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Efficient Enantioselective Synthesis of a β-Hydroxyepoxide Building Block for the Construction of Macrocyclic Natural Products

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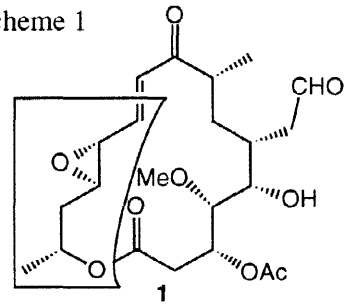
Abstract: The synthesis of a protected β-hydroxyepoxide macrolide building block in seven steps from commercially available (*R*)-3-hydroxybutyric acid methyl ester in 68% overall yield is described.

Macrocyclic natural products like macrolides and macrolactams display a variety of biological activities and are widely used in the treatment of disease.[1] Therefore, they have been the subject of numerous intense research activities which culminated in a variety of elegant total syntheses.[2] Recently, this area of research has gained a new impulse by mingling the approaches of solid phase chemistry and natural product total synthesis. Thus, the macrolides epothilon A and B as well as numerous analogs thereof could be synthesized on a solid support by employing a versatile and flexible building block strategy.[3] The application of this principle to other natural products requires that the building blocks to be employed as well as analogs thereof must be accessible in an efficient and flexible manner.

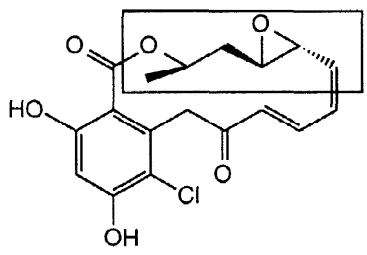
Numerous macrocyclic natural products like the aglycon of carbomycin A[4a] **1**, radicicol[4b] **2** and decarestrictine F[4c] **3** embody a β-hydroxyvinyl epoxide unit (Scheme 1).

Scheme 1



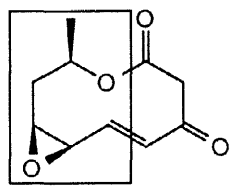
1

Aglycon of Carbomycin A



2

Radicicol



3

Decarestrictine F

The presence of this highly electrophilic fragment strongly influences the biological activity of these natural products. For instance the anti-fungal and anti-tumor activity of radicicol is not shared by the related compounds monocillin II-V which lack either a double bond or the epoxide or even both.[5] Therefore, in order to construct such natural products and analogs thereof via the approach mentioned above, the development of an efficient synthetic access to a chiral building block, e.g. **10**, would be highly desirable which might be incorporated in total syntheses, and which might also be amenable to the construction of analogs. In this communication we describe a synthetic route which fulfils these demands.

Thus, (*R*)-3-hydroxybutyric acid methyl ester **5** was converted into the α,β-unsaturated ester **8**[6] as shown in Scheme 2. To this end, the alcohol present in **5** was protected as the thexyldimethylsilyl (TDS) ether and the ester was subsequently reduced to the alcohol **6** with DIBAH (94% over two steps). Swern oxidation afforded the respective aldehyde which due to its volatility was used immediately and without further purification for the following step. The crude aldehyde was subjected to a Horner reaction with diethylphosphonoacetate **7** under the conditions developed by Masamune and Roush et al.[7]. Thereby the ester **8** was obtained in excellent yield (92% over two steps) and with complete *E*-selectivity.

The reduction of the ethyl ester of **8** to the allyl alcohol presented unexpected difficulties since the intermediary formed alcoholate added to the activated double bond of unreacted **8**. However, strict control of the reaction temperature (2h at -20°C, 1h at 0°C, 12h at room temperature) circumvented this problem and the desired allyl alcohol was obtained in nearly quantitative yield. Its highly stereoselective conversion to the epoxide **9** (diastereomeric ratio 94:6) was accomplished by following the Sharpless protocol,[8] employing (-)-diethyl tartrate as stereodirecting ligand. Finally, the alcohol **9** was converted in high yield to the desired epoxyaldehyde **10**[9] by Swern oxidation. Overall by means of this synthetic route the epoxyaldehyde **10** was built up in multigram (up to 5 g) amounts from commercially available (*R*)-3-hydroxybutyric acid methyl ester **5** in seven steps with an overall yield of 68%. By means of this efficient and convenient reaction sequence various analogs of **10** should

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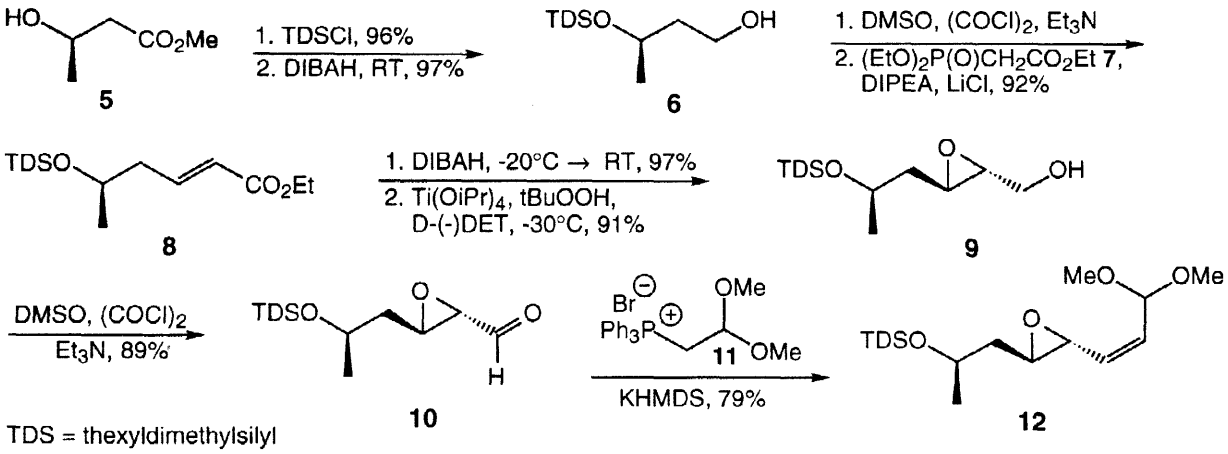
Scheme 2



be readily preparable. Thus, various β-hydroxy esters analogous to **5** are available in both enantiomeric forms e.g. via racemate resolution or enantioselective reduction of the corresponding β-ketocarbonyl compounds.[10]In addition, instead of the phosphonate **7** other nucleophiles can be used allowing for the attachment of further substituents to the double bond of **8**. Furthermore, the level of diversity can be raised further by means of the Sharpless epoxidation, i.e. via use of D(-) or L(+) diethyl tartrate.

Finally, in order to demonstrate that aldehydes like **10** can successfully be employed as reagents for the construction of the β-hydroxyvinyl epoxide moiety present in several macrocyclic natural products (see Scheme 1), in a model study **10** was converted to the vinyl epoxide **12** by means of a Wittig reaction with the phosphonium bromide **11** (Scheme 2). Thus, the silyl-protected vinyl epoxide **12** could be obtained in high yield and with high *Z*-selectivity from **10**. During this reaction the epoxide moiety remained unattacked.

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9) **10:** colorless oil; $[\alpha]_D^{23}$ = -66.7° (c = 0.76, CH_2Cl_2); **^{1}H NMR** (250 MHz, $CHCl_3$): δ (ppm) = 0.03 (s, 3H); 0.08 (s, 3H); 0.79 (s, 6H); 0.84 (d, *J* = 7.1 Hz, 6H); 1.20 (d, *J* = 5.8 Hz, 3H); 1.51-1.79 (m, 3H); 3.16 (dd, *J* = 6.2, 2.0 Hz, 1H); 3.43 (dt, *J* = 5.8, 2.0 Hz, 1H); 4.09 (sext, *J* = 5.8 Hz, 1H); 8.97 (d, *J* = 6.2 Hz, 1H); **^{13}C NMR** (62.8 MHz, $CDCl_3$): δ (ppm) = -3.05, -2.53, 18.43, 18.51, 20.04, 20.17, 23.48, 24.65, 34.02, 40.84, 54.12, 58.56, 66.05, 198.31. **IR** (film): 2960, 2868, 1733, 1466, 1440, 1379, 1252, 1211, 1142, 1128, 1106, 1077, 1032, 997, 969, 875, 835, 816, 777, 726, 679, 662.
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