Synthesis of Enantiomerically Enriched Homoallylic Alcohols and of 1,2-Dien-4-ols Using Chiral Tin(IV) Complexes Containing Diethyl Tartrate as an Auxiliary Ligand

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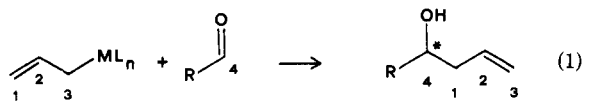
Chiral allylic tin(IV) complexes **3** are prepared by treatment of tin dichloride with 2 equiv of doubly deprotonated diethyl tartrate followed by addition of an allylic bromide. The reaction of **3** with aldehydes affords optically active homoallylic alcohols in 50–80% yield and in 40–60% ee. When applied to propargyl bromide this procedure leads to optically active 1,2-dien-4-ols, and when 2-carbethoxyallyl bromide is used chiral γ-substituted α-methylene-γ-butyrolactones can be easily obtained.

Homoallylic alcohols often get involved in organic synthesis as versatile intermediates, owing to the flexibility of both the alcohol group and the C=C double bond, which allow easy entries to a variety of bifunctionalized molecules. Particularly, it is worth mentioning the Pd(II)-catalyzed oxidation and the oxidative cleavage (e.g., ozonization) of the C=C bond which make homoallylic alcohols stable and convenient precursors of the less easily manageable and storable β-hydroxy carbonyl or carboxylic compounds. This interest, as a consequence, has urged on a lot of efforts aimed at working out regio- and stereocontrolled routes to homoallylic alcohols.

One of the most widely used aproaches relies on the addition of η^1-allylic metal complexes to carbonyl compounds according to general eq 1. Allylic complexes of



(1)

Sn(IV), Al, B, Ti(IV), Cr(III), Mg, Zn, Si, etc. have been used to this purpose.[1] The following features are worth mentioning: (i) the reaction is regioselective since it takes place with complete allylic inversion, and (ii) if a substituent is present on C-1, the relative stereochemistry of C-4 and C-1 centers is mainly controlled by the nature of the metal involved, and so a given diastereoisomer can be obtained simply by "tuning" on the appropriate metal.[2]

Moreover the continuing quest for improved asymmetric syntheses has also brought about the development of enantioselective processes leading to optically active homoallylic alcohols. In order to control the absolute configuration of the stereogenic C-4 hydroxylated center, chirality has to be placed in one or in both the reaction partners,[3] and in this second case we exploit a double asymmetric induction.[4]

In the literature examples it is reported that chirality is located (i) on the R group (Cram/anti-Cram selectivity[5]), (ii) on a chiral auxiliary group temporary added to the carbonyl group (e.g., chiral acetals[6]), (iii) on the metal ligands,[7] (iv) on the allylic group,[8] and, finally, (v) on the

(1) Tin: (a) Tagliavini, G. *Silicon, Germanium, Tin Lead Compds.* **1985**, *8*, 237. Aluminum: (b) Collum, D. B.; McDonald J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118. (c) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943. Boron: (d) Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966. (e) Hoffmann, R. W.; Metternich, R. *Liebigs Ann. Chem.* **1985**, 2390. (f) Hoffmann, R. W.; Kemper, B.; Metternich, T.; Lehmeier, T. *Liebigs Ann. Chem.* **1985**, 2246. (g) Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 1039. (h) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. (i) Roush, W. R.; Straub, J. A. *Tetrahedron Lett.* **1986**, *27*, 3349. (j) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. Titanium: (k) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31. (l) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421. (m) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441. Chromium: (n) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (o) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. (p) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343. (q) Mulzer, J.; deLasalle, P.; Freissler, A. *Liebigs Ann. Chem.* **1986**, 1152. Zinc: (r) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1983**, *48*, 4108. Silicon: (s) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. (t) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761. (u) Parnes, Z. N.; Bolestova, G. I. *Synthesis* **1984**, 991. Lithium and other metals: (v) Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932. (w) Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

(2) The diastereoselectivity of the addition of crotyl metal complexes to aldehydes in some cases reflects the geometry of the allylic moiety (B, Al, Sn), in other cases (Ti, Cr, Zr, Si, and Sn in the presence of Lewis acids) the reactions are threo- or erythroselective independently of the allyl group geometry. For a discussion, see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (b) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (c) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. (d) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311.

(3) (a) Hoffmann, R. W.; Endesfelder, A.; Zeiss, H.-J. *Carbohydr. Res.* **1983**, *123*, 320. (b) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (c) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (d) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316. (e) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 320. (f) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 953.

(4) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *29*, 1.

(5) (a) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. (c) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. (d) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879. (e) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (f) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. *Chem. Lett.* **1984**, *335*. (g) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. (h) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31. (i) Yamamoto, Y.; Taniguchi, K.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1429. (j) Yamamoto, Y.; Nishii, S.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1986**, 102. (k) Roush, W. R.; Adam, M. A.; Harris, D. J. *J. Org. Chem.* **1985**, *50*, 2000. (l) Roush, W. R.; Michaelides, M. R. *Tetrahedron Lett.* **1986**, *27*, 3353. (m) Williams, D. R.; Klingler, F. D. *Tetrahedron Lett.* **1987**, *28*, 869.

(6) (a) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (b) Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513. (c) Johnson, W. S.; Crackett, P. H.; Elliott, J. D. *Tetrahedron Lett.* **1984**, *25*, 3951. (d) Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 765. (e) Seebach, D.; Imwinkelried, R.; Stucky, G. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 178.

(7) Boron: (a) Herold, T.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 768. (b) Herold, T.; Schrott, U.; Hoffmann, R. W. *Chem. Ber.* **1981**, *114*, 359. (c) Hoffmann, R. W.; Herold, T. *Chem. Ber.* **1981**, *114*, 375. (d) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564. (e) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (f) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. Chromium: (g) Cazes, B.; Vernière, C.; Goré, J. *Synth. Commun.* **1983**, *13*, 73. Tin: (h) Otera, J.; Yoshinaga, Y.; Yamaji, T.; Yoshioka, T.; Kawasaki, Y. *Organometallics* **1985**, *4*, 1213. (i) Mukaiyama, T.; Minowa, N.; Oriyama, T.; Narasaka, K. *Chem. Lett.* **1986**, 97.

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Table I. Enantioselective Allylation of Benzaldehyde[a]

entry	$(RO_2CCH(OH))_2$, R[b]	reacn temp, °C	reacn time, h	tartrate/tin molar ratio	product yield,[c] %	ee,[d] %
1	C_2H_5	20	92	1/1	38	20
2	C_2H_5	20	23	1.5/1	54	40
3	C_2H_5	20	6	2/1	84	47
4	C_2H_5	0	17	2/1	82	62
5	i-C_3H_7	0	17	2/1	71	48
6	$[(CH_3)_2CH]_2CH$	0	17	2/1	61	42

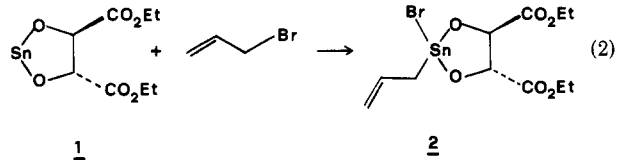
[a] The reactions are carried out on 10-mmol scale of $SnCl_2$. See Experimental Section. [b] All the esters quoted derive from (+)-(*R*,*R*)-tartaric acid. [c] Yields refer to pure 1-phenyl-3-buten-1-ol isolated by flash chromatography on silica gel. [d] Determined by optical rotation measurements. The product has the *S* configuration.

metal itself.[9]

Recently we reported some preliminary results concerning the use of chiral allylic tin(IV) complexes containing (+)-diethyl tartrate as an auxiliary ligand;[10] we now wish to go deeply to this reaction examining more widely its features.

Results and Discussion

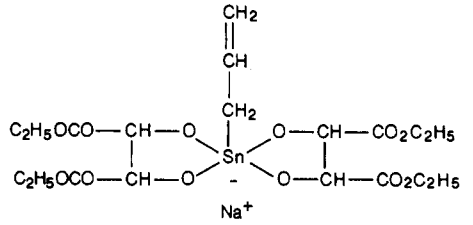
At the outset our plan was to prepare the allylic complex **2** by oxidative addition of tin(II)–diethyl tartrate **1** to allyl bromide[11] as shown in eq 2, in order to test the stereochemical outcome of condensation reactions with aldehydes. The tin complex **1** was in turn prepared by the



(2)

1 **2**

reaction between tin dichloride and 1 equiv of diethyl tartrate disodium salt in tetrahydrofuran (THF).[12] The reaction of **2** with benzaldehyde in tetrahydrofuran at room temperature gave rise to (*S*)-1-phenylbut-3-en-1-ol in 20% yield after 19 h and 40% yield after 92 h with a 20% ee (Table I, entry 1). Several attempts were made to improve the chemical and optical yields by changing the experimental conditions: we found that, while changing the temperature (20 to −40 °C), the solvent (dichloromethane; 1,2-dimethoxyethane), and the ester group (diisopropyl, bis(2,4-dimethyl-3-pentyl)) had neglegible effects, both the reaction rate and the enantioselectivity considerably increased when an excess of diethyl tartrate disodium salt was used with respect to tin dichloride. A typical procedure was as follows: to (*R*,*R*)-diethyl tartrate disodium salt, prepared as a white precipitate at 0 °C in THF under an inert atmosphere from the corresponding ester and 2 equiv of NaH, was added tin dichloride (0.5 equiv), causing a fast fluidization of the reaction mixture. After 30 min allyl bromide (1.5–2 equiv) was added, and the reaction mixture was stirred at 0 °C for 5 h.[13] Unfortunately we were not able to obtain single crystals of the allylic tin(IV) complex suitable for X-ray investigation; anyway, we tentatively suggest structure **3** as a likely arrangement of ligands around the tin atom.[14] In order to roughly evaluate the



3

yield of the oxidative addition step an aliquot of the reaction mixture was removed, the solvent and the excess of allyl bromide were distilled off under vacuum, and the ^1H NMR spectrum of the residue dissolved in hexadeuteriated dimethyl sulfoxide was recorded. On the basis of the integrals of the allylic (doublet at δ 2.1) and ethoxylic (CH_3CH_2O multiplet at δ 1.2) proton signals we could estimate a 80 ± 5% conversion, and this will also represent the maximum theoretical yield of the successive condensation reactions. Benzaldehyde (10% excess with respect to tin) was then added, and the reaction course was monitored by gas chromatography.

In Table I we collected the results obtained in condensation reactions of this complex with benzaldehyde when some experimental details are changed. As apparent from entries 2 and 3, reactions considerably speeded up when passing from the complex **2** to **3**. Particularly a virtual complete formation of the homoallylic alcohol is obtained in 6 h at 20 °C by using the complex **3**, and, at the same time, the product exhibited a two-fold enantiomeric excess. A further increase of the ee to 62% was achieved by car-

(8) Boron: (a) Hoffmann, R. W.; Landmann, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 437. (b) Hoffmann, R. W.; Dresely, S. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 189. (c) Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, *119*, 2013. (d) Midland, M. M.; Preston, S. B. *J. Am. Chem. Soc.* **1982**, *104*, 2330. (e) Wuts, R. G. M.; Bigelow, S. S. *J. Chem. Soc., Chem. Commun.* **1984**, 736. Silicon: (f) Hayashi, T.; Konishi, M.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 281. (g) Mikami, K.; Maeda, T.; Kishi, N.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 5151. Tin: (h) Jephcote, V. J.; Pratt, A. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1984**, 800. Lithium: (i) Roder, H.; Helmchen, G.; Peters, E. M.; Peters, K.; von Schnering, M.-G. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 898. (j) Hoppe, D.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 160.

(9) Reetz, M. T.; Kyung, S.-H.; Westermann, J. *Organometallics* **1984**, *3*, 1716.

(10) Boldrini, G. P.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1986**, 685.

(11) Concerning preparations of allylic tin(IV) complexes via oxidative addition of tin(II) species to allylic halides, see, for example: (a) Shoda, S.; Mukaiyama, T. *Chem. Lett.* **1981**, 723. (b) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 1109. (c) Mukaiyama, T.; Yamaguchi, M.; Kato, J. *Chem. Lett.* **1981**, 1505. (d) Nokami, J.; Tamaoka, T.; Ogawa, H.; Wakabayashi, S. *Chem. Lett.* **1986**, 541.

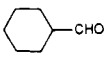
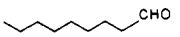
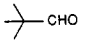
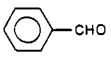
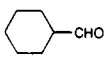
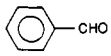
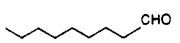
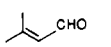
(12) The complex **1** was also prepared according to the general procedure reported by: Honnick, W. D.; Zuckerman, J. J. *Inorg. Chem.* **1978**, *17*, 501. The complex **1** had correct elemental analysis. $C_8H_{12}O_6Sn$ requires: C, 29.76; H, 3.75. Found: C, 30.03; H, 4.13.

(13) If diethyl tartrate disodium salt is treated at 0 °C with an excess of allyl bromide in the absence of tin dichloride the corresponding di- and mono-O-allylated products are obtained in large amount. These products are absent in the reaction mixture when tin dichloride is present.

(14) This assumption is made on the basis of the stoichiometric ratios of the reagents used and on the possible expansion of the tin atom valence shell. In fact it is known that the tin atom in monoalkylstannanes can expand its valence shell to give penta-, hexa-, and even heptacoordinated species (for a discussion, see: Tzschach, A.; Jurkschat, K. *Comments Inorg. Chem.* **1983**, *3*, 35). Of course we cannot also rule out the formation of polynuclear species with bridging tartrate ligands. In any case the absence of self-condensation products when enolizable aldehydes are used and of O-allylated tartrate esters[13] should exclude the presence of residual sodium alkoxides appendages.

(15) Poulter, C. D.; March, L. L.; Hughes, J. M.; Argyle, J. C.; Satterwhite, D. M.; Goodfellow, R. J.; Moesinger, S. G. *J. Am. Chem. Soc.* **1977**, *99*, 3816.

Table II. Enantioselective Synthesis of Homoallylic Alcohols[a]

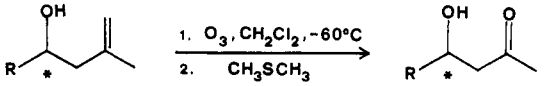
entry	allyl halide	aldehyde	reacn time, h	homoallylic alcohol: yield, %[b]	ee, %[c]	config.	$[\alpha]^{23}_D$, deg (c, solv)	ref
1			18	53	65	S	−6.5 (0.6, EtOH)	3b
2			22	78	54	R	+5.8 (2.5, CCl_4)	6a
3			18	64	36	S	−4.2 (11, C_6H_6)	1h
4			19	65	46	S	−22.8 (9.9, Et_2O)	7c
5			18	68	51	S	+2.0 (1.4, CCl_4)	6c
6			16[d]	76	58[e]	S	−15.7 (1.3, CH_2Cl_2)	
7			18	68	16[f]	R[g]	−4.7 (3.0, Et_2O)	
8			16	72	25	R	+4.4 (0.35, CCl_4)	15

[a] The reactions are carried out on a 10-mmol scale of $SnCl_2$ and 20 mmol of (+)-diethyl tartrate. [b] Yields refer to the homoallylic alcohol purified by flash chromatography on silica gel. [c] Values determined by optical rotation measurements. [d] Reaction quenching has to be performed with a pH 7 phosphate buffer solution. [e] Determined after conversion into γ-phenyl-α-methylene-γ-butyrolactone (eq 4). [f] Determined after conversion into diastereomeric carbamates (see Experimental section). [g] Predicted in analogy to the configurations of the other homoallylic alcohols obtained by using (+)-diethyl tartrate.

rying out the reaction at 0 °C (at lower temperatures, owing to the insolubility of the tin complex, the reaction slows down heavily and virtually stops at −30 °C). Finally we observed that bulky alkyl groups in tartrate esters negatively affect the reaction selectivity (entries 6, 7).

The results of reactions of **3** or other related allylic complexes with some representative aldehydes are summarized in Table II. Yields are good and often get near the 80% limit value, and the ee values fluctuate in the 50–60% range when unsubstituted or 2-substituted allylic complexes are used. The enantioselectivity drops to lower levels when the steric demand of the aldehyde increases (entry 3) or γ-substituents are present in the allylic moiety (entries 7, 8). The reactions take place cleanly, no byproducts are observed, and the separation of homoallylic alcohols from the excess of aldehyde and from diethyl tartrate freed by the complex in the alkaline workup is very readily accomplished by flash chromatography on silica gel.

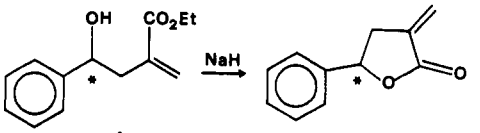
As stated in the introduction, the condensation of η^1-allylic complexes with aldehydes can be considered equivalent by a synthetic point of view to the aldol reaction since homoallylic alcohols can be easily converted into aldols by oxidative cleavage of the C=C bond. Exploiting this simple chemical correlation we could assign the *S* configuration to the levogire 4-phenyl-4-hydroxy-2-butanone and 4-cyclohexyl-4-hydroxy-2-butanone[16] by ozonizing (*S*)-1-phenyl-3-methyl-3-buten-1-ol and (*S*)-1-cyclohexyl-3-methyl-3-buten-1-ol, respectively (eq 3).



(3)

R = phenyl, cyclohexyl

Let us now inspect entry 6: given the interest for sesquiterpene lactones possessing the α-methylene-γ-butyrolactone ring, which confers to the parent molecule important cytotoxic, antineoplastic, and bactericidal properties,[17] we envisioned 2-carbethoxyallyl bromide as an interesting candidate for applying our procedure to the synthesis of this class of compounds in an enantiomerically enriched form. It is noteworthy that the 2-carbethoxyallyltin complex adds in a very good yield to benzaldehyde at 0 °C, forming the corresponding homoallylic alcohol without undergoing the expected spontaneous lactonization which is usually observed in related reactions exploiting zinc,[1r,18] chromium,[19] silicon,[20] and tin[21] complexes. Anyway the unsaturated hydroxy ester **4** can be cleanly converted to the corresponding optically active (*S*)-γ-phenyl-α-methylene-γ-butyrolactone (**5**) (eq 4) upon short



4 **5** (4)

contact (2 min) with NaH in THF at 0 °C. This reaction can be regarded as a useful complement of the few asymmetric syntheses of this class of biologically active compounds so far appeared in the literature.[22]

Besides the addition to prochiral aldehydes, we also inspected the addition of **3** to glyceraldehyde acetonide, extensively used as a probe of diastereofacial selectivity in reactions with nucleophiles.[23] For this purpose we prepared the complex **3** starting from allyl bromide and (+)-diethyl tartrate and (−)-diethyl tartrate, in this way

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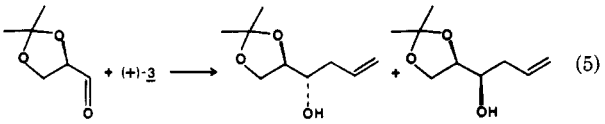
obtaining two enantiomeric allylic tin complexes, the first labeled as (+)-3 and the second as (−)-3. The reactions of (+)-3 and (−)-3 with (*R*)-glyceraldehyde acetonide are reported in eq 5 and 6, respectively. It is apparent in this

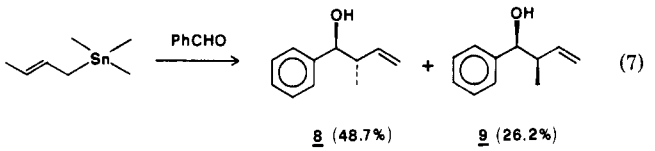


(5)

(6)

case of double asymmetric induction that the facial selectivity of the aldehyde outweighs the facial preference of the chiral allylic complex; in fact the anti isomer **6**,[24] which generally prevails in the reactions of this aldehyde with nucleophiles with very few exceptions,[25] predominates with both (+)- and (−)-3, passing from a 92% de with the former (matched pair) to 75% de with the latter (mismatched pair).

A further aspect we have examined is the diastereoselectivity of the reaction with benzaldehyde of a tin complex prepared according to the previously reported conditions for the preparation of **3** starting from (*E*)-crotyl bromide (*E*/*Z* = 85/15) and (+)-diethyl tartrate. After 15 h at 0 °C the reaction mixture contained the threo **8** and the erythro **9** adducts in the 65/35 ratio (eq 7). As expected



(7)

in the addition of (*E*)-crotylstannanes to aldehydes in the absence of added Lewis acid catalysts,[2] the threo isomer is the prevailing product, but the diastereomeric excess is lower (de 30%) than that expected on the basis of the configurational purity of the starting crotyl bromide (the theoretical de should be 70%). This could be due to a partial *E*/*Z* isomerization as a result of a 1,3-metallotropic rearrangement or to a concurrence of cyclic and open transition states which lead to different diastereomeric products.[26] Furthermore, in order to establish the enantiomeric composition of **8** and **9**, we converted them into chiral carbamates using (−)-(*R*)-α-phenylethyl isocyanate. Capillary gas chromatography (Carbowax 20M, OV 1, SE 52) could not acceptably resolve the enantiomeric alcohols **8**, while the erythro product **9** was perfectly separated into two peaks in 2.2:1 ratio (corresponding to a 37.4% ee), the majority of which was assigned to (1*S*,2*R*)-1-phenyl-2-methylbut-3-en-1-ol[27] in analogy to the configurations of the products reported in Tables I and II. As previously observed the asymmetric induction level depends on the

Scheme I

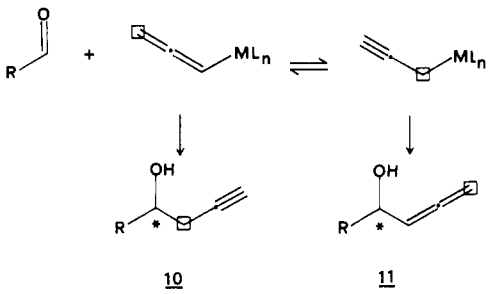


Table III. Enantioselective Synthesis of 1,2-Dien-4-ols[a]

		CH_2=C=CHCHOHR			
entry	RCHO, R	yield, %[b]	ee, %[c]	config[d]	$[\alpha]^{22}_D$, deg (*c*, solv)
1	phenyl	58	47	*S*	+45.6 (1.2, CCl_4)
2	cyclohexyl	61	42	*R*	−9.8 (2.0, C_6H_6)
3	*n*-octyl	56	39	*R*	+6.4 (1.3, C_6H_6)

[a] The reactions are carried out on a 10-mmol scale of $SnCl_2$ and 20 mmol of (+)-diethyl tartrate disodium salt and 15 mmol of propargyl bromide using the same procedure reported in the Experimental Section. After the addition of the aldehyde, the reaction mixture was stirred at 0 °C for 18 h and finally quenched with aqueous $NaHCO_3$ (5%). [b] Yields determined by gas chromatography (Carbowax 20M). The isomeric homopropargylic alcohols are present in 5–10% yield. [c] See Experimental Section. [d] The configurations were determined by comparing the optical properties of the saturated alcohols obtained upon hydrogenation (5% Pd on carbon, MeOH, 1 atm of H_2) of the 1,2-dien-4-ols with those of the same alcohols obtained upon hydrogenation of the corresponding homoallylic alcohols reported in Tables I and II, whose absolute configurations are known.

presence of substituents on the γ-position of the allylic moiety, and the ee value observed in the case of the crotyl group is halfway to those obtained with the allyl and the γ,γ-dimethylallyl groups.

The last feature we wish to discuss here is the use of propargyl bromide in this reaction. It is known that propargylic metal derivatives add to carbonyl compounds to produce both homopropargylic alcohols and allenylcarbinols. The often observed lack of regioselectivity arises from the fact that the starting complexes are actually an equilibrating mixture of allenylic and propargylic organometallic species which, upon reaction with a carbonyl compound give, according to a S_E2' mechanism, homopropargylic alcohols **10** and allenylcarbinols **11**, respectively[28] (Scheme I).

In the last years considerable progress has been recorded toward the preparation of static (not equilibrating) propargylic and allenylic metal complexes so to attain the regiochemical control of their reaction with electrophiles.[29]

(24) GLC analysis of the crude reaction mixture (Carbowax, temperature program starting from 70 to 220 °C at 10 °C/min) shows the peaks of the syn **7** and anti **6** products at 9.1 and 9.8 min, respectively. The stereochemical assignment was done by comparison of the ^{13}C NMR spectrum with that reported by Hoffmann.[3a]

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(26) GLC analysis of the crude reaction mixture (Carbowax, 125 °C) shows the peaks of the threo and erythro adducts at 14.8 and 15.4 min, respectively.

(27) GLC analyses of the diastereomeric carbamates gave these results: (a) (Carbowax, 215 °C) three peaks at 32.0, 33.0, and 33.8 min in a 66.5/23/10.5 ratio; (b) (OV1, 200 °C) three peaks at 19.5, 19.9, and 20.4 min in a 67/22.7/10.3 ratio.

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As concerns the use of tin complexes, diallenyltin dibromide in THF[30] and allenyldibutyltin chloride in water[29d] were reported to add to aldehydes, affording pure homopropargylic alcohols in good yields; on the other hand, mixtures of homopropargylic and allenylic alcohols are obtained starting from propargyl iodide and tin dichloride in aprotic dipolar solvents.[31]

We found that the tin complex prepared starting from propargyl bromide according to the same procedure described for the preparation of **3**, mainly affords with aldehydes allenylcarbinols **11** (Table III) in 40–50% ee, and this represents, at our knowledge, the first report of asymmetric synthesis of this class of unsaturated alcohols via condensation reactions. The only byproduct observed in these condensation reactions are the regioisomeric homopropargylic alcohols which are formed in 5–10% yield.

In conclusion, we believe that the procedure here described, although inferior in terms of absolute asymmetric induction with respect to the related boron chemistry exploiting chiral allylic boranes and boronates, is a useful contribution to the widely studied tin chemistry at the level of the control of the absolute configuration of the newly formed chiral centers. Moreover the simple and clean method reported, where the most tricky reagent is NaH and the most expensive chemical is anhydrous tin dichloride, could be also attractive from a synthetic point of view, particularly in the case of optically active γ-substituted α-methylene-γ-butyrolactones and allenylcarbinols for which very few or no alternatives using boron complexes are presently available.

Experimental Section

General. Proton ^1H NMR spectra were measured in $CDCl_3$ at 90 MHz on a Varian EM390 instrument; chemical shifts are reported in δ units using Me_4Si as internal standard. ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ with a Varian FT-80A instrument; chemical shifts are expressed as δ units using internal Me_4Si and external 85% H_3PO_3, respectively, as standard. Infrared (IR) spectra were measured on a Perkin-Elmer PE 682 spectrophotometer, absorptions are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a Perkin-Elmer PE 241 polarimeter. Mass spectra (MS) were taken on a double-focusing Varian MAT 112S instrument at an ionizing voltage of 70 eV. Capillary gas chromatography (GLC) was performed on a Carlo Erba HRGC 5300 Mega Series apparatus using a OV1 (0.1-μm film thickness, 15 m, 3 mL/min flow rate of helium, 45/1 split ratio) and a Carbowax 20M (0.4-μm film thickness, 20 m, 2 mL/min flow rate of hydrogen, 50/1 split ratio) column. Flash chromatographic separations were performed by using 70–230 mesh silica gel (Merck). TLC analyses were carried out by using Merck plastic sheets coated with silica gel 60 F_{254} (layer thickness, 0.2 mm). All reactions were conducted in flame-dried glassware under an atmosphere of argon. Tetrahydrofuran (THF) was distilled over $LiAlH_4$. (+)-Tartaric acid bis(2,4-dimethyl-pent-3-yl) ester,[29f] α-(bromomethyl)acrylic acid ethyl ester,[32] 3-methyl-2-butenal,[33] and 2,3-*O*-isopropylidene-D-glyceraldehyde[23b] were prepared according to known procedures. Anhydrous tin dichloride was purchased from Merck. All the other chemicals were commercially available from Fluka and Aldrich at satisfactory purity levels and were used without further purification. The homoallylic alcohols reported in this paper had correct elemental analyses (C ± 0.3%, H ± 0.25%) and were identified by comparison of their spectroscopic properties with the literature data.

General Procedure for Reactions of Allylic Tin(IV) Tartrate Complexes with Aldehydes. The reaction of the complex **3** with benzaldehyde (Table I, entry 4) is described as an illustrative case. In a three-necked round-bottom flask equipped with mechanical stirrer and argon inlet, a 60% dispersion of NaH in mineral oil (1.6 g, 40 mmol) was washed with anhydrous pentane (3 × 5 mL), covered with THF (20 mL), and cooled at 0 °C. A solution of (+)-diethyl tartrate (4.12 g, 20 mmol) in THF (30 mL) was added with vigorous stirring over a 30-min period at 0 °C. The white coagulated product was further stirred 30 min at 0 °C, and then anhydrous $SnCl_2$ (1.90 g, 10 mmol) was added, causing a fast fluidization of the reaction mixture. After the mixture was stirred 30 min at 0 °C, allyl bromide (1.82 g, 15 mmol) was added, and the reaction mixture was stirred for 5 h at 0 °C and finally treated with benzaldehyde (1.17 g, 11 mmol). The reaction was allowed to proceed at 0 °C and was monitored by GLC. When a stable ratio between benzaldehyde and 1-phenyl-3-buten-1-ol was reached (usually 15–20 h) the reaction was quenched by adding 10% aqueous $NaHCO_3$ (20 mL) and stirred for 15 min at 0 °C. The aqueous layer was extracted with ether (3 × 30 mL), the combined extracts were dried (Na_2SO_4) and concentrated under vacuum, and the product (1.21 g, 82%) was purified by flash chromatography using cyclohexane–ether (95:5) as eluent. 1-Phenylbut-3-en-1-ol has $[\alpha]^{23}_D$ −29.0° (*c* 7.4, benzene), corresponding to the *S* isomer in 62% ee (lit.[1h] $[\alpha]^{23}_D$ −44.92° (*c* 7.4, benzene) for a sample of *S* alcohol reported to be 96% ee): IR (neat) 3420, 3035, 3010, 1640, 910, 755, 695; ^1H NMR 1.9 (s, 1 H, OH), 2.3–2.6 (m, 2 H), 4.6–5.0 (m, 1 H), 5.0–5.5 (m, 2 H), 5.5–6.4 (m, 1 H), 7.5 (s, 5 H); ^{13}C NMR 143.7, 134.3, 128.2, 127.3, 125.7, 118.0, 73.1, 43.6; MS, *m/e* (relative intensity) 148 (M^+, 3), 108 (70), 107 (100), 105 (46), 91 (11), 80 (26), 79 (82), 78 (30), 77 (65), 51 (58).

Data for 4-Phenyl-4-hydroxy-2-methylenebutanoic Acid, Ethyl Ester 4 (Table II, Entry 6). The product was purified by flash chromatography using cyclohexane–ether (9:1) as eluent: IR (neat) 3450, 1710, 1630, 950, 760, 700; ^1H NMR 1.25 (t, J = 7.5 Hz, 3 H), 2.6–2.9 (m, 2 H), 3.0 (s, 1 H, OH), 4.2 (q, J = 7.5 Hz, 2 H), 4.9 (dd, J = 7.5 Hz, J = 5.4 Hz, 1 H), 5.55 (s, 1 H), 6.2 (s, 1 H); ^{13}C NMR 168.1, 144.1, 137.2, 128.3, 128.0, 127.4, 125.8, 73.1, 61.0, 42.5, 14.2; MS, *m/e* (relative intensity) 220 (M^+, 2), 206 (2), 205 (4), (82 (10), 74 (63), 59 (100), 45 (95), 41 (45). To establish the absolute configuration and the ee of the levogire hydroxy ester **4**, we converted it into the γ-phenyl-α-methylene-γ-butyrolactone, whose optical rotation is known. The title hydroxy ester (0.3 g, 1.36 mmol) dissolved in THF (1 mL) was added to a suspension of NaH (33.6 mg, 1.4 mmol) in THF (2 mL) cooled at 0 °C. After 2 min the reaction mixture was quenched with a pH 7 phosphate buffer solution (5 mL). Longer reaction times cause product decomposition. After extraction with ether (3 × 5 mL) and concentration of the collected organic phases under vacuum, γ-phenyl-α-methylene-γ-butyrolactone (**5**) (201 mg, 85%) was isolated by flash chromatography using cyclohexane–CH_2Cl_2 (1:1) as eluent: $[\alpha]^{15}_D$ +11.0° (*c* 1, $CHCl_3$) corresponding to the *S* isomer in 58% ee (lit.[22d] $[\alpha]^{15}_D$ −19.0° (*c* 1, $CHCl_3$) for a sample of configurationally pure *R* isomer); mp 55–56 °C; IR (KBr) 1760, 1660, 810, 750, 700; ^1H NMR 2.7–3.1 (ddt, J = 17 Hz, J = 8 Hz, J = 2.5 Hz, 1 H), 3.2–3.7 (ddt, J = 17 Hz, J = 8 Hz, J = 2.5 Hz), 5.5 (m, 1 H), 5.7 (t, J = 2.5 Hz, 1 H), 6.3 (t, J = 2.5 Hz, 1 H), 7.4 (s, 5 H).

Data for 3,3-Dimethyl-1-dodecen-4-ol (Table II, Entry 7). The crude reaction mixture was washed with sodium bisulfite until most of the unreacted nonanal was eliminated, and then the title alcohol was purified by flash chromatography using cyclohexane–ether (9:1) as eluent: IR (neat) 3420, 3070, 910; ^1H NMR (C_6D_6) 0.95 (t, 3 H), 1.1–1.8 (14 H), 2.3 (s, 1 H, OH), 3.15 (m, 1 H), 4.95 (dd, J = 0.84 Hz, J = 18.3 Hz, second-order coupling, 1 H), 5.0 (dd, 0.84 Hz, J = 9.9 Hz, second-order coupling, 1 H), 5.8 (dd, J = 9.9 Hz, J = 18.3 Hz); MS, *m/e* (relative intensity) 171 ($M^+ - C_3H_5$, 5), 143 (5), 141 (4), 103 (20), 83 (38), 71 (39), 70 (100), 69 (88), 55 (85). To ascertain the enantiomeric composition, the title alcohol (30 mg) was heated with (*S*)-(−)-1-phenylethyl isocyanate (40 mg) in a sealed ampule at 60 °C for 1 h. The reaction mixture was then diluted to 0.5 mL with CH_2Cl_2 and directly analyzed by capillary GLC (OV1) at 240 °C: the retention times of the two diastereomeric products were 9.49 and 9.72 min, and the integral ratio between the second (higher) and the first

(30) Nokami, J.; Tamaoka, T.; Koguchi, T.; Okawara, R. *Chem. Lett.* **1984**, 1939.
(31) Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 621.
(32) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.
(33) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Organomet. Chem.* **1985**, *280*, 307.

peak was 58/42.

Data for 1-Phenyl-2,3-butadien-1-ol (Table III, Entry 1). TLC analysis (cyclohexane–ether, 8:2) of the crude reaction mixture shows two spots, the first with R_f 0.30, which takes up an orange color upon spraying with 2,4-dinitrophenylhydrazine and corresponding to the title dienol, the second with R_f 0.24 corresponding to 1-phenyl-3-butyn-1-ol as established by its spectra: IR (neat) 3400, 3300, 2120, 865, 755, 700; ^{1}H NMR (CCl_4) 1.2 (s, 1 H, OH), 1.9 (t, J = 2.6 Hz, 1 H), 2.5 (dd, J = 2.6 Hz, J = 7 Hz, 2 H), 4.75 (t, J = 7 Hz, 1 H), 7.3 (m, 5 H). GLC analysis of the same mixture (Carbowax, 150 °C) shows two peaks having retention times 3.9 and 4.6 min in 12/88 area ratio, the latter corresponding to the title dienol. 1-Phenyl-2,3-butadien-1-ol was purified by flash chromatography using cyclohexane–ether (9:1; two elutions): IR (neat) 3360, 3090, 3060, 3025, 1955, 1020, 920, 850, 760, 700; ^{1}H NMR (CCl_4) 3.6 (s, 1 H, OH), 4.6–4.85 (dd, J = 2.5 Hz, J = 5.5 Hz, 2 H), 4.85–5.5 (m, 2 H), 7.25 (pseudo s, 5 H); MS, m/e (relative intensity) 146 (M^+, 4), 128 (7), 108 (35), 107 (100), 105 (21), 79 (91), 77 (82), 51 (34), 39 (49). In order to establish the absolute configuration and the ee, the title dienol (150 mg) was hydrogenated in methanol in the presence of 5% Pd on carbon to 1-phenyl-1-butanol having $[\alpha]^{25}_D$ −21.5° (c 10, benzene) (lit.[34] $[\alpha]^{22}_D$ −31.6° (c 10, benzene) for a sample reported to be 69% ee).

Data for 1-Cyclohexyl-2,3-butadien-1-ol (Table III, Entry 2). GLC analysis (Carbowax, temperature program starting from 80 to 220 °C at 10 °C/min) shows the homopropargylic alcohol peak at 8.3 min and the dienol peak at 9.0 min in 7.7/92.3 area ratio. The title dienol has R_f 0.32 (cyclohexane–ether, 8:2) and was isolated by flash chromatography (cyclohexane–ether, 9:1; two elutions): IR (neat) 3350, 1950, 1450, 1020, 895, 865, 840; ^{1}H NMR 0.9–1.5 (m, 6 H), 1.5–2.0 (m, 4 H), 1.95 (s, 1 H, OH), 3.85 (m, 1 H), 4.75 (m, 2 H), 5.15 (dd, J = 13.5 Hz, J = 6.5 Hz, 1 H); MS, m/e (relative abundance) 113 ($M^+ - C_3H_3$, 37), 95 (100), 70 (23), 69 (59), 67 (32), 55 (56), 41 (61), 39 (28). The ee of the title dienol was established according to the Feringa's procedure:[35] the alcohol (110 mg) was dissolved in $CDCl_3$ (2 mL) and pyridine (60 mg) and treated at 0 °C with PCl_3 (34 mg) dissolved in $CDCl_3$ (2 mL) to give three diastereomeric phosphonates. The ^{31}P NMR spectrum showed three peaks at δ 6.4, 6.0, and 5.6 in the 14:71:15 area ratio.

Data for 1,2-Dodecadien-4-ol (Table III, Entry 3). GLC analysis of the reaction mixture (Carbowax, temperature program starting from 80 to 220 °C at 10 °C/min) shows the homopropargylic alcohol peak at 10.9 min and the dienol peak at 11.6 min in the 15/85 area ratio. The dienol has R_f 0.38 (cyclohexane–ether, 8:2) and is isolated by flash chromatography (cyclohexane–ether, 9:1; two elutions): IR (neat) 3430, 1950, 840; ^{1}H NMR 0.9 (t, 3 H), 1.1–1.9 (14 H), 2.2 (s, 1 H, OH), 4.2 (m, 1 H), 4.8 (m, 2 H), 5.2 (dd, J = 6.0 Hz, J = 12.9 Hz, 1 H); MS, m/e (relative intensity) 143 ($M^+ - C_3H_3$, 9), 107 (100), 79 (69), 69 (64), 55 (24), 41 (53), 43 (15), 39 (22). The ee was established by conversion of the dienol into diastereomeric phosphonates as in the case of 1-cyclohexyl-2,3-butadien-1-ol: the ^{31}P NMR contains three peaks at δ 5.6, 5.3, and 5.0 in the 16:69.5:14.5 ratio.

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Registry No. (+)-**3**, 109958-05-6; (−)-**3**, 109907-86-0; **5**, 109958-04-5; **6**, 79364-35-5; **7**, 87604-46-4; (±)-**8**, 63553-62-8; **9**, 103882-39-9; (*R,R*)-*i*-PrOC(O)CH(OH)CH(OH)C(O)O-*i*-Pr, 2217-15-4; (*R,R*)-[$(CH_3)_2CH]_2$CHOC(O)CH(OH)CH(OH)C(O)-OCH[$(CH(CH_3)_2]_2$, 99686-56-3; CH_2=C(CH_3)CH_2Br, 1458-98-6; EtOC(O)C(=CH_2)CH_2Br, 17435-72-2; $(CH_3)_2$C=CHCH_2Br, 870-63-3; c-C_6H_{11}CHO, 2043-61-0; $CH_3(CH_2)_7$CHO, 124-19-6; $(CH_3)_3$CCHO, 630-19-3; $(CH_3)_2$C=CHCHO, 107-86-8; PhCHO, 100-52-7; (*R*)-$CH_3(CH_2)_7$CH(OH)CH_2CH=CH_2, 85029-09-0; (*S*)-$(CH_3)_3$CCH(OH)CH_2CH=CH_2, 67760-86-5; (*S*)-PhCH-(OH)CH_2C(CH_3)=CH_2, 77127-91-4; (*S*)-c-C_6H_{11}CH(OH)CH_2C-(CH_3)=CH_2, 94340-24-6; (*S*)-PhCH(OH)CH_2C(=CH_2)c(O)OEt, 109907-81-5; (*R*)-$CH_3(CH_2)_7$CH(OH)C(CH_3)CH=CH_2, 109927-25-5; (*R*)-$(CH_3)_2$C=CHCH(OH)C$(CH_3)_2$CH=CH_2, 77363-66-7; (*S*)-CH_3CH(Ph)N=C=O, 14649-03-7; (*R,S*)-$CH_3(CH_2)_7$CH[OC-(O)NHCH(Ph)CH_3]C$(CH_3)_2$CH=CH_2, 109907-82-6; (*S,S*)-CH_3-$(CH_2)_7$CH[OC(O)NHCH(Ph)CH_3]C$(CH_3)_2$CH=CH_2, 109907-83-7; (*S*)-c-C_6H_{11}CH(OH)CH_2CH=CH_2, 94340-22-4; (*S*)-CH_2=C=CHCH(OH)Ph, 104516-09-8; (*R*)-CH_2=C=CHCH(OH)-c-C_6H_{11}, 109907-84-8; (*R*)-CH_2=C=CHCH(OH)$(CH_2)_7CH_3$, 109907-85-9; (*S*)-CH_2=CHCH_2CH(OH)Ph, 77118-87-7; (*S*)-$CH_3(CH_2)_2$CH-(OH)Ph, 22135-49-5; (+)-diethyl tartrate, 87-91-2; (−)-diethyl tartrate, 13811-71-7; allyl bromide, 106-95-6; propargyl bromide, 106-96-7; (*R*)-glyceraldehyde acetonide, 15186-48-8; (*E*)-crotyl bromide, 29576-14-5; (*Z*)-crotyl bromide, 39616-19-8.

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Absolute Configuration of A-32′287 [Conocandin] and Total Synthesis of Its Methyl and *tert*-Butyl Esters

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The first total synthesis of *ent*-conocandin *tert*-butyl ester and conocandin methyl ester is described. The synthetic route involves initial stereoselective construction of the unsaturated aldehyde **3**, its homologation into the enantiomerically pure 2-alkoxy aldehyde **19**, and subsequent addition of an α-acrylate anion equivalent. Further functional group modifications afforded the desired targets. A chemical correlation with the natural product allowed absolute configuration assignment.

In 1976 J. M. Muller and co-workers[1] isolated a new compound from *Hormococcus conorum* cultures which exhibited a marked activity against yeasts and fungi. This new and interesting antibiotic, named conocandin (A-32′287), was assigned structure **1** (R = H), the absolute configuration remaining unknown; Figure 1.

A total synthesis of such a compound involves the achievement of three main goals: (a) A stereoselective synthesis of the C-9/C-10 trisubstituted double bond. (B)

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