Similar time curves were obtained for the following sieve cuts: <210, 250–297, and >420 μm. No difference in kinetics was observed between silated and unsilated glassware or between the presence and absence of an N_2 purge. Decarboxylation could not be induced photochemically (450-W Hanovia medium-pressure bulb for 24 h in an argon atmosphere).

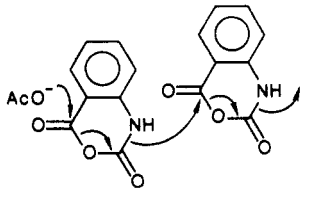
Microscopy. A single isatoic anhydride crystal was heated to 200 °C while viewed under 40× magnification (Vickers polarizing microscope). Photomicrographs taken periodically show no evidence of a "reaction front". Instead, small bits of solid break off from the crystal as the surface becomes progressively more pitted. After 25 min, the original "chunk" appears completely amorphous—although most of the isatoic anhydride has yet to react. Visual inspection suggests, therefore, that the reaction initiates at the surface (in apparent conflict with the rate insensitivity to particle size).

Thermal Stability of Product. The product, a remarkably stable organic solid, softens to the touch of a probe at T_g = 254 °C and melts with discoloration at T_m = 354 °C. A thermal stability curve was secured by heating the product at 300 °C (ambient atmosphere) and plotting "percent weight loss vs. time". There is only about a 11% weight loss after 5 h; an additional 13 h of heating does not further diminish the weight. By way of comparison, the polyamide formed from terephthalyl chloride and *p*-phenylenediamine loses 7.4% of its weight at 300 °C for 40 h.[7]

Solution Chemistry. Isatoic anhydride in DMF (1.1 M), dioxane (1.1 M), or diglyme (0.6 M) was heated at 220 °C for 24 h in a sealed glass tube purged with nitrogen. Starting material was recovered in >90% yield. In contrast to the crystalline state, the solution phase lacks the molecular constraints necessary for a rapid oligomerization reaction. In current parlance, the reaction is under "lattice control".[8]

***N*-Methylisatoic Anhydride.** *N*-Methylisatoic anhydride (recrystallized 3× from EtOH, mp 170–178 °C) does not decompose when heated at 160–185 °C as a solid or a melt. In fact, no decomposition was observed at 270 °C, a marked difference in reactivity from the N-protonated analogue.

Catalysis by Dopants. Isatoic anhydride (100 mg) was added to a solution or slurry of a dopant (1 mg) in 5 mL of water. The water was then removed with the aid of a rotary evaporator. Isatoic anhydride, "doped" in this manner, was dried over P_2O_5 and subjected to 200 °C for 20 min. Samples doped with anthranilamide and sodium acetate expelled 14% and 81% of the theoretical CO_2 volume, respectively, compared to only 2% for undoped isatoic anhydride. The catalysis could be "physical", arising from irregularities or local melting produced in the crystal lattice. Alternatively, the catalysis could be "chemical" with the dopant (included or otherwise in the lattice) serving as a nucleophilic initiator:



Not only does sodium acetate accelerate the decarboxylation, it affects the molecular weight distribution of the product. Thus, 1% sodium acetate increases the weight average M_w from 740 to 1280. Moreover, the "polydispersity index" (defined as the weight average M_w/number average M_w) increases almost 3-fold; this means that the sodium acetate induced product has a much broader range of molecular weights.

Crystal Structure. The crystal structure of isatoic anhydride has been reported previously.[9] Each unit cell contains four molecules. These are arranged as two pairs of centrosymmetric dimers engaged in intermolecular amide–amide hydrogen bonding. An analysis using published X-ray data[5] in conjunction with the SHELXTL MOLECULAR GEOMETRY program (Nicolet, Inc.) shows that 6.79 Å separates the nitrogens from their nearest electrophilic carbonyl carbon. Obviously, coupling between two molecules in the course of oligomer formation would require a major disruption of lattice organization (including H-bond cleavage). Hence, it is likely that loci of crystalline disorder provide intermolecular contacts which initiate the reaction. This is consistent with the observed rate sensitivity to impurities and dopants.

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(7) Dine-Hart, R. A.; Moore, B. J. C.; Wright, W. W. *Polym. Lett.* **1964**, *2*, 369.
(8) Karch, N. J.; McBride, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 5092.
(9) Kashino, S.; Nakashima, S.; Haisa, M. *Acta Crystallogr., Sect. B* **1978**, *B34*, 2191.

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Reactions of Diisopropyl Tartrate Modified Allyl- and (*E*)- and (*Z*)-Crotylboronates with β-Alkoxy-α-methylpropionaldehydes: A Reagent Based Solution to the Acyclic Dipropionate Problem

Summary: Compounds **5**, **6**, **7**, **9**, and **10** are now available each with a minimum of diastereoselectivity of 87% from the reactions of β-alkoxy-α-methylpropionaldehyde **4** and the diisopropyl tartrate modified crotyl- and allylboronates **1–3**.

Sir: The development of concise, highly stereoselective methods for the synthesis of the 1,3-dimethyl-2-hydroxy or 1,3-dihydroxy-2-methyl stereochemical relationships present in macrolide, ansamycin, and other natural products of propiogenic/acetogenic biosynthetic origin is a topic of considerable current interest.[1] Many studies have focused on the construction of synthetic equivalents of **5–10**. Although several ingenious but multistep solutions have been reported,[1a-f] until now a general one-step protocol for elaboration of a chiral aldehyde (e.g., **4**) with a family of suitable enolates or allylmetal reagents has been lacking.[2]

(1) (a) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343. (b) Nagaoka, H.; Rutsch, W.; Schmid, G.; Iio, H.; Johnson, M. R.; Kishi Y. *J. Am. Chem. Soc.* **1980**, *102*, 7962. (c) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (d) Oikawa, Y.; Nishi, T.; Itaya, H.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 1987. (e) Nakata, T.; Fukui, M.; Ohtsuka, H.; Oishi, T. *Tetrahedron* **1984**, *40*, 2225. (f) Suzuki, K.; Katayama, E.; Tomooka, K.; Matsumoto, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1985**, *26*, 3707. (g) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Ibid.* **1985**, *26*, 5627. (h) Danishefsky, S.; Harvey, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 6647. (i) Ziegler, F. E.; Wester, R. T. *Tetrahedron Lett.* **1986**, *27*, 1225.

0022-3263/87/1952-0316$01.50/0

Scheme I

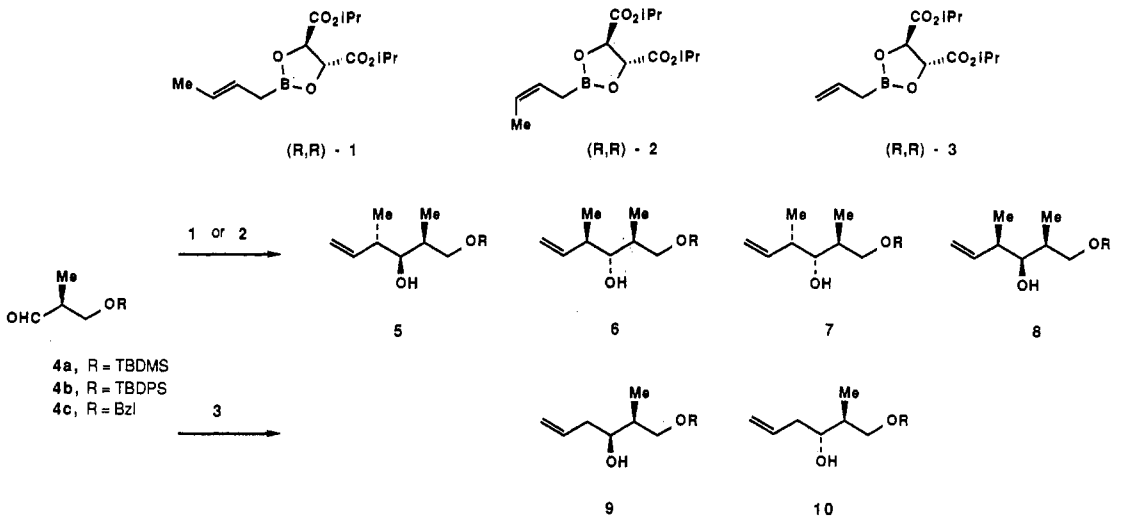

Table I. Reactions of 4 with Achiral Allylmetal Reagents

			product ratios					
entry	aldehyde	reagent	5	6	7	8	9	10
1	4a[a]	pinacol (*E*)-crotylboronate	61	39				
2	4b[a]	pinacol (*E*)-crotylboronate	62	38				
3	4c[a]	pinacol (*E*)-crotylboronate	68	32				
4	4a[a,c]	pinacol (*Z*)-crotylboronate	9	7	55	29		
5	4b[a,c]	pinacol (*Z*)-crotylboronate	11	8	45	36		
6	4c[a,c]	pinacol (*Z*)-crotylboronate	8	6	55	31		
7[2b]	4c	$CH_3CH{=}CHCH_2I/CrCl_2$	61	39				
8[2a]	4a	$CH_3CH{=}CHCH_2SnBu_3/BF_3$			5	[95]		
9[2a]	4c	$CH_3CH{=}CHCH_2SnBu_3/MgBr_2$	2	7	81	10		
10	4a[b]	pinacol allylboronate					52	48
11	4b[b]	pinacol allylboronate					54	46
12	4c[b]	pinacol allylboronate					54	46
13[2a]	4c	$CH_2{=}CHCH_2SnBu_3/SnCl_4$					2	[98]
14[2a]	4c	$CH_2{=}CHCH_2SnBu_3/BF_3$					48	52
15[2d]	4c	$CH_2{=}CHCH_2SiMe_3/SnCl_4$					8	92

[a] Reaction performed in toluene at 23 °C; see ref 6a for pertinent experimental details. [b] Reaction performed in toluene at −78 °C. [c] The reagent used in these cases was of low isomeric purity (ca. 90%).

Table II. Reactions of 4 with Chiral Reagents 1–3[a]

				product ratios[d,e]					
entry	aldehyde[b]	reagent	yield,[c] %	5	6	7	8	9	10
1	4a	(*R,R*)-1	80	[97]	3				
2	4b	(*R,R*)-1		82	16	1	2		
3	4c	(*R,R*)-1		93	5	1	1		
4	4a	(*S,S*)-1		16	81	3			
5	4b	(*S,S*)-1	85	11	[88]	1			
6	4c	(*S,S*)-1		14	85	1			
7	4a	(*S,S*)-2	71		4	[95]	1		
8	4b	(*S,S*)-2			4	85	12		
9	4c	(*S,S*)-2			3	88	9		
10	4a	(*R,R*)-2		12	2	45	41		
11	4b	(*R,R*)-2		9	3	24	[64]		
12	4c	(*R,R*)-2		8	2	45	45		
13	4a	(*R,R*)-3	71					[89]	11
14	4b	(*R,R*)-3						79	21
15	4c	(*R,R*)-3						83	17
16	4a	(*S,S*)-3						19	81
17	4b	(*S,S*)-3	72					13	[87]
18	4c	(*S,S*)-3						20	80

[a] All reactions were performed in toluene (0.2 M) at −78 °C in the presence of 4A molecular sieves (typically 25–50 mg/mL) with 1.5 equiv of reagent. All reactions were complete within 4 h and were worked up as described in ref 3a. [b] See ref 4a. [c] Combined yield of isolated reaction products (see ref 4b). [d] Diastereomer ratios were determined by HPLC analysis (4.6 × 250 mm ChemcoPak column packed with 3μ Chemcosorb silica gel) of unseparated product mixtures. Products of all reactions of aldehydes **4a** and **4b** were analyzed by using 3% EtOAc in hexane as eluant. Reaction of **4c** with reagents 1 and 2 (entries 3, 6, 9, 12) were analyzed using 10% EtOAc–hexane, whereas 5% EtOAc–hexane was used for the analysis of **9c**/**10c** mixtures (entries 15, 18). [e] For a discussion of stereochemical assignments, see ref 10.

We disclose herein our recent findings that diisopropyl tartrate modified crotyl- and allylboronates **1–3**[3] undergo highly diastereoselective reactions with aldehyde **4**,[4] providing compounds **5**, **6**, **7**, **9**, and **10** each with a *minimum* diastereoselectivity of 87% (Scheme I). Since Keck has already shown that **8a** can be prepared with 95% diastereoselectivity via the $BF_3{\cdot}Et_2O$-catalyzed reaction of **4a** and crotyltributylstannane,[2a] the first reagent based solution to the acyclic "dipropionate problem" is at hand.

Use of optically active reagents **1–3** to achieve high levels of diastereofacial selectivity in reactions with chiral, nonracemic aldehydes such as **4** is necessary since **4** does not possess a sufficiently large intrinsic diastereofacial bias in reactions with most achiral allylmetal or aldol reagents.[5,6] Some typical results are summarized in Table I. These data show that only **8** and **10** are accessible with acceptable, synthetically useful levels of diastereoselection, but only when type II allylmetal reagents are employed (entries 8, 13, 15).[7,8]

Results of reactions of **4** with chiral reagents **1–3** are summarized in Table II. Several points are noteworthy. First, although the overall sense of asymmetric induction is controlled by the tartrate auxiliaries of **1–3**, the absolute levels of stereoselectivity appears to be dependent on the hydroxyl protecting group in **4**. The TBDMS unit consistently gave best results in the matched double asymmetric reactions leading to **5**, **7**, and **9** (entries 1, 7, 13), whereas selectivity in the mismatched direction leading to **6**, **8**, and **10** is best when a TBDPS blocking group is employed (entries 5, 11, 17). We do not fully understand the role played by the protecting groups in this chemistry and intend to explore this point further in subsequent studies. Second, the diastereoselectivity in the matched double asymmetric reactions of **4a** (R = TBDMS) with crotyl reagents (*R,R*)-**1** (leading to **5a**, entry 1) and (*S,S*)-**2** (leading to **7a**, entry 7) is outstanding (33:1 and 95:1, respectively). The 4% of **6a** produced in the latter case presumably results from stereochemical crossover or from reaction of the small amount of (*S,S*)-**1** present in **2** as an isomeric impurity. Matched diastereoselection, however, is somewhat lower (8:1) in the reaction of **4a** and allyl reagent (*R,R*)-**3** (entry 13). Nevertheless, this reaction still provides compound **9** with greater selectivity than any other method reported to date (see Table I, entries 10–15). Third, acceptable levels of mismatched diastereoselection were realized in the reactions of **4b** and (*S,S*)-**1** (entry 5, 88:11 ratio of **6b**/**5b**) and (*S,S*)-**3** (entry 17, 87:13 ratio of **10b**/**9b**) but not in the reaction with (*Z*)-crotyl reagent (*R,R*)-**2** (entries 10–12). The poor performance of **2** in this mismatched series undoubtedly reflects the fact that **2** is somewhat less enantioselective than **1**.[9] Since compounds with the syn,syn stereochemistry of **8** are accessible with very high selectivity by using crotylstannane methodology (e.g., Table I, entry 8),[2a,11] it is probable that **2** will be of limited utility for preparation of syn,syn diastereomers.

In summary, compounds **5–10** are now available each with a minimum diastereoselectivity of 87% by using allylmetal methodology. Compounds **5**, **6**, **7**, and **9** are best prepared by using the diisopropyl tartrate modified crotyl- and allylboronates **1–3**, whereas **8** and **10** are best prepared by using allylic stannane reagents. Applications of these observations in total synthesis will be reported shortly.

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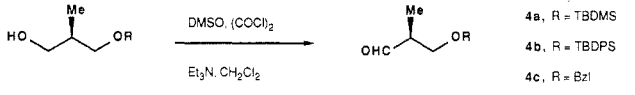
(2) For previous studies on the reactions of **4** with achiral allylmetal or aldol reagents, see: (a) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. (b) Lewis, M. D.; Kishi, Y. *Ibid.* **1982**, *23*, 2343. (c) Gennari, C.; Bernardi, A.; Scolastico, C.; Potenza, D. *Ibid.* **1985**, *26*, 4129. (d) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. (e) For a review of earlier examples from the aldol arena, see: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(3) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Halterman, R. L. *Ibid.* **1986**, *108*, 294. (c) The preparation of (*Z*)-crotyl reagent **2** starting from (*Z*)-2-butene is analogous to the preparation of **1** described in ref 3b (Roush, W. R.; Halterman, R. L., unpublished research results).

(4) (a) Aldehydes **4a–c** were prepared from methyl 3-hydroxy-2-methylpropionate, both enantiomers of which are commercially available (Aldrich), by using standard procedures (e.g., see ref 1c and: Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015). The final step in each case was the Swern oxidation of alcohol i. The optical purity of crude **4** was >98% ee as determined



by Mosher ester analysis of i recovered after $LiAlH_4$ reduction of **4**. Attempts to purify **4** by silica gel chromatography resulted in 5–7% racemization (85–90% ee). Since the diastereoselectivity of the reactions of **4** with chiral reagents **1–3** depends on the optical purity of **4**, crude aldehyde was used in all studies described in text. (b) The yields reported herein are for two steps including the oxidation of i.

(5) For a review of double asymmetric synthesis, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(6) (a) For a discussion of the factors that influence aldehyde diastereofacial selectivity in reactions of chiral aldehydes and achiral allylboronates, see: Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (b) See also: Hoffmann, R. W.; Weidmann, U. *Chem. Ber.* **1985**, *118*, 3966.

(7) For the definition of type II allylmetal reagents, see: Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta.* **1983**, *66*, 1655. See also: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555.

(8) (a) Gennari has reported the preparation of a compound stereoanalogues to **7c** with 99% diastereoselection via the $TiCl_4$-mediated reaction of **4c** and a (*Z*)-*O*-propionate thio ester silyl ketene acetal (ref 2c). A substantial amount of racemization occurred in this reaction (85% ee), however, which detracts from the synthetic potential of this method. (b) After this manuscript was submitted, Evans reported a highly stereoselective synthesis of **6c** via the reaction of **4c** and a chiral crotonate imide: Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.

(9) The reactions of **1** with representative achiral aldehydes exhibit greater enantioselectivity than those with **2** (Roush, W. R.; Halterman, R. L., unpublished research). Data for **1**: decanal (88% ee for anti diastereomer); cyclohexanecarboxaldehyde (88% ee); 2-decenal (77% ee); benzaldehyde (70% ee). Data for **2**: decanal (82% ee for syn diastereomer); cyclohexanecarboxaldehyde (86% ee); 2-decenal (60% ee); benzaldehyde (59% ee).

(10) Compounds **5a,b,c–8a,b,c**, **9c**, and **10c** have been previously described in the literature (ref 2a,d). The ^1H NMR spectra of HPLC purified samples of **5b,c–7b,c** and **8a–c** were in excellent agreement with spectral data provided by Prof. Keck. Structural assignments for **5a–7a** are by analogy to **6b,c–8b,c** and are based on the similarities of the ^1H NMR spectra and identical HPLC profiles in the three series. The assignments for **5a–7a** are also fully consistent with predictions based on the expected behavior of **4a** with **2** and **3**. The spectroscopic data obtained for **9c** and **10c** were fully consistent with published values (ref 2d). Compounds **9a,b** and **10a,b** were correlated with **9c**/**10c**, respectively, by deprotection and hydrogenation of each to the corresponding *syn*- or *anti*-1,3-dihydroxy-2-methylhexanes.

(11) For other examples of reactions of α-methyl branched aldehydes and crotyltributylstannane, see ref 1f and: (a) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239. (b) Nakajima, N.; Hamada, T.; Tanaka, T.; Oikawa, Y. Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 4645.

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