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CONSTRUCTION OF FOUR CONSECUTIVE ASYMMETRIC CENTERS I. ANTI- AND SYN-SELECTIVE EPOXIDATION OF β-METHYL-CIS-HOMOALLYLIC ALCOHOLS

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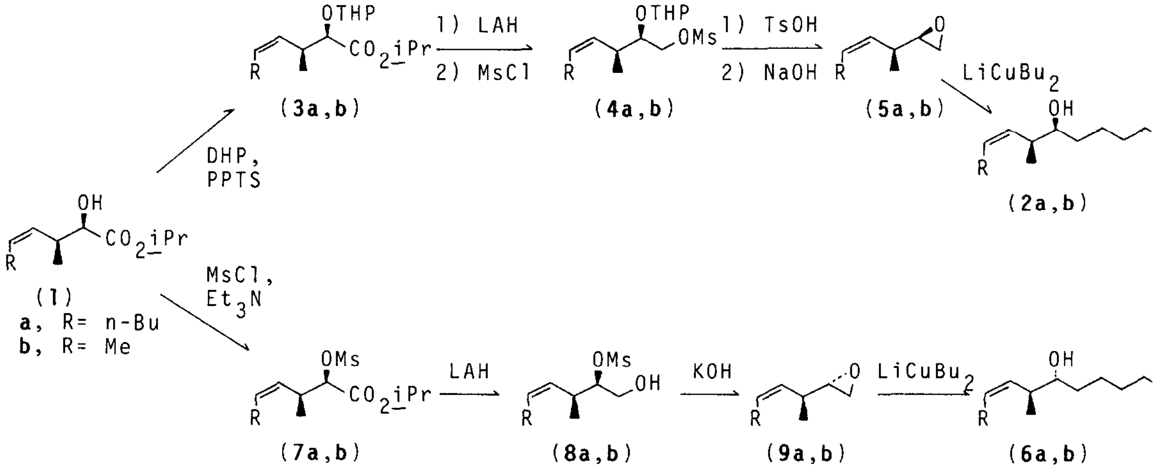
Summary: All the diastereomers of 2,3-cis-epoxy-4-methyl-5-decanol and of 8,9-cis-epoxy-7-methyl-6-tridecanol were stereoselectively synthesized as key intermediates in a model approach toward the stereoselective construction of four consecutive asymmetric centers.

Since the total synthesis of rifamycin S,[1)] several stereoselective syntheses of consecutive asymmetric centers of the type R[CH(CH$_3$)CH(OH)]$_n$R' have appeared.[2)] They are, however, mainly concerned with configurations of particular interest and the methodology which enables the stereocontrolled construction of any desired configurations of four or more consecutive asymmetric centers at our disposal, has not been reported until recently.[3)]

Here, we wish to describe a general methodology for the stereoselective construction of four consecutive asymmetric centers from two common starting materials taking isomeric 6,8-dihydroxy-5,7-dimethyltridecanes as model targets, wherein a combination of the epoxidation of β-methylhomoallylic alcohols and the subsequent alkylative opening of epoxide rings was utilized.

Although either a trans- or a cis-homoallylic alcohol derivative was considered to be the possible starting material in the present approach, we adopted the cis compound because Sato et al. recently described that the epoxidation of β-methyl-γ-trimethylsilyl-trans-homoallylic alcohols did not give high stereoselection except for limited cases.[4)] For cis-β-methylhomoallylic alcohols, Mihelich et al. have already shown that the epoxidation with a VO(acac)$_2$-TBHP system generally gives epoxides anti to the β-methyl group with high diastereoselectivity.[5)] Therefore, the remaining problem was the syn-selective epoxidation of the same substrates and it has been solved by introducing a new combination of the reagent and the modification of substrates. Thus, the stereoselective synthesis of all the diastereomers of 2,3-cis-epoxy-4-methyl-5-decanol and of 8,9-cis-epoxy-7-methyl-6-tridecanol could be achieved, which is described in the present communication. These epoxy alcohols serve as the crucial intermediates for the construction of all the diastereomers of the above dihydroxydimethyltridecane through regioselective alkylation of epoxide rings, which will be discussed in the following communication.

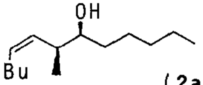
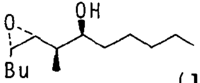
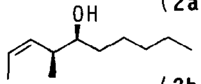
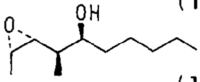
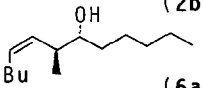
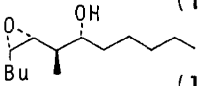
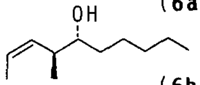
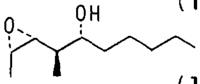
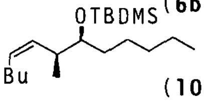
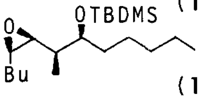
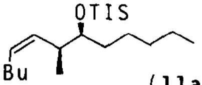
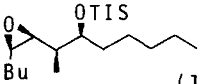
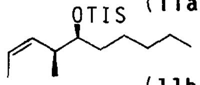
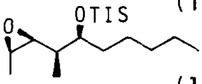
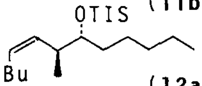
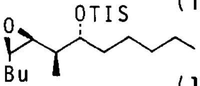
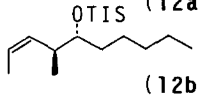
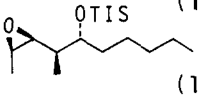
Preparation of β-methyl-cis-homoallylic alcohols (**2a, 2b, 6a,** and **6b**). Two starting materials, isopropyl dl-cis-2-hydroxy-3-methyl-4-nonenoate (**1a**) and isopropyl dl-cis-2-hydroxy-3-methyl-4-hexenoate (**1b**), were stereoselectively prepared by zirconium-mediated [2,3]Wittig rearrangement which we reported recently.[6)] One advantage of this reaction is that optically active **1a** or **1b** is readily prepared if desired, though in the present study *dl*-compounds were used. Another advantage was that the configuration of the α-asymmetric carbon atoms of **1a** and **1b** were readily invertible by conventional procedures. **1a** and **1b** were transformed into the *syn*-β-methyl-*cis*-homoallylic alcohols (**2a** and **2b**; overall yield **1a**–**2a**, 50%; **1b**–**2b**, 53%), with the retention of the configuration at the α-carbon atom by the reaction sequence: i) Protection of the hydroxyl group by treatment with dihydropyran and PPTS(7) in dichloromethane to the THP ethers (**3a** and **3b**), ii) LAH reduction of the ester group in THF at 0 °C followed by reaction with methanesulfonyl chloride in the presence of triethylamine to form the mesylates (**4a** and **4b**), iii) deprotection of the THP ether with toluenesulfonic acid in methanol and ring closure by using aqueous NaOH to give the *syn*-epoxides (**5a** and **5b**), and iv) epoxide ring opening with lithium dibutylcuprate. **1a** and **1b** were also transformed into the *anti*-β-methyl-*cis*-homoallylic alcohols (**6a** and **6b**; overall yield **1a**–**6a**, 45%; **1b**–**6b**, 47%), with the inversion of stereochemistry at the α-carbon atom by the following sequence: i) Reaction with methanesulfonyl chloride in the presence of triethylamine, ii) LAH reduction followed by treatment of the resulting hydroxy mesylates (**8a** and **8b**) with aqueous KOH to give the epoxides (**9a** and **9b**), and iii) epoxide ring opening with lithium dibutylcuprate (Scheme 1).



Scheme 1

*Epoxidation of homoallylic alcohols(**2a, 2b, 6a,** and **6b**).* The transformation of **2a**, **2b**, **6a**, and **6b** into the respective epoxides (**13a**, **13b**, **14a**, and **14b**) in which the epoxy group has *anti* stereochemistry with respect to β-methyl group, was carried out with high diastereoselectivity (>30:1) and good yield by a known vanadium catalyzed *t*-butyl hydroperoxide epoxidation (Table 1, entries 1-4).(5) In order to obtain the reversed *syn*-selectivity, the protection of the hydroxyl group with a bulky protective group and the use of an epoxidizing agent having a

Table 1. Epoxidation of <u>cis</u>-homoallylic alcohols and their TIS ethers.[a,b]

Entry	Substrate	Reagent	The major epoxy alcohol	anti	:	syn [c]	Yield[d]
1	 (**2a**)	V^{5+}-TBHP	 (**13a**)	>30	:	1	85
2	 (**2b**)	V^{5+}-TBHP	 (**13b**)	>30	:	1	81
3	 (**6a**)	V^{5+}-TBHP	 (**14a**)	>30	:	1	94
4	 (**6b**)	V^{5+}-TBHP	 (**14b**)	>30	:	1	95
5	 (**10**)	MoO_5.HMPA	 (**15**)	1	:	5	74
6	**10**	WO_5.HMPA	**15**	1	:	5.5	82
7	 (**11a**)	WO_5.HMPA	 (**16a**)	1	:	10.8	80
8	 (**11b**)	WO_5.HMPA	 (**16b**)	1	:	16.7	89
9	 (**12a**)	WO_5.HMPA	 (**17a**)	1	:	8.2	74
10	 (**12b**)	WO_5.HMPA	 (**17b**)	1	:	7.4	67

a) A typical experimental procedure for <u>syn</u>-epoxidation: A mixture of **11b** (7.1 mg) and WO_5.HMPA (30 mg) in dichloroethane was stirred overnight at room temperature. After removal of the solvent in vacuo, the residue was dissolved in ether and filtered through a short silica gel column. The filtrate was concentrated to give a mixture of <u>syn</u>- and <u>anti</u>-isomers in a ratio of 16.7:1 (^{1}H NMR, 400MHz). The mixture was chromatographed at medium pressure by using Lobar column with hexane-ethyl acetate (300:1) to give the epoxide **16b** in 84% yield. b) All the new compounds obtained in the present study gave satisfactory ^{1}H NMR (400 MHz) and elementary analyses. c) Diastereomeric ratio was determined by ^{1}H NMR (400 MHz). d) The combined yield of <u>syn</u>- and <u>anti</u>-isomers.

poor affinity to the ether oxygen atom are considered to be favorable.[8)] Thus, the compound (**2a**) was first converted to the corresponding <u>t</u>-butyldimethylsilyl (TBDMS) ether (**10**) and treated with $MoO_2(acac)_2$-TBHP, MoO_5.HMPA, or WO_5.HMPA.[9)] The epoxidation with TBHP-$MoO_2(acac)_2$ system did not give the desired epoxide but only the deprotected compound (**2a**).[10)] On the other hand, the reaction with MoO_5.HMPA and with WO_5.HMPA gave the <u>syn</u>-epoxide as a major isomer in a ratio of 5:1 and 5.5:1, respectively. Protection by triethylsilyl group was fairly sensitive and cleaved under the reaction conditions using MoO_5.HMPA or WO_5.HMPA. Then, **2a** was converted to the triisopropylsilyl (TIS) ether (**11a**).[11] Epoxidation of **11a** with WO_5.HMPA in dichloroethane proceeded smoothly with high stereoselectivity (10.8:1) (entry 7). The remaining three TIS ethers (**11b**, **12a**, and **12b**) could be also epoxidized in good *syn*-selectivities (7.4-16.7:1), as can be seen in the Table 1 (entries 8-10).

Thus, starting from **1a** and **1b**, all the possible isomers of 2,3-*cis*-epoxy-4-methyl-5-decanol (**13b**, **14b**, **16b**, and **17b**) and 8,9-*cis*-epoxy-7-methyl-6-tridecanol (**13a**, **14a**, **16a**, and **17a**), necessary intermediates for further elabolation to four consecutive asymmetric carbons, were stereoselectively synthesized by using a set of epoxidations, a known *anti*-selective and a new *syn*-selective ones, as key reactions.

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References and notes

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