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Synthetic Studies Directed Towards Epothilone A: Enantioselective Synthesis of a C_7 - C_{15} Carboxaldehyde Segment

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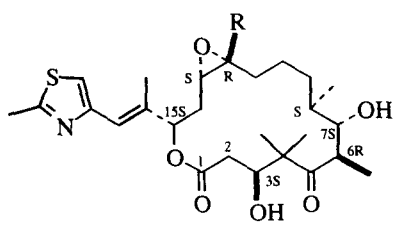
Abstract: Enantioselective syntheses of a protected C_7-C_{15} fragment of epothilone A is reported in ten manipulations in good overall yield. An alkynyl-aluminum induced opening of a chiral epoxide followed by reordering of functionality furnished the iodide **18**. Chain elongation with N-propionyl-1*S*-(-)-2,10-camphorsultam **19** afforded the elaborated acylsultam **20** which was reduced and reoxidized to furnish a protected chiral aldehyde **6** suitable for aldol condensation, representing the C_7-C_{15} portion of epothilone A.

Epothilone B (**1**) and epothilone A (**2**) were first isolated by Höfle et al. from the myxobacterium *Sorangium cellulosum* and represent a new group of macrocyclic lactones with novel molecular architecture and taxol-like antitumor activity.[1] Along with their antifungal and microtubule binding properties, these new compounds have the advantage of better solubility than taxol, can be obtained in multigram quantities and have high relative potency compared to taxol against taxol-resistant cancer cell lines.[2,3] The importance of the epothilones as synthetic targets is clearly indicated by an intense flurry of activity towards their total synthesis within a short peroid of time after their stucture and biological activity was established. Thus far, five total syntheses have been reported[4-8] along with communications of partial syntheses.[9-12]



Epothilone B, **1**, R = Me
Epothilone A, **2**, R = H

Retrosynthetic analysis of the epothilones indicated to us the three fragments **3**, **4** and **5** as key intermediates once appropriately protected (Scheme I). With these structures in hand, crucial construction in the analysis was imagined as a diastereoselective Aldol condensation employing double stereodifferentiation to form the C_6-C_7 bond; macrolactonization; epoxidation, and Wadsworth-Emmons reaction of a methyl ketone with the phosphonate reagent **4**. Herein we wish to report the efficient enantioselective synthesis of the C_7-C_{15} aldehyde subunit **6**, a suitably protected equivalent of the retrosynthon **3**.

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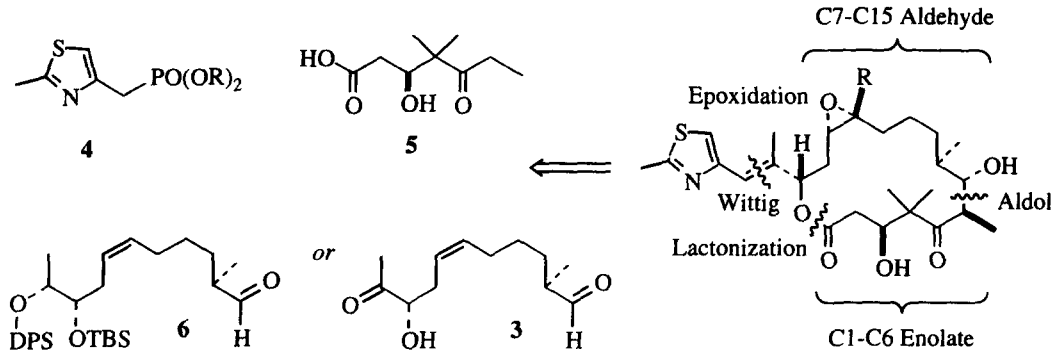
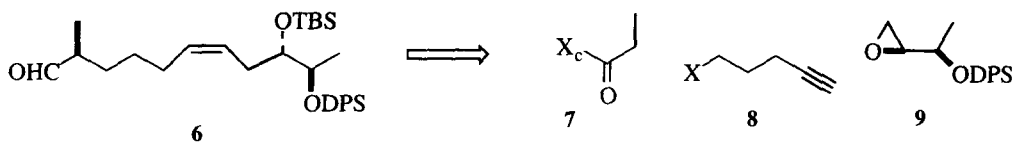
Scheme I



Our plan for the synthesis of **6** was dependent upon the ring opening of an alkyne **8** with a chiral epoxide **9**, with the final three carbon atoms to be introduced from a chiral propionate **7** as indicated in Scheme II. The C_{15} and C_8 asymmetric centers were sought to be generated by Sharpless asymmetric epoxidation and enantioselective alkylation using an appropriate chiral auxilary, respectively. Incorporation of the *Z*-olefin was planned by coupling the acetylenic subnit **8**, followed by partial hydrogenation.

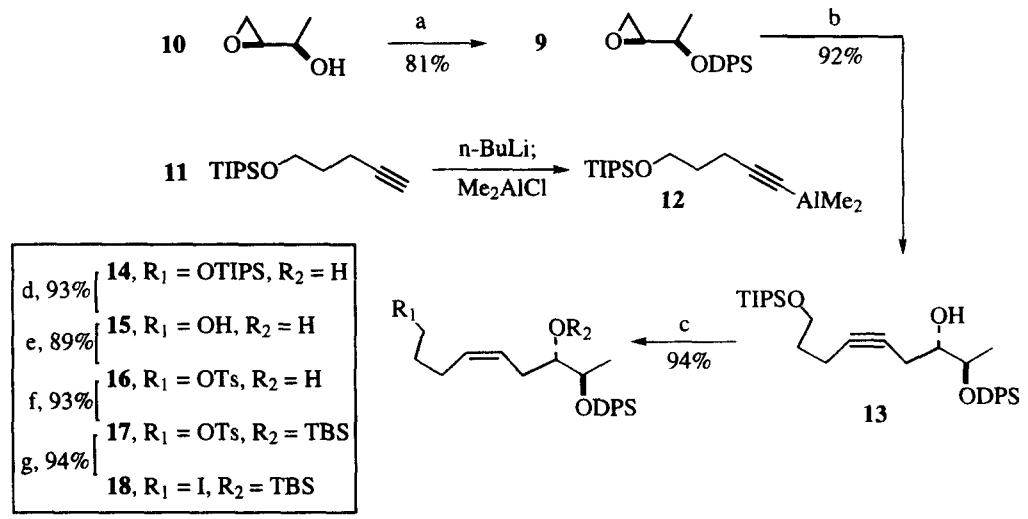
Scheme II



As can be seen in Scheme III, the synthesis of **6** was intitiated by silylating the (2*S*,3*R*)-1,2-epoxy-3-butanol **10**[13] with DPSCl (*tert*-butyldiphenylsilyl chloride) and imidazole to form the epoxy-silyl ether **9**. Regioselective opening of this epoxide could be achieved upon reaction with the alane **12**, itself derived from the lithium salt of the protected pentynol **11** reacted with dimethylaluminum chloride, to provide **13** in excellent overall yield. With careful monitoring of reaction progress, partial hydrogenation of **13** using Lindelar's catalyst yielded the *Z*-olefin **14** in high yield. Selective cleavage of the TIPS ether **14** in alcoholic aqueous 0.1N HCl provided the diol **15**, which was then selectivley tosylated with *p*-toluenesulfonyl chloride to give the primary tosylate **16**. Introduction of a *tert*-butyldimethylsilyl (TBS) protecting group was readily achieved upon reaction with the corresponding silyl triflate, giving rise to the fully protected triol **17**. Finally, in anticipation of ensuing alkylation reaction, the primary tosylate **17** could be converted to its analogous iodide **18** under conventional conditions of sodium iodide in refluxing acetone.

The iodide **18** has displayed good stability when stored cold in the absence of light and oxygen, and has been conveniently reacted with the propionyl derivative of Oppolzer's sultam **19**[14] to furnish the desired *S* alkylation product **20** in 68% with > 99% d.e. (Scheme IV).

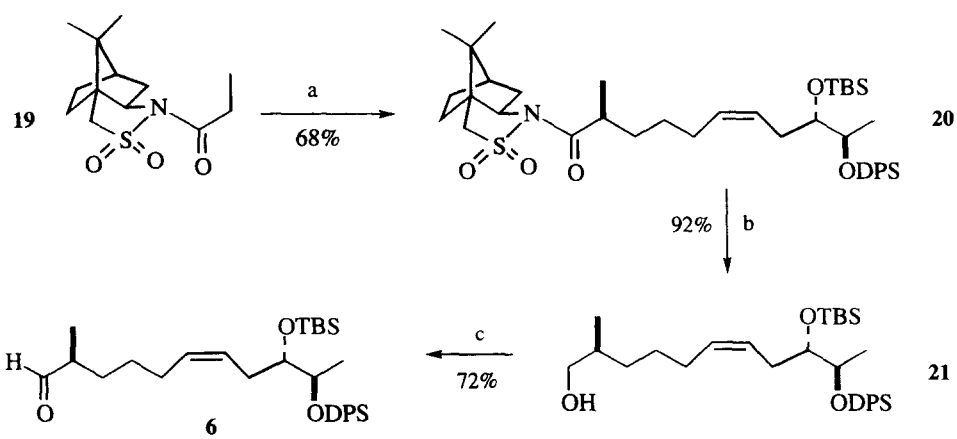
Scheme III



Key: a) *tert*-Butyldiphenylsilyl chloride (DPSCl), imidazole, 4-N,N'-dimethylaminopyridine (DMAP), CH_2Cl_2; b) **12** in Toluene, 0 °C; add **9**, warm to ambient temperature; c) H_2, Lindelar's Catalyst, quinoline, EtOH; d) 0.1N HCl, EtOH, ; e) *p*-toluenesulfonyl chloride, pyridine, 10 mole% DMAP, CH_2Cl_2; f) *tert*-butyldimethylsilyl triflate, 2,6-lutidine, CH_2Cl_2 ; g) NaI, acetone, .

After reduction of **20** with $LiAlH_4$, the alcohol **21** could be isolated in 92% yield. Finally, the aldehyde **6** could be generated by Swern oxidation conducted at -78 °C in 72% unoptimized but isolated yield.[15]

Scheme IV



Key: a) *n*-BuLi, THF-HMPA; -78 °C, then **18** and warm to 0 °C; b) $LiAlH_4$, THF, 0 °C; c) $(COCl)_2$, DMSO, **21**; then Et_3N, CH_2Cl_2, -78 °C.

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References

1. Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem.* **1996,** *108*, 1671-1673; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567-1569.
2. Grever, M. R.; Schepartz, S. A.; Chabner, B. A. *Seminars in Oncology* **1992,** *19*, 622-638.
3. Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995,** *55*, 2325-2333.
4. 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- 2803.
5. Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y. H.; Chou, T. C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997,** *119*, 2733 - 2734.
6. Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Yang, Z. *Angew. Chem.* **1997,** *109*, 539 - 540; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 525-527.
7. Nicolaou, K. C.; Winssinger, N.; Pastor, J. A.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P. Hamel, E. *Nature* **1997**, *387*, 268-272.
8. Schinzer, D.; Limberg, A.; Bauer, A.; Bohm, O. M.; Cordes, M. *Angew. Chem. Int. Ed. Engl.* **1997,** *36*, 523 - 524.
9. Mulzer, J.; Mantoulidis, A. *Tetrahedron Lett.* **1996,** *37*, 9197 -9181.
10. Claus, E.; Pahl, A.; Jones, P. G.; Meyer, H. M.; Kalesse, M. *Tetrahedron Lett* **1997,** *38*, 1359 - 1362.
11. Gabriel, T.; Wessjohann, L. *Tetrahedron. Lett.* **1997,** *38*, 1363 - 1366.
12. Taylor, R. E.; Haley, J. D. *Tetrahedron Lett.* **1997**, *38*, 2061-2064.
13. White, J. D.; Kang, M. C.; Sheldon, B. G. *Tetrahedron Lett.* **1983,** *24*, 4539-4542.
14. Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, 5603-5606.
15. Data for **6**: $[\alpha]^{21}_D$ = 7.48 ° (c = 1.85, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H); 0.05 (s, 3H); 0.88 (s, 9H); 0.97 (d, J = 6.3 Hz, 3H); 1.06 (s, 9H); 1.07 (d, J = 6.4 Hz, 3H); 1.27-1.41 (m, 3H); 1.68 (dddd, J = 14.6, 9.2, 5.0, 2.6 Hz, 1H); 1.93-2.03 (br q, 2H); 2.15-2.24 (br q, 2H); 2.31 (ddq, J = 8.5, 6.7, 1.8 Hz, 1H); 3.67 (ddd, J = 6.2, 6.2, 3.0 Hz, 1H); 3.78 (dq, J = 6.3, 3.0 Hz, 1H); 5.31 (overlapping ddd, J = 11.2, 9.4, 5.8 Hz, 1H); 5.34 (overlapping ddd, J = 11.2, 9.4, 5.8 Hz, 1H); 7.32-7.46 (m, 6H); 7.67 (dd, J = 1.6, 1.6 Hz, 2H); 7.70 (dd, J = 1.5, 1.5 Hz, 2H); 9.59 (d, J = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.4, -4.3, 13.2, 18.0, 18.1, 19.1, 25.8, 26.7, 27.0, 27.2, 30.0, 31.8, 46.1, 72.5, 77.0, 126.6, 127.2, 127.3, 129.3, 129.4, 130.3, 134.0, 134.7, 135.8, 204.9. IR (film): 2929, 2858, 1727, 1461, 1421, 1110, 703 cm^{-1}. HRMS (FAB): m/z calcd for $C_{30}H_{45}O_3Si_2$ (M-*tert*-Bu): 509.2908; found: 509.2903.