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Synthesis of methyl dihydrohardwickiate and its C-4 epimer. Structural amendment of natural crolechinic acid

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Abstract

Reduction of the α,β-unsaturated ester moiety of (+)-methyl hardwickiate with magnesium in methanol afforded methyl (4a*S*,6*S*,8a*S*,1*R*,5*R*)-5,6,8a-trimethyl-5-[2′-(3″-oxoyl)-ethyl-perhydro-1-naphthalenyl]-carboxaylate, while reduction with sodium in *n*-propanol, followed by esterification with diazomethane, furnished its C-4 epimer. After comparison of the ^{1}H- and ^{13}C-NMR data of these compounds with those reported for crolechinic acid isolated from *Croton lechleri*, a stereochemical revision for the natural product is suggested.

Keywords: Reduction; (+)-Methyl hardwickiate; Stereochemistry; Crolechinic acid

1. Introduction

Crolechinic acid is a clerodane diterpene isolated from *Croton lechleri*, (Cai, Chen, & Phillipson, 1993) a plant widely used as a traditional medicine in South America for the treatment of wounds, inflammation and cancer (Hartwell, 1969; Bettolo & Scarpati, 1979; Cai, Evans, Roberts, Phillipson, Zenk & Gleba, 1991). Its structure was depicted as **1** based on the analysis of its ^{1}H- and ^{13}C-NMR spectral data, including a COSY experiment, and also by comparison of the data with those of crolechinol (**2**) isolated from the same plant. The most intriguing aspect of this diterpene is the axial orientation of the carboxyl group at carbon C-4. During our studies on the chemical transformation of (+)-methyl hardwickiate (**3**) (Costa, Fujiwara & Imamura 1998), one of the products which we have prepared is **4**, obtained through catalytic hydrogenation of **3b**. Since the catalytic hydrogenation of an olefin is sensitive to sterical hindrance, it was assumed that hydrogenation will occur from the α-face leading to a carbomethoxy group with an equatorial orientation (House, 1972). On comparing the ^{13}C-NMR spectral data of crolechinic acid reported in the literature (Cai et al., 1993) and **4**, we observed that the chemical shifts of the A, B ring were almost identical, which suggests that in both cases, the relative stereochemistry at C-4 should be the same, i.e., an equatorial orientation for carboxyl group. This prompted us to prepare compounds **5** and **6b** from **3**, in order to compare all the spectroscopic data with those of crolechinic acid and to establish the correct stereochemistry of the natural product.

2. Results and discussion

Reduction of α,β-unsaturated esters is well known in the literature, and particularly the use of magnesium in methanol (Zechmeister & Rom, 1929) was extended in the past few years after the discovery that it can selectively reduce the C–C double bond (Youn, Yon & Pak, 1986; Walkup & Park, 1990; Zarecki & Wicha, 1996; Ho, Lee & Chen, 1997). Actually, only a few examples of the reduction of α,β-unsaturated esters

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Table 1
^{13}C-NMR chemical shifts[a] of **4**, **5**, **6b**, **7** and **8**

Carbon	4	5	6b	7	8
1	21.5	21.0	21.0	21.5	21.5
2	26.5	22.6	26.2	26.9	22.4
3	25.0	24.3	24.9	25.4	23.6
4	57.6	53.9	57.6	54.4	51.3
5	37.4	36.7	37.3	37.0	36.9
6	39.9	38.3	39.9	39.5	37.0
7	27.2	27.2	27.1	27.3	27.3
8	36.6	36.5	36.6	36.5	37.0
9	38.8	38.6	38.9	38.9	38.8
10	49.3	39.9	49.3	49.7	42.2
11	37.1	38.3	38.3	38.5	38.2
12	26.2	18.2	18.1	18.1	18.2
13	40.1	125.9	125.6	125.9	125.7
14	32.8	111.1	111.0	111.2	111.0
15	68.1	142.5	142.7	142.9	142.7
16	73.8	138.5	138.4	138.6	138.4
17	16.0	16.0	16.0	16.1	16.0
18	175.3	175.8	175.0	63.6	62.1
19	14.8	21.6	14.8	15.2	23.0
20	18.2	18.1	18.1	18.1	18.1
OMe	51.0	50.8	50.9		

[a] δ in ppm from TMS, in $CDCl_3$ solution.

linked to the cyclopentene system were reported in the literature (Boyle et al., 1986; Hudlicky, Sinai-Zingde & Natchus, 1987) and there is no example for the cyclohexene system. Thus submitting (+)- methyl hardwickiate (**3b**) to the magnesium in methanol reduction technique according to the procedure described by Hudlicky et al. (1987), we obtained a clean reaction which after purification afforded a single product.To our surprise, after analysis of the spectroscopic data, the product was characterized as **5**. The stereochemistry at C-4 of **5** was determined by careful analysis of its ^{1}H- and ^{13}C-NMR spectral data, and by NOE experiments. On irradiating 4-H at δ 2.22, an enhancement in the intensity of the signal for the C-19 methyl group at δ 1.04 (3.9%) was observed. Following irradiation of the C-19 methyl group, enhancements in the intensities of the signals for 4-H (3.6%) and of the C-20 methyl group at δ 0.69 (2.5%) were observed. When the ^{13}C-NMR spectral data of this reduction product were compared with those of **4**, we observed, as expected due to the γ-gauche effect (Wehrli & Wirthlin, 1976), a significant difference of the chemical shifts for C-2 ($\Delta\delta = -3.9$), C-10 ($\Delta\delta = -9.4$) and C-19 ($\Delta\delta = +6.8$) confirming that the carbomethoxy group of **5** should be oriented axially. To provide further confirmation, the reduction of **3b** was carried out with sodium in *n*-propanol (Ferrari, Pelizzoni & Ferrari, 1971) to furnish the acid **6a**, which was esterified with diazomethane to give ester **6b** in 45% yield and the over-reduction product **7** in 50% yield.

By comparison of the ^{13}C-NMR spectral data, presented in the Table 1, of the esters **5** and **6b**, and alcohols **8** (obtained by reduction of **5**) and **7**, we could observe clearly the γ-effect shielding (Wehrli & Wirthlin, 1976) at C-2 and C-10 for **5** (respectively, $\Delta\delta = -3.6$ and -9.4) and for **8** (respectively, $\delta = -4.5$ and -7.5), and the deshielding at C-19 due to the lack of a γ-effect of shielding ($\Delta\delta = 6.8$ for **5** and $\Delta\delta = 7.8$ for **8**). The ^{13}C-NMR chemical shifts of the bicyclic system observed for **7** are in good agreement with those reported for the enantiomer (Rosa, Minale, Riccio & Sodano, 1976).

On comparing the chemical shifts of the ^{13}C-NMR spectral data of ester **6b** with those reported for crolechinic acid, we observed, except for the methoxy group, a good agreement, which indicates that they should have same relative stereochemistry. A good agreement was also observed by comparing the bicyclic system for the alcohols **7** and **2**, which suggests that the orientation of the hydroxymethyl group at C-4 should also be equatorial. Thus, the results of the ^{13}C-NMR data observed above for **5** and **6b** led us to suggest that the structure of natural crolechinic acid should be revised as depicted in **9**[1] and structure **10** for natural crolechinol.

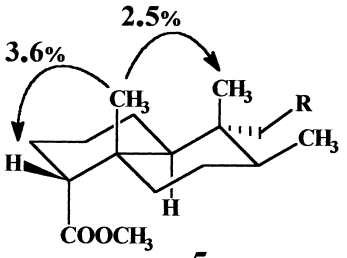
3. Experimental

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz, respectively, with a Bruker AC 300/P spectrometer (TMS as internal standard). IR spectra of neat samples were measured with a Perkin–Elmer 1600 series FTIR. Mass spectra of purified compounds were recorded with a Hewlett-Packard 5890 GC equipped with a Model 5970 mass-selective detector. Elemental analyses were performed with a Perkin–Elmer 2400 CHN analyzer. Optical rotations were measured with a Carl Zeiss photoelectric polarimeter.

*3.1. Methyl (1S,4aS,6S,8aS,5R)-5,6,8a-trimethyl-5-[2′-(tetrahydrofuranyl)-ethyl-perhydro-1-naphthalenyl]-carboxylate (**4**)*

A solution of **3b** (66 mg, 0.20 mmol) was dissolved in EtOAc (15 ml) and hydrogenated on a Parr instrument (1 atm) with PtO_2 (3 mg). After 4 h, the mixture was filtered through Celite and washed with EtOAc (10 ml). After removal of solvent, **4** (67 mg, 100%) was obtained: IR (film): $\nu = 2933$, 2871, 1727, 1450, 1383, 1187, 1140, 1038 cm^{-1}. ^{1}H-NMR spectral data ($CDCl_3$, TMS): $\delta = 0.68$ (*s*, 3H), 0.77 (*d*, 3H, $J = 6.2$ Hz), 1.00 (*s*, 6H), 0.80–1.60 (*m*, 26H), 1.70–1.90 (*m*,

[1] Since there is no report of the optical rotation of the natural product, the absolute configuration remains unknown.



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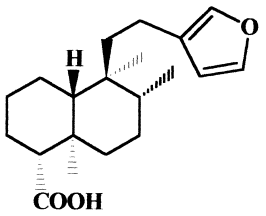

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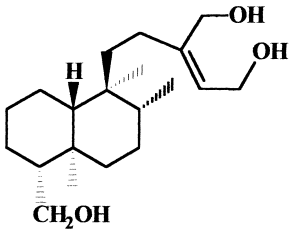
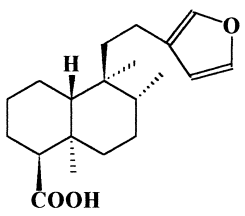


10

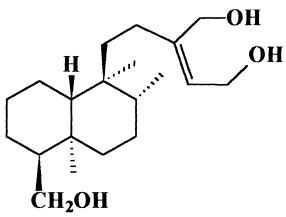
6H), 2.0–2.30 (*m*, 6H), 3.25–3.35 (*m*, 2H), 3.62 (*s*, 6H), 3.65–3.95 (*m*, 8H); ^{13}C-NMR spectral data (see Table 1).

3.2. Methyl (4aS,6S,8aS,1R,5R)-5,6,8a-trimethyl-5-[2′-(3″-oxoyl)-ethyl-perhydro- 1-naphthalenyl]-carboxylate (5)

Mg turnings (40.8 mg, 1.68 mmol) were added to a stirred solution of **3b** (55.4 mg, 0.17 mmol) in dry MeOH (10 ml). The reaction mixture was cooled, 3 M HCl was added carefully until the excess of Mg dissolved and the mixture was extracted with Et_2O (4 × 5 ml). The organic layer was washed with brine (10 ml), dried ($MgSO_4$) and concentrated in vacuum. The residue was purified by silica gel chromatography (*n*-hexane/Et_2O, 99:1) to give **5** (33.4 mg, 60%): colorless oil; $[\alpha]_D^{25}$ −12° (*c* 1.74, $CHCl_3$) spectral data. IR (film): $\nu = 2921, 2867, 1732, 1446, 1377, 1150, 1026, 874, 777$ cm^{-1}. ^{1}H-NMR spectral data ($CDCl_3$, TMS): $\delta = 0.69$ (*s*, 3H), 0.80 (*d*, 2H, $J = 6.5$ Hz), 1.04 (*s*, 3H), 1.20–2.40 (*m*, 17H), 3.64 (*s*, 3H), 6.27 (*br s*, 1H), 7.21 (*br s*,



1



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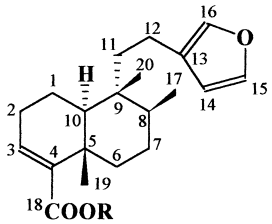
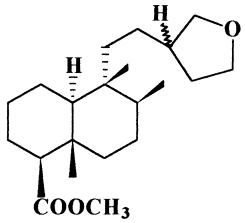


3a R = H
3b R= CH_3



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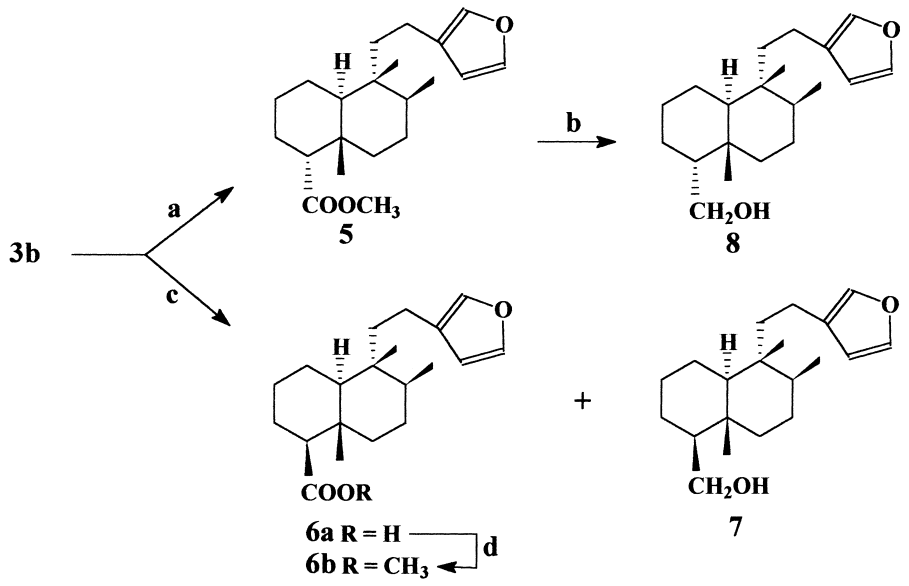

Scheme 1. (a) Mg/MeOH; (b) $LiAiH_4$, Et_2O; (c) Na/*n*-PrOH; (d) CH_2N_2, Et_2O.

1H), 7.33 (*t*, 1H, $J = 1.6$ Hz); ^{13}C-NMR spectral data (see Table 1); MS: *m/z* (%) = 332 (M^+, 6), 237 (20), 205 (20), 177 (32), 96 (8), 81 (100), 41 (60); Anal. calcd. for $C_{21}H_{32}O_3$ (332.5): C 75.86; H 9.70; Found: C 75.72; H 9.64.

*3.3. Methyl (1S,4aS,6S,8aS,5R)-5,6,8a-trimethyl-5-[2′-(3″-oxoyl)-ethyl-perhydro- 1-naphthalenyl]-carboxylate (**6b**) and (1S,4aS,6S,8aS,5R)-5,6,8a-trimethyl-5-[2′-(3″-oxoyl)-ethyl-perhydro-1 -naphthalenenyl]-methanol (7)*

Small pieces of sodium (23.6 mg, 1.0 mmol) were added to a stirred solution of **3a** (68.2 mg, 0.21 mmol) in dry *n*-propanol (15 ml). The reaction mixture was stirred for 6 h at room temperature, the solution acidified by adding HCl 1 M (pH ~ 5) and extracted with Et_2O (4 × 20 ml). The ethereal solution was washed with brine (2 × 30 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel chromatography (*n*-hexane/EtOAc, 99:1) to give **7** (31.4 mg, 50%) as colorless oil. Further elution (*n*-hexane/EtOAc, 9:1) furnished **6a**, which was esterified with CH_2N_2 to give **6b** (30.9 mg, 45%) as colorless oil.

Compound **6b**: $[\alpha]_D^{25}$ +52° (*c* 2.37, $CHCl_3$) [for enantiomer (Boyle et al., 1986): $[\alpha]_D$ −56°, ($CHCl_3$)]; IR (film): $\nu = 2947$, 2870, 1731, 1447, 1384, 1320, 1191, 1144, 1026, 873, 777, 600 cm^{-1}. ^{1}H-NMR spectral data ($CDCl_3$, TMS): $\delta = 0.72$ (*s*, 3H), 0.81 (*d*, 3H, $J = 6.5$ Hz), 1.02 (*s*, 3H), 1.10–1.90 (*m*, 14H), 2.10–2.40 (*m*, 3H), 3.63 (*s*, 3H), 6.25 (*br s*, 1H), 7.20 (*br s*, 1H), 7.34 (*t*, 1H, $J = 1.6$ Hz); ^{13}C-NMR spectral data (see Table 1); MS: *m/z* (%) = 332 (M^+, 10), 237 (100), 205 (78), 177 (75), 81 (95), 55 (40); Anal. calcd. for $C_{21}H_{32}O_3$ (332.5): C 75.86; H 9.70; Found: C 75.70; H 9.88.

Compound **7**: $[\alpha]_D^{25}$ +21.7° (*c* 5.87, $CHCl_3$) [for enantiomer (Boyle et al., 1986): $[\alpha]_D$ −30.5°, ($CHCl_3$)]; IR (film): $\nu = 3346$, 2925, 2868, 1446, 1161, 1026, 874, 779 cm^{-1}. ^{1}H-NMR spectral data ($CDCl_3$, TMS): $\delta =$ 0.71 (*s*, 3H), 0.81 (*d*, 3H, $J = 6.5$ Hz), 0.83 (*s*, 3H), 1.00-1.90 (*m*, 16H), 2.10-2.40 (*m*, 2H), 3.27 (*dd*, 1H, $J = 8.0$, 10.3 Hz), 3.84 (*dd*, 1H, $J = 2.4$, 10.3 Hz), 6.26 (*br s*, 1H), 7.20 (*br s*, 1H), 7.35 (*t*, 1H, $J = 1.6$ Hz); ^{13}C-NMR spectral data (see Table 1); Anal. calcd. for $C_{20}H_{32}O_2$ (304.5): C 78.90; H 10.59; Found: C 78.88, H 10.45.

*3.4. (4aS,6S,8aS,1R,5R)-5,6,8a-trimethyl-5-[2′-(3″-oxoyl)-ethyl-perhydro- 1-naphthalenyl]-methanol (**8**)*

A solution of **5** (25.2 mg, 0.07 mmol) in dry Et_2O (5 ml) was added to a suspension of $LiAlH_4$ (27.7 mg, 0.76 mmol) in dry Et_2O at 0°C, and the reaction mixture was stirred for 6 h under nitrogen. Excess $LiAlH_4$ was destroyed by the careful addition of 10% aqueous NaOH. The solid was removed by filtration through a Celite pad, and the ethereal solution was dried ($MgSO_4$) and concentrated in vacuum. The residue was purified by flash chromatography (*n*-hexane/EtOAc, 9:1) to give **8** (22.3 mg, 97%): colorless oil; $[\alpha]_D^{25}$ −28.0° (*c* 1.4, $CHCl_3$). IR (film): $\nu = 3356$, 2931, 2868, 1448, 1026, 874, 779 cm^{-1}. ^{1}H-NMR spectral data ($CDCl_3$, TMS): $\delta = 0.70$ (*s*, 3H), 0.81 (*d*, 2H, $J =$ 6.5 Hz), 1.07 (*s*, 3H), 1.20–1.80 (*m*, 16H), 1.90–2.40 (*m*, 2H), 3.66 (*dd*, 1H, $J = 7.6$, 10.6 Hz), 3.97 (*dd*, 1H, $J = 5.4$, 10.6 Hz), 6.26 (*br s*, 1H), 7.20 (*br s*, 1H), 7.34 (*t*, 1H, $J = 1.6$ Hz); ^{13}C-NMR spectral data (see Table 1); Anal. Calcd. for $C_{20}H_{32}O_2$ (304.5): C 78.90; H, 10.59; Found: C 78.89, H 10.40.

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