

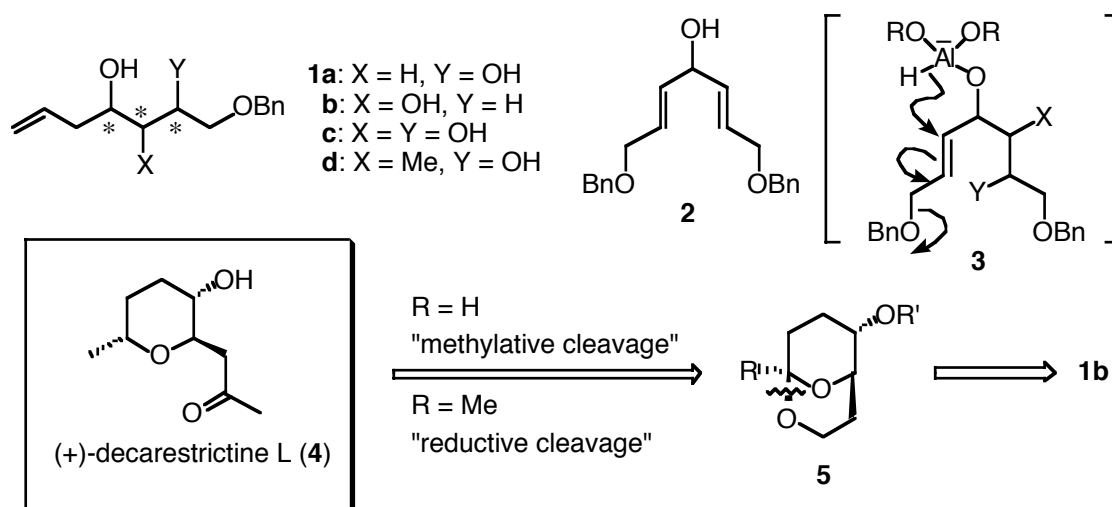
ENANTIOSELECTIVE SYNTHESIS OF (+)-DECARESTRICTINE L FROM (2E,5E)-DIBENZYLOXY-2,5-HEPTADIEN-4-OL

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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 Me_2AlCl 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.

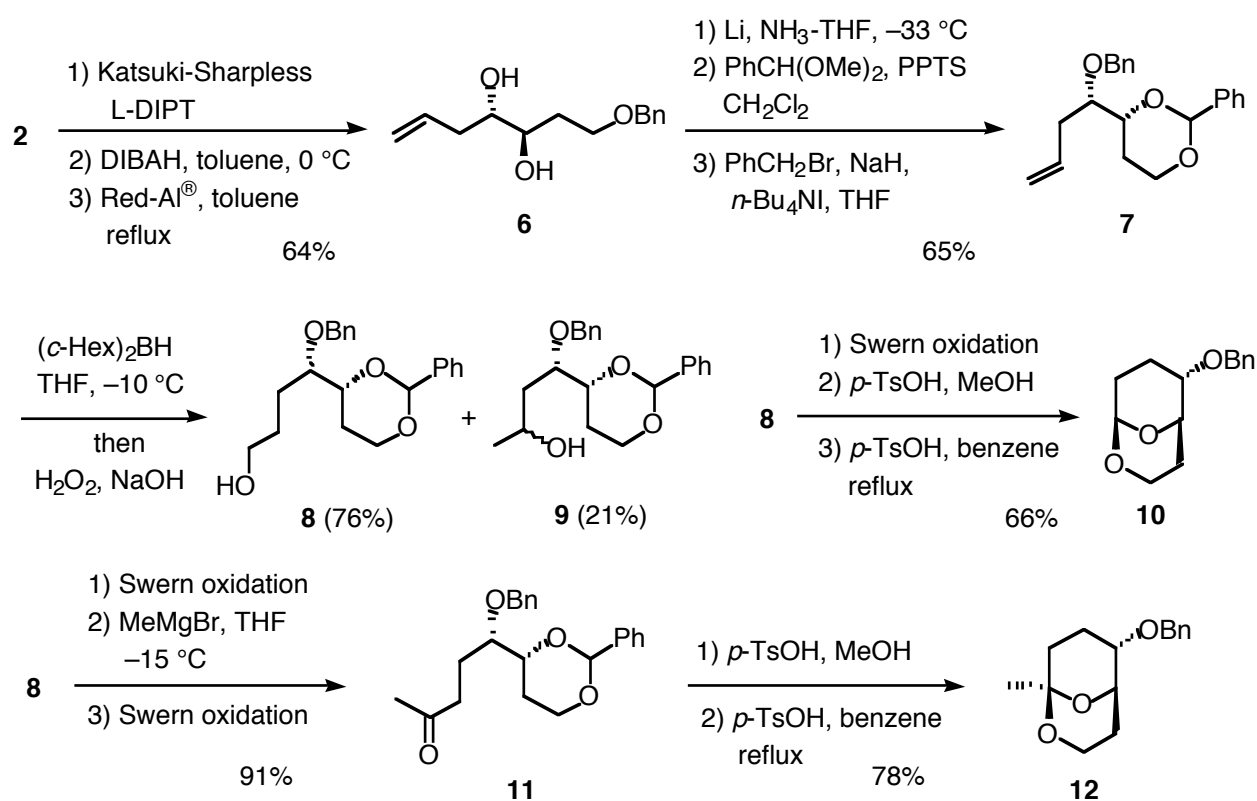
Recently we have developed an efficient method for the preparation of all stereoisomers of (**1a~d**) in enantiomerically pure form starting from σ -symmetrical (2E,5E)-1,7-dibenzyloxy-2,5-heptadien-4-ol (**2**) based on Red-Al[®] promoted reaction as depicted in **3**.¹ In order to demonstrate the synthetic utility of our methodology, we envisaged its application towards a synthesis² of (+)-decarestrictine L (**4**),³ a member of the decarestrictine family^{3,4} 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.



Scheme 1

According to our established procedure,^{1a} 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

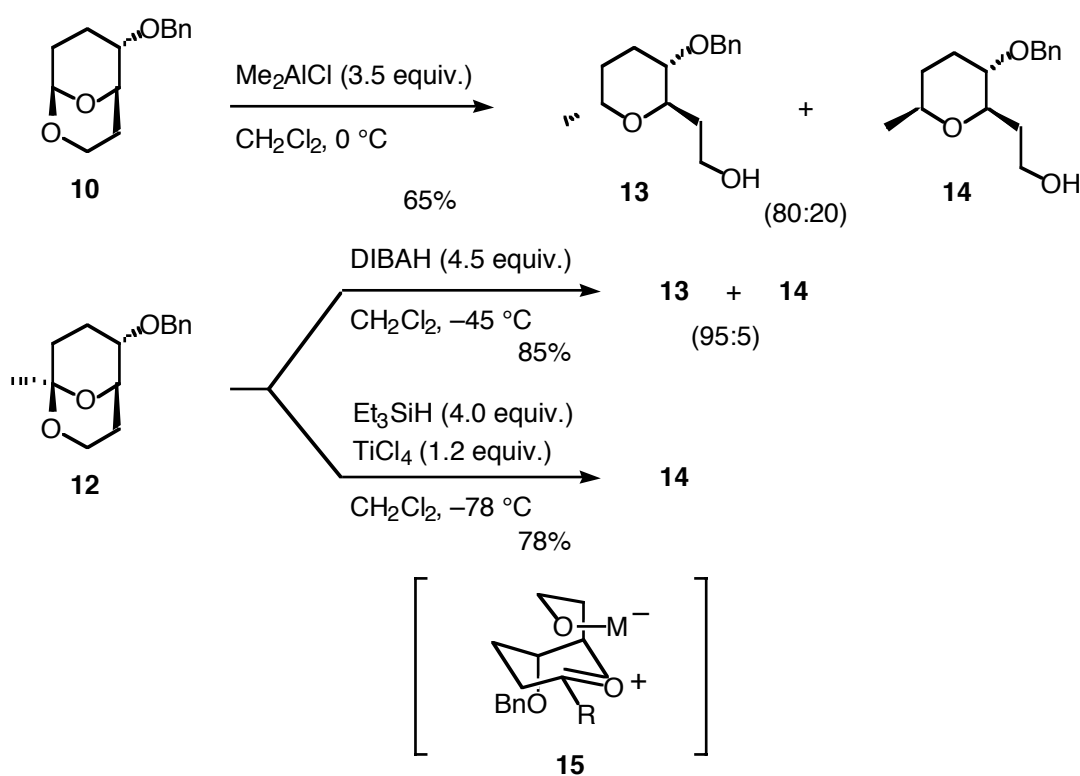
epoxidation, regioselective DIBAH reduction, and Red-Al[®] promoted reductive cleavage of the benzyloxy group. Upon sequential Birch reduction, benzyldiene acetalization, and benzylation, **6** afforded benzyldiene acetal (**7**),⁵ $[\alpha]_{\text{D}}^{20} +9.8^\circ$ (*c* 1.03, CHCl₃), in 65 % overall yield. Hydroboration of **7** with dicyclohexylborane followed by oxidation afforded primary alcohol (**8**), $[\alpha]_{\text{D}}^{27} -1.4^\circ$ (*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 benzyldiene acetal group, and intramolecular acetalization to give (1*R*,5*R*,6*S*)-6-benzyloxy-2,9-dioxabicyclo[3.3.1]nonane (**10**), $[\alpha]_{\text{D}}^{20} +139.6^\circ$ (*c* 0.90, CHCl₃), in 61% overall yield. Alternatively, alcohol (**8**) was converted to (1*R*,5*R*,6*S*)-6-benzyloxy-1-methyl-2,9-dioxabicyclo[3.3.1]nonane (**12**), $[\alpha]_{\text{D}}^{26} -7.9^\circ$ (*c* 1.16, CHCl₃), via methyl ketone **11**, $[\alpha]_{\text{D}}^{24} -14.7^\circ$ (*c* 1.30, CHCl₃), in 71% overall yield through a five-step sequence involving Swern oxidation, Grignard reaction, Swern oxidation, methanolytic removal of the benzyldiene acetal group, and intramolecular ketalization.



Scheme 2

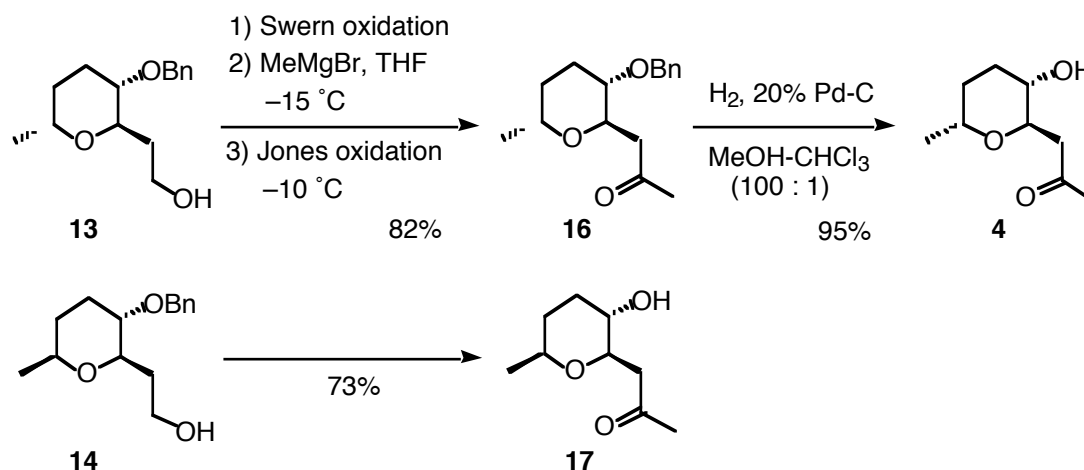
With the required bicyclic compounds (**10**) and (**12**) in hand, we then investigated their transformations into the key intermediate (**13**). Although methylative cleavage⁶ of dioxabicyclo[3.3.1]nonane derivatives are unprecedented, we found that Me₂AlCl caused the cleavage of **10** with moderate 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**), $[\alpha]_{\text{D}}^{23} +55.6^\circ$ (*c* 1.19, CHCl₃), and its epimer (**14**), $[\alpha]_{\text{D}}^{26} +60.1^\circ$ (*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 TiCl_4 in CH_2Cl_2 at $-78\text{ }^\circ\text{C}$,⁸ 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^{8a} and can be explained on the basis of their interpretation^{8c} 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**) ($\text{M} = i\text{-Bu}_2\text{AlH}$, $\text{R} = \text{Me}$). In the cases of the triethylsilane reduction and the Me_2AlCl promoted reaction, the observed stereoselectivities would arise from preferential bottom-face attack of the reagent to ion paired intermediate (**15**) ($\text{M} = \text{TiCl}_4$ or Me_2AlCl , $\text{R} = \text{H}$ or Me).



Scheme 3

Compound (**13**) thus obtained was converted to methyl ketone (**16**), $[\alpha]_{\text{D}}^{28} +54.0^\circ$ (c 0.66, CHCl_3), by Swern oxidation, Grignard reaction, and Jones oxidation in 82% overall yield. Finally, hydrogenolytic debenzoylation of **16** furnished (+)-decastrictine L (**4**), $[\alpha]_{\text{D}}^{26} +34.4^\circ$ (c 0.59, MeOH) [lit.,^{1d} $[\alpha]_{\text{D}}^{20} +26.0^\circ$ (c 0.7, MeOH)], in 95% yield. The ^1H and ^{13}C NMR spectra were identical with those of (+)-decastrictine L synthesized by Kibayashi and co-workers.^{1a} Similarly, (+)-6-epidecastrictine L (**17**), $[\alpha]_{\text{D}}^{21} +31.5^\circ$ (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 (+)- decastrictine L as well.



Scheme 4

ACKNOWLEDGMENT

We gratefully thank Professor Chihiro Kibayashi (Tokyo University of Pharmacy and Life Science) for providing us with spectral data of (+)-decaresstrictine L.

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