Total Synthesis of (*S*)-(–)-Curvularin: A Ring-Closing-Metathesis-Based Construction of the Macrocyclic Framework

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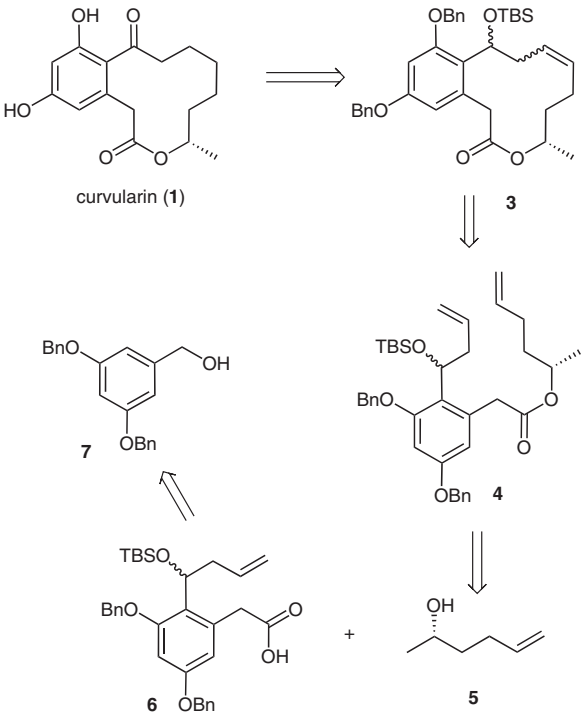
Abstract: A convergent, flexible, and efficient approach to the synthesis of curvularin is described. Key step is the high-yielding macrocyclic ring formation by ring-closing metathesis (RCM) using the Grubbs second-generation catalyst.

Key words: curvularin, cytotoxic, ring-closing metathesis, Pinnick oxidation, Wittig reaction

Curvularin belongs to a unique class of 12-membered fused resorcinylic macrolides. Curvularin (**1**)[1,2] and related compounds have been reported as metabolites produced by members of the *Curvularia*,[3,4] *Alternaria*,[5,6] and *Penicillium*[7–9] genera. 11,12-Dehydrocurvularin (**2**) co-occurs with curvularin in *Drechslera australiensis*.[10] These macrolides possess interesting biological properties, including phytotoxicity,[5] cytotoxicity toward sea urchin embryogenesis,[8] inhibition of cell division,[8] inhibition of expression of human inducible nitric oxide synthase,[11] and growth-promoting activity in farm animals.[12] The interesting 12-membered fused lactone family and their potent biological activities attracted our attention for the total synthesis.

Despite the great number of reports[13] regarding the synthesis of curvularin, no effort was made for the construction of macrocyclic framework using ring-closing metathesis. During the final step of our synthesis, Kunz et al.[13j] for the first time reported the ring-closing metathesis approach for the synthesis of curvularin and its homologues. The retrosynthetic strategy was envisaged utilizing a highly convergent coupling sequence for two intermediates **5** and **6**. The first coupling would entail esterification of an appropriately substituted aromatic acid **6** with an optically pure secondary alcohol **5** containing the single stereogenic center present in curvularin. In the concluding coupling, ring-closing metathesis of a diene **4** would lead to the desired 12-membered macrolide **3**. The substituted aromatic acid could be achieved from readily available alcohol **7**[14] through a tactical combination of functional group manipulation, that is, one-carbon Wittig homologation, sequential hydroboration–oxidation, allylation by Grignard reaction and Pinnick oxidation (Scheme 1).



Scheme 1 Retrosynthetic analysis of curvularin (**1**)

Synthesis of densely functionalized, substituted aromatic acid began with commercially available 3,5-benzyloxybenzyl alcohol **7**,[15] which was oxidized to aldehyde using PDC, followed by one-carbon Wittig olefination with incipient methylenetriphenyl phosphorane generated in situ from $MeP^+Ph_3I^-$ and *n*-BuLi in THF to provide olefin **8**. The styrene derivative **8** was subjected to the sequential hydroboration–oxidation,[16] protection of the hydroxy group as its PMB ether to provide **9** (Scheme 2). Formylation[17] was effected with $POCl_3$, DMF to give aldehyde **10**,[18] which on Grignard reaction with allylmagnesium bromide gave the hydroxyl compound **11**.[19] The alcohol was protected as its TBS ether using TBSCl[20] to

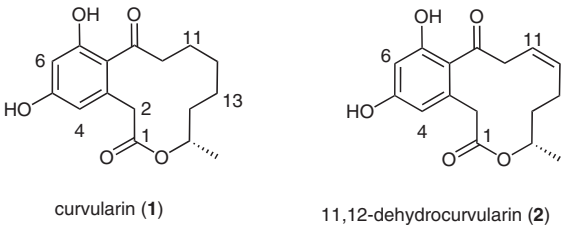


Figure 1

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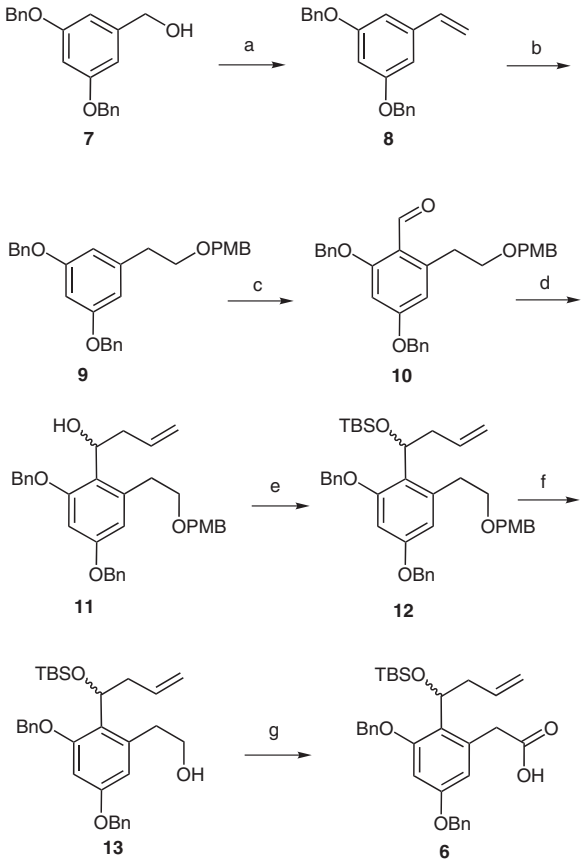
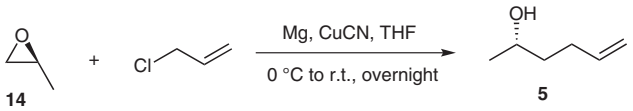


Scheme 2 *Reagents and conditions*: a) (i) PDC, MS 4 Å, CH_2Cl_2, 0 °C to r.t., 1.5 h; (ii) $P^+Ph_3MeI^-$, *n*-BuLi, THF, 0 °C, overnight, 91% (in two steps); b) (i) BH_3·DMS, THF, 0 °C, 3 h, 89%, (ii) PMB-Cl, NaH, DMF, 0 °C, 3 h, 81%; c) DMF, $POCl_3$, 0–75 °C, 2 h, 82%; d) allyl bromide, Mg, Et_2O, r.t., 3 h, 88%; e) TBSCl, imidazole, DMF, 0 °C, 4 h, 98%; f) DDQ, CH_2Cl_2, buffer (pH = 7), r.t., 1.5 h, 93%; g) (i) IBX, DMSO, THF, r.t., 1 h, 97%, (ii) $NaClO_2$, NaH_2PO_4, *t*-BuOH, THF, H_2O, 2-methyl-2-butene, 2 h, 94%.



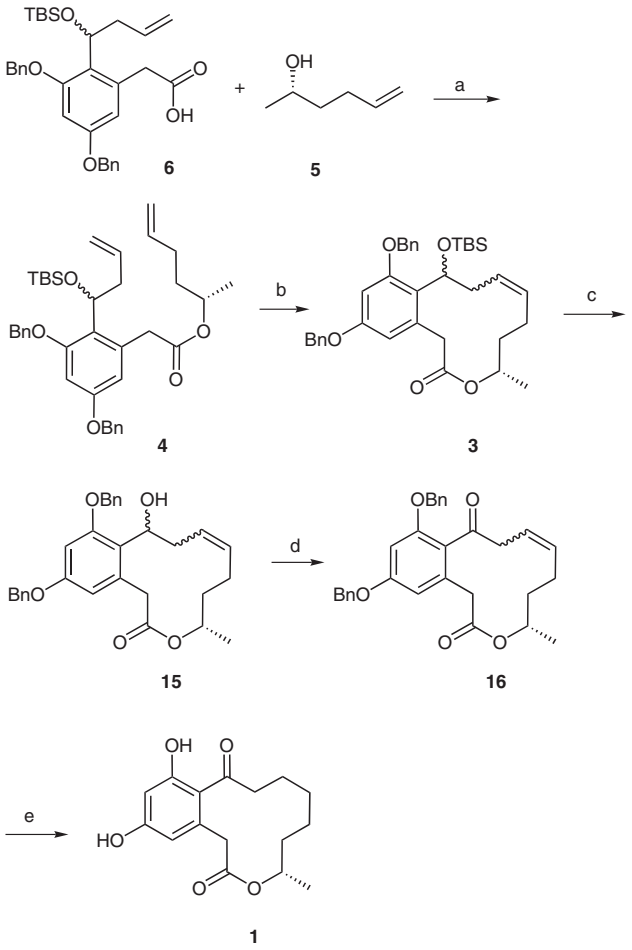
Scheme 3 Synthesis of fragment **5**

obtain **12**. Cleavage of PMB ether by treating with DDQ[21] followed by IBX oxidation of alcohol **13** afforded the corresponding aldehyde which on Pinnick[22] oxidation gave the required acid **6**.[23]

With the aromatic segment readily in hand, our next attention was to obtain the desired alcohol **5** with commercially available (*S*)-(–)-methyloxirane (**14**) as delineated in Scheme 3.

The epoxide **14** was subjected to CuCN coordinated regioselective nucleophilic opening[24] with allylmagnesium chloride to provide the alcohol **5** in 87% yield, the structure of which was adequately substantiated by spectral studies.[25]

With two subunits in hand, we proceeded to couple both intermediates **5** and **6** as described in Scheme 4. Accord-



Scheme 4: *Reagents and conditions:* a) DCC, DMAP, CH_2Cl_2, 0 °C to r.t., 2 h, 91%; b) Grubbs' second-generation catalyst, toluene, 70 °C, overnight, 83%; c) TBAF, THF, r.t., 48 h, 97%; d) IBX, DMSO, THF, r.t., 1.5 h, 98%; e) 10% Pd/C, H_2, EtOAc, r.t., 1.5 h,

ingly, the esterification was accomplished using DCC,[26] DMAP in CH_2Cl_2 to furnish **4**.[27] After having synthesized the diene derivative **4**, the stage was finally set for the construction of macrocyclic framework. Accordingly, on exposure of **4** to the Grubbs second-generation catalyst[28] in toluene at 70 °C led to the formation of an *E*/*Z* mixture of unsaturated macrocycle **3** in 83% yield. The newly generated double bond of **3** was of no consequence, as it would finally be hydrogenated in the later stage of synthetic sequence. All the spectral and elemental analysis secured the assigned structure. Macrolactone **3** was converted into hydroxyl lactone **15** by treating with TBAF (1 M) in THF at ambient temperature.

The IBX oxidation of the secondary hydroxyl functionality in **15** led to the ketolactone **16**.[29] Finally, global deprotection and concomitant reduction of the olefin with catalytic hydrogenation[13b] using 10% Pd/C afforded curvularin (**1**) in 90% yield. The spectroscopic (^1H NMR, ^{13}C NMR)[30] and analytical data were in all respects identical to those reported in the literature.[8,13j]

In conclusion, a convergent synthesis of (*S*)-curvularin has been achieved via ring-closing metathesis reaction as

the key step starting from readily available starting materials. This protocol is promising for gram-quantity synthesis of the above molecule and its analogues.

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(18) **Analytical and Spectral Data of 10**
IR (neat): 3032, 2933, 1673, 1598, 1572, 1513, 1436, 1384, 1320, 1247, 1152, 1090, 1031, 820, 754, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.21 (t, *J* = 6.6 Hz, 2 H), 3.59 (t, *J* = 6.6 Hz, 2 H), 3.67 (s, 3 H), 4.35 (s, 2 H), 4.95 (s, 2 H), 4.99 (s, 2 H), 6.40 (d, *J* = 2.2 Hz, 1 H), 6.42 (d, *J* = 2.2 Hz, 1 H), 6.73 (d, *J* = 8.6 Hz, 2 H), 7.12 (d, *J* = 8.7 Hz, 2 H), 7.22–7.32 (m, 10 H), 10.45 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.9, 55.2, 70.1, 70.2, 70.6, 72.3, 98.4, 110.1, 113.6, 117.4, 127.3, 127.6, 128.2, 128.3, 128.7, 129.2, 130.7, 135.9, 135.9, 145.3, 159.0, 163.4, 164.4, 190.3 ppm. Anal. Calcd for $C_{31}H_{30}O_5$: C, 77.16; H, 6.27. Found: C, 77.46; H, 6.21.
(19) **Analytical and Spectral Data of 11**
IR (neat): 3400, 2930, 1600, 1512, 1454, 1383, 1302, 1247, 1151, 1084, 1030, 822, 738, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.42–2.55 (m, 1 H), 2.64–2.79 (m, 1 H), 2.84–3.03 (m, 2 H), 3.51–3.67 (m, 2 H), 3.77 (s, 3 H), 4.39 (d, *J* = 11.5 Hz, 1 H), 4.45 (d, *J* = 11.6 Hz, 1 H), 4.85–4.95 (m, 2 H), 4.97 (s, 2 H), 5.01–5.02 (m, 1 H), 5.05 (s, 2 H), 5.66–5.87 (m, 1 H), 6.42 (d, *J* = 2.4 Hz, 1 H), 6.51 (d, *J* = 2.4 Hz, 1 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 7.20 (d, *J* = 8.5 Hz, 2 H), 7.33–7.41 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.6, 55.2, 70.0, 70.1, 70.4, 72.6, 99.2, 108.2, 113.7, 114.3, 116.0, 118.7, 126.3, 126.9, 127.2, 127.6, 127.8, 128.0, 128.5, 128.6, 129.3, 130.4, 132.0, 134.0, 136.7, 136.8, 138.9, 139.3, 158.1, 158.3, 159.1. Anal. Calcd for $C_{34}H_{36}O_5$: C, 77.84; H, 6.92. Found: C, 77.69; H, 6.82.
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(23) **Analytical and Spectral Data of 6**
IR (neat): 3065, 3031, 2927, 2855, 1730, 1602, 1454, 1385, 1254, 1105, 836, 756, 616 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = –0.11 (s, 3 H), 0.05 (s, 3 H), 0.88 (s, 9 H), 2.40–2.54 (m, 1 H), 2.61–2.75 (m, 1 H), 3.96 (d, *J* = 16.7 Hz, 1 H), 4.45 (d, *J* = 16.7 Hz, 1 H), 4.97–5.08 (m, 6 H), 5.55–5.58 (m, 1 H), 5.68–5.89 (m, 1 H), 6.52–6.60 (m, 2 H), 7.30–7.48 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.7, 17.9, 25.6, 34.8, 40.2, 70.0, 70.2, 77.5, 99.1, 104.2, 114.3, 114.7, 119.3, 126.9, 127.1, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 131.8, 132.4, 136.2, 136.3, 136.6, 136.9, 141.7, 154.9, 159.8, 170.4 ppm. Anal. Calcd for $C_{32}H_{40}O_5Si$: C, 72.14; H, 7.57. Found: C, 72.31; H, 7.39.
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(25) **Analytical and Spectral Data of 5**
$[\alpha]_D^{25}$ +9.89 (*c* 1.1, $CHCl_3$). IR (neat): 3435, 3019, 1598, 1403, 1215, 1118, 758, 669 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 6.2 Hz, 3 H), 1.46–1.58 (m, 2 H), 1.99 (br s, 1 H), 2.06–2.20 (m, 2 H), 3.79 (quin, *J* = 6.2 Hz, 1 H), 4.90–5.07 (m, 2 H), 5.71–5.91 (m, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.4, 30.1, 38.2, 67.4, 114.7, 138.4 ppm. Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.89; H, 12.11.
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(27) **Analytical and Spectral Data of 4**
$[\alpha]_D^{25}$ +7.86 (*c* 1.5, $CHCl_3$). IR (neat): 2929, 2371, 2361, 2341, 1730, 1604, 1383, 1257, 1146, 1068, 773, 696, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = –0.16 (s, 3 H), 0.01 (s, 3 H), 0.86 (s, 9 H), 1.22 (d, *J* = 5.7 Hz, 1.5 H), 1.25 (d, *J* = 5.7 Hz, 1.5 H), 1.47–1.79 (m, 2 H), 1.99–2.16 (m, 2 H), 2.37–2.50 (m, 1 H), 2.61–2.75 (m, 1 H), 3.70–3.88 (m, 1 H), 4.37–4.50 (m, 1 H), 4.92–5.07 (m, 9 H), 5.50–5.56 (m, 1 H), 5.67–5.91 (m, 2 H), 6.48 (d, *J* = 2.3 Hz, 1 H), 6.53 (br s, 1 H), 7.31–7.42 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.2, –4.9, 18.2, 19.9, 20.0, 25.9, 29.6, 29.7, 35.1, 69.9, 70.2, 70.5, 70.6, 98.9, 108.5, 108.6, 115.0, 116.4, 124.2, 126.9, 127.2, 127.5, 127.7, 128.0, 128.4, 128.5, 128.6, 135.9, 136.8, 137.0, 137.7, 158.2, 158.3, 170.9, 171.9 ppm. Anal. Calcd for $C_{38}H_{50}O_5Si$: C, 74.23; H, 8.20. Found: C, 74.01; H, 8.22.

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(29) **Analytical and Spectral Data of 16**
$[\alpha]_D^{25}$ +45.05 (*c* 1.0, $CHCl_3$). IR (neat): 3208, 2928, 1728, 1687, 1655, 1601, 1429, 1311, 1154, 1105, 754 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6.3 Hz, 3 H), 1.47–1.62 (m, 2 H), 1.91–1.99 (m, 1 H), 2.14–2.26 (m, 1 H), 3.05–3.55 (m, 4 H), 4.94–5.02 (m, 5 H), 5.15–5.25 (m, 1 H), 5.38–5.51 (m, 1 H), 6.46 (d, *J* = 2.1 Hz, 1 H), 6.52 (s, 1 H), 7.22–7.36 (m, 10 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.9, 30.4, 33.7, 38.0, 49.0, 70.2, 70.6, 72.4, 99.6, 109.5, 120.1, 124.3, 127.2, 127.6, 128.0, 128.1, 128.6, 134.1, 136.2, 136.5, 137.2, 156.6, 160.2, 170.8, 204.6 ppm. Anal. Calcd for $C_{30}H_{30}O_5$: C, 76.57; H, 6.43. Found: C, 76.42; H, 6.49.

(30) **Analytical and Spectral Data of 1**
$[\alpha]_D^{25}$ –31.89 (*c* 2.0, EtOH); lit[14] $[\alpha]_D^{25}$ –33.0 (*c* 2.0, EtOH). IR (Nujol): 3419, 3176, 2933, 2869, 2254, 1719, 1661, 1607, 1589, 1463, 1316, 1264, 1105, 1006, 823, 616. cm^{-1}. ^1H NMR (500 MHz, acetone-d_6,): δ = 1.13 (d, *J* = 6.3 Hz, 3 H), 1.24–1.28 (m, 2 H), 1.40–1.50 (m, 3 H), 1.52–1.57 (m, 1 H), 1.59–1.64 (m, 1 H), 1.73–1.80 (m, 1 H), 2.78 (ddd, *J* = 2.9, 9.8, 15.5 Hz, 1 H), 3.12 (ddd, *J* = 2.9, 8.7, 15.5 Hz, 1 H), 3.71 (d, *J* = 15.7 Hz, 1 H), 3.79 (d, *J* = 15.6 Hz, 1 H), 4.90–4.96 (m, 1 H), 6.36 (d, *J* = 2.2 Hz, 1 H), 6.41 (d, *J* = 2.2 Hz, 1 H), 8.82 (br s, 1 H), 9.19 (br s, 1 H) ppm. ^{13}C NMR (50 MHz, acetone-d_6): δ = 20.5, 23.4, 24.5, 27.4, 32.8, 39.6, 44.0, 72.6, 102.4, 112.2, 121.3, 136.9, 158.2, 160.1, 171.0, 206.7 ppm. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.68; H, 6.91.

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