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The first stereoselective total synthesis of (Z)-cryptomoscatone D2, a natural G_2 checkpoint inhibitor ☆

Gandolla Chinna Reddy [a], Penagaluri Balasubramanyam [a], N. Salvanna [a], Thummala Sreenivasulu Reddy [b], Biswanath Das [a,*]

[a] Organic Chemistry Division-I, Indian Institute of Chemical Technology (CSIR), Hyderabad 500 007, India
[b] Department of Chemistry, Sri Krishnadevaraya University, Anantapur 515 003, India

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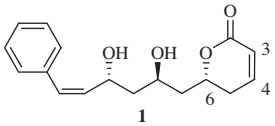
ABSTRACT

The first stereoselective synthesis of (*Z*)-cryptomoscatone D2, a naturally occurring G_2 checkpoint inhibitor, was accomplished using propane-1,3-diol as the starting material. The Maruoka asymmetric allylation, ring closing metathesis and the hydrogenation of the triple bond employing Lindlar's catalyst were involved as the key steps.

The α,β-unsaturated δ-lactones (γ-pyrone derivatives) have frequently been isolated from various natural sources.[1] They are known to posses different interesting biological properties including cytotoxic, antiviral and antibacterial activities.[2] (*Z*)-cryptomoscatone D2 (**1**), a novel compound of this group, was isolated from *Cryptocarya concinna*, a tree of the laurel family.[3] The compound contains an α,β-unsaturated δ-lactone ring along with two hydroxyl groups having opposite stereostructure and an olefinic system with (*Z*)-configuration. The bioactivity of this compound was studied and it was identified as a G2 checkpoint inhibitor while examining in human breast carcinoma MCF-7 cells.[3b] However, to our knowledge, the synthesis of this compound has not yet been synthesized though some structurally related compounds with (*E*)-configuration have earlier been reported.[4] In continuation of our work[5] on the construction of bioactive naturally occurring compounds we accomplished the synthesis of **1** which we would like to describe here.



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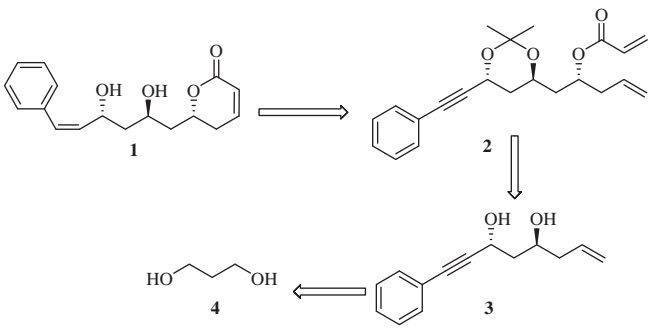

1 **2** **3** **4**

Scheme 1.

The retrosynthetic analysis (Scheme 1) revealed that the compound **1** can be prepared from the ester **2** which in turn can be synthesized from the unsaturated diol **3** generated from propane-1,3-diol (**4**).

The synthesis of (*Z*)-cryptomoscatone D2 (**1**) was initiated (Scheme 2) by protecting one of the hydroxyl groups of propane-1,3-diol (**4**) as the benzyl ether by treatment with BnBr using NaH and TBAI to form the compound **5**. The compound **5** was oxidized with PCC to the corresponding aldehyde which underwent Maruoka asymmetric allylation[6] employing (S)-binol titanium complex, (*S,S*)-**I** and allyl tributyl stannane to produce the chiral homoallylic alocohol **6** (ee 96%).[7] The hydroxyl group of this

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* Corresponding author. Tel./fax: +91 40 7160512.
E-mail address: biswanathdas@yahoo.com (B. Das).

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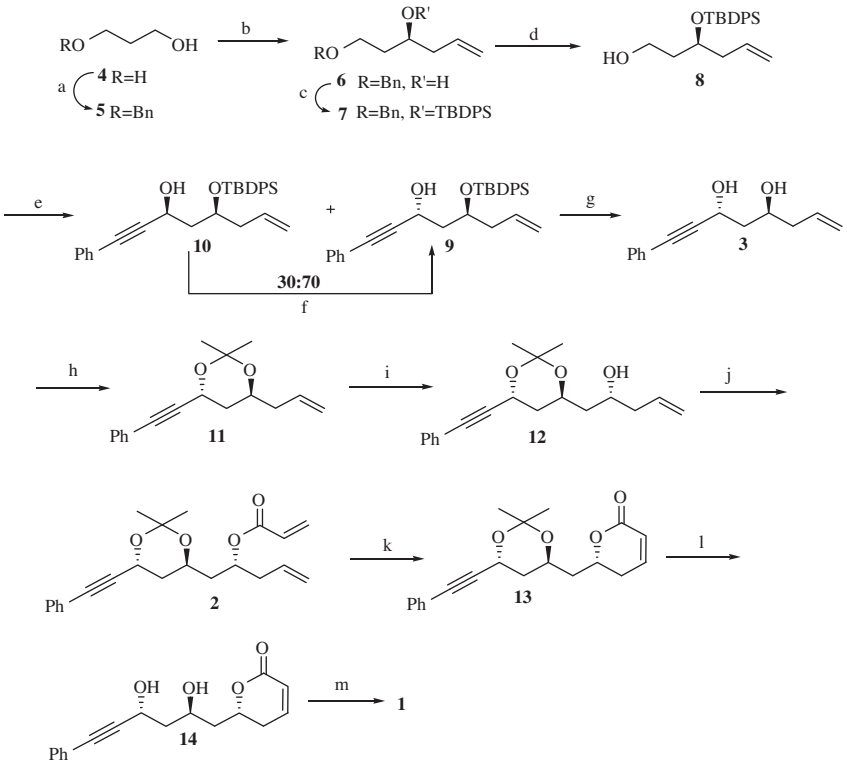
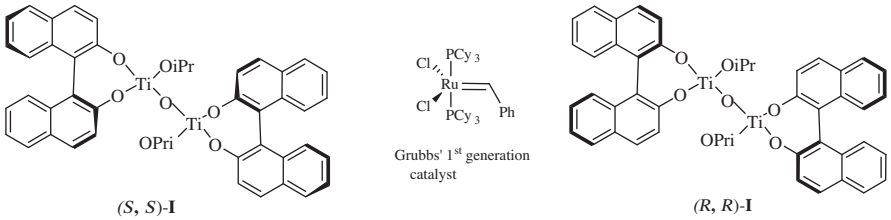


Scheme 2. Synthesis of (*Z*)-cryptomoscatone D2 (**1**). Reagents and conditions: (a) BnBr, NaH, TBAI, THF. 0 °C to rt, 2 h, 87%; (b) (i) PCC, celite, CH_2Cl_2, rt, 2 h; (ii) (*S,S*)-**I** (10 mol %), allyltributyltin, 4 Å MS, CH_2Cl_2, −20 °C, 72 h, ee 96%, 85% (over two steps); (c) TBDPSCl, imidazole, cat. DMAP, CH_2Cl_2, 0 °C to rt, 4 h, 88%; (d) Li in naphthalene, −20 °C, 3 h, 91%; (e) (i) IBX, CH_2Cl_2/DMSO, 0 °C to rt, 6 h; (ii) Phenyl acetylene, *n*-BuLi, anhyd THF, −20 °C, 3 h, 84% (over two steps); (f) (i) $4NO_2$-PhCOOH, TPP, DIAD, anhyd THF, 0 °C to rt, 12 h (ii) K_2CO_3, MeOH, 1 h, 87% (over two steps); (g) TBAF, dry THF, 0 °C to rt, 4 h, 95%; (h) 2,2-DMP, PPTS, CH_2Cl_2, 0 °C, 30 min, 91%; (i) (i) OsO4, NMO, acetone/H_2O, $NaIO_4$, 27 °C, 4 h; (ii) (*R,R*)-**I** (10 mol %), allyltributyltin, 4 Å MS, CH_2Cl_2, −20 °C, 72 h, 75% (over two steps); (j) acryloyl chloride, $^iPr_2NEt$, CH_2Cl_2, −78 °C, 2 h, 90%; (k) Grubbs' 1st generation catalyst (10 mol %), CH_2Cl_2, reflux, 12 h, 72%; (l) 4*N* HCl, MeOH, 0 °C, 30 min, 92%; (m) Pd/$CaCO_3$, H_2, quinoline, EtOAc, rt, 6 h, 90%.

alcohol **6** was protected as the TBDPS ether by treatment with TBDPS-Cl and imidazole to form **7** which was subsequently treated with Li in naphthalene to generate the primary alcohol **8**. The alcohol **8** was then oxidized with IBX to the corresponding aldehyde which was reacted with phenyl acetylene using *n*-BuLi to afford the diastereoisomeric propargyl alcohols **9** (major) and **10** (minor) (diastereoisomeric ratio 70:30). Both the compounds were separated by column chromatography. The minor alcohol **10** was subsequently converted into **9** under Mitsunobu conditions[8] by reaction with 4-nitro benzoic acid, TPP and DIAD followed by treatment with methonolic K_2CO_3. Next, the deprotection of TBDPS ether group of **9** with TBAF yielded the required diol **3** which on treatment with DMP and PPTS afforded the acetonide **11**. The 1,3-*anti* relationship in **11** was realized[9] by analysis of its ^{13}C NMR spectrum which showed that the methyl carbons resonated at δ 24.8 and the acetonide carbon at δ 100.3. Compound **11** was treated with OsO_4 and NMO in aqueous acetone and subsequently the resulting diol was treated with $NaIO_4$ to form an aldehyde which was again subjected to Maruoka asymmetric allylation using (*R*)-binol titanium complex (*R,R*)-**I** to form the homoallyl alcohol **12**. The alcohol **12** was converted into the acryloyl ester **2** which underwent the ring closing metathesis[10] using Grubbs' 1st generation catalyst to form the α,β-unsaturated lactone **13**. The deprotection of the acetonide group (4*N* HCl, MeOH) of **13** furnished the diol **14**. Finally the hydrogenation of the later one employing Lindlar's catalyst[11] yielded the target molecule,(*Z*)-cryptomoscatone D2 (**1**) whose optical and spectral properties were found to be identical to those of the natural product.[3b]



(*S*, *S*)-**I** (*R*, *R*)-**I**

In conclusion, we have developed[12] the first stereoselective total synthesis of a natural bioactive lactone (*Z*)-cryptomoscatone D2 starting from propane-1,3-diol by utilizing the Maruoka allylation, ring closing metathesis and selective reduction of the alkyne as the key steps. This strategy can be applied for the preparation of (*Z*)-isomers of several naturally occurring lactones having olefinic side chain with (*E*)-configuration and both the (*E*)- and (*Z*)-isomers can be utilized to study and compare their biological properties.

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12. The spectral data of some selected compounds are given below. *Compound* ***3***: $[\alpha]_D^{25}$ = +32.4 (*c* = 2.4, $CHCl_3$); IR: 3357, 1641, 1490, 1332 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.45–7.36 (2H, m), 7.30–7.22 (3H, m), 5.81 (1H, m), 5.19–5.08 (2H, m), 4.88 (1H, br s), 4.22 (1H, m), 3.81 (1H, br s), 2.95 (H, br s), 2.32–2.22 (2H, m), 1.93–1.87 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.2, 131.9, 128.5, 128.4, 122.8, 118.5, 89.9, 85.1, 68.3, 61.1, 42.2, 42.0; ESIMS: *m*/*z* 239 $[M+Na]^+$; Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.78; H, 7.41. Found: C, 77.62; H, 7.38.
Compound ***12***: $[\alpha]_D^{25}$ = −6.6 (*c* = 0.7, $CHCl_3$); IR: 3449, 1625, 1436, 1254 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.43–7.35 (2H, m), 7.32–7.22 (3H, m), 5.81 (1H, m), 5.27–5.01 (2H, m), 4.92 (1H, t, *J* = 7.0 Hz), 4.71 (1H, br s), 4.49 (1H, m), 3.90 (1H, m), 2.32–2.14 (2H, m), 1.99 (1H, m), 1.80 (1H, m), 1.68 (3H, s), 1.69–1.57 (2H, m), 1.35 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 134.9, 131.9, 128.5, 128.4, 123.8, 118.7, 95.2, 89.8, 85.2, 65.3, 61.4, 61.3, 42.9, 42.0, 41.7, 25.0, 24.8; ESIMS: *m*/*z* 323 $[M+Na]^+$; Anal. Calcd for $C_{19}H_{24}O_3$: C, 76.00; H, 8.00. Found: C, 76.21; H, 8.06.
Compound ***13***: $[\alpha]_D^{25}$ = +49.0 (*c* = 0.8, $CHCl_3$); IR: 1712, 1639, 1463, 1258 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.49–7.42 (2H, m), 7.38–7.29 (3H, m), 6.90 (1H, m), 6.03 (1H, d, *J* = 8.0 Hz), 4.99 (1H, t, *J* = 7.0 Hz), 4.68 (1H, m), 4.51 (1H, m), 2.42–2.32 (2H, m), 1.98–1.88 (2H, m), 1.82–1.71 (2H, m), 1.70 (3H, s), 1.39 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.2, 145.1, 131.3, 128.4, 128.3, 124.0, 121.4, 100.4, 89.5, 86.0, 74.1, 62.0, 60.0, 42.0, 37.1, 29.6, 23.4; ESIMS: *m*/*z* 349 $[M+Na]^+$; Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75. Found: C, 73.78; H, 6.71.
Compound ***1***: $[\alpha]_D^{25}$ = +119.4 (*c* = 0.1, CH_2Cl_2); IR: 3444, 1709, 1630, 1388, 1256 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.41–7.20 (5H, m), 6.90 (1H, m), 6.56 (1H, d, *J* = 11.0 Hz), 6.03 (1H, d, *J* = 9.0 Hz), 5.81 (1H, dd, *J* = 110, 9.0 Hz), 4.98 (1H, m), 4.73 (1H, m), 4.40 (1H, m), 2.40–2.32 (2H, m), 1.91–1.78 (2H, m), 1.71–1.53 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 164.5, 145.4, 136.3, 133.6, 130.8, 128.7, 128.4, 127.4, 121.3, 74.9, 65.8, 64.6, 43.1, 42.1, 29.9; ESIMS: *m*/*z* 311 $[M+Na]^+$; Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94. Found: C, 70.72; H, 6.90.