Natural Product Synthesis

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Total Synthesis of (+)-Isomigrastatin**

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Isomigrastatin (**1**), recently isolated[1] from *S. platensis*, has been a target for total synthesis in our laboratory. It is structurally related to migrastatin (**2**).[1,2] The ability of migrastatins to retard cell migration might conceivably be exploitable in inhibiting the progression of clinically manageable tumors to less containable metastatic states. Earlier, we had described a successful inaugural total synthesis of **2**[3a,b] and how that effort had paved the way for a program in diverted total synthesis (DTS).[4b,c] DTS in turn enabled the discovery of migrastatin-inspired structures which are considerably more potent than **2** in suppressing colonization of tumors in vivo.[4]

Our interest in isomigrastatin was further enhanced by its chemical vulnerability. Thus, Shen and co-workers demonstrated[5a,b] that the ester (lactonic) linkage in **1** is rapidly hydrolyzed, thereby leading to a family of previously known biologically active systems, that is, the dorrigocins (Figure 1, see bold black and gray arrows). Moreover, as very elegantly shown, compound **1** undergoes extremely ready solvolytic and thermally induced rearrangement to migrastatin itself (Figure 1, see thin arrows). Indeed, **2** may actually not be a primary metabolite. Rather, it might well arise through a biosynthesis pathway leading to isomigrastatin (**1**), which, in turn, is transformed to **2** under isolation conditions.

Presumably, the ready transformation of **1** to **2** reflects the fact that the two *E*-configured double bonds in the macrolactone are better accommodated in the context of a 14-membered (cf. **2**) rather than a 12-membered (cf. **1**) macrolide. The pursuit of the total synthesis of compounds at the margins of viability can be conducive to the discovery of new chemistry.[6] Despite the deceptively simple allylic relationship between **1** and **2**, the present target presents a much greater challenge and the route required to reach **1** had very little homology with that used for **2**.

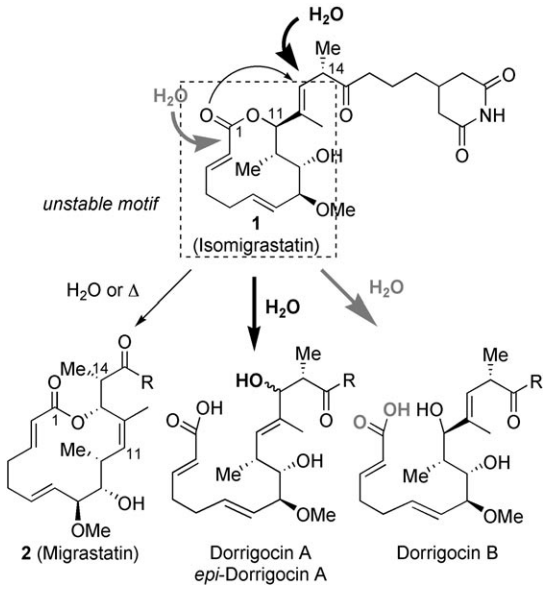

Figure 1. Isomigrastatin rearrangements (see text for details).

As the lability of **1** probably arises from the strain inherent in its *trans–trans* dienolide core, a responsive total synthesis strategy (Figure 2) would seek to delay implementation of the two *E*-configured double bonds until the latest possible stages of the effort. Another area of challenge in reaching **1** by total chemical synthesis is in the C11–C14 region. Of course, we hoped to take advantage of lessons learned from our earlier total synthesis of **2**. However, the sp^3-configurational information in migrastatin (**2**), from C11 outward, is vested solely

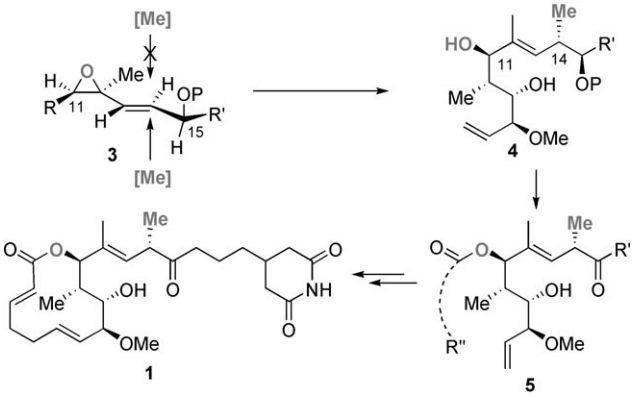

Figure 2. Synthetic strategy to **1** (P: protecting group).

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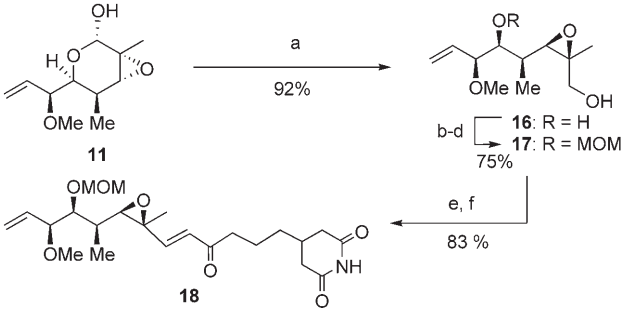
in the vicinal C13–C14 relationship. Accordingly, the migrastatin experience[3] does not inform as to the means for management of the relatively remote C11–C14 stereoconnectivity in **1** flanking the C12–C13 *E*-configured double bond. In Figure 2 is adumbrated the logic we hoped to employ in organizing the stereochemistry and functionality of the isomigrastatin, beyond C11. In the key stereo-defining step (see structure **3**), chirality information from a C11–C12 oxirane and possibly from C15 would hopefully govern the stereochemical sense of nucleophilic attack at C14, thereby establishing the C11–C14 stereoconnectivity. With its stereoguidance role (if any) accomplished, the C15 oxygen atom would eventually be converted to the ketone level (see structure **5**) in the context of paving the way for the ring-closure phase of the synthesis to generate the dienolide en route to **1**.

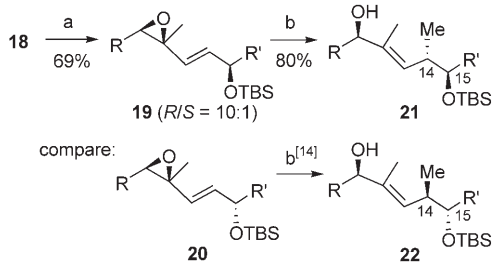
The initial steps of the venture, drawn from our migrastatin synthesis[3a] occurred smoothly (Scheme 1). LACDAC reaction of **6** and **7** led to **8** and thence to **9**. Following Luche reduction[7] and aqueous Ferrier rearrangement,[8] as shown, **10** was in hand. Epoxidation of **10** afforded the α-oxirane **11** in 43% yield (after recrystallization) along with approximately 5% of the β-oxiranyl isomer (not shown).[9] In a route featuring maximum convergence, the known Wittig reagent **13**[10] served to alkylidenate the known aldehyde **12**.[11] Hydrogenation of **14** afforded the appropriately functionalized Wittig reagent **15**.

In principle, coupling of **11** with **15** would be ultimately convergent in reaching the required series. In practice, this union could not be effected in our hands,[12] thus obliging us to proceed in a more circumspect manner. Reduction of the lactol arrangement in **11** was accomplished (Scheme 2) with lithium borohydride, leading to alcohol **16**. This compound could be converted into its C9 MOM ether, **17**. Oxidation followed by coupling with phosphorane **15** afforded the required aldehyde **18**.

Precedent from the pioneering work of Marshall et al.[13] could have been taken to suggest S_N2' attack (Scheme 3) by a first-order cyanocuprate at C14 would occur *anti* to the epoxide, regardless of the configuration of the proximal C15 OTBS group. Enone **18** was reduced with sodium borohydride to give a 1:1.2 mixture of epimeric allylic alcohols. This step was followed by protection, as shown, to afford the

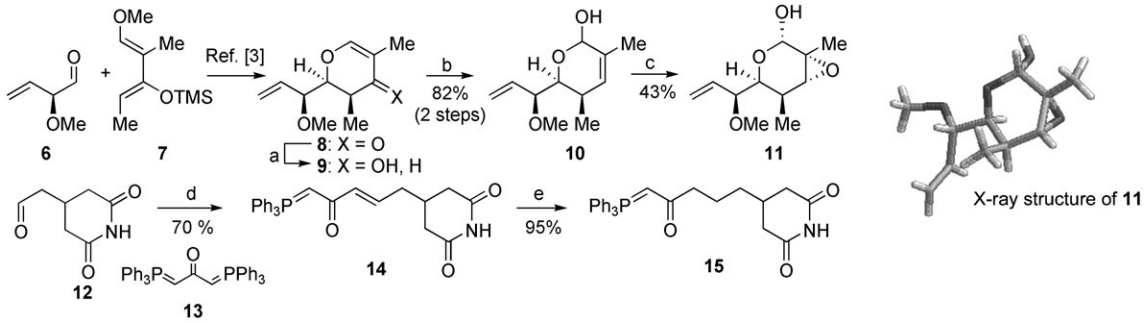


Scheme 2. Fragment coupling. Reagents and conditions: a) $LiBH_4$, THF/H_2O; b) Ac_2O, pyridine; c) MOMCl, iPr_2NEt; d) K_2CO_3, MeOH; e) $(COCl)_2$/DMSO, −78 °C, then iPr_2NEt; f) **15**, $DMSO/CHCl_3$, room temperature, 18 h. MOM: methoxymethyl.



Scheme 3. Matched–mismatched S_N2' epoxide opening. Reagents and conditions: a) 1.5 equiv (*S*)-Me-CBS, 1.1 equiv BH_3-Me_2S, then TBSCl, DMAP, Et_3N; b) MeCuCNLi, Et_2O, −20 °C→RT (see Ref. [14]). (*S*)-Me-CBS: (*S*)-methyl oxazaborolidine; TBS: *tert*-butyldimethylsilyl; DMAP: 4-dimethylaminopyridine.

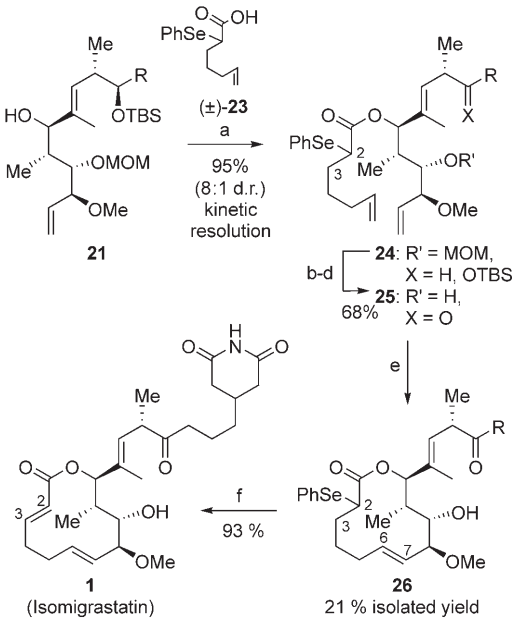
corresponding mixture of TBS ethers **19** and **20** (Scheme 3). In the event, both components of the mixture[15] underwent clean S_N2' displacement with lithium cyanomethylcuprate with high selectivity for attack *anti* to the C15 OTBS group as implied in Figure 2, conformer **3**. Thus, unlike the case of Marshall et al., the configuration at C15 is apparently a very important stereochemical marker in determining the sense of the S_N2' substitution.[13] This connectivity provided a strong incentive to reach a particular (in this case *R*) C15 epimer with stereocontrol. As indicated above, metal borohydride



Scheme 1. Fragment synthesis. Reagents and conditions: a) $NaBH_4$, $CeCl_3$-H_2O, MeOH, −20→0 °C, 2 h; b) CSA, THF/H_2O 9:1, reflux, 3 h; c) mCPBA, K_2CO_3, CH_2Cl_2, 0 °C, 24 h; d) DMSO, room temperature; e) H_2, Pd/C, THF/MeOH, 16 h. TMS: trimethylsilyl; CSA: camphorsulfonic acid; mCPBA: *m*-chloroperbenzoic acid; DMSO; dimethyl sulfoxide.

reduction drawing upon resident stereochemical biases had led to a mixture of C15 epimers. Fortunately for our purpose, the powerful reagent-controlled technology of Corey et al.[15] provided the required solution. In our case, use of the (*S*)-Me-CBS Corey catalyst[15b] in the reduction of **18** afforded **19** with good *R* selectivity (approximately 10:1).

Following addition of lithium cyanomethylcuprate to the enriched mixture, purification was possible, providing **21** in 80% yield. After extensive exploration of macroannulation strategies, it was determined that successful olefin metathesis macrocyclization hinged on the absence of a double bond at C2–C3.[16] Acylation of the C11 alcohol **21** with racemic selenoacid **23**[17] proceeded with substantial kinetic resolution, providing **24** as an approximately 8:1 mixture of inseparable C2 epimers (Scheme 4). After removal of the TBS protecting

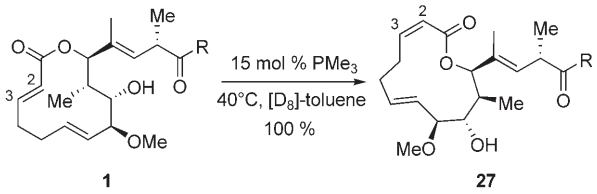


Scheme 4. Synthesis of (+)-isomigrastatin (**1**). Reagents and conditions: a) (±)-**23** (excess), EDCI, DMAP, (3 equiv each) CH_2Cl_2, 0°C; b) pyridine-HF (1.1:1 mol/mol), 40°C; c) $(COCl)_2$, DMSO, −78°C, then iPr_2NEt; d) Me_2BBr, iPr_2NEt, −78°C, then THF/$NaHCO_3$(aq); e) 20 mol% Grubbs' second-generation catalyst, toluene, 110°C, 2 min; f) mCPBA, −78°C, then iPr_2NEt, −78°C→RT. EDCI: 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide.

group, oxidation at C15, and MOM deprotection, ring-closing metathesis of **25** afforded the desired *E*-configured cyclized product **26** in 21% isolated yield, along with 36% of the C6–C7 *Z* isomer[18] (not shown). At this stage, the C2 epimers of **26** could be separated. Gratifyingly, oxidative deselenation of either C2 epimer afforded isomigrastatin (**1**) with very high selectivity for the *E* geometry at C2–C3.[19] ^1H and ^{13}C NMR spectra of synthetic **1** were identical with those obtained from a naturally derived sample of isomigrastatin.[20]

Moreover, synthetic and natural **1** exhibited identical behavior on TLC and provided the same product distribution under the hydrolytic conditions reported by Shen and co-workers,[5a,b] as monitored by LC/MS analysis. Finally, the optical rotation of synthetic **1** ($[\alpha]_D = +178$, $CHCl_3$, $c = 0.18$) agreed, within error, with that of the natural sample ($[\alpha]_D = +170$, $CHCl_3$, $c = 0.18$), confirming the absolute configuration as drawn.

Action of trimethylphosphine[21] (Scheme 5) on synthetic **1** resulted in its complete conversion into **27**, showing rigorously that, as expected, the *Z*-configured 2,3 double-



Scheme 5. Isomerization of **1** to the 2,3-*cis* isomer.

bond linkage is more stable than the *E* variant.[22] This stability order raises the question as to what factors are responsible for selective *E*-olefin formation (in **26**→**1**). We would argue that the preference for a *pro-E* over a *pro-Z syn* selenoxide transition state must be governed by minimization of vicinal nonbonded (van der Waals) interactions. Apparently, the transannular steric strain factors which eventually make the *E* isomer less stable than the *Z* isomer are not felt at this early point along the reaction coordinate.[23]

In summary, the inaugural total synthesis of the very elusive isomigrastatin, while still a work in progress from a process perspective (see the low yield of **26**), illustrates important principles in the control of sp^3-level stereochemistry and provides several pleasing examples of convergence. The properties of the broad family of migrastatins continue to stimulate research in our laboratory.

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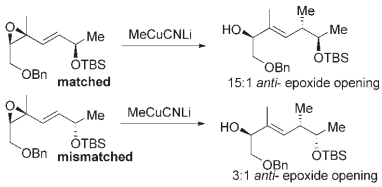
[12] There is precedent for Wittig and Horner–Emmons couplings directly with 2,3-epoxylactols: see J. E. Harvey, S. A. Raw, R. J. K. Taylor, *Org. Lett.* **2004**, *6*, 2611 – 2614. The difficulty in our case may have been due to the presence of an additional methyl group adjacent to the anomeric carbon center.

[13] a) J. A. Marshall, J. D. Trometer, B. E. Blough, T. D. Crute, *J. Org. Chem.* **1988**, *53*, 4274 – 4282; b) J. A. Marshall, B. E. Blough, *J. Org. Chem.* **1990**, *55*, 1540 – 1547; c) J. A. Marshall, B. E. Blough, *J. Org. Chem.* **1991**, *56*, 2225 – 2234. A substantial matched–mismatched effect is seen in Marshall's example (below). In the case of **20**, the mismatch is enough to overturn selectivity to a *syn* S_N2' result, possibly owing to the larger size of the glutarimide appendage (R′, Scheme 3) relative to the methyl group in Marshall's system.



[14] Compound **20** was subjected to the cuprate S_N2' reaction as a mixture with **19**, from which it was virtually inseparable. However, the corresponding products **21** and **22** were easily separated and isolated with a combined yield of 75%.

[15] a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551 – 5553; b) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092 – 2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986 – 2012; c) E. J. Corey, C. K. Bakshi, S. Shibata, C. P. Chen, V. K. Singh, *J. Am. Chem. Soc.* **1987**, *109*, 7925 – 7926.

[16] Numerous ring-closing metathesis strategies failed to give the required (2,3),(6,7)-dienolide directly, whether closure was attempted at the 2,3- or 6,7-positions. This was likely due to decomposition of this unstable motif under metathesis conditions.

[17] See the Supporting Information for preparation of **24**.

[18] Integration of crude ^{1}HNMR signals showed a 1.6:1 ratio favoring the *Z* geometry at C6–C7 for each C2 epimer. Future efforts will be directed toward enhancement of yield and selectivity. For a promising direction, see: A. Fürstner, K. Radkowski, C Wirtz, R. Goddard, C. W. Lehmann, R. Mynott, *J. Am. Chem. Soc.* **2002**, *124*, 7061 – 7069.

[19] The major C2 epimer eliminated along C2–C3 to give a separable 9:1 mixture of *E* and *Z* products. The minor C2 epimer afforded exclusively the *E* isomer.

[20] Natural material was graciously provided by B. Shen and co-workers.

[21] Previous examples of phosphine-catalyzed *E*–*Z* equilibration: a) C. Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906 – 2908; b) S. Ganguly, D. M. Roundhill, *J. Chem. Soc. Chem. Commun.* **1991**, 639 – 640.

[22] This isomerization could also be effected by excessive exposure to silica gel or weak nucleophiles such as pyridine. The silica-promoted rearrangement also afforded a substantial quantity of migrastatin (**2**).

[23] For a discussion of the Curtin–Hammet principle, which is relevant to this discussion, see: J. I. Seeman, *Pure Appl. Chem.* **1987**, *59*, 1661 – 1672.

