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ORGANOMETALLIC COMPOUNDS FOR STEREOREGULATED SYNTHESIS OF ACYCLIC SYSTEMS. THEIR APPLICATION TO THE SYNTHESIS OF THE PRELOG-DJERASSI LACTONIC ACID

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Dedicated to Professor Herbert C. Brown on the occasion of his 70th birthday

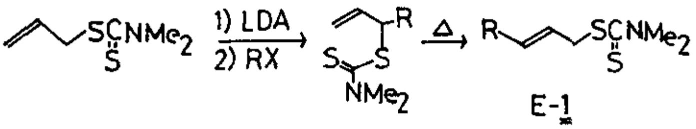
Abstract - Acyclic stereoselection via organometallic compounds (M = Li, Mg, Zn, Cd, Cu, B, Al, Si, Sn, Ti, Zr, Cr, and Pd) is surveyed. Application of the organometallics to the synthesis of the Prelog-Djerassi lactonic acid is described along with other approaches.

One of the challenging problems for the organic chemist today is control of stereochemistry in conformationally nonrigid complex molecules, such as polyether, ansamycin, and macrolide antibiotics. Their biological activities and considerable commercial importance, coupled with the intriguing structural problems, have stimulated intense efforts directed toward their total synthesis.[1] The methods for the stereoregulated synthesis of their key intermediates generally commence with the crossed aldol reactions,[2] the condensation of organometallic compounds with carbonyl compounds, the ring opening reactions of cyclic compounds,[3] the epoxidation of allylic alcohols,[4] the hydroboration of olefinic compounds,[5] the reduction of carbonyl derivatives,[6] the sigmatropic rearrangement,[7] and the reaction of carbohydrates.[8] The first chapter of this review reports the currently available methods via organometallic compounds for the stereoregulated synthesis of acyclic systems. The crossed aldol reaction, in which the metal cation plays an important role in the stereocontrol, is not involved in this article. In the second chapter, the synthetic methods of the Prelog-Djerassi lactonic acid, which holds a conspicuous position as a stereochemical touchstone in the chemistry of the macrolide antibiotics, are summarized. It is indicated that the strategy via the organometallic compound is short and efficient.

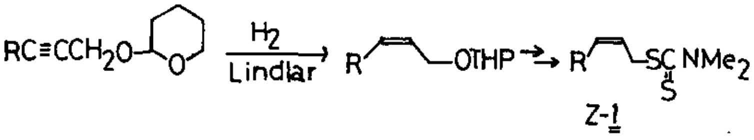
Chapter 1. Organometallic Way to Control Stereoselection

[1] Organolithium compounds

(E) and (Z)-2-Alkenyl-N,N-dimethyldithiocarbamates (1) are prepared as shown in eqs. 1 and 2.[9,10]

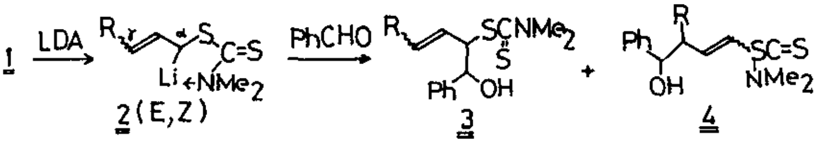


(1)



(2)

Treatment of 1 with lithium diisopropylamide in THF/hexane at -60°C, followed by the addition of benzaldehyde at -90°C, gives a mixture of α and γ-adducts (3 and 4, respectively)(eq 3). The ratio of four possible isomers of 4 are summarized in the Table 1.[11]



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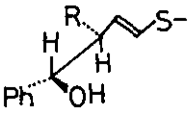
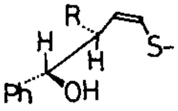
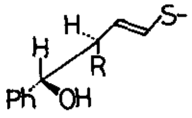


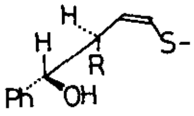
4-threo-(E)



4-threo-(Z)



4-erythro-(E)

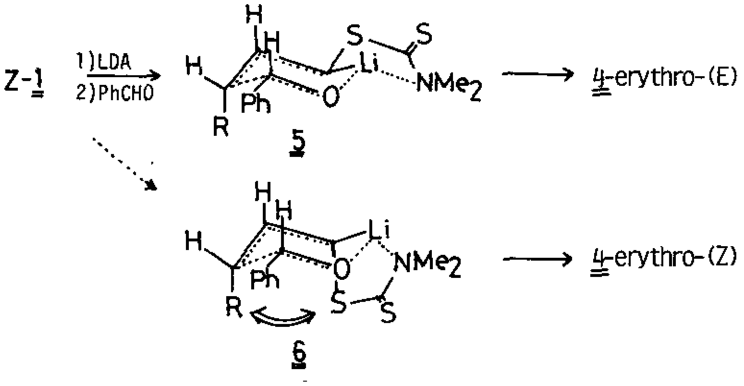


4-erythro-(Z)

Table 1. Regio and Stereoselectivities in Reaction of 2 with Benzaldehyde

Anion 2		Yield of	γ/α	Isomer ratio of 4			
	R	3 + 4 (%)	ratio	threo(E)	threo(Z)	erythro(E)	erythro(Z)
2(Z)	Me	85	9 : 1	11.0	0	89.0	0
2(Z)	Et	84	9 : 1	8.0	0	92.0	0
2(E)	Me	92	9 : 1	50.7	7.2	23.7	18.4
2(E)	Et	87	9 : 1	53.6	2.6	25.1	18.7
2(E)	i-Pr	85	9 : 1	74.6	7.1	9.8	8.5

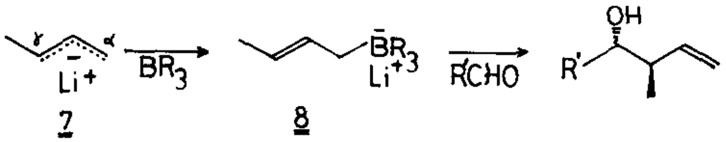
As evident, Z-2 gives the erythro isomer stereoselectively and the ratio of E/Z of 4 is exceptionally high; erythro selectivity = ~90 %, and E selectivity = 100 %. On the other hand, although E-2 affords the threo isomer predominantly, both the threo selectivity and E selectivity are not so high. These stereochemical characteristics are explained by a six-membered cyclic transition state. An analogous transition state is frequently used to understand the stereochemical aspects of the aldol condensation reaction.[1] The strong preference for a chair



(4)

conformation (5) explains the stereoselective formation of 4-erythro-(E) (eq 4), though the relatively low selectivity of E-2 can not be explained completely. At least in the reaction of Z-2, the transition state (6) leading to 4-erythro-(Z) is destabilized in comparison with 5 owing to the steric repulsion.

The threo selective coupling between crotyllithium and aldehydes without the use of the pure E-isomer is realized; merely the addition of BR_3 before the addition of aldehydes to crotyllithium (7) produces the threo selectivity (eq 5).[13] Such an improvement of the stereo- and regio-selectivity of 7 via a simple procedure is noteworthy, since 7 itself produces both α and γ-adducts and does not exhibit the stereoselectivity (erythro/threo = 50/50). The "ate" complex (8) is involved as an intermediate, whose crotyl unit possesses predominantly E-configuration despite of the fluctionality of 7.[14] The E-configuration is confirmed by the ^{1}H and ^{13}C NMR spectra.[14]

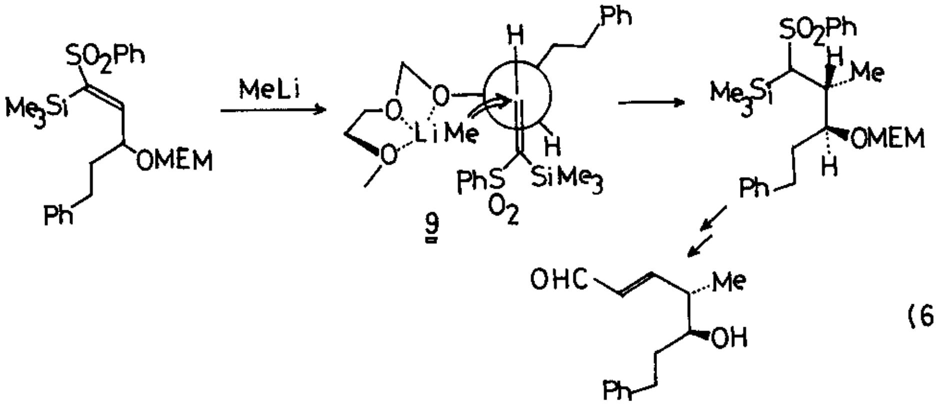


(5)

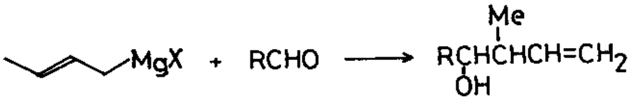
Stereoselective "heteroconjugate addition" of alkyllithiums to the activated olefins substituted with heteroatoms, such as silicon and sulfur, is an useful method for erythro selective synthesis of the β-methyl alcohol unit (eq 6).[15] The stereochemical control is understood by consideration of the conformation (9), where the methyl group is forced to attack from the one side because of the coordination of lithium cation to the MEM group.

[2] Organomagnesium, zinc, and cadmium compounds

Aldehydes react with crotyl and secondary-butyl Grignard reagents to form pairs of diastereoisomeric alcohols (eqs 7 and 8). In both cases, the stereoselectivity is quite low or even



(6)



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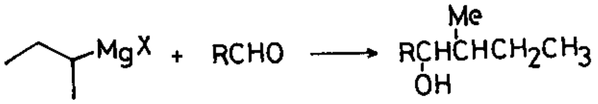
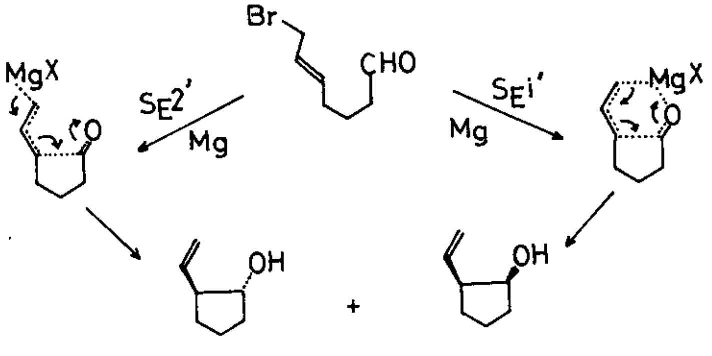
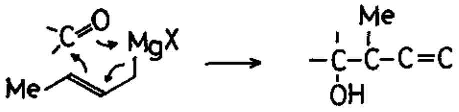


(8)

negligible.[16] Cyclization of 7-bromohept-5-enal in the presence of Mg preferentially affords trans-2-vinylcyclopentanal in low yield. These stereochemical findings suggest that the reaction proceeds through a non-cyclic bimolecular electrophilic substitution mechanism (S_E2').[16a]



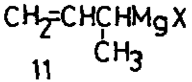
On the other hand, a six-membered cyclic mechanism has often been proposed, since the reaction of crotylmagnesium bromide with carbonyl compounds gives an α-methylallyl product (eq 9).[17] However, this product can also be explained by consideration of the allylic rearrangement; 10 would predominate in the equilibrium, but 11 would be more reactive. If the cyclic mechanism is operative,



(9)

$CH_3CH=CHCH_2MgX$

10

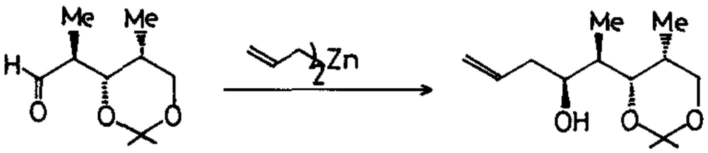


$CH_2=CH\underset{CH_3}{C}HMgX$

11

trans-crotyl Grignard reagent will give the threo product predominantly, and the cis derivative the erythro isomer as discussed above. Such an experiment using the stereochemically defined crotyl derivative has not been performed yet.[18] Furthermore, it should be noted that the addition of certain allylic organometallic compounds to a carbonyl compound is reversible.[19] For example, as the steric bulk of the carbonyl compound increases, there is a concomitant increase in the crotyl product at the expence of the α-methylallyl product. This tendency depends on the nature of the organometallic compound; the order of the reversibility is Zn $\rangle$ Li $\rangle$ Mg. The stereochemical aspects of the reaction with epoxides are not investigated yet.[16b] This reaction may produce an interesting stereoselectivity. Although Grignard reagent does not exhibit an useful stereoselectivity in the above reaction types, recent investigations reveal that some Grignard reactions are quite useful in the chelation controlled nucleophilic addition to carbonyl compounds. This subject is discussed in the section of organocopper compounds.

Diallylzinc reacts with aldehyde (12) stereoselectively to give 13; the ratio of 13 to its isomer is 4.3 : 1 (eq 10).[20] Allylmagnesium bromide yields a 1.1 : 1.0 mixture favoring the undesired product. Diallylcadmium and diallylmanganese fail to react with 12.



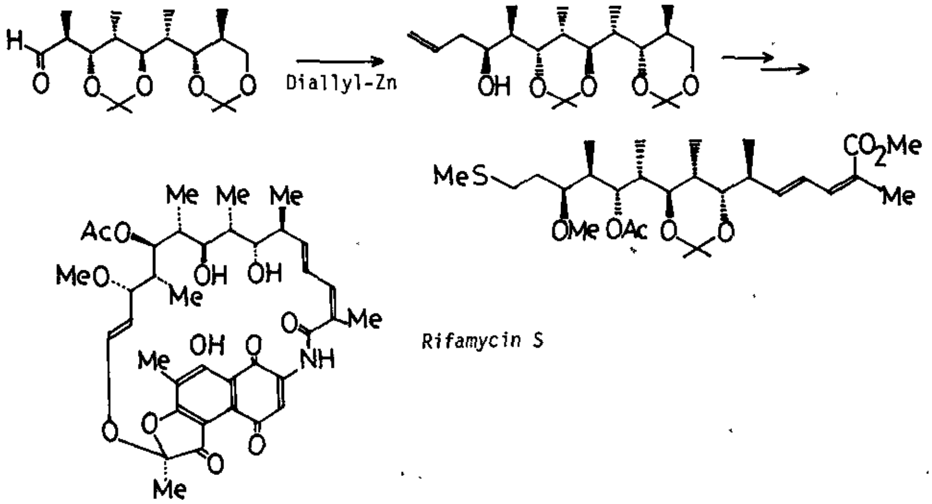
12

13

(10)

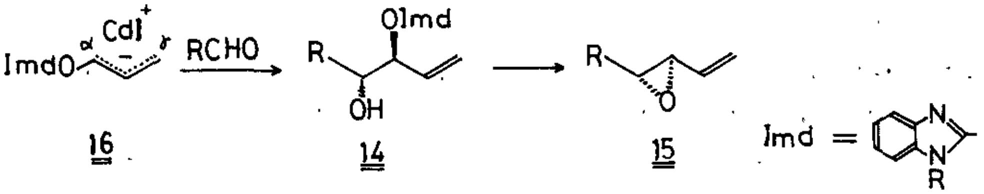
This process is used to construct the aliphatic building block of rifamycin S (eq 11).[20]

Allylcadmium derivative reacts with aldehydes to produce selectively the α-adduct (eq 12).[21] The adduct (14) is converted to trans-vinyloxirane (15) stereoselectively in good yield on treatment with sodium hydride. It is noteworthy that the threo adduct (14) is obtained



Rifamycin S

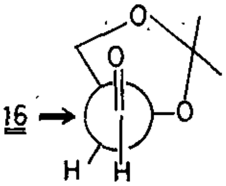
(11)

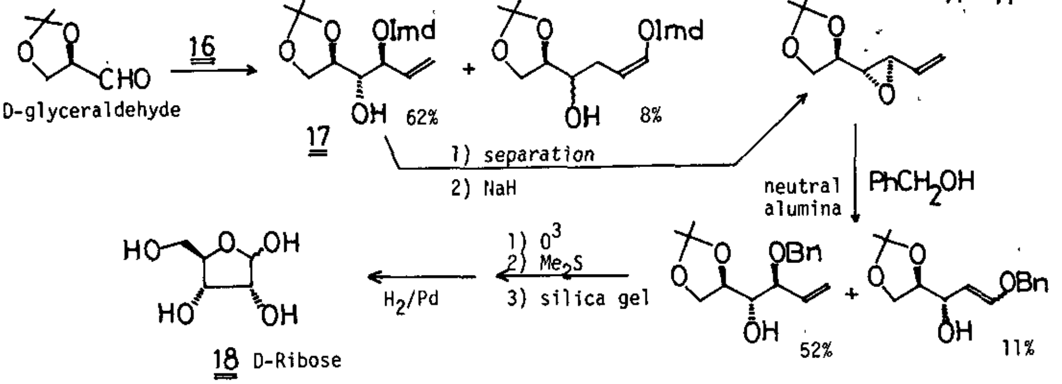


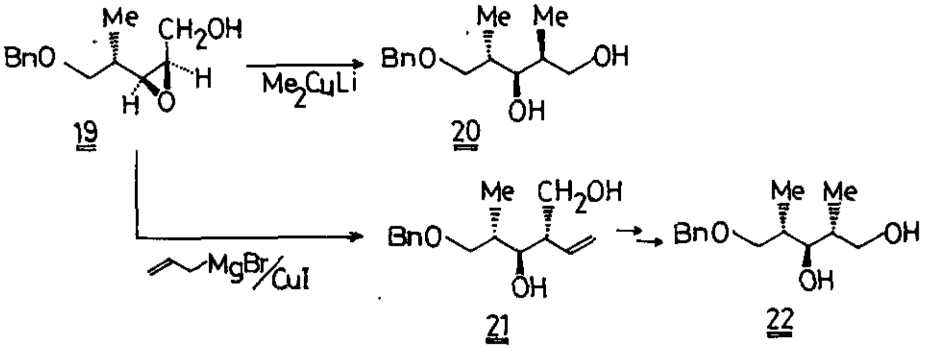
(12)

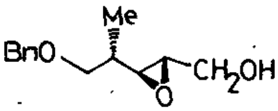
stereoselectively. Presumably, oxygen-substituted allylcadmium (16) possesses the trans configuration in the transition state. This reaction is applied to the stereoselective synthesis of L- and D-ribose (18).[22] The reaction of 16 with 2,3-O-isopropylidene-D-glyceraldehyde gives stereoselectively 17 along with small amounts of the regioisomer (γ-adduct). The stereoselective formation of 17 is explained by the Felkin model (Fig 1). L-Ribose, quite rare in nature, is synthesized via the same procedure from L-glyceraldehyde.

Fig 1





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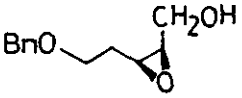
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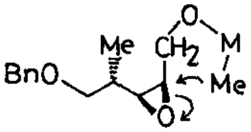
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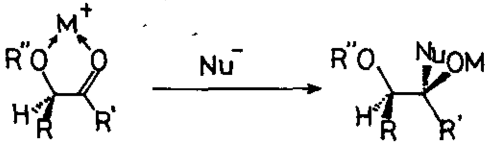
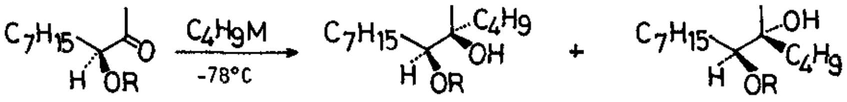
[3] Organocopper compounds

The ring opening of cis epoxide (19) with lithium dimethylcuprate proceeds in a regio- and stereoselective manner giving exclusively the alcohol (20) in 95 % yield.[23] Similarly, the ring opening with divinylcuprate affords exclusively the alcohol (21) in 90 % yield. Since 21 can be converted into 22 via selective reduction of the OH group, two diastereoisomers can be prepared independently. The cuprate opening of trans epoxide (23) gives 22 exclusively. On the other hand, the cuprate opening of epoxide (24) yields a 1 : 1 mixture of two possible alcohols. Therefore, the high regio- and stereoselectivity are presumably a reflection of the steric hindrance caused by Me group and of the presence of OH group (25). This opening reaction is applied to the synthesis of rifamycin S.[20]



(13)

Originally, Cram and coworkers examined the reaction of a variety of α-alkoxyketones with nucleophiles and found that the major products can be explained by a cyclic model in which the nucleophile adds to the less hindered side of a chelated carbonyl (eq 13).[24] The α-induction via this method was not so high (from ~2 : 1 to 9 : 1). Recently, highly stereoselective

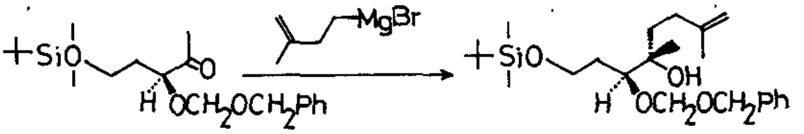


(14)

R = MEM Threo Erythro

		Threo/Erythro	
		M = Li	M = MgBr
Solvent:	C_5H_{12}	2	9
	CH_2Cl	3	14
	Et_2O	1	9
	THF	0.7	>100

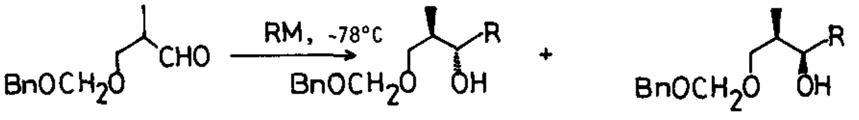
addition of organometallic compounds to chiral α-alkoxyketones and aldehydes is reported. The Grignard reagent in THF at -78°C gives extremely high stereoselectivity for the threo product (eq 14).[25] *This high stereoselectivity* is also observed with other protecting groups, such as R = methoxymethyl, methylthiomethyl, CH_2Ph, and CH_2OCH_2Ph. Further, a chiral complex diol is readily constructed by this method (eq 15), which is applied for the synthesis of monensin.[26]



(15)

Threo (50 : 1)

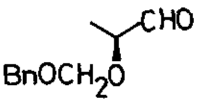
The highly stereoselective addition to β-alkoxyaldehydes is realized by using organocuprate (eq 16).[27] The stereoselective addition is not limited to the aldehyde with Bn (benzyoxymethyl) protecting group; high threo selectivity is also achieved with THP and CH_2Ph protecting groups.



(16)

Threo Erythro

		Threo/Erythro
R = CH_3	RM = CH_3Li	0.7
	CH_3MgBr	1.0
	$(CH_3)_2CuLi$	30.0
R = n-C_4H_9	RM = C_4H_9Li	1.7
	$(C_4H_9)_2CuLi$	17.0



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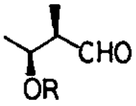

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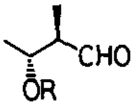

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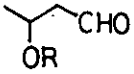

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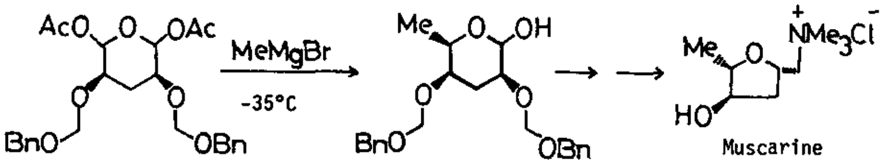
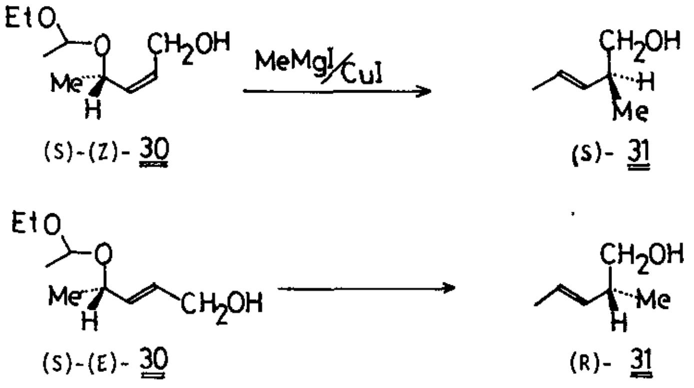
The high stereoselectivity to β-alkoxyaldehydes is not extended to the corresponding α-alkoxyaldehyde (26). The addition of dimethylcuprate gives a 2 : 1 mixture of two isomers. Further, the selectivity highly depends upon the substituents both at the α and β positions (27 - 29). The isomer ratio in the dimethylcuprate addition is as follows; 27 (>20 : 1), 28 (2.3 : 1), and 29 (~1 : 1). Consequently, the cuprate or Grignard addition is highly useful in certain cases, but the mechanism of such high selectivity remains obscure. The chelation controlled reaction is applied to the synthesis of (±)-muscarine (eq 17).[28]

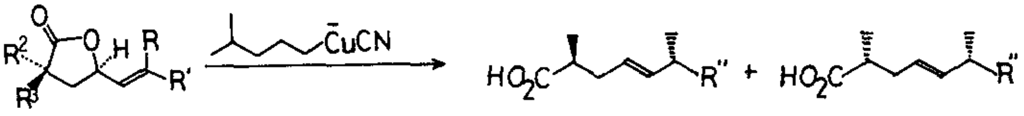


(17)

threo/erythro
= 5-6/1

Normally, the S_N2' type substitution reaction of allylic substrates with organocopper reagents proceeds via an anti (trans) stereoselectivity.[29] For example, (s)-cis-4-(1-ethoxyethoxy)pent-2-en-1-ol (30) gives (s)-trans-31 upon treatment with methylmagnesium iodide in the presence of CuI, while (s)-trans-30 affords the (R)-enantiomer.[30] It is suggested that π-allyl complex Cu^{III} is involved as an intermediate.





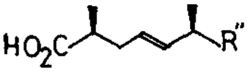
32 a, R = R^2= CH_3, R'= R^3= H

b, R = R^3= CH_3, R'= R^2= H

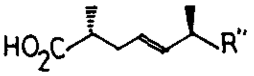
c, R = R^2= H, R'= R^3= CH_3

d, R = R^3= H, R'= R^2= CH_3

33a R'' = i-C_6H_{13} 33b



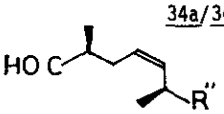
34a



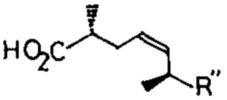
35a

34a/34b = 77/23

35a/35b = 84/16

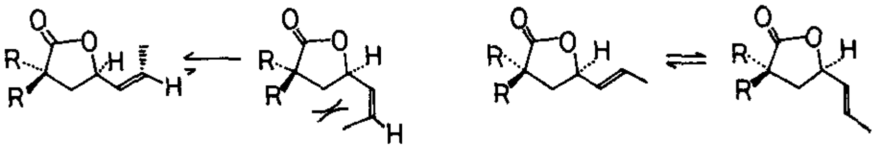


34b



35b

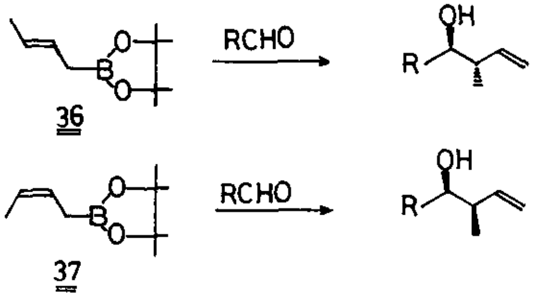
The anti-S_N2' reaction of organocopper compounds is useful for the chirality transfer in acyclic systems.[31] Treatment of the Z-olefin isomers (32a and b) with the alkylcyanocuprate gives in each case a single product (33a and b, respectively). On the other hand, the reaction of the E-isomers (32c and d) leads to a mixture of two isomers(32c ⟶ 34a + 34b , 32d ⟶ 35a + 35b). These results are consistent with an anti S_N2' substitution. The reaction of the Z-isomers occurs from the one conformer (32a, b - anti), while that of the E-isomers from both conformers (32c, d - anti and syn). Presumably, 32a, b - syn form is destabilized owing to the nonbonded interactions, forcing the ionization of the OC(O)- group from the anti form. On the other hand, the difference between 32c, d - anti and -syn is much less, though some preference still exists for products from the anti form. The result of the E-isomers is in a marked contrast to the palladium mediated reaction as discussed later.

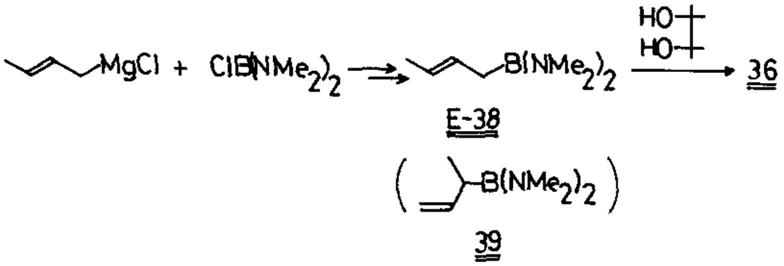


32a, b anti 32a, b syn 32c, d anti 32c, d syn

[4] Organoboranes and alanes

E-Crotylboronate (36) reacts with aldehydes to produce the threo adduct with $\geq$ 94 % stereoselectivity, while Z-isomer (37) gives the erythro adduct with similarly high stereoselectivity.[32] Although the reaction is very clean and proceeds in high yields and in highly stereoselective manner, the preparation of the stereochemically defined crotyl derivatives (36 and 37) seems to be not easy (eqs 18 and 19).[33]





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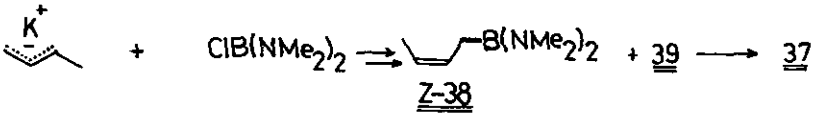
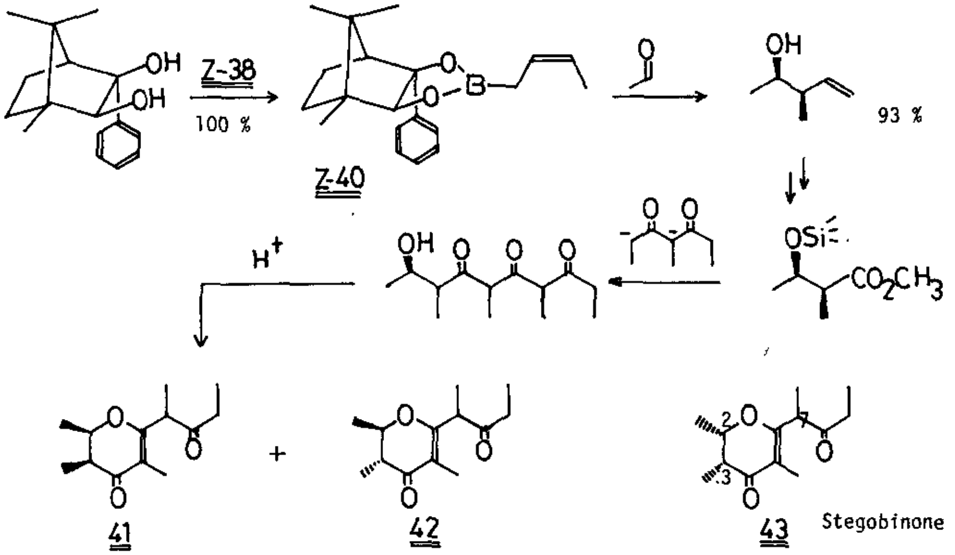


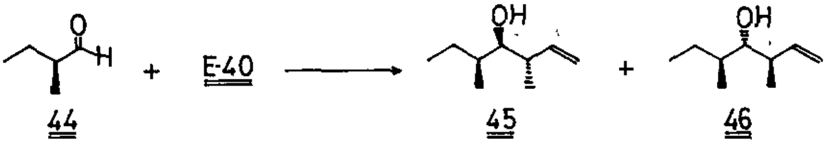
(19)

The reaction of crotylmagnesium chloride with bis(dimethylamino)chloroborane, followed by heating in the presence of $ZnBr_2$, produces a 7 : 3 mixture of E-38 and Z-38. The similar reaction of crotylpotassium affords a 10 : 1 mixture of Z-38 and 39. Therefore, the separation by a spinning band column is required before the treatment with pinacol. The advantage of this method is that the enantioselective synthesis of secondary homoallyl alcohols is possible by using a chiral diol. Use of the glycol, obtained from (+)-camphor via the ketol and its reaction with phenyllithium in ether, instead of pinacol produces a chiral Z-crotylboronate (Z-40). Reaction of Z-40 with acetaldehyde gives the erythro 3-methylpent-1-en-4-ol in 93 % yield along with 2 % of the threo isomer. The enantiomeric purity of the erythro isomer is about 60 - 70 %. Further transformation leads to a 2 : 1 mixture of 41 and 42. The stereochemistry at C-3 is



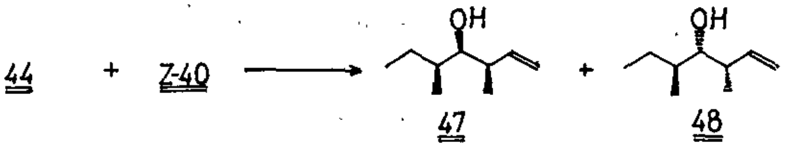
lost presumably during the cyclization process. This synthesis enables the correct stereochemistry of stegobinone (43), the sex pheromone of the drugstore beetle.[34]

"Double stereodifferentiation"[35] is also examined in crotylboronate systems (eqs 20 and 21).[36] Reaction of racemic E-40 with the (S)-(+) aldehyde (44) gives the alcohols (45 and 46) in the ratio of 3 : 1, with the Cram product (45) predominantly. Use of chiral E-40 increases the diastereoselectivity to ca. 11 : 1. This result indicates that the tendency toward predominant



(20)

(S)-(+)	(-)	92	:	8
(S)-(+)	(±)	76	:	24
(±)	(-)	75	:	25

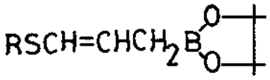


(21)

(S)-(+)	(-)	56	:	44
(S)-(+)	(±)	30	:	70
(±)	(-)	30	:	70

formation of the Cram product and that of the reagent to form an alcohol with (R) configuration at C-4 cooperate. The increase from 3 : 1 to 11 : 1 is the enhancement caused by the chirality of the reagent. It can be deduced that the combination between the (R)-(-) aldehyde and (-)-E-40 is an unmatched pair. The anti-Cram product (48) predominates in the ratio of 2.3 : 1 on the reaction of racemic Z-40 with (S)-(+)-44. Although the amount of 47 increases by using the chiral (-)-Z-40, it is not possible to overcompensate the anti-Cram preference. The anti-Cram preference in the reaction of 44 with Z-40 should be noted. This may be a result of the more compact cyclic transition state via boron reagents.

Heteroatom substituted allylboronates (49,[37] 50,[37, 38] 51,[39, 40] 52[40]) react similarly; the Z-isomer gives the erythro adduct and the E-isomer affords the threo alcohol. Heteroatom substituted allylic aluminum "ate" complex[41] (53) reacts with aldehydes regioselectively at the α-position to produce 54.[40] The alcohol (54) possesses the threo configuration, and hence the elimination reaction (trans) gives the corresponding trans 1,3-diene. This process can be applied to the synthesis of a sex pheromone of Diparopsis castanea (55).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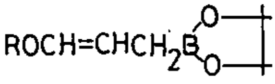
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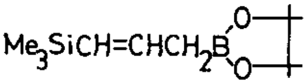
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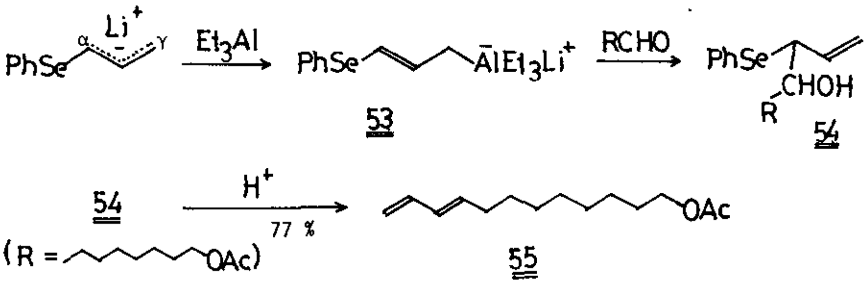
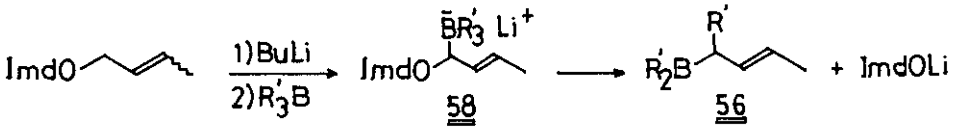
$PhSeCH{=}CHCH_2BR_2$

52



Allylic borane (56), generated in situ from trialkylboranes (BR'_3) and 2-butenyloxybenzimidazole, reacts with aldehydes and ketones to give the threo homoallyl alcohol (57) (eq 22).[42] The threo and E selectivity can be explained by assuming a preference of the E-form in the "ate"



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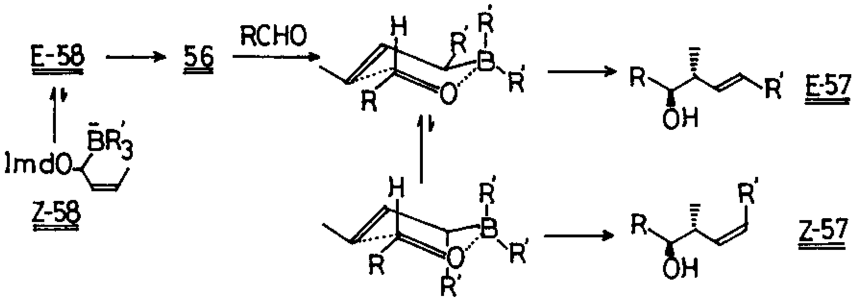
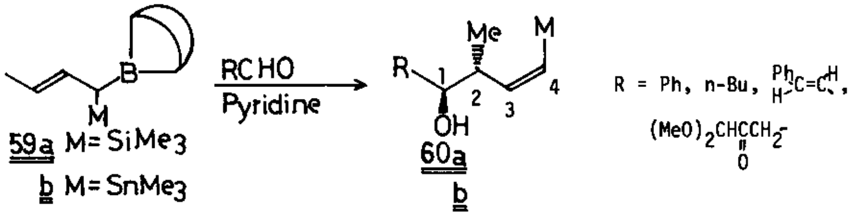


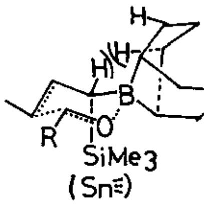
Threo selectivity > 95 %, E/Z = 90/10

complex (58), which leads to the E-56, and by consideration of a six-membered chair transition state. The transition state with an equatrial R' group is more stable than that with an axial R', leading to the preferential formation of E-57.

α-Silyl- or stannyl-substituted crotyl-9-borabicyclo[3.3.1]nonane (59) is a useful reagent for the stereoregulated synthesis of four consecutive carbon units in acyclic systems (60)[43]; the threo relation between C-1 and C-2, and the cis configuration at C-3 and C-4. It is essential to use an additive such as pyridine or n-butyllithium.



The high threo and Z selectivity can be understood by a six-membered cyclic transition state (61). The allylic borane (59) consists of a mixture of E and Z forms. The coordination of pyridine or n-butyllithium stops the allylic rearrangement of 59 and makes the crotyl unit to possess preferentially the E-form[14] (see also eq 5). Bulky Me_3Si or Me_3Sn group occupies the axial position owing to the steric repulsion by the protons of the 9-BBN ring,



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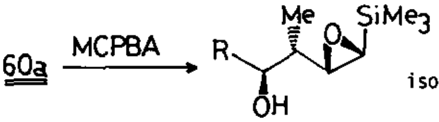
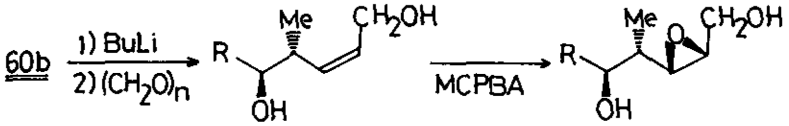


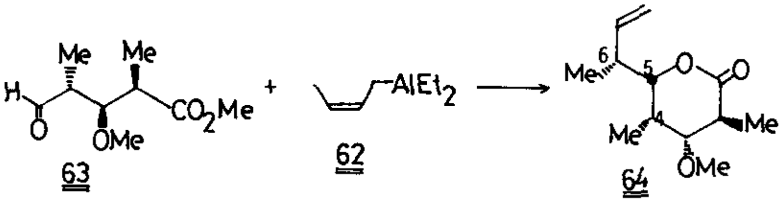
isomer ratio = 85 : 15



isomer ratio = 88 : 12

leading to the selective formation of 60 among 8 possible combinations. The preferential formation of the threo Z isomer (60) is in marked contrast with that of the threo E isomer (E-57) in eq 22. This is a reflection of the wing shaped structure of the 9-BBN ring. The threo, cis (60) thus obtained is useful for the further elaboration of complex molecules. The epoxidation of 60a with MCPBA gives the corresponding epoxide with reasonably high stereoselectivity. Transmetallation of 60b with n-BuLi, followed by treatment with formaldehyde, produces stereoselectively the one carbon homologated alcohol, which subsequently undergoes the epoxidation with MCPBA. These epoxides can undergo the cuprate opening reaction (see 19 ⟶ 20).

Z-Crotylaluminum compound (62) reacts with aldehyde (63) to give 64 with reasonably good stereoselectivity (eq 23).[26] It should be noted that the relation between C-5 and C-6 is erythro, which is expected from the Z configuration of 62, and more importantly the stereochemistry between C-4 and C-5 is produced via the Cram's rule. The latter observation should be compared with the reaction of crotyltin - BF_3 system as mentioned later(104A). The reaction of 62 is applied to the synthesis of monensin.[26]

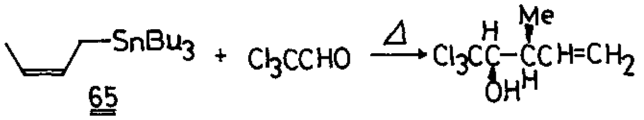


(23)

the ratio of isomers = 3 : 1

[5] Organosilanes and stannanes

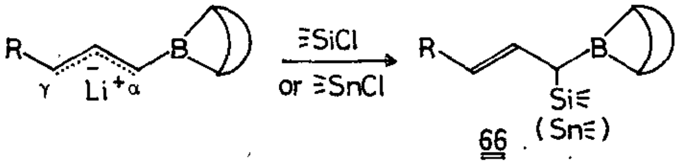
It is reported that the thermal reaction of Z-crotyltributyltin (65) with an aldehyde bearing an electron withdrawing group must give an erythro alcohol (eq 24).[44] However, these authors do not use a stereochemically pure Z-65, instead the above conclusion is deduced from the reaction with a mixture of E and Z crotyltins.



(24)

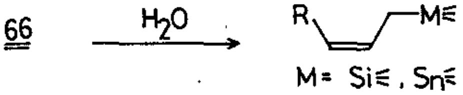
It is not so easy to prepare stereochemically pure Z-crotylsilane and stannane, though such compounds are useful for erythro selective synthesis of β-alkyl alcohol derivatives. The reaction of allylic magnesium or lithium compounds with R_3SiX or with R_3SnX, or that of allylic halides with R_3MLi (M = Si or Sn), gives a mixture of E and Z-2-alkenyl derivatives. The cis hydrogenation of the propargyl derivatives is promising. However, the preparation of such a compound always accompanies the allenic derivatives. Use of the boron-substituted allyl carbanion solves this problem.[45]

(25)



(26)

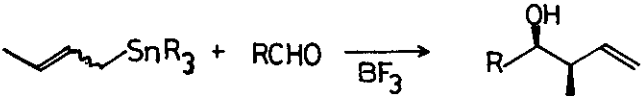
Although a boron-substituted allyl carbanion bearing a bulky siamyl group directs trimethylsilyl group at the γ-position (eq 25),[46] that with a sterically less bulky 9-BBN directs at the α-position to produce (66) (eq 26). Hydrolysis of 66 gives stereodefined Z-crotylsilane and stannane (eq 27). Completely erythro selective coupling is realized via the thermal or Lewis acid mediated reaction of Z-crotyltin , as expected. On the other hand, titanium tetrachloride mediated,



(27)

reaction of Z-2-alkenylsilanes with propanal produces a mixture of the erythro and threo alcohols in the ratio of 60 : 40.

If a six-membered cyclic transition state is also involved in the reaction of 2-alkenyltins, E-crotyltin must give the threo alcohol. Actually, the thermal reaction of E-crotyltributyltin with Cl_3CCHO affords the threo alcohol.[44] To our surprise, BF_3 mediated reaction of E-crotyltin with aldehydes produces the erythro alcohol (eq 28).[47] Consequently, the erythro alcohol



(28)

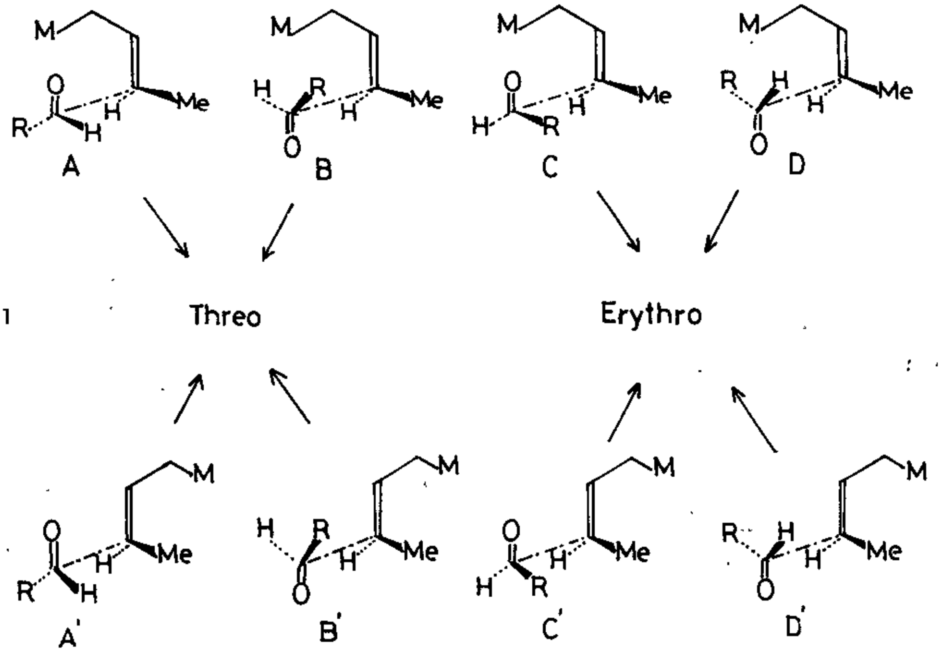
is obtained regardless of the geometry of the crotyl unit. The results are summarized in the Table 2.

Table 2. Erythro Selective Synthesis of β-Methylhomoallyl Alcohols

crotyltin (trans and/or cis)	aldehyde	Yield, %	erythro/threo
$CH_3CH=CHCH_2Sn(n\text{-}Bu)_3$ (t)	C_6H_5CHO	90	98 : 2
$CH_3CH=CHCH_2Sn(n\text{-}Bu)_3$ (t 90%,c10%)	C_6H_5CHO	90	98 : 2
$CH_3CH=CHCH_2Sn(n\text{-}Bu)_3$ (t 60%,c40%)	C_6H_5CHO	90	96 : 4
$CH_3CH=CHCH_2Sn(n\text{-}Bu)_3$ (c)	C_6H_5CHO	90	99 : 1
$CH_3CH=CHCH_2SnMe_3$ (t)	C_6H_5CHO	90	95 : 5
$CH_3CH=CHCH_2SnMe_3$ (t)	$(CH_3)_2CHCHO$	89	95 : 5

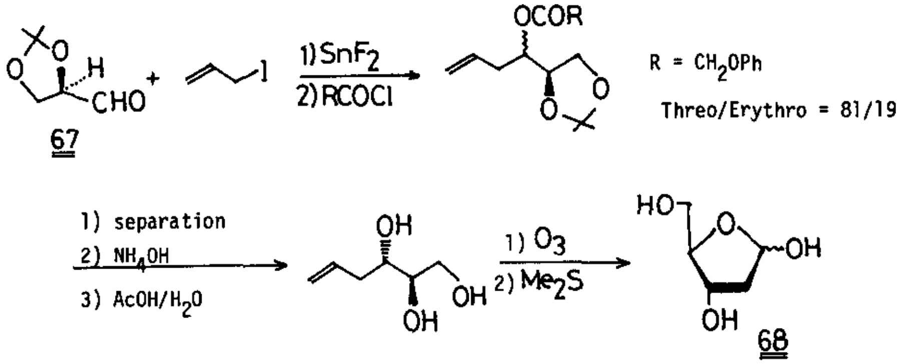
Such an independence from the stereochemistry of the starting materials is particularly useful for synthetic application and , more importantly, highly interesting for the mechanistic consideration. We propose an acyclic mechanism (Scheme 1). It is easily understood that two configurations

Scheme 1

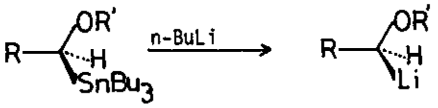


(D and D') leading to the erythro isomer should be favored for steric reasons. The reaction via Li, Mg, Cd, B, Al, and Sn (thermal reaction)[44, 45] must proceed through a six-membered cyclic *transition state, as frequently* mentioned above. The carbonyl group in the present reaction is coordinated by BF_3, and hence no coordination site on the C=O group is available for the tin atom. Moreover, the affinity of Sn toward oxygen atom is weaker than that of Si. These combined effects force crotyltins to take an acyclic mechanism.

Difluorotin mediated addition of allyl iodide to aldehyde(67) is used to the synthesis of 2-deoxy-D-ribose (68).[48]



Conformationally stable organolithium compounds are highly useful for the stereocontrolled synthesis of acyclic systems. These reagents have been limited to vinyl- and cyclopropyllithiums. *Recently, sp*^{3} *hybridized, acyclic configurationally stable lithium derivatives are prepared from*



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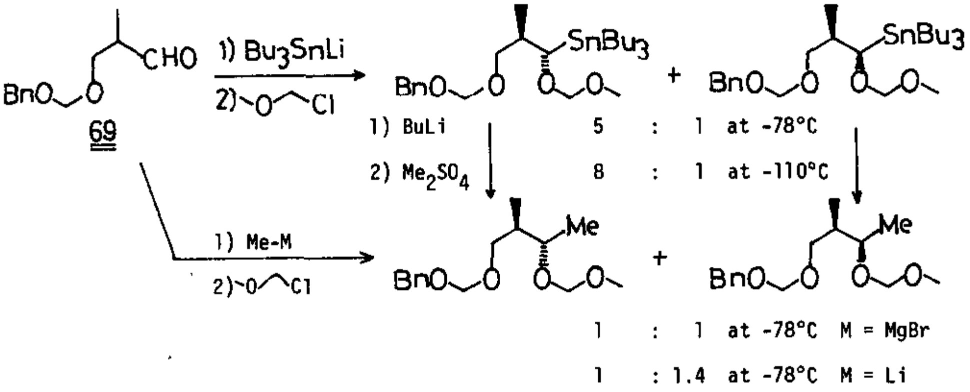
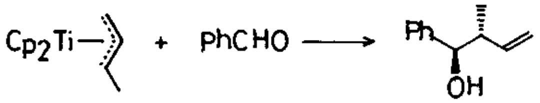


(30)

the corresponding organostannanes (eq 29).[49] When β-alkoxy aldehyde (69) is treated with tributylstannyllithium in THF, a 5 : 1 (at -78°C) or 8 : 1 (at -110°C) mixture of diastereomers is obtained (eq 30). These isomers are independently converted stereoselectively into the corresponding Me derivatives via the transmetallation - methylation. When 69 is reacted with methylmagnesium bromide or methyllithium, an almost equivalent amount of two diastereomers is obtained.

[6] Organotitanium and zirconium compounds

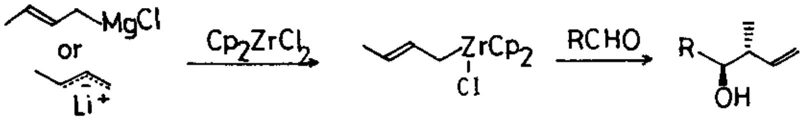
π-Crotyldicyclopentadienyltitanium (III) complex reacts with aldehydes and ketones regioselectively and stereoselectively to afford the threo homoallyl alcohols (eq 31).[50]



(31)

threo/erythro = 95/5

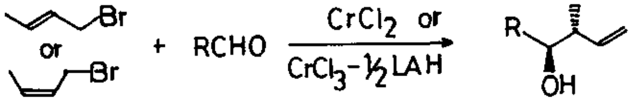
Crotylzirconium derivatives, prepared in situ from the reaction of crotylmagnesium chloride or crotyllithium with bis(cyclopentadienyl)zirconium dichloride, undergo a facile reaction with aldehydes to give the threo alcohols predominantly (eq 32).[51] The ratio of Cram/anti-Cram product via this reagent is ca. 75/25 ∼ 60/40.



(32)

[7] Organochromium compounds

Allyl halides react with aldehydes and ketones in the presence of Cr(II) to give homoallylic alcohols.[52] The reaction between benzaldehyde and crotyl bromide gives only one stereoisomer,[52] which is determined to be the threo alcohol (eq 33).[53] With Z-crotyl bromide, the threo alcohol is again obtained.[54] Presumably, the isomerization occurs at the step of the formation of the crotylchromium species.



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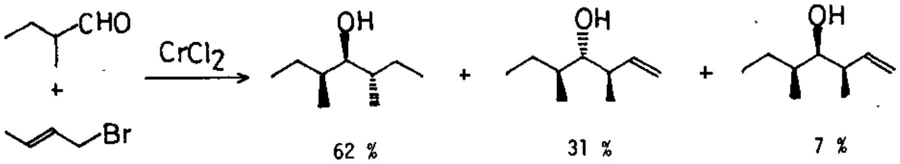


(34)

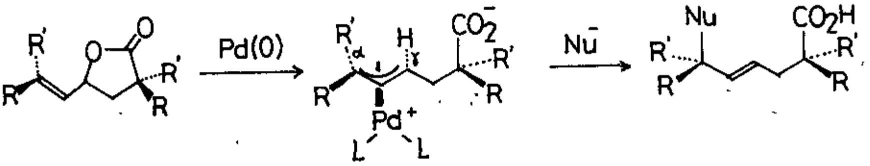
threo/erythro = 93/7

Cram/anti-Cram = 69/31

The threo selectivity can be explained on the basis of a six-membered cyclic transition state. Although the threo selectivity is very high, the Cram/anti-Cram product ratio is low (eq 34).

[8] Organopalladium compounds

The ring stereochemistry of lactone (32) can be relayed to the stereochemistry of acyclic systems via a π-allylic palladium complex (eq 35).[55] Such a 1,5-stereochemical control is realized when (1) the ionization of the vinyl lactone occurs from one conformation, (2) the π-allylic palladium complex retains its stereochemistry, and (3) the nucleophile attacks regioselectively at the α-position. Actually, the high degree of stereoregulation is achieved. The lactone (70) is treated with methyl sodiomalonate and 3 mol % tetrakis(triphenylphosphine)-palladium in refluxing THF to give 71 in 90 % yield as a single product (70a → 71a, 70b → 71b).



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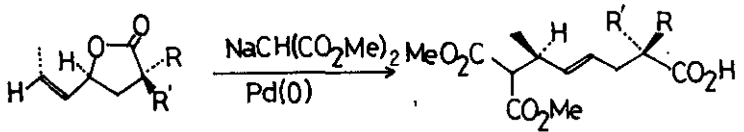
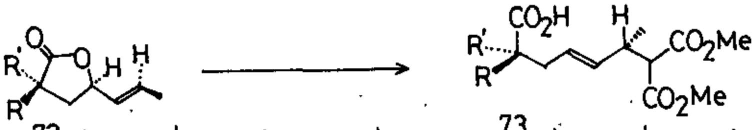


70 a) R=CH_3, R'=H
b) R=H, R'=CH_3

71 a) R=CH_3, R'=H
b) R=H, R'=CH_3

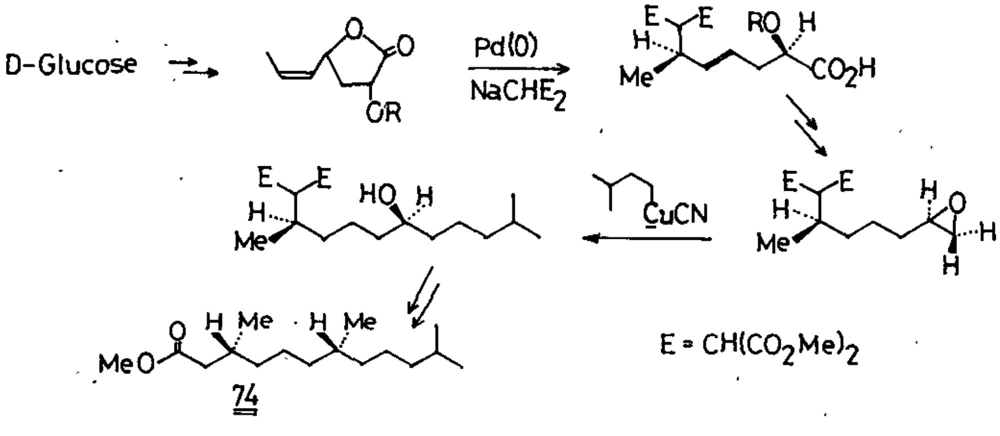


72 a) R=H, R'=CH_3; b) R=CH_3, R'=H

73 a) R=H, R'=CH_3; b) R=CH_3, R'=H

Similarly, E-olefins (72a and b) give stereoselectively 73a and b, respectively. This high stereoselectivity should be compared with the selectivity of organocopper reactions (34 and 35). The difference presumably reflects the ability of the increased bulk of the palladium catalyst to accentuate the steric differences in the transition state. The ionization of OC(O)- group from the anti form (32c, d anti) must occur more readily than that from the syn form (32c, d syn), since the former produces the more stable π-allylic syn-syn palladium complex and the latter produces the less stable syn-anti complex. Consequently, net S_N2' reaction with either retention or inversion is available by choosing either palladium or copper compound, respectively.

Optically active vitamin E side chain is synthesized from D-glucose by using the chirality transfer method via organopalladium compound.[56] The alkylation of the vinyl lactone in the presence of catalytic amounts of Pd(0) proceeds smoothly to yield the expected open chain compound in 95 % yield. The epoxide opening via cyanocuprate gives the enantiomerically pure alcohol. Tosylation of the alcohol, followed by dimethylcuprate coupling, produces the desired 74 contaminated by elimination products.

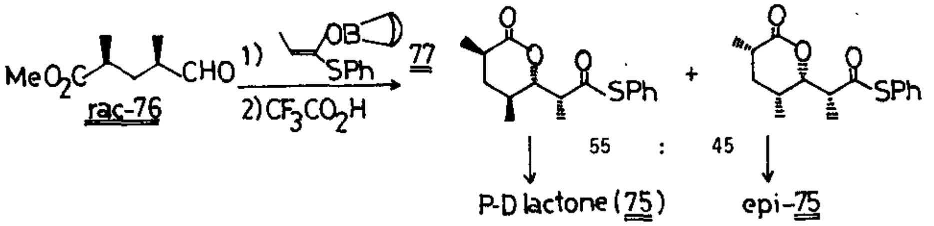


Chapter 2. Synthesis of the Prelog-Djerassi Lactonic Acid

The synthesis of the Prelog-Djerassi lactonic acid (75, P-D lactone) has been realized via the aldol condensation, the ring opening reaction of cyclic compounds, the reaction of carbohydrates, the ene reaction, the reduction of carbonyl compound, and the organometallic reaction. Therefore, most of the methods for the synthesis of acyclic systems have been examined to this particular compound.

[1] Aldol condensation

Treatment of (rac)-76 with boron enolate (77) gives a 55 : 45 mixture of the corresponding



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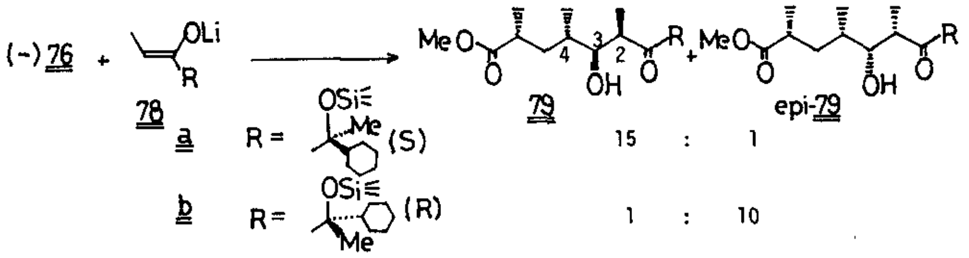
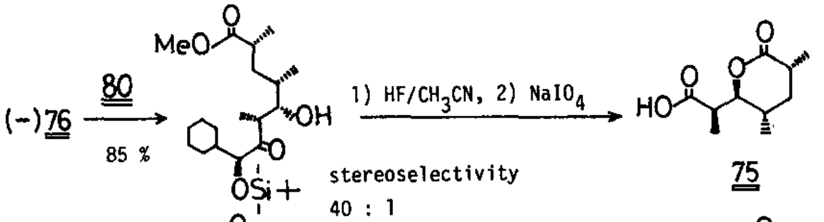


(37)

condensation products. Interestingly, the anti-Cram product predominates, though only slightly (eq 36).[57] *The concept of double stereodifferentiation is examined for the reaction of* optically pure (-)-76 with optically active lithium enolate (78).[35b] S-Chiral reagent (78a) gives a mixture of 79 and epi-79 in a ratio of 15 : 1, while R-78 affords in a ratio of 1 : 10 (eq 37). 79 can be converted into P-D lactone. Therefore, this method can be used to control the 3, 4-stereochemistry of 79 with high diastereoselection. The double stereodifferentiation



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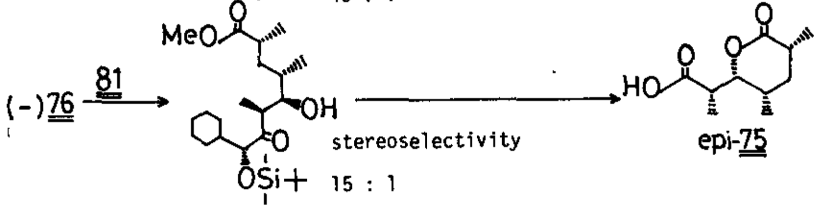

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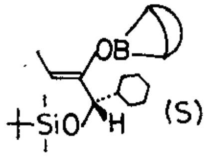
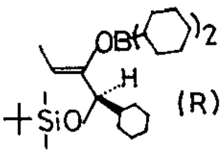


80

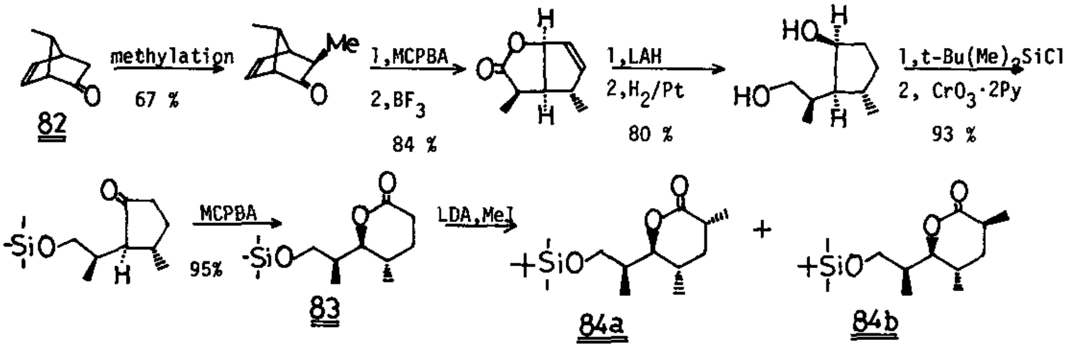


81

is also examined with the chiral boron enolates (80 and 81), and exceptionally high diastereoselection is achieved.[58] The reaction of (-)-76 with S-chiral reagent (80) proceeds with the stereoselectivity of 40 : 1 (eq 38), and the reaction with R-chiral reagent (81) gives a 15 : 1 mixture of the diastereomers.

[2] The ring opening reaction of cyclic compounds

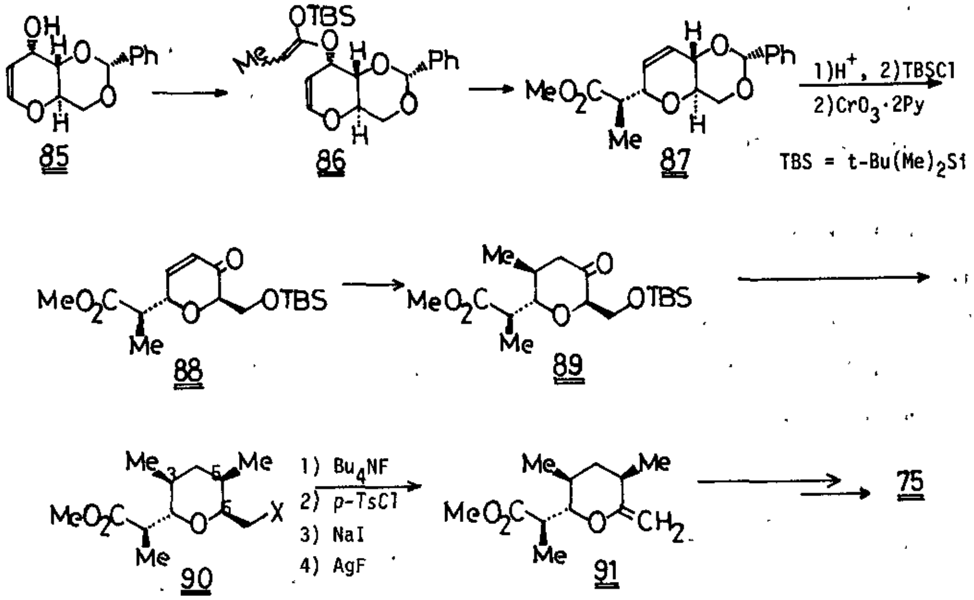
Three different methods in this category (Masamune,[59] White,[60] and Stork[61]) are amply demonstrated in the previous review article,[1] and hence these syntheses are not described here. Another type of the ring opening reaction is carried out by Grieco's group, which starts from optically pure bicyclo[2.2.1]heptanone (82).[62]



Treatment of lactone (83) with LDA followed by the addition of MeI in HMPA gives a 1 : 1 mixture of 84a and b. Reaction of a THF solution of this mixture with LDA at -78°C followed by kinetic protonation (10 % citric acid) of the lactone enolate produces a 3.5 : 1 mixture of 84a and b in 85 % yield. Separation of 84a, followed by desilylation and oxidation with Jones reagent, gives optically pure P-D lactone in 82 % yield.

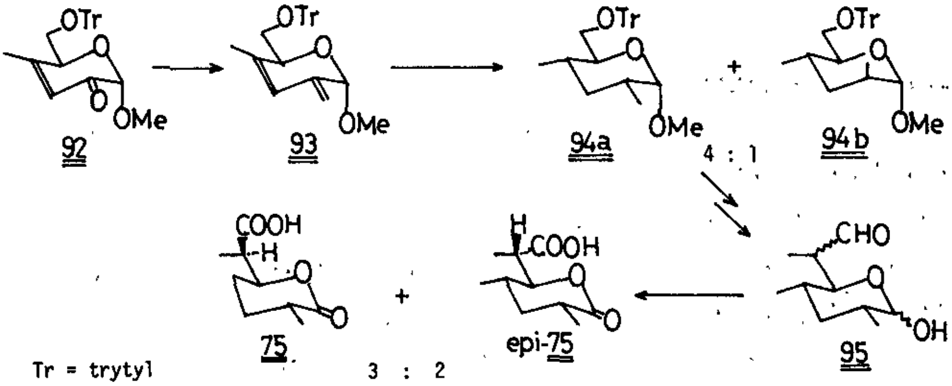
[3] Synthesis from carbohydrates

Optically pure P-D lactone is prepared from glycal 4,6-O-benzylidene-D-allal (85).[63] The ester-enolate Claisen rearrangement of 86 gives a 9 : 1 mixture of 87 and its diastereomer. The predominant formation of 87 implies that a boat-like transition state is followed with the (Z)-silyl ketene acetal. Further transformation of 87 leads to the enone 88. Conjugate addition of dimethylcuprate to 88 produces 89 stereoselectively in an isomer ratio of 94 : 6. Wittig methylenation of the ketone 89 , followed by the catalytic hydrogenation, produces 90 having the two required ring methyl groups with the desired β-configuration. After conversion of the



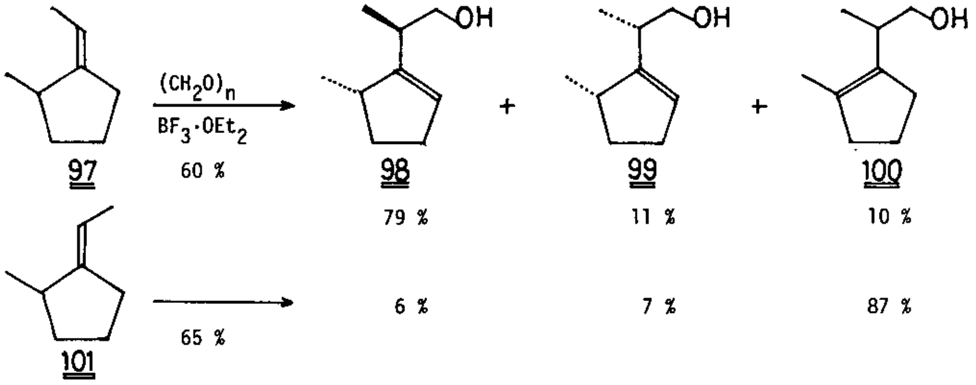
C-6 oxygen function (X) through the tosylate to the iodide, AgF-Py promoted elimination leads to the enol ether (91). Ozonolysis followed by saponification gives optically pure P-D lactone.

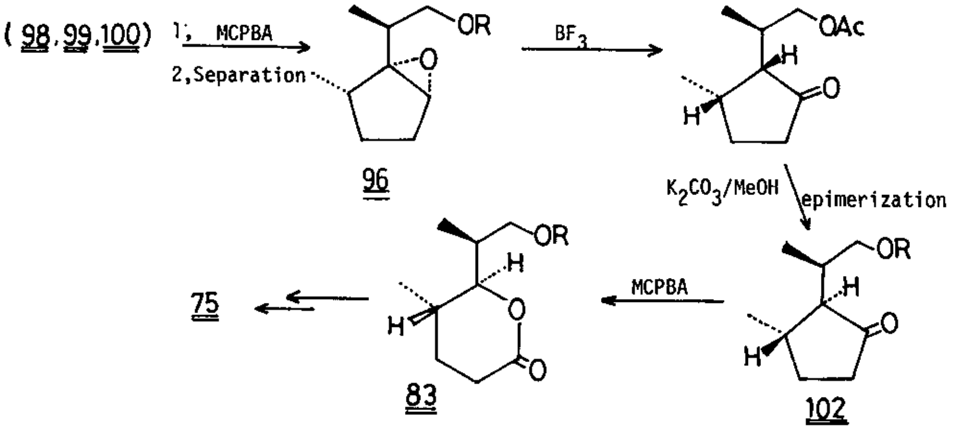
Optically pure methyl α, D-glucopyranoside is used as a starting material (92).[64] Wittig methylenation of 92 produces 93. The hydrogenation of 93 gives a mixture of 94a and b in a ratio of 4 : 1. *Separation of 94a, and further transformations (i, removal of Tr protecting* group; ii, PCC oxidation; iii, MeLi then PCC; iv, $Ph_3P{=}CHOMe$) lead to 95. Jones oxidation of 95 yields a 3 : 2 mixture of P-D lactone (75) and its epimer. Optical purity of 75 thus obtained is not described.



[4] The ene reaction

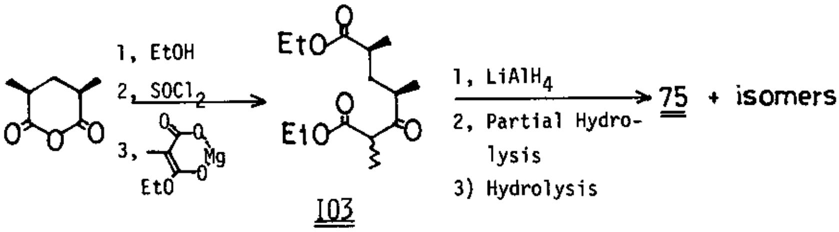
The Lewis acid mediated ene reaction of 97 with formaldehyde gives 98 as a major product along with 99 and 100, while the similar reaction of 101 affords 100 as a major product.[65] The high regioselectivity of this ene reaction should be noted; (98 + 99)/100 from 97 = 9/1, and that from 101 = 1/9. The stereoselectivity in the reaction of 97 is also high (98/99 = 7/1), presumably due to the steric effect of Me group. The ene products undergo an epoxidation with MCPBA, and epoxide(96) is opened with BF_3. Baeyer-Villiger oxidation with MCPBA gives the lactone (83). Methylation of 83 produces P-D lactone and its epimer as mentioned above (83 ⟶ 84).





[5] Reduction

Reduction of 103 with $LiAlH_4$ gives all of the four possible isomers. Separation of each isomer and further transformations produce four possible isomers including the desired P-D lactone. The racemic P-D lactone has been resolved by using L-threo-2-amino-1-(4-methylthiophenyl)-1,3-propanediol.[66]



[6] Organometallic way to P-D lactone

Intramolecular oxymercuration is used for the synthesis of P-D lactone,[67] though the stereoselectivity is not so high. This subject is already discussed in the earlier review.[1] Our method is based on the observation that the reaction of crotyltrialkyltins with aldehydes gives an erythro alcohol regardless of the geometry of the crotyl unit (eq 28), which predicts the correct stereochemical relation between C-3 and C-4 of 104. The important problem is whether the stereochemistry between C-4 and C-5 produced by this method is opposite to the usual Cram's rule or not. The result is quite surprising since the condensation proceeded through almost complete violation of the Cram's rule (Table 3).[68]

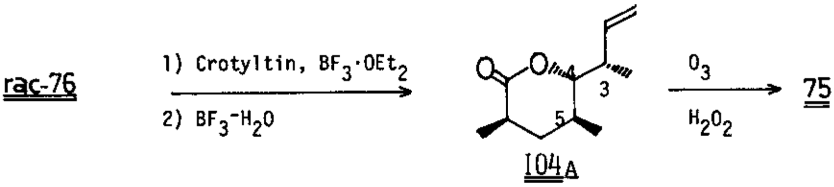
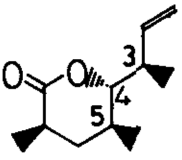


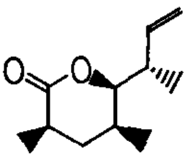
Table 3. Reaction with crotyl organometallic reagents

Crotyl metal	104a (%)	104b (%)	104c (%)	104d (%)	Total
M =	erythro, anti-Cram	erythro, Cram	threo, Cram	threo, anti-Cram	yield
$SnBu_3$					
1 eq $BF_3 \cdot OEt_2$	94 - 97	3 - 4	1	1	92
2 eq $BF_3 \cdot OEt_2$	83 - 91	5 - 9	1 - 3	2 - 5	90
3 eq $BF_3 \cdot OEt_2$	41	10	17	32	90
$ZrCp_2Cl$	10	2	47	41	85
	27	13	9	51	90

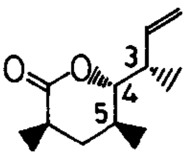
[a] The isomer ratio was determined by the Glc analysis (CW 6000) of the reaction mixture.



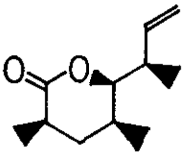
104 a



104 b

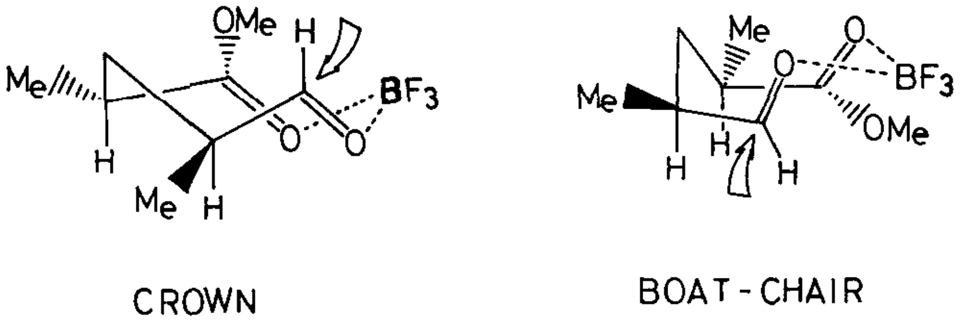


104 c



104 d

The reaction of crotyltin in the presence of 1 eq $BF_3 \cdot OEt_2$ produces P-D lactone with at least 94 % stereoselectivity. The stereoselectivity decreases with the increase of $BF_3 \cdot OEt_2$. As is expected, crotyl zirconium and crotyl-9-BBN give the threo products predominantly; threo/erythro = 88/12 for Zr, and 60/40 for B. The ratio of Cram/anti-Cram product is 49/51 for Zr and 22/78 for B. The high stereoselectivity via crotyltin can be explained by the eight-membered cyclic intermediate (Scheme 2).



CROWN

BOAT - CHAIR

Scheme 2. Eight-membered cyclic intermediate

The crown form leads to the anti-Cram products, since the molecular model clearly indicates that a nucleophile is forced to attack from the direction indicated by an arrow owing to the steric repulsion. On the other hand, the boat-chair form gives the Cram products. Since the crown form is more stable than the boat-chair form, the reaction must proceed through the crown type. Excess $BF_3 \cdot OEt_2$ permits the coordination at each carbonyl group to prevent the formation of the eight-membered cyclic intermediate. The boron atom of crotyl-9-BBN presumably acts as a similar chelating agent, while such a chelation does not occur with the zirconium reagent.

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