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

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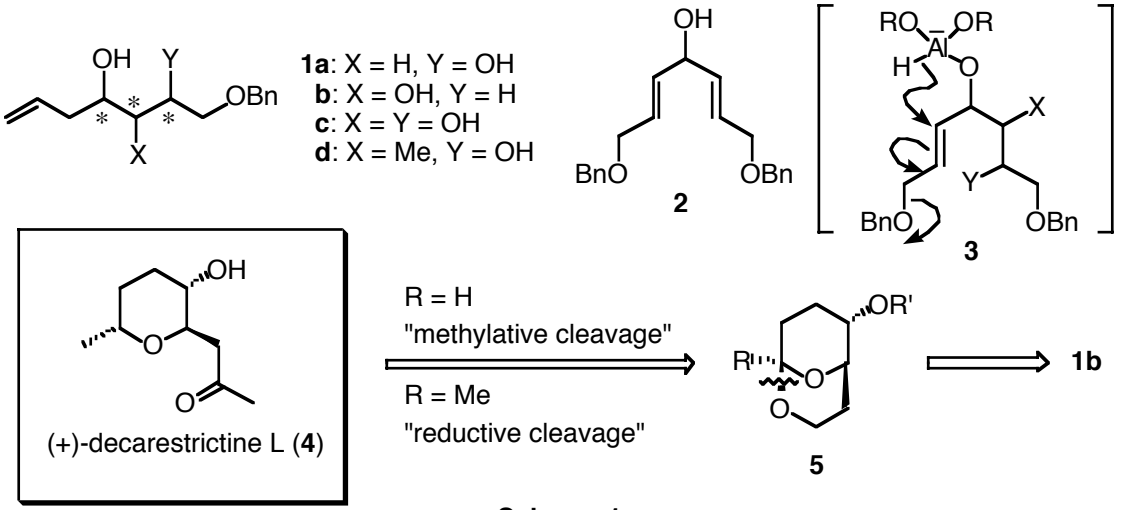
Abstract - *(+)-Decarestrictine L has been synthesized in enantiomerically pure form from (3R,4S)-1-benzyloxy-6-heptene-3,4-diol, prepared from (2E,5E)-1,7-dibenzyloxy-2,5-heptadien-4-ol, employing either Me_2AlCl promoted methylative cleavage of (1R,5R,6S)-6-benzyloxy-2,9-dioxabicyclo[3.3.1]nonane or DIBAH promoted reductive cleavage of (1R,5R,6S)-6-benzyloxy1-methyl-2,9-dioxabicyclo[3.3.1]nonane for the construction of the substituted pyran ring system.*

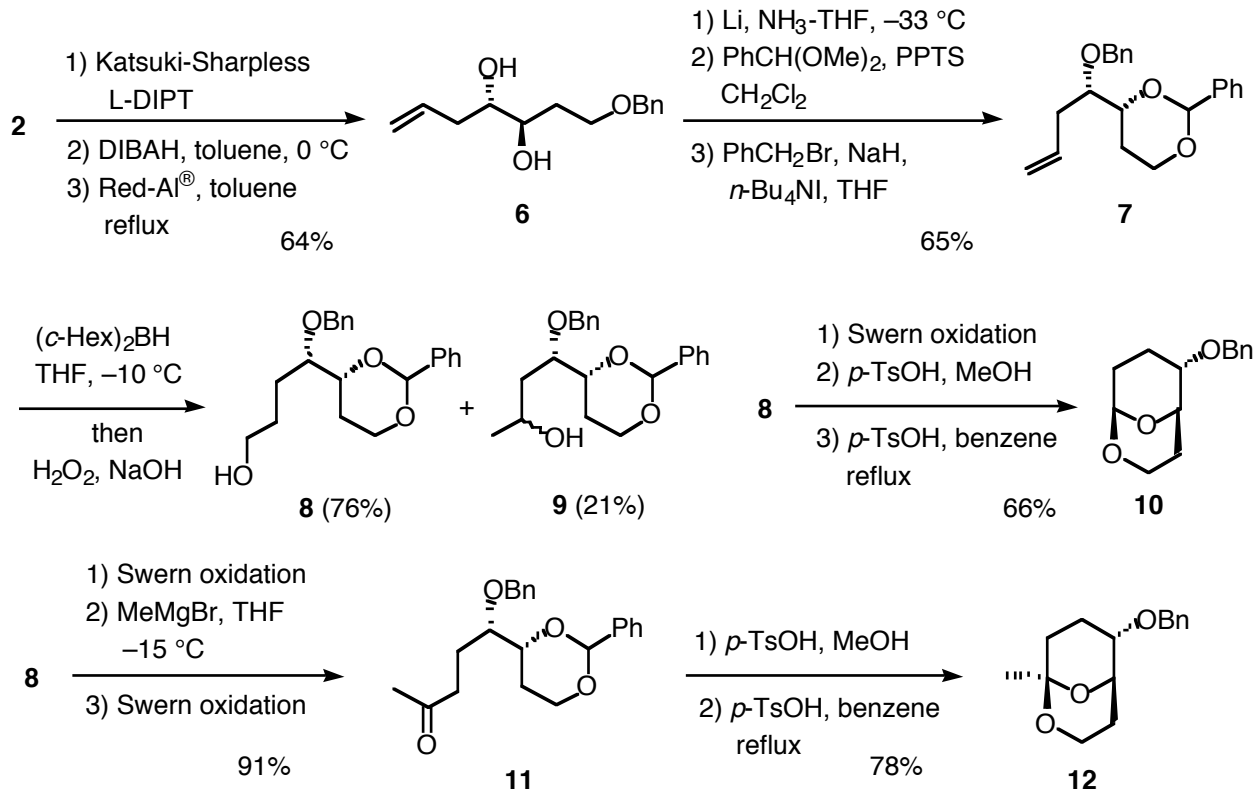
Recently we have developed an efficient method for the preparation of all stereoisomers of (**1a~d**) in enantiomerically pure form starting from σ-symmetrical (2*E*,5*E*)-1,7-dibenzyloxy-2,5-heptadien-4-ol (**2**) based on Red-Al® promoted reaction as depicted in **3**.[1] In order to demonstrate the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

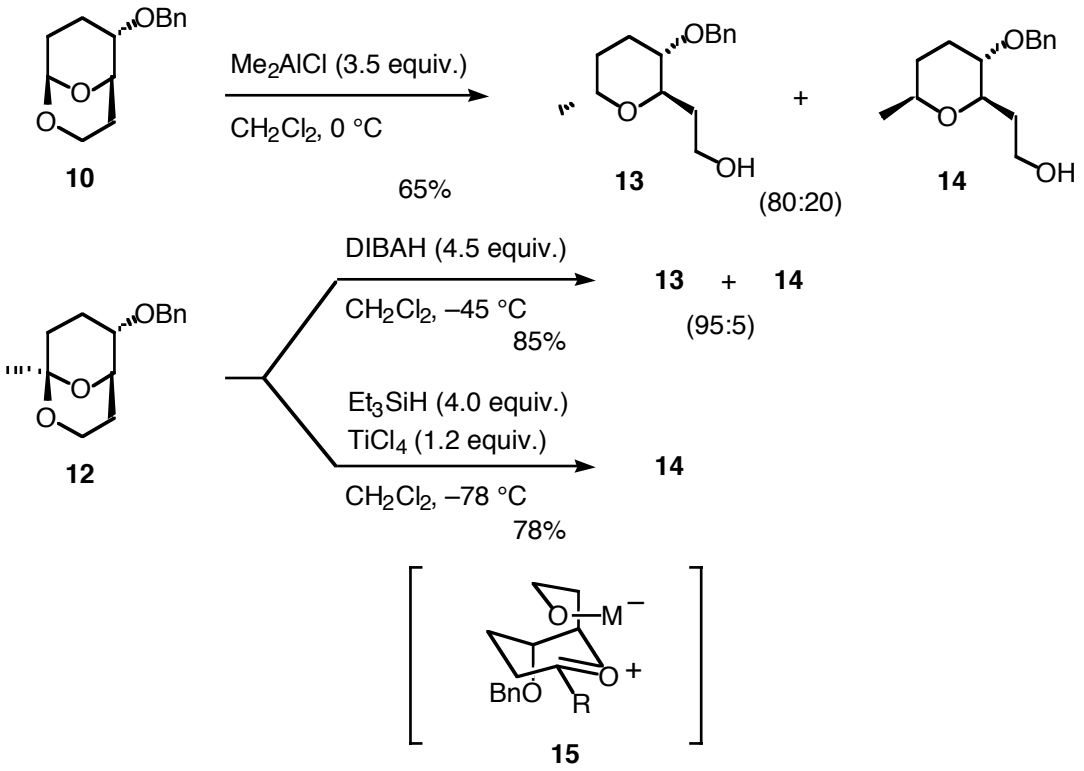
epoxidation, regioselective DIBAH reduction, and Red-Al® promoted reductive cleavage of the benzyloxy group. Upon sequential Birch reduction, benzylidene acetalization, and benzylation, **6** afforded benzylidene acetal (**7**),[5] $[\alpha]^{20}_{D}$ +9.8° (*c* 1.03, $CHCl_3$), in 65 % overall yield. Hydroboration of **7** with dicyclohexylborane followed by oxidation afforded primary alcohol (**8**), $[\alpha]^{27}_{D}$ –1.4° (*c* 1.08, $CHCl_3$), 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 (1*R*,5*R*,6*S*)-6-benzyloxy-2,9-dioxabicyclo[3.3.1]nonane (**10**), $[\alpha]_D^{20}$ +139.6° (*c* 0.90, $CHCl_3$), 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**), $[\alpha]_D^{26}$ –7.9° (*c* 1.16, $CHCl_3$), via methyl ketone **11**, $[\alpha]_D^{24}$ –14.7° (*c* 1.30, $CHCl_3$), 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.



Scheme 2

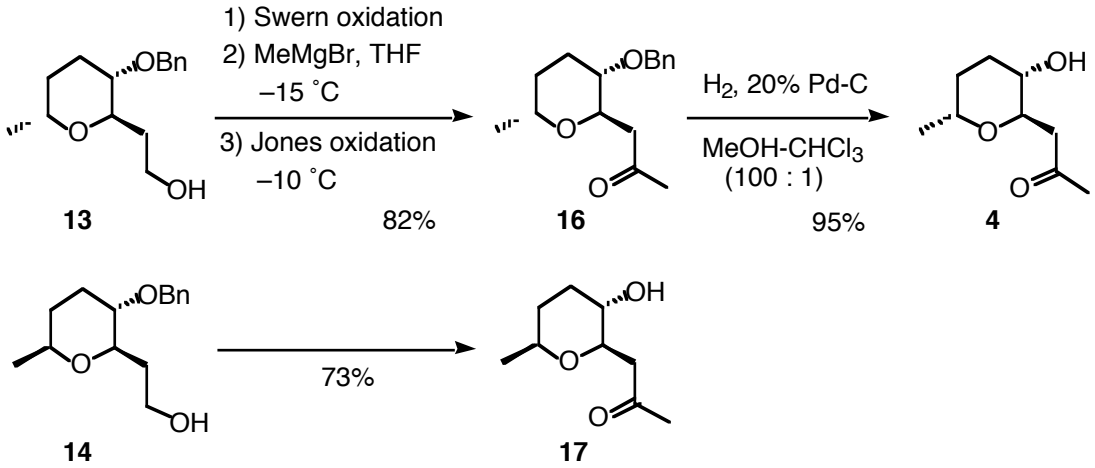
With the required bicyclic compounds (**10**) and (**12**) in hand, we then investigated their transformations into the key intermediate (**13**). Although methylative cleavage[6] of dioxabicyclo[3.3.1]nonane derivatives are unprecedented, we found that Me_2AlCl caused the cleavage of **10** with moderate diastereoselectivity, whereas Me_3Al itself resulted in no reaction[7]. Thus, treatment of **10** with 3.5 equivalents of Me_2AlCl inCH_2Cl_2at 0 °C produced the desired pyran (**13**), $[\alpha]_D^{23}$ +55.6° (*c* 1.19, $CHCl_3$), and its epimer (**14**), $[\alpha]_D^{26}$ +60.1° (*c* 1.35, $CHCl_3$), in a ratio of 80:20 in 65% yield. On the other hand, reductive cleavage[8] 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 °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**) (M = *i*-Bu_2AlH, R = 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**) (M = $TiCl_4$ or Me_2AlCl, R = H or Me).



Scheme 3

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



Scheme 4

ACKNOWLEDGMENT

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