

Radical-induced Opening of Trisubstituted Epoxides: Application in the Synthesis of C₁-C₁₂ Segment of Epothilones

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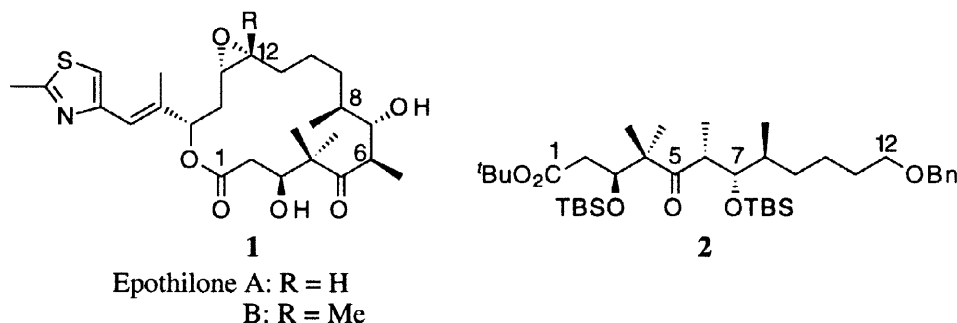
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Abstract: Diastereo- and regioselective opening of a trisubstituted epoxy ketone at the more substituted carbon using samarium(II) iodide presents an alternate approach to the C₅-C₇ aldol moiety with β -hydroxyketo framework in the stereoselective synthesis of C₁-C₁₂ segment of epothilones.

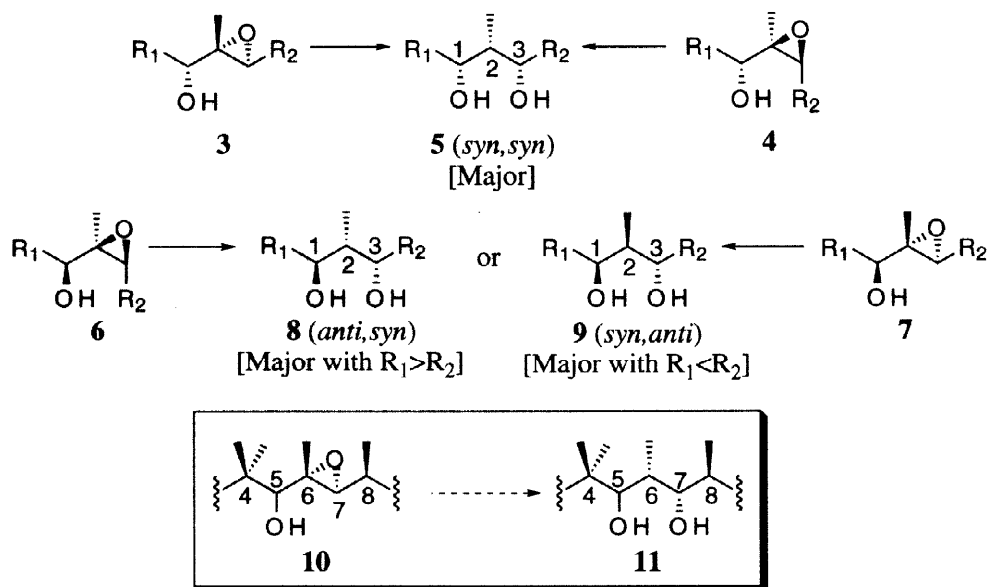
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The unique biological profiles of epothilones (**1**)¹ as powerful antifungal and antitumor agents with taxol-like microtubule-stabilizing properties, even in taxol-resistant cell lines,² have generated tremendous interests amongst the organic chemists worldwide. In less than one year's time, no fewer than six total syntheses of epothilones and several studies directed toward their syntheses have been reported.³ Herein, we report the synthesis of the C₁-C₁₂ moiety of epothilones A and B (**2**), an advanced stage intermediate similar to the one used by Schinzer *et al* in their total synthesis.^{3h}

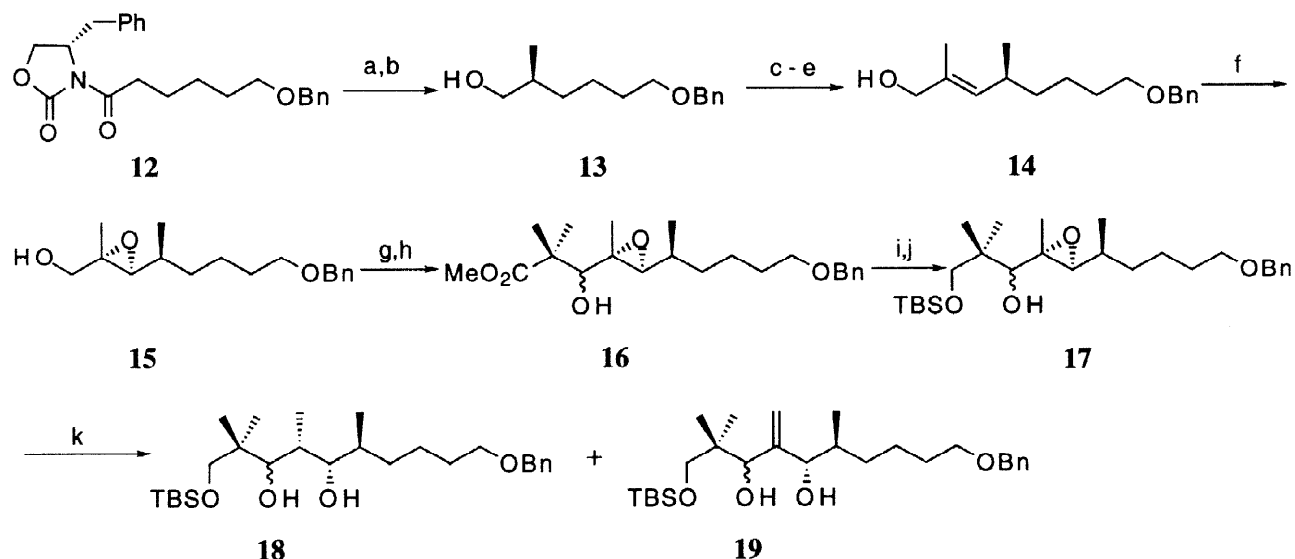


To begin with, our aim was to show the applicability of our recently developed method for the synthesis of 2-methyl-1,3-diols by radical-mediated anti-Markovnikov opening of trisubstituted epoxy alcohols at the more substituted carbon using Cp₂TiCl-cyclohexa-1,4-diene⁴ in the construction of the C₆ and C₇ stereocenters of epothilones which have, so far, been made mostly by aldol approach³ except in the synthesis by Danishefsky *et al*^{3d} who have built these stereocenters following a Diels-Alder route. According to our study,⁴ both *syn* and *anti* epoxy alcohols, **3** and **4** respectively, on epoxide ring opening with Cp₂TiCl-cyclohexa-1,4-diene give *syn,syn* diol **5** as the major product, whereas the products from epoxy alcohols **6** and **7** depend on the relative sizes of R₁ and R₂. When R₁ is bigger than R₂ the major product is *anti,syn* diol **8**.

With smaller R_1 , the *syn,anti* product **9** predominates. This prompted us to build an epoxy alcohol like **10**, as a target intermediate in our present study, which could be subjected to our epoxide ring opening reaction. The stereochemistry at C_5 was not considered important since either isomer, R_1 group (C_4) being bigger than R_2 (C_8), was expected to provide the desired 6,7-*syn* product **11**. Moreover, the C_5 hydroxyl was anyway to be oxidized, later on, to keto.



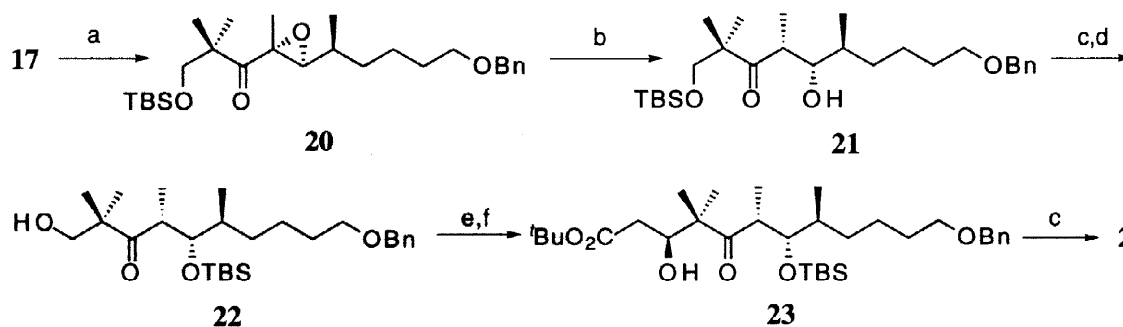
Our synthesis started with oxazolidinone **12** prepared from mono-benzyl-protected hexane-1,6-diol in three steps. Diastereoselective alkylation of the sodium enolate of **12** with MeI⁵ (scheme 1) was followed by



Scheme 1. a) NaHMDS, MeI, THF, -78 °C; b) LiBH₄, H₂O, Et₂O, 0 °C; c) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 to 0 °C; d) Ph₃P=C(CH₃)CO₂Et, CH₂Cl₂, 25 °C; e) DIBAL, CH₂Cl₂, -78 °C; f) Ti(OⁱPr)₄, (+)-DET, TBHP, CH₂Cl₂, -78 °C to -40 °C; g) same as step c; h) (CH₃)₂CHCO₂Me, LDA, THF, -78 °C; i) LiBH₄, THF, 0 °C; j) TBSCl, Et₃N, CH₂Cl₂, 0 to 25 °C; k) Cp₂TiCl, 1,4-cyclohexadiene, THF, -20 to 25 °C.

reductive removal of the chiral auxiliary⁶ (80% in two steps). The resulting alcohol **13**⁷ was then subjected to oxidation, olefination, and, finally, reduction to get the *E*-allylic alcohol **14**⁷ in 75% overall yield. Epoxidation of **14** by Sharpless epoxidation method⁸ using molar equivalents of reagents at -78 °C and allowing to reach -40 °C slowly over 3-4 hours time gave epoxide **15**⁷ with de $\geq 95\%$ (80% yield). Swern oxidation of the epoxy alcohol **15** gave an aldehyde which was reacted with lithium enolate of methyl isobutyrate to get diastereomeric mixture of alcohols **16**⁷ (90% from **15**). Reduction of **16** with LiBH₄ was followed by selective TBS-protection to furnish the epoxy alcohol **17**⁷ (85% yield) having the requisite structural framework of **10**.

The stage was now set to try the opening of the epoxy ring of **17** following our method. But, when **17** was treated with Cp₂TiCl-cyclohexa-1,4-diene according to the procedure described earlier,⁴ the desired intermediate **18** was formed as a minor product, the major one being an unwanted olefin **19**. This came as a surprise to us since no such product was ever encountered by us with the substrates used in our earlier study.⁴ All our efforts to obtain **18** as the major product failed. This forced us to look for an alternate, but preferably a radical-mediated method, to carry out the desired epoxide opening. After trying several reagents unsuccessfully,⁹ the choice fell on samarium(II) iodide (SmI₂) which is known to open epoxy ketones at the α -carbon.¹⁰ We wanted to use this reagent to open our trisubstituted epoxide.



Scheme 2. a) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 to 0 °C; b) SmI₂, MeOH, THF, -90 °C; c) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C; d) CSA, MeOH-CH₂Cl₂, 0 to 25 °C; e) SO₃-Py, Et₃N, DMSO-CH₂Cl₂, 25 °C; f) H₂C=C(O^tBu)OTBS, BF₃-Et₂O, CH₂Cl₂, -78 °C.

Accordingly, epoxy alcohol **17** was oxidised to the ketone **20** (scheme 2) which was selectively opened, as expected, by SmI₂ (2.5 molar equiv., 0.1 M sol. in THF) in MeOH-THF (1:1) at the more substituted carbon to give the desired product **21** as a single diastereomer (90% yield). The *J*_{6,7} of 6.7 Hz as reported for similar compounds³ confirmed the assigned stereochemistry. Silylation of **21** was followed by selective removal of the primary silyl group (80% overall). The resulting alcohol **22** was oxidised to an aldehyde which was subjected to Mukaiyama aldol reaction¹¹ with silyl ketene acetal to get a mixture (3:1) of diastereomers in 85% yield with the major product having the desired stereochemistry as determined by NMR coupling constants. The C₃-H of the major isomer **23** came at δ 4.28 as a dd with 5.7 and 3.6 Hz coupling constants which were matching with the reported values for similar compounds.³ Finally, silylation of the C₃-hydroxyl gave the target compound **2**.¹²

In conclusion, a novel approach based on diastereo- and regioselective opening of a trisubstituted epoxy ketone with SmI₂ to get the crucial β -hydroxy ketone moiety is presented here which supplements earlier approaches based on aldol and Diels-Alder reactions. An intermediate very similar to **2** has already been converted to epothilone A.^{3h}

ACKNOWLEDGEMENTS

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12. ¹H NMR (CDCl₃, 200 MHz): δ 7.3-7.2 (m, 5 H, aromatic), 4.48 (s, 2 H, OCH₂Ph), 4.28 (dd, *J* = 5.7, 3.6 Hz, 1 H, C₃-H), 3.77 (d, *J* = 6.7 Hz, 1 H, C₇-H), 3.43 (t, *J* = 6.7 Hz, -CH₂OBn), 3.11 (dq, *J* = 6.7 Hz, 1 H, C₆-H), 2.37 (dd, *J* = 17.1, 3.6 Hz, 1 H, C₂-H), 2.16 (dd, *J* = 17.1, 5.7 Hz, 1 H, C₂-H'), 1.6-1.2 (m, 7 H, CH₂ and CH), 1.4 (s, 9 H, CO₂C(CH₃)₃), 1.25 and 1.2 (two s, 6 H, C₄-Me₂), 1.02 (d, *J* = 6.4 Hz, 3 H, C₈-CH₃), 1.0 (d, *J* = 6.7 Hz, 3 H, C₆-CH₃), 0.88 and 0.86 (two s, 18 H, Si-'Bu), 0.094, 0.045, 0.038, and 0.011 (four s, 12 H, SiMe); MS (LSIMS): *m/e* 691 (M⁺-1).