ENANTIOSELECTIVE SYNTHESIS OF (+)-DECARESTRICTINE L FROM (2E,5E)-DIBENZYL-OXY-2,5-HEPTADIEN-4-OL

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Abstract - (+)-Decarestrictine L has been synthesized in enantiomerically pure form from (3R,4S)-1-benzyloxy-6-heptene-3,4-diol, prepared from (2E,5E)-1,7-dibenzyloxy-2,5-heptadien-4-ol, employing either Me₂AlCl promoted methylative cleavage of (1R,5R,6S)-6-benzyloxy-2,9-dioxabicyclo[3.3.1]nonane or DIBAH promoted reductive cleavage of (1R,5R,6S)-6-benzyloxy-1-methyl-2,9-dioxabicyclo[3.3.1]nonane for the construction of the substituted pyran ring system.

Recently we have developed an efficient method for the preparation of all stereoisomers of (1a~d) in enantiomerically pure form starting from σ-symmetrical (2E,5E)-1,7-dibenzyloxy-2,5-heptadien-4-ol (2) based on Red-Al® promoted reaction as depicted in Scheme 1. In order to demonstrate the synthetic utility of our methodology, we envisaged its application towards a synthesis of (+)-decarestrictine L (4), a member of the decarestrictine family which is a novel class of inhibitors of cholesterol biosynthesis. We now report an enantioselective synthesis of (+)-decarestrictine L (4) employing a strategy based on stereoselective methylative or reductive cleavage of dioxabicyclo[3.3.1]nonane intermediate (5) (R = H or Me) which is accessible from a 1b-type chiral building block.

According to our established procedure, the required 1b-type chiral building block (6) was prepared from 2 in optically pure form in 64% yield by combination of catalytic Katsuki-Sharpless asymmetric
epoxidation, regioselective DIBAH reduction, and Red-Al® promoted reductive cleavage of the benzyloxy group. Upon sequential Birch reduction, benzylidene acetalization, and benzylation, 6 afforded benzylidene acetal (7), \([\alpha]^{20}_D +9.8^\circ\) (c 1.03, CHCl₃), in 65% overall yield. Hydroboration of 7 with dicyclohexylborane followed by oxidation afforded primary alcohol (8), \([\alpha]^{27}_D -1.4^\circ\) (c 1.08, CHCl₃), and secondary alcohol (9) in a ratio of 78:22 almost quantitatively. Alcohol (8) was successively subjected to Swern oxidation, methanolytic removal of the benzylidene acetal group, and intramolecular acetalization to give (1R,5R,6S)-6-benzyloxy-2,9-dioxabicyclo[3.3.1]nonane (10), \([\alpha]^{20}_D +139.6^\circ\) (c 0.90, CHCl₃), in 61% overall yield. Alternatively, alcohol (8) was converted to (1R,5R,6S)-6-benzyloxy-1-methyl-2,9-dioxabicyclo[3.3.1]nonane (12), \([\alpha]^{26}_D -7.9^\circ\) (c 1.16, CHCl₃), via methyl ketone 11, \([\alpha]^{24}_D -14.7^\circ\) (c 1.30, CHCl₃), in 71% overall yield through a five-step sequence involving Swern oxidation, Grignard reaction, Swern oxidation, methanolytic removal of the benzylidene acetal group, and intramolecular ketalization.

With the required bicyclic compounds (10) and (12) in hand, we then investigated their transformations into the key intermediate (13). Although methylative cleavage⁶ of dioxabicyclo[3.3.1]nonane derivatives are unprecedented, we found that Me₂AlCl caused the cleavage of 10 with moderate diastereoselectivity, whereas Me₃Al itself resulted in no reaction.⁷ Thus, treatment of 10 with 3.5 equivalents of Me₂AlCl in CH₂Cl₂ at 0 °C produced the desired pyran (13), \([\alpha]^{23}_D +55.6^\circ\) (c 1.19, CHCl₃), and its epimer (14), \([\alpha]^{26}_D +60.1^\circ\) (c 1.35, CHCl₃), in a ratio of 80:20 in 65% yield. On the other hand, reductive cleavage⁸ of 12 with DIBAH took place with excellent diastereoselectivity to give 13 and 14 in a ratio of 95:5 in 85% yield. When 12 was
treated with triethylsilane in the presence of TiCl₄ in CH₂Cl₂ at –78 °C, the reductive cleavage occurred with perfect but opposite diastereoselectivity to give 14 exclusively in 78% yield. These stereochemical outcomes are well consistent with the results reported by Yamamoto and co-workers and can be explained on the basis of their interpretation which suggests participation of the tight ion paired intermediates. Thus, in the case of the DIBAH promoted reaction, the highly stereoselective reductive cleavage would occur via intramolecular hydride transfer from the coordinated aluminum reagent of ion paired intermediate (15) (M = i-Bu₂AlH, R = Me). In the cases of the triethylsilane reduction and the Me₂AlCl promoted reaction, the observed stereoselectivities would arise from preferential bottom-face attack of the reagent to ion paired intermediate (15) (M = TiCl₄ or Me₂AlCl, R = H or Me).

Scheme 3

Compound (13) thus obtained was converted to methyl ketone (16), [α]D²⁸ +54.0° (c 0.66, CHCl₃), by Swern oxidation, Grignard reaction, and Jones oxidation in 82% overall yield. Finally, hydrogenolytic debenzylation of 16 furnished (+)-decarestrictine L (4), [α]D²⁶ +34.4° (c 0.59, MeOH) [lit.,²⁺ [α]D²⁰ +26.0° (c 0.7, MeOH)], in 95% yield. The ¹H and ¹³C NMR spectra were identical with those of (+)-decarestrictine L synthesized by Kibayashi and co-workers.²⁺ Similarly, (±)-6-epidecarestrictine L (17), [α]D²¹ +31.5° (c 0.36, MeOH), was also synthesized from 14 in 73% overall yield. The stereochemistries of 4 and 17 were confirmed further by NOE experiments (500 MHz ¹H NMR), making those of 13 and 14 unambiguous at this stage. Since all stereoisomers of 1b-type chiral building block are available from 2, the present method enables us to synthesize all stereoisomers of (+)- decarestrictine L as well.
1) Swern oxidation
2) MeMgBr, THF
   –15 °C
3) Jones oxidation
   –10 °C

\[
\begin{align*}
13 & \xrightarrow{1) \text{Swern oxidation}} \xrightarrow{2) \text{MeMgBr, THF}} \xrightarrow{3) \text{Jones oxidation}} 16 \\
14 & \xrightarrow{73\%} 17
\end{align*}
\]

\[
\begin{align*}
16 & \xrightarrow{82\%} 17 \\
16 & \xrightarrow{95\%} 17
\end{align*}
\]

\[
\begin{align*}
16 & \xrightarrow{95\%} 17
\end{align*}
\]

\[
\begin{align*}
16 & \xrightarrow{95\%} 17
\end{align*}
\]

Scheme 4

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REFERENCES
5. All new compounds exhibited satisfactory spectral data (1H and 13C NMR, IR, HRMS).
7. When 10 was treated with Me3Al (3 equiv.) in the presence of AlCl3 (1 equiv.) in CH2Cl2 at room temperature, compound (13) was obtained in 35% yield.