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Radical-induced Opening of Trisubstituted Epoxides: Application in the Synthesis of C_1-C_{12} Segment of Epothilones

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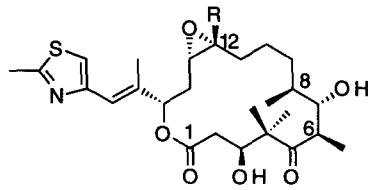
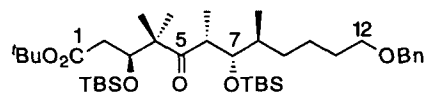
Abstract: Diastereo- and regioselective opening of a trisubstituted epoxy ketone at the more substituted carbon using samarium(II) iodide presents an alternate approach to the C_5-C_7 aldol moiety with β-hydroxyketo framework in the stereoselective synthesis of C_1-C_{12} segment of epothilones.

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 C_1-C_{12} 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]



1

Epothilone A: R = H
B: R = Me



2

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 Cp_2TiCl-cyclohexa-1,4-diene[4] in the construction of the C_6 and C_7 stereocenters of epothilones which have, so far, been made mostly by aldol approach[3] 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 Cp_2TiCl-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 R_1 and R_2. When R_1 is bigger than R_2 the major product is *anti,syn* diol **8**.

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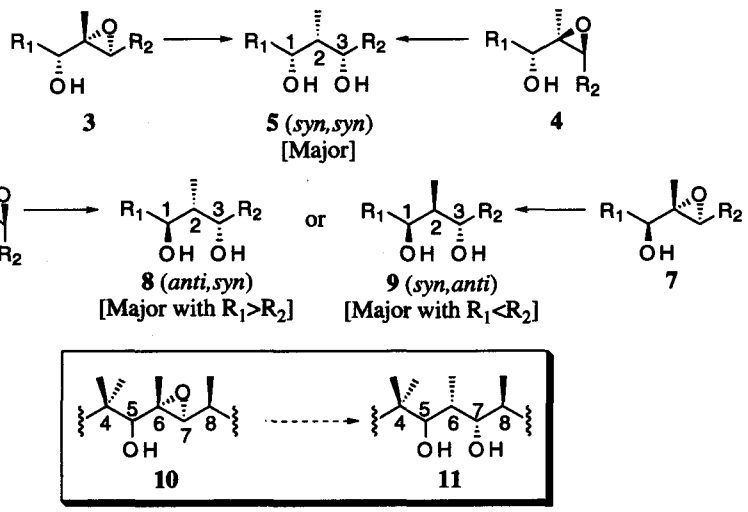
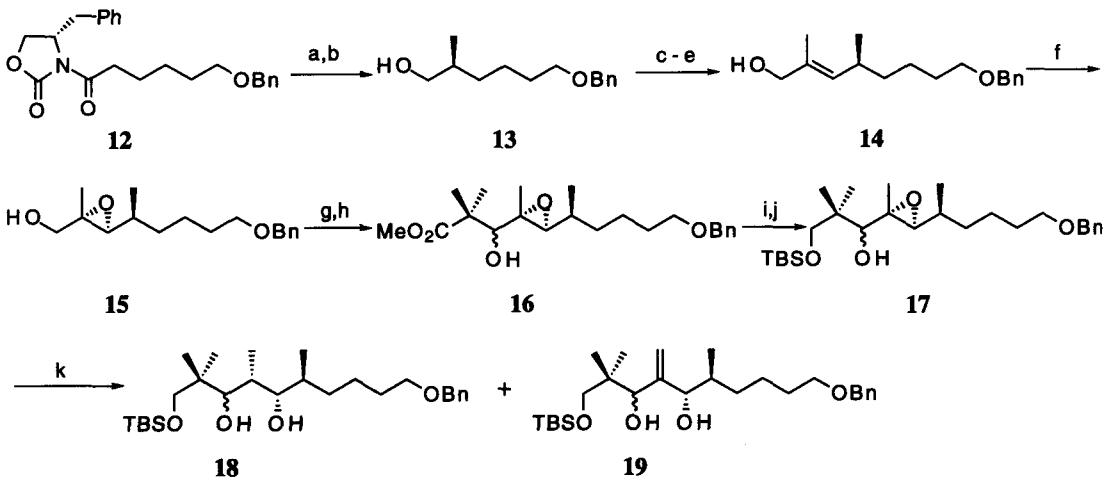
With smaller R_1, the *syn,anti* product **9** predominates. This prompted us to build an epoxy alcohol like **10**, as a target intermediate in our present study, which could be subjected to our epoxide ring opening reaction. The stereochemistry at C_5 was not considered important since either isomer, 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.



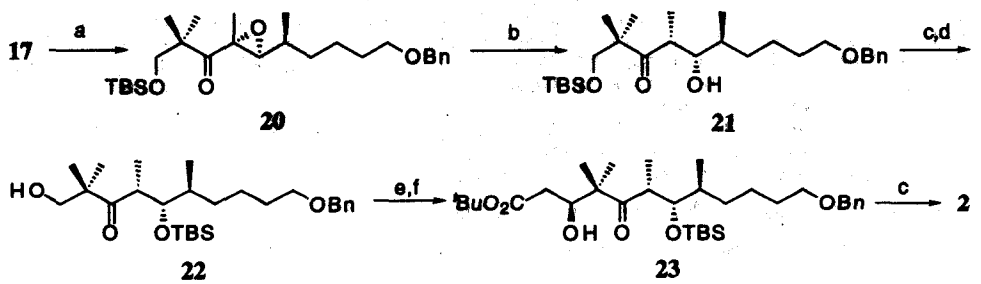
Our synthesis started with oxazolidinone **12** prepared from mono-benzyl-protected hexane-1,6-diol in three steps. Diastereoselective alkylation of the sodium enolate of **12** with MeI[5] (scheme 1) was followed by



Scheme 1. a) NaHMDS, MeI, THF, -78 °C; b) $LiBH_4$, H_2O, Et_2O, 0 °C; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 0 °C; d) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, 25 °C; e) DIBAL, CH_2Cl_2, -78 °C; f) $Ti(O^iPr)_4$, (+)-DET, TBHP, CH_2Cl_2, -78 °C to -40 °C; g) same as step c; h) $(CH_3)_2CHCO_2Me$, LDA, THF, -78 °C; i) $LiBH_4$, THF, 0 °C; j) TBSCl, Et_3N, CH_2Cl_2, 0 to 25 °C; k) Cp_2TiCl, 1,4-cyclohexadiene, THF, -20 to 25 °C.

reductive removal of the chiral auxiliary[6] (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 method[8] 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 ≥ 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 $LiBH_4$ 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 Cp_2TiCl-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 (SmI_2) 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, Et_3N, CH_2Cl_2, -78 to 0 °C; b) SmI_2, MeOH, THF, -90 °C; c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; d) CSA, MeOH-CH_2Cl_2, 0 to 25 °C; e) SO_3-Py, Et_3N, DMSO-CH_2Cl_2, 25 °C; f) $H_2C{=}C(O^tBu)OTBS$, BF_3-Et_2O, CH_2Cl_2, -78 °C.

Accordingly, epoxy alcohol **17** was oxidised to the ketone **20** (scheme 2) which was selectively opened, as expected, by SmI_2 (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 compounds[3] 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 reaction[11] 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 C_3-*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 C_3-hydroxyl gave the target compound **2**.[12]

In conclusion, a novel approach based on diastereo- and regioselective opening of a trisubstituted epoxy ketone with SmI_2 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]

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12. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.3-7.2 (m, 5 H, aromatic), 4.48 (s, 2 H, OCH_2Ph), 4.28 (dd, *J* = 5.7, 3.6 Hz, 1 H, C_3-*H*), 3.77 (d, *J* = 6.7 Hz, 1 H, C_7-*H*), 3.43 (t, *J* = 6.7 Hz, -CH_2OBn), 3.11 (dq, *J* = 6.7 Hz, 1 H, C_6-*H*), 2.37 (dd, *J* = 17.1, 3.6 Hz, 1 H, C_2-*H*), 2.16 (dd, *J* = 17.1, 5.7 Hz, 1 H, C_2-*H'*), 1.6-1.2 (m, 7 H, CH_2 and C*H*), 1.4 (s, 9 H, $CO_2C(CH_3)_3$), 1.25 and 1.2 (two s, 6 H, C_4-Me_2), 1.02 (d, *J* = 6.4 Hz, 3 H, C_8-CH_3), 1.0 (d, *J* = 6.7 Hz, 3 H, C_6-CH_3), 0.88 and 0.86 (two s, 18 H, Si-^{t}Bu), 0.094, 0.045, 0.038, and 0.011 (four s, 12 H, SiMe); MS (LSIMS): *m/e* 691 (M^+-1).