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Total Synthesis of (-)-Decarestrictine D Through a Stereoselective Intramolecular Nozaki-Hiyama-Kishi Reaction

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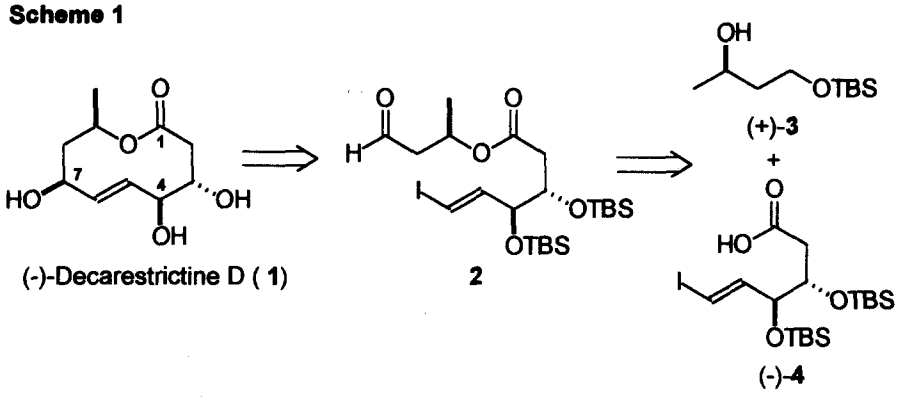
Abstract: A concise total synthesis of (-)-decarestrictine D (1) from 1,3-propanediol and polyhydroxybutyrate (PHB) is described. The approach involves the stereoselective intramolecular Nozaki-Hiyama-Kishi coupling to construct the decanolide ring and to set the proper configuration at C-7.

Decarestrictine D (**1**) is a 10-membered lactone isolated from *Penicillium corylophilum* and *P. simplicissimum*[1] and from *Polyporus tuberaster*[2] which has been demonstrated to inhibit cholesterol biosynthesis in HEP-G2 liver cells and *in vivo* studies with normolipidemic rats. Recently, Andrus and Shih reported the first total synthesis of decarestrictine D (**1**) which also established its absolute configuration.[3]

Here we would like to report our approach to decarestrictine D (**1**) which features a stereoselective construction of the 10-membered lactone and of its stereogenic center at C-7 through an intramolecular Nozaki-Hiyama-Kishi coupling reaction[4] with vinylic iodide **2** (**Scheme 1**).

Scheme 1



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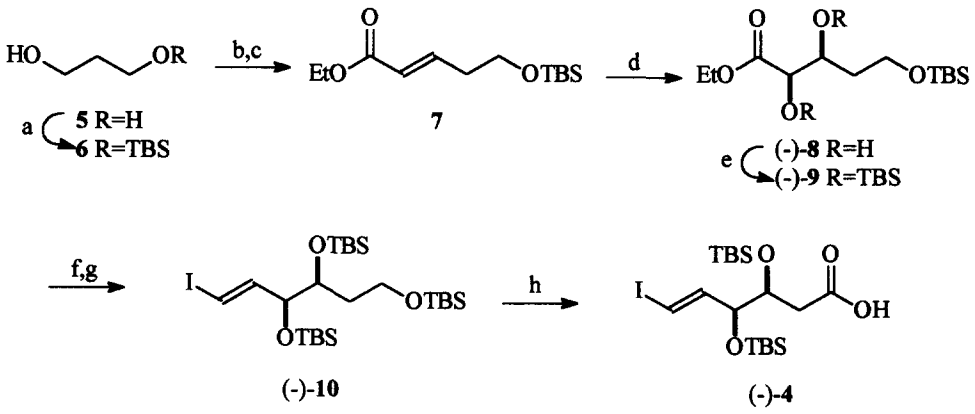
We reasoned that the proper configuration at C-7, which requires the approach of the vinylic Cr(II) species to the *re* face of the aldehyde, would be favored due to the minimization of torsional and transannular interactions in the forming decanolide.[5] Additionally, we hoped that such topology would be reinforced by the conformational bias imposed by the bulky OTBS groups at C-3 and C-4.

Our synthesis started with the reductive depolymerization of polyhydroxybutyrate (PHB), according to the procedure described by Seebach[6], which afforded (-)-1,3-butanediol in 85% yield. Selective protection of the primary hydroxyl group with TBSCl gave (+)-**3** in 83% yield and >99% ee, as determined by chiral GC analysis.[7]

Scheme 2



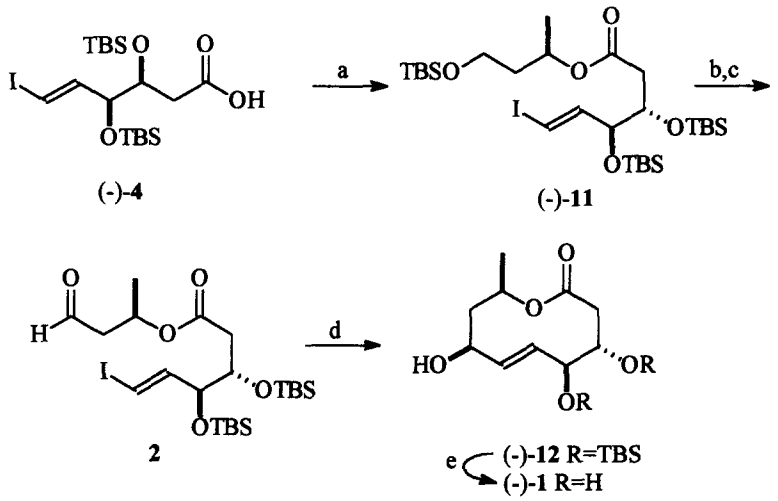
Key: a) i. NaH, THF, 0°C; ii. TBSCl(91%); b) i. $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; ii. Et_3N, -78°C->rt; c) $(EtO)_2P(O)CHNaCH_3$, THF, 0°C (70%, 2 steps); d) AD-mix α, $CH_3SO_2NH_2$, H_2O/ *tert*-BuOH (94%); e) TBSCl, DMF, imidazole (100%); f) DIBAL-H (2.0 equiv.), toluene, -95°C; g) $CrCl_2$ (12 equiv.), CHI_3 (4 equiv.), THF, 55°C; h) Jones reagent, acetone, 0°C (53%, 3 steps).

The preparation of (-)-**4** required monosilylation of 1,3-propanediol (**5**)[8] (91% yield), followed by Swern oxidation of **6** and Wittig olefination to give the unsaturated ester **7** as a 22:1 mixture of **E** and **Z** isomers (**Scheme 2**). The **E** isomer **7** was isolated in 70% yield after column chromatography on silica gel and submitted to Sharpless dihydroxylation[9] (AD-mix α reagent in the presence of methanesulfonamide). Diol (-)-**8** was formed in 94% yield (91% ee by chiral GC analysis[7]) and it was fully protected as the corresponding TBS ether (-)-**9** (quantitative yield).

The final transformation of (-)-**9** to the C1-C6 fragment in (-)-**4** required extensive experimentation: DIBAL-H reduction of (-)-**9** to the corresponding aldehyde required 2.0 equivalents of the reducing agent at -95°C and the crude aldehyde was immediately submitted to modified Takai's conditions[10] ($CrCl_2$, CHI_3, THF, 55°C) to afford **E-10** in 53% yield (2 steps). Selective desilylation (HF.pyr, pyridine, THF), followed by Jones oxidation afforded carboxylic acid (-)-**4** in 64% yield (2 steps). As the final steps in the

sequence above (desilylation and oxidation to the carboxylic acid) could conceivably be carried out sequentially with Jones reagent[11] and we had observed partial desilylation of (-)-**10** during its purification by silica gel chromatography, we employed crude iodide (-)-**10** in a one-pot desilylation-oxidation step with Jones reagent, under which conditions the carboxylic acid (-)-**4** was obtained in 53% overall yield from (-)-**9** after column chromatography on silica gel.

Scheme 3



(-)-**4** (-)-**11** **2**

Key: a) i. 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF; ii. (-)-**3**, DMAP (2 equiv.), C_6H_6 (83%); b) HF.pyr, C_5H_5N, THF; c) Dess-Martin periodinane, CH_2Cl_2, H_2O; d) $CrCl_2$-0.5% $NiCl_2$ (15 equiv.), $5x10^{-3}$ M in DMF (30% yield from (-)-**11**; e) TBAF, HF, CH_3CN (80%).

At this stage the two requisite fragments were coupled using Yamaguchi's protocol[12] to afford (-)-**11**, in 83% yield. Attempts to purify by column chromatography on silicagel the alcohol resulting from the deprotection of (-)-**11** with HF.pyr led to extensive migration of the acyl moiety from the secondary hydroxyl group to the primary one. Therefore, we employed the crude mixture in the Dess-Martin oxidation step to afford **2** which was immediately submitted to the Nozaki-Hiyama-Kishi coupling reaction in DMF to give (-)-**12** (30% yield, 3 steps) as a single diastereoisomer, as determined by capillary GC analyses and from the ^{1}H-NMR spectrum (300 MHz) of the crude reaction mixture (**Scheme 3**).[13]

The stereochemistry at C-7 in (-)-**12** was revealed by NOE difference spectroscopy (4.3% enhancement of the H-7 signal upon irradiation of H-9) and by its conversion to (-)-decarestrictine D (**1**), in 80% yield. The optical rotation ($[\alpha]_D$ = -70.9 (c 1.0, $CHCl_3$) and the ^{1}H- and ^{13}C-NMR spectra of the synthetic material[14] fully agreed with those reported by Andrus and Shih.[3]

In summary, an efficient (13 steps, 6.3% overall yield from 1,3-propanediol) and stereoselective route to (-)-decarestrictine D (**1**) was developed with a reduced number of purification steps. Studies are

currently underway aiming to probe the structural features controlling the stereochemical outcome of the Nozaki-Hiyama-Kishi coupling as applied to the formation of 10-membered lactones.

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7. Column: heptakis(2,6-methyl-3-pentyl)-β-cyclodextrine 20% in OV 1701, 25m, 0.25mm id.

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13. When the Nozaki-Hiyama step in the above sequence was carried out in DMSO the formation of a 2:1 mixture of **(-)-12** and its C-7 epimer was observed.

14. ^{1}H NMR (500MHz, CD_3OD) of **(-)-1**: δ 5.83 (1H, ddd, J=15.9Hz, J=9.3Hz, J=1.5Hz), 5.74 (1H, dd, J=15.9Hz, J=3.1Hz), 5.17 (1H, dqd, J=11.3Hz, J=6.5Hz, J=1.6Hz), 4.19 (1H, ddd, J=4.5Hz, J=3.2Hz, J=1.5Hz), 4.07 (1H, ddd, J=10.7Hz, J=9.3Hz, J=3.4Hz), 3.94 (1H, ddd, J=6.8Hz, J=4.6Hz, J=2.4Hz), 2.59 (1H, dd, J=14.0Hz, J=2.3Hz), 2.31 (1H, dd, J=14.1Hz, J=6.9Hz), 1.85 (1H, ddd, J=13.9Hz, J=3.6Hz, J=1.5Hz), 1.72 (1H, dt, J=13.9Hz, J=11.2Hz), 1.21 (3H, d, J=6.7Hz); ^{13}C NMR (75MHz, $CDCl_3$) of **(-)-1**: δ 175.3, 133.9, 130.1, 73.9, 72.5, 72.2, 68.2, 42.9, 33.0, 21.0.