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A Short Synthesis of (±)-Decarestrictine L

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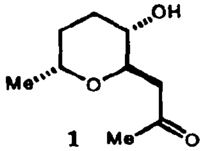
Abstract: A stereoselective synthesis of (±)-decarestrictine L (**1**) from protected pentane-1,4-diol (**2**) is described. The key intermediate, tetrahydropyran-3-one **5a**, was obtained by a tandem intramolecular carbenoid insertion and ylide rearrangement reaction.

The metabolite decarestrictine L (**1**) was recently isolated as a minor component from a culture broth of *Penicillium simplicissimum* (**Figure**), and shown to inhibit the biosynthesis of cholesterol.[1] While other members of the decarestrictine family of metabolites are lactonic in structure, decarestrictine L is unique in possessing a tetrahydropyranyl nucleus. The interesting structure, intriguing biological properties, and relative scarcity of decarestrictine L, make it an attractive synthetic target.[2] Herein, we describe a short stereoselective synthesis of this natural product.

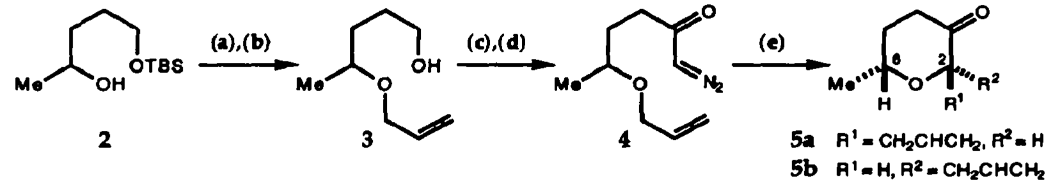


1

Decarestrictine L

Figure

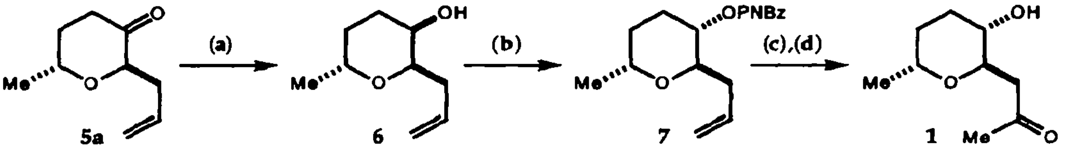
Our synthetic route to (±)-decarestrictine L commenced from the mono-protected diol **2** (**Scheme 1**).*O*-Allylation of **2** was accomplished by deprotonation with sodium hydride followed by reaction with allyl bromide. Fluoride mediated deprotection of the primary hydroxyl group afforded **3**. This alcohol was then oxidised with PDC in DMF, and the resulting carboxylic acid converted to the corresponding acid chloride. Treatment of the crude acid chloride with diazomethane gave the diazo ketone **4**, the cyclisation precursor. Reaction of **4** with a catalytic amount of copper(II) hexafluoroacetylacetonate in dichloromethane at reflux, afforded the required tetrahydropyran-3-one system in 68% yield as a chromatographically separable mixture of diastereoisomers (**5a**:**5b**, 77:23).[3,4] The reaction proceeded by intramolecular insertion of the copper carbenoid derived from **4** into a lone pair of the ether oxygen followed by rearrangement of the resulting oxonium ylide species.[5] We have shown previously that copper-catalysed tandem heteroatom insertion and ylide rearrangement reactions of this type can be used for the stereoselective synthesis of 2,5-dialkyl tetrahydrofuran-3-ones and the preparation of cyclic ethers with ring sizes 6 to 8.[6,7] This is the first example of the application of the reaction to the stereoselective synthesis of a 2,6-dialkyl tetrahydropyran-3-ones, and is a further demonstration of the scope and synthetic utility of the reaction.



Reagents: (a) NaH, CH_2CHCH_2Br, THF, reflux (97%); (b) Bu_4NF, THF, RT (95%); (c) PDC, DMF, RT (62%); (d) (i) $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C→RT, (ii) CH_2N_2, Et_2O, 0 °C (68%); (e) $Cu(CF_3COCHCOCF_3)_2$ (2 mol%), CH_2Cl_2, reflux (68%, 77:23, **5a**:**5b**)

Scheme 1

The conversion of **5a** into (±)-decarestrictine L was completed in four steps (**Scheme 2**). Reduction of **5a** with L-Selectride afforded the alcohol **6** as a single diastereoisomer.[8] Protection of the hydroxyl group as the *p*-nitrobenzoyl ester under Mitsunobu conditions, proceeded with inversion of configuration at the 3-position to give **7**.[9] The methyl ketone functionality was then installed in high yield by palladium-catalysed oxidation of the alkene **7**.[10] Deprotection of the hydroxyl group afforded (±)-decarestrictine L (**1**) which was spectroscopically identical to the natural product.[1] Thus, the synthesis of (±)-decarestrictine L from **2** was achieved in nine steps.



Reagents: (a) L-Selectride, THF, −78 °C (88%); (b) $p\text{-}O_2NC_6H_4CO_2H$, DEAD, PPh_3, RT (45%); (c) $PdCl_2$ (0.2 equiv.), CuCl (1 equiv.), DMF–H_2O (10:1), O_2, RT (83%); (d) K_2CO_3, MeOH–H_2O (30:1), RT (63%)

Scheme 2

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References and Notes

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2. For a recent synthesis of (+)-decarestrictine L, see: Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.*, **1993**, *34*, 5739.
3. The stereochemical assignment was based on NMR analysis of both isomers. Significant NOEs were observed between the C-2 and C-6 protons of **5b** which were absent for **5a**.
4. Treatment of **5a** or **5b** with K_2CO_3 in methanol at room temperature gave an equilibrium mixture of isomers with a ratio of 80:20 in favour of **5b**.
5. For a recent review of the formation of ylides from metal carbenoids, see: Padwa, A.; Hornbuckle S. F. *Chem. Rev.*, **1991**, *91*, 263.
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7. Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.*, **1993**, *34*, 4385.
8. Although many other reducing agents were examined, **6** was the major diastereoisomer in all cases.
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