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# STEREO- AND REGIOCONTROL OF ACYCLIC SYSTEMS VIA THE LEWIS ACID MEDIATED REACTION OF ALLYLIC STANNANES WITH ALDEHYDES

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**Abstract**—The reaction of crotyltrialkylstannanes (**1**) with aldehydes in the presence of $BF_3 \cdot OEt_2$ produces the corresponding *erythro* homoallyl alcohols (**2**) predominantly regardless of the geometry of the double bond. Further, the Lewis acid mediated reaction exhibits the enhanced Cram selectivity in comparison with other allylic organometallic reactions which proceed in the absence of Lewis acids. Use of $AlCl_3$–i-PrOH as the Lewis acid entirely changes the reaction course; the linear adduct (**12**) is produced rather than the branched adduct (**13**). The reaction of 1–$BF_3 \cdot OEt_2$ system is applied to the short and stereoselective synthesis of the (±) Prelog–Djerassi lactonic acid (**16**) and (−) verrucarinolactone (**19**).

Allylation of aldehyes with allylic organometallic compounds has recently received wide attention as a basic synthetic method for control of acyclic stereochemistry.[1] Generally speaking, the *trans* crotylmetal compound, such as M = Li, Mg, B, Al, Zn, Cd, Ti, Zr or Cr . . . , reacts with aldehydes to produce the corresponding threo homoallyl alcohol predominantly if the geometry of the double bond is retained during the reaction, while the *cis* derivative to give the *erythro* isomer preferentially.

On the other hand, the Lewis acid mediated reaction of allylic stannanes and silanes exhibits an entirely different stereoselectivity; the reaction of crotyltrialkylstannanes (**1**) and silanes with aldehydes in the presence of $BF_3 \cdot OEt_2$ gives the *erythro* homoallyl alcohol (**2**) preferentially regardless of the geometry of the double bond.[2] Here we report the full details of that work together with the application to the synthesis of the natural products.

## RESULTS AND DISCUSSION

*Diastereoselectivity.* The diastereoselectivity in the reaction of **1** with various aldehydes in the presence of $BF_3 \cdot OEt_2$ is summarized in Table 1. Although other Lewis acids, such as $TiCl_4$, $SnCl_4$, $BCl_3$ and cyclopentyldichloroborane, were examined, $BF_3 \cdot OEt_2$ gave the best result both in the diastereoselectivity and the yield. As is apparent from Table 1, the *erythro*-selective (> 90%) condensation is realized regardless of the geometry of the crotyl unit. Such stereochemical convergence is particularly useful for synthetic application, since the preparation of **2** through other allylic organometallics requires the stereochemically fixed *Z*-crotyl derivative.[3] More importantly, however, the *erythro*-selectivity irrespective of the geometry of the starting material cannot be understood by the conventional 6-membered chair transition state.[4] We propose an acyclic transition state. Lewis acids coordinate to the O atom preventing the coordination of the Sn atom. It is easily decided that among several possible transition state geometries two conformations (A and B) leading to the *erythro* isomer must be favored for steric reasons. Therefore, the Lewis acid plays an important role for the stereochemical convergence.

On the other hand, the stereochemistry in thermal

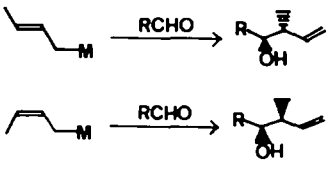


Fig. 1.

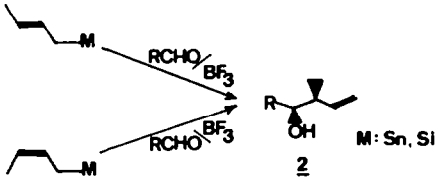


Fig. 2.

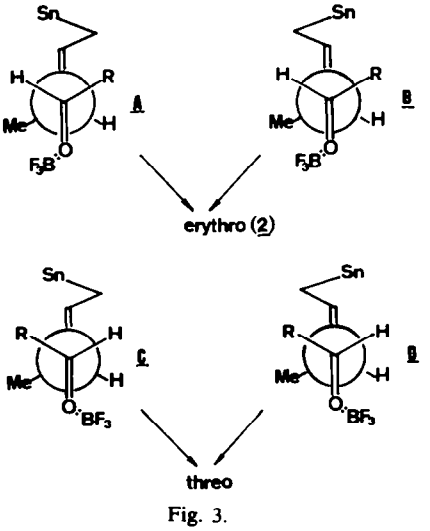


Fig. 3.

Table 1. Diastereoselectivity in the 1–$BF_3$·$OEt_2$ system

| 1 (trans and/or cis) | aldehyde | erythro/threo | yield, %[a] |
|---|---|---|---|
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t) | $C_6H_5CHO$ | 98/2 | 90 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t 90%, c 10%) | $C_6H_5CHO$ | 98/2 | 90 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t 60%, c 40%) | $C_6H_5CHO$ | 96/4 | 90 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (c) | $C_6H_5CHO$ | 99/1 | 90 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t)[b] | $C_6H_5CHO$ | 99/1 | 70 |
| $CH_3CH=CHCH_2Sn(Me)_3$ (t) | $C_6H_5CHO$ | 95/5 | 90 |
| $CH_3CH=CHCH_2Sn(Me)_3$ (t) | $(CH_3)_2CHCHO$ | 95/5 | 89 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t) | $(CH_3)_2CHCHO$ | 91/9 | 90 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t) | $(C_2H_5)_2CHCHO$ | 98/2 | 92 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t) | $(CH_3)_2CHCH_2CHO$ | 90/10 | 90 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t) | $CH_3CH_2CHO$ | 91/9 | (87) |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t) | $CH_3CHO$ | 91/9 | (82) |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t) | $CH_3CH=CHCHO$ | 91/9 | 88 |
| $CH_3CH=CHCH_2Sn(Me)_3$ (t) | $CH_3CH=CHCHO$ | 91/9 | 90 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ (t) | $CH_3O_2CCH_2CH_2CHO$ | 96/4 | 90 |
| $CH_3CH=CHCH_2Sn(Me)_3$ (t) | $CH_3O_2CCH_2CH_2CHO$ | 98/2 | 89 |

[a] Isolated yield (GLPC yield). [b] $Me_3SiI$ was used instead of $BF_3$·$OEt_2$.

Considerable amounts of the linear adduct (12) was formed as a by-product.

reactions ( < 200°) of **1** generally depends upon the geometry of the crotyl unit[5] as observed in ordinally allylic organometallic reactions. To help clarify the factors responsible for this striking stereochemical difference and to get better insight into the structure of the transition state, we examined the reaction of allylic stannanes with aldehydes under high pressure (10 Kbar, 1 GPa).[6] To our surprise, the allylation occurred at room temperature under neutral condition. The results are summarized in Table 2. Evidently, the *threo* isomer is formed predominantly from the *trans*-crotylstannane. Therefore, the reaction proceeds essentially via a 6-membered chair transition state. The Lewis acid coordination entirely alters the structure of the transition state, resulting in the stereochemical convergence. In conclusion, Lewis acids serve as a stereosteering group as well as an activator of CO group.[7]

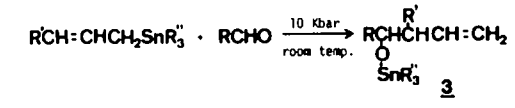


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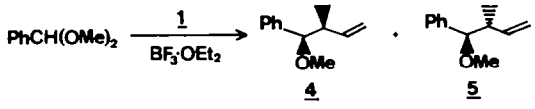
Fig. 4.

The diastereoselectivity in the reaction of **1** with benzaldehyde dimethy acetal was also examined. Unfortunately, the selectivity was low; **4**:**5** = 56:44.

*Cram/anti-Cram selectivity.* The Cram/anti-Cram problem was investigated both in the Lewis acid mediated reaction and in the high pressure reaction.




4 5

Fig. 5.

Table 2. Allylation of aldehydes under high pressure

| allylstannane | aldehyde | time/day | solvent | erythro/threo | yield,% |
|---|---|---|---|---|---|
| $CH_3CH=CHCH_2Sn(Bu)_3$ | $C_6H_5CHO$ | 3 | $Et_2O$ | 35/65 | 41 |
| $CH_2=CHCH_2Sn(Me)_3$ | $C_6H_5CHO$ | 5 | $Et_2O$ | | 100 |
| $CH_3CH=CHCH_2Sn(Bu)_3$ | $p$-$MeC_6H_4CHO$ | 7 | $Et_2O$ | 20/80 | 17 |
| $CH_2=CHCH_2Sn(Me)_3$ | $p$-$MeC_6H_4CHO$ | 7 | $Et_2O$ | | 100 |
| $CH_2=CHCH_2Sn(Me)_3$ | $p$-$MeOC_6H_4CHO$ | 6 | $CH_2Cl_2$ | | 40 |
| $CH_2=CHCH_2Sn(Me)_3$ | $p$-$O_2NC_6H_4CHO$ | 6 | $CH_2Cl_2$ | | 100 |
| $CH_2=CHCH_2Sn(Me)_3$ | $C_6H_5CH=CHCHO$ | 6 | $CH_2Cl_2$ | | 83 |
| $CH_2=CHCH_2Sn(Me)_3$ | $CH_3(CH_2)_2CHO$ | 7 | $CH_2Cl_2$ | | 70 |

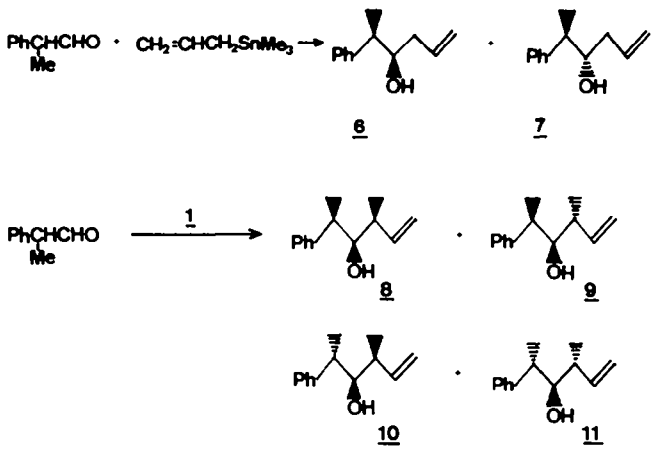


Fig. 6.

The results are summarized in Table 3. The high pressure reaction under neutral condition gives diastereomers (Cram and anti-Cram product) in ratios of about 2:1. The ratio in the reaction of allyl-9-borabicyclo[3.3.1]-nonane or allylmagnesium chloride is about 1.2–2.0:1. On the other hand, the ratio is enhanced up to 7.3:1 in the Lewis acid mediated reaction. The enhanced diastereofacial selectivity may be due to the coordination of Lewis acids to the O atom, which causes change of the directionality[8] of the nucleophilic addition as suggested by Heathcock.[9]

*Regiocontrol of the allylation reaction.* The reaction of unhindered carbonyl compounds with crotylmetal reagents such as M = Li, Mg, Cu, Zn, Cd, B, Al, Si, Sn, Ti, Zr, Cr, Mn . . . , generally results in products in which the allylic group is attached at the more highly substituted position (the branched adduct, **13**).[10] In fact, the reaction of crotylstannanes in the presence of ordinary Lewis acids, such as $TiCl_4$, $SnCl_4$ and $BF_3{\cdot}OEt_2$, affords **13** exclusively. The regioreversed addition to produce the linear adduct (**12**) is totally unprecedented despite its great potential importance. We found that the reaction of **1** with certain aldehydes in the presence of $AlCl_3$–i–PrOH gives **12** either predominantly or exclusively. The results are summarized in Table 4. Benzaldehyde and linear aldehydes give **12**, while the branched aldehyde, crotonaldehyde and acetophenone afford **13**.

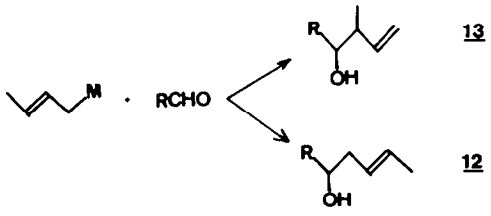


Fig. 7.

Isovaleraldehyde is a borderline case. The presence of i-PrOH is essential for the regioreversed addition; use of $AlCl_3$ itself leads to exclusive formation of **13**. The effect of the ratio of $AlCl_3$–i-PrOH upon the regioselectivity was investigated, and the best result was obtained in the ratio of 1:1. Other alcohols such as methanol, t-butanol, camphor, menthol, and $\beta$-pinene were also examined. Although the regioselectivity with $AlCl_3$–t-BuOH system was similar to that with $AlCl_3$–i-PrOH system, the selectivity with other alcohol systems was relatively low. Another important factor to control the regioselectivity is the order of the addition of the reagents; the sequence of the addition must be in the order of (i) $AlCl_3$, (ii) i-PrOH, (iii) **1**, (iv) aldehyde, and the addition of aldehydes prior to the addition of **1** results in the low regioselectivity.

Table 3. Cram/anti-Cram selectivity in the reaction of 2-phenylpropionaldehyde

| allylstannane | conditions | Cram : anti-Cram | erythro : threo |
|---|---|---|---|
| | | 6 : 7 | |
| $CH_2{=}CHCH_2Sn(Me)_3$ | $AlCl_3$, $CH_2Cl_2$ | 5.1 : 1 | |
| | $BF_3{\cdot}OEt_2$, $CH_2Cl_2$ | 4.0 : 1 | |
| | $TiCl_4$, $CH_2Cl_2$ | 2.2 : 1 | |
| | 10 Kbar, $CH_2Cl_2$ | 2.0 : 1 | |
| | | 8 + 9 : 10 + 11 | 8 + 10 : 9 + 11 |
| $CH_3CH{=}CHCH_2Sn(Bu)_3$ | $BF_3{\cdot}OEt_2$, $CH_2Cl_2$ | 6.1 : 1 | >99 : 1 |
| | 10 Kbar, $CH_2Cl_2$ | 2.3 : 1 | 1 : 2.2 |
| $CH_3CH{=}CHCH_2Sn(Me)_3$ | $BF_3{\cdot}OEt_2$, $CH_2Cl_2$ | 7.3 : 1 | >99 : 1 |

Table 4. Regioreversed addition of crotyltributylstannane

| aldehyde | product ratio, 12/13 | E/Z ratio of 12 | Total yield, %[a] |
|---|---|---|---|
| PhCHO | 83/17 | 90/10 | 80 |
| EtCHO | 98/2 | 90/10 | 67 |
| n-PrCHO | 95/5 | 85/15 | 72 |
| n-BuCHO | 90/10 | 87/13 | 73 |
| $n\text{-}C_9H_{19}CHO$ | 61/39 | 84/16 | 70 |
| $Me_2CHCH_2CHO$ | 58/42 | 87/13 | 68 |
| $Me_2CHCHO$ | 0/100 | | 80 |
| MeCH=CHCHO | 0/100 | | 80 |
| PhC(O)Me | 0/100 | | 85 |

[a] GLPC yield; for 13, a mixture of two diastereoisomers was obtained.

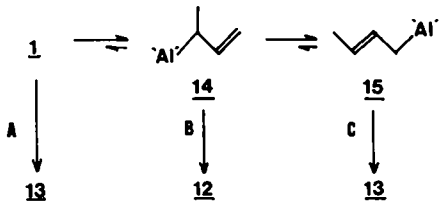



Fig. 8.

The regioreversed addition can be understood by the following routes. Transmetallation from **1** with the aid of $AlCl_3$–i-PrOH, presumably $AlCl_2$(O–i-Pr), would proceed through $S_E2'$ process[11] to produce the α-metallylaluminum derivative (**14**), which reacts with aldehydes to give **12**. At higher temperature and/or over a prolonged period of time, **14** undergoes rearrangement to the more stable isomer (**15**), which reacts with aldehydes to give **13**. Moreover, **1** may react with aldehydes in the presence of $AlCl_3$–i-PrOH to give **13**. $AlCl_3$ and other strong Lewis acids produce **13** via path A. The combination of the soft Lewis acid ($AlCl_3$–i-PrOH) and the reactive aldehydes gives **12** via path B. Unreactive aldehydes and ketones permit further rearrangement to **15**, resulting in **13** via path C. Presumably, the addition of aldehydes prior to the addition of **1** makes path A favourable. In conclusion, either the branched or the linear adduct can be obtained by merely choosing Lewis acids.

*The Prelog–Djerassi lactonic acid* (**16**). The *erythro*-selectivity exhibited by **1**–$BF_3$·$OEt_2$ system was applied to the stereoselective synthesis of **16**.[12] The reaction of **17** with **1** in the presence of 1 eq $BF_3$·$OEt_2$ produced **18a** in 92% yield. The ozonolytic cleavage of the double bond of **18a** gave the desired lactonic acid (**16**) in 85% yield. Therefore, the present reaction may provide an efficient and one of the most convenient method[13] for the synthesis of **16**.[14] The stereoselectivity in the reaction of **1**– 1 eq $BF_3$·$OEt_2$ with **17** was very high (> 94%); **18a**: (**18b** + **18c** + **18d**) = > 94:6. The highly stereoselective formation of **18a** attracted our attention, since the stereochemical relationship between C-4 and C-5 required that the reaction must proceed through the anti-Cram's rule. Presumably, the reac-

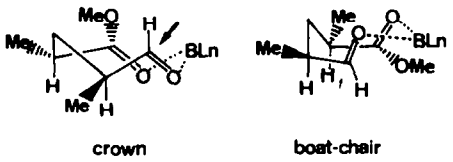



Fig. 10.

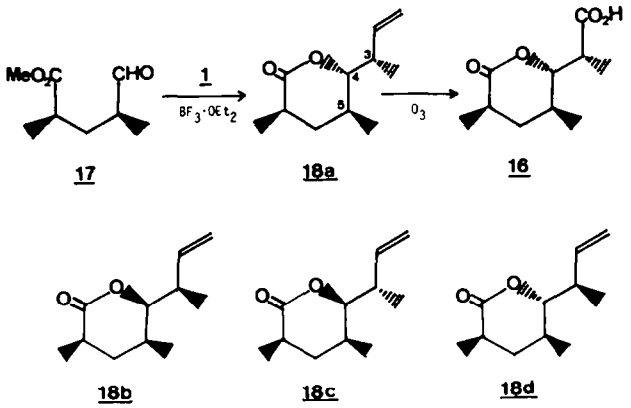



Fig. 9.

tion proceeds through the 8-membered cyclic transition state which involves boron chelation.

The crown form leads to the anti-Cram products, since the nucleophile is forced to attack from the direction indicated by an arrow owing to the steric factor. The boat-chair form produces the Cram products. Generally speaking, the crown form of cyclooctane is more stable than the boat-chair form.[15]

Therefore, the reaction must proceed via the crown type transition state. Use of 2 eq $BF_3$·$OEt_2$ caused decrease of the stereoselectivity (*ca* 83–91%). Further, use of 3 eq $BF_3$·$OEt_2$ lead to loss of the stereoselectivity (41%). This result supports the 8-membered cyclic transition state. Excess $BF_3$·$OEt_2$ permits the coordination at each CO group to prevent the formation of the cyclic transition state.

*Verrucarinolactone* (**19**). We chose **19**,[16] the left half of the macrocyclic portion of verrucarin A, as the target molecule. It was thought that **1** would attack the CO group of the glyoxylate ester of 8-phenyl-menthol (**20**)[17] from the si-face, since the phenyl group would block the attack from the re-face. It is clear that **21a** and **21b** result from attack at the si-face of **20**, and **21c** and **21d** from attack at the re-face of **20**. The *erythro* selectivity of **1**–$BF_3$·$OEt_2$ system predicts the predominant formation of **21a** and **21c**. Therefore, it was expected that **21a** would be produced predominantly among 4 diastereomers. In fact, the reaction of **20** with **1** in the presence of 1 eq $BF_3$·$OEt_2$ gave **21a** as a major product; **21a**:**21b**:**21c** + **21d** = 84:9:7. Hydroboration-oxidation of the mixture of these isomers (**21**) gave the diol (**22**) in 70% yield. Treatment of **22** with toluen-*p*-sulphonic acid produced white crystals. $^1$H NMR spectroscopy showed a ratio of **19** to its epimer of 9:1. Recrystallization from ether gave pure


Fig. 12.

**19**, m.p. 101–102°, $[\alpha]_D^{21.5}$ −8.82°, 91% e.e. Consequently, as we assumed in **20**, both CO groups take the *syn* geometry rather than the *anti* geometry.

Perhaps, the coordination of B to both carbonyl O atoms is more favourable than that to the ester O and carbonyl O atom. The simple procedure and high levels of enantio- and diastereoselectivity via **1**–$BF_3$·$OEt_2$ system may provide a practical method for the asymmetric synthesis of **19**.

## EXPERIMENTAL

General information concerning instrumentation and materials is described previously.[18] Allylic stannanes were prepared according to the reported procedure.[19] *Z*-Crotyltributylstannane was prepared by the method which we previously developed.[3]

*General procedure for the Lewis acid mediated reaction.* The preparation of *erythro*-2-methyl-1-phenyl-3-buten-1-ol is representative. To a soln of benzaldehyde (2 mmol, 0.22 mL) in dry $CH_2Cl_2$ (4 mL) was added $BF_3$·$OEt_2$ (4 mmol, 0.52 mL) at −78° under $N_2$. Subsequently, crotyltributylstannane (2 mmol, 0.8 mL) was added, and the mixture was allowed to warm to 0°. The reaction was quenched with $H_2O$, and the organic phase was separated, dried and condensed. Filtration through a column of silica gel with hexane–ether (10:1) as an eluant gave the desired product in an essentially pure form: 0.29 g, 90%, b.p. 80–85° (0.5 mmHg) (Kugelrohr), $^1$H NMR and other data of both *erythro* and *threo* isomer are described previously.[18]

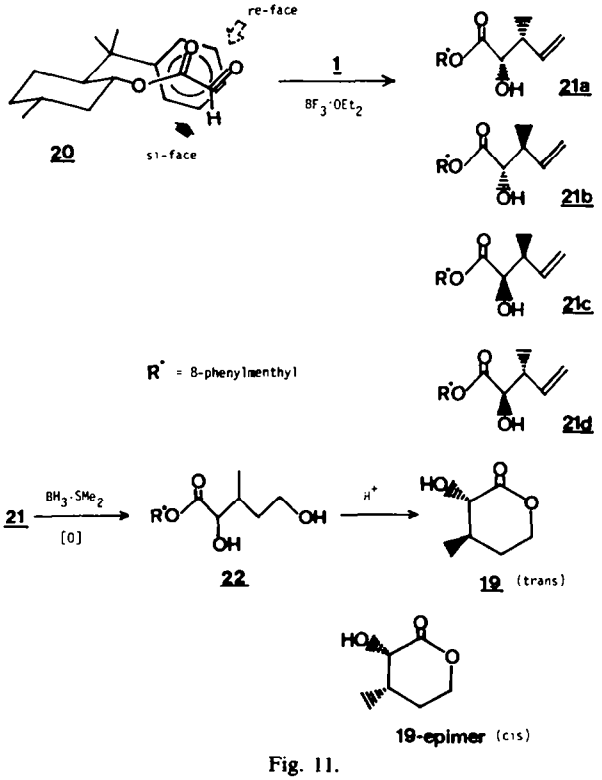
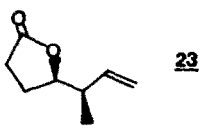



Fig. 11.

3-Methyl-4-penten-2-ol (from acetaldehyde), 4-methyl-5-hexen-3-ol (from propionaldehyde) and 2,4-dimethyl-5-hexen-3-ol (from isobutyraldehyde) were identical with authentic samples.[4] Erythro-3,6-dimethyl-1-hepten-4-ol (from isovaleraldehyde): b.p. 90–94° (18 mmHg) (Kugelrohr); $^1$H NMR ($CCl_4$): $\delta$ 0.93 (dd, 6, J = 6.6 and 2.4 Hz), 0.96 (d, 3, J = 6.6 Hz), 1.28 (m, 4), 2.14 (m, 1), 3.60 (bs, 1), 4.85–5.10 (m, 2), 5.45–5.90 (m, 1); IR ($CCl_4$) 3620, 3020, 1270, 1030, 990, 910 cm$^{-1}$; MS: *m/e* ($M^+$) 142; Anal. ($C_9H_{18}O$) C, H. Erythro-3-methyl-5-ethyl-1-hepten-4-ol (from 2-ethylbutyraldehyde): b.p. 98–100° (18 mm Hg) (Kugelrohr); $^1$H NMR ($CCl_4$) $\delta$ 0.96 (d, 3, J = 6.6 Hz), 0.98 (t, 6, J = 6.6 Hz), 1.30 (m, 6), 2.10 (m, 1), 3.58 (bs, 1), 4.85–5.10 (m, 2), 5.50–5.90 (m, 1); IR ($CCl_4$) 3620, 3020, 1270, 1030, 990, 910 cm$^{-1}$; MS: *m/e* ($M^+$) 156; Anal. ($C_{10}H_{20}O$) C, H. Erythro-3-methyl-1,5-heptadien-4-ol (from crotonaldehyde); b.p. 80–85° (18 mmHg) (Kugelrohr); $^1$H NMR ($CCl_4$) $\delta$ 0.97 (d, 3, J = 6.6 Hz), 1.70 (d, 3, J = 5.0 Hz), 2.24 (m, 1), 2.50 (bs, 1), 3.80 (t, 1, J = 6.7 Hz), 4.86–5.04 (m, 2), 5.40–5.90 (m, 3); IR ($CCl_4$) 3600, 1620, 990, 960, 910 cm$^{-1}$; MS: *m/e* ($M^+$) 126; Anal. ($C_8H_{14}O$) C, H. Methyl erythro-4-hydroxy-5-methyl-6-heptenoate (from methyl 4-oxobutanoate); $^1$H NMR ($CCl_4$) $\delta$ 1.11 (d, 3, J = 6.6 Hz), 1.50–2.50 (m, 5), 2.84 (bs, 1), 3.35 (m, 1), 3.64 (s, 3), 4.92–5.20 (m, 2), 5.50–5.92 (m, 1). This alcohol quite easily underwent lactonization under the $BF_3$ mediated reaction condition to produce the lactone (**23**), and the isomer ratio was determined after the lactonization. **23**: b.p. 80–85°



**23**

(20 mmHg) (Kugelrohr); $^1$H NMR ($CCl_4$) $\delta$ 1.14 (d, 3, J = 6.6 Hz), 1.75–2.40 (m, 5), 4.18 (quartet, 1, J = 6.0 Hz), 5.00–5.20 (m, 2), 5.50–5.86 (m, 1); IR ($CCl_4$) 1788, 1640, 1180, 995, 920 cm$^{-1}$; MS: *m/e* ($M^+$) 140; Anal. ($C_8H_{12}O_2$) C, H. The ratio of *erythro/threo* in Table 1 was determined by using GLC (CW 6000, 2m),[4,18] except for the ratio in the reaction of benzaldehyde which was determined by $^1$H NMR spectroscopy.[18] It was very difficult to isolate the minor *threo* isomer via the Lewis acid mediated reaction. We prepared authentic *threo* isomers through crotylzirconium reagents,[20] whose data will be published in due course.

*High pressure allylation.* In a Teflon capsule (1.5 mL capacity) were placed the aldehyde (1 mmol), the allylic stannane (1 mmol), and the solvent (*ca* 1 mL). High pressure (10 Kbar) experiments were performed in a stainless steel die and compressed at room temp via a piston.[21] After the period indicated in Table 2, the pressure was released and the solvent was removed *in vacuo*. The product was directly analyzed by $^1$H NMR spectroscopy. When the reaction was incomplete, the aldehyde and the allylic stannane were recovered without change. The yield was determined by the area ratio of the $^1$H NMR spectra of **3**. The *erythro/threo* ratio was determined from the $^1$H NMR spectra and/or GLC analysis of the hydrolysis product, homoallyl alcohol. Erythro-2-methyl-1-p-tolyl-3-buten-1-ol; b.p. 78–82° (0.1 mmHg) (Kugelrohr); $^1$H NMR ($CCl_4$) $\delta$ 0.84 (d, 3, J = 6.6 Hz), 1.20–1.64 (m, 2), 2.32 (s, 3), 4.22 (d, 1, J = 7.0 Hz), 4.96–5.12 (m, 2), 5.48–5.80 (m, 1), 7.08 (bs, 4); IR ($CCl_4$) 3610, 1620, 1050, 990, 910 cm$^{-1}$; MS: *m/e* ($M^+$) 176. Threo isomer; $^1$H NMR ($CCl_4$) $\delta$ 0.96 (d, 3, J = 6.6 Hz), 1.20–1.64 (m, 2), 2.32 (s, 3), 4.39 (d, 1, J = 6.0 Hz), 4.96–5.12 (m, 2), 5.48–5.80 (m, 1), 7.08 (bs, 4); the same IR and MS spectra as above. 1-p-Anisyl-3-buten-1-ol; b.p. 90–95° (0.1 mmHg) (Kugelrohr); $^1$H NMR ($CCl_4$) $\delta$ 2.24 (bs, 1), 2.40 (t, 2, J = 6.0 Hz), 3.72 (s, 3), 4.54 (d, 1, J = 7.0 Hz), 6.70–7.20 and 7.70–7.80 (m, 4). 1-p-Nitrophenyl-3-buten-1-ol; b.p. 100–105° (0.1 mmHg) (Kugelrohr); $^1$H NMR ($CDCl_3$) $\delta$ 2.56 (t, 2, J = 6.0 Hz), 2.60 (bs, 1), 4.88 (d, 1, J = 7.0 Hz), 5.04–5.20 (m, 2), 5.60–5.96 (m, 1), 7.70–7.60 and 8.15–8.22 (m, 4). 1-Phenyl-1,5-hexadien-3-ol; b.p. 80–85° (0.1 mmHg) (Kugelrohr); $^1$H NMR ($CCl_4$) $\delta$ 2.34 (t, 2, J = 6.0 Hz), 2.60 (bs, 1), 4.22 (m, 1), 5.00–5.20 (m, 2), 5.60–6.00 (m, 1), 6.56 (d, 1, J = 16.0 Hz), 7.20 (m, 6). 1-Hepten-4-ol; b.p. 70° (18 mm Hg) (Kugelrohr); $^1$H NMR ($CCl_4$) $\delta$ 0.93 (t, 3, J = 6.0 Hz), 1.40 (bs, 5), 2.16 m, 2), 3.60 (m, 1), 4.94–5.08 (m, 2), 5.52–5.95 (m, 1). All these products were compared with authentic samples prepared by the other procedure.[22]

*The reaction of benzaldehyde dimethyl acetal.* The same procedure as above was employed, except for the reaction time. The reaction was kept at room temp overnight and then quenched: b.p. 140–145° (18 mmHg) (Kugelrohr), 82% yield. The ratio of *erythro/threo* was determined by $^1$H NMR spectroscopy. Erythro-1-methoxy-1-phenyl-2-methyl-3-butene (**4**): $^1$H NMR ($CCl_4$) $\delta$ 0.93 (d, 3, J = 6.6 Hz), 2.34 (m, 1), 3.04 (s, 3), 3.76 (d, 1, J = 6.0 Hz), 4.68–4.86 (m, 2), 5.30–5.80 (m, 1), 7.16 (bs, 5); IR ($CCl_4$) 1600, 1060, 990, 910 cm$^{-1}$; MS: *m/e* ($M^+$)176. Threo isomer (**5**): $^1$H NMR ($CCl_4$) $\delta$ 0.74 (d, 3, J = 6.6 Hz), 2.34 (m, 1), 3.06 (s, 3), 3.76 (d, 1, J = 6.0 Hz), 4.68–4.86 (m, 2), 5.30–5.80 (m, 1), 7.16 (bs, 5); the similar IR and MS spectra were obtained. Authentic samples of **4** and **5** were prepared by the reaction of *erythro* and *threo* 2-methyl-1-phenyl-3-buten-1-ol with Na/MeI in THF.

*Cram/anti-Cram selectivity.* The Lewis acid mediated and high pressure reaction were carried out as described above. The ratio of **6**/**7** was determined by $^1$H NMR spectroscopy. **6**; $^1$H NMR ($CCl_4$) $\delta$ 1.29 (d, 3, J = 7.0 Hz), 1.72 (bs, 1), 2.00 (m, 2), 2.65 (quintet, 1), 3.60 (m, 1), 4.86–5.06 (m, 2), 5.90–5.52 (m, 1), 7.16 (bs, 5). **7**; $^1$H NMR ($CCl_4$) $\delta$ 1.27 (d, 3, J = 7.0 Hz), 1.72 (bs, 1), 2.00 (m, 2), 2.65 (quintet, 1), 3.60 (m, 1), 4.86–5.06 (m, 2), 5.90–5.52 (m, 1), 7.16 (bs, 5). **8** and **10** were obtained from the reaction of **1**, and pure **8** was isolated through the column of silica gel by using hexane–ether (20:1) as an eluant. However, **10** could not be isolated in pure form and the $^1$H NMR spectra was easily analyzed from the mixture of **8** and **10**. **9** and **11** were isolated from the reaction of crotylzirconium compounds.[20] **8**; $^1$H NMR ($CCl_4$) $\delta$ 0.96 (d, 3, J = 7.0 Hz), 1.24 (d, 3, J = 7.0 Hz), 1.40 (bs, 1), 2.15 (m, 1), 2.80 (quintet, 1), 3.48 (m, 1), 4.90–5.10 (m, 2), 5.58–5.94 (m, 1), 7.14 (bs, 5). **9**; 0.99 (d, 3, J = 7.0 Hz), 1.27 (d, 3, J = 7.0 Hz), 2.16 (bs, 2), 2.72 (quintet, 1), 3.44 (bs, 1), 4.80–5.10 (m, 2), 5.64–6.00 (m, 1), 7.14 (bs, 5). **10**; 0.11 (d, 3, J = 7.0 Hz), 1.30 (d, 3, J = 7.0 Hz), 2.16 (m, 1), 2.22 (bs, 1), 2.80 (quintet, 1), 3.48 (m, 1), 4.95–5.10 (m, 2), 5.80–6.00 (m, 1), 7.20 (bs, 5). **11**; $\delta$ 1.07 (d, 3, J = 7.0 Hz), 1.21 (d, 3, J = 7.0 Hz), 1.40 (bs, 1), 2.24 (m, 1), 2.72 (quintet, 1), 3.36 (m, 1), 4.90–5.08 (m, 2), 5.64–6.00 (m, 1), 7.20 (bs, 5). Each isomer was subjected to ozonolysis in the similar manner as described later to produce the corresponding acid, which was converted into the crystalline diol via $LiAlH_4$ reduction.[23] The diol was compared with the authentic sample.[24]

*Regioreversed addition.* In a dry 50 mL flask, maintained under a static pressure of $N_2$ and kept at −78°, were placed dry $CH_2Cl_2$ (4 mL) and $AlCl_3$–diethyl ether soln (2 M, 1 mmol). Propan-2-ol (1 mmol) was added and then crotyltributylstannane (1 mmol). After 1–3 min, the aldehyde (1 mmol) was added and stirring continued for 15 min at this temp. The reaction was quenched at 0° and analyzed by GLC (PEG, 5%, 2m). **12** was isolated through the column of silica gel (hexane–ether = 20:1) as a mixture of *trans* and *cis* isomer, whose ratio was determined by GLC. The major isomer was determined to be the *trans* isomer because of the strong IR absorption at 960 cm$^{-1}$. 1-Phenyl-3-penten-1-ol; $^1$H NMR ($CCl_4$) $\delta$ 1.56 (d, 3, J = 6.0 Hz), 2.00 (bs, 1), 2.40 (t, 2, J = 6.6 Hz), 4.52 (t, 1, J = 6.6 Hz), 5.40 (m, 2), 7.20 (bs, 5). 5-Hepten-3-ol; $\delta$ 0.96 (t, 3, J = 6.6 Hz), 1.40 (m, 2), 1.64 (d, 3, J = 6.0 Hz), 1.50 (bs, 1), 2.20 (t, 2, J = 6.6 Hz), 3.50 (m, 1), 5.44 (m, 2). 6-Octen-4-ol; $\delta$ 0.95 (bs, 3), 1.38 (bs, 5), 1.64 (d, 3, J = 6.0 Hz), 2.14 (t, 2, J = 6.6 Hz), 3.53 (bs, 1), 5.44 (m, 2). 2-Nonen-5-ol; $\delta$ 0.93 (bs, 3), 1.40 (bs, 7), 1.67 (d, 3, J = 6.0 Hz), 2.18 (t, 2, J = 6.6 Hz), 3.58 (bs, 1), 5.56 (m, 2).

2-Tetradecan-5-ol: $\delta$ 0.92 (bs, 3), 1.26 bs, 17), 1.63 (d, 3, J = 6.0 Hz), 2.13 (t, 2, J = 6.3 Hz), 3.45 (bs, 1), 5.44 (m, 2). All products in Table 4 were compared with authentic samples.[25]

*Synthesis of* **16**. Meso-2,4-dimethylglutaric acid monomethyl ester, prepared from meso-2,4-dimethylglutaric acid anhydride,[26] was converted into the corresponding carboxylic–carbonic anhydride by the literature procedure.[27] Treatment of this anhydride with 1/4 eq $NaBH_4$ in glyme at 0–20° under $N_2$ gave the corresponding alcohol, 2-methyl-4-carbomethoxypentanol, together with **17**. The mixture was treated with 1.2 eq PCC in dry $CH_2Cl_2$.[28] **17** was obtained in 70% overall yield from the meso ester; $^1$H NMR ($CCl_4$) $\delta$ 1.09 (d, 3, J = 7.0 Hz), 1.15 (d, 3, J = 7.0 Hz), 1.10–1.40 (m, 1), 1.50–1.80 (m, 1), 2.06–2.62 (m, 2), 3.63 (s, 3), 9.5 (bs, 1); IR ($CCl_4$) 1735, 1720 cm$^{-1}$. The $BF_3$ mediated reaction of **17** (1 mmol) was carried out as described above. The reaction was quenched with $H_2O$ at 0°. $BF_3{\cdot}OEt_2$ (2 mmol) was added and stirring was continued for 2 hr. Extraction with ether, drying, evaporation of the solvents, and filtration through silica gel gave **18a** in 92% yield. Although GLC analysis (CW 6000, 5%, 2m) of the mixture indicated the presence of small amounts of isomers (**18b–d**, < 6%), an appreciable amount of these isomers could not be isolated via silica gel column chromatography. **18a**; $^1$H NMR ($CCl_4$) $\delta$ 1.01 (d, 3, J = 7.0 Hz), 1.04 (d, 3, J = 7.0 Hz), 1.22 (d, 3, J = 7.0 Hz), 1.30–2.20 (m, 3), 2.20–2.70 (m, 2), 3.91 (dd, 1, J = 2.3 and 10 Hz), 5.11 (dd, 1, J = 1.5 and 10 Hz), 5.14 (dd, 1, J = 1.5 and 18 Hz), 6.07 (ddd, 1, J = 8, 10 and 18 Hz). The minor isomer (**18b–d**) increased with increase of $BF_3{\cdot}OEt_2$, and the structure was deduced from the product mixture of the reaction through crotylzirconium[20] or crotyl-9-borabicyclo[3.3.1]nonane.[18] Ozone was introduced into an ethyl acetate soln (5 mL) of **18a** (30 mg, 0.17 mmol) at *ca* −75°. After the color of the soln changed to blue, the mixture was allowed to warm to room temp. Treatment with $H_2O_2$ (30%, 0.5 mL)–$H_2O$ (0.5 mL), subsequent heating at 60° for 10 hr, followed by the addition of 2 N NaOH (0.7 mL) produced **16** in 85% yield. Recrystallization from hexane–ether gave a pure **16**, m.p. 116.5–117.5° (lit[29] 116–117°); $^1$H NMR ($CDCl_3$) $\delta$ 1.02 (d, 3, J = 6.2 Hz), 1.19 (d, 3, J = 7.0 Hz), 1.29 (d, 3, J = 6.8 Hz), 1.38–2.90 (m, 5), 4.59 (dd, 1, J = 2.3 and 10 Hz), 7.32 (bs, 1); IR ($CDCl_3$) 3450–2700, 1720 cm$^{-1}$. We are grateful to Prof. Satoru Masamune for providing us with $^1$H NMR spectra of **16** and its epimer.

*Synthesis of* **19**. **20** was prepared from (+)pulegone by the method of Corey[17] and Kornblum;[30] $^1$H NMR ($CCl_4$) $\delta$ 0.7–2.3 (m, 17), 4.88 (td, 1, $J_t$ = 10.3 and $J_d$ = 4.0 Hz), 7.20 (m, 5), 8.37 (s, 1). The $BF_3$ mediated reaction of **20** was carried out similarly. **21a** + **21b** and **21c** + **21d** were isolated through the column of silica gel by using hexane–ether (20:1). The ratio of **21a**/**21b** (*erythro*/*threo*) was 9:1, as judged from the $^1$H NMR spectra of the mixture. This mixture was converted into verrucarinolactone and the ratio of **19** to **19**-epimer was 9:1. Since separation at the initial stage was not so easy, we decided to separate and purify **19** at the final stage. The ratio of **21a**, **21b** and **21c** + **21d** was determined by GLC (DC 550, 10%, 3 m). **21c** and **21d** could not be separated. **21** was separated from the stannane residue by using a short column of silica gel (hexane–ether = 10:1). Without any further separation and purification **21** was treated with 1.2 eq $BH_3{\cdot}SMe_2$ at 0° in hexane, and then the reaction was kept at 20–25° for 1 hr. The usual oxidation with 30% $H_2O_2$ (0.2 mL)-aq NaOH (1N, 0.4 mL) gave **22** in 70% yield; $^1$H NMR ($CCl_4$) $\delta$ 0.6–2.2 (m, 23), 2.63 (bs, 1), 3.20 (s, 1), 3.60 (m, 3), 4.94 (td, 1, $J_t$ = 10.3 and $J_d$ = 4.1 Hz), 7.26 (m, 5); IR ($CCl_4$) 3630, 3600–3150, 1740 cm$^{-1}$. Without any further purification, this diol was directly treated with 0.5 eq *p*-TsOH in $CH_2Cl_2$ at 30–35° for 24 hr. Ether extraction, drying, condensation and addition of hexane to the product gave white crystals, m.p. 93–94°. $^1$H NMR examination at this stage revealed that the ratio of **19** to **19**-epimer was 9:1; the Me proton of **19** appeared at $\delta$ 1.21, while that of its epimer appeared at $\delta$ 1.02. Recrystallization from ether gave pure **19**, m.p. 101–102° [lit[16] m.p. 102–102.5° (Koga's) or 101.5–103° (Mohr's)]; $[\alpha]_D^{25}$ − 8.82° (10 cm cell, c 0.57, $CHCl_3$)), 91% enantiomeric excess; $^1$H NMR ($CCl_4$) $\delta$ 1.21 (d, 3, J = 6.6 Hz), 1.52–2.22 (m, 3), 3.43 (bs, 1), 3.84 (d, 1, J = 10.2 Hz), 4.32 (m, 2).

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