Communication

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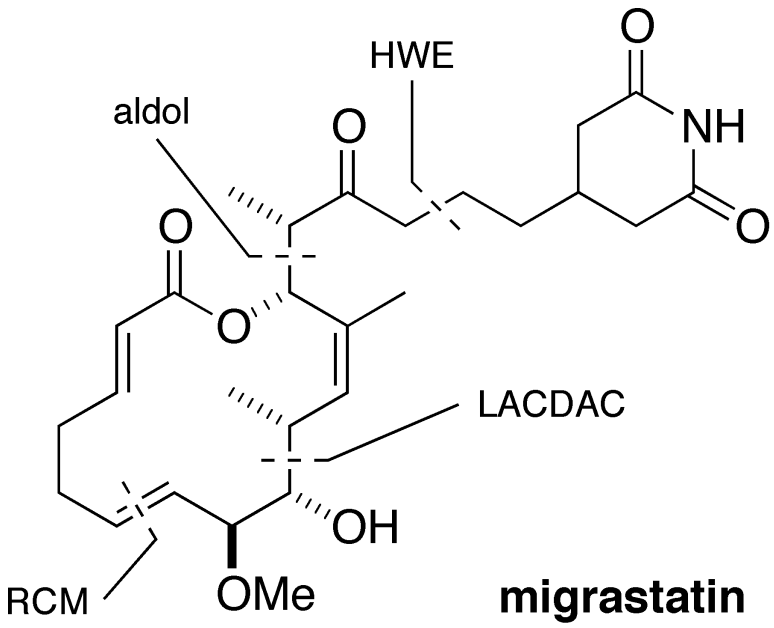

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The Total Synthesis of (+)-Migrastatin

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Apropos of our ongoing program to exploit natural products as leads for new anticancer agents, we initiated experiments directed to the total synthesis of migrastatin (**1**) (Scheme 1). This novel macrolide, recently isolated from two different strains of *Streptomyces*, inhibits human tumor cell migration.[1,2] Because in vivo cellular motility and fusion are key elements of the complex phenomenology of metastasis, small molecules which might modulate the relocation of cells with metastatic potential are of great interest, particularly if the effect could be realized in a clinical setting.[3] Minimally, such agents could be useful as in vitro probes aimed at the deconvolution of the transduction sequence which culminates in metastasis.

Given our long-term commitment to the thorough evaluation of the migrastatins, substantial amounts of material could well be necessary. Accordingly, high priority was assigned to a total synthesis that would be characterized by conciseness, workable yields, and high margins of selectivity.

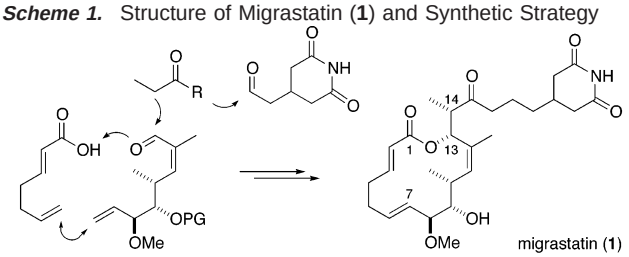
In an earlier paper, we formulated a general vision toward a synthesis of migrastatin and demonstrated that the approach could be used to reach a stripped-down core system.[4] An important component of the plan involved the use of the chelation controlled Lewis acid-catalyzed diene aldehyde cyclocondensation (LACDAC)[5] to build the stereocenters at future carbons 8, 9, and 10 as well as the otherwise potentially difficult C11−C12 (*Z*)-olefin. As described below, in a major advance directed to conciseness and convergence, we took recourse to the rather interesting β,γ-unsaturated aldehyde **5** (Scheme 2), *prepared and used here for the first time*. We note parenthetically that **5**, derived from L-tartrate, serves as a valuable bridging intermediate from the well-established chiral pool to optically defined migrastatin (vide infra).

A second element of our scheme contemplated resort to the ring-closing olefin metathesis (RCM) to fashion the migrastatin macrolactone ring from an appropriate ester precursor. The *seco* system would presumably be assembled by an acylation reaction, joining a dienoic acid to the secondary C13 alcohol. Unexpectedly, this seemingly straightforward projected union brought with it significant complications in the total synthesis relative to the core model system, wherein a corresponding acylation was conducted at a primary alcohol. Of course, the total synthesis goal also brought with it the need to accommodate new stereogenic centers at C13 and C14 and a keto function at C15, leading, ultimately, to a γ-substituted glutarimide moiety. A comprehensive solution to this multifaceted problem is provided below.

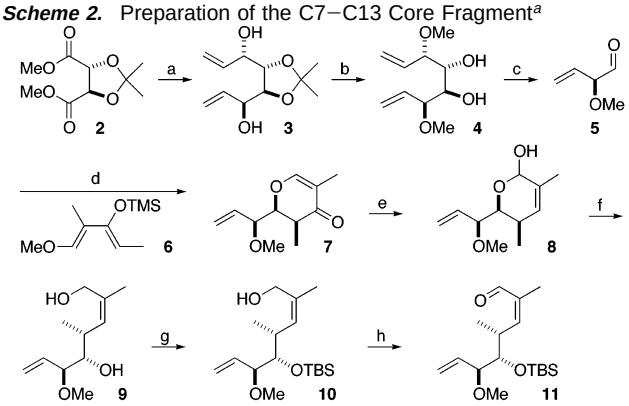
Our synthesis commenced with commercially available dimethyl 2,3-*O*-isopropylidene-l-tartrate **2** (Scheme 2). Reduction of **2**, followed by a highly diastereoselective divinylzinc addition to the in situ generated dialdehyde, produced the desired vinyl carbinol **3**.[6] Methylation of the two hydroxyl groups and removal of the acetonide protecting group led to diol **4**,[7] which was subjected to glycol cleavage to yield α-methoxy-β-vinyl aldehyde **5**. This sensitive aldehyde was used directly for the LACDAC sequence:[5] Reaction of **5** with the synergistically activated diene **6**[8] under the influence of $TiCl_4$ furnished the α-chelation controlled dihydropyrone product **7** as a single diastereoisomer.[9] The cyclocondensation had thus enabled proper presentation of the three contiguous stereocenters of the macrolide (carbons 8, 9, and 10) and set the stage for establishing the trisubstituted (*Z*)-alkene C11−C12. Luche reduction[10] of enone **7** afforded the corresponding allylic alcohol, which smoothly underwent aqueous Ferrier rearrangement[11] to give lactol **8**. Reductive opening of **8**, protection of the secondary hydroxyl group, and oxidation of the primary alcohol yielded the C7−C13 core fragment **11**.

Construction of the C13−C14 bond called for an *anti*-selective aldol-type union. We found that a recently disclosed protocol was particularly well suited for this task.[12] Propionyl oxazolidinone **12** added smoothly to the angelic-like aldehyde **11**, in the presence of $MgCl_2$ and TMSCl, thereby delivering exclusively the aldol product **13** in good yield (Scheme 3). Protection of the resulting secondary

Scheme 1. Structure of Migrastatin (**1**) and Synthetic Strategy



Scheme 2. Preparation of the C7−C13 Core Fragment[a]



[a] Reagents and conditions: (a) DIBALH, then $ZnCl_2$, $H_2C{=}CHMgBr$, PhMe, −78 °C to room temperature, 75% (ds > 90%); (b) (i) NaH, MeI, DMF, room temperature, (ii) 3 N HCl, THF, reflux, 80%; (c) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, room temperature; (d) (i) $TiCl_4$, CH_2Cl_2, −78 °C, (ii) TFA, CH_2Cl_2, room temperature, 75% from **4**; (e) (i) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, (ii) CSA, H_2O, THF, reflux; (f) $LiBH_4$, H_2O, THF, room temperature, 44% from **7**; (g) (i) Ac_2O, DMAP, pyridine, CH_2Cl_2, room temperature, (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, room temperature, (iii) K_2CO_3, H_2O, MeOH, room temperature, 90%; (h) Dess−Martin periodinane, CH_2Cl_2, room temperature.

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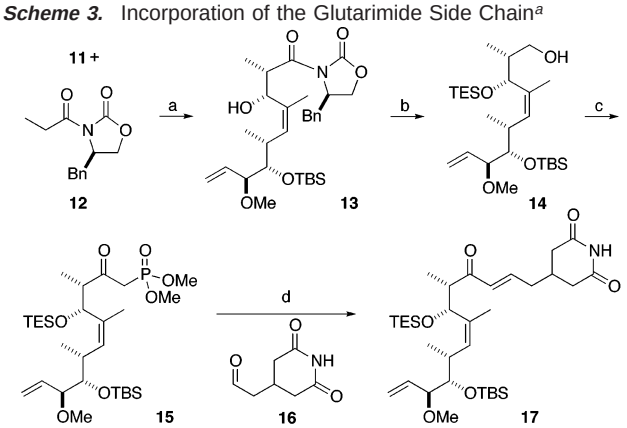
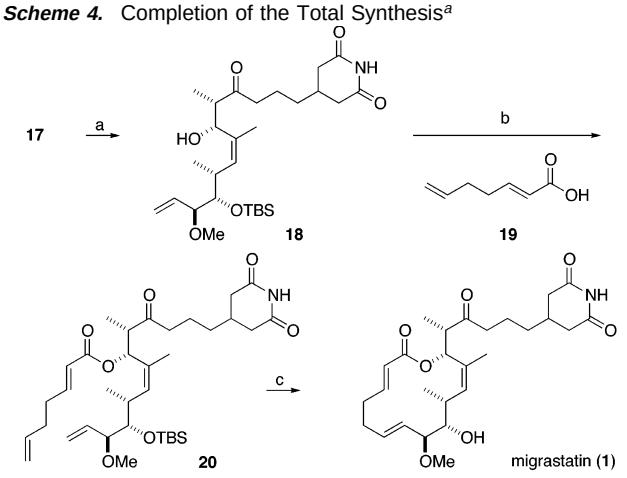
Scheme 3. Incorporation of the Glutarimide Side Chain[a]



[a] Reagents and conditions: (a) (i) $MgCl_2$, Et_3N, TMSCl, EtOAc, room temperature, (ii) TFA, MeOH, room temperature, 67% from **10**; (b) (i) TESCl, imidazole, CH_2Cl_2, room temperature, (ii) $LiBH_4$, MeOH, THF, room temperature, 83%; (c) (i) Dess−Martin periodinane, CH_2Cl_2, room temperature, (ii) methyl dimethylphosphonate, BuLi, THF, −78 °C to room temperature, (iii) Dess−Martin periodinane, CH_2Cl_2, room temperature; (d) LiCl, DBU, MeCN, room temperature, 57% from **14**.

Scheme 4. Completion of the Total Synthesis[a]



[a] Reagents and conditions: (a) (i) $[(Ph_3P)CuH]_6$, PhMe, room temperature, (ii) HOAc, H_2O, THF (3:1:1), room temperature, 82%; (b) 2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, pyridine, PhMe, room temperature, 66%; (c) (i) second generation Grubbs catalyst (20 mol %), PhMe (0.5 mM), reflux, 70%, (ii) HF·pyridine, THF, room temperature, 95%.

hydroxyl group and reductive cleavage of the chiral auxiliary furnished alcohol **14**. After considering a number of possibilities for connecting the glutarimide moiety to the backbone, we chose to start with the Masamune−Roush variant of the Horner−Wadsworth−Emmons reaction, hoping to exploit its generality and mildness.[13] Alcohol **14** was converted to β-ketophosphonate **15** via a straightforward protocol (see Scheme 3). Treatment of the phosphonate with LiCl and DBU in the presence of glutarimide aldehyde **16**[14] resulted in efficient formation of the desired enone **17**. The ability to conduct this sequence and the remaining steps of the total synthesis without protection of the glutarimide nitrogen proved to be particularly valuable.

Conjugate reduction of enone **17** with the Stryker reagent[15] and removal of the TES protecting group yielded alcohol **18** (Scheme 4). Surprisingly, the acylation of **18** with dienoic acid **19**[16] turned out to be challenging. Various coupling conditions employed led to either extensive decomposition of starting material or products containing significant amounts of β,γ-unsaturated ester. The latter presumably arose via acylation of **18** with the vinylketene derived upon activation of the acyl group of **19**. Finally, the joining was realized efficiently by a modified Yamaguchi procedure,[17] leading to RCM precursor **20**. In the event, when this *seco* compound was subjected to ring-closing metathesis under the conditions shown,[18] only the desired (*E*,*E*,*Z*)-trienyl 14-membered macrolactone was obtained. This result is in accord with our expectations that the ruthenium carbene would be initially formed at the less congested of the two terminal olefins and would then cyclize onto the most accessible of the three remaining double bonds. Finally, cleavage of the silyl ether yielded (+)-migrastatin (**1**), whose physical properties are identical to those reported for natural migrastatin.

In summary, a total synthesis of (+)-migrastatin has been accomplished for the first time. In retrospect, success was achieved by interfacing the dihydropyrone matrix chemistry, developed in our laboratories in the 1980s,[5] with the RCM methodology of Grubbs[18] and the powerful auxiliary-dominated stereochemical control of Evans.[12] The flexible approach provided above will allow us to enter the biological phase of the program.[19] Toward this end, efforts to establish an SAR profile for the migrastatins and to identify the targets of its action are currently underway.

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Supporting Information Available: Physical data for key intermediates **4**, **7**, **10**, **14**, **18**, and (+)-migrastatin (**1**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Fully synthetic migrastatin was tested in a wound healing assay, and the results confirmed the findings of Imoto et al. for natural migrastatin.[1]

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