Tetrahedron Letters 51 (2010) 946–948

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

First total synthesis of (+)-crassalactone A

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ARTICLE INFO

Article history:
Received 18 November 2009
Revised 6 December 2009
Accepted 9 December 2009
Available online 16 December 2009

Dedicated to Professor N. S. Sarma, Andhra University, Visakhapatnam on his 60th birth day and his excellent contributions in marine natural products

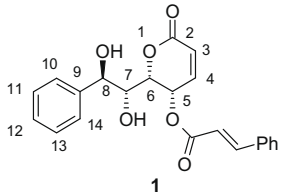
Keywords:
Goniothalamus
Polyalthia crassa
Styrllactones
(+)-Crassalactone A
Lactonization
Cis-hydroxylation

ABSTRACT

A simple and highly efficient first total synthesis of cytotoxic (+)-crassalactone A starting from (*R*)-mandelic acid is described. The strategy involves the osmium tetroxide-catalyzed cis-hydroxylation and the stereoselective addition of ethyl lithiopropiolate to a chiral aldehyde intermediate as key steps.

1. Introduction

Plants of the genus *Goniothalamus* (family; *Annonaceae*) in South East Asia have been known for a long time for their proven use in folk medicine. The extract of the seeds of *Goniothalamus amuyon* is reported to be employed for the treatment of edema and rheumatism.[1] The other applications include its use as painkillers[2] and mosquito repellents. In view of the medicinal properties, these plants are considered as a potential source of biologically active compounds. Styryl lactones, a group of important secondary metabolites is known for their significant cytotoxicity against several human cancer cell lines,[3] are widely present in the genus *Goniothalamus*.[4,5] Among which goniotriol is an important member of this family occurring in two enantiomeric forms[6] with a significant cytotoxicity in the potato disc and the brine shrimp tests. More recently (+)-crassalactone A (**1**) a 5-*O*-cinnamoyl derivative of (+)-goniotriol was isolated from the ethyl acetate extract of the leaves and twigs of *Polyalthia crassa*.[7] The new compound **1** shows cytotoxic activity against a panel of mammalian cancer cell lines. The structure was determined on the basis of spectroscopic methods. In continuation of our interest towards the total synthesis of biologically active natural products[8a–c] we report here the first total synthesis of (+)-crassalactone A (**1**).



1

The retro-synthesis analysis of compound **1** is shown Scheme 1. It was envisioned that (+)-crassalactone A (**1**) could be synthesized from **2** by cis hydrogenation, functional group transformations, elaboration, and lactonization. While in turn **2** could be originated from α,β-dihydroxy ester **3** which could be derived from the commercially available (*R*)-mandelic acid **4** (Scheme 1).

The journey of the synthesis was started from the commercially available chiral source (*R*)-mandelic acid **4.** Since the C8 chiral center is matched with compound **4** it was chosen as the starting compound for the synthesis. The other C6, C7, and C5 chiral centers were achieved via osmium tetroxide cis-dihydroxylation and anionic addition of ethyl lithiopropiolate to the chiral intermediate aldehyde.

2. Results and discussion

Initially (*R*)-mandelic acid **4** was converted into its methyl ester derivative **5** using the reported literature procedure with 93%

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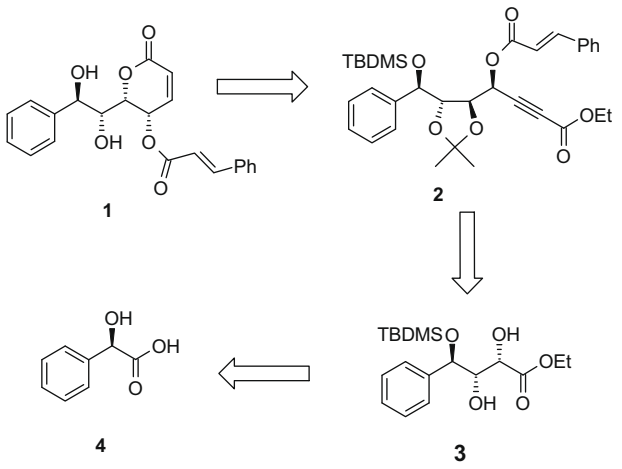
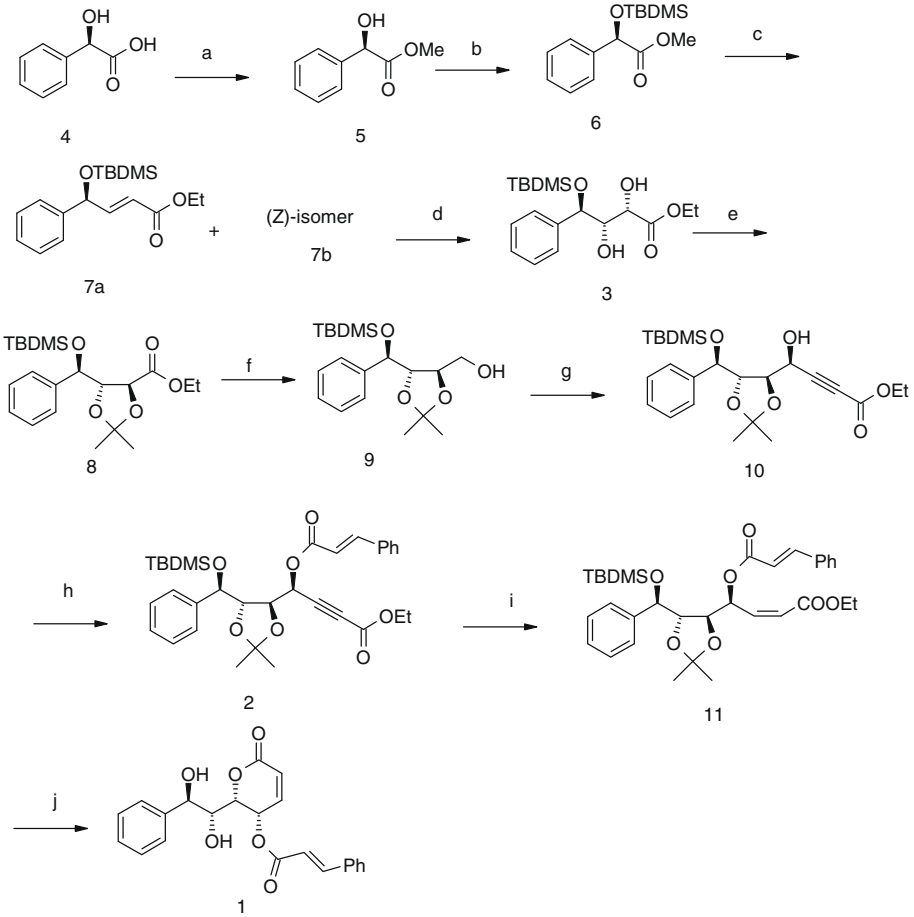
doi:10.1016/j.tetlet.2009.12.038



Scheme 1.

yield.[8d] The hydroxyl group in the methyl-(*R*)-mandelate was protected with TBDMS group using *tert*-butyldimethylsilyl chloride in an anhydrous DCM afforded compound **6.** Ester **6** was reduced with DIBAL-H at −78 °C to give good yield the corresponding aldehyde, which was treated with (ethoxycarbonylmethylene)triphenylphosphoranecarbonyl in an anhydrous DCM to furnish the Wittig product α,β-unsaturated esters **7a** and **7b** in 87% yield with the ratio of (*E*/*Z* = 93:7). After chromatographic separation of the two geometrical isomers, the *E*-isomer (**7a**) [*E*-configuration in **7a** supported by ^{1}H NMR coupling constant (*J* = 15.3 Hz) was reacted with a catalytic amount of OsO_4 in the presence of excess *N*-methylmorpholine N-oxide in acetone–water (5:1) system to afford α,β-dihydroxy ester **3**. The reaction afforded high *anti*-selectivity (90:10 ratio of *anti*: *syn*)[9] with respect to the existing C8 chiral center, and the anti isomer **3** was separated chromatographically in 85% yield. The formation of compound **3** was established by its ^{1}H NMR spectral data due to the presence of two hydroxy methine protons at δ 3.83 (1H, td, *J* = 8.3, 1.1 Hz, CHOH-CHOSi) and 4.52 (1H, dd, *J* = 5.6, 0.94 Hz, CHOH-CO_2Et). The dihydroxy ester **3** masked by acetonide protection using 2,2-dimethoxypropane in the presence of catalytic amount of *p*-TSA to give compound **8** in 87% yield, which was reduced with DIBAL-H, furnished alcohol **9** in an excellent yield. Primary alcohol **9** upon oxidation with Dess–Martin reagent[10] afforded the intermediate chiral aldehyde, which on treatment with ethyl lithiopropiolate[11] at −78 °C in the presence of LDA generated **10** as the almost single isomer[12] along with the negligible amount of other diastereomer (recognized by ^{1}H NMR) in good yield (75%). The formation of compound **10** was confirmed by its ^{1}H NMR spectral data due to hydroxyl methine proton vicinal to alkyne at δ 3.96 (1H, d, *J* = 9.9 Hz, CHOH). Compound **10** was esterified with cinnamic acid in the presence of standard DCC and DMAP procedure to give compound **2** in 65% yield. The triple bond in compound **2** on partial hydrogenation into *cis*-alkene using Lindlar's catalyst (5 w/w% Pd on $CaCO_3$/Pb, 70 w/w%) in hexane afforded **11** in 90%



Scheme 2. Reagents and Conditions: (a) MeOH, cat *P*-TSA, reflux 4 h, 93%; (b) TBSCl, Imidazole, dry DCM, 3 h, rt, 95%; (c) i). DIBAL-H, dry DCM, −78 °C, 1 h; (ii) $P(Ph)_3CHCO_2Et$.DCM, 6 h, rt, 70% (for two steps); (d) OSO_4, NMO, Acetone–H_2O (5:1), rt, 8 h, 85%; (e) 2,2-DMP, *p*-TSA (cat), Dry acetone, 6hr, rt, 87%; (f) 1) DIBAL-H, dry DCM, 0 °C, 1 h, 90%; (g) i) Dess–Martin Periodinane, dry DCM, 1 h; ii) $CHCCO_2Et$, −78 °C, LDA, THF, 12 h, 62% (for two steps); (h) DCC, Cinnamic acid, DMAP, dry DCM, rt, 3 h, 65%; (i) H2 (1bar), Lindlar's catalyst.(70 w/w%), quinoline, hexane, rt, 90%; (j) 3% MeOH/HCl,0 °C to rt, 5 h; 65%.

yield. Finally the deprotection of TBS and acetonide groups followed by cyclization of compound **11** was achieved on treating with 3% methanolic HCl, which afforded (+)-crassalactone A (**1**) in a single step with 65% yield. The formation of compound **1** was established by ^{1}H NMR spectral data in which the double bond signals in the lactone appeared at δ 6.19 (1H, d, J = 9.6 Hz) and 7.0 (1H, dd, J = 9.5, 6.0 Hz) and the lactonic methane proton appeared at 4.75 (dd, J = 5.8, 2.6 Hz). Compound **1** also characterized by ^{13}C NMR spectral data due to the carbonyl in δ-lactone appeared at δ 162.4, carbonyl in a cinnamate group at δ 165.7 and the carbons C-3, C-4, C-5, C-6, C-7, and C-8 appeared at δ 123.5, 140.4, 62.5, 77.5, 73.3, and 73.5, respectively. The double bond carbons in cinnamate group appeared at δ 116.4 and 146.6. The physical {white solid, mp 132 °C; $[\alpha]_D^{25}$ +319 (c 0.1, $CHCl_3$)} and spectral data[13] of the synthesized compound **1** were found to be in good agreement with the reported literature data[7] (Scheme 2).

In conclusion, we have accomplished the first total synthesis of the cytotoxic of (+)-crassalactone A (**1**) in 10 steps with an overall yield of 11% from (*R*)-mandelic acid.

Acknowledgments

The authors V.S., D.K.R., V.S., D.C.B. are thankful to CSIR, New Delhi, for the financial support and Dr. J. S. Yadav Director, Indian Institute of Chemical Technology (IICT), for his encouragement.

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13. *Spectral data for selected compounds*:
Compound **3**: $[\alpha]_D^{25}$ −32.9 (c 2.5, $CHCl_3$); IR (neat): 3488, 2995, 2942, 2860, 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.42 (m, 5H), 4.68 (d, 1H, J = 8.3 Hz), 4.52 (dd, 1H, J = 5.6, 0.94 Hz), 4.22–4.31 (m, 2H), 3.83 (td, 1H, J = 8.3, 1.1 Hz), 3.05 (d, 1H, J = 5.4 Hz), 1.62 (d, 1H, J = 7.6 Hz), 1.32 (t, 3H, J = 7.1 Hz), 0.9 (s, 9H), 0.1 (s, 3H), -0.2 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 141.5, 128.3, 127.9, 127.1, 77.3, 76.4, 75.1, 70.0, 61.8, 25.7, 18.0, 14.1, −4.7, −5.3; MS-ESIMS: m/z 377 $[M+Na]^+$; HRMS calcd for $C_{18}H_{30}NaO_5Si$ 377.1755, found 377.1754; *Compound* **10**: $[\alpha]_D^{25}$ −5.2 (c 0.3, $CHCl_3$); IR (neat): 3445, 2929, 2859, 2239, 1713, 1459, 1375, 1248, 1075, 840, 771, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.35 (m, 5H), 4.81 (d, 1H, J = 5.6 Hz), 4.20–4.30 (m, 3H), 4.12 (dd, 1H, J = 7.6, 5.6 Hz), 3.96 (d, 1H J = 9.9 Hz), 1.46 (s, 3H), 1.40 (s, 3H), 1.29 (t, 3H, J = 6.8 Hz), 0.90 (s, 9H), 0.07 (s, 3H), −0.14 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 152.6, 138.6, 128.5, 128.2, 126.5, 109.8, 80.9, 79.6, 77.2, 75.3, 74.1, 71.5, 61.8, 61.3, 127.7, 27.2, 26.1, 19.0, 14.2, −4.4, −4.6; MS-ESIMS: m/z 466 $[M+NH_4]^+$; HRMS calcd for $C_{24}H_{40}NO_6Si$ 466.2619, found 466.2618; *Compound* **2**: $[\alpha]_D^{25}$ −13.4 (c 0.3, $CHCl_3$); IR (neat): 3438, 2932, 2857, 2246, 1719, 1636, 1454, 1371, 1251, 1149, 1087, 1016, 840, 773, 702 cm^{-1}; ^{1}H NMR (300 Mz, $CDCl_3$): δ 7.7 (d, 1H, J = 15.8 Hz), 7.22–7.55 (m, 10H), 6.38 (d, 1H, J = 15.8 Hz), 5.33 (d, 1H, J = 3.7 Hz), 4.77 (d, 1H, J = 5.2 Hz), 4.35 (dd, 1H, J = 6.7, 3.7 Hz), 4.17–4.25 (m, 2H), 4.08 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.32 (t, 3H, J = 6.7 Hz), 0.9 (s, 9H), 0.1 (s, 3H), −0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 152.5, 146.4, 140.7, 134.3, 128.9, 128.3, 128.2, 126.7, 126.5, 116.7, 110.8, 81.4, 78.4, 77.6, 75.2, 74.8, 63.0, 60.2, 27.9, 26.0, 18.4, 14.1, −4.5, −4.6; ESI-MS: m/z 596 $[M+NH_4]^+$; HRMS calcd for $C_{33}H_{46}NO_7Si$; 596.3038, found 596.3039; *Compound* **1**: $[\alpha]_D^{25}$ +319 (c 0.1, $CHCl_3$); IR (neat): 3425, 2922, 1748, 1634, 1451, 1266, 1169, 1112, 1043, 939, 822, 763, 701, 554 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, 1H, J = 15.8 Hz), 7.29–7.50 (m, 10H), 7.0 (dd, 1H, J = 9.5, 6.0 Hz), 6.35 (d, 1H, J = 15.8 Hz), 6.19 (d, 1H, J = 9.6 Hz), 5.28 (dd, 1H, J = 6.0, 2.6 Hz), 4.90 (d, 1H, J = 5.8 Hz), 4.75 (dd, J = 5.8, 2.6 Hz), 4.26 (m, 1H), 2.00 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7 (C1′), 162.4 (C2), 146.6 (C3′), 140.4 (C4), 139.8 (C9), 133.6 (C4′) 130.8 (C7′), 128.9 (C6′,C8′), 128.7 (C11,C13), 128.3 (C12), 128.2 (C5′,C9′), 126.5 (C10,C14), 123.5 (C3), 116.4 (C2′), 77.5 (C6), 73.5 (C8), 73.3 (C7), 62.5 (C5); MS-ESIMS: m/z 398 $[M+NH_4]^+$; HRMS calcd for $C_{22}H_{24}NO_6$; 398.1598, found 398.1596.