Diastereodivergent Control in the Reactions of Allylic and Allenic Organometallic Reagents with Pyruvates[1]

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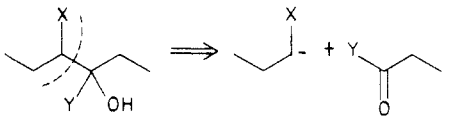
The reaction of crotyl-9-BBN (**4a**) with pyruvates (**3**) produced the threo (anti) isomer **5** either predominantly or exclusively. On the other hand, the reaction of allenic organometallic reagents **18** (M = B or Ti) gave the erythro (syn) isomer **20** preferentially. The diastereochemical difference between both organometallic reagents is discussed.

Diastereo- and enantiodivergent control at the chiral centers is of current importance in synthetic organic chemistry. Although the stereoselective synthesis of secondary alcohols **1a** from the reaction of aldehydes **2a** with organometallic compounds has been extensively investigated,[2] the diastereoselective synthesis of tertiary alcohols **1b** from ketones **2b** has been scarcely reported[3] (eq 1).



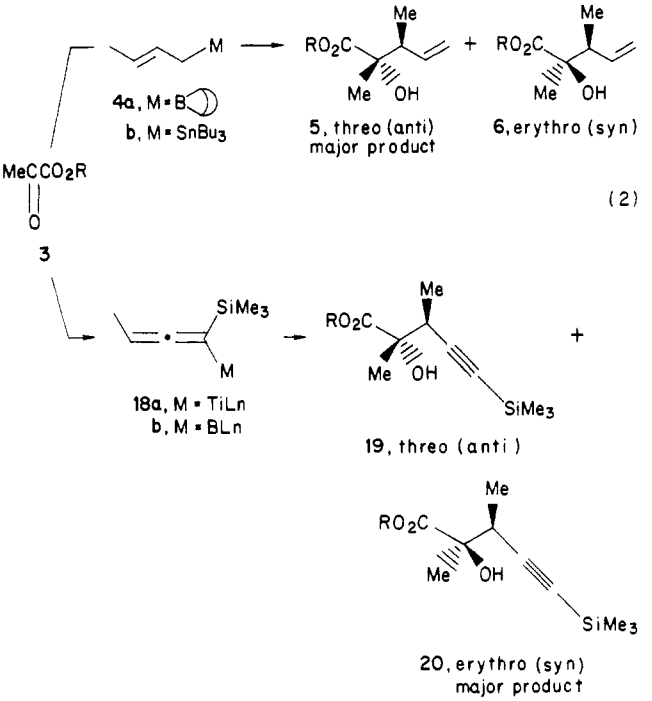
(1)

1a, Y = H
b, Y = R(alkyl, aryl, ...)
c, Y = CO_2R

2a, Y = H
b, Y = R
c, Y = CO_2R

Tertiary alcohols such as **1c** constitute a framework of pyrrolidizine alkaloids,[4] and thus the diastereodivergent control in the reaction of pyruvates (**3**) is synthetically important. Moreover, a systematic study on the diastereoselectivity in the tertiary derivatives may serve to elucidate the stereoselection in acyclic systems.

Previously, we[1] and others[3] reported diastereoselective C–C bond formation with generation of tertiary alcohols, but unfortunately both approaches provided only one of a stereopair. We now wish to report that both stereoisomers **5** and **20** can be obtained predominantly from **3** by merely changing the organometallic reagents (eq 2).



(2)

Results and Discussion

Reaction of 4 with 3. The reaction of crotyl-9-BBN (**4a**) and crotyltributylstannane (**4b**) was examined and the results are summarized in Table I. By increasing the steric bulk of the ester groups, the threo[5] (anti[6]) isomer **5** can be obtained either predominantly or exclusively (entry 8) via the reaction with **4a**. On the other hand, the stereoselective synthesis of the erythro[5] (syn[6]) isomer **6** is difficult, and the best result so far obtained is ca. 60% via the reaction with **4b** (entry 5). These stereochemical features can be explained by the previously proposed six-membered chair[2] or acyclic transition state[7] (Scheme I).

In the six-membered chair transition state from **4a**, **7** gives **5** and **8** produces **6**. Increase of the steric bulk of R destabilizes **8** relative to **7** owing to the CO_2R - L interaction. In the reaction of **4b** in the presence of Lewis acids which proceeds through acyclic transition state,[7] **9** is only slightly stabilized relative to **10** with a small R group. With a large R group this is reversed (entries 5 - 7). Consequently, the reaction of **4b** results in low diastereoselectivity. The stereochemistry of **5** and **6** was determined by converting into crobarbatic acid as mentioned later.

(1) For a preliminary report on some aspects of the present study, see: Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1983**, 191.

(2) Review articles: (a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (c) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *33*, 1. (d) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31. (e) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (f) Heathcock, C. H. In "Comprehensive Carbanion Chemistry"; Durst, T., Buncel, E., Eds.; Elsevier: New York 1984. (g) Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203. (h) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (i) Hoppe, D. *Ibid.* **1984**, *23*, 932. (j) Mulzer, J. *Nachr. Chem. Tech. Lab.* **1984**, *32*, 16. (k) Bartlett, P. D. *Tetrahedron* **1980**, *36*, 2. (l) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125.

(3) (a) Seebach, D.; Widler, L. *Helv. Chim. Acta* **1982**, *65*, 1972. (b) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441.

(4) For example: (a) Huang, J.; Meinwald, J. *J. Am. Chem. Soc.* **1981**, *103*, 861. (b) Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guedin-Vuong, D. *Ibid.* **1984**, *106*, 2954. (c) Devlin, J. A.; Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1117.

(5) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521.

(6) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1981**, *103*, 2106.

(7) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107. Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239.

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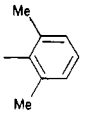
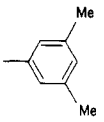
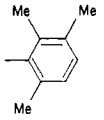
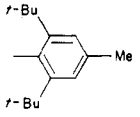
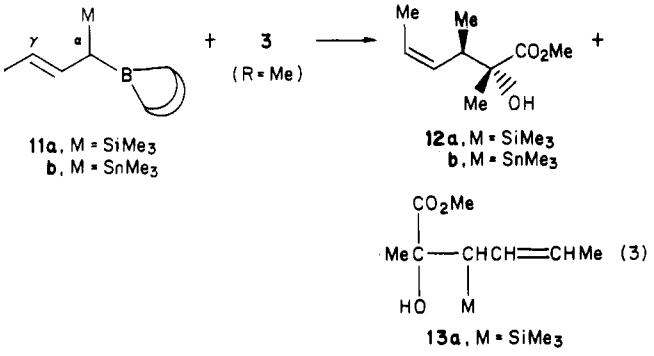
Table I. Reaction of 4 with 3

entry	3, R	4a yield,[a] %	4a 5:6	4b yield,[a] %	4b 5:6
1	Me	96	73:27	88	60:40
2	CH_2CMe_3	90	85:15	86	54:46
3	CH_2Ph	94	80:20	89	50:50
4	Ph	89	80:20	78	70:30
5		79	75:25	84	43:57 (35:65)[b]
6		88	65:35	82	50:50
7		80	70:30	83	45:55
8		90	100:0		

[a] Isolated yield. The ratio of **5**/**6** was determined by ^1H NMR analysis of the reaction mixture. [b] $EtAlCl_2$ was used in place of $BF_3{\cdot}OEt_2$ as the Lewis acid.

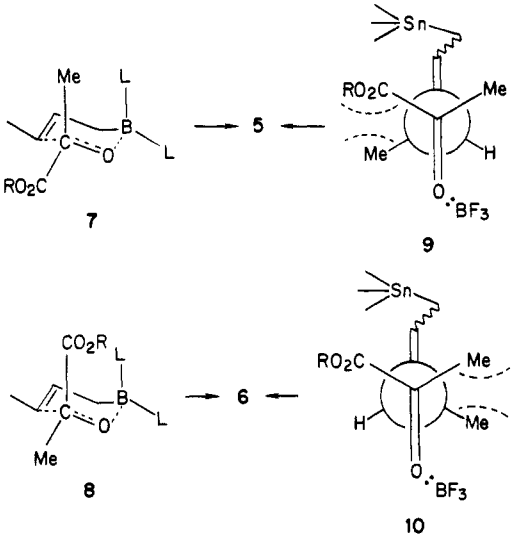
Reaction of α-Trimethylsilyl- and α-Trimethylstannyl-Substituted Crotyl-9-BBN (11). We have already reported that the threo selectivity in the reaction of **11** with aldehydes is extremely enhanced in comparison with that of crotyl-9-BBN itself owing to the 1,3-diaxial repulsion between the α-substitutents (Me_3Si or Me_3Sn) and the methyl group of crotyl unit in the chair transition state.[8,9] Actually, even methyl pyruvate gave the threo-cis isomer **12b** as a single product in 60% yield from the reaction of **11b** (eq 3). Unfortunately, the reaction of **11a**



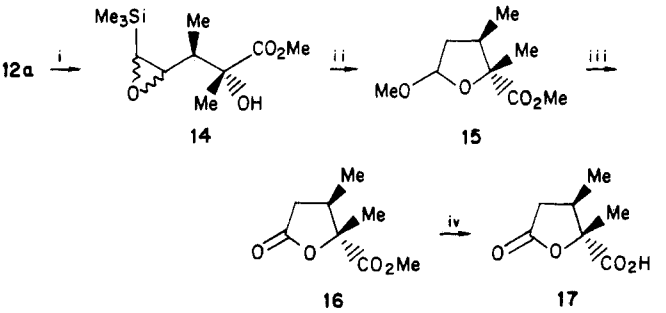
was accompanied by the formation of the α-adduct **13a** (**12a**/**13a** = 63/37). The threo-cis adduct **12a** was easily separated from **13a** by silica gel column chromatography. Protodesilylation or protodestannylation of **12** followed by hydrolysis produced **5** (R = H). The reaction products of Table I were converted into the corresponding acids by hydrolysis, and thus those stereochemistries were correlated to the stereochemistry of **12**.

The threo-cis isomer **12a** was converted into *cis*-crobarbatic acid methyl ester (**16**) via the procedure of Magnus[10] (Scheme II). The usual hydrolysis produced

Scheme I

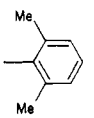
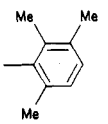


Scheme II[a]



[a] (i) MCPBA–CH_2Cl_2, 95%; (ii) $BF_3{\cdot}OEt_2$–MeOH, 90%; (iii) CrO_3–H_2SO_4, acetone, 80%; (iv) LiOH, MeOH–H_2O, 64%.

Table II. Reaction of 18 with 3

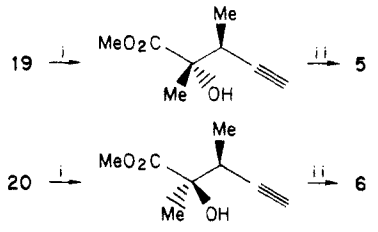
entry	3, R	18	temp, °C	isomer ratio[a] 19:20	total yield,[a] %
1	Me	18a	−78	15:85	93
2	Me		−20	23:77	93[b]
3	Me		0 → 25	27:73	86[c]
4	Me	18b	−78	15:85	95
5	Me		0	17:83	95
6	Et	18a	−78	24:76	92
7	Et	18b	−78	25:75	90
8	CH_2CMe_3	18a	−78	24:76	90
9	Ph		−78	39:61	88
10			−78	50:50	80
11			−78	50:50	82

[a] Isolated yield. The isomer ratio was determined by ^1H NMR spectroscopy and GLPC analysis. [b] Partial ester exchange from methyl to isopropyl was observed. [c] The ester group was completely exchanged.

the corresponding acid **17**. The structure of **16** was determined by comparison with an authentic material prepared with the literature procedure (trans/cis = 10/1).[11] Since the synthetic procedure for the trans isomer is

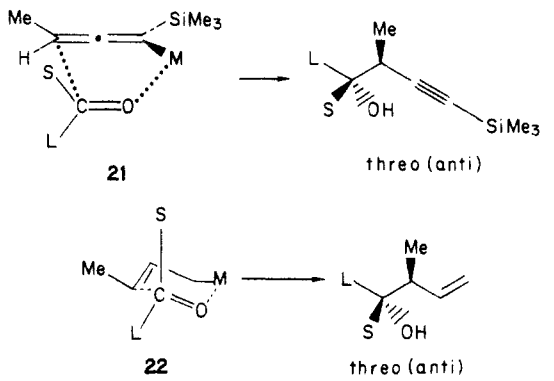
(8) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 3229.
(9) See also: Tsai, D. J. S.; Matteson,D. S. *Organometallics* **1983**, *2*, 236. Midland, M. M.; Preston, S. B. *J. Am. Chem. Soc.* **1982**, *104*, 2330. Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 993.
(10) Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 5004.
(11) (a) Bradbury, R. B.; Masamune, S. *J. Am. Chem. Soc.* **1959**, 81, 5201. (b) Ref 4a.

Scheme III[a]



[a] (i) NaOMe–MeOH; (ii) H_2, catalyst Pd–$BaSO_4$.

Scheme IV



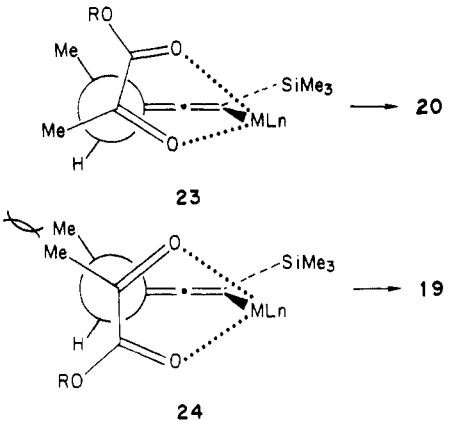
well-known,[11] both isomers of crobarbatic acid are now available.

Reaction of Allenic Organometallic Compounds (18). The reaction of **18** with **3** was examined and the results are summarized in Table II. In contrast with crotylorganometallic reagents, the allenic derivatives[12] gave the erythro (syn) isomer **20** predominantly. Although the ester group exchange was observed at higher reaction temperature (entries 2 and 3), the reaction at −78 °C prevented such an exchange. Further, the stereoselectivity was somewhat higher at −78 °C (entries 1,3 and 4,5). Both titanium (**18a**) and boron (**18b**) reagents[13] produced similar erythro selectivity (entries 1 vs. 4 and 6 vs. 7). Quite interestingly, with increase of the steric bulk of R, the erythro selectivity decreases and finally both isomers are produced in 1:1 ratio at entries 10 and 11.

The structure of **19** and **20** was determined as follows (Scheme III). Trimethylsilyl group of **19** and **20** was removed with NaOMe–MeOH. The resulting acetylenic derivative was reduced to the corresponding homoallyl alcohol (**5** and **6**) with Lindlar catalyst. These homoallyl alcohols were compared with authentic samples prepared previously.

Generally speaking, the diastereoselectivity trend exhibited in the reaction of **18** with ordinary carbonyl compounds is identical with the trend in the reaction of (*E*)-2-butenylmetallic compounds (M = B, Ti, Zr, ...).[14]

Scheme V



This is a reasonable conclusion when the two types of cyclic six-membered transition states (**21** and **22**) are taken into consideration (Scheme IV). In the reaction of **18**, **21** is a stabilized conformation in which Me favors the S (small) group and H favors the L (large) group.[12] In the reaction of (*E*)-2-butenylorganometallics, L goes to the equatorial position and S goes to the axial position (**22**).[2a,b]

As mentioned in the reaction of **4a** with **3**, S of **22** corresponds to Me and L corresponds to CO_2R (Scheme I). Therefore, at the outset of this investigation, we anticipated that the reaction of **18** would produce **19** predominantly, but the reverse was the case as shown in Table II. A possible explanation for this unexpected result is given in Scheme V. The metal (MLn) can coordinate to both carbonyl groups of **3**, and hence in the transition state the carbonyl group must somewhat rotate from the originally proposed position for the ordinary aldehydes (Scheme IV, **21**).[15] In such models (**23** and **24**), the steric interaction between two methyl groups destabilizes **24** which produces **19**. Therefore, the erythro isomer is predominantly produced in entries 1–9. With increase of the steric bulk of R, the steric repulsion between Me and OR groups destabilizes **23**, which gives **20**.

In conclusion, we are now in a position to synthesize both isomers in a diastereodivergent way by a proper choice of reagents, either allylic or allenic organometallic compounds. This method may provide an useful approach for the synthesis of naturally occurring tertiary alcohols such as pyrrolizidine alkaloids and related compounds.

Experimental Section

General information concerning instrumentation and materials is described previously.[16] The reagents **4b**,[7] **11**,[8] and **18**[12] were prepared by the literature procedures. Methyl and ethyl pyruvates were purchased from Tokyo Kasei Co. LTD. Neopentyl and benzyl pyruvates were prepared according to the general procedure reported previously.[17] **Neopentyl pyruvate**:[18] bp 100 °C (15 mmHg; Kugelrohr); ^{1}H NMR (CCl_4) δ 0.99 (9 H, s), 2.41 (3 H, s), 3.84 (2 H, s); IR (neat, cm^{-1}) 1140, 1730, 1750, 2900; mass spectrum, *m/e* 158 (M^+). **Benzyl pyruvate**:[18] bp 63 °C (0.5 mmhg; Kugelrohr); ^{1}H NMR (CCl_4) δ 2.24 (3 H, s), 5.09 (2 H, s), 7.28 (5 H, s); IR (CCl_4, cm^{-1}) 1130, 1290, 1730, 1750, mass spectrum, *m/e* 178 (M^+). Phenyl, 3,5-dimethylphenyl, 2,6-dimethylphenyl, and 2,3,6-trimethylphenyl pyruvates were prepared

(12) (a) "The Chemistry of the Carbon–Carbon Triple Bond"; Patai, S., Ed.; Wiley: New York, 1978. (b) "The Chemistry of Ketenes, Allenes, and Related Compounds"; Patai, S., Ed.; Wiley: New York, 1980. (c) Brandsma, L.; Verkruijsse, H. D. "Synthesis of Acetylenes, Allenes and Cumulenes"; Elsevier: Amsterdam, 1981. (d) "The Chemistry of Allenes"; Landor, S. R., Ed.; Academic Press: London, 1982; Vol. 1–3. (e) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768. (f) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667. (g) Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565. (h) Yamamoto, Y.; Ito, W.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1984**, 1004. (i) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376. (j) Nikam, S. S.; Wang, K. K. *Ibid.* **1985**, *50*, 2193.

(13) For titanium reagents, see: (a) Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1. (b) Seebach, D. *Mod. Synth. Methods* **1983**, *3*, 216.

(14) This rule of thumb is not applicable to the imine reaction (ref 12h).

(15) A referee points out that the distances between the carbonyl oxygens and the metal center would appear to be too long for an appreciable attractive interaction if the proximity of the reactive centers is retained.

(16) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969.

(17) "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. 3, p 610.

(18) "Dictionary of Organic Compounds"; Maruzen: Tokyo, 1965; Vol. 5, p 2829.

according to Hassner's procedure.[19] Pyruvic acid (10 mmol), phenol (10 mmol), and pyridine (10 mmol) were dissolved in 30 mL of dry CH_2Cl_2. To this solution was added a solution of dicyclohexylcarbodiimide (11 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The ratio of phenol to ester was monitored by GLPC (DC 550, 5%, 3 m, 160 °C). White precipitates were filtered off and the product was purified by a short column of silica gel. **Phenyl pyruvate**: 70% yield; mp 73–73.5 °C (colorless needles recrystallized from hexane–CH_2Cl_2); ^1H NMR (CCl_4) δ 2.62 (3 H, s), 7.1–7.6 (5 H, m); IR (KBr, cm^{-1}) 1120, 1590, 1720, 1740; mass spectrum, m/e 164 (M^+). Anal. ($C_9H_8O_3$) C, H. **2,6-Dimethylphenyl pyruvate** was prepared similarly, but the reaction was very slow in comparison with the case of phenyl pyruvate. Therefore, 0.05 equiv of *p*-(*N*,*N*-dimethylamino)pyridine (DMAP) was added and 1.5 equiv of pyruvic acid was used.[19] The desired ester was obtained in 75% yield: bp 95 °C (1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ 2.09 (6 H, s), 2.44 (3 H, s), 6.94 (3 H, s); IR (neat, cm^{-1}) 1120, 1160, 1730, 1760; mass spectrum, m/e 192 (M^+). Anal. ($C_{11}H_{12}O_3$) C, H. **3,5-Dimethylphenyl pyruvate** was prepared as described above: bp 95 °C (1 mmHg; Kugelrohr); 75% yield; ^1H NMR (CCl_4) δ 2.22 (6 H, s), 2.37 (3 H, s), 6.64 (2 H, s), 6.72 (1 H, s); IR (CCl_4, cm^{-1}) 1120, 1160, 1725, 1760; mass spectrum, m/e 192 (M^+). Anal. ($C_{11}H_{12}O_3$) C, H. **2,3,6-Trimethylphenyl pyruvate**: bp 100 °C (1 mmHg; Kugelrohr); 70% yield: ^1H NMR (CCl_4) δ 1.95 (3 H, s), 2.03 (3 H, s), 2.18 (3 H, s), 2.41 (3 H, s), 6.87 (2 H, s); IR (CCl_4, cm^{-1}) 1120, 1160, 1725, 1760; mass spectrum, m/e 206 (M^+). Anal. ($C_{12}H_{14}O_3$) C, H. **2,6-Di-*tert*-butyl-4-methylphenyl pyruvate** could not be prepared by the above method, and thus Heathcock's procedure was employed.[20] Pyruvyl chloride was prepared according to the literature procedure.[21] To a solution of 10 mmol of 2,6-di-*tert*-butyl-4-methylphenol dissolved in dry THF (15 mL) was added a solution of 11 mmol of BuLi in hexane at 0 °C under N_2. After a few minutes, pyruvyl chloride (15 mmol) was added, and the mixture was kept at room temperature for 24 h. A mixture of the ester and the phenol was obtained in a ratio of 1:10. The product was purified by a column chromatography on silica gel using hexane/ether (15:1) as eluent: R_f of the ester was 0.9, while that of the phenol was 1.0. The desired ester was obtained in 8% yield:[22] mp 72–73 °C (recrystallized from hexane); ^1H NMR (CCl_4) δ 1.26 (18 H, s), 2.31 (3 H, s), 2.49 (3 H, s), 6.98 (2 H, s); IR (CCl_4, cm^{-1}) 1120, 1180, 1595, 1735, 1760; mass spectrum, m/e 290 (M^+). Anal ($C_{18}H_{26}O_3$) C, H.

Reaction of 4a. The following procedure for the synthesis of methyl 2,3-dimethyl-2-hydroxy-4-pentenoate is representative. To a solution of 1 mmol of methyl pyruvate (0.091 mL) dissolved in 5 mL of dry ether was added 1.1 mmol of **4a** (0.19 mL) under N_2 at −76 °C. After 30 min, the reaction mixture was allowed to warm to 0 °C. The reaction was quenched with 1 mL of MeOH and 2 mmol of monoethanolamine (0.12 mL). The solvent was removed under vacuum, and then 15 mL of hexane was added. The resulting viscous yellow oil (or precipitates) was washed several times with hexane. The homoallyl alcohol was purified by using a short column of silica gel and hexane–ether (15 : 1) as eluent.

Reaction of 4b. To a solution of 1 mmol of methyl pyruvate dissolved in 5 mL of dry CH_2Cl_2 was added 2 mmol of $BF_3{\cdot}OEt_2$ (0.26 mL) at −76 °C under N_2. Subsequently, 1 mmol of **4b** (0.40 mL) was added, and the reaction mixture was allowed to warm to 0 °C. The reaction was quenched with aqueous NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and condensed. The homoallyl alcohol was purified as described above.

Methyl 2,3-dimethyl-2-hydroxy-4-pentenoate: bp 100 °C (20 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [threo isomer] 1.03 (3 H, d, J = 7 Hz), 1.30 (3 H, s), 2.2–2.6 (1 H, m), 3.0 (1 H, s), 3.71 (3 H, s), 4.8–5.2 (2 H, m), 5.5–6.0 (1 H, m), [erythro isomer] 0.89 (3 H, d, J = 7 Hz), 1.25 (3 H, s), 2.2–2.6 (1 H, m), 3.0 (1 H, m), 3.76 (3 H, s), 4.8–5.2 (2 H, m), 5.5–6.0 (1 H, m); IR (CCl_4, cm^{-1}) 915, 980, 1175, 1250, 1730, 2980, 3530; mass spectrum, m/e 158 (M^+). Anal. ($C_8H_{14}O_3$) C, H.

Neopentyl 2,3-dimethyl-2-hydroxy-4-pentenoate: bp 100 °C (2 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [threo isomer] 0.96 (9 H, s), 1.03 (3 H, d, J = 7 Hz), 1.31 (3 H, s), 2.2–2.6 (1 H, m), 3.16 (1 H, s), 3.64 (1 H, d, J = 10 Hz), 3.88 (1 H, d, J = 10 Hz), 4.8–5.1 (2 H, m), 5.5–5.9 (1 H, m), [erythro isomer] 0.92 (3 H, d, J = 7 Hz), 0.96 (9 H, s), 1.29 (3 H, s), 2.2–2.6 (1 H, m), 3.16 (1 H, s), 3.64 (1 H, d, J = 10 Hz), 3.88 (1 H, d, J = 10 Hz), 4.8–5.1 (2 H, m), 5.5–5.9 (1 H, m); IR (CCl_4, cm^{-1}) 910, 980, 1170, 1250, 1730, 2960, 3520; mass spectrum, m/e 214 (M^+). Anal. ($C_{12}H_{22}O_3$) C, H.

Benzyl 2,3-dimethyl-2-hydroxy-4-pentenoate: bp 100 °C (1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [threo isomer] 1.00 (3 H, d, J = 7.5 Hz), 1.29 (3 H, s), 2.41 (1 H, m), 3.22 (1 H, s), 5.00 (2 H, s), 4.64–5.08 (2 H, m), 5.40–5.84 (1 H, m), 7.22 (5 H, s), [erythro isomer] 0.86 (3 H, d, J = 7.5 Hz), 1.26 (3 H, s), 2.41 (1 H, m), 3.22 (1 H, s), 5.00 (2 H, s), 4.64–5.08 (2 H, m), 5.40–5.84 (1 H, m), 7.22 (5 H, s); IR (CCl_4, cm^{-1}) 915, 1000, 1175, 1250, 1730, 2980, 3520; mass spectrum, m/e 234 (M^+). Anal. ($C_{14}H_{18}O_3$) C, H.

Phenyl 2,3-dimethyl-2-hydroxy-4-pentenoate: mp 78–80 °C (white needles); ^1H NMR (CCl_4) δ [threo isomer] 1.13 (3 H, d, J = 7 Hz), 1.47 (3 H, s), 2.4–2.8 (1 H, s), 3.0 (1 H, s), 4.9–5.2 (2 H, m), 5.5–6.0 (1 H, m), 6.9–7.5 (5 H, m), [erythro isomer] 1.06 (3 H, d, J = 7 Hz), 1.43 (3 H, s), 2.4–2.8 (1 H, m), 3.0 (1 H, s), 4.9–5.2 (2 H, m), 5.5–6.0 (1 H, m), 6.9–7.5 (5 H, m); IR (CCl_4, cm^{-1}) 920, 980, 1190, 1750, 2920, 3400; mass spectrum, m/e 220 (M^+). Anal. ($C_{13}H_{16}O_3$) C, H.

2,6-Dimethylphenyl 2,3-dimethyl-2-hydroxy-4-pentenoate: bp 130 °C (1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [threo isomer] 1.15 (3 H, d, J = 7 Hz), 1.50 (3 H, s), 2.08 (6 H, s), 2.4–2.8 (1 H, m), 3.4 (1 H, s), 4.9–5.2 (2 H, m), 5.7–6.2 (1 H, m), 6.94 (3 H, s), [erythro isomer] 1.12 (3 H, d, J = 7 Hz), 1.48 (3 H, s), 2.08 (6 H, s), 2.4–2.8 (1 H, m), 3.4 (1 H, s), 4.9–5.2 (2 H, m), 5.7–6.2 (1 H, m), 6.94 (3 H, s); IR (CCl_4, cm^{-1}) 920, 1000, 1170, 1240, 1750, 2940, 3450; mass spectrum, m/e 248 (M^+). Anal. ($C_{15}H_{20}O_3$) C, H.

3,5-Dimethylphenyl 2,3-dimethyl-2-hydroxy-4-pentenoate: bp 130 °C (1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [threo isomer] 1.11 (3 H, d, J = 7 Hz), 1.42 (3 H, s), 2.28 (6 H, s), 2.4–2.7 (1 H, m), 2.84 (1 H, s), 4.96–5.22 (2 H, m), 5.60–6.04 (1 H, m), 6.58 (2 H, s), 6.75 (1 H, s), [erythro isomer] 1.02 (3 H, d, J = 7 Hz), 1.38 (3 H, s), 2.28 (6 H, s), 2.4–2.7 (1 H, m), 2.84 (1 H, s), 4.96–5.22 (2 H, m), 5.60–6.04 (1 H, m), 6.58 (2 H, s), 6.75 (1 H, s); IR (CCl_4, cm^{-1}) 920, 990, 1190, 1750, 2940, 3460; mass spectrum, m/e 248 (M^+). Anal. ($C_{15}H_{20}O_3$) C, H.

2,3,6-Trimethylphenyl 2,3-Dimethyl-2-hydroxy-4-pentenoate: bp 100 °C (0.1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [threo isomer] 1.13 (3 H, d, J = 7 Hz), 1.48 (3 H, s), 1.94 (3 H, s), 2.03 (3 H, s), 2.18 (3 H, s), 2.5–2.8 (1 H, m), 3.04 (1 H, s), 4.96–5.20 (2 H, m), 5.6–6.2 (1 H, m), 6.77 (2 H, s), [erythro isomer] 1.06 (3 H, d, J = 7 Hz), 1.46 (3 H, s), 1.94 (3 H, s), 2.03 (3 H, s), 2.18 (3 H, s), 2.5–2.8 (1 H, m), 3.08 (1 H, s), 4.96–5.20 (2 H, m), 5.6–6.2 (1 H, m), 6.80 (2 H, s); IR (CCl_4, cm^{-1}) 920, 995, 1170, 1240, 1750, 2940, 3450; mass spectrum, m/e 262 (M^+). Anal. ($C_{16}H_{22}O_3$) C, H.

2,6-Di-*tert*-butyl-4-methylphenyl 2,3-dimethyl-2-hydroxy-4-pentenoate: mp 66–67 °C; ^1H NMR (CCl_4) δ [threo isomer] 1.12 (3 H, d, J = 7 Hz), 1.29 (18 H, s), 1.45 (3 H, s), 2.28 (3 H, s), 2.34 (1 H, s), 2.5–2.9 (1 H, m), 5.0–5.3 (2 H, m), 5.8–6.2 (1 H, m), 7.01 (2 H, s); IR (CCl_4, cm^{-1}) 910, 990, 1170, 1240, 1750, 2940, 3450; mass spectrum, m/e 346 (M^+). Anal. ($C_{22}H_{34}O_3$) C, H. The linear isomer, 2,6-di-*tert*-butyl-4-methylphenyl 2-methyl-2-hydroxy-4-hexenoate, was accompanied in the reaction of **4b** with 2,6-di-*tert*-butyl-4-methylphenyl pyruvate: bp 130 °C (0.1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ 1.30 (18 H, s), 1.49 (3 H, s), 1.70 (3 H, d, J = 6 Hz), 2.29 (3 H, s), 2.51 (1 H, s), 2.5–2.8 (2 H, m), 5.2–5.7 (2 H, m), 7.00 (2 H, s); IR (CCl_4, cm^{-1}) 965, 1170, 1750; mass spectrum, exact mass calcd for $C_{22}H_{34}O_3$ m/z 346.2508, found m/z 346.2501. The ratio of the branched/linear homoallyl alcohol was ca. 60/40.

Hydrolysis of 5 and 6. The adducts in entries 1–7 of Table I were converted into the corresponding acids (erythro and threo)

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by the reported procedure.[21] The ^1H NMR data of the acid thus obtained were compared with the reported data.[23] The hydrolysis of the 2,6-di-*tert*-butyl-4-methylphenyl derivative was very difficult, and hence the stereochemistry could not determined by the hydrolysis method. The ester was reduced to 2,3-dimethyl-4-pentene-1,2-diol with $(i\text{-Bu})_2AlH$ (4 equiv) at 0 °C in hexane according to the usual procedure; ^1H NMR ($CDCl_3$) δ 0.84–1.04 (6 H, br s), 2.1–2.5 (1 H, m), 3.0–4.2 (4 H, br), 4.8–5.1 (2 H, m), 5.4–6.1 (1 H, m); IR ($CDCl_3$) cm^{-1}) 920, 1000, 3500; exact mass calcd for $C_7H_{14}O_2$ m/z 130.0994, found m/z 130.0990. This diol was compared with the diols obtained from the methyl derivatives (**5** and **6**, R = Me).

Reaction of 11. The same procedure as described in the reaction of **4a** was employed. When pyridine or *n*-BuLi was used as an additive,[8] the yield of **13a** increased. The similar workup gave **12a** + **13a** in 65% yield and **12b** in 60% yield. **Methyl 2,3-dimethyl-2-hydroxy-5-(trimethylsilyl)-4-pentenoate (12a)**: ^1H NMR (CCl_4) δ 0.09 (9 H, s), 0.97 (3 H, d, J = 7 Hz), 1.30 (3 H, s), 2.3–2.6 (1 H, m), 3.06 (1 H, s), 3.68 (3 H, s), 5.39 (1 H, d, J = 14 Hz), 6.21 (1 H, dd, J = 10, 14 Hz); IR (CCl_4, cm^{-1}) 840, 1210, 1245, 1725, 2950, 3520; exact mass calcd for $C_{11}H_{22}O_3Si$ m/z 230.1338 found m/z 230.1332. To dry CH_3CN saturated with HCl was added **12a** at room temperature. After 10 h, the reaction was quenched with dry MeOH, and the mixture was neutralized. The usual workup gave **5** (R = Me). During this desilylation process, the methyl ester was partially hydrolyzed to give the corresponding threo acid. The α-isomer **13a** was separated by using hexane/ether (15:1) as eluent: ^1H NMR (CCl_4) δ 0.08 (9 H, s), 1.42 (3 H, s), 1.56 (3 H, d, J = 6 Hz), 2.2–2.4 (1 H, m), 3.23 (1 H, s), 3.64 (3 H, s), 5.2–5.5 (2 H, m); IR (CCl_4, cm^{-1}) 840, 860, 1210, 1245, 1725, 2950, 3015, 3520; exact mass calcd for $C_{11}H_{22}O_3Si$ m/z 230.1338 found m/z 230.1344. **Methyl 2,3-dimethyl-2-hydroxy-5-(trimethylstannyl)-4-pentenoate (12b)**: ^1H NMR (CCl_4) δ −0.05 (9 H, s), 0.79 (3 H, d, J = 7 Hz), 1.11 (3 H, s), 1.9–2.3 (1 H, m), 3.25 (1 H, s), 3.45 (3 H, s), 5.55 (1 H, d, J = 12 Hz), 6.19 (1 H, dd, J = 10, 12 Hz); IR (CCl_4, cm^{-1}) 835, 1250, 1725, 2920, 3520; exact mass calcd for $C_{11}H_{22}O_3Sn$ m/z 322.0591, found m/z 322.0600. To a solution of 0.117 g of **12b** dissolved in ether was added 2 equiv of $BF_3{\cdot}OEt_2$ and 1 equiv of ethyl chloroformate at room temperature. After 10 h, the reaction was quenched with brine. The usual workup gave **5** (R = Me) in nearly quantitative yield.

Synthesis of 16 and 17. The epoxidation of **12a** gave **14** in 95% yield;[10] ^1H NMR (CCl_4) δ [major isomer] 0.00 (9 H, s), 0.92 (3 H, d, J = 8 Hz), 1.20 (3 H, s), 1.3–1.6 (1 H, m), 1.9–2.1 (1 H, m), 2.8–3.1 (1 H, m), 3.63 (3 H, s), 3.6 (1 H, br), [minor isomer] 0.00 (9 H, s), 0.92 (3 H, d, J = 8 Hz), 1.26 (3 H, s), 1.3–1.6 (1 H, m), 1.9–2.1 (1 H, m), 2.8–3.1 (1 H, m), 3.6 (1 H, br), 3.65 (3 H, s); IR (CCl_4, cm^{-1}) 830, 1210, 1245, 1720, 2950, 3015, 3500; exact mass calcd for $C_{11}H_{22}O_4Si$ m/z 246.1287, found m/z 246.1282. Without further purification, **14** was converted into **15** in 90% yield according to the literature procedure:[10] ^1H NMR (CCl_4) δ [major isomer] 0.94 (3 H, d, J = 8 Hz), 1.10 (3 H, s), 1.3–2.8 (3 H, m), 3.18 (3 H, s), 3.57 (3 H, s), 4.73 (1 H, d, J = 4 Hz), [minor isomer] 0.95 (3 H, d, J = 8 Hz), 1.25 (3 H, s), 1.3–2.8 (3 H, m), 3.22 (3 H, s), 3.57 (3 H, s), 4.97 (1 H, dd, J = 4, 6 Hz); IR (CCl_4, cm^{-1}) 1055, 1120, 1220, 1735, 2960; exact mass calcd for $C_9H_{16}O_4$ m/z 188.1048, found m/z 188.1054. The Jones oxidation[10] of **15** gave **16** in 80% yield: ^1H NMR (CCl_4) δ 1.15 (3 H, d, J = 7 Hz), 1.51 (3 H, s), 2.0–2.4 (1 H, m), 2.5–3.0 (2 H, m), 3.77 (3 H, s); IR (CCl_4, cm^{-1}) 1125, 1740, 1785, 2960; exact mass calcd for $C_8H_{12}O_4$ m/z 172.0735, found m/z 172.0742.

To a mixture of 10 mL of MeOH and 10 mL of saturated aqueous LiOH solution was added 0.1 mmol of **16**, and the mixture was stirred for 2 days at room temperature. The mixture was acidified with 5% HCl solution and saturated with NaCl. The usual workup gave **17** (*cis*-crobarbatic acid) in 60% yield: ^1H NMR (CCl_4) δ 1.14 (3 H, d, J = 7 Hz), 1.49 (3 H, s), 2.0–2.4 (1 H, m), 2.6–3.0 (2 H, m), 10.1 (1 H, br). An authentic *trans*-crobarbatic acid was prepared according to the literature:[11] ^1H NMR (CCl_4) δ 1.14 (3 H, br s), 1.64 (3 H, s), 2.3–2.9 (3 H, m), 10.28 (1 H, br). The literature procedure gave a mixture of trans and cis isomers in a ratio of 10:1. Further, *trans*-crobarbatic acid methyl ester was prepared: ^1H NMR (CCl_4) δ 1.05 (3 H, d, J = 6.5 Hz), 1.60 (3 H, s), 2.2–2.8 (3 H, m), 3.82 (3 H, s). Both methyl esters (trans and **16**) were analyzed by GLPC (DC 550, 5%, 3 m, 150 °C); the retention time of the trans isomer was 6.9 min, while that of **16** was 8.2 min.

Reaction of 18. To a solution of 1 mmol (0.1 mL) of 1-(trimethylsilyl)-1-butyne[24] dissolved in 5 mL of dry THF was added 1.2 equiv of *t*-BuLi under N_2 at 0 °C. The resulting pale yellow solution was stirred at 0 °C for 1 h, and then cooled to −78 °C. Subsequently, 1.1 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ (0.34 mL) or $B(OMe)_3$ (0.13 mL) was added,[12e] and the mixture was stirred for 10 min. To this solution was added 1 mmol of pyruvates at −78 °C. After being stirred for 3 h at this temperature, the reaction was quenched with MeOH and water. The reaction mixture was extracted with ether, dried over anhydrous $MgSO_4$, and condensed. Chromatography of the resulting oil on a silica gel column (10 : 1 hexane:ether) gave the desired product. The other isomer, the allenic derivative, was not obtained.

Methyl 2,3-dimethyl-2-hydroxy-5-(trimethylsilyl)-4-pentynoate: bp 90 °C (2 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [erythro isomer] 0.14 (9 H, s), 1.09 (3 H, d, J = 7 Hz), 1.41 (3 H, s), 2.72 (1 H, q, J = 7 Hz), 3.03 (1 H, br), 3.77 (3 H, s), [threo isomer] 0.11 (9 H, s), 1.16 (3 H, d, J = 7 Hz), 1.32 (3 H, s), 2.69 (1 H, q, J = 7 Hz), 3.03 (1 H, br), 3.71 (3 H, s); IR (CCl_4, cm^{-1}) 840, 1110, 1180, 1250, 1380, 1450, 1720, 2160, 2990, 3520; exact mass calcd for $C_{11}H_{20}O_3Si$ m/z 228.1182, found m/z 228.1188.

Ethyl 2,3-dimethyl-2-hydroxy-5-(trimethylsilyl)-4-pentynoate: bp 100 °C (2 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [erythro isomer] 0.14 (9 H, s), 1.10 (3 H, d, J = 6 Hz), 1.31 (3 H, t, J = 7 Hz), 1.41 (3 H, s), 2.7 (1 H, m), 2.9–3.2 (1 H, br), 4.20 (2 H, q, J = 7 Hz), [threo isomer] 0.11 (9 H, s), 1.17 (3 H, d, J = 6 Hz), 1.31 (3 H, t, J = 7 Hz), 1.32 (3 H, s), 2.7 (1 H, m), 2.9–3.2 (1 H, br), 4.20 (2 H, q, J = 7 Hz); IR (CCl_4, cm^{-1}) 1720, 3500; exact mass calcd for $C_{12}H_{22}O_3Si$ m/z 242.1338, found m/z 242.1330.

Neopentyl 2,3-dimethyl-2-hydroxy-5-(trimethylsilyl)-4-pentynoate: bp 130 °C (1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [erythro isomer] 0.14 (9 H, s), 0.96 (9 H, s), 1.10 (3 H, d, J = 6 Hz), 1.44 (3 H, s), 2.76 (1 H, q, J = 6 Hz), 3.82 (3 H, m), [threo isomer] 0.11 (9 H, s), 0.97 (9 H, s), 1.16 (3 H, d, J = 6 Hz), 1.36 (3 H, s), 2.74 (1 H, q, J = 6 Hz), 3.82 (3 H, m); IR (CCl_4, cm^{-1}) 1720, 2165, 3520; exact mass calcd for $C_{15}H_{28}O_3Si$ m/z 284.1807, found 284.1814.

Phenyl 2,3-dimethyl-2-hydroxy-5-(trimethylsilyl)-4-pentynoate: bp 90 °C (0.1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [erythro isomer] 0.11 (9 H, s), 1.12 (3 H, d, J = 6 Hz), 1.36 (3 H, s), 2.77 (1 H, q, J = 6 Hz), 6.8 (3 H, m), 7.1 (2 H, m), [threo isomer] 0.11 (9 H, s), 1.26 (3 H, d, J = 6 Hz), 1.48 (3 H, s), 2.77 (1 H, q, J = 6 Hz), 6.8 (3 H, m), 7.1 (2 H, m); IR (CCl_4, cm^{-1}) 1725, 2160, 3500; exact mass calcd for $C_{16}H_{22}O_3Si$ m/z 290.1338, found m/z 290.1330. The ^1H NMR peak of OH was not observed.

2,6-Dimethylphenyl 2,3-dimethyl-2-hydroxy-5-(trimethylsilyl)-4-pentynoate: bp 110 °C (0.1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [erythro isomer] 0.15 (9 H, s), 1.31 (3 H, d, J = 7 Hz), 1.65 (3 H, s), 2.16 (6 H, s), 3.01 (1 H, q, J = 6 Hz), 3.10 (1 H, s), 7.00 (3 H, s), [threo isomer] 0.11 (9 H, s), 1.31 (3 H, d, J = 7 Hz), 1.57 (3 H, s), 2.19 (6 H, s), 3.01 (1 H, q, J = 6 Hz), 3.10 (1 H, s), 7.00 (3 H, s); IR (CCl_4, cm^{-1}) 1725, 2160, 3520; exact mass calcd for $C_{18}H_{26}O_3Si$ m/z 318.1651, found m/z 318.1664.

2,3,6-Trimethylphenyl 2,3-dimethyl-2-hydroxy-5-(trimethylsilyl)-4-pentynoate: bp 120 °C (0.1 mmHg; Kugelrohr); ^1H NMR (CCl_4) δ [erythro isomer] 0.18 (9 H, s), 1.32 (3 H, d, J = 7 Hz), 1.66 (3 H, s), 1.90 (3 H, s), 2.12 (3 H, s), 2.28 (3 H, s), 3.01 (1 H, q, J = 7 Hz), 3.11 (1 H, br), 6.88 (2 H, s), [threo isomer] 0.14 (9 H, s), 1.33 (3 H, d, J = 7 Hz), 1.65 (3 H, s), 1.92 (3 H, s), 2.14 (3 H, s), 2.28 (3 H, s), 3.01 (1 H, q, J = 7 Hz), 3.11 (1 H, br), 6.88 (2 H, s); IR (CCl_4, cm^{-1}) 1725, 2160, 3500; exact mass calcd for $C_{19}H_{28}O_3Si$ m/z 332.1807, found m/z 332.1814.

Desilylation and Reduction. To a solution of 0.2 mL of NaOMe (28% solution in MeOH) in 5 mL of THF was added dropwise 0.5 mmol of **19** (or **20**) dissolved in THF at room temperature. The mixture was stirred for 3 h, and then 10% H_2SO_4 (5 mL) was added. Ether was added and the organic layer was

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separated. The usual workup gave **methyl 2,3-dimethyl-2-hydroxy-4-pentynoate**: ^{1}H NMR (CCl_4) δ [erythro isomer] 1.12 (3 H, d, J = 7.5 Hz), 1.44 (3 H, s), 2.01 (1 H, m), 2.75 (1 H, q, J = 7.5 Hz), 3.03 (1 H, br), 3.78 (3 H, s), [threo isomer] 1.19 (3 H, d, J = 7.5 Hz), 1.35 (3 H, s), 2.01 (1 H, m), 2.76 (1 H, q, J = 7.5 Hz), 3.03 (1 H, br), 3.71 (3 H, s); IR (CCl_4, cm^{-1}) 1720, 2150, 3500; exact mass calcd for $C_8H_{12}O_3$ m/z 156.0786, found m/z 156.0777. The R group of **19** and **20** was converted to Me group during the desilylation step. The acetylenic ester was reduced with Lindler catalyst. To a solution of 20 mg of Pd–$BaSO_4$ dissolved in 5 mL of MeOH was added the ester (0.5 mmol) in MeOH. The usual hydrogenation gave **5** and **6** (R = Me).

Enantio- and Diastereoselectivity in the Periodate Oxidation of Sulfides Catalyzed by Bovine Serum Albumin. 2[1]

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The asymmetric oxidation of aliphatic, aromatic, and heterocyclic sulfides in the presence of a catalytic amount of bovine serum albumin (BSA) affords the corresponding sulfoxides with enantiomeric excess (ee) up to 80%. The diastereoselectivity of the process has also been examined in comparison with the enzymatic oxygenation with cytochrome P-450. Electronic and CD spectral data indicate that the sulfides are not tightly bound to BSA in the reaction conditions.

Natural and synthetic polypeptides have been recently used to promote asymmetric induction. In spite of the increasing availability of enzymes as chiral catalysts, nonenzymic catalytic asymmetric synthesis is still a powerful tool in organic chemistry. Almost enantioselective reactions have been performed, inter alia, in the cyanohydrin synthesis catalyzed by a synthetic cyclic dipeptide[2] and in the epoxidation of electron-poor olefins in the presence of poly(α-amino acids).[3]

On the other hand, natural globular proteins, which also present a chiral environment, have the unique property of specific binding sites for hydrophobic organic molecules. They are available in large quantity in a optically pure form, and this constitutes a big advantage with respect to synthetic polypeptides. Outstanding results have been reported by Whitesides[4] and Sugimoto[5] in the asymmetric hydrogenation of 2-acetamidoacrylic acid with a modified avidin and in the stereoselective oxidation of aromatic sulfides catalyzed by bovine serum albumin (BSA), respectively.

More recently the versatility of BSA as chiral catalyst has been emphasized by the enantioselective hydroxylation of alkenes[6] and in the Darzens condensation.[7]

Previously, we have shown that the asymmetric periodate oxidation of functionalized sulfides with BSA proceeds smoothly to give the corresponding sulfoxide with satisfactory optical purity.[1] In order to verify the generality of this type of asymmetric synthesis, we have now investigated the metaperiodate oxidation of aliphatic, aromatic, and heterocyclic sulfides. Furthermore it was interesting to establish the diastereoselectivity of the reaction and to compare it to that of enzymatic oxygenation with cytochrome P-450.[8]

The effect on the stereoselectivity of a number of variables such as (i) pH, (ii) the nature of the oxidizing agent, and (iii) the addition of denaturing agents has also been studied.

In this context it must be stressed that there are still several uncertainties in the understanding of the mechanism responsible for these asymmetric syntheses. An investigation of the electronic and CD spectra of BSA in the presence of the sulfides and the oxidizing agent was therefore undertaken to the end of establishing whether substrate binding to the protein occurs in the conditions employed for the catalytic oxidations.

The reactions were carried out by stirring at room temperature a heterogeneous mixture of substrate (1 mol) and $NaIO_4$ (2 mol) in the presence of BSA in a buffer solution (0.05 mol). In ancillary experiments with sulfides **4** and **10** we found that the use of lower amounts of BSA (0.02 mol) slowed down the reaction rate, affording the corresponding sulfoxides **18** and **24**, respectively, with comparable or lower enantioselectivity. On the other hand the use of a higher amount of BSA (0.1 mol) resulted in an increase of the chemical yields but in a lowering of the stereoselectivity.[1]

$$\underset{\textbf{1-14}}{RSR'} \xrightarrow[\text{BSA}]{\text{aqueous } NaIO_4} \underset{\textbf{15-28}}{RS^*(=O)R'}$$

The sulfides used were *tert*-butyl *n*-butyl sulfide (**1**), dodecyl methyl sulfide (**2**), mesityl phenyl sulfide (**3**), bis(*p*-tolylthio)methane (**4**), 1,3-dithiane (**5**), 2-methyl-2,3-dihydrobenzothiophene (**6**), 1-thiochroman (**7**), 2-methyl-1-thiochroman (**8**), *sec*-butyl *p*-tolyl sulfide (**9**),

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