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Total Synthesis of (+)-Decarestrictine L

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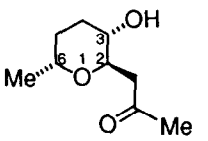
Abstract: The first total synthesis of (+)-decarestrictine L, a member of a new family of inhibitors of cholesterol biosynthesis, has been achieved utilizing a C_2 symmetrical diepoxide chiral synthon. The approach involves the construction of the tetrahydropyranyl nucleus by fully stereocontrolled intramolecular 1,4-conjugate addition.

Decarestrictine L (**1**) was isolated very recently by the joint group[1] of Hoechst and University of Göttingen from the culture broth of *Penicillium simplicissimum* as a very minor component (yield: 0.3 mg/L) of the decarestrictine family which is a novel class of inhibitors of cholesterol biosynthesis,[1-3] and was proposed to have the relative stereochemistry shown in **1**. This decarestrictine is characterized by the tetrahydropyranyl nucleus instead of the lactone ring which is usually found in other members of the decarestrictine family such as decarestrictine A to K,[1-3] and M.[1] The intriguing biological activity in this series and the extreme scarcity of natural material make the synthesis of decarestrictines an important goal.

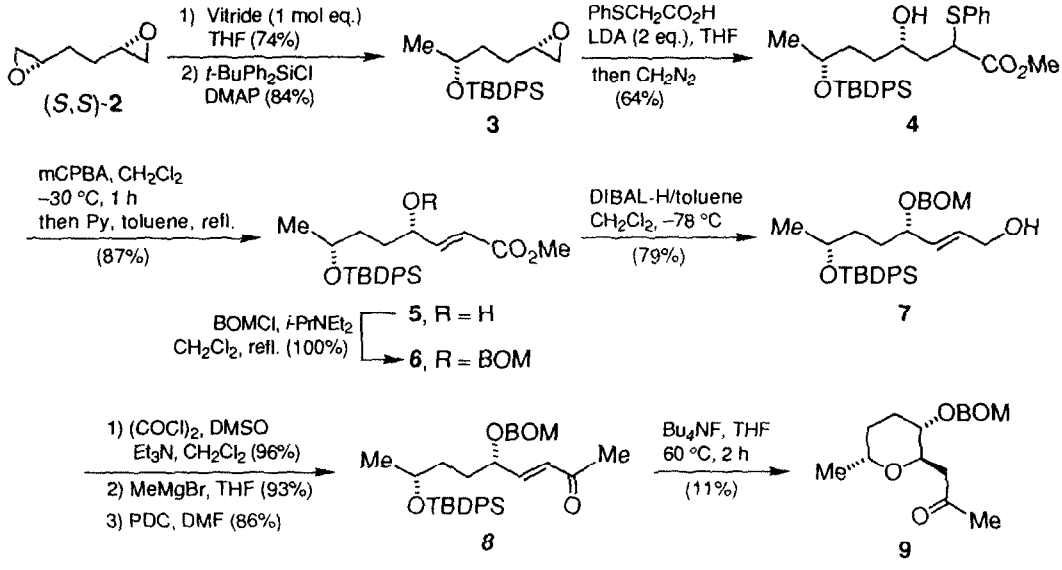
Recent investigations from this laboratory have revealed that the optically active C_6 unit with C_2 symmetry, i.e. 1,2:5,6-diepoxyhexane (**2**), economically available in both enantiomeric forms from D-mannitol,[4,5] serves as a multi-purpose chiral synthon in the preparation of various natural products including alkaloids[5,6] and macrodiolides.[7] As part of our continuing studies, we have sought to expand the versatility of this chiron protocol utilizing the diepoxide **2** to the enantioselective preparation of the naturally occurring decarestrictine family (no member of which has been synthesized to date). In this communication, we now report the first total synthesis of (+)-decarestrictine L (**1**) starting from the enantiomerically pure (*S,S*)-diepoxide **2** by an approach involving intramolecular 1,4-conjugate addition[8] of an oxygen nucleophile to an α,β-unsaturated ester with complete stereocontrol, thereby establishing the relative and absolute configurations of natural decarestrictine L as depicted in **1**.[9]



(+)-Decarestrictine L (**1**)

The (*S,S*)-diepoxide **2**[4,5] was converted to the (*E*)-α,β-unsaturated hydroxy ester **5** according to our own route previously described[7] for the preparation of the opposite enantiomer of **5** with a slight modification as outlined in Scheme I. The hydroxy group of **5** was protected as the benzyloxymethyl (BOM) ether giving

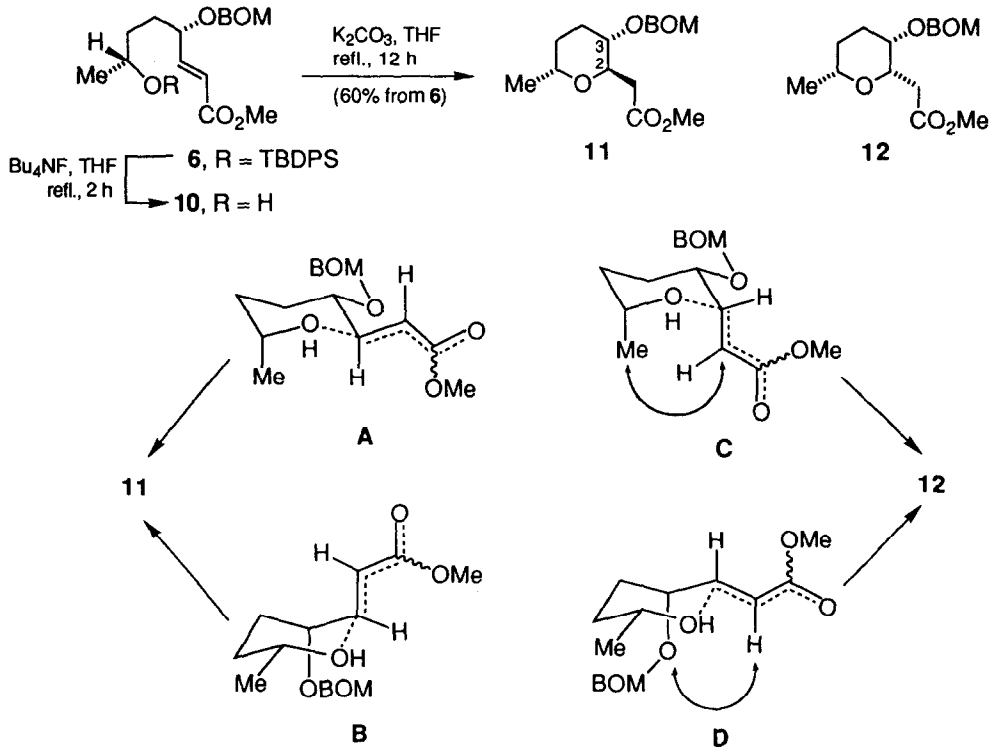
Scheme I



rise to **6** in quantitative yield. Reduction of this compound with DIBAL-H (CH_2Cl_2, –78 °C) afforded the allylic alcohol **7** (79% yield), which was transformed into the α,β-unsaturated ketone **8** (77% overall yield) by a three-step sequence involving Swern oxidation,[10] Grignard reaction of the resulting aldehyde, and PDC oxidation of the secondary alcohol. Desilylation of **8** was carried out with Bu_4NF in THF at 60 °C for 2 h. During this reaction intramolecular 1,4-conjugate addition of the alcohol to the alkenone occurred to form the tetrahydropyranyl nucleus **9** (for the stereochemical outcome, see below) which is BOM protected decarestrictine L. This route, however, provided poor yield (11%) of the adduct **9** and was accompanied with the formation of a complicated reaction mixture. On the other hand, after treating **8** with Bu_4NF, application of basic conditions (*t*-BuOK in THF) resulted in the formation of an inseparable complex mixture with no trace of **9**.

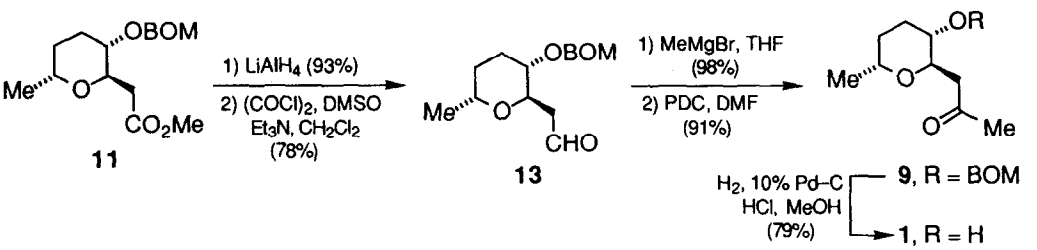
The intramolecular 1,4-conjugate addition could be accomplished effectively by using the foregoing α,β-unsaturated ester **6** as shown in Scheme II. Accordingly, this ester underwent desilylation with Bu_4NF (*THF, reflux, 2 h*) to form ***10*** (and probably 1,4-conjugate adduct(s) in part), which was without isolation subjected to subsequent 1,4-addition under thermodynamically equilibrated conditions (K_2CO_3, THF, reflux, 12 h) to afford **11** in 60% overall yield with exclusive trans (with respect to C-2 and C-3) selectivity.[11] Trans stereochemistry of the C-2 and C-3 substituents in **11** was secured by H-2–H-3 coupling constant of 6.7 Hz indicating *trans*-diaxial relationship.[12] The rationale for this selectivity is evident from an analysis of the possible chair-like transition states (Scheme II). The transition states **C** and **D** leading to the undesired cis adduct **12** are destabilized substantially by 1,3-diaxial interaction and 1,3-allylic strain,[13] respectively. In the trans-predictive transition states **A** and **B**, the latter conformer **B** would be energetically less favorable since both the sterically larger substituents adapt axial orientation. Consequently, the energetically most favorable process would occur via the transition state **A**, thus providing predominantly the trans adduct **11**.

Scheme II



With the *trans*-tetrahydropyranyl derivative **11** thus in hand, the synthesis of decarestrictine L is completed as follows: Sequential reduction with $LiAlH_4$ and oxidation under Swern conditions led to the aldehyde **13**, which was then converted to the ketone **9** by Grignard reaction with MeMgBr followed by PDC oxidation. Hydrogenolytic removal of the BOM protecting group with palladium on carbon in the presence of a catalytic amount of HCl furnished (+)-decarestrictine L (**1**), $[\alpha]^{25}_D$ +28.8° (*c* 0.49, $CHCl_3$); $[\alpha]^{25}_D$ +52.5° (*c* 0.48, MeOH) [lit.[1] $[\alpha]_D$ +21.8° (*c* 0.5, MeOH)], in 79% yield. On comparison of spectroscopic data (^1H and ^{13}C NMR), the synthetic substance was found to be identical with natural decarestrictine L.[1]

Scheme III



In conclusion, our approach to (+)-decarestrictine L (**1**) has allowed us to demonstrate the additional versatility and flexibility of the diepoxide chiral synthon **2** in natural products synthesis and represents the first example of the synthesis of the decarestrictine, confirming the absolute natural configuration of **1** as 2*R*,3*S*,6*R*. Further experiments are in progress to extend this chiron approach to other decarestrictines.

References and Notes

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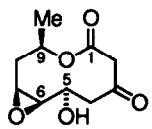
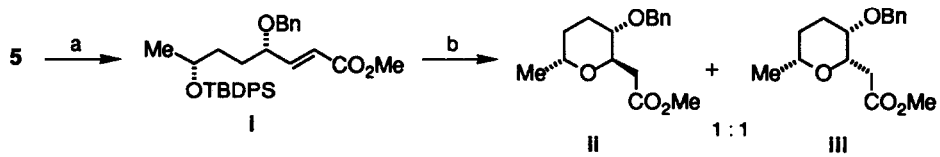
7. Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 841.
8. For a recent excellent review, see: Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.
9. At the beginning of this work, we tentatively inferred the C-2, C-3, and C-6 absolute configurations for decarestrictine L as depicted in **1** from the analogy with the corresponding C-5, C-6, and C-9 asymmetric centers of decarestrictine B,[3] the only naturally occurring decarestrictine to which the absolute stereochemistry has been assigned.



Decarestrictine B

10. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
11. When the conjugate addition was conducted by using the α,β-unsaturated ester **i**, prepared from **5**, for a short period of time (1 h), it resulted in a ca. 1:1 mixture (60% yield) of trans and cis adducts **ii** and **iii**.



(a) $PhCH_2OC(=NH)CCl_3$, $MeSO_3H$ (65%); (b) Bu_4NF, THF, refl., 2 h, then K_2CO_3, THF, refl., 1 h (60%).

12. For the axial-oriented protons at C-2 and C-3 in decarestrictine L, the trans coupling constant of 6.6 Hz has been reported.[1]
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