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A cross metathesis approach to the synthesis of the C11–C23 fragment of (−)-16-normethyldictyostatin☆

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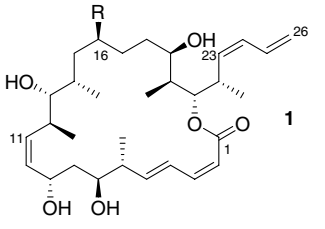
Abstract—The synthesis of the C11–C23 fragment **2** of (−)-16-normethyldictyostatin has been achieved by cross metathesis between two olefinic fragments **4** and **5** followed by a reduction of the double bond at C16–C17. Both the olefinic fragments are easily synthesized in a diastereoselective manner from the common precursor alcohol **7**.

Around half of the drugs currently in clinical use are of a natural product origin.[1,2] Among them marine macrolides have recently gained a significant importance as potent disrupters of cell cycle events. Dictyostatin (Fig. 1) is a marine-derived macrolide that was first isolated by Pettit et al. from *Spongia* sp.[3] It was demonstrated that dictyostatin inhibited the growth of human cancer cells with GI_{50} from 50 pm to 1 nM.[4] Most importantly, it retains the activity against taxol resistant cancer cells that express an active P-glycoprotein. Initial studies demonstrated that dictyostatin arrests the cell in the G2/M phase by potently inducing tubulin polymerization and suppressing microtubule dynamics, leading to an apoptosis similar to that seen in cells exposed to palcitaxel.[5] With the promising antimitotic properties of dictyostatin and other polyketides of marine origin, which include laulimalide,[6] peloruside A[7] and discodermolide,[8] natural products may lead to the development of anticancer drugs. The significant biological properties of dictyostatin coupled with its scarcity in nature and densely functionalized structure has prompted numerous studies directed towards its synthesis. So far, the total synthesis of dictyostatin has been achieved by the groups of Curran[9] and Paterson.[10] More recently, an analogue (−)-16-normethyldictyostatin was shown to be essentially equipotent to its parent compound against human ovarian carcinoma 1A9 cells and its clones 1A9PTX22.[11] In considering a strategy for the synthesis of (−)-16-normethyldictyostatin, herein we report a cross metathesis approach for the synthesis of the C11–C23 fragment.



(-)-dictyostatin, R = Me
(-)-16-normethyldictyostatin, R = H

Figure 1.

The retrosynthetic analysis revealed that the C11–C23 fragment of (−)-16-normethyldictyostatin **2** can be assembled by following a cross metathesis approach between **4** and **5**, followed by the reduction of the double bond at the C16–C17 position in **3**. Both the olefinic fragments **4** and **5** with the desired stereochemistry are easily accessible from the common precursor aldehyde **6**, which in turn can be synthesized from alcohol **7** in a diastereoselective manner in a few steps (Scheme 1).

As depicted in Scheme 2, our synthesis commenced with the addition of the titanium enolate derived from the acyloxazolidinone to aldehyde **8** (synthesized from

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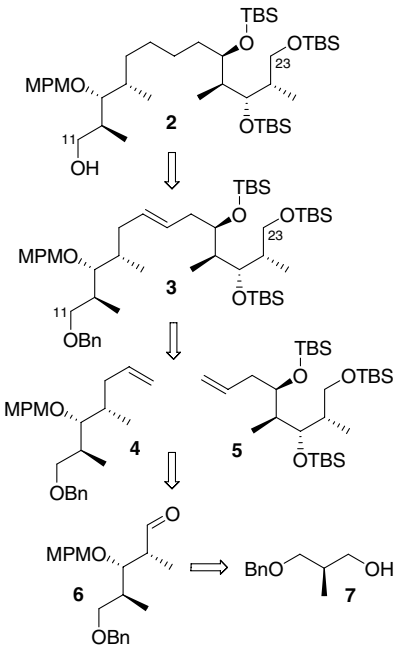
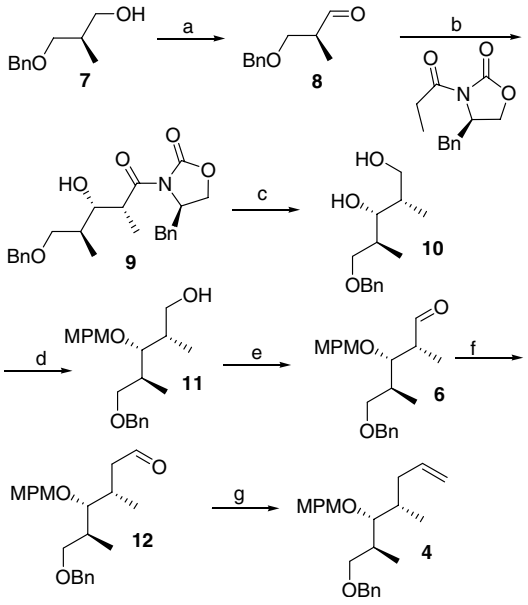


Scheme 1. Retrosynthesis of the C11–C23 fragment **2**.



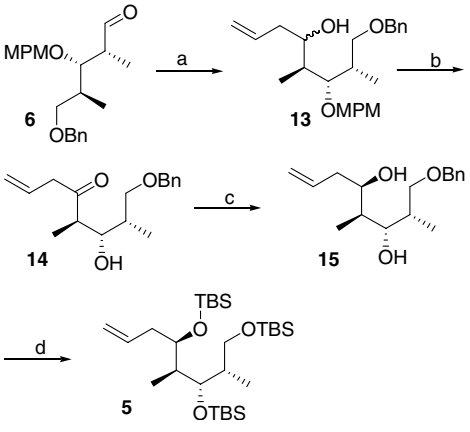
Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then **7**, Et_3N, −78 to rt, 1 h, 95%; (b) $TiCl_4$, (−)-sparteine, CH_2Cl_2, 0 °C, 1.5 h, 97%; (c) $NaBH_4$, THF/H_2O 5:1, 0 °C to rt, 12 h, 90%; (d) (i) $(OMe)_2CHC_6H_4OMe$, CSA, CH_2Cl_2, rt, 4 h, 70%; (ii) DIBAL-H, CH_2Cl_2, 0 °C, 3 h, 80%; (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 0 °C, 1 h, 91%; (f) (i) $MeOCH_2PPh_3Cl$, NaHMDS, THF, −40 to 0 °C, 2 h; (ii) PPTS, dioxane/H_2O 9:1, 50 °C, 12 h, 85%; (g) CH_3PPh_3Br, NaHMDS, Et_2O, 0 °C, 4.5 h, 90%.

alcohol **7**[12] by Swern oxidation[13]) resulting in the formation of *syn* aldol product **9**[14] in a 97% yield and excellent diastereoselectivity (⩾96%). A reductive removal of the chiral auxiliary with $NaBH_4$ in THF/H_2O[15] gave 1,3-diol **10**,[16] which was protected with 4-methoxybenzaldehyde dimethylacetal[17] followed by a selective opening of the benzylidene ring using DIBAL-H to give primary alcohol **11**.[18] Swern oxidation of **11** yielded the crucial aldehyde **6** with the required contiguous stereocentres. The two step sequential homologation[19] of aldehyde **6** via **12** followed by Wittig olefination[20] afforded fragment **4**[21] in a 76% yield over three steps.

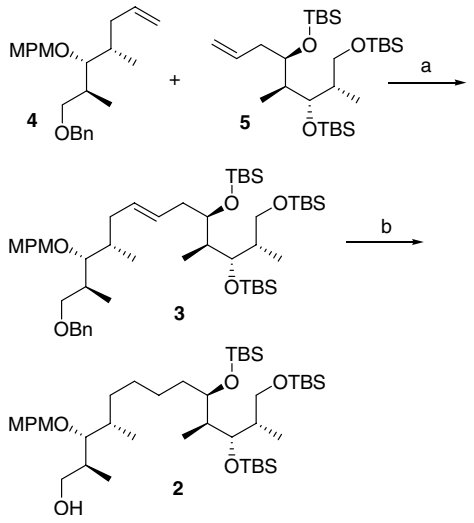
The synthesis of the olefinic fragment **5** via $SnCl_4$ mediated diastereoselective addition of allyltributyltin to aldehyde **6** gave a 70:30 ratio in favour of the undesired stereocentre at C19 of alcohol **13**.[22] This result can be explained by considering the *syn* diastereomeric (nonreinforcing) relationship between α-alkyl and β-alkoxy substituents[23] influencing the incoming nucleophile to the aldehyde in the anti-Felkin mode. The oxidation of **13** using Dess–Martin periodinane[24] followed by deprotection of the MPM group with DDQ[25] yielded the hydroxy ketone **14** in a 77% yield (Scheme 3). The reduction of **14** with DIBAL-H in THF produced 1,3-*syn* diol **15** with a high diastereoselectivity (⩾90%).[26] Finally, the benzyl group of **15** was deprotected using boron trichloride[22,27] followed by a global protection of the resulting triol with TBSOTf[28] to afford **5**[29] in a 93% yield.

With the two main fragments **4** and **5** in hand, the cross metathesis[30] (CM) strategy was adopted using Grubbs' 2nd generation catalyst (10 mol %) to yield the desired product **3**[31] in a 50% yield along with the homodimer of the starting olefinic compound **4**. Deprotection of the benzyl ether and reduction[32] of the double bond of compound **3** using excess Raney Ni under a H_2 atmosphere provided the required C11–C23 core fragment **2** in a good yield and with the required stereocentres (Scheme 4).[33]

In summary, we have developed an efficient route for the synthesis of the C11–C23 fragment of (−)-16-normethyldictyostatin using a cross metathesis approach. The most interesting feature of this synthesis is that both the olefinic partners required for cross metathesis were synthesized from a common intermediate **6** and the cross



Scheme 3. Reagents and conditions: (a) $Bu_3SnCH_2CH{=}CH_2$, $SnCl_4$, CH_2Cl_2, −90 °C, 1 h, 90%; (b) (i) DMP, CH_2Cl_2, rt, 1 h, 90%; (ii) DDQ, CH_2Cl_2/H_2O 20:1, 0 °C, 1 h, 77%; (c) DIBAL-H, THF, −78 °C, 5 h, 70%; (d) (i) BCl_3, toluene, −78 to 0 °C, 3 h, 65%; (ii) TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 1.5 h, 93%.



Scheme 4. Reagents and conditions: (a) Grubbs' II catalyst (10 mol %), rt, 36 h, 50%; (b) H_2, Raney Ni (excess), EtOH, rt, 85%.

metathesis between fragments **4** and **5** gave an appreciable yield of the desired product **3**. This flexible approach has provided us with a robust route towards the total synthesis of (−)-16-normethyldictyostatin and structural analogues for biological studies, which are currently under way in our laboratory.

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29. Spectral data for compound **5**: $[\alpha]_D^{20}$ −22.8 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 2957, 2930, 2858, 1472, 1463, 1255, 1078, 1031, 836, 773; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.88–5.79 (m, 1H), 5.06–5.02 (m, 2H), 3.72–3.63 (m, 3H), 3.42–3.38 (m, 1H), 2.33–2.29 (m, 2H), 1.83–1.68 (m, 2H), 0.93–0.86 (m, 33H), 0.07–0.00 (m, 18H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 134.73, 117.00, 73.84, 72.80, 65.01, 40.55, 39.80, 39.51, 26.22, 25.98, 25.71, 18.54, 18.32, 18.16, 14.77,

10.27, −2.95, −3.43, −3.72, −3.93, −4.41, −5.33; MS (ESI) 531 [M+H$^+$].

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31. Experimental procedure and spectral data for compound **3**: In a 10 mL round bottom flask charged with **5** (270 mg, 0.51 mmol) and **4** (375 mg, 1.02 mmol) and Grubbs' 2nd generation catalyst was added as a solid (0.051 mmol, 43.2 mg) to the flask and the dark purple reaction mixture was stirred at room temperature for 36 h. The crude reaction mixture was purified directly by flash chromatography (0.8–1% EtOAc/Hexane) to provide 222 mg (50%) of cross product **3** as a colourless oil: $[\alpha]_D^{20}$ −19.3 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 2956, 2931, 2858, 1465, 1252, 1083, 1034, 835, 773; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.33 (m, 5H), 7.20 (d, $J = 8.60$ Hz, 2H), 6.84 (d, $J = 8.60$ Hz, 2H), 5.46–5.42 (m, 2H), 4.50–4.39 (m, 4H), 3.79 (s, 3H), 3.70–3.63 (m, 3H), 3.56–3.50 (m, 2H), 3.42–3.25 (m, 2H), 2.27–1.71 (m, 8H), 1.00 (d, $J = 6.98$ Hz, 3H), 0.92–0.86 (m, 36H), 0.06–0.00 (m, 18H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.99, 138.81, 131.64, 129.05, 128.29, 127.59, 127.41, 126.36, 113.67, 83.94, 74.45, 74.06, 73.06, 72.74, 64.98, 55.23, 40.48, 40.15, 39.78, 38.31, 36.97, 26.23, 25.99, 18.53, 18.31, 18.17, 15.18, 14.87, 13.16, 10.24, −3.40, −3.68, −3.88, −4.38, −5.27; MS (ESI) 893 [M+Na$^+$]; HRMS calcd for $C_{50}H_{90}O_6NaSi_3$ [M+Na$^+$] 893.5942, found: 893.5924.
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33. Spectral data for compound **2**: $[\alpha]_D^{20}$ −15.6 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3421, 2929, 2857, 1716, 1513, 1464, 1251, 1109, 838, 666; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (d, $J = 8.60$ Hz, 2H), 6.87 (d, $J = 8.60$ Hz, 2H), 4.59 (d, $J = 10.48$ Hz, 1H), 4.48 (d, $J = 10.75$ Hz, 1H), 3.80 (s, 3H), 3.70–3.58 (m, 5H), 3.43–3.39 (m, 1H), 3.26–3.23 (m, 1H), 2.74 (br s, –OH, 1H), 1.91–1.81 (m, 2H), 1.80–1.70 (m, 2H), 1.54–1.41 (m, 2H), 1.39–1.26 (m, 6H), 0.97–0.81 (m, 39H), 0.07–0.03 (m, 18H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.30, 130.53, 129.39, 113.88, 88.53, 74.90, 74.27, 73.39, 66.68, 64.99, 55.25, 40.49, 39.83, 37.64, 36.28, 34.87, 29.69, 28.23, 26.22, 25.99, 24.56, 18.54, 18.31, 18.17, 15.49, 15.05, 14.24, 10.58, 1.01, −3.47, −3.66, −3.91, −4.29, −5.23, −5.32; MS (ESI) 783 [M$^+$]; HRMS calcd for $C_{43}H_{86}O_6Si_3$ [M$^+$] 783.5810, found: 783.5801.