Pergamon

Tetrahedron Letters 42 (2001) 7341–7344

TETRAHEDRON LETTERS

# Total synthesis of epothilone A

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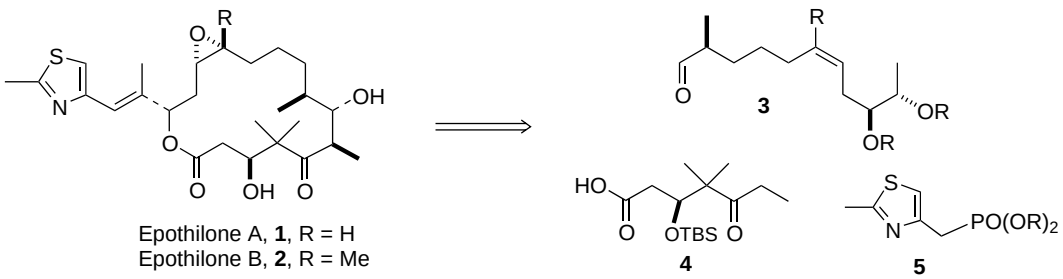
Received 6 August 2001; revised 20 August 2001; accepted 23 August 2001

**Abstract**—A convergent total synthesis of epothilone A (**1**) is described. The key steps are diastereoselective aldol condensation of aldehyde **3** to form the $C_6$–$C_7$ bond; macrolactonization and Wadsworth–Emmons reaction of methyl ketone with phosphonate reagent **5**. 

The naturally occurring macrolactones, epothilone A (**1**) and epothilone B (**2**), possess novel molecular architecture and a taxol-like antitumor mechanism of action. They have been a popular synthetic target since their isolation and characterization from *Sorangium cellulosum* several years ago.[1] Along with their antifungal and microtubule binding properties, these compounds have the advantage of better solubility than taxol, can be obtained in multigram quantities and demonstrate increased potency over taxol multi-drug resistant cancer cell lines.[2,3] The numbers of completed syntheses, partial syntheses, and patents relating to these compounds within the last 4 years is remarkable.[4–6]

Retrosynthetic analysis of the epothilones indicated to us that synthons **3**, **4** and **5** could serve as key intermediates once appropriately protected. With these structures in hand, a diastereoselective aldol condensation of **3** with the enolate of **4**, employing double stereodifferentiation to form the $C_6$–$C_7$ bond, could be followed by macrolactonization and Wadsworth–Emmons reaction of **5** with a methyl ketone to complete the synthesis of **1**. A few aspects of this work have been published.[7] Herein we wish to report our convergent total synthesis of epothilone A **1**.

The synthesis of aldehyde unit **3**, the top half of epothilone A **1** was dependent upon the ring opening of the epoxide **7** by an alkynylalane, with the final three carbon atoms to be introduced from a chiral propionate. The synthesis was initiated by silylating the (2*S*,3*R*)-1,2-epoxy-3-butanol **6**[8] with TBDMSCl and imidazole to form the epoxy silyl ether **7**, as outlined in Scheme 1. Regioselective opening of this epoxide to afford diol **10** in excellent overall yield could be achieved upon reaction with alane **9**. The alkynylalane **9** was prepared in situ with dimethylaluminium chloride. Selective hydrogenation of the alkyne **10** using Lindlar's catalyst furnished the *Z*-olefin **11**. A sequence of simple reactions transformed **11** into iodide **12**: selective tosylation of the primary alcohol; protection of the secondary alcohol as the TMS (trimethylsilyl) ether with TMS triflate and 2,6-lutidine; and finally, NaI displaced the tosylate to give the iodide **12**.

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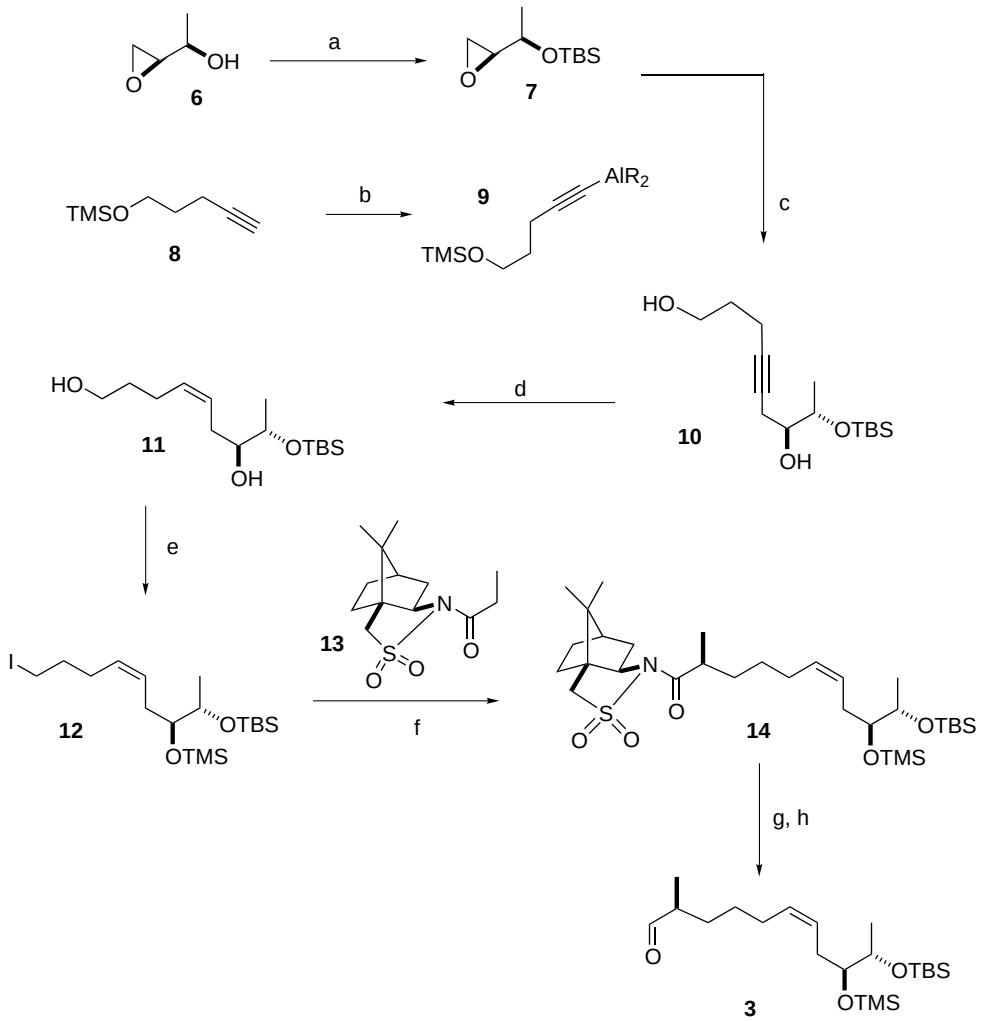
PII: S0040-4039(01)01585-4




**Scheme 1.** *Reagents*: (a) TBDMSCl, imidazole, $CH_2Cl_2$, 0°C to rt, 91%; (b) *n*-BuLi, $Me_2AlCl$, toluene, 0°C; (c) **7** in toluene, 0°C; add **9**, warm to rt, then aq. AcOH, rt, 92%; (d) $H_2$, Lindlar's catalyst, quinoline, EtOH, rt, quant.; (e) i. *p*-toluenesulfonyl chloride, pyridine, mol% DMAP, $CH_2Cl_2$, 0°C to rt, 89%; ii. trimethylsilyltriflate, 2,6-lutidine, $CH_2Cl_2$, 0°C to rt, 98%; iii. NaI, acetone, reflux, 94%; (f) **13**, *n*-BuLi, THF–HMPA; −78°C, then add **12** and warm to −30°C, 68%; (g) DIBALH, $CH_2Cl_2$, −30°C; (h) $SO_3$-Py, DMSO, TEA, $CH_2Cl_2$, 0°C, 80% for two steps.

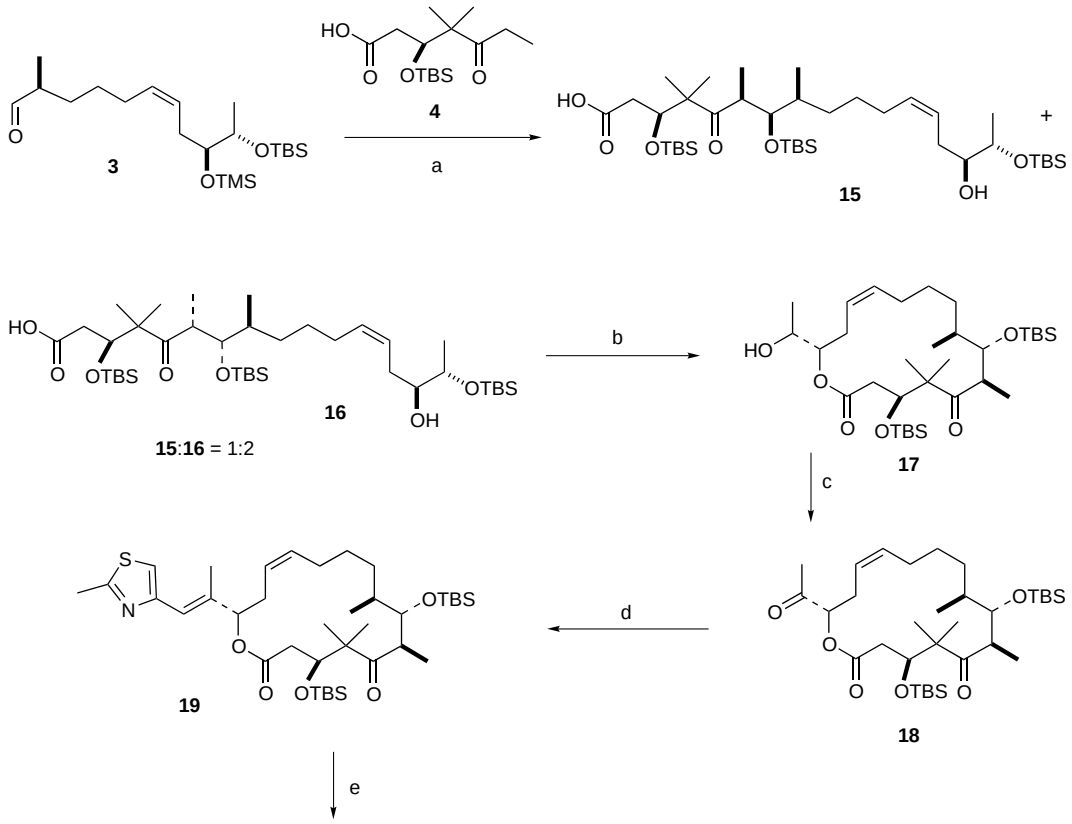
Alkylation of iodide **12** with the enolate of propionyl amide **13**,[9] prepared from (−)-camphor sultam, afforded the desired *S* homologated material **14**, auxiliary intact in 68% yield with >99% d.e. DIBALH-reduction of the adduct resulted in the formation of the corresponding alcohol which was then oxidized using $SO_3$–py complex to furnish the desired aldehyde **3**. The overall process could be accomplished in eight steps from the pentynyl derivative **8**.

For the aldol condensation outlined in retrosynthesis, the silyl protected keto acid **4** was required. This acid could be prepared as reported in our earlier work via enantioselective aldol reaction based on Evans chiral oxazolidinones.[6] The optimum conditions for the ensuing aldol condensation with aldehyde **3** required generation of the dilithio derivative **4** with LDA [−78 to −40°C] followed by exchange with Zn for Li using $ZnCl_2$ at −78°C, and then addition of aldehyde **3** resulted in the formation of aldol products, as shown in Scheme 2.[10]

This mixture was then treated with excess of TBSOTf and 2,6-lutidine to furnish a mixture of tetra-silylated products which was treated with aq. acetic acid to deprotect TMS ether with simultaneous deprotection of TBS esters. At this stage the aldol product mixture was separated from the unreacted keto acid **4** using flash column chromatography to obtain compounds **15** and **16** in a 1:2 diastereomeric ratio.

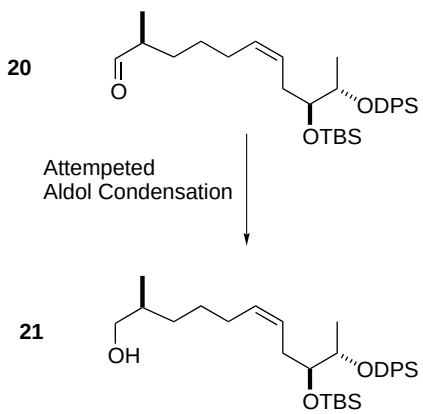
It is worth noting that this aldol condensation was sensitive to a number of factors. Transmetallation of the dilithium enolate of **4** with $ZnCl_2$ to generate a Zn enolate had a beneficial effect on the diastereoselective aldol reaction providing an excess (2:1) of the required *syn*,*syn* diastereomer **16** over the unwanted *syn*,*anti* diastereomer **15**.

In addition, choice of primary structure and/or protecting groups for the aldehyde side-chain in the aldol reaction was critical for success. An earlier reported protecting scheme for the diol side chain of the alde-




**Scheme 2.** *Reagents*: (a) i. **4** in THF, 2LDA, −78 to −40°C then $ZnCl_2$, −78 to −50°C; then add **3**, THF, 1 h; ii. TBDMSOTf, 2,6-lutidine, $CH_2Cl_2$, 0°C to rt, iii. aq. AcOH, rt, 72%. (b) i. 2,4,6-trichlorobenzoyl chloride, TEA, THF, DMAP, toluene, rt, 1 h; ii. $H_2SiF_6$, *tert*-BuOH, MeCN, $CH_2Cl_2$, rt, 24 h, 70%; (c) oxalyl chloride, DMSO, TEA, $CH_2Cl_2$, −78°C, 93%; (d) **5**, *n*-BuLi, THF, −78°C to rt, 60%; (e) i. 20% TFA in $CH_2Cl_2$, 0°C, 1 h, 92%; ii. methyl(trifluoromethyl)dioxirane, MeCN, 0°C, 56%.

hyde **3**, in which the TBS and TMS groups were replaced with bulkier DPS and TBS groups, respectively (i.e. **20**),[7] gave reduction product **21** upon attempted aldol condensation. This mechanistically obscure outcome could be alleviated as we outlined after a number of other protecting groups were examined and discarded due to this side reaction.




Macrolactonization of the mixture of hydroxy acids was accomplished using the Yamaguchi method[11] to obtain the corresponding lactones. Selective deprotection of the TBS ether using fluorosilicic acid and chromatographic separation gave the desired alcohol **17**. Oxidation of **17** under Swern conditions provided the methyl ketone **18**, which underwent Wadsworth–Emmons reaction with the phosphonate reagent **5**[12] to furnish the *E*-alkene **19** in good yield and with nearly complete regioselectivity. Removal of both TBS groups from **19** furnished the corresponding diol. Finally, treatment of **19** with methyl(trifluoromethyl) dioxirane[13] led cleanly to epothilone A **1**, whose spectral data was in accord with the reported data for epothilone A.

## Acknowledgements

We thank the Elsa U. Pardee Foundation for partial financial support of these efforts, and Dr. Höfle for communications regarding the stereochemistry of **1** in December of 1995.

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