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A convergent synthesis of the macrolide core of migrastatin☆

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Abstract—We describe an efficient synthesis of the 14-membered macrolide core **2** of migrastatin via key intermediate **3** employing a diastereoselective aldol condensation, Lewis acid mediated diastereoselective addition and an exclusive (*Z*)-olefination sequence. Yamaguchi esterification of the key intermediate **3** followed by ring-closing metathesis (RCM) produced macrolide **2** with high selectivity and good yield.

Around half of the drugs currently in clinical use are of natural product origin.[1,2] The synthesis of natural products of therapeutic use, in particular, anticancer agents, is an important area of research in drug discovery. Research has led to the total synthesis of several antitumor natural products such as epothilones,[3] taxol,[4] radicicol[5] and TMC-95A/B.[6] The recent entry of 16-aza-epothilone B (BMS-247550)[7] and 12,13-desoxyepothilone B (KOS-862)[8] in clinical trials has further elicited interest in this area of research. It is generally observed that in cancer chemotherapy, cytotoxic molecules inhibit tumor cell proliferation and cause cell death. Thus, the principle of targeting cell migration as an alternative strategy for the development of anticancer therapies has recently attracted considerable interest.[9] Migrastatin **1** (Fig. 1) is a novel macrolide natural product, isolated from a cultured broth of *Streptomyces* sp.Mk 929-43F$_1$ by Imoto and co-workers[10] and has the potential for metastasis suppression through its ability to inhibit tumor cell migration ($IC_{50} = 29\ \mu M$ in $4T_1$ cells).[11] The specific inhibition property of migrastatin in tumor cell migration renders it an interesting target for medicinal chemists.[12] Following their successful total synthesis of migrastatin,[13] Danishefsky and co-workers have synthesized various closely related analogues of migrastatin[14] and found that the macrolide core **2** of migrastatin exhibits a maximum biological activity of $IC_{50} = 22$ nM. The combination of novel structure and promising biological activity prompted us to explore a general strategy for the synthesis of this macrolide core and its analogues. We herein report our efforts on the synthesis of the core of migrastatin from a commercially available starting material.

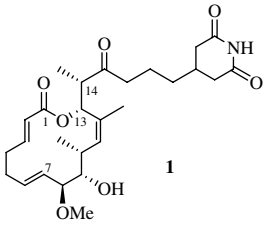

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Figure 1. Structures of migrastatin.

The retrosynthetic analysis revealed that the macrolide core can be assembled using a Yamaguchi esterification between **3** and 2,6-heptadienoic acid, followed by ring-closing metathesis (RCM) as earlier reported by Danishefsky and co-workers.[13] The key intermediate **3** can be synthesized from **4** by employing a (*Z*)-olefination reaction (Scheme 1). Compound **4** can be achieved by diastereoselective addition of vinylmagnesium bromide to aldehyde **6**, which in turn can be accessed in a diastereoselective manner in a few steps.

As depicted in Scheme 2, our synthesis commenced with dibutylboron triflate mediated Evans aldol condensation of (*S*)-benzyl oxazolidinone and acrolein to furnish the aldol product **8** in good yield and with excellent diastereoselectivity.[15] Reductive removal of the chiral

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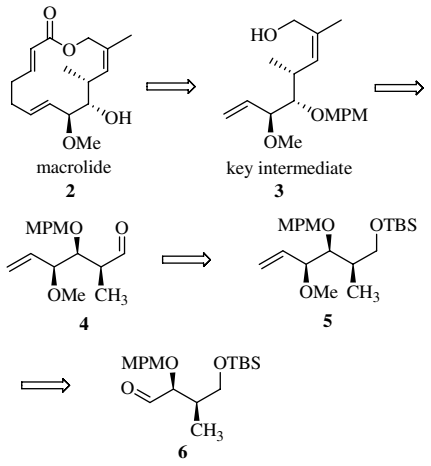
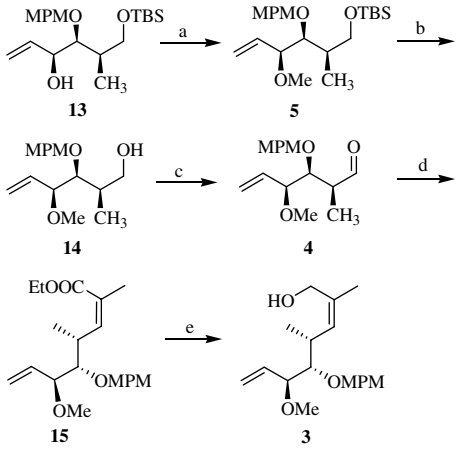


Scheme 1. Retrosynthesis of macrolide **2**.



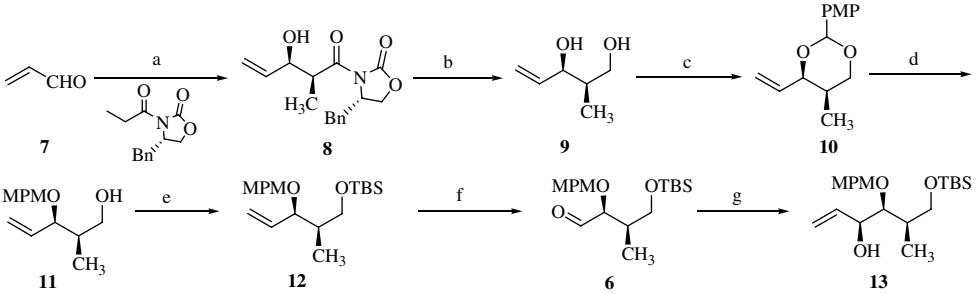
Scheme 3. Reagents and conditions: (a) MeOTf, 2,6-di-*tert*-butyl-4-methyl pyridine, CH_2Cl_2, reflux, 6 h, 62%; (b) TBAF, THF, rt, 12 h, 94%; (c) DMP, CH_2Cl_2, rt, 40 min, 85%; (d) $(PhO)_2P(O)CH(CH_3)$-$CO_2C_2H_5$, DBU/NaI, THF, −78 °C to 0 °C, 3 h, 60%; (e) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 96%.

auxiliary by lithium borohydride in THF gave **9**, which on 1,3-diol protection with 4-methoxybenzaldehyde dimethyl acetal[16] afforded the corresponding acetal **10** in high yield. At this stage, we conceived the selective opening of the acetal to furnish the primary alcohol to be crucial, since this functionality can be transformed to the aldehyde necessary for the crucial (*Z*)-olefination at a later stage. Hence, the acetal **10** was selectively opened using DIBAL-H[16] and the resulting primary alcohol was protected as its TBS ether to enable selective deprotection of this functionality in the presence of MPM protection at a later stage of the synthesis. With this intermediate in hand, we pursued the oxidative cleavage of the terminal olefin which was successfully accomplished using OsO_4–$NaIO_4$[17] in the presence of 2,6-lutidine to afford aldehyde **6** in good yield.

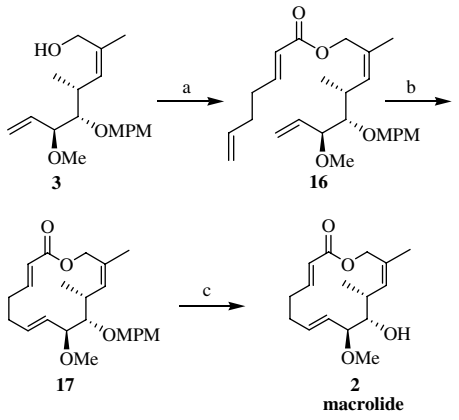
Lewis acid mediated diastereoselective addition of vinylmagnesium bromide to aldehyde **6** yielded compound **13** with high diastereoselectivity ($dr = 7{:}1$) and good yield (72%) at rt. However, at this stage due to the close R_f values we failed to isolate the pure required diastereomer. Later the required diastereomer was separated after protecting the secondary hydroxyl (Scheme 3) as its methyl ether using MeOTf.[18] Deprotection of the TBS group in **5** using TBAF followed by the oxidation of the primary alcohol with Dess–Martin periodinane[19] afforded the desired aldehyde **4** required for the (*Z*)-olefination reaction. Exclusive (*Z*)-olefination was achieved by reacting Ando's phosphonate[20] with aldehyde **4** in the presence of DBU as base. Reduction of the resulting ethyl ester **15** with DIBAL-H yielded the crucial C7–C13 core fragment **3**[21] possessing the required stereocentres.

With the key intermediate **3** in hand, the primary hydroxyl group was reacted with 2,6-heptadienoic acid following the Yamaguchi esterification protocol[22] (Scheme 4) to produce the acylated product **16** in 64% yield. The versatile ring-closing metathesis[23] (RCM) strategy using Grubbs' II generation catalyst (20 mol %, 0.5 mM) was employed on **16** to give **17**.[24] Finally, deprotection of the MPM group using DDQ[25] gave the desired (*E*,*E*,*Z*)-trienyl 14-membered macrolide **2**.[14]

In summary, we have developed an efficient synthesis of the macrolactone core of migrastatin utilizing a diastereoselective aldol condensation, an exclusive (*Z*)-olefination reaction followed by Yamaguchi esterification and ring-closing metathesis (RCM) as key steps. This flexible approach starting from an inexpensive and commercially available starting material has provided us with a robust route to generate structural analogues of



Scheme 2. Reagents and conditions: (a) *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C to 0 °C, 1 h, 84%; (b) $LiBH_4$, MeOH, THF, 0 °C, 2 h, 96%; (c) $(OMe)_2CHC_6H_4OMe$, CSA, CH_2Cl_2, rt, 12 h, 70%; (d) DIBAL-H, CH_2Cl_2, −78 °C to 0 °C, 2 h, 95%; (e) TBDMSCl, imidazole, DMF, rt, 12 h, 88%; (f) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O (3:1), rt, 3 h, 82%; (g) $H_2C{=}CHMgBr$, $MgBr_2{\cdot}OEt_2$, CH_2Cl_2, rt, 2 h, 72%.



Scheme 4. Reagents and conditions: (a) 2,6-heptadienoic acid, 2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, pyridine, toluene, rt, 24 h, 64%; (b) Grubbs' II catalyst (20 mol %), toluene (0.5 mM), reflux, 15 min, 50%; (c) DDQ, CH_2Cl_2/H_2O (20:1), rt, 30 min, 73%.

the macrolide for further biological investigation, these studies are currently underway in our laboratory.

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21. *Spectral data for compound* **3**: $[\alpha]_D^{20}$ +2.6 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3420, 2934, 1613, 1514, 1455, 1248; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 5.89–5.80 (m, 1H), 5.31–5.26 (m, 2H), 5.14 (d, $J = 10.2$ Hz, 1H), 4.62 (d, $J = 11.0$ Hz, 1H), 4.51 (d, $J = 11.0$ Hz, 1H), 4.16 (d, $J = 11.8$ Hz, 1H), 3.96 (d,

$J = 11.5$ Hz, 1H), 3.79 (s, 3H), 3.67–3.64 (m, 1H), 3.24 (s, 3H), 3.18–3.15 (m, 1H), 2.90–2.84 (m, 1H), 1.78 (d, $J =$ 1.3 Hz, 3H), 0.99 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.10, 136.02, 134.43, 131.05, 130.71, 129.60, 118.30, 113.58, 85.64, 84.12, 74.68, 61.70, 56.24, 55.17, 34.32, 21.76, 17.30; MS (ESI) 343 [M+Na$^+$]; HRMS calcd for $C_{19}H_{28}O_4Na$ [M+Na$^+$] 343.1885, found 343.1876.

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24. *Spectral data for compound* **17**: $[\alpha]_D^{20}$ +9.6 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 2927, 1726, 1612, 1513, 1247; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (d, $J = 8.6$ Hz, 2H), 6.90 (d, $J = 8.6$ Hz, 2H), 6.88–6.76 (m, 1H), 5.72 (d, $J = 15.8$ Hz, 1H), 5.60–5.52 (m, 1H), 5.38 (dd, $J = 9.7$, 1.3 Hz, 1H), 5.18 (dd, $J = 15.4$, 8.4 Hz, 1H), 4.90 (d, $J = 11.3$ Hz, 1H), 4.67 (d, $J = 15.8$ Hz, 1H), 4.59 (d, $J = 15.6$ Hz, 1H), 4.52 (d, $J = 11.3$ Hz, 1H), 3.80 (s, 3H), 3.64 (t, $J = 8.3$ Hz, 1H), 3.29 (s, 3H), 3.25–3.21 (m, 1H), 3.03–2.99 (m, 1H), 2.46–2.36 (m, 2H), 2.32–2.19 (m, 2H), 1.59 (s, 3H), 0.86 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.34, 158.95, 149.77, 131.86, 130.50, 130.06, 129.33, 126.97, 121.92, 113.61, 86.59, 84.25, 75.36, 65.48, 56.42, 55.26, 32.61, 32.34, 30.00, 29.67, 22.34, 13.51; MS (ESI) 423 [M+Na$^+$]; HRMS calcd for $C_{24}H_{32}O_5Na$ [M+Na$^+$] 423.2147, found 423.2131.
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