Pergamon

Tetrahedron Letters 39 (1998) 5261–5264

TETRAHEDRON LETTERS

Epoxide Opening with Acetylide for Synthesis of Epothilone A C_{7-21} Segment

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Received 23 January 1998; revised 18 May 1998; accepted 22 May 1998

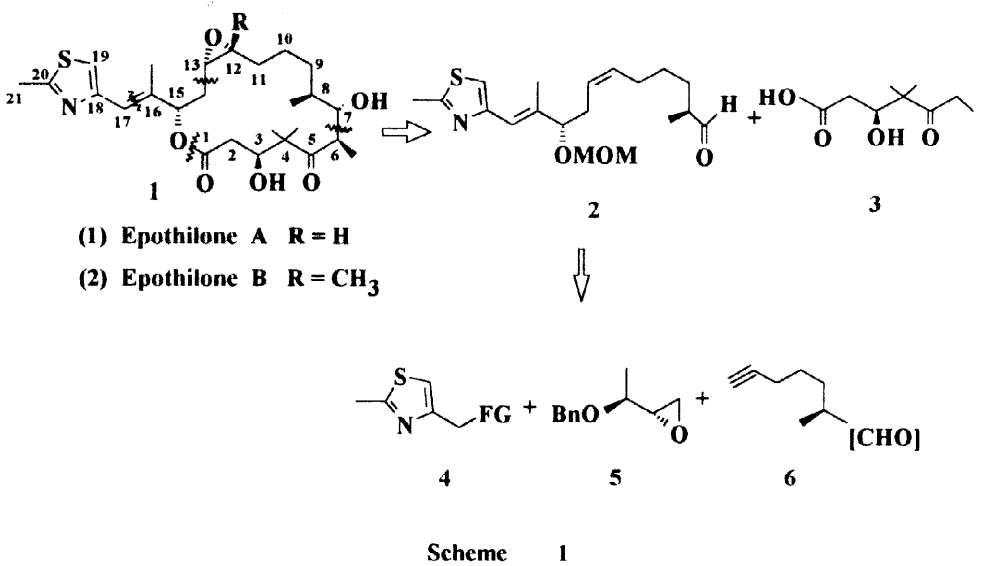
Abstract: A Chiral synthesis of epothilone A C_{7-21} segment **2** is described using epoxide opening with acetylide for the construction of the C_{12-13} *cis* double bond and a modified Wittig reaction for introduction of the thiazole side chain .

Epothilone A and B are a new class of macrolide, first identified as antigungal cytotoxic agents.[1] Most importantly, Merck scientists discovered that epothilones have all the biological effects of taxol with the same mechanism of action. In contrast to taxol, epothilones retain a much greater toxicity against P-glycoprotein-expressing multiple drug resistant cells and better water solubility. This observation suggests that epothilones as antineoplastic agents could provide an important advantage over taxol.[2] However the stucture of epothilones, 16-membered macrolactones, are totally different from taxol.

Epothilones were first isolated by the Höfle group from myxobacteria Sorangium cellulosum culture So ce90.[1] Due to their very interesting biological activity and new chemical structure, these biological analogues of taxol immediately attracted much attention. Three groups have already synthesized epothilones[3-5] and several groups have reported their approaches to epothilones.[6-9] Herein we report our preliminary result for the synthesis of epothilone A C_{7-21} segment **2**.

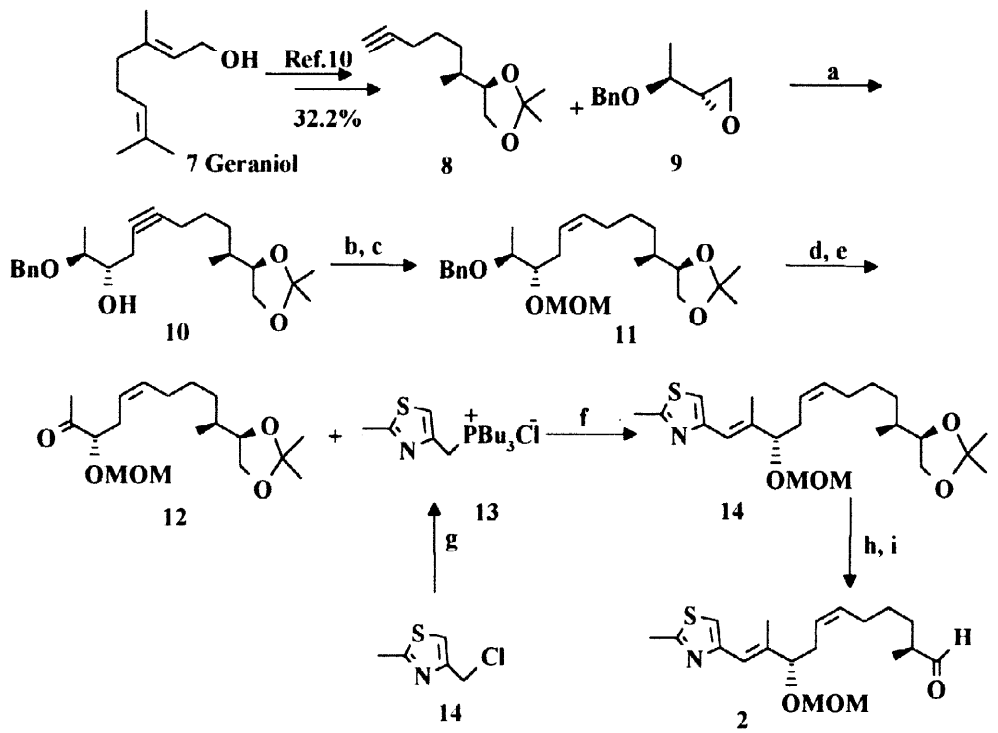
Retrosynthetic analysis of synthesis of the segment **2** is shown in **Scheme 1**.

0040-4039/98/$19.00
PII: S0040-4039(98)01060-0



Scheme 1

This strategy is different from the others reported so far for synthesis of epothilone A $C_{7\text{-}21}$ segment and allows use of acetylide for the introduction of the desired *cis* double bond at $C_{12\text{-}13}$. Our synthetic route is shown in **Scheme 2** .



Scheme 2. *Reagents and conditions*: a. n-BuLi (1.0 equi.), THF, -78°C ~ -20°C, 30min then $BF_3 \bullet Et_2O$ (1.0 equi.), -78°C, 10min, then epoxide **9** (1.5 equi.), 30min, 84%; b. H_2, Pd-$BaSO_4$, quinoline, MeOH, 25min, 100%; c. MOM-Cl (3 equi.), i-Pr_2NEt (3 equi.), CH_2Cl_2, -20°C → 0°C, 4h, 81.5%; d. Na (1.5 equi.), NH_3 (L), -60°C, 35min, 83%; e. $(COCl)_2$ (1.4 equi.), DMSO

(2.8 equi.), CH_2Cl_2, then Et_3N, -78°C, 2 h, 76%; f. compound **13** (3.5 equi.), t-BuOK (3.2 equi.), toluene, 0°C → rt, 23 h, 72%. g. n-Bu_3P, no solvent, 70°C, 3h, 86.7%; h. HOAc : H_2O = 8:2, rt, 2.5 h, then 45°C, 0.5 h, 98%; i. $NaIO_4$-Silica gel, CH_2Cl_2, rt, 15min, 96%.

The synthesis started from the acetylide **8**, prepared from geraniol **7** in eight steps and 32.3% overall yield.[10, 11] Lithium acetylide, prepared by treatment of **8** with n-butyl lithium, opened the epoxide **9**[12] in the presence of BF_3•OEt_2 to give **10**. Partial hydrogenation of **10** with Lindlar catalyst, followed by protection of the hydroxy group provided the desired *cis* double bond of compound **11**. Reductive cleavage of the benzyl group and oxidation of the resulting alcohol afforded ketone **12**. In order to stereospecificially introduce the thiazole side chain with the *trans* double bond, we chose Armstrong's procedure[13] with a Schlosser's modification of the Wittig reaction. The tributylphosphonium salt **13** (highly hygroscopic crystal) was synthesized from the chloride **14**. [14] Condensation of **13** by treatment of potassium t-butoxide with ketone **12** furnished compound **14**, which contains the whole carbon skeleton of the segment **2**. Deprotection of the vicinal diol acetonide and cleavage of the resulting diol[15] gave epothilone A $C_{7\text{-}21}$ segment **2** in 25.4% overall yield from **8.** Thus an efficient synthesis of a main segment of epothilone A has been achieved and its elaboration to the epothilone A is in progress. [17]

REFERENCES AND NOTES

1. (a) Höfle, G.; Bedorf, N.; Gerth, K. and Reichenach, H., DE 4, 138, 042, 1993, *Chem. Abstr.*, **1993**, *120*, 52841; (b) Höfle, G.; Bedorf, N.; Steinmertz, H.; Schomburg, D.; Gerth, K. and Reichenbach, H., *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567.
2. Bollag, D. M.; Mcqueney, P. A.; Zhu, J.; Kaupal, L.; Leisch, J.; Goetz, M.; Lazarides, E. and Woods, C. M., *Cancer Res.*, **1995**, *55*, 2325.
3. A)Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.-S.; Sorensen, E. J. and Danishefsky, S. J., *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801; b)Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L. and Horwitz, S. B., *J. Am. Chem. Soc.*, **1997**, *119*, 2733; c)Su, D.-S.; Meng, D.; Bertinato, P.; Balog, A.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L. and Horwitz, S. B., *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 757 and cited references therein.
4. (a) Nicolaou, K. C.; Sarabia, F. and Yang, Z., *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 525 and cited reference therein; (b) Nicoloau, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Glannakakou P. and Hamel, E., *Nature*, **1997**, *387*, 15.
5. Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M. and Cordes, M., *Angew. Chem. Int. Ed. Engl.*, **1997**, *36*, 523 and cited reference therein.
6. Mulzer, J. and Mantoulidis, A., *Tetrahedron Lett.*, **1996**, *37*, 9179.
7. Claus, E.; Pahl, A.; Jones, P. G.; Meyer, H. M. and Kalesse, M., *Tetrahedron Lett.*, **1997**, *38*, 1359.
8. Gabriel, T. and Wessjohann, L., *Tetrahedron Lett.*, **1997**, *38*, 1363.
9. Brabander, J.D.; Rosset, S.; Bernardinelli, G., *Synlett*, **1997**, 824.
10. Liu, Z.-Y.; Yu, C.-Z.; Yang, J.-D., *Synlett*, 1997, 1383.
11. All the yields mentioned in this paper are not optimum.
12. (a) the compound **9** was prepared from vitamin C with the modification of the Abushanab's procedure: Abushanab, E.; Vemishetti, P.; Leiby, R.W.; Singh, H.K.; Mikkilineni, A.B.; Wu, D.C.-J.; Saibaba, R.; Panzica, R.P., *J.Org. Chem.*, **1988**, *53*, 2598. (b)Abushanab, e.;Bessodes, M.; Antonakis., *Tetrahedron Lett.*, **1984**, *25*, 3841.
13. Zhao, Z.; Scarlato, G.R.; Armstrong, R.W., *Tetrahedron Lett.*, **1991**, *32*, 1609.
14. Hooper, F.E.; Johnson, T.B.; *J.Am.Chem.Soc.*, **1934**, 56, 470.
15. Zhong Y.-L. and Shing, T. K. M., *J. Org. Chem.*, **1997**, *62*, 2622-2624.

16. Selected data for **11**: R_f = 0.6(PE : AE = 6 :1), $[\alpha]_D^{25}$: +14 4° (c = 1.86, $CHCl_3$), IR(film): 3481, 3030, 2984, 2932, 1497, 1455, 1379, 1370, 1214, 1070, 736, 699. ^{1}HNMR(300MHz, $CDCl_3$): 7.36-7.26(m, 5H, Ph), 5.51-5.46(m, 2H), 4.67(d, J=11.47Hz, 1H), 4.44(d, J=11.46Hz, 1H), 3.99(dd, J=6.21, 7.69Hz, 1H), 3.87(dd, J=13.48, 6.79Hz, 1H), 3.59(t, J=7.58Hz, 1H), 3.55-3.40(m, 2H), 2.53(brs, 1H), 2.35-2.19(m, 2H), 2.14-1.98(m, 2H), 1.68-1.02(14H, singlets at 1.40, 1.35, doublet at 1.22), 0.96(d, J=6.74Hz, 3H). MS(EI): 376(M^+-CH_3, 1.71), 361(M-Me, 3.42), 301(31.13), 285(M-Bn, 3.67), 241(2.61), 211(37.66), 101(20.31). Analysis($C_{23}H_{36}O_4$): calcd. for C 73.37 H 9.64, found C 73.42 H 9.71.

14: R_f = 0.4(PE : AE = 8 : 1), $[\alpha]^{25}$: -74.7° (c=0.99, $CHCl_3$), IR(film): 3097, 1506, 1456, 1378, 1369, 1249, 1214, 1150, 917, 863cm^{-1}. ^{1}HNMR(300MHz, $CDCl_3$): 6.94(d, J= 2.17Hz, 1H), 6.48(s, 1H), 5.48-5.35(m, 2H), 4.64(d, J=6.56Hz, 1H), 4.51(d, J=6.64Hz, 1H), 4.13-4.02(m, 1H), 4.01-3.95(m, 1H), 3.90-3.80(dd, J=13.65, 6.85Hz, 1H), 3.57(t, J=7.59Hz, 1H), 3.37(s, 3H), 2.69(s, 3H), 2.52-2.25(m, 2H), 2.20-1.95(m, 5H), 1.65-1.00(m, 11H, singlets at 1.38, 1.32, 3H each), 0.95(d, J=6.63Hz, 3H). MS(m/e): 424(M+1, 2.83), 408(M-Me, 4.57), 378(M-CH_3OCH_2, 1.21), 362(21.93), 322(2.61), 212(100.00), 101(7.63). HRMS: calcd. for $C_{23}H_{37}O_4NS$ 423.2443 , found 423.2426.

2: R_f = 0.8 (PE : AE = 1 : 1), $[\alpha]^{25}$: -22.9° (c = 1.78, $CHCl_3$), IR(film): 3107, 2822, 2711, 1726, 1655, 1506, 1459, 1150, 1098, 1031, 919cm^{-1}. ^{1}HNMR(300MHz, $CDCl_3$): 9.59(s, 1H), 6.95(s, 1H), 6.48(d, J=4.45Hz, 1H), 5.46-5.41(m, 2H), 4.66(d, J=6.63Hz, 1H), 4.51(d, J=6.62Hz, 1H), 4.09(t, J=6.86Hz, 1H), 3.37(s, 3H), 2.70(s, 3H), 2.44-2.28(m, 3H), 2.08-1.98(m, 5H), 1.72-1.67(m, 2H), 1.44-1.31(m, 2H), 1.07(d, J=7.01Hz, 3H). MS(m/e): 352(M+1, 1.31), 306(0.66), 290(18.94), 272(0.96), 212(89.68), 166(17.42), 152(19.22).

17. During the revision of this manuscript, Avery, M. A. and coworkers published their synthesis of $C_{7\text{-}15}$ segment: Bijoy, P.; Avery, M. A., *Tetrahedron Lett.*, **1998**, *39*, 209.