film): ν_{max} 3006, 2917, 2850, 1612, 1514, 1248, 1080, 1035, 823 cm^{-1}; ESI-MS m/z 243.2 ([M + Na]$^+$); ESI-HRMS calcd for $C_{13}H_{20}O_3N$ ([M + NH_4]$^+$) 238.1438, found 238.1436.

3.2.5. Synthesis of (S)-1

A mixture of **8** (11 mg, 0.05 mmol) and DDQ (15 mg, 0.065 mmol) in CH_2Cl_2 (1.5 mL) and H_2O (0.075 mL) was stirred at ambient temperature for 20 min (during which the initial dark-green solution became a yellow suspension). When TLC showed completion of the reaction, Et_2O (50 mL) and H_2O (2 mL) were added. The phases were separated. The organic layer was washed with aq. sat. $NaHCO_3$ (10 mL × 8, until the aqueous layer became neutral), water (20 mL) and brine (20 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:1 *n*-pentane/Et_2O) on silica gel gave

(*S*)-**1** as a colourless oil (4.0 mg, 0.04 mmol, 80%): $[\alpha]_D^{26}$ –6.3 (*c* 0.25, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33 (dd, *J* = 4.0, 2.0 Hz, 1H), 5.14 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.58 (m, 1H), 4.50 (dt, *J* = 14.0, 3.0 Hz, 1H), 4.27 (dt, *J* = 14.0, 2.0 Hz, 1H), 3.92 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.77 (dd, *J* = 10.0, 4.0 Hz, 1H), 1.89 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.8, 108.0, 75.3, 73.1, 70.1; FT-IR (film): ν_{max} 3404 (br), 2857, 1421, 1064, 909 cm^{-1}; EI-MS *m/z* (%) 100 (M^+, 3), 70 (100); EI-HRMS calcd for $C_5H_8O_2$ (M^+): 100.0524, found 100.0527.

4. Conclusions

In summary, the structure previously proposed for a natural product isolated from the leaves of *Michelia compressa* var. *lanyuensis* (Magnoliaceae) was synthesised in an enantiopure form. Apart from clear-cut ^{1}H and ^{13}C NMR spectra, the relation between absolute configuration and the optical rotation was also established for the proposed structure for the first time. However, the synthetic sample showed an optical rotation incompatible with that reported for the natural sample. Significant differences were also found in ^{1}H and ^{13}C NMR. On the basis of the newly acquired data, it is concluded that the structure previously assigned to the title natural product must be incorrect.

Disclosure statement

No potential conflict of interest was reported by the author.

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