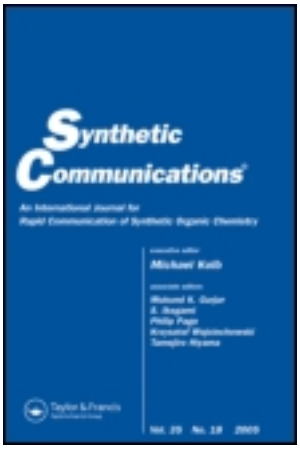

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 15 Aug 2006.

To cite this article: Kyoko Nakagawa-Goto, Jiu-Hong Wu & Kuo-Hsiung Lee (2005) First Total Synthesis of Desmosdumotin C, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:13, 1735-1739, DOI: 10.1081/SCC-200063907

To link to this article: http://dx.doi.org/10.1081/SCC-200063907

Synthetic Communications®, 35: 1735–1739, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200063907

First Total Synthesis of Desmosdumotin C†

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Abstract: Desmosdumotin C (**1**), a novel compound isolated from the roots of *Desmos dumosus*, was synthesized from 2,4,6-trihydroxyacetophenone (**2**), confirming the assigned structure of the natural product.

Keywords: Antitumor, cytotoxicity, desmosdumotin C, total synthesis

INTRODUCTION

Desmosdumotin C, a novel compound,[1] was isolated recently by our group from the roots of *Desmos dumosus*. The structure of **1**, which was established mainly by NMR and X-ray analyses, has a cyclohexe-4-ene-1,3-dione skeleton with a conjugated cinnamoyl moiety on the C-2 position and a *gem*-dimethyl group on the C-6 position. Similar compounds, safflomin C,[2] syzygiol,[3] and uliginosin A analog,[4] are known. Although these latter compounds exist as tautomeric mixtures, the isolated desmosdumotin C exists as one enolic tautomer.

Received in the USA June 27, 2004
†Antitumor agent 242
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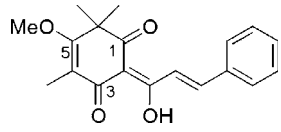


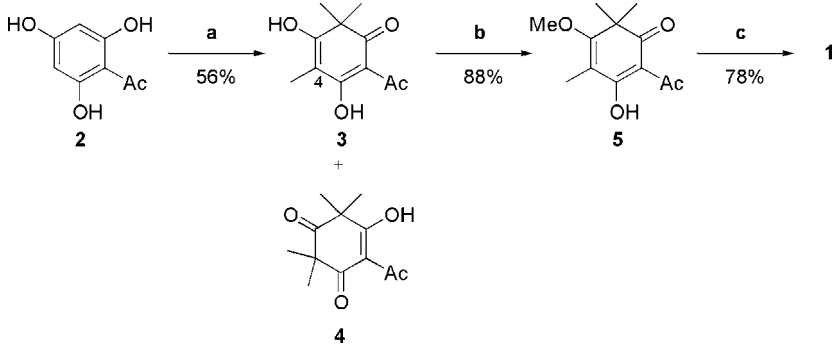
Desmosdumotin C (**1**)

Figure 1. The structure of Desmosdumotin C.

Desmosdumotin C (**1**) represents a promising new anticancer lead structure for further new analog development based on its in vitro evaluation against a panel of six cancer cell lines.[1] Thus, to obtain a larger quantity than available from the plant source and to confirm the structure of the natural product, we herein report the first simple total synthesis of **1**.

EXPERIMENTAL

Reaction of 2,4,6-trihydroxyacetophenone (**2**) with three equivalents of methyl iodide in the presence of sodium methoxide produced 2-acetyl-3-hydroxy-4,6,6-trimethylcyclohexa-2,4-dienone (**3**)[5] in 56% yield along with tetramethyl **4** in 9% yield. The selective methoxylation of **3** to give **5** was achieved in 88% yield by treatment with $TMSCHN_2$ at a low temperature. Employing a higher temperature gave a low yield of the desired compound, because of the production of unknown side product(s). The use of other conditions, such as K_2CO_3 and MeI or Li_2CO_3 and MeI,[6] yielded only tetramethyl derivative **4**, because of the presence of a strongly acidic proton on the C-4 position (Scheme 1).



Scheme 1. Reagents and conditions: a) MeI (3.3 mol eq.), 30% NaOMe in MeOH (3.7 mol eq.), MeOH, reflux, 7 h; b) 2.0 M $TMSCHN_2$ in Et_2O (excess), EtOAc/MeOH, −78 °C, 3 h; c) 50% KOH aq., EtOH, PhCHO, rt, 23 h.

Finally, desmosdumotin C (**1**) was obtained in 78% yield by the aldol condensation of **5** with benzaldehyde in 50% KOH aqueous solution. Recrystallization from $CHCl_3$–MeOH gave **1** as yellow needles. The synthetic product has identical spectral data with those of the natural product.

All melting points were taken on Fisher-Johns and Mel-Temp II melting-point instruments and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1320 spectrophotometer. ^{1}H NMR spectra were obtained using a Varian Gemini 2000 (300-MHz) NMR spectrometer with TMS as the internal standard. All chemical shifts are reported in ppm. FABMS and HRFABMS spectral analyses were determined on a JOEL HX-110 instrument. Analytical thin-layer chromatography (TLC) was carried out on Merck precoated aluminum silica-gel sheets (Kieselgel 60 F-254). All target compounds were characterized by ^{1}H, IR, and MS analyses.

2-Acetyl-3,5-dihydroxy-4,6,6-trimethylcyclohexa-2,4-dione (3)

A solution of 2,4,5-trihydroxyacetophenone (**2**, 487 mg, 2.9 mmol) and sodium methoxide (1.95 mL, 10.8 mmol, 30% MeOH solution) in anhydrous MeOH (3 mL) containing methyl iodide (0.6 mL, 9.6 mmol) was refluxed for 7 h. The reaction mixture was cooled to 0 °C and acidified with 1 N of aqueous HCl, then extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc–hexane (1:9 to 1:4, v/v) as an eluent to provide **3** (343 mg, 56%). Pale yellow prisms, mp: 164–165 °C (EtOAc–hexane). IR (KBr): 3099 (br), 1656, 1590, 1525, 1474, 1387, 1331, 1278, 1193, 1153 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 18.94$ (br s, 1H, chelated-O*H*), 2.42 [s, 3H, C(O)CH_3], 1.73 (s, 3H, CH_3), 1.23 (s, 6H, C$H_3 \times 2$). ^{13}C NMR (300 MHz, DMSO-d_6): $\delta = 199.4$ (*C*=O), 196.0 (*C*=O), 188.7 (*C*–OH), 176.2 (*C*–OCH$_3$), 105.0 (*C*-2), 101.7 (*C*-6), 48.2 [*C*(CH$_3$)$_2$], 27.8 [C(O)*C*H$_3$], 24.3 (*C*H$_3 \times 2$), 7.3 (*C*H$_3$). MS m/z 209 ($M^+ - 1$).

2-Acetyl-3-hydroxy-5-methoxy-4,6,6-trimethylcyclohexa-2,4-dione (5)

To a solution of **3** (447 mg, 2.13 mmol) in anhydrous EtOAc–MeOH (5:1, 6 mL), a solution of $TMSCHN_2$ in diethyl ether (5 mL, 10 mmol, 2 M) was added slowly at −78 °C under argon atmosphere, and the mixture was stirred for 2 h. At this time, a second aliquot of $TMSCHN_2$ (4 mL, 8 mmol, 2 M) was added and stirring was continued at −78 °C. Acetic acid was then added to destroy the excess $TMSCHN_2$. The mixture was concentrated in vacuo, and the residue was purified by silica-gel column chromatography with EtOAc–hexane (1:2) as an eluent to obtain **5** (418 mg, 88%). Yellow oil: IR (KBr): 2979, 2937, 2874, 1659, 1636, 1536, 1469, 1374, 1202, 1131,

978, 915 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 18.93$ (s) and 18.14 (s) (2:1, 1H, chelated-O*H*), 3.93 (s) and 3.85 (s) (2:1, 3H, OCH_3), 2.69 (s) and 2.59 (s) [1:2, 3H, C(O)CH_3], 1.95 (s) and 1.90 (s) (2:1, 3H, CH_3), 1.43 (s) and 1.31 (s) (1:2, 6H, $CH_3 \times 2$). ^{13}C NMR (300 MHz, $CDCl_3$) δ C–H COSY (*gem*-dimethyl), 7.3. MS m/z 223 ($M^+ - 1$).

Desmosdumotin C (1)

A solution of **4** (62 mg, 0.28 mmol) in EtOH (1 mL) and 50% KOH in water (1 mL) containing benzaldehyde (0.1 mL, 0.99 mmol) was stirred at rt for 23 h. The reaction mixture was poured into 1 N of ice-cold HCl, then extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc–hexane (1:9, v/v) as an eluent to afford a crystalline solid (80 mg). Recrystallizaton from CH_2Cl_2–MeOH gave desmosdumotin C (39 mg without its tautomer) as yellow needles (Figure 1). A second recrystallization of the mother liquor using CH_2Cl_2–hexane gave 29 mg of **1**, as a mixture with its tautomer. In sum, 68 mg (78%) of **1** were obtained. Yellow needles, mp 98–99 °C ($CHCl_3$–MeOH, lit.: 96–97 °C). IR (KBr): 3101, 2978, 2936, 1656, 1623, 1514, 1448, 1425, 1203, 1152, 1119, 977, 944, 759, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 19.17$ (s, 1H, chelated-O*H*), 8.33 (d, 1H, $J = 15.5$ Hz), 7.92 (d, 1H, $J = 15.5$ Hz), 7.71–7.62 (m, 2H, Ar-2″, 6″-*H*), 7.42–7.34 (m, 3H, Ar-3″, 4″, 5″-*H*), 3.95 (s, 3H, OCH_3), 1.99 (s, 3H, Ar-CH_3), 1.37 (s, 6H, $CH_3 \times 2$). ^{13}C-NMR (300 MHz, $CDCl_3$): $\delta = 198.0$ (C-1), 192.4 (C-3), 187.2 (C-1′), 176.6 (C-5), 144.9 (C-2′, C-3′), 135.2 (C-1″), 130.6 (C-3″, C-5″), 128.8 (C-4″), 123.2 (C-2″, C-6″), 113.6 (C-2), 106.6 (C-4), 62.1 (OCH_3), 50.4 (C-6), 24.3 ($CH_3 \times 2$), 9.8 (Ar-CH_3). MS m/z 313 ($M^+ + 1$).

ACKNOWLEDGMENTS

This study was supported by NIH Grant CA17625 awarded to K. H. L. Thanks are also due to Grant No. 30271533 awarded to J. H. W. from the National Natural Science Foundation of China.

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