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Chemo- and stereoselective epoxidation of 12,13-desoxyepothilone B using 2,2′-dimethyldioxirane

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Abstract—Epoxidation of 12,13-desoxyepothilone B (dEpoB) to epothilone B (EpoB), using DMDO, reproducibly gives excellent stereoselectivity with high confidence and yield. © 2001 Published by Elsevier Science Ltd.

The epothilones have continued to attract interest as potential alternatives to the taxanes, which are clinically important anticancer agents. Epothilone B and its 15-aza congener have each been advanced through phase I studies.[1] In 1997, we reported on the total synthesis of epothilones A and B, and more recently on epothilone F.[2] The ultimate step in those syntheses involved the epoxidation of 12,13-desoxyepothilones to the epothilones. Remarkably, these epoxidations proved to be highly chemo- and stereoselective.

The success of the late stage epoxidation in the needed sense was by no means assured at the outset. We had suspected that installation of the 12,13-epoxide might be attainable from two considerations. First, attack of the oxidizing agent might occur from the β-face of the macrocycle on the basis of local conformational preferences.[3] Secondly, we presumed that installation of the epoxide functionality, in nature's biosynthesis, occurs as the last step in the sequence and were optimistic that some reagent could be found to mimic this admittedly enzymatically mediated outcome. This presumption indeed turned out to be the case. Recently the gene cluster responsible for epothilone biosynthesis was cloned and completely sequenced.[4] As hypothesized, it was discovered that a cytochrome P450 epoxidase enzyme (*EpoK*) catalyzes the conversion of desoxyepothilones into epothilones as the final step in epothilone biosynthesis.

Our original synthesis of epothilone B from the 12,13-desoxy precursor was chemoselectively accomplished using 2,2′-dimethyldioxirane.[5] By contrast, Höfle had found that when *m*CPBA was used as the oxidant, at least with dEpoA, three regions are susceptible to oxidation, namely the thiazole ring (either N or S), the 16,17-olefin, and the 12,13-olefin, with the 12,13-olefin as the major product.[6] We subsequently noted, with some consternation, that later workers studying the epoxidation of dEpoA and dEpoB were, in several instances, unable to duplicate our earlier claims.[7] These failures to meet expectations based on our results have led to the use of other less effective reagents or even redesigns of epothilone syntheses to circumvent the epoxidation step which we felt to be eminently selective.[8] Accordingly, we reinvestigated the terminal epoxidation step. Our results fully confirm our earlier claims but point to the need for close adherence to the conditions described. Failure to follow these protocols does indeed lead to slippage in selectivity.

We have found that the diastereoselectivity of the epoxidation is highly temperature dependent (Table 1). At room temperature the C_{12}–C_{13} diastereoselectivity was modest (8:1) favoring the desired β-stereoisomer. However, when the reaction is performed at −78°C the diastereoselectivity increases to >20:1. To achieve high levels of stereoselectivity, it is critical that the DMDO solution be precooled to the desired temperature. Since the epoxidation reaction is rapid at higher temperature, failure to precool the DMDO solution results in degraded diastereoselectivity. Even though the diastereoselectivity of the reaction is highest when the epoxidation is carried out at −78°C, the required reaction time increases correspondingly (∼24 h). For this reason, the most convenient temperature, with the

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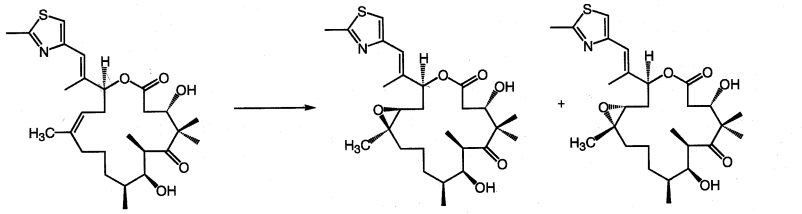
Table 1.



12,13-Desoxyepothilone B Epothilone B Epothilone B, α-epoxide

Reaction	Temperature (°C)	DR (β:α)	Time	Yield (%)
1	−78	>25:1	12 h	100
2	−50 (fresh DMDO)	16:1	2 h	85
3	−50 (1 week DMDO)	16:1	2 h	85
4	−50 (4 months DMDO)	16:1	2 h	85
5	−20	14:1	45 min	85
6	0	11:1	30 min	75
7	25	8:1	15 min	70

Reaction 1 through 5 were performed by addition of freshly titrated DMDO (2.2 equiv.) to a dichloromethane solution containing dEpoB. The excess dioxirane was quenched at the designated temperature with dimethylsulfide followed by concentrated in vacuo. Reactions 6 and 7, which were run at temperatures >0°C, utilized only 1.0 equiv. of DMDO to minimize secondary oxidation reactions.

highest level of stereoselectivity for the reaction is −50°C. At this temperature, complete consumption of starting material is realized within 2 h with a diastereoselectivity of 16:1. Under these conditions we encounter little or no competition from the vinyl thiazole sector for oxidation.[10]

We also suspected that alternative reagents for the epoxidation reaction have been utilized due to the fact that DMDO is not commercially available. Recognizing that long term storage of acetone solutions of DMDO may lead to some decomposition, we assessed the stereoselectivity and yield of the epoxidation relative to the apparent age of the DMDO solutions. Remarkably, when the reaction was carried out at the optimal temperature of −50°C, *no difference in product was observed using DMDO solutions up to 4 months old!* This result is significant in the fact that although solutions of DMDO are not commercially available, prepared solutions are stable upon prolonged storage.[9]

In summary, 2,2′-dimethyldioxirane is a convenient and efficient reagent for the chemo- and stereoselective oxidation of the epothilone 12,13-olefinic linkage to the corresponding epoxide. We have demonstrated that the reaction diastereoselectivity decreases as the reaction temperature is increased. In addition, we have demonstrated that dilute acetonic solutions of DMDO, when stored at −78°C, retain their potency and do not result in adventitious reactions. In conclusion, when strict experimental protocols are followed the epoxidation of dEpoB to EpoB, using DMDO, reproducibly gives excellent stereoselectivity with high confidence. We see no benefit in recourse to other epoxidizing agents which are either more difficult to prepare or which produce inconvenient debris thereby complicating workup.

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9. DMDO solutions ($\sim$0.08 M in acetone) were routinely stored over 4 Å molecular sieves at −78°C.
10. Typical procedure: A solution of dEpoB (0.01 g, 0.021 mmol) in dichloromethane (1 mL) was cooled to −78°C. In a separate flask DMDO (0.1 M in acetone, 0.46 mL, 0.46 mmol) was cooled to −78°C and cannulated into the flask containing dEpoB. After the addition was complete the solution was warmed to −50°C and stirred for 2 h. The excess DMDO was quenched at −50°C by the addition of dimethylsulfide (0.1 mL). The solvent was removed in vacuo. Purification by preparatory thin layer chromatography (prep TLC, 70% EtOAc/hexanes) provided EpoB (0.009 g, 85%, ds 16:1).