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Synthesis of the macrolide core of migrastatin†

Christoph Gaul[a] and Samuel J. Danishefsky[a,b,*]

[a]*Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10021, USA*

[b]*Department of Chemistry, Columbia University, Havemayer Hall, 3000 Broadway, New York, NY 10027, USA*

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Abstract—A concise and efficient synthesis of the macrolactone core of migrastatin, a new natural product with potent anticancer properties, has been achieved. The key features of our synthetic strategy encompass a Lewis acid catalyzed diene aldehyde condensation (LACDAC) to install the three contiguous stereocenters and the trisubstituted (*Z*)-double bond of migrastatin, and a (*E*)-selective ring-closing metathesis (RCM) to construct the macrocycle. © 2002 Published by Elsevier Science Ltd.

Migrastatin (**1**, Fig. 1) is a novel macrolide natural product, isolated from a cultured broth of *Streptomyces* sp. MK929-43F1 by Imoto and co-workers in 2000.[1,2] Recently, it was shown by Kosan Bioscience researchers that cultures of *Streptomyces platensis* (strain NRRL 18993) also produce migrastatin.[3]

Migrastatin displays a remarkable inhibitory effect on the migration of human tumor cells.[4] The suppression of tumor cell migration is of great interest, potentially as a model for a therapeutic approach to the treatment of tumor metastasis. Furthermore, migrastatin selectively inhibits the anchorage-independent growth of human small cell lung carcinoma Ms-1 cells.[4]

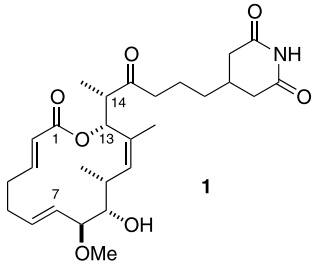

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Figure 1. Structure of migrastatin.

These potent anticancer properties render migrastatin an interesting target for total synthesis. A successful undertaking of this sort would supply adequate amounts of material to investigate its biological mode of action, and even more importantly, could provide means for preparing structural analogs of **1**. From such a focused collection of congeners might arise agents with improved biological profiles.

In 2002, the relative and absolute configuration of migrastatin was determined by X-ray crystal structure analysis of a derivative of **1**.[5] Migrastatin was revealed to be a 14-membered lactone with a glutarimide side chain. The molecule contains five stereogenic centers and three double bonds. Our general synthetic strategy toward the total synthesis of migrastatin envisaged the preparation of key fragment C7–C13 via a Lewis acid catalyzed diene aldehyde condensation (LACDAC). For the construction of the macrocycle, we envisioned ester bond formation, followed by ring-closing metathesis (RCM) to set up the C6–C7 double bond. In this letter, we describe a rapid and efficient synthesis of the macrolide core of migrastatin following these ideas. Happily, the solution for most of the stereochemical issues takes advantage of chemistry first promulgated in our laboratories 20 years earlier.

The assembly of the C7–C13 subunit began with the preparation of α-methoxy,β-siloxy aldehyde **4** (Scheme 1). Selective silylation of the primary hydroxyl group of (*S*)-3-benzyloxy-1,2-propanediol **2**,[6] methylation of the secondary alcohol, and reductive cleavage of the benzyl ether yielded **3**, which was oxidized to aldehyde **4** under Swern conditions.

Keywords: migrastatin; tumor cell migration; natural product macrolide; LACDAC; ring-closing metathesis.

* Corresponding author. Tel.: +1-212-639-5501; fax: +1-212-772-8691; e-mail: s-danishefsky@ski.mskcc.org

† We dedicate this paper on the occasion of his 65th birthday to Professor Dieter Seebach for his many contributions to science.

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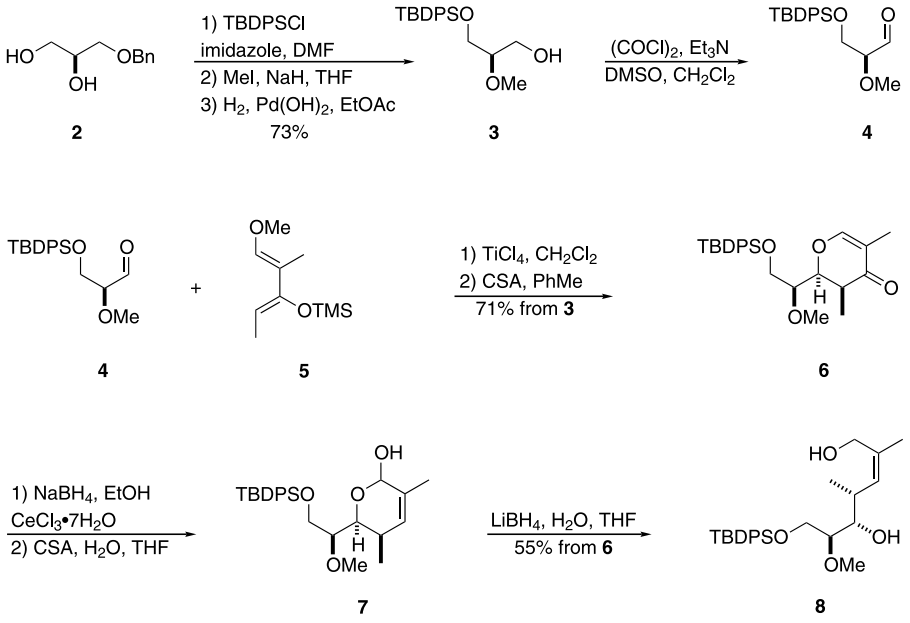


Scheme 1. Synthesis of the C7–C13 fragment **8**.

It is known that α-chelation control in Lewis acid mediated reactions of aldehydes of type **4** with carbon nucleophiles can be achieved, while competing β-chelation is suppressed by the bulky silylether protecting group.[7] Hence, reaction of aldehyde **4**[8] and diene **5** under the influence of $TiCl_4$, followed by cyclization with camphorsulfonic acid (CSA), yielded the α-chelation controlled dihydropyrone product **6** (Scheme 1).[9] The cyclocondensation allowed the construction of the three contiguous stereocenters of the macrolide and set the stage for establishing the trisubstituted (*Z*)-alkene C11–C12. Treatment of cycloadduct **6** with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ (Luche reduction)[10] led to the corresponding reduced compound, which underwent a Ferrier rearrangement in aqueous acidic THF to produce lactol **7**.[11] Reductive opening of lactol **7** with $LiBH_4$ afforded diol **8** with the desired (*Z*)-olefin in 55% overall yield from dihydropyrone **6**. We were able to obtain single crystals of compound **8** (mp 101–102°C) by crystallization from ethyl acetate. X-Ray analysis led to a decisive structural confirmation, revealing the relative configuration of the three stereogenic centers and the geometry of the double bond to be as proposed on the basis of our precedents.[12] The structure is depicted in Fig. 2.

With key intermediate **8** in hand, we explored the viability of an RCM approach (Scheme 2),[13] even before addressing issues that are associated with the incorporation of the glutarimide-containing side chain. Thus, acid chloride **9** was prepared by treatment of the copper dianion of crotonic acid with allyl bromide,[14] followed by the reaction of the resultant acid with oxalyl chloride.[15] Selective acylation of the primary hydroxyl group of **8** with acid chloride **9** proceeded smoothly in the presence of DMAP. Interestingly, use of triethylamine rather than DMAP led to an acylation product in which the C2–C3 double bond had moved out of conjugation into the β,γ-position (possibly via vinylketene formation).

Protection of the secondary hydroxyl group as a MOM ether and cleavage of the TBDPS group with HF·py afforded intermediate **11** in 79% yield. A simple two step sequence (oxidation of the primary alcohol with Dess–Martin periodinane (DMP) and Tebbe olefination[16] of the resulting aldehyde) provided access to metathesis precursor **12**. Anticipating that the risk of competitive participation of the electron-poor C2–C3 and the sterically hindered C11–C12 double bonds in the metathesis step is rather low, compound **12** was subjected to 20 mol% Grubbs Ru–dihydroimidazolylidene catalyst[17] in refluxing toluene (0.5 mM).[18] Gratifyingly, the migrastatin macrolide core **13** was generated under these conditions[19] in 50% yield as a single olefinic isomer (the desired (*E*)-congener).[20] Noteworthy, treatment of **12** with the first generation Grubbs catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$ in refluxing CH_2Cl_2 led exclusively to the dimeric product derived from cross metathesis of the terminal double bond of the acyl moiety.

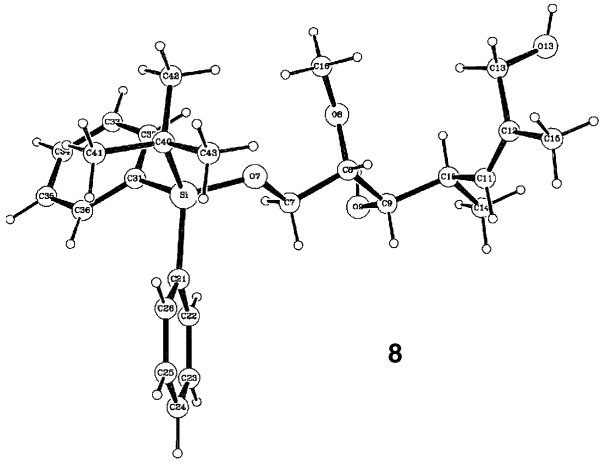
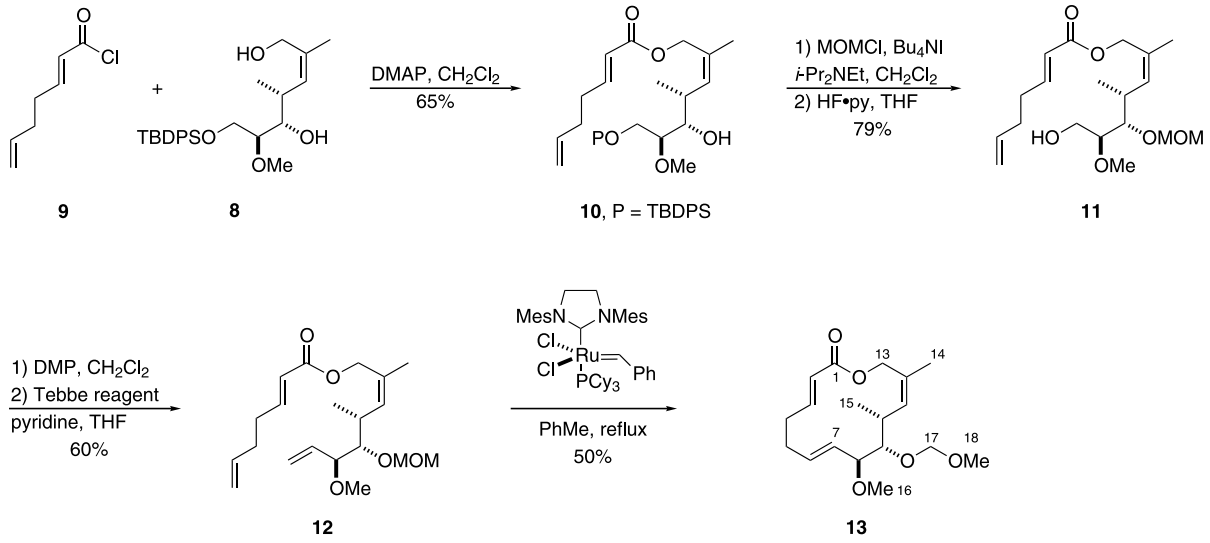


Figure 2. ORTEP plot of the X-ray crystal structure of **8**.



Scheme 2. Synthesis of the macrolide core **13** of migrastatin.

In conclusion, we have developed a direct and efficient synthesis of the macrolactone core of migrastatin utilizing a LACDAC/RCM combination as the key feature. Having demonstrated that macrocyclization can be achieved via RCM and with the versatile intermediate **8** in hand, we have now begun efforts to adapt our synthesis to accomodate incorporation of the glutarimide-containing side chain. The results of this ongoing investigation will be reported in due course.

Acknowledgements

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6. (*S*)-3-Benzyloxy-1,2-propanediol **2** is commercially available (Fluka, Aldrich), but only at a high cost. Compound **2** can be easily prepared from inexpensive starting materials. See: (a) Kitaori, K.; Furukawa, Y.; Yoshimoto, H.; Otera, J. *Tetrahedron* **1999**, *55*, 14381–14390; (b) Xiang, G.; McLaughlin, L. W. *Tetrahedron* **1998**, *54*, 375–392.
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8. The TBDPS group actually serves a dual purpose: It does not only prevent competing β-chelation, but is also a protecting group that is sufficiently stable toward acidic hydrolysis (see the use of CSA in the following transformations).
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12. Crystallographic data (excluding structural factors) for compound **8** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as deposition no. CCDC 195014.
13. The reaction sequence described in Scheme 2 was actually conducted starting from compound *ent*-**8**. For our early studies toward the total synthesis of migrastatin it was more convenient to commence the synthesis with the known aldehyde *ent*-**4** (prepared from D-mannitol: Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem. Eur. J*. **1995**, *1*, 318–333), leading to diol *ent*-**8**. Later, we addressed this problem and developed an efficient synthesis of aldehyde **4** (see Scheme 1).
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20. Spectroscopic data of **13** ($C_{18}H_{28}O_5$): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.81 (dt, 1H, $J=15.6$, 7.4, C3-H), 5.75 (d, 1H, $J=15.6$, C2-H), 5.61–5.53 (m, 2H, C6-H, C11-H), 5.15 (dd, 1H, $J=15.4$, 8.6, C7-H), 4.90 (d, 1H, $J=6.5$, C17-H), 4.75 (d, 1H, $J=6.5$, C17-H), 4.73 (d, 1H, $J=15.9$, C13-H), 4.63 (d, 1H, $J=15.9$, C13-H), 3.55 (app. t, 1H, $J=8.6$, C8-H), 3.46 (s, 3H, C18-H), 3.34 (dd, 1H, $J=8.6$, 1.7, C9-H), 3.25 (s, 3H, C16-H), 3.09–3.02 (m, 1H, C10-H), 2.48–2.15 (m, 4H, C4-H, C5-H), 1.68 (s, 3H, C14-H), 0.89 (d, 3H, $J=6.9$, C15-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.55, 149.97, 132.82, 130.33, 129.99, 127.49, 122.15, 99.05, 85.99, 83.42, 65.69, 56.51, 56.24, 32.56, 32.22, 30.21, 22.66, 13.67; MS (ESI): 347 ($[M+Na]^+$).