ORGANIC LETTERS

1999
Vol. 1, No. 6
913−916

Phorboxazole Synthetic Studies. 2. Construction of a C(20–28) Subtarget, a Further Extension of the Petasis–Ferrier Rearrangement

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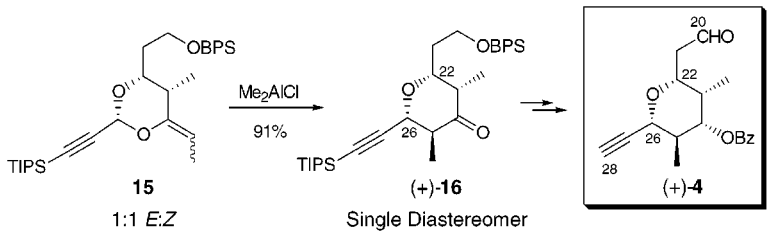
Received July 19, 1999

ABSTRACT



In this, the second of two Letters, we describe the efficient assembly of (+)-4, a C(20–28) subtarget for the total synthesis of phorboxazoles A (1) and B (2). The synthesis was achieved in 12 linear steps (20% overall yield) via Petasis–Ferrier rearrangement of an *E/Z* mixture of trisubstituted enol ethers (15) to assemble the C(22–26) *cis*-tetrahydropyran. A mechanism for the observed diastereoconvergence of 15 is proposed. In addition, a new tactic for the synthesis of enol ethers (e.g., 15) based on the elegant work of Julia is described.

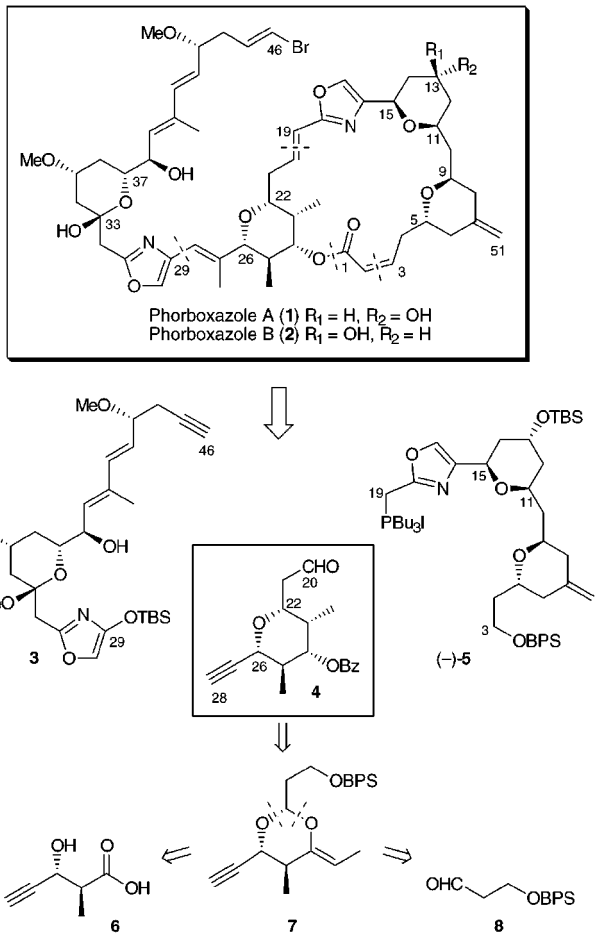
Phorboxazoles A (**1**) and B (**2**), rare marine macrolides comprised of three tetrahydropyrans, two oxazoles, and a 21-membered macrolactone, display extraordinary cancer cell growth inhibition, and as such have attracted considerable interest in the synthetic community.[1−3] In the preceding Letter,[4] we outlined a strategy for the construction of **1** and **2**, in conjunction with an efficient synthesis of the C(3−19) subtarget (−)-**5**, exploiting an extension of the Petasis−Ferrier rearrangement[5,6] to assemble the C(11−15) tetrahydropyran ring (Scheme 1). The success of the Petasis−Ferrier rearrangement encouraged us to explore a similar tactic for construction of the fully substituted C(22−26) tetrahydropyran moiety present in the C(20−28) subtarget **4**.

Our modification of the Petasis−Ferrier rearrangement permits direct conversion of a 4-alkylidenyl-1,3-dioxane (**9**)- to the corresponding *cis*-tetrahydropyranone (**10**) when Me_2-AlCl is employed as the Lewis acid. This protocol avoids the Meerwein−Ponndorf−Verley reduction of the initially derived tetrahydropyranone by *i*-Bu_3Al, as observed by Petasis. To extend the Petasis−Ferrier rearrangement to assemble a fully substituted tetrahydropyran such as **4** (Scheme 1), trisubstituted enol ether **7** would be required. No information on the stereochemical outcome for trisubstituted enol ethers however was available. To explore this stereochemical issue, we prepared and rearranged (−)-**11**,[7] a model of enol ether **7** (Scheme 2).

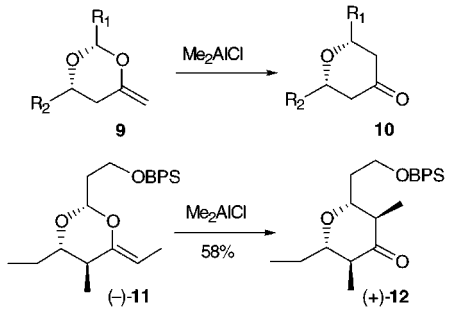
(1) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126.
(2) (a) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422. (b) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879.
(3) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597. For references to other synthetic efforts, see ref 4.
(4) Smith, A. B., III.; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909.
(5) Petasis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1996**, *36*, 141.
(6) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779.

10.1021/ol990829m CCC: $18.00
Published on Web 08/31/1999

Scheme 1

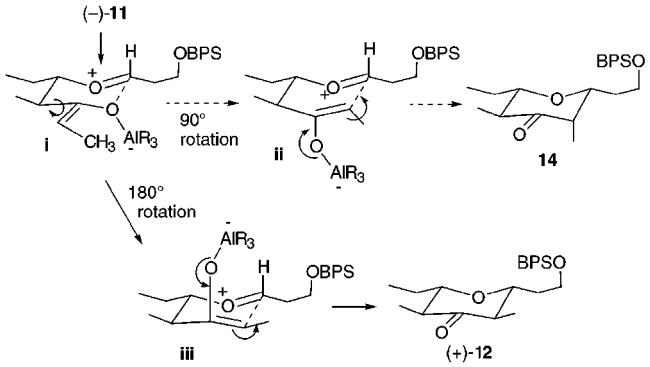


Scheme 2



Although Petasis suggests the rearrangement proceeds via a chair conformation, we rationalized that a least motion mechanism involving a boat conformation (**i** → **ii**, Scheme 3) held promise of delivering the required stereochemical outcome (e.g., **14**). In the event, however, Petasis−Ferrier rearrangement of (−)-**11** furnished only the all equatorial tetrahydropyran (+)-**12** (58% unoptimized); the configuration of (+)-**12** was secured via 1D-NOE experiments.[8] Presumably, Lewis acid complexation at the enol ether oxygen of (−)-**11** triggers ring opening, reversibly liberating the

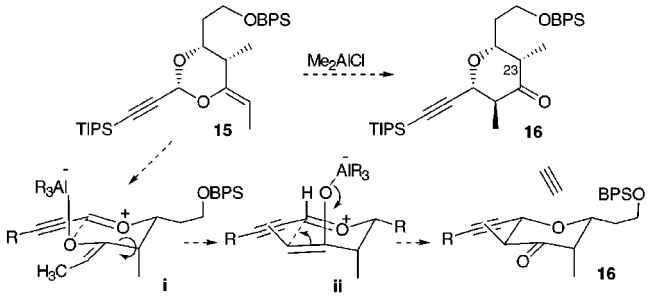
Scheme 3



aluminum enolate; rotation of the enolate by 180° (**i** → **iii**) and reclosure via a chair conformation would afford (+)-**12**.

Armed with this insight, we envisioned the oxygen-transposed enol ether **15** to be an appropriate substrate for the construction of **4** (Scheme 4). Rearrangement involving

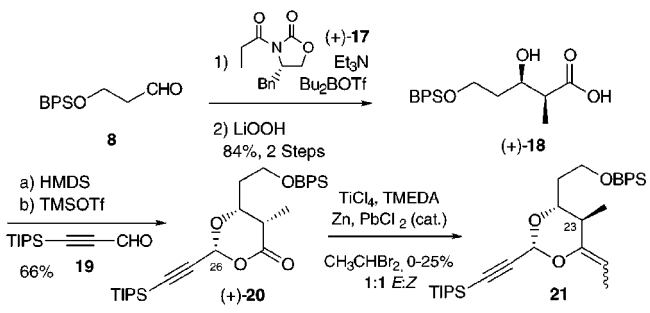
Scheme 4



bond rotation of 180° would lead via a chair conformation to **16** possessing the requisite axial methyl at C(23).

Assembly of **15** began with aldol condensation of the boron enolate derived from Evans oxazolidinone (+)-**17**[9] with aldehyde **8**;[7c] hydrolysis (LiOH, H_2O_2) afforded β-hydroxy acid (+)-**18**[10] in 84% yield for the two steps (Scheme 5). Bis-silylation with hexamethyldisilazane (HMDS),[11] followed by TMSOTf[12]-promoted condensation with alde-

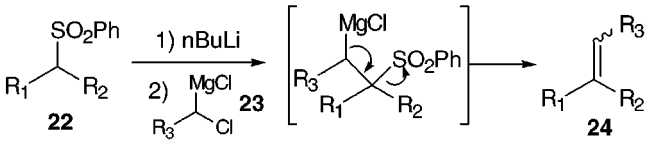
Scheme 5



hyde **19**[13] furnished dioxanone (+)-**20**[10] in 66% yield, along with 19% of the C(26) epimer, the latter readily removed by flash chromatography.[14] The configuration of (+)-**20** was again determined by 1D-NOE experiments. Unfortunately, ethylidenation via the Takai protocol[7d] failed to yield **15**, furnishing instead the C(23) epimeric enol ether as a *E*/*Z* mixture (**21**). Related olefination strategies were equally unsuccessful.[15]

Undaunted, we explored the Julia protocol for olefination of sulfones with electrophilic carbenoids.[16] This protocol calls for α-alkylation of a sulfone (**22a**) with α-halo Grignard reagents (**23**); subsequent elimination furnishes the alkene (**24a**; Scheme 6). We reasoned that a similar reaction with

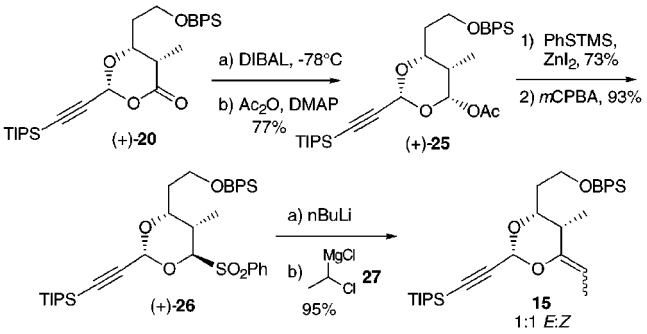
Scheme 6



a) $R_1 = R_2 =$ alkyl
b) $R_1 =$ alkyl; $R_2 =$ OR

sulfone **22b** (R_2 = OR) would afford **24b**, contingent on preferential expulsion of phenyl sulfinate over the alkoxide.[17]

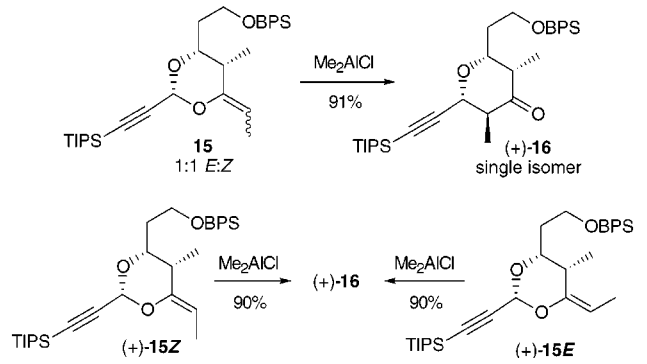
Scheme 7



Toward this end, reduction of dioxanone (+)-**20** (DIBAL) followed by in situ acylation of the alkoxide (Ac_2O, DMAP) afforded acetal (+)-**25**[10] (Scheme 7).[18] Treatment of (+)-**25** with PhSTMS in the presence of ZnI_2[19] then led to the corresponding sulfide which upon oxidation (*m*CPBA) generated sulfone (+)-**26**[10] in 68% yield for the two steps. Deprotonation of (+)-**26** with *n*-BuLi and exposure to Grignard **27**[16,20] furnished the desired enol ether **15** in excellent yield (95%), albeit with no *E*/*Z* selectivity. Careful flash chromatography permitted separation of the *E* and *Z* diastereomers; again the stereochemistry was secured by NOE experiments.

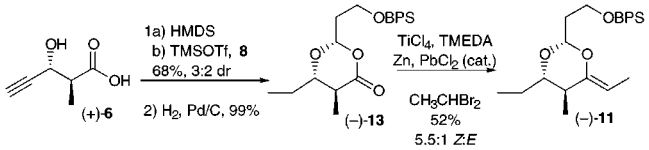
To our delight, treatment of the 1:1 mixture of enol ethers (**15**) with Me_2AlCl afforded *only the desired tetrahydropyran* (+)-**16**[10,21] in a 91% yield (Scheme 8). The individual diastereomers also rearranged to tetrahydropyran (+)-**16** in similarly high yields.

Scheme 8



Although (+)-**15*Z*** presumably rearranges through a chair transition state as anticipated in Scheme 3, formation of (+)-**16** from (+)-**15*E*** implies that the unfavorable 1,3-diaxial interactions in transition state **ii** (Scheme 9) preclude a chair

(7) (a) Enol ether (−)-**11** was prepared by condensation of β-hydroxy acid (+)-**6**[7b] and aldehyde **8**,[7c] hydrogenation of the resultant dioxanone, and Takai ethylidenation.[7d] (b) (+)-**6** was prepared according to Oppolzer's protocol: Oppolzer, W.; Lienard, P. *Tetrahedron Lett.* **1993**, *34*, 4321. (c) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553. (d) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410.



(8) That **12** is not the result of epimerization of the axial methyl group was demonstrated via exposure of **14** to the reaction conditions; no epimerization occurred.

(9) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(10) The structure assigned to each new compound is in accord with its infrared, 500 MHz ^{1}H NMR, and 125 MHz ^{13}C NMR spectra, as well as appropriate ion identification by high-resolution mass spectrometry.

(11) (a) Harada, T.; Yoshida, T.; Kagamihara, Y.; Oku, A. *J. Chem. Soc, Chem. Commun.* **1993**, 1367. (b) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448.

(12) Initial difficulties in the scale-up of this reaction suggested that TfOH is the actual catalyst. Advantageous water, more pronounced on smaller scale, may generate TfOH in situ from TMSOTf (as well as TMS_2O). Large-scale reactions do not proceed until catalytic TfOH (2−4 mol %) is added. Yields and diastereoselectivity were similar with the added TfOH.

(13) (a) Lange, T.; van Loon, J.-D.; Tykwinski, R. R.; Schreiber, M.; Diederich, F. *Synthesis*, **1996**, 537. (b) For an improved general route to α,β-acetylenic aldehydes, see: Journet, M.; Cai, D.; DiMichele, L. M.; Larsen, R. D. *Tetrahedron Lett.* **1998**, *39*, 6427.

(14) Although all attempts to epimerize the undesired C(26) isomer to (+)-**20** were unsuccessful (e.g., with TMSOTf), hydrolysis of the epimer (LiOH, H_2O/THF) afforded (+)-**18** in 97% yield.

(15) Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.

(16) De Lima, C.; Julia, M.; Verpeaux, J.-N. *Synlett* **1992**, 133.

(17) α-Amido sulfones in a similar reaction, see: Alonso, D. A.; Alonso, E.; Najera, C.; Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **1997**, *53*, 4835.

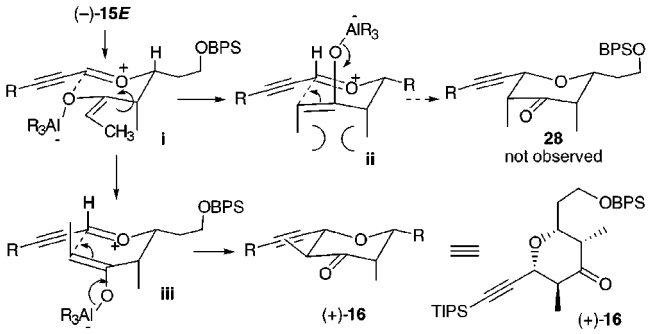
(18) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317.

(19) Evans, D. A.; Trotter, B. W.; Coté, B.; Coleman, P. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 24, 2741.

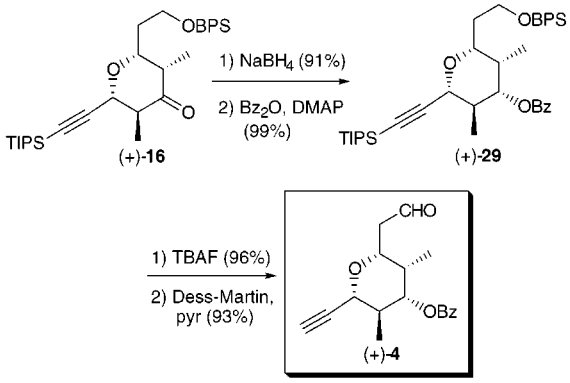
(20) Simpson, M. M. *Bull. Soc. Chem. Fr.* **1879**, *31*, 411.

(21) The stereochemistry of (+)-**16** was secured by NOE experiments and coupling constant analysis.

Scheme 9



Scheme 10



conformation and instead lead to a boatlike transition state (**iii**), wherein the *re* face of the enolate approaches the oxocarbenium species. Presumably, the small steric requirements of the alkyne as well as the propargylic stabilization of the oxocarbenium ion[22] lower the transition state energy of **ii** and **iii** comparably. However, the 1,3 diaxial interactions in **ii** evidently outweigh the energetic penalty of adopting the boat conformation in **iii**.

An alternative mechanism would entail *E* to *Z* isomerization of the enol ether followed by rearrangement through a chair conformation.[23] All attempts, however, to observe **15*Z*** upon interruption of the Petasis−Ferrier rearrangement failed to provide evidence for this isomerization.

With an efficient synthesis of tetrahydropyranone (+)-**16** in hand, four steps remained to complete subtarget **4** (Scheme 10): reduction of (+)-**16** with $NaBH_4$ (91% yield, 15:1 dr) followed by protection of the alcohol (Bz_2O, >99% yield) provided benzoate (+)-**29**.[10] Desilylation (TBAF, 96% yield) and Dess−Martin[24] oxidation then furnished aldehyde (+)-**4**[10] in 93% yield.

In summary, the Petasis−Ferrier rearrangement has been extended to permit assembly of the fully substituted C(22−26) tetrahydropyran in subtarget (+)-**4**. The synthesis proceeded in 12 linear steps and 20% overall yield. In addition, we have developed a new tactic for enol ether synthesis, extending the elegant work of Julia. Finally, a mechanistic rationale for the diastereoconvergent Petasis−Ferrier rearrangement of *E* and *Z* trisubstituted enol ethers is presented. Studies to assemble the phorboxazole macrocycle and ultimately phorboxazoles A (**1**) and B (**2**) continue in our laboratory.

Acknowledgment. Support was provided by the National Institutes of Health (National Cancer Institute) through grant CA-19033.

Supporting Information Available: Spectroscopic and analytical data for **4**, **6**, **11**−**13**, **15**, **16**, **18**, **20**, **25**, **26**, and **29** and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) For an example of an acetylene stabilizing an oxocarbenium ion in an acetal opening, see: Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089.

(23) For an example of silyl enol ether isomerization, see: Duffy, J. L.; Yoon, T. P.; Evans, D. A. *Tetrahedron Lett.* **1995**, *36*, 9245.

(24) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.