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The synthesis and evaluation of 12,13-benzodesoxyepothilone B: a highly convergent route

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Abstract

The title compound retains some of the affinity for microtubule assemblies as does 12,13-desoxyepothilone B.

The advent of paclitaxel as a clinically valuable antitumor drug[1] was followed by the discovery of several other agents that seem to share its mechanistic mode of action, i.e. stabilization of cellular microtubules. Of these post-paclitaxel agents which apparently target microtubules, those which have attracted the greatest attention have been epothilones A and B[2] as well as eleutherobin[3] and discodermolide.[4] On considerations of 'seniority' of discovery, availability from fermentation, and in vivo potency, epothilones A and B have advanced the furthest of the post paclitaxel agents.[2]

Our laboratory and others have been addressing the epothilones in terms of total synthesis[5] and development of SAR profiles.[6] In the light of the potency of the epothilones and their apparently robust performance against otherwise resistant tumor cell lines,[7] we undertook a strong commitment directed toward the synthesis of epothilones A and B. These compounds were not available to us from natural fermentation sources. Given materials obtained from our initial stereospecific total synthesis,[8a] and from its highly concise second generation variation,[8b] we were able to conduct the first and thus far only published in vivo studies on a variety of xenograft models.[6a,9,10] The results of these efforts, in the aggregate, identified apparently serious in vivo toxicity problems with epothilones A and B (derived solely from total synthesis). If extrapolated to the clinical situation, these findings could foreshadow

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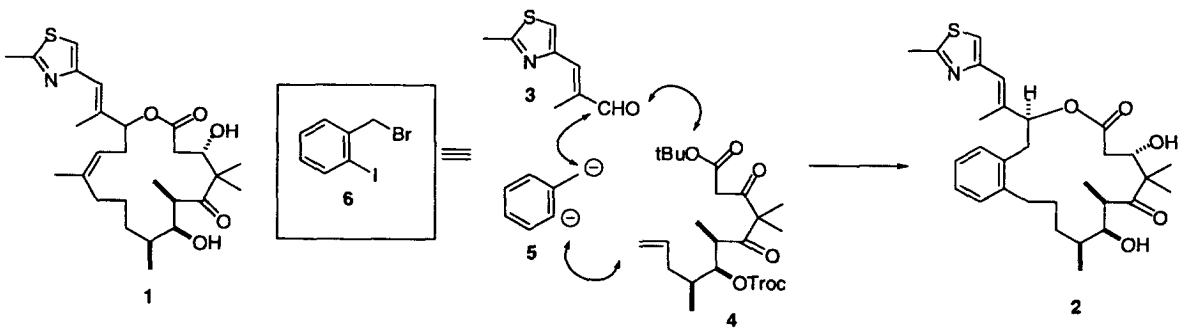
a poor therapeutic index for human therapy for the A and B drugs themselves. Remarkably our investigations revealed that the peripheral toxicity manifested by the intact epothilone B is dramatically attenuated through the use of 12,13-*Z*-12,13-deoxyepothilone B (**1**).[11] The results of extensive in vivo investigations, detailed elsewhere,[10] have identified deoxy system **1** as a promising drug candidate.

A collaborative effort, combining chemical synthesis, molecular modeling, and tubulin binding assays revealed a common pharmacophore that embraces nonataxel, epothilone B, eleutherobin, and discodermolide.[12] We noted that the 12,13 epoxidic oxygen of epothilones A and B does not fall within the dimensions of the common pharmacophore model which embraces the four drugs. In these terms, the non-requirement of the epoxide for tubulin binding was readily accommodated.

In the work described here, we undertook examination of the consequences of a bold invasion of apparently 'non-pharmacophore space' in the epothilone series in the area of C12 and C13. For this purpose we defined as our target, the 12,13 benzo-derivative of desoxyepothilone A. Quite aside from our interest in the consequences of this major departure from the epothilone motif at the modeling level, the synthetic issues to be faced in addressing target **2** were not without considerable inherent challenge. We describe first a concise solution to the synthetic problem. The approach has ramifications for other targets of opportunity in the epothilone area.

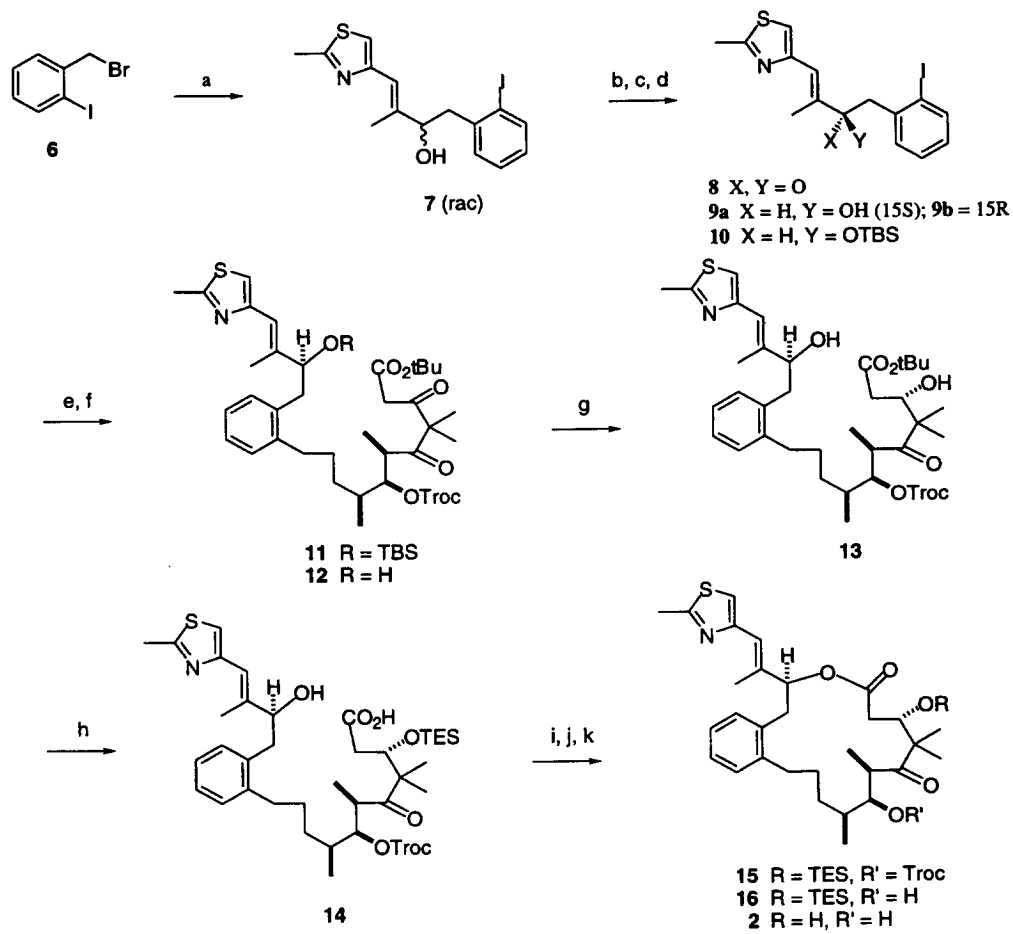
Our strategy for the synthesis of **2** was much influenced by our earlier work in various generations of our epothilone total synthesis effort (Scheme 1). In fact we took advantage of two building blocks, **3** and **4**, from the total synthesis of **1**.[8a,b] This approach clearly identified the need to interpolate the equivalent of dianion **5** between subunits **3** and **4**. For reduction to practice, we elected to work with 2-iodobenzyl bromide[13] (**6**). Success in the synthesis effort would depend on the ability to exercise strict control over the iodine and bromine functions in the interpolation phase.



Scheme 1.

To begin the synthesis, selective metallation of 2-iodobenzyl bromide (**6**) at the benzylic position with zinc and subsequent transmetallation to the higher-order cuprate[14] provided a nucleophile that added in a 1,2-fashion to enal **3** to give the racemic alcohol (Scheme 2). To reach the required stereochemistry of the alcohol at C_{15}, **7** *rac* was oxidized, and the resultant ketone **8** reduced with the Corey pro-S CBS reagent.[15] In the event, after extensive examination of conditions and reagents, a 4:1 mixture of **9***S* and **9***R* was obtained. This mixture was carried forward until the macrolactonization step (vide infra) at which point the last vestiges of the minor product were removed. The CBS reduction products **9***S* and **9***R* were converted to **10** (only the C_{15} S product is shown). The stage was set for the critical merger of the major fragments. In the event, hydroboration of alkene **4**, as shown, afforded the presumed borane (**4a**) which was subjected to B-alkyl Suzuki coupling[8a] with **10**. Following deprotection of the silyl group, **12** (plus a small amount of its C_{15} epimer) were in hand.

At this point, the β-keto ester functionality of **12** was reduced by adaptation of Noyori hydrogenation



Scheme 2. (a) Zn; CuCN, LiCl, $BF_3 \cdot OEt_2$; **3** (67%); (b) Swern oxidation; (c) (*R*)-2-Me-CBS-oxazolidinone, $BH_3 \cdot SMe_2$; (d) TBSOTf, lutidine (92%); (e) **4**, 9-BBN, THF; $Pd(dppf)Cl_2$, Ph_3As, $CsCO_3$, DMF (70%); (f) HF·pyridine (72%); (g) (*R*)-Ru-BINAP catalyst, H_2 (1200 psi) (82%); (h) TESOTf, TEA; HCl, MeOH, THF (65%); (i) 2,4,6-trichlorobenzoyl chloride, TEA; DMAP (57%); (j) SmI_2 (70%); (k) HF·pyridine (86%)

conditions[8b] in a highly diastereoselective fashion to afford the hydroxy ester **13**. This product was readied for macrolactonization as indicated (see **14**, only C_{15} *S* isomer shown). Cyclization proceeded cleanly affording after chromatographic purification a diastereomerically pure product (**15**). A two step deprotection sequence, conducted as shown,[8b] afforded the target molecule (**2**).

The synthetic aryl-containing epothilone analog (**2**) was evaluated for tubulin binding in the standard assay, and was found at 60 min, to retain 40% of the activity of the parent structure, dEpoB (Fig. 1). In cytotoxicity results against a variety of cancer cell lines (CCRF-CEM, CCRF-CEM/VBL, and CCRF-CEM/VM1), the IC_{50} of **2** tended to be in the low micromolar range. Thus, **2** manifests reduced cytotoxicity relative to **1** by a factor of ca. 500. This result may be due to drug transport and drug availability problems of the more hydrophobic, less soluble benzo analog. Having shown that the area surrounding the 12,13 double bond can, in principle, be encompassed in a ring without serious loss of affinity for microtubule assembly, and having developed a convergent synthetic route to reach such agents, we will continue to explore the possibilities for generating novel epothilones.

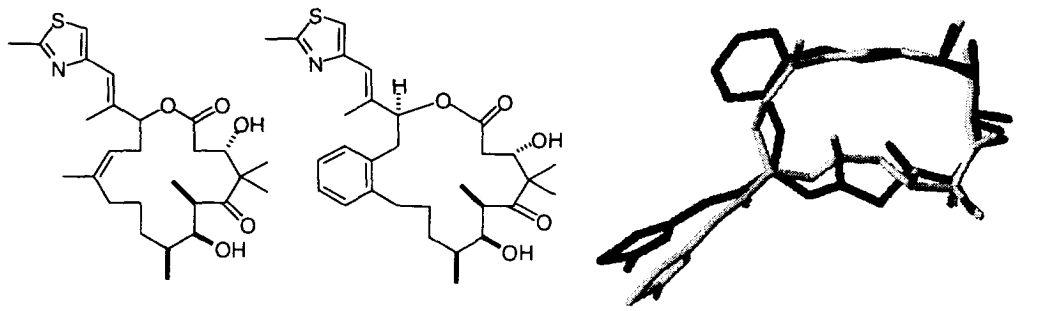


Figure 1.

Acknowledgements

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