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En Route to a Plant Scale Synthesis of the Promising Antitumor Agent 12,13-Desoxyepothilone B

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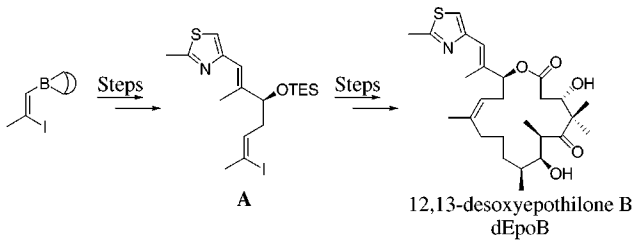
ABSTRACT



Efficient and processable syntheses of key building blocks of the antitumor agent 12,13-desoxyepothilone B (dEpoB) by catalytic asymmetric induction are herein described.

Interest in the epothilone family of natural products on the part organic chemists was incubated, no doubt, by the promising biological profiles of the A and B isomers, particularly the latter.[1,2] These compounds seem to share a common tubulin-centered mechanistic framework with paclitaxel, yet offer potential advantages in terms of formulability and performance in vitro toward Taxol insensitive tumor cells.[3] Likewise, the interesting and insightful structural features of the epothilones challenge the collective ingenuity of the science of organic synthesis. The field has benefited from a continuing series of disclosures,[2,4] seeking to improve upon the three initial feasibility demonstrations.[5−7]

As early as 1997, using our then intricate (though stereospecific) academic type synthesis,[5b] enough epothilone B was garnered to show for the first time that the initial Merck reports[3] on the favorable in vitro biological profiles of epothilones were extendable to human tumors transplanted in murine hosts in a xenograft setting.[8] However, during these

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(1) Hofle, G. H.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567.

(2) For extensive reviews in this field, see: (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem., Int. Ed.* **1998**, *37*, 2015. (b) Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434.

(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.

(4) For some recent total syntheses of epothilone B, see: (a) Mulzer, J.; Mantoulidis, A.; Ohler, E. *Tetrahedron Lett.* **1998**, *39*, 8633. (b) White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999**, *64*, 684. (c) May, S. A.; Grieco, P. A. *Chem. Commun.* **1998**, 1597. (d) Sawada, D.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 209.

(5) (a) For the synthesis of epothilone A, see: Su, D. S.; Meng, D. F.; Bertinato, P.; Balog, A.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2801. (b) For the synthesis of epothilone B, see: Su, D. S.; Meng, D. F.; Bertinato, P.; Balog, A.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L. F.; Horwitz, S. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 757.

(6) (a) For the synthesis of epothilone A, see: Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166. (b) For the synthesis of epothilone B, see: 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.

(7) (a) For the synthesis of epothilone A, see: Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523. (b) For the synthesis of epothilone B, see: Schinzer, D.; Bauer, A.; Schieber, J. *Synlett* **1998**, 861.

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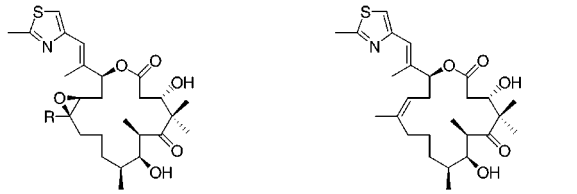
investigations, some potentially serious toxicity problems were uncovered using agent **2** (Figure 1). These findings cast



1 epothilone A (R = H)
2 epothilone B (R = CH_3)

3 12,13-desoxyepothilone B (dEpoB)

Figure 1. Epothilones.

some doubt as to whether exploitable therapeutic indices could be found with epothilone B (EpoB). During this era, we demonstrated that much of the toxicity of EpoB could be abrogated through the use of 12,13-desoxyepothilone B (dEpoB, **3**).[9,10] Vast superiority of dEpoB relative to EpoB and to paclitaxel has been demonstrated in a variety of competitive in vivo settings, and the results have been published elsewhere.[2b,11] Presently, dEpoB has advanced to toxicology and efficacy studies in dogs, en route to a full-scale clinical evaluation.[12]

Since our laboratory lacks access to fermentation-derived epothilones, total synthesis constituted our only recourse to produce material for biological investigations. Indeed, all of the in vivo evaluations have been conducted on fully synthetic dEpoB. The present goal is to develop a practical total synthesis of dEpoB which can furnish material appropriate for a full scale evaluation in humans if, as expected, findings in higher and larger animals so indicate.

In our previously described improved routes to dEpoB,[13,14] three subunits were built and combined. The route to building block **C** (see Figure 2) has already been shown to be

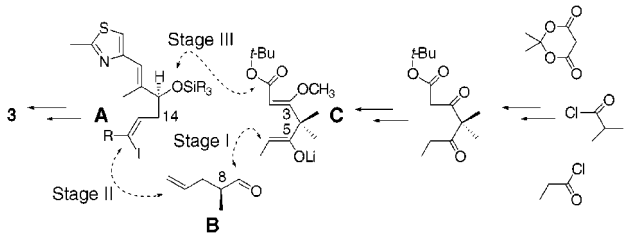
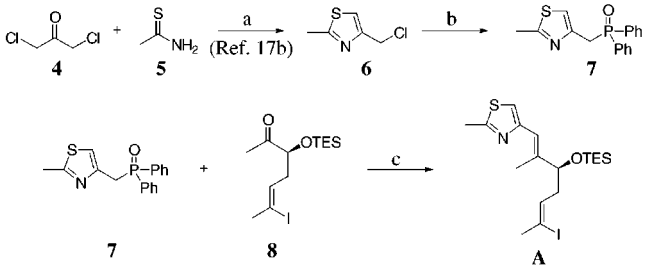


Figure 2. Epothilone building blocks.

amenable to major scale-up. As previously described by Overman,[15] building block **B** was prepared by auxiliary-mediated allylation of a suitable propionate derivative, using methodology first promulgated by Evans and associates.[16] The largest impediment to major scale-up was in the synthesis of the **A** subunit, which had previously required eight steps, exclusive of generating the required reagents. Several of these maneuvers required rather sophisticated and expensive chemistry, and prospects for serious scale-up of these protocols were daunting. The disclosure herein now describes new synthetic developments which render the **A** fragment readily available in multigram quantities, utilizing easily processable chemistry. These advances have major favorable consequences for a plant-level synthesis of dEpoB.

The new route for the synthesis of the key vinyl iodide fragment required smooth access to large quantities of phosphine oxide **7**. This subunit is in fact easily prepared *in two steps* on a 100 g scale as shown in Scheme 1.[17] The

Scheme 1[a]



[a] (a) (i) acetone, (ii) $ZnCl_2$, MeOH, reflux, 60%; (b) $HOPPh_2$, Cs_2CO_3, Bu_4NI, CH_2Cl_2, 97%; (c) (i) **7**, *n*-BuLi. THF, −78 °C, 30 min, (ii) **8**, −78 °C to rt, 98%.

second subunit required for building the **A** segment is methyl ketone **8** (vide infra). The Horner-like condensation[18] between **7** and **8** is conducted in 98% yield on a multigram scale to afford **A**. However, for this chemistry to be valuable, a straightforward synthesis of **8**, amenable to plant-level scale-up, had to be accomplished.

Fortunately, two such routes have now been developed. In the first approach (Scheme 2) following conversion of **9**

(8) Su, D. S.; Balog, A.; Meng, D. F.; Bertinato, P.; Danishefsky, S. J.; Zeng, Y. H.; Chou, T.-C.; He, L. F.; Horwitz, S. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2093.

(9) Chou, T.-C.; Zhang, X. G.; Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K. A.; Bertino, J. R.; Danishefsky, S. J. *Proc. Nat. Acad. Sci.* **1998**, *95*, 15798.

(10) Chou, T.-C.; Zhang, X. G.; Balog, A.; Su, D. S.; Meng, D. F.; Savin, K.; Bertino, J. R.; Danishefsky, S. J. *Proc. Nat. Acad. Sci.* **1998**, *95*, 9642.

(11) Harris, C.; Savin, K.; Danishefsky, S. J.; Chou, T.-C.; Zhang, X.-G. *Soc. Chim. Ther.* **1999**, *25*, 187.

(12) This work was done in collaboration with Dr. T.-C. Chou, Dr. W. Tong, Dr. O. O'Conner, and Dr. J. Bertino at the Sloan-Kettering Institute for Cancer Research.

(13) Balog, A.; Harris, C.; Savin, K.; Zhang, X. G.; Chou, T. C.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2675.

(14) Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K.; Glunz, P. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 7050.

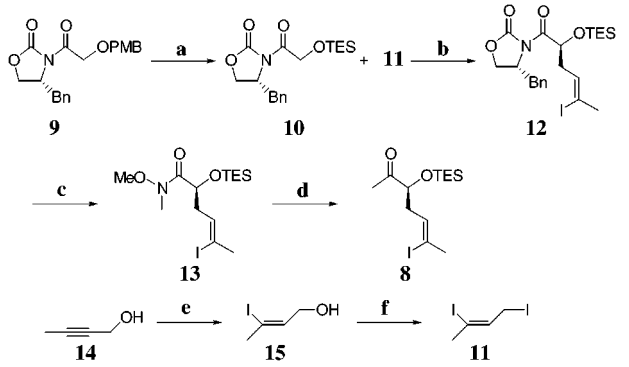
(15) Lin, N.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062.

(16) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(17) (a) For an earlier synthesis of **7** and its application to this type of Wittig reaction, see: Bertinato, P.; Sorensen, E. J.; Meng, D. F.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 7998. (b) Gellis, A.; Vanelle, P.; Kaafarani, M.; Benakli, K.; Crozet, M. P. *Tetrahedron Lett.* **1997**, *53*, 5471.

(18) (a) Lythgoe, B.; Nambudiry, M. E. N.; Ruston, S.; Tideswell, J.; Wright, P. W. *Tetrahedron Lett.* **1975**, *40*, 3863. (b) Lythgoe, B. *Chem. Soc. Rev.* **1981**, 449. (c) Toh, H. T.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 1414. (d) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Batcho, A. D.; Sereno, J. F.; Uskokovic, M. R. *J. Org. Chem.* **1986**, *51*, 3098.

Scheme 2[a]

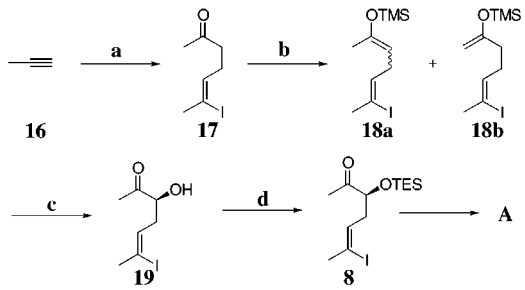


[a] (a) (i) $TiCl_4$, 0 °C, 87%, (ii) TESCl, imidazole, DMF, 84%; (b) LHMDS, 11, −78 °C, 81%; (c) (i) HOAc:THF:H_2O (3:1:1), (ii) CH_3ONHCH_3, $AlMe_3$, (iii) TESCl, DMF, 88% overall; (d) MeMgB, 0 °C, 93%; (e) (i) RedAl, 0 °C to rt, (ii) I_2, −78 °C to rt, Et_2O; (f) TMSI, CH_2Cl_2, 0 °C, 81%−two steps.

to **10** (84%),[19,20] a highly diastereoselective alkylation of lithio **10** with **11** produces **12** (>25:1 de) in 81% yield.[19,20] As was previously reported,[21] diiodide **11** is available from 2-butynol in two steps as shown. Finally, compound **12** was advanced in three steps to **8** by recourse to the Weinreb amide **13**.[22]

A second route, while somewhat less selective, reaches **8** even more easily, in only four steps via asymmetric dihydroxylation[23] (Scheme 3). This synthesis begins with the

Scheme 3[a]

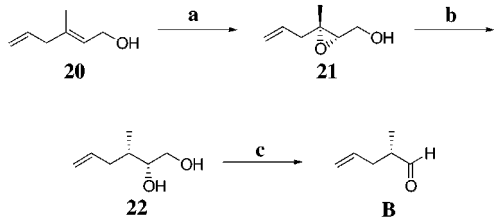


[a] (a) (i) I-9-BBN, hexanes, (ii) methyl vinyl ketone, hexanes, (iii) 3 N NaOH, PhMe, 100 °C, 65%; (b) TMSI, HMDS, CH_2Cl_2, −20 °C to rt; (c) 1 mol % of OsO_4, AD-mix-α, $MeSO_2NH_2$, *t*-BuOH:H_2O (1:1), 55%−two steps; (d) TESCl, imidazole, DMF, 85%.

known reaction of propyne with *B*-iodo-9-BBN and methyl vinyl ketone to produce **17**,[24] which reacts (in multigram scale) with trimethylsilyl iodide to provide an 88:12 (**18a**:**18b**) mixture of silyl enol ether isomers **18**.[25] Asymmetric dihydroxylation[23] of this material, under the conditions shown, afforded **19** (87% ee, 55% yield−two steps). Finally, triethylsilylation of **19** completes the synthesis of ketone **8** and therefore **A**.

With a view to generating fragment **B** by strictly catalytic asymmetric methods, its synthesis was revisited (Scheme 4).

Scheme 4[a]



[a] (a) *t*-BuOH, Ti(O*i*-Pr)$_4$, (+)-DET, CH_2Cl_2, 98%, 82% ee; (b) $NaCNBH_3$, BF_3·OEt_2, THF, 52%; (c) $NaIO_4$, THF:H_2O, 81%.

For this purpose, we synthesized subunit **20**, which is prepared from isoprene by known chemistry.[26] Asymmetric epoxidation[27] of **20** provides **21**, which undergoes reductive cleavage[28] at the more substituted center to furnish diol **22**. Following periodate cleavage as shown, building block **B** is in hand. While this method bypasses recourse to a chiral auxiliary, its ultimate advantage in terms of scale-up to the multigram levels in a plant-type setting awaits demonstration.

As previously described,[13,14] a novel aldol condensation joins fragments **B** and **C**. Subsequently, a palladium-mediated *B*-alkyl Suzuki[29] merger joins **A** with **B**−**C**. With the carbon skeleton in place, a catalytic Noyori reduction[30] provides the desired stereochemistry at C3 and macrolactonization leads, shortly afterward, to dEpoB.[14] While we always remain open to possibilities for still greater practicality, we are now already confident that compound availability through total synthesis will support a full and searching evaluation of dEpoB and other promising epothilones at the clinical level.

(19) Hitherto, glycolates have been prepared by auxiliary chemistry through hydroxylation of the alkanoate rather than through alkylation of the glycolate: Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346.

(20) See however: Paterson, I.; Bower, S.; McLeod, M. D. *Tetrahedron Lett.* **1995**, *36*, 175.

(21) Gras, J.-L.; Kong Win Chan, Y.-Y.; Bertrand, M. *Tetrahedron Lett.* **1982**, *23*, 3571.

(22) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.

(23) (a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768 and references therein. (c) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067.

(24) Satoh, Y.; Serizawa, H.; Hara, S.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 5225.

(25) Quitschalle, M.; Kalesse, M. *Tetrahedron Lett.* **1999**, *40*, 7765.

(26) Babler, J. H.; Buttner, W. J. *Tetrahedron Lett.* **1976**, *4*, 239.

(27) (a) Pfenninger, A. *Synthesis* **1986**, 89. (b) Bolitt, V.; Mioskowski, C.; Bhatt, R. K.; Falck, J. R. *J. Org. Chem.* **1991**, *56*, 4238.

(28) Hutchins, R. O.; Taffer, I. M.; Burgoyne, W. *J. Org. Chem.* **1981**, *46*, 5214.

(29) (a) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014.

(30) (a) Noyori, R. *Tetrahedron* **1994**, *50*, 4259. (b) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227. (c) Taber, D. F.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639.

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