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New methodologies for the synthesis of natural products

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Abstract — syn,Z-Selective [2,3]sigmatropic rearrangement of 2-alkenyloxyacetic acid ester enolates, syn,E-selective [2,3]sigmatropic rearrangement of the corresponding enolates bearing an additional oxygen functionality on the ether alkenyl, and syn-selective epoxidation of β-methylhomoallylic alcohols were newly developed. These stereoselective reactions were successfully applied to the synthesis of compounds having four of more asymmetric centers, such as all eight diastereomers of 5,7-dimethyl-6,8-tridecanediol, the Kishi's intermediate for rifamycin S, and Ireland alcohol.

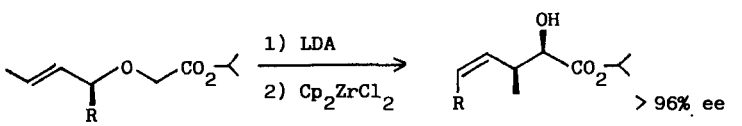
INTRODUCTION

Structures with consecutive asymmetric centers often appear in natural products, especially, of polyketide origin, such as macrolides, macrolactams, polyethers etc. Because of the importance of these natural products from the structural and biological points of view, much effort was directed to their synthesis, wherein the stereocontrolled construction of consecutive asymmetric center systems was one of the crucial tasks. However, most of these studies have been focused on the syntheses of the structures having particular configurations, namely, those of natural ones, and only a few general methodologies were developed which enabled the synthesis of any configurations other than those of natural compounds, though it was considered to be quite meaningful for the elucidation of structure-biological activity relationship.

Recently, we developed new methodologies, zirconium mediated syn,Z-selective and titanium mediated syn,E-selective [2,3]sigmatropic rearrangement of ester enolates and syn-stereoselective epoxidation of β-methylhomoallylic alcohols. These methodologies were considered to provide quite useful means for the syntheses of polyketide natural products, and some applications related to the synthesis of compounds having consecutive asymmetric centers were undertaken as described below.

ZIRCONIUM MEDIATED [2, 3]SIGMATROPIC REARRANGEMENT

Recently we developed trans-2,5-disubstituted pyrrolidine chiral auxiliaries, in which C_2-symmetry and the periplanarity of five-membered ring structure were combined, and showed that they were quite effective for a wide veriety of asymmetric reactions, such as α-alkylation or acylation of carboxylic acids and their derivatives, aldol condensation, and Diels-Alder reaction, with high enantioselectivity. The method was successfully applied to [2,3]sigmatropic rearrangement of alkenyloxyacetic acid amide enolates into β-alkyl-α-hydroxy-γ-unsaturated amides, and found that they also proceeded with high enantio- and syn-diastereoselectivity, when zirconium enolates of E-alkenyloxy substrates were used. The selectivity seemed to arise from a chelate structure of the enolate, and, therefore it was considered that the selectivity was not confined to amide enolates but also expected from the corresponding esters.



1 2

Thus, we examined the rearrangement of alkenyloxyacetic acid ester enolates (ref. 1). Although lithium enolate did not give good selectivity, the addition of zirconocene

dichloride to the lithium enolate solution gave quite high syn-diastereoselectivity (syn:anti=50:1–100:1) in the products 2, when E-substrates 1 were used. With optically active substrates bearing an asymmetric carbon atom at the ether linkage, a remarkably high chirality transfer (>96% ee) was observed besides the high syn-selectivity. The most striking outcome of this rearrangement was, however, the exclusive formation of Z-double bond in the products, because it had been accepted that sigmatropic rearrangement usually exhibited E-selectivity. The unusual Z-selectivity was explained as follows. Because of the coordination of the ether oxygen to zirconium atom, the transition state of the rearrangement took a dioxazirconabicyclo[3,3,0]octene like structure as illustrated by Fig. 1, where the substituent R occupied a sterically favored exo-position, leading to the formation of the Z-double bond.

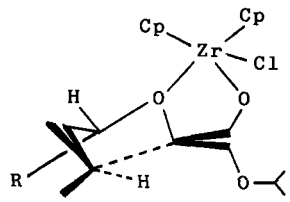
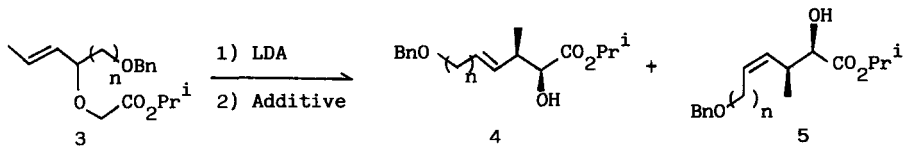


Fig. 1. Transition state leading to Z-double bond formation

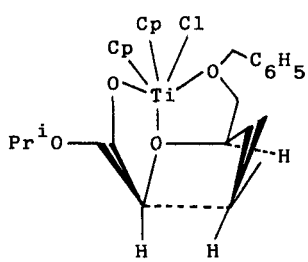
TITANIUM MEDIATED [2, 3]SIGMATROPIC REARRANGEMENT

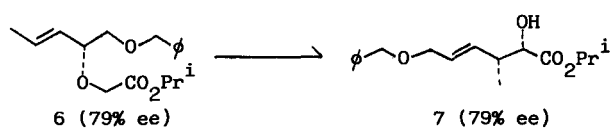
Then we proceeded to the rearrangement of another type of substrates (3, n=1, 2, or 3), with an oxygen functionality at a different chain length position on the ether alkenyls, hoping the formation of stereodefined ω-oxygenated α-hydroxy-β-methyl-γ-unsaturated esters, 4 or 5 (ref. 2). These products carried two different oxygen functionalities, benzyl ether and ester, they were considered to serve as versatile synthons for further site selective transformations.



3 4 5

Although the rearrangement of lithium enolate only showed poor to moderate stereoselectivity in all cases, the addition of zirconocene dichloride to lithium enolates gave high syn- and Z-selectivity for the substrates of n=2 and 3. However, for the substrate of n=1, the ratio of the syn,Z- to the syn,E-isomer was 1:1.5, exhibiting an obvious trend to E-double bond formation. This result suggested that the use of more oxygenophilic titanium ion would result in the further enhancement of E-selectivity. As a fact, the addition of titanocene dichloride to the lithium enolate remarkably improved the E-selectivity to 58:1. The formation of E-double bond in the products of this rearrangement is considered to be due to the high Lewis acidity of titanium. The strong coordination of benzyloxyl oxygen to titanium as shown by Fig. 2, is considered to promote the otherwise disfavored endo-orientation of the benzyloxymethyl substituent on a dioxatitanabicyclooctene like transition state, resulting in the predominant formation of the syn,E-isomer.





6 (79% ee) 7 (79% ee)

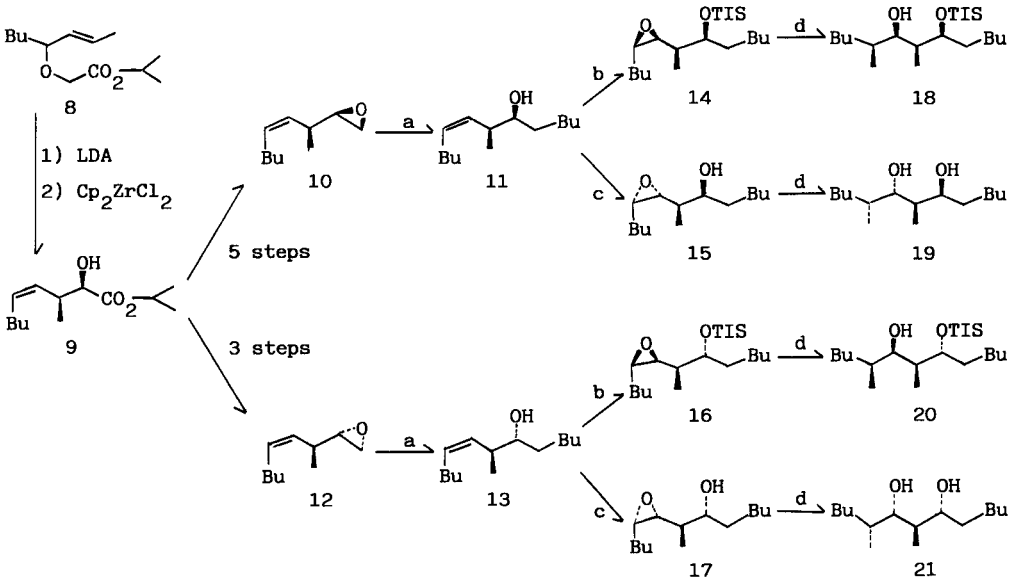
Fig. 2. Transition state leading to E-double bond formation

The titanium mediated rearrangement of an optically active substrate 6, bearing a chiral center at the allyl ether carbon atom, led to 7 with a high chirality transfer, where the sense of asymmetric induction was opposite to that observed in the above zirconium mediated rearrangement of the alkenyloxy esters, supporting the proposed transition state represented by Fig. 2.

GENERAL CONSTRUCTION OF FOUR CONSECUTIVE ASYMMETRIC CENTERS

For the study on the general methodology for the construction of four consecutive asymmetric centers, the synthesis of all possible isomers of 5,7-dimethyl-6,8-tridecanediol was chosen as the model example (ref. 3). The synthesis consisted of two alike series. The reaction sequence of one series is outlined in Scheme 1 and will be discussed in some detail here. The starting material in the series, isopropyl syn,Z-2-hydroxy-3-methyl-4-nonenoate 9, was readily prepared in quantity by the above zirconium mediated rearrangement from an ally ether 8. Although the experiments were carried out with racemic materials throughout the work, it is obvious that the synthesis with optically active compounds is also feasible because optically active allylic alcohols necessary for the preparation of 8 are readily available by various methods, by, for example, Katsuki-Sharpless kinetic resolution of secondary allyl alcohols. The compound 9 was transformed into a syn,Z-homoallylic alcohol 11 by a sequence of conventional reactions, THP protection of hydroxyl group, LAH reduction of ester, mesylation of the resulting alcohol, removal of THP protection, alkali treatment to an epoxide 10, and lithium dibutylcuprate treatment, with 50% overall yield. The anti,Z-homoallylic alcohol 13, was obtained also from the same starting material 9 by a sequence of reactions, mesylation, reduction, base treatment, and cuprate treatment, with 47% overall yield. The syn- and anti-homoallylic alcohols in the other series were prepared in a similar manner starting from isopropyl syn,Z-2-hydroxy-3-methyl-4-hexenoate.

Scheme 1



a: $LiCuBu_2$
b: 1) TISOTF, 2,6-Lutidine, CH_2Cl_2 2) WO_5 HMPA, $ClCH_2Ch_2Cl$
c: $VO(acac)_2$, TBHP, CH_2Cl_2
d; $Me_2Cu(CN)Li_2$, $n\text{-}Bu_3P$, Me_2S, Et_2O

Synthetic sequence to four diastereomers of dimethyltridecanediol

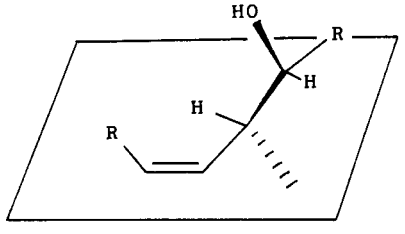


Fig. 3. Conformation of β-methyl-homoallylic alcohol

Here, the present approach needed the epoxidation of these homoallylic alcohols both in anti- and syn-fashion. The epoxidation of β-methylhomoallylic alcohols to the epoxides in which

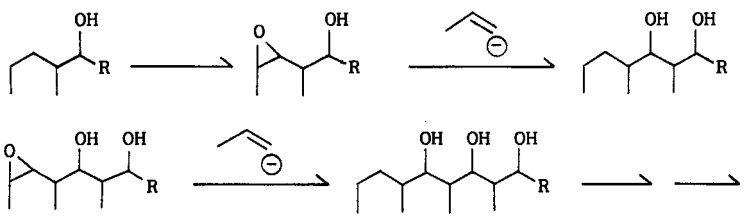
the epoxy group had an anti-stereochemistry with respect to β-methyl group, had already been established by Mihelich et al. by using vanadyl catalyzed t-butylhydroperoxide oxidation (ref.4). For our substrates, 11 and 13, in this series and two substrates in the other series, the method proceeded with high diastereoselectivity (>30:1). On the other hand, however, no good method had been developed for the syn-epoxidation. On considering the conformation of β-methylhomoallylic alcohols in the above anti-epoxidation as shown by Fig. 3, where the attachment of the catalyst metal onto the hydroxyl oxygen promoted the oxidation from the upper face of the double bond. Therefore, it was thought that if the hydroxyl group was protected by a very bulky group and if a poorly oxygenophilic metal oxidant was used, epoxidation from the bottom face would take place. Some experiments were carried out along this line with trialkylsilyl groups for protection and oxides of molybdenum and tungsten as catalysts or oxidants, and it was found that a combination of triisopropylsilyl (TIS) protection and tungsten pentoxide-hexamethylphosphoric triamide (WO_5-HMPA) complex (ref. 5) gave a fairly good result. Then the method was applied to four homoallylic alcohols of both the series with practicable stereoselectivity of 7.4:1–16.7:1.

Thus, the necessary epoxides 14, 15, 16, and 17 in the series and other four in the other series could be secured. These epoxides were regioselectively opened by higher order mixed dimethylcuprate in this series and by the corresponding dibutylcuprate in the other series, completing the synthesis of all eight isomers of 5,7-dimethyl-6,8-tridecanediol 18, 19, 20, 21 and other four, after deprotection. It is well recognized that the regiochemistry in the opening of epoxide ring is quite dependent on reaction conditions, reagents, and protective groups, and in our cases also some modifications in the protection of the hydroxyl group and in reaction conditions were necessary depending on the substrates. There was an obvious trend that for desired regiochemistry, syn-epoxides preferred the hydroxyl group protected form while anti-epoxides the non-protected form. The major by-product was β-hydroxyketones formed by the rearrangement of epoxide group.

SYNTHESIS OF KISHI'S INTERMEDIATE FOR THE SYNTHESIS OF RIFAMYCIN S

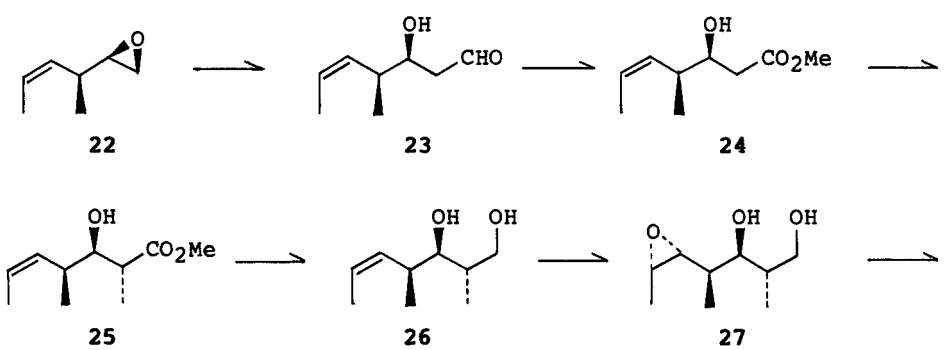
The practicability of the above strategies suggested a simple route to the successive addition of two consecutive asymmetric centers of anti-type by repeating the epoxide ring opening with a cis-vinyl anion equivalent followed by stereoselective reepoxidation as shown in Scheme 2.

Scheme 2



Successive addition of two consecutive asymmetric centers

As an example of this approach, the synthesis of the Kishi's intermediate 38 (ref. 6) for the synthesis of rifamycin S will be described next (ref. 7). The synthetic sequence is shown by Scheme 3.



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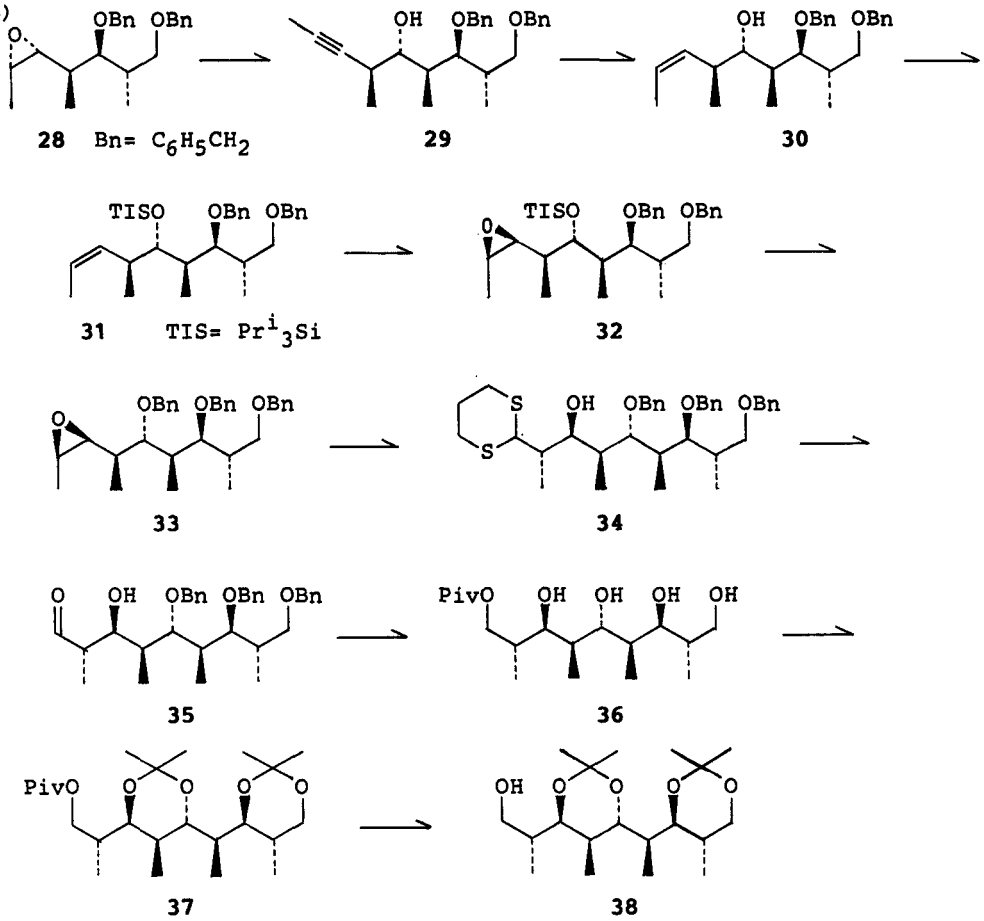
Scheme 3 (contd.)

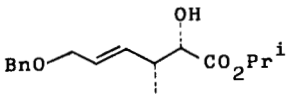


Synthetic sequence to Kishi's intermediate for rifamycin S

The epoxide 22 was treated with lithiated 1,3-dithiane and the product was hydrolysed to an aldehyde 23, which was transformed into 26 by a sequence of conventional reactions. Mihelich's anti-epoxidation gave 27 with rather modest selectivity of 7:1. After benzyl protection of two hydroxyl groups, methylacetylene was introduced as a cis-vinyl equivalent by the boron trifluoride promoted procedure (ref. 8) to give 29. Catalytic hydrogenation led to a cis-homoallylic alcohol 30, the hydroxyl group of which was triisopropylsilylated to 31. The syn-epoxidation of 31 by our procedure proceeded with quite high syn-diastereoselectivity (30:1) this time, to give 32. After protective manipulation, the introduction of a formyl group led to 35, via a dithiane derivative 34. The reduction of formyl group followed by conventional protective manipulations led to the Kishi's intermediate 38 which carried seven consecutive asymmetric centers. The proton NMR spectrum coincided in detail with the authentic datum (ref. 9).

SYNTHESIS OF IRELAND ALCOHOL

As am application of the titanium mediated [2,3]sigmatropic rearrangement, the synthesis of so-called Ireland alcohol 44 is described next (ref. 10). The compound was synthesized by Ireland et al. (ref. 11) as an intermediate for the synthesis of tirandamycic acid, a degradation product of an antibiotic tirandamycin isolated from Streptomyces tirandaris. The synthesis started with isopropyl (2,3-syn,4E)-6-benzyloxy-2-hydroxy-3-methyl-4-hexenoate 39 readily prepared by the above rearrangement. The ester 39 was hydrolysed and then subjected to iodolactonization to give 40. The treatment of 40 with methanolic sodium carbonate gave an epoxide 41. After the THP protection, reduction, and pivaloylation to the compound 42, the foruth chiral center was introduced by lithium dimethylcuprate to afford a 1,3-dilol 43, as a single isomer, thus completing the construction of four necessary consecutive asymmetric centers. The compound 43 could be uneventfully transformed into the Ireland alcohol 44 by a sequence of conventional conversions.



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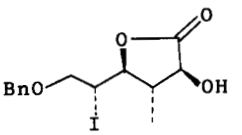

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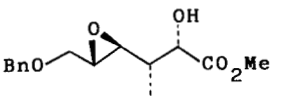

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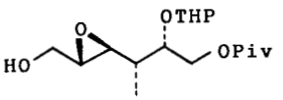

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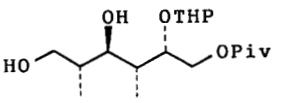

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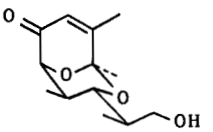

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