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Stereoselective Synthesis of Decarestrictine D from a Previously Inaccessible (2*Z*,4*E*)-Alkadienyl Alcohol Precursor

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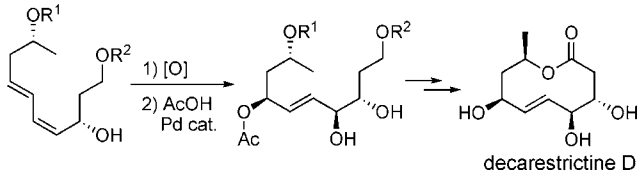
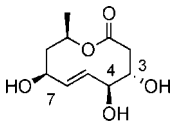
ABSTRACT



The core structure of decarestrictine D was constructed by stereoselective oxygenation of (2*Z*,4*E*)-alkadienyl alcohol, which could be synthesized by a nickel-catalyzed coupling reaction between the corresponding cis bromide and trans borate. Efficiency in macrocyclization of the seco acid with Yamaguchi reagent was found to be protective-group-dependent, and the best yield of 40% was obtained with the seco acid with tri-MOM protective groups.

Decarestrictine D (**1**), isolated from *Penicillium corylophilum* and *Polyporus tuberaster*,[1] shows inhibitory activity against cholesterol biosynthesis at 10^{-7} M,[1a] and the structural difference of **1** from that of other well-known inhibitors such as mevinolin and compactin implies another mode of action to be operative with **1**. In addition, **1** exhibits no other effects such as antibacterial or antifungal activities. Taking together its strong and selective biological profile, **1** is an attractive compound for developing a new cholesterol-lowering drug. So far, the synthesis of **1** and the seco acid has been reported by three groups.[2−4] However, the syntheses suffer from the low 1,3-chiral induction at C(7) by the C(9) alkoxyl group in the construction of the central core structure by Andrus[2] and Chapleur[4] and excess use of the toxic Cr reagent twice in Pilli's synthesis.[3] In addition, the macrolactonization and macrocyclization at C(7)−C(8) have been accomplished with rather low yields of <33%.



decarestrictine D (**1**)

Previously, we have reported a nickel-catalyzed coupling reaction between alkenyl borates and highly congested (*Z*)-3-alkoxy-1-alkenyl halides to furnish hitherto hardly accessible (2*Z*,4*E*)-alkadienyl alcohol derivatives,[5] and later, the reaction has been applied to the synthesis of korormicin[6] and

(1) (a) Grabley, S.; Granzer, E.; Hütter, K.; Ludwig, D.; Mayer, M.; Thiericke, R.; Till, G.; Wink, J.; Philipps, S.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 56−65. (b) Göhrt, A.; Zeeck, A.; Hütter, K.; Kirsch, R.; Kluge, H.; Thiericke, R. *J. Antibiot.* **1992**, *45*, 66−73. (c) Ayer, A. W.; Sun, M.; Browne, L. M.; Brinen, L. S.; Clardy, J. *J. Nat. Prod.* **1992**, *55*, 649−653.

(2) Andrus, M. B.; Shih, T.-L. *J. Org. Chem.* **1996**, *61*, 8780−8785.

(3) (a) Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **1998**, *39*, 4421−4424. (b) Pilli, R. A.; Victor, M. M. *J. Braz. Chem. Soc.* **2001**, *12*, 373−385.

(4) Colle, S.; Taillefumier, C.; Chapleur, Y.; Liebl, R.; Schmidt, A. *Bioorg. Med. Chem.* **1999**, *7*, 1049−1057.

(5) Kobayashi, Y.; Nakayama, Y.; Mizojiri, R. *Tetrahedron* **1996**, *54*, 1053−1062.

(6) Kobayashi, Y.; Yoshida, S.; Nakayama, Y. *Eur. J. Org. Chem.* **2001**, 1873−1881.

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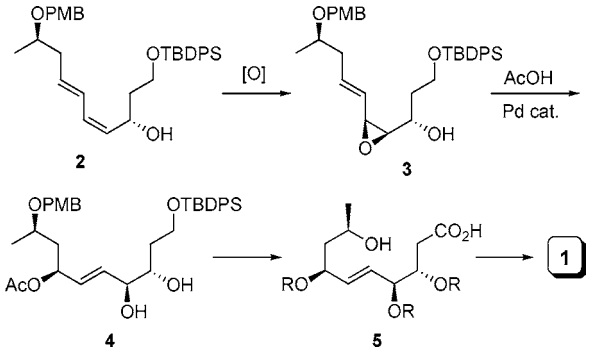
dihydro-leukotriene B_4,[7] both of which molecules possess this structural unit. These simple but successful applications of this coupling reaction prompted another, higher use of the dienyl alcohols coupled with an oxygenation reaction in construction of highly oxygenated compounds. This conceptual idea inspired a practical transformation as delineated in Scheme 1 of dienyl alcohol **2** into diol-acetate **4** through

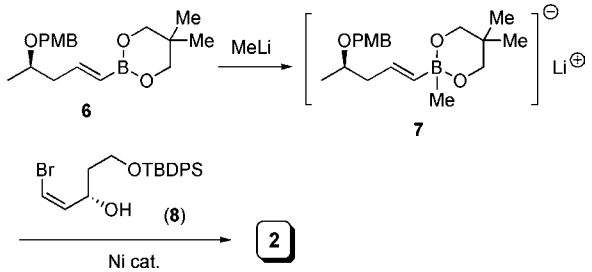
Scheme 1. Key Transformation to Decarestrictine D (**1**)



the hydroxyl-group-directed epoxidation and a palladium-catalyzed reaction of the resulting epoxide **3** with AcOH. Product **4** possesses the full functionality and correct chirality found in decarestrictine D (**1**), and we thought the transformation meets the criterion of chirality economy. Herein, we report results along this line, and lactonization of seco acid **5**, for which the protective groups of the hydroxyl groups at C(3) and C(4) play a crucial role for success.

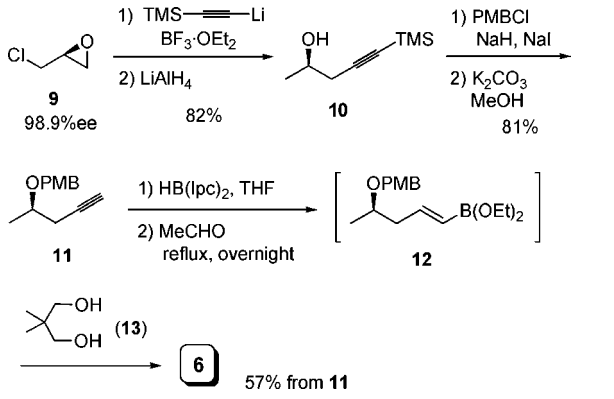
Scheme 2 shows the coupling reaction of the boronate ester **6** and cis alkenyl bromide **8** to produce the key dienyl alcohol

Scheme 2. Preparation of Dienyl Alcohol **2**



2, and the synthesis of each coupling partner is delineated in Schemes 3 and 4, respectively. The first step in the synthesis of **6** was a $BF_3{\cdot}OEt_2$-assisted reaction[8] of epichlorohydrin **9** of 98.9% ee with the lithium anion derived from TMS acetylene, and the resulting chloro alcohol was reduced to **10**[9] in 82% yield from **9**. Protection of **10** with PMBCl

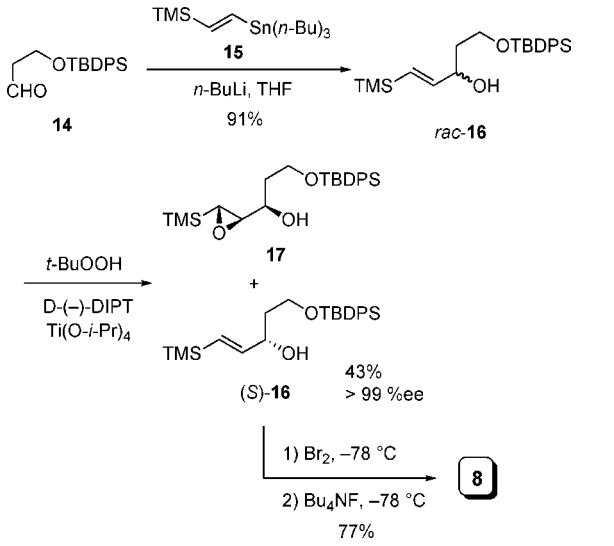
Scheme 3. Preparation of the C(6)−C(10) Intermediate **6**



(PMB = p-$MeOC_6H_4CH_2$-) under the literature conditions (NaH and NaI in THF)[10] resulted in concomitant removal of the TMS group, though incompletely, to afford a mixture of **11** and the PMB ether of **10** in a 1:2 ratio. Without separation, the mixture was treated with K_2CO_3 in MeOH to produce **11** in 81% from **10**. The reverse sequence, i.e., removal of the TMS group from **10** followed by PMB protection was less productive since most of the volatile alcohol produced in the first step was lost during isolation. Finally, acetylene **11** was converted into the boronate ester **6** in 57% yield by hydroboration with $(Ipc)_2BH$, ligand exchange with MeCHO,[11] and transesterification of the resulting diethyl boronate **12** with diol **13**.

Synthesis of the other key intermediate **8** (Scheme 4) was commenced with addition of the lithium anion derived from

Scheme 4. Preparation of the C(1)−C(5) Fragment **8**



15 and *n*-BuLi to aldehyde **14**. Racemic alcohol *rac*-**16** produced in 91% yield was then subjected to the kinetic

(7) Nakayama, Y.; Kumar, G. B.; Kobayashi, Y. *J. Org. Chem.* **2000**, *65*, 707−715.

(8) (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391−394. (b) Subburaj, K.; Okamoto, S.; Sato, F. *J. Org. Chem.* **2002**, *67*, 1024−1026.

(9) White, D. J.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991−4998.

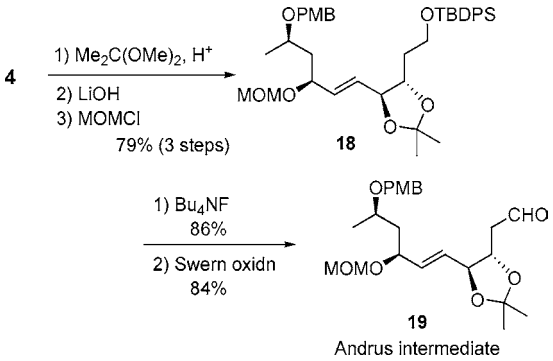
resolution[12] by using Sharpless asymmetric epoxidation[13] to furnish a mixture of epoxy alcohol **17** and the remaining allylic alcohol (*S*)-**16**. The ee of (*S*)-**16**, obtained in 43% yield based on *rac*-**16** after chromatography, was >99% by ^{1}H NMR spectroscopy of the derived MTPA ester. Bromination of (*S*)-**16** with Br_2 at −78 °C took place without injuring the TBDPS group, and subsequent treatment of the bromine adduct with Bu_4NF at −78 °C afforded cis bromide **8** with complete stereoselection as judged by ^{1}H NMR and ^{13}C NMR spectroscopy.

Nickel-catalyzed coupling of **6** and **8** (Scheme 2) was executed by addition of MeLi (1.1 equiv) to a mixture of boronate ester **6** (1 equiv) and $NiCl_2$(dppf) (0.067 equiv) in THF followed by reaction with cis bromide **8** (0.67 equiv) at room temperature for 14 h to furnish dienyl alcohol **2** in 76% yield based on **8**. Noteworthy here is that the hydroxyl group present in **8** did not quench the anionic borate **7**, and thus the molar ratio of the boronate ester **6** could be reduced to less than 2 equiv of the bromide **8**.

Epoxidation of dienyl alcohol **2**, the first step of the key transformation (Scheme 1), proceeded with *m*-CPBA (1.3 equiv) in a completely stereoselective manner, and subsequent palladium-catalyzed reaction of epoxide **3** with AcOH (2 equiv) furnished **4** in 68% yield from **2**. Neither the regioisomer nor the C(7) diastereomer (structure not shown) was detected by NMR spectroscopy and TLC analysis. The two chiral centers, thus created, should have the configurations depicted in **4** on the basis of the literature precedents for the respective steps.[14,15] This speculation was later confirmed to be correct by transformation to the known compounds (see the next paragraph).

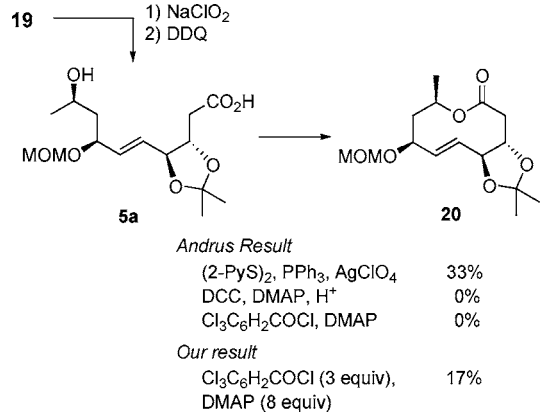
The remaining tasks toward completion of the synthesis were functional group manipulation and macrolactonization. First, **4** was converted into the Andrus acetonide **19**[2] by a sequence of reactions depicted in Scheme 5 in good overall yield. The ^{1}H NMR and ^{13}C NMR spectra of synthetic **19** were all consistent with the data reported.[2] A formal synthesis of decarestrictine D (**1**) was thus achieved. In addition, the chiral centers at C(4) and C(7) of **4** constructed by the key transformation were thus established.

Scheme 5. Synthesis of Known Intermediate **19**



In the previous synthesis,[2] macrolactonization of seco acid **5a** was achieved by using the Corey−Nicolaou reagent ((2-PyS)$_2$, PPh_3, $AgClO_4$) to produce lactone **20** in 33% yield, whereas the Keck reagent (DCC, DMAP, H^+) and the Yamaguchi reagent ($Cl_3C_6H_2COCl$, DMAP) did not afford the lactone (Scheme 6). To improve the yield, lactonization

Scheme 6. Macrolactonization of Acetonide Seco Acid **5a**



of the same seco acid **5a**, derived from the above aldehyde **19** by the literature procedure ($NaClO_2$ then DDQ), was studied with the Yamaguchi reagent,[16] since we were familiar with this reagent through the syntheses of other macrolides.[17] Under slightly modified conditions, the cyclization was accomplished but furnished **20** only in 17% yield. One reason we speculated for the failure reported by Andrus (0%) and the low yield described above (17%) is that the two reaction sites (CO_2H and OH) are projected into opposite directions of the acetonide plane, thus rendering the unfavorable 10-membered lactonization[18] even more difficult.

(10) Paquette, L. A.; Barriault, L.; Pissarnitski, D.; Johnston, J. N. *J. Am. Chem. Soc*. **2000**, *122*, 619−631.

(11) Kamabuchi, A.; Moriya, T.; Miyaura, N.; Suzuki, A. *Synth. Commun*. **1993**, *23*, 2851−2859.

(12) Kinetic resolution of γ-silylallylic alcohols: Kitano, Y.; Matsumoto, T.; Sato, F. *Tetrahedron* **1988**, *44*, 4073−4086.

(13) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B.*J. Am. Chem. Soc*. **1981**, *103*, 6237−6240. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc*. **1987**, *109*, 5765−5780.

(14) Epoxidation of cis allylic alcohols: (a) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett*. **1979**, 4733−4736. (b) Narula, A. S. *Tetrahedron Lett*. **1981**, *22*, 2017−2020. (c) Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1982**, *23*, 3387−3390. (d) Adam, W.; Kumar, R.; Reddy, T. I.; Renz, M. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 880−882.

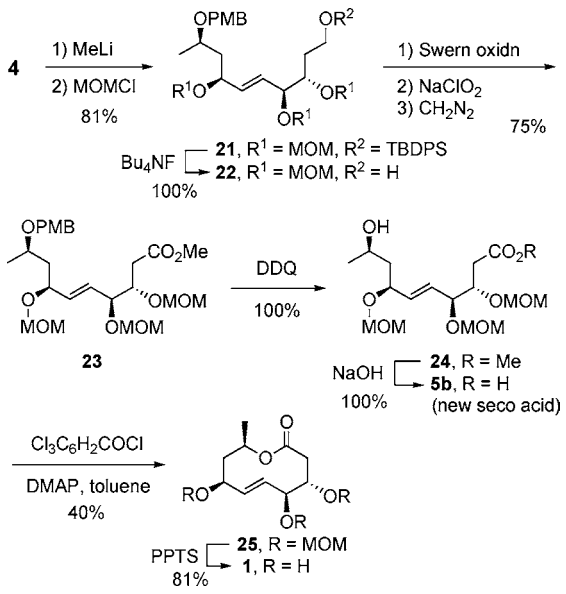
(15) (a) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc*. **1981**, *103*, 5969−5972. (b) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett*. **1981**, *22*, 2575−2578. (c) Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett*. **1985**, *26*, 5615−5618. (d) Deardorff, D. R.; Shambayati, S.; Linde II, R. G.; Dunn, M. M. *J. Org. Chem*. **1988**, *53*, 189−191. (e) Echavarren, A. M.; Tueting, D. R.; Stille, J. K. *J. Am. Chem. Soc*. **1988**, *110*, 4039−4041. (f) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc*. **1995**, *117*, 6224−6233.

(16) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989−1993.

(17) (a) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem*. **1998**, *63*, 7505−7515. (b) Kobayashi, Y.; Okui, H. *J. Org. Chem*. **2000**, *65*, 612−615. (c) Kobayashi, Y.; Matsuumi, M. *J. Org. Chem*. **2000**, *65*, 7221−7224. (d) Kobayashi, Y.; Kumar, G. B.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem*. **2001**, *66*, 2011−2018. (e) Kobayashi, Y.; Wang, Y.-G. *Tetrahedron Lett*. **2002**, *43*, 4381−4384.

The above hypothesis led us to examine another seco acid **5b**, in which such a negative bias against lactonization is eliminated (Scheme 7). The acetyl group of **4** was first

Scheme 7. Synthesis of Decarestrictine D (**1**) through a New seco Acid **5b**



removed by using MeLi, and the resulting triol was converted to MOM ether **21**. After removal of the TBDPS protection, the resulting alcohol **22** was converted to ester **23** in 75% yield. The PMB group was then removed with DDQ, and the ester group was hydrolyzed to afford seco acid **5b**, which upon Yamaguchi lactonization furnished lactone **25** in 40% yield.[19] The ^{1}H NMR and ^{13}C NMR spectra of lactone **25** indicated the existence of a single conformational isomer.[20]

(18) Difficulty in formation of medium ring lactones: Rousseau, G. *Tetrahedron* **1995**, *51*, 2777−2849.

Deprotection of the MOM group of **25**, the last step, was attempted under the conditions using CF_3CO_2H/CH_2Cl_2, Dowex-50/MeOH, $BF_3{\cdot}OEt_2$, and $(CH_2SH)_2/CH_2Cl_2$ to provide a mixture of products, whereas PPTS in refluxing *n*-BuOH was found to produce decarestrictine D (**1**) cleanly in 81% yield. The ^{1}H and ^{13}C NMR spectra of **1** measured in $CDCl_3$ and in CD_3OD were identical with those reported.[1c,2,3] In addition, the specific rotation ($[\alpha]^{24}_D$ −68 (*c* 0.066, MeOH)) and mp (121−123 °C, recrystallized from CH_2Cl_2/hexane) were also in good agreement with the reported data: $[\alpha]^{20}_D$ −62 (*c* 1.0);[1a] 118−120 °C (synthetic);[2] 116 °C (natural).[1b]

In summary, synthesis of decarestrictine D (**1**) was accomplished through dienyl alcohol **2**, which was prepared by the nickel-catalyzed coupling reaction. The key transformation of **2** to **4** proceeded efficiently with creation of the C(4) and C(7) chiral centers. Moreover, lactonization was achieved in higher yield with a new seco acid **5b** than the previous seco acid **5a**.

Acknowledgment. Epichlorohydrin **9** was kindly gifted by Takasago International Corporation. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Experimental procedures and copies of the ^{1}H amd ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Perhaps, lactonization of **5b** with $(2\text{-PyS})_2$, PPh_3, and $AgClO_4$ may furnish a better yield of **25** by extrapolation of the results summarized in Scheme 6. However, this possibility was not studied partly because of the explosive nature of $AgClO_4$: (a) Brinkley, S. R., Jr. *J. Am. Chem. Soc.* **1940**, *62*, 3524. (b) Hein, F. *Chem. Tech. (Berlin)* **1957**, *9*, 97; *Chem. Abstr.* **1957**, *51*, 54429.

(20) On the other hand, lactone **20** derived from **5a** (Scheme 6) exists as a mixture of the three conformational isomers on the basis of the ^{1}H NMR spectrum, according to Andrus (ref 2).