Communications to the Editor

Remote Effects in Macrolide Formation through Ring-Forming Olefin Metathesis: An Application to the Synthesis of Fully Active Epothilone Congeners

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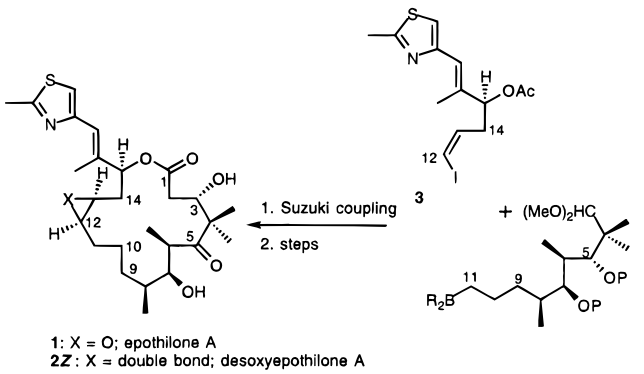
Recently, we achieved the first synthesis of epothilone A (structure **1**).[1] Aside from numerous chemical issues which must be addressed in accomplishing such a synthesis, interest in the epothilone class of compounds is further heightened by claims (thus far based solely on *in vitro* measurements) that the epothilones may constitute a useful group of anticancer agents, operating through the same mechanism of action as paclitaxel.[2] It has further been suggested, again on the basis of *in vitro* data, that the epothilones offer advantages relative to paclitaxel in terms of ease of formulation and potency toward drug resistant cell lines.

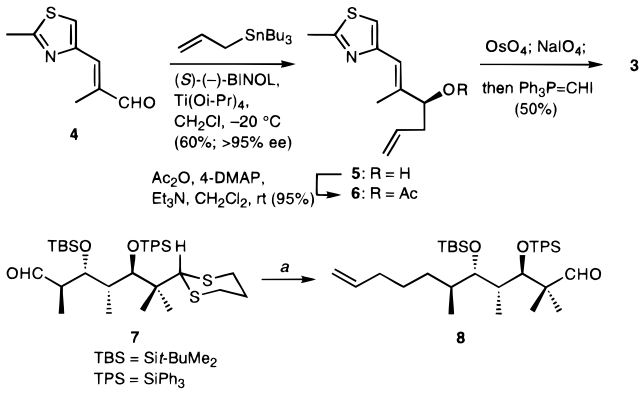
In our synthesis of epothilone A (**1**), we passed through the desoxycompound **2*Z***. We showed, for the first time, that the action of dimethyldioxirane on compound **2*Z*** results in a highly diastereoselective epoxidation, providing compound **1**. The strategy we employed to construct compound **2*Z*** provided strict control over the geometry of the C12−C13 double bond through a *B*-alkyl Suzuki coupling reaction of *cis* vinyl iodide **3** with an appropriate borane (Scheme 1).

The studies described herein focused on a different method for the construction of desoxyepothilone A (**2*Z***). In particular, we investigated the possibility of a ring-forming olefin metathesis reaction to construct the C12−C13 bond.[3] We were particularly mindful of a precedent furnished by Hoveyda et al.[3b] It was hoped that such an assembly strategy involving components of the type **6** and **8** might lead to an even more direct route to the natural series and analogs thereof. *These studies became of particular interest when it was found, surprisingly, that desoxyepothilone A (**2Z**) has the full biological activity of epothilone A as manifested through independent investigations at the level of cytotoxicity and polymerization of stable microtubules in the absence of GTP*. Herein we describe a straightforward route to reach substrates needed for olefin metathesis. We also disclose the results of these cyclizations which indicate a remarkable sensitivity to permutations of functionality and stereochemistry at centers far removed from the site of olefin metathesis. Finally, we describe some early but exciting SAR results which indicate that significant structural variances can be introduced in this series with maintenance of full biological function.

Scheme 1



Scheme 2[a]



[a] Key: (a) (i) 3-butenylmagnesium bromide, Et_2O, −78 to 0 °C (92%); (ii) thiocarbonyldiimidazole, DMAP, 95 °C; (iii) Bu_3SnH, AIBN, C_6H_6, 80 °C (83% for two steps); (iv) $(CF_3CO_2)_2IC_6H_5$, MeOH, THF; (v) *p*TSA, dioxane, H_2O, 50 °C (85% for two steps).

Our new strategy commences with aldehyde **4**, a substance available in multigram quantities.[1b,c] An important technological advance in the area was registered when it was found that subjection of aldehyde **4** to the catalytic asymmetric allylation protocol previously described by Keck leads to **5** in >95% enantiomeric excess (Scheme 2).[4] As an aside, we note that **5** was converted in two steps to the previously mentioned vinyl iodide **3**, thereby effecting a major economy in the earlier synthesis. For purposes to be described, compound **5** was simply converted to the ester **6**. The pre-acyl construct **8** was assembled from the dithiane aldehyde **7**[1a,b] in the manner indicated in Scheme 2. We thus had in hand the two subunits required to study ring forming olefin metathesis *en route* to the C12−C13 bond.

The compounds **6** and **8** were joined through a simple intermolecular aldol addition. That this reaction produced an approximately 1:1 mixture of the epimers **9** and **10** was *per se*

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(1) (a) Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.-S.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2801. (b) Meng, D.; Sorensen, E. J.; Bertinato, P.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 7998. (c) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000.

(2) See: Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomberg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567 and references therein.

(3) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* 1995, *28*, 446. (b) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943.

(4) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.

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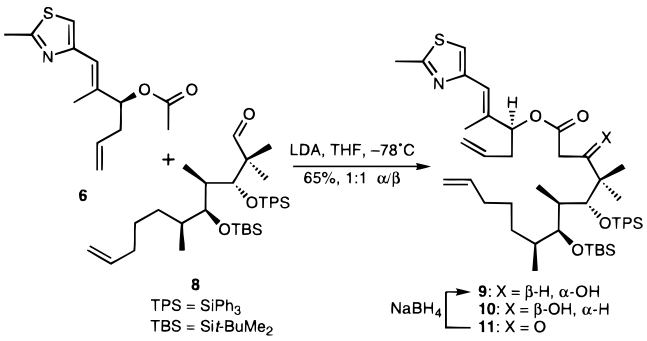
Scheme 3



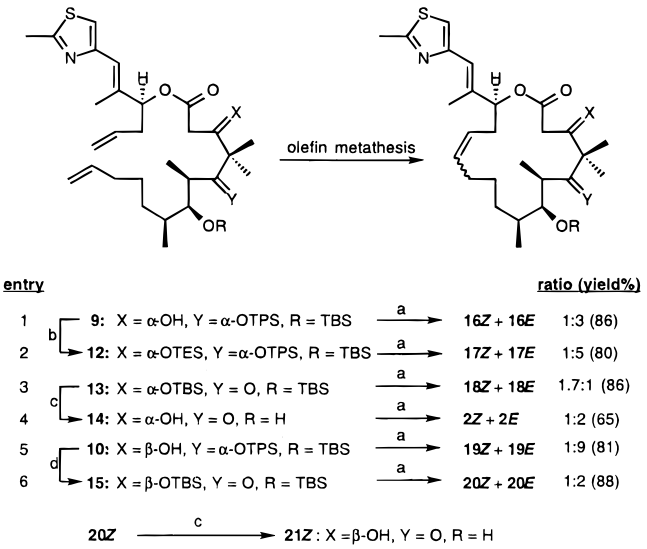
of no consequence, since the latter could be converted to the former through an oxidation/reduction sequence (i.e., **10** → **11** → **9**) (Scheme 3). Indeed, much was learned chemically and biologically from having both the 3*S* (cf. **9**) and 3*R* (cf. **10**) series available to us. From the core compounds **9** and **10**, we could easily fashion substrates **12**−**14**. We were then in a position to study the ring-forming olefin methathesis (ROM) reaction (Scheme 4).

Cyclization reactions were conducted under the conditions shown in Scheme 4 for compounds **9**, **10**, and **12**−**14**. As seen, we could readily obtain products containing the *E* C12−C13 double bond (see formation of **19*E*,*Z***). However, at this writing the highest ratio for the *Z* product is only 1.7:1 (see formation of **18***E*,*Z*). We note that, with all protecting groups identical, the proportion of *E* product increases upon changing from the 3*S* to 3*R* series (see formation of **19*E*,*Z*** and **20*E*,*Z***). Similarly, keeping C-3 and C-7 constant but permutating C-5 (see ROM substrates **13** and **14**) affords more of the *Z* olefin product (see formation of **18*E*,*Z*** and **2*E*,*Z***).

Using this chemistry, we could easily access the fully deprotected *cis*-desoxyepothilone A (**2*Z***). Of course, this work constitutes a second synthesis of **2*Z*** and a formal total synthesis of **1**.[5] It is noteworthy that the concise route to enantiomerically pure vinyl iodide **3** (see Scheme 2) renders our initial approach to **2*Z*** more practical. Nevertheless, the ROM chemistry described herein provides an eminently more workable route to *trans*-desoxyepothilone A (***2E***). *Remarkably, compound (**2E**) is fully active as measured by cytotoxicity and microtubule assays. Perhaps equally surprising, biological activity is abrogated in the 3R compounds **21Z** and 3-epi-epothilone A (3-epi-**1**).*[6]

(5) It has been brought to our attention through the popular media that another total synthesis of epothilone A has been subsequently completed utilizing ring-closing olefin metathesis. Nicolaou, K. C.; et al. *Angew. Chem., Int. Ed. Engl.* **1997**, *37*, 166.

Scheme 4[a]



[a] Key: (a) $RuBnCl_2(PCy_3)_2$ (50 mol %), C_6H_6, 0.001 M, rt, 24 h; (b) TESCl, imidazole, DMF, (80%); (c) pyridine hydrofluoride, THF, rt; (d) (i) pyridine hydrofluoride, pyridine, THF, rt, (93%); (ii) TBSOTf, 2,6-lutidine, −35 °C, (95%); (iii) Dess−Martin periodinane, (87%) (TBS = *tert*-butyldimethylsilyl; TPS = triphenylsilyl; TES = triethylsilyl).

In summary, a route to (*E*)- and (*Z*)-desoxyepothilones using ROM technology has been accomplished. Through this and related methodology to be described soon, highly biologically active congeners have been obtained, and a total synthesis driven mapping of the SAR of epothilones is well underway.

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Supporting Information Available: Preparation of substrates for olefin methathesis (**9, 10** and **12**−**15**) and compounds **21*Z*** and 3-*epi*-epothilone A and relevant biological data (IC_{50} values) as well as all relevant spectral data for compounds **2**−**21** (43 pages). See any current masthead page for ordering and Internet access instructions.

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(6) The compound 3-*epi*-epothilone A was produced by treatment of 3-*epi*-desoxyepothlone A (**21*Z***) with dimethyldioxirane at −35 °C.