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Stereoselective syntheses of 11-α-methoxycurvularin and 11-β-methoxycurvularin

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ABSTRACT

A stereoselective synthesis of potent cytotoxic macrolides, 11-α-methoxycurvularin and 11-β-methoxycurvularin has been accomplished. The synthesis entailed Maruoka asymmetric allylation to introduce the stereocentres at C-11 and the key fragment was installed by using Grubbs cross-metathesis followed by CBS-reduction.

Macrolides, particularly lactones with medium-sized rings (10–12 membered), attracted considerable attention from medicinal chemists as well as chemical biologists because of their fascinating structural diversity and important biological activities.[1] Curvularins, which fall into this class, constitute group of structurally unique naturally occurring macrolides isolated from various *Curvularia*, *Penicillium* and *Alternaria* species are known to elicit diverse biological effects ranging from phytotoxicity to antibacterial and antifungal activity.[2] As shown in Figure 1, these macrolides encompasses a 12-membered lactone ring fused with the 1,3-dihydroxybenzene ring containing two stereocentres.

11-α-methoxycurvularin (**3**) and 11-β-methoxycurvularin (**4**), isolated from hybrid strain ME 005 derived from *Penicillium citreoviride*[3] have been found to exhibit cytotoxicity towards panel of human cancer cell lines (NCI-H460, MCF-7, and SF-268).[4] This ability is likely to have originated from the conformation of their macrocyclic ring, which mimics the M-helicity of the colchicines skeleton.[5] Further, it has also been demonstrated that stereochemical features are important for tubulin binding of these agents.[6] Structurally, these two compounds differ only in the stereochemistry at C-11 in the 12-membered lactone ring.

Recently, first total synthesis of these natural products was reported by Liang et.al.[7] which led to the revision of the spectral data of originally proposed structures (**3** and **4**). In the present Letter, we report a new route for the stereoselective synthesis of 11-α-methoxycurvularin and 11-β-methoxycurvularin featuring a Maruoka allylation to install stereocentre at C-11 and Grubbs cross-metathesis reaction for the construction of the key fragment. The most distinguished feature of this synthesis is the efficient and reagent controlled asymmetric construction of key fragment **8a** in six steps from inexpensive 1,3-propanediol in 55.8% overall yield.

As outlined in Scheme 1, disconnection of the unique 12-membered lactone ring leads to **6a**, which we envisioned could readily arise via esterification of 1,3-dimethoxyphenyl acetic acid **7** with the fragment **8a**. The key fragment **8a** in turn could be prepared from the Grubbs cross-metathesis of **10a** and **9** followed by reduction. The fragment **10a** was prepared in four-step sequence from

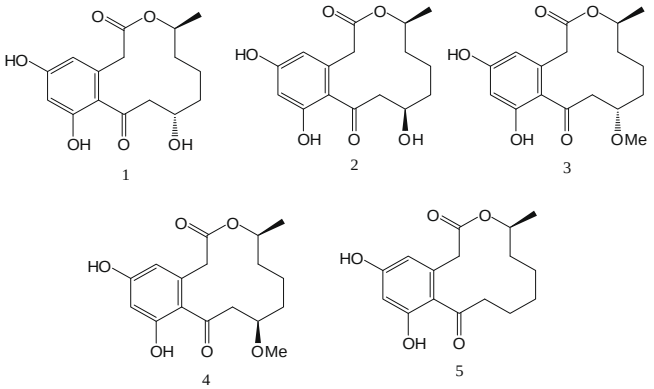

Figure 1. 11-α-Hydroxycurvularin (**1**), 11-β-hydroxycurvularin (**2**), 11-α-methoxycurvularin (**3**), 11-β-methoxycurvularin (**4**) and curvularin (**5**).

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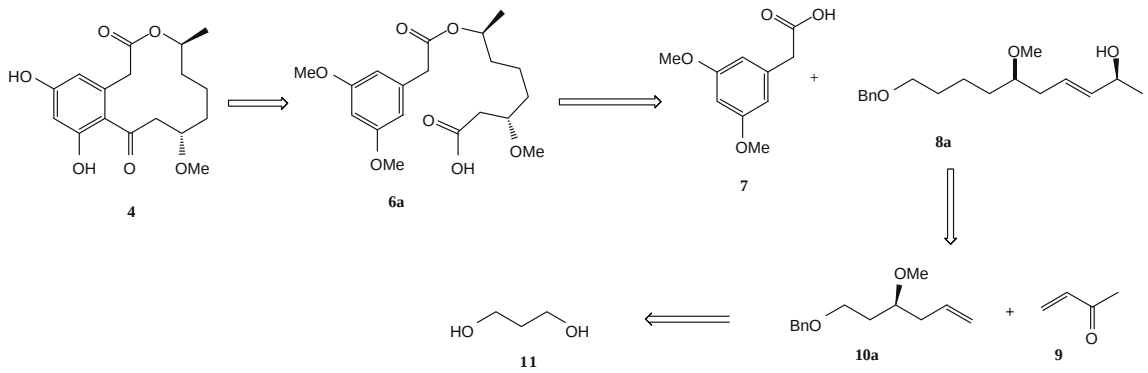


Scheme 1. Retrosynthetic analysis of the 11-α-methoxycurvularin.

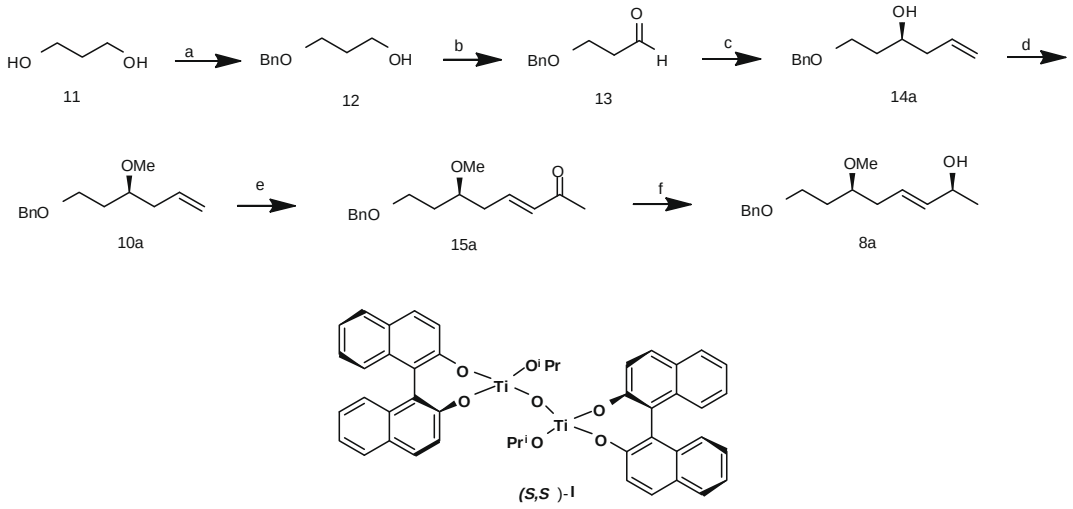
inexpensive 1,3-propanediol. The necessary variation at C-11 stereocentre would be accessible by taking advantage of synthetic transformations.

The total synthesis based on the above-mentioned plan was initiated with the known 1,3-propanediol (**11**), which was selectively protected as benzyl ether **12** using BnBr, NaH and a catalytic amount of TBAI (Scheme 2). IBX[8] oxidation of **12** gave aldehyde **13**, which was subjected to an enantioselective Maruoka allylation[9] using titanium complex (***S,S*)-I** and allyltri-*n*-butyltin to furnish the homoallylic alcohol **14a** in 86% yield with excellent enantioselectivity of 97.96% ee (determined by chiral HPLC).[10] Homoallylic alcohol **14a** was then converted to its corresponding methyl ether **10a** using MeI and NaH in THF in 96% yield (Scheme 2).

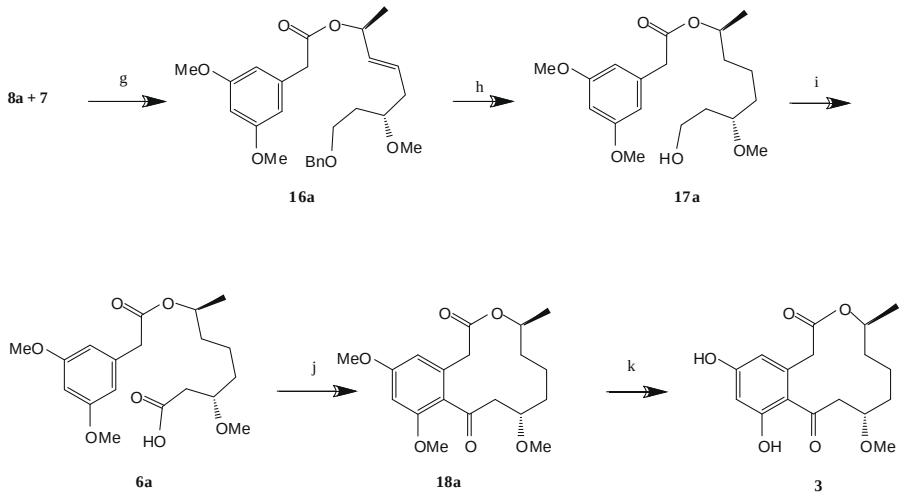
The merging of two alkenes **14a** and **9** was then investigated via olefin cross-metathesis reaction. Treatment of the fragments **10a** and methyl vinyl ketone **9** (2 equiv) with second generation Grubbs catalyst (5 mol % Grubbs II) in dichloromethane under reflux conditions provided the cross-metathesis product **15a** in 86% yield.[11] The α,β-unsaturated ketone **15a** was treated with (*R*)-(+)-2-methyl-CBS-oxazaborolidine[12] and BH_3·DMS at −40 °C to furnish allyl alcohol **8a** with an (***S***)-configuration in 90% yield with 97% de.[13]

Once the desired product **8a** was in hand, we then focused on the construction of the macrolide ring system of **3**. As shown in Scheme 3, esterification of **8a** with 3,5-dimethoxyphenyl acetic acid **7**[14] using DCC and DMAP at room temperature afforded **16a** in 96% yield. Subsequent deprotection of benzyl group and reduction of double bond were carried out by hydrogenation[15] using 10% Pd/C in ethyl acetate to furnish alcohol **17a** in 90% yield. After oxidation of **17a** using Jones' reagent (CrO_3, H_2O, H_2SO_4, acetone, 0 °C to room temperature), the desired carboxylic acid **6a** was obtained in 85% yield.[16] The macrolide **18a** was obtained by intramolecular Friedel–Crafts reaction of the carboxylic acid **6a** in a mixture of trifluoroacetic acid and trifluoroacetic acid anhydride in 42% yield (60 °C, reflux, 30 min).[17] Finally, treatment of **18a** with freshly prepared AlI_3 in benzene completed the synthesis of 11-α-methoxycurvularin (**3**)[18] in 68% yield as colourless oil.

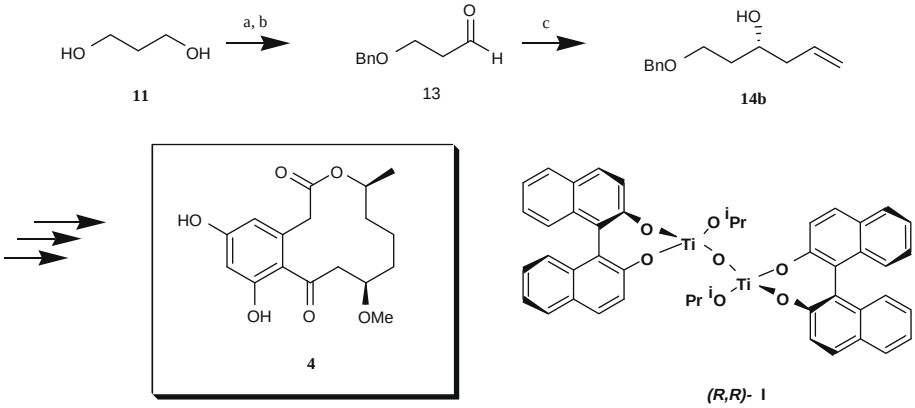
After the successful completion of synthesis of 11-α-methoxycurvularin, we also attempted the synthesis of 11-β-methoxycurvularin and achieved by using the same strategy as that used in the synthesis of 11-α-methoxycurvularin (**3**). In a similar fashion to the Schemes 2 and 3, synthesis was commenced from the commercially available 1,3-propanediol **11**. To establish the desired stereocentre, the aldehyde was subjected to Maruoka allylation[9] using titanium complex (***R,R*)-I** and allyltri-*n*-butyltin to furnish the homoallylic alcohol **14b** with required stereocentre. The rest of the synthesis (Scheme 4) consisted of repeating all the steps as in the case of 11-α-methoxycurvularin. We ultimately, reached 11-β-methoxycurvularin, with absolute configuration as shown in Figure 1 (Scheme 4). Indeed, the optical rotation of the fully synthetic 11-β-methoxycurvularin was found to be consistent with



Scheme 2. Reagents and conditions: (a) BnBr, NaH, THF, 0 °C to rt, 2 h, 95%; (b) IBX, DMSO, THF, rt, 1 h, 92%; (c) ***(S,S)*-I** (10 mol %), $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, −15 °C to 0 °C, 24 h, 86%; (d) MeI, NaH, 0 °C to rt, 3 h, 96%; (e) methyl vinyl ketone (2 equiv), 5 mol %, Grubbs second generation catalyst, CH_2Cl_2, reflux, 6 h, 86%; (f) *R*-CBS catalyst, THF, −40 °C, BH_3.DMS, 3 h, 90%, 97% de.



Scheme 3. Reagents and conditions: (g) DCC, DMAP, Et_2O, rt, 3 h, 96%; (h) H_2, 10% Pd/C, EtOAc, 10 h, 90%; (i) Jones' reagent, 0 °C, 15 min, 85%; (j) TFA, TFAA, reflux, 30 min, 42%; (k) AlI_3, $Bu_4N^+I^-$, benzene, 10 °C, 15 min, 68%.



Scheme 4. Reagents and conditions: (a) BnBr, NaH, THF, 0 °C to rt, 2 h, 95%; (b) IBX, DMSO, THF, rt, 1 h, 92%; (c) ***(R,R)*-I** (10 mol %), $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, −15 °C to 0 °C, 24 h, 86%.

the reported values. The spectral data[19] (^{1}H NMR and ^{13}C NMR) derived from each of these compounds were in full accordance with those of the assigned structures. Furthermore, chirooptical data obtained were in complete agreement with the data reported by Liang et.al.[7]

In conclusion, we have demonstrated stereoselective synthesis of both α-methoxycurvularin and β-methoxycurvularin using Maruoka allylation and Grubbs cross-metathesis as key steps. This general strategy also paves the way for synthesizing the macrolide skeletons and structurally related analogues. On the basis of the route described herein, further work towards preparation of the library of macrolide analogues for biological analysis is in progress in our laboratory.

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19. *Spectral data for selected compounds*: Compound **15a**: Light brown liquid. $[\alpha]_D^{25}$ +21.2 (*c* 0.83, $CHCl_3$); IR (KBr) ν_{max} 3460, 2925, 2857, 1698, 1678, 1454, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.20 (m, 5H), 6.84–6.69 (m, 1H), 6.12–6.02 (m, 1H), 4.47 (s, 2H), 3.60–3.44 (m, 3H), 3.33 (s, 3H), 2.54–2.30 (m, 2H), 2.23 (s, 3H), 1.85–1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): 198.13, 143.93, 138.16, 133.24, 128.19, 127.46, 76.57, 72.87, 66.34, 56.79, 36.46, 33.98, 26.62; HRMS (ESI): *m/z* 224.1542 [M^+] (calcd for $C_{16}H_{22}O_3$, 262.1569).Compound **15b**: Liquid, $[\alpha]_D^{25}$ −22.1 (*c* 0.83, $CHCl_3$). Compound **8a**: pale yellow oil, $[\alpha]_D^{25}$ +20.6 (*c* 0.83, $CHCl_3$); IR (KBr) ν_{max} 3444, 2924, 2920, 2858, 1639, 1632, 1496, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H), 5.64–5.47 (m, 2H), 4.45 (s, 2H), 4.27–4.15 (m, 1H), 3.60–3.44 (m, 2H), 3.42–3.30 (m, 1H), 3.27 (s, 3H), 2.20 (t, 2H, *J* = 5.66 Hz), 1.80–1.66 (m, 2H), 1.29–1.16 (d, 3H, *J* = 6.42 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 138.38, 136.92, 128.27, 127.57, 127.48, 126.00, 77.41, 72.92, 68.55, 66.75, 56.65, 36.05, 33.86, 23.23; HRMS (ESI): *m/z* 264.1772 [M^+] (calcd for $C_{16}H_{24}O_3$, 264.1725).Compound **8b**: Oil, $[\alpha]_D^{25}$ −13.9 (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.25 (m, 5H), 5.69–5.52 (m, 2H), 4.5 (s, 2H), 4.31–4.22 (m, 1H), 3.62–3.51 (m, 2H), 3.45–3.36 (m, 1H), 3.33(s, 3H), 2.26 (t, 2H, *J* = 5.84 Hz), 1.82–1.72 (m, 2H), 1.28–1.23 (d,3H, *J* = 6.23 Hz); ^{13}C NMR (75 MHz,$CDCl_3$): 138.48, 136.94, 128.34, 127.63, 127.53, 126.21, 77.50, 73.01, 68.76, 66.83, 56.77, 36.14, 33.96, 23.29. HRMS (ESI): *m/z* 264.1730 [M^+] (calcd for $C_{16}H_{24}O_3$, 264.1725).Compound **16a**: Colourless oil. $[\alpha]_D^{25}$ +1.7 (*c* 0.83, $CHCl_3$); IR (KBr) ν_{max} 3444, 2924, 2920, 2858, 1639, 1632, 1496, 1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.39–7.22 (m, 5H), 6.41 (d, 2H, *J* = 2.26 Hz), 6.33 (t, 1H, *J* = 2.26 Hz), 5.72–5.60 (m, 1H), 5.55–5.44 (m, 1H), 5.38–5.26 (m, 1H), 4.48 (s, 2H), 3.76 (s, 6H), 3.60–3.52 (m, 1H), 3.51 (s, 3H), 3.41–3.26 (m, 4H), 2.22 (t, 2H, *J* = 6.23 Hz), 1.79–1.63 (m, 2H), 1.29 (d, 3H, *J* = 6.42 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 170.33, 160.61, 138.36, 136.08, 131.74, 128.69, 128.16, 127.46, 127.35, 107.06, 99.00, 77.22, 72.78, 71.17, 66.61, 56.71, 55.05, 41.73, 36.27, 33.89, 20.05; HRMS (ESI): *m/z* 443.2402 [M+1]$^+$ (calcd for $C_{26}H_{35}O_6$, 443.2434).Compound **16b**: Colourless oil, $[\alpha]_D^{25}$ −23.1 (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.42–7.27 (m, 5H), 6.44 (d, 2H, *J* = 2.07 Hz), 6.36 (t, 1H, *J* = 2.26 Hz), 5.75–5.61 (m, 1H), 5.59–5.47 (m, 1H), 5.40–5.29 (m, 1H), 4.49 (s, 2H), 3.76 (s, 6H), 3.59–3.46 (m, 4H), 3.40–3.28 (m, 4H), 2.34–2.14 (m, 2H), 1.79–1.52 (m, 2H), 1.29 (d, 3H, *J* = 6.42 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 170.52, 160.75, 138.48, 136.22, 131.90, 128.80, 128.31, 127.61, 127.50, 107.23, 99.17, 77.41, 72.95, 71.40, 66.77, 56.90, 55.24, 41.89, 36.43, 34.04, 20.22. HRMS (ESI): *m/z* 443.2426 [M+1]$^+$ (calcd for $C_{26}H_{35}O_6$, 443.2434).