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Total synthesis of (–)-(3*R*,6*S*,9*R*)-decarestrictine C_2

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Abstract

Enantioselective synthesis of the proposed structure of (−)-(3*R*,6*S*,9*R*)-decarestrictine C_2 (**4**) has been accomplished using (2*S*,5*S*)-1,2,5,6-hexanetetrol (**9**) as a C_2-symmetric chiral synthon, in which the diastereoselective aldol-type reaction of a tin(II) enolate of 3-acetyl-4(*S*)-isopropyl-1,3-thiazolidine-2-thione with the α,β-unsaturated aldehyde was used as a key step.

Keywords: medium-ring heterocycles; aldol reactions; lactonization; X-ray crystal structures.

In 1992, the joint group of Hoechst AG and University of Göttingen reported[1] the isolation of a family of 10-membered lactones, named decarestrictines A–D, as the first representatives of a new class of fungal metabolites from cultures of *Penicillium simplicissimum* and *P. corylophilum*. Subsequent research by the same group on these cultures led to the further discovery of decarestrictines E–M as minor components of this class of fungal metabolites.[2] These metabolites were found to show more or less potent inhibitory effects on cholesterol biosynthesis in cell line tests with HEP-G2 liver cells.[1,2] Of these decarestrictines, decarestrictine A and decarestrictine C seemed to be homogeneous on TLC, however, their ^{1}H NMR spectra revealed that both decarestrictines actually consist of two components; A_1 and A_2 (**1** and **2**), and C_1 and C_2 (**3** and **4**) in the ratios of 3:1 and 1:1, respectively. The structural elucidation of both components of each diastereomeric mixture epimeric at C-3 could be possible because of the well separated signal patterns in their ^{1}H NMR spectra, and the relative and absolute stereochemistries of these compounds have been presented as shown. The interesting biological activity of decarestrictines has been responsible for recent synthetic activity, including the total syntheses of decarestrictines D (**5**),[3] J (**6**),[4] and L (**7**).[5]

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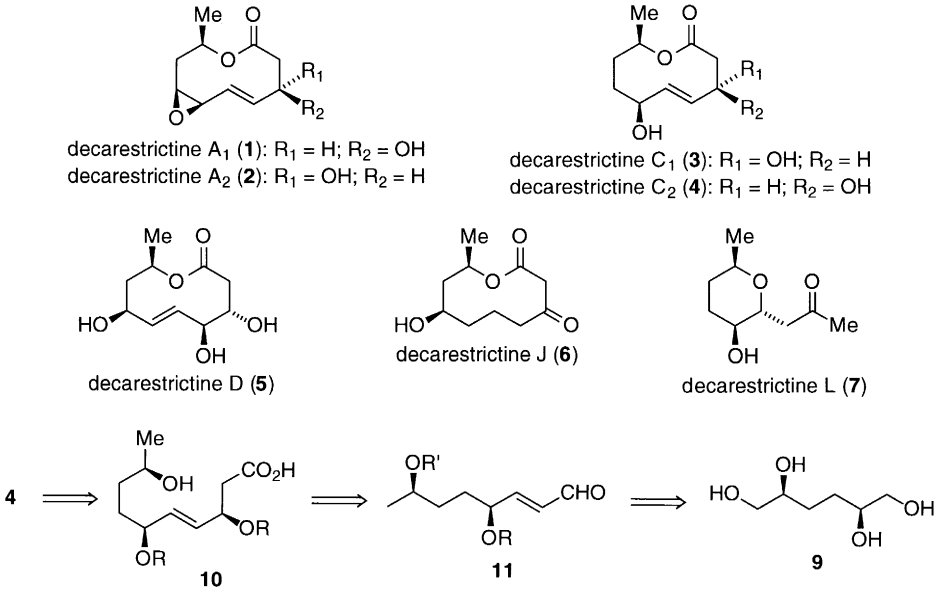
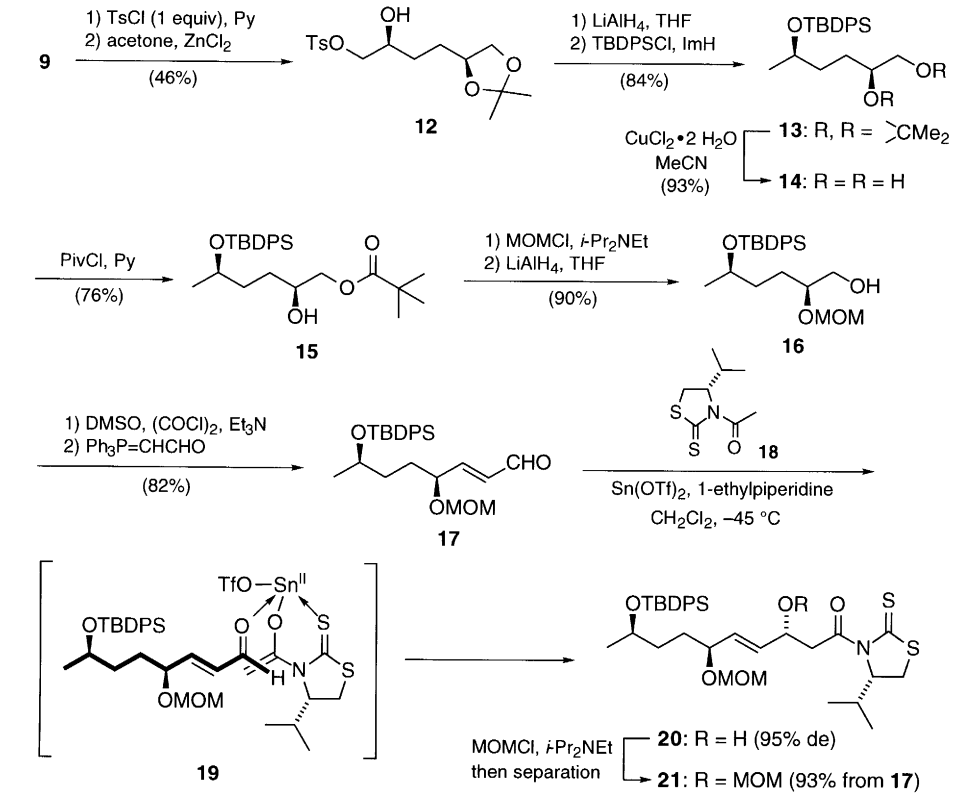


Scheme 1.

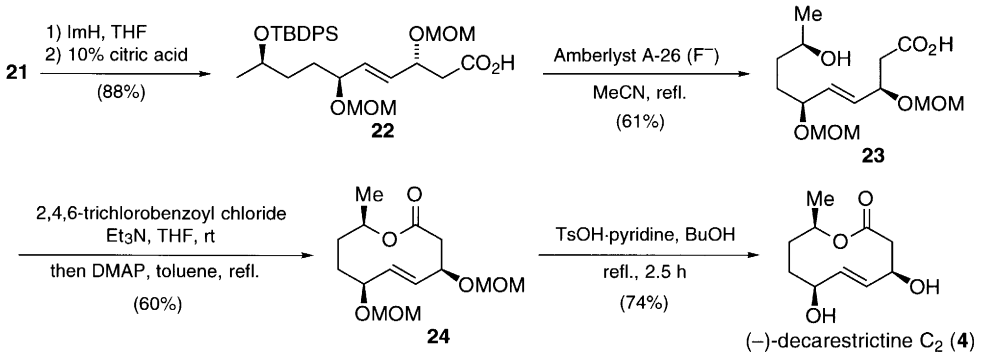
We have previously published transformation of D-mannitol into (*S*,*S*)- and (*R*,*R*)-1,2,5,6-diepoxyhexane (**8**)[6] via a key intermediate C_2-symmetric (*S*,*S*)-tetrol **9**, and the diepoxide **8** has been used as a multi-purpose chiral building block in the enantioselective syntheses of various natural products[6a,c,7] including decarestrictine L (**7**).[5a] In connection with this synthetic strategy based on the C_2-symmetrical chiral synthon approach, we envisioned the use of the (*S*,*S*)-tetrol **9** for the synthesis of decarestrictine C_2 (**4**) revealed by the retrosynthetic approach as briefly outlined in Scheme 1. In this paper, we report the first total synthesis of (−)-(3*R*,6*S*,9*R*)-decarestrictine C_2 according to this synthetic strategy.

The synthesis began with monotosylation of the primary alcohol in **9**,[8] followed by protection of the 1,2-diol to give the hydroxy tosylate **12** in 46% overall yield (Scheme 2). Reduction of the tosylate **12** using $LiAlH_4$ followed by protection of the secondary alcohol with the *t*-butyldiphenylsilyl (TBDPS) group gave the fully protected triol **13**. In selective cleavage of the acetal group in **13**, conventional acid treatment (HCl or CF_3CO_2H) resulted in unsatisfactory yields of the 1,2-diol **14**. Upon treatment with copper(II) chloride dihydrate[9] in acetonitrile, however, **14** was obtained in excellent yield (93%). Subsequent selective pivaloylation of the primary alcohol yielded **15**, which was converted to the alcohol **16** in 90% yield by hydroxyl protection and $LiAlH_4$ reduction. Swern oxidation of **16** followed by Wittig olefination of the resulting aldehyde afforded the 2(*E*)-octenal **17** as a single geometrical isomer. For the enantioselective introduction of the hydroxyl-bearing asymmetric center, **17** was subjected to diastereoselective aldol-type reaction using tin(II) enolates.[10] Thus, the chiral tin(II) enolate, prepared from (*S*)-acetyl-1,3-thiazolidine-2-thione **18** and $Sn(OTf)_2$ in the presence of 1-ethylpiperidine, was allowed to react with **17** to provide the 3(*R*)-hydroxy-4-decenamide **20** with 95% de, which required immediate hydroxyl protection because of its lability, and then **21** was isolated in 93% overall yield from **17**. The creation of the new stereogenic center with the desired *R* configuration is understandable by consideration of the chelated transition state **19**.[10]

Removal of the chiral auxiliary was accomplished effectively by applying a mild aminolysis.[11] Thus, treatment of **21** with imidazole in THF followed by hydrolysis of the resulting imidazolide with 10% citric acid provided the carboxylic acid **22** in 88% yield (Scheme 3). The TBDPS-protection of **22**



Scheme 2.



Scheme 3.

was selectively removed by the use of polymer-supported fluoride[12] in refluxing acetonitrile to give the seco-acid **23** in 61% yield. Subsequent lactonization of **23** by the Yamaguchi method[13] afforded the 10-membered lactone **24** in 60% yield. Deprotection of the MOM groups furnished (−)-(3*R*,6*S*,9*R*)-decarestrictine C_2 (**4**), mp 182–183.5°C (acetone–$CHCl_3$); $[\alpha]_D^{27}$ −35.0 (*c* 0.66, MeOH), in 74% yield. Spectroscopic data[14] and the result of X-ray crystallographic analysis (Fig. 1) for our synthetic material unambiguously confirmed the structure and stereochemistry of **4** proposed for decarestrictine C_2, however, there were significant differences between the ^1H and ^{13}C NMR spectral data for this material and the corresponding data[1b] for decarestrictine C_2 (as well as C_1) assigned by NMR analysis of natural decarestrictines C_1/C_2. We have previously synthesized[15] decarestrictines C_1 and C_2 (**3** and **4**)

as an inseparable 1:1 epimeric mixture at C-3 starting with the (*S*,*S*)-diepoxide (**8**). The synthetic material was found to be identical with a diastereomeric mixture of natural decarestrictines C_1/C_2[1b] on ^1H and ^{13}C NMR spectral comparison. On the basis of these results, it is strongly suggested that the observed discrepancy in the spectral data may be due to the formation of a 1:1 molecular complex in a solution resulting from the intermolecular hydrogen bonding between decarestrictines C_1 and C_2.

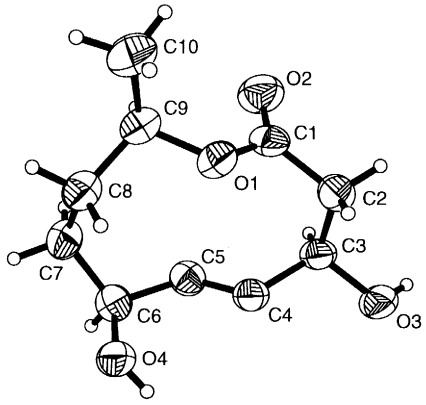


Fig. 1. The single-crystal X-ray structure of **4**

In conclusion, we have achieved the first enantioselective total synthesis of (−)-(3*R*,6*S*,9*R*)-decarestrictine C_2 (**4**) utilizing the C_2 symmetric (*S*,*S*)-tetrol **9** as a simple chiral synthon.

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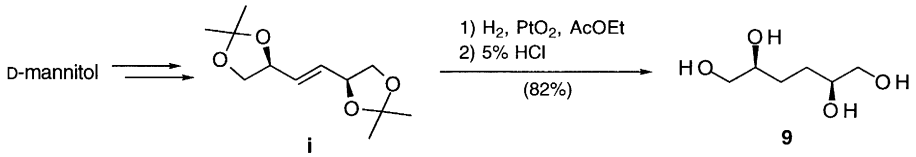
8. The preparation of **9** has been carried out starting from D-mannitol via hydrogenation of **i** using Rh–Al_2O_3 as a catalyst (Ref. 6c). However, this method was found to be less reproducible, often leading to the formation of by-products. We have found that this problem is solved by the use of PtO_2 as a catalyst as follows (unpublished result).



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14. NMR data for synthetic **4**: ^{1}H NMR (400 MHz, CD_3OD) δ 1.13 (3H, d, *J*=6.5 Hz), 1.43 (1H, dd, *J*=16.0, 7.1 Hz), 1.62 (1H, br t, *J*=12.3 Hz), 1.79–1.93 (2H, m), 2.30 (1H, t, *J*=10.5 Hz), 2.58 (1H, dd, *J*=10.2, 5.3 Hz), 4.28 (1H, m), 4.33 (1H, ddd, *J*=10.7, 8.7, 5.3 Hz), 4.73 (1H, m), 5.42 (1H, br d, *J*=16.0 Hz), 5.72 (1H, ddd, *J*=16.0, 8.7, 1.6 Hz); ^{13}C NMR (100.6 MHz, CD_3OD) δ 22.8, 29.9, 36.9, 48.0, 69.5, 74.6, 75.3, 132.2, 135.2, 173.4.
15. A 1:1 epimeric mixture of decarestrictines C_1/C_2 (**3**/**4**) has been synthesized by the following sequence starting from (*S*,*S*)-**8** via a nonstereoselective Reformatsky-type cyclization (Machinaga, N. PhD Thesis, Tokyo University of Pharmacy & Life Science, 1993).