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Convergent Syntheses of 3,6-Dihydroxydec-4-enolides

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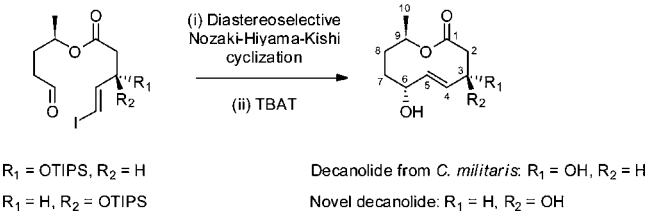
ABSTRACT



The total syntheses of the 3,6-dihydroxydecanolide from *Cordyceps militaris* and the novel C-3 epimer are reported using a diastereoselective Nozaki–Hiyama–Kishi reaction in the key cyclization to generate the 6*R* stereocenter.

Natural products assembled on the 9*R*-methyl decanolide core have been isolated from a wide variety of sources and include for example tuckolide,[1] the diplodialides,[2] and the decarestrictines.[3] They differ in their oxygenation patterns and the presence or absence of double bonds. Many are biologically active. For example, the decarestrictines isolated from *Penicillium simplicissimum* are inhibitors of cholesterol biosynthesis in *in vitro* HEP-G2 cell assays and have potential as leads to highly selective cholesterol lowering drugs.[1,3b] The bioactivity of these compounds, combined with the challenge of constructing the medium-sized ring, has inspired a number of total syntheses.[4]

As part of our ongoing synthetic and biosynthetic work on polyketide derived natural products, we have focused on 3,6-dihydroxydecanolides with a 4*E*-double bond for which there are four possible diastereomers **1**–**4** (Figure 1).

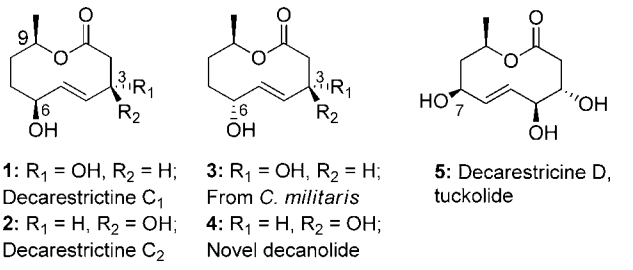


Figure 1. Structures of decanolides.

Decarestrictines C_1 **1** and C_2 **2** isolated from *P. simplicissimum* were originally proposed to be epimeric at C-3 and have the *S* configuration at C-6. The total synthesis of decarestrictine C_2[5] and a 1:1 C_1/C_2 mixture[6] was completed by Kibayashi et al. Later, Mohapatra[4b] reported the synthesis of decarestrictines **1** and **2** and suggested that decarestrictines C_1 and C_2 isolated from *P. simplicissimum* are in fact equilibrating conformers of the (3*S*,6*S*)-isomer decarestrictine C_1 **1** rather than a H-bonded dimer of the 1:1 mixture of **1** and **2** suggested by Kibayashi. The (3*S*, 6*R*)-diol **3** was isolated from *Cordyceps militaris* BCC 2816,

(1) Ayer, W. A.; Sun, M.; Browne, L. M.; Brinen, L. S.; Clardy, J. *J. Nat. Prod.* **1992**, *55*, 649.

(2) (a) Ishida, T.; Wada, K. *J. Chem. Soc., Chem. Commun.* **1975**, 209. (b) Wada, K.; Ishida, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1154.

(3) (a) Gohrt, A.; Zeeck, A.; Hutter, K.; Kirsch, R.; Kluge, H.; Thiericke, R. *J. Antibiot.* **1992**, *45*, 66. (b) Grabley, S.; Granzer, E.; Hutter, K.; Ludwig, D.; Mayer, M.; Thiericke, R.; Till, G.; Wink, J.; Philips, S.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 56. (c) Grabley, S.; Hammann, P.; Hutter, K.; Kirsch, R.; Kluge, H.; Thiericke, R.; Mayer, M.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 1176.

(4) (a) For a review, see: Riatto, V. B.; Pilli, R. A.; Victor, M. M. *Tetrahedron* **2008**, *64*, 2279. See also: (b) Mohapatra, D. K.; Sahoo, G.; Ramesh, D. K.; Rao, J. S.; Sastry, G. N. *Tetrahedron Lett.* **2009**, *50*, 5636. (c) Krishna, P. R.; Rao, T. J. *Org. Biomol. Chem.* **2010**, *8*, 3130. (d) Krishna, P. R.; Rao, T. J. *Tetrahedron Lett.* **2010**, *51*, 4017. (e) Binanzer, M.; Fang, G. Y.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 4264.

(5) Arai, M.; Morita, N.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **2000**, *41*, 1199.

(6) Machinaga, N. PhD Thesis, Tokyo University of Pharmacy & Life Science, 1993

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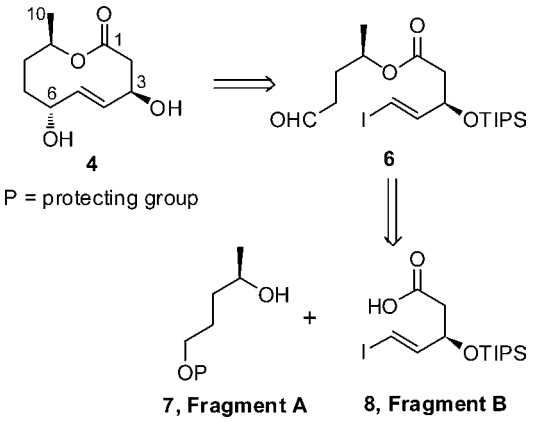
and the structure was confirmed through X-ray crystallography and total synthesis.[7] However to date neither the isolation nor synthesis of the final diastereomer **4** has been reported. Our aim was to prepare **4** which would be of value when screening extracts from organisms known to produce decanolides. The synthetic approach needed to be flexible, enabling access to other diastereomers (e.g., **3**), as well as amenable for the incorporation of vicinal carbon-13 labels for biosynthetic studies.

Diastereomers **1**, **2**, and **3** have all been prepared using a ring closing metathesis to generate the 4,5-double bond in the cyclization step.[4b−d,8] In contrast, we proposed a convergent route in which the two fragments A and B would be coupled using a Yamaguchi esterification to **6** followed by a Nozaki−Hiyama−Kishi reaction (NHK) to form the decanolide ring (Scheme 1).

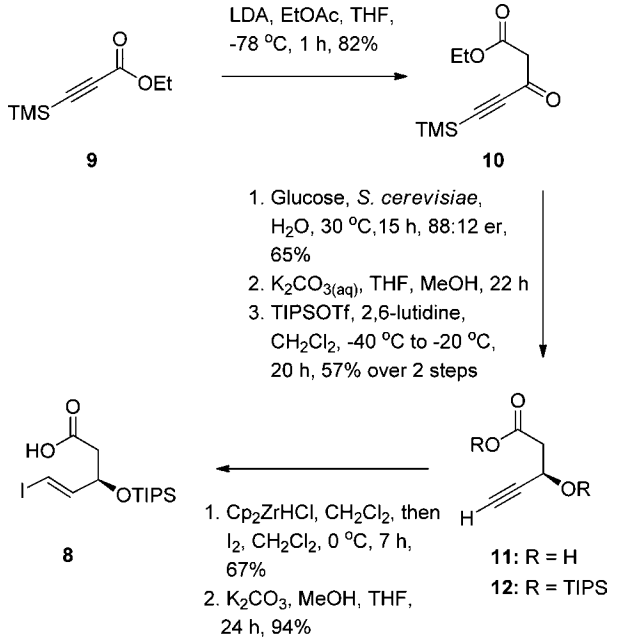
Scheme 1. Retrosynthesis of Decanolide **4**



In their synthesis of decarestrictine D **5**, Pilli and Victor used the NHK reaction to close the ring with formation of the C_6-C_7 bond.[9] The required 7*S*-alcohol was formed preferentially, but the protecting groups on the 3- and 4-hydroxyl groups influenced both the yield and stereoselectivity of this step. We aimed to prepare both enantiomers of vinyl iodide **8** to further investigate how the conformational bias in the acyclic precursor influences the stereocontrol in NHK cyclizations.

An enzymatic reaction was used in the synthesis of the C_1-C_5 fragment **8** required for synthesis of our first target, diol **4**. First Claisen condensation of ethyl acetate with protected ethyl propiolate **9** gave β-keto ester **10** in 82% yield (Scheme 2). Reduction of **10** using *Saccharomyces cerevisiae*[10] gave the C-3 alcohol in 88:12 er as determined by conversion to the 2-phenylethyl ester and analysis by chiral HPLC. Concomitant removal of the TMS group and hydrolysis of the ester were achieved using aqueous K_2CO_3 to give **11**. The final step was conversion of the alkyne to the (*E*)-vinyl iodide. It proved necessary to protect both the acid and alcohol as the TIPS derivative **12** to provide sufficient steric hindrance for the Schwartz hydrozirconium/iodination to proceed in good yield without competing zirconium complexation by the ester group.[11] The exclusive formation of the *E* double bond was apparent from the ^{1}H NMR (δ 6.42, dd, *J* 14.5, 0.9 Hz, 5-H; δ 6.63, dd *J* 14.5, 6.8 Hz, 4-H). Finally hydrolysis of the TIPS ester provided the required vinyl iodide **8**.

Scheme 2. Synthesis of C_1-C_5 Fragment **8**



For the synthesis of the C_6-C_{10} fragment, a chemoenzymatic approach was again used starting in this case from commercially available pentane-1,4-diol (Scheme 3). The primary alcohol was protected as the trityl ether **14** to achieve high enantioselectivity (99:1 er as determined by chiral HPLC) in the resolution with vinyl acetate and Amano lipase from *P. cepacia*.[12] The resultant acetate **15** was readily hydrolyzed to the required secondary alcohol **16** in 99% yield.

With both fragments in hand, coupling to the requisite ester was investigated and Yamaguchi conditions proved best giving **17** in 99% yield (Scheme 4). The trityl group was removed using Et_2AlCl, thus unmasking the primary alcohol **18**. This was oxidized with DMP to provide aldehyde **6** required for the key cyclization. Treatment of **6** with $CrCl_2$ and $NiCl_2$ in DMF gave a 3:1 mixture of epimers at C_6 which were readily separable by SiO_2 column chromatography. NOE studies ($CDCl_3$) revealed the stereochemistry of the major isomer (Figure 2).

(7) Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953.
(8) Mohapatra, D. K.; Ramesh, D. K.; Giardello, M. A.; Chorghade, M. S.; Gurjar, M. K.; Grubbs, R. H. *Tetrahedron Lett.* **2007**, *48*, 2621.
(9) (a) Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **1998**, *39*, 4421. (b) Pilli, R. A.; Victor, M. M. *J. Braz. Chem. Soc.* **2001**, *12*, 373. (c) Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **2002**, *43*, 2815.
(10) Salit, A. F.; Meyer, C.; Cossy, J.; Delouvrie, B.; Hennequin, L. *Tetrahedron* **2008**, *64*, 6684.
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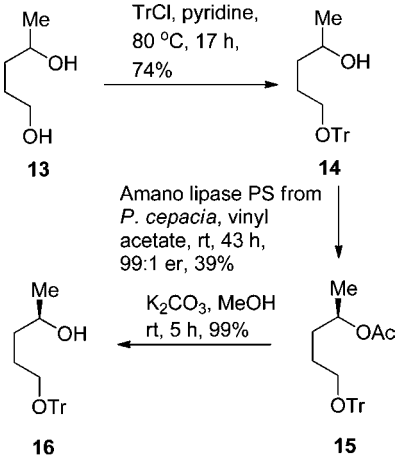
(12) Kim, M. J.; Lim, I. T.; Choi, G. B.; Whang, S. Y.; Ku, B. C.; Choi, J. Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 71.

Scheme 3. Synthesis of C_6-C_{10} Fragment



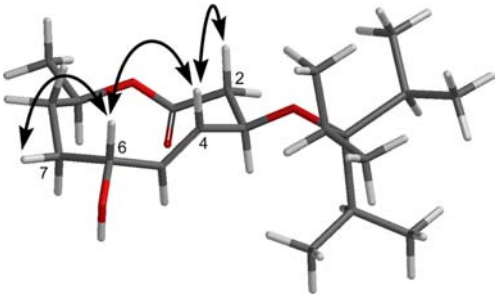


Figure 2. NOEs observed on major epimer **19** (Hartree–Fock 6-31G* energy minimized structure).

Irradiation of the signal assigned to 4-H led to enhancements of 2-H_{ax} and 6-H, and NOE interactions were apparent between 6-H and 7-H_{eq}.

The final deprotection to the novel decanolide **4** was accomplished by treatment of **19** with tetrabutylammoniumtriphenyldifluorosilicate (TBAT),[13] achieving significantly better yields than with the more conventional TBAF-mediated method (26%).

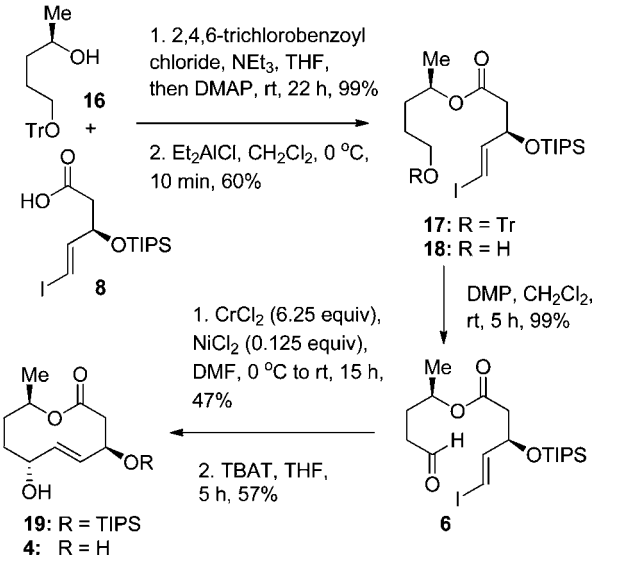
The above approach may be adapted for the incorporation of vicinal carbon-13 labels at C-1 and C-2 of decanolide **4** starting with $^{13}CH^{13}CO_2Et$ for the synthesis of **10**. However, ideally, when working with expensive ^{13}C-labeled compounds the isotopes should be introduced as late as possible in the synthetic sequence.

With this in mind we examined alternative strategies for the synthesis of the two fragments required for dihydroxydiolide **3** which may be adapted for ^{13}C-labeling of C-5 and C-6. First the C_1-C_5 fragment was prepared from L-malic acid (Scheme 5).

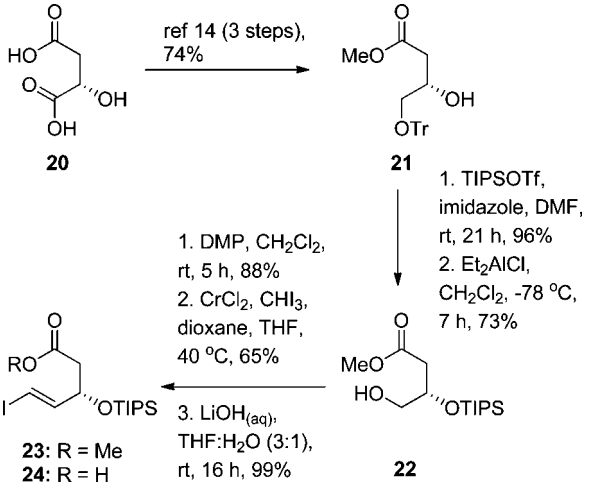
(13) Pilcher, A. S.; Ammon, H. L.; Deshong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.

(14) Prasad, K.; Chen, K. M.; Repic, O.; Hardtmann, G. E. *Tetrahedron: Asymmetry* **1990**, *1*, 307.

Scheme 4. Completing the Total Synthesis of **4**



Scheme 5. Alternative C_1-C_5 Fragment Synthesis



The synthesis of **21** was accomplished in three steps following a literature precedent.[14] The secondary alcohol was then protected with TIPS, the primary alcohol deprotected giving **22** which was oxidized to an aldehyde. Takai olefination gave vinyl iodide **23** which was hydrolyzed to acid **24** ready for coupling with the C_6-C_{10} fragment. This final step may be adapted for the incorporation of a carbon-13 label using $^{13}CHI_3$ prepared from [^{13}C]-acetophenone[15] followed by a haloform reaction.[16]

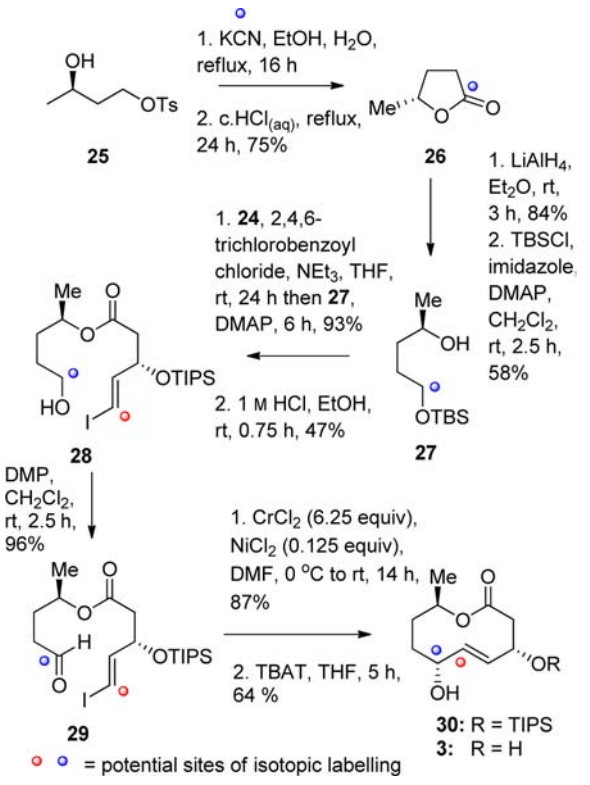
A revised synthesis of the C_6-C_{10} fragment was also developed which would enable incorporation of a carbon-13 label at C-6 (decanolide numbering) using potassium [^{13}C]-cyanide (Scheme 6). Treatment of the known[17] tosylate **25**

(15) Baldwin, J. E.; Barden, T. C. *J. Am. Chem. Soc.* **1984**, *106*, 5312.

(16) Baker, K. V.; Brown, J. M.; Cooley, N. A. *J. Labelled Compds. Radiopharm.* **1988**, *25*, 1229.

(prepared from ethyl *R*-3-hydroxybutanoate) with KCN and *in situ* hydrolysis of the resultant nitrile gave lactone **26** in 75% yield.

Scheme 6. Completing the Synthesis of **3**



Reduction of **26** with $LiAlH_4$ followed by selective protection of the primary alcohol as the silyl ether gave **27**.

Aldehyde **29** required for the key NHK reaction was prepared following a similar strategy to that used for diastereomer **6**. Yamaguchi coupling (93%) was followed by a selective deprotection of the primary TBS group in the presence of a secondary TIPS group using aqueous HCl. The resultant alcohol **28** was oxidized with DMP to afford **29** which, on treatment with $CrCl_2$ and $NiCl_2$ in DMF, gave a 5:1 mixture of epimers at C_6 in 87% yield. The stereochemistry of the major isomer was assigned as 3*S*, 6*R*, 9*R* on the basis of NOE data which were similar to those obtained for diastereomer **19** (Figure 3). TBAT was again used for the final deprotection step giving the target diol **3** in 64% yield. There was an excellent correlation of the spectral data of synthetic **3** with the decanolide isolated from *C. militaris* BCC 2816,[7] and an X-ray crystal structure of synthetic **3** confirmed that the structures were identical. Full spectral data of both isomers **3** and **4** and data for previously synthesized **1** and **2** are presented for comparison in the Supporting Information accompanying this paper.

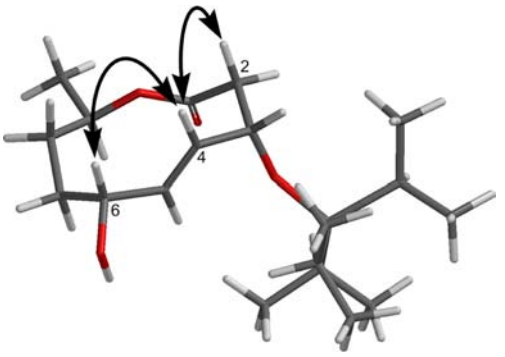


Figure 3. NOEs observed on major epimer **30** (Hartree−Fock 6-31G* energy minimized structure).

It is interesting to note that, in the key NHK reactions with diastereomers **6** and **29**, attack occurs preferentially on the *Re* face of the aldehyde giving the *R*-alcohol as the major product. The same preference is observed in Pilli's decarestrictine D synthesis, in this case leading to the 7*S*-alcohol.[8] In their synthesis of (−)-7-deacetoxyalcyonin acetate, MacMillan and Overman suggest that the NHK reaction proceeds *via* an intermediate in which the vinyl chromium species chelates with the aldehyde carbonyl.[18] Transannular steric interactions are proposed to be minimized if this chelation occurs in a pseudoequatorial position relative to the forming decanolide ring. This proposal is consistent with both Pilli and our observations.

In conclusion the convergent synthesis of the novel (3*R*,6*R*,9*R*)-dihydroxy decanolide **4** and the known[7] natural product **3** are reported. The two fragments were coupled efficiently under Yamaguchi conditions, and cyclization was achieved using the NHK reaction to generate the required 10-membered rings with the 6*R*-stereocenter. The approach may be readily adapted for the incorporation of vicinal ^{13}C labels required for biosynthetic studies, and the results of these investigations will be reported in due course.

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Supporting Information Available. Preparation and characterization of the compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) (a) Najera, C.; Yus, M.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 289. (b) O'Neill, J. A.; Simpson, T. J.; Willis, C. L.; Lindell, S. D. *Tetrahedron: Asymmetry* **1994**, *5*, 117.

(18) Macmillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.

The authors declare no competing financial interest.