complete by TLC after being stirred for an additional 1.5 h. The reaction mixture was concentrated in vacuo and the residue purified by CHP 20 (3:1 H_2O/MeCN). The appropriate fractions were combined and concentrated to remove MeCN. The remaining aqueous solution was millipore filtered and lyophilized to afford 92 mg (89%) of pure **3a** as its lithium salt. TLC: R_f = 0.28 (20:1:1 CH_2Cl_2/MeOH/AcOH, visualization by PMA). Mp = 186–188 °C. MS: $(M - H)^-$ 441, $(M + Li)^+$ 449. IR: (KBr) 3432, 2934, 2879, 1724, 1583, 1391, 1248, 1165. $[\alpha]_D$ = +1.4° [c = 0.5, MeOH]. ^1H (CD_3OD): 0.79 (d, 3 H, J = 7.6), 0.80 (s, 3 H), 0.85 (t, 3 H, J = 7.0), 0.86 (d, 3 H, J = 7.6), 0.95 (s, 3 H), 1.14 (s, 3 H), 1.16 (s, 3 H), 1.0–1.95 (m, 14 H), 2.24 (dd, 1 H, J = 7.9, 15.2), 2.35 (dd, 1 H, J = 4.7, 15.2), 3.7 (quint, 1 H), 4.0 (d, 1 H, J = 11.7), 4.08 (quint, 1 H), 4.36 (dd, 1 H, J = 1.7, 11.7). Anal. Calcd for $C_{25}H_{45}LiO_6 \cdot 0.7\ H_2O$: C, 65.11; H, 10.14. Found: C, 65.07; H, 10.40.

Preparation of 3b. 1 N LiOH (250 μL, 0.25 mmol) was added to a solution of the ester **25** (110 mg, 0.222 mmol) in freshly distilled dioxane (5 mL). After 2 h, additional 1 N LiOH (100 μL, 0.1 mmol) was added, and the reaction was judged to be complete by TLC after being stirred for an additional 1 h. The reaction mixture was concentrated in vacuo and the residue purified by CHP 20 (3:1 H_2O/MeCN). The appropriate fractions were combined and concentrated to remove MeCN. The remaining aqueous solution was millipore filtered and lyophilized to afford 85 mg (84.5%) of pure **3b** as its lithium salt. TLC: R_f = 0.24 (20:1:1 CH_2Cl_2/MeOH/AcOH, visualization by PMA). Mp = 168–178 °C. MS: $(M + Li)^+$ 447. IR: (KBr) 3420, 2961, 1725, 1585, 1422, 1250, 1164. $[\alpha]_D$ = +21.1° [c = 0.5, MeOH]. ^1H (CD_3OD): 0.8 (d, 3 H, J = 7), 0.85 (t, 3 H, J = 7.0), 0.86 (s, 3 H), 0.89 (s, 3 H), 0.92 (d, 3 H, J = 7), 1.14 (s, 3 H), 1.15 (s, 3 H), 1.1–1.4 (m, 3 H), 1.45–1.65 (m, 6 H), 1.66–1.74 (m, 1 H), 1.85–1.90 (m, 2 H), 2.23 (dd, 1 H, J = 7.7, 15.4), 2.38 (dd, 1 H, J = 4.4, 15.4), 3.93 (dd, 1 H, J = 2.2, 11.7), 4.02 (m, 1 H), 4.22 (dd, 1 H, J = 2.2, 11.7), 4.26–4.29 (m, 1 H), 5.37–5.48 (m, 2 H). Anal. Calcd for $C_{25}H_{43}LiO_6 \cdot 0.5H_2O$: C, 65.92; H, 9.73. Found: C, 66.14; H, 9.86.

Acknowledgment. We wish to thank Dr. Carl P. Ciosek for the biological testing of compounds, and Drs. Donald S. Karanewsky and Scott A. Biller for helpful discussions during the course of this work.

Registry No. **3a**·Li, 144225-27-4; **3b**·Li, 144225-28-5; **4**, 69153-92-0; **5**, 144225-29-6; **6**, 144225-30-9; **7**, 144225-31-0; **8** (isomer 1), 144225-32-1; **8** (isomer 2), 144300-60-7; **8** (isomer 3), 144300-61-8; **8** (isomer 4), 144300-62-9; (*E*)-**9**, 144225-33-2; (*Z*)-**9**, 144300-63-0; **10a**, 144225-34-3; **10b**, 144300-64-1; **11**, 96555-58-7; **13**, 144225-35-4; **14a** (isomer 1), 144225-36-5; **14a** (isomer 2), 144300-65-2; **14b** (isomer 1), 144225-37-6; **14b** (isomer 2), 144300-66-3; **14b** (isomer 3), 144300-67-4; **14b** (isomer 4), 144300-68-5; **15**, 119673-72-2; **17**, 144225-38-7; **18**, 144225-39-8; **19**, 144225-40-1; **20**, 144225-41-2; **21**·Li, 144225-42-3; **22**, 144225-43-4; **23**, 144225-44-5; **24**, 144225-45-6; **25**, 144225-46-7; **26**, 144225-47-8; **27**, 6553-64-6; **28**, 144225-48-9; **30**, 144225-49-0; **31**, 144225-50-3; **32** (isomer 1), 144225-51-4; **32** (isomer 2), 144300-69-6; **33** (isomer 1), 144225-52-5; **33** (isomer 2), 144300-70-9; **34** (isomer 1), 144225-53-6; **34** (isomer 2), 144300-71-0; **35**, 144225-54-7; **36** (isomer 1), 144225-55-8; **36** (isomer 2), 144300-72-1; (*S*)-HYTRA, 95061-51-1; (*R*)-(−)-carvone, 6485-40-1; HMT-CoA reductase, 9028-35-7; cholesterol, 57-88-5.

Zaragozic Acid A, a Potent Inhibitor of Squalene Synthase: Initial Chemistry and Absolute Stereochemistry

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Chemical studies on the highly potent squalene synthase inhibitor zaragozic acid A (1) have led to the determination of the total absolute stereochemistry of the molecule as shown in Figure 3 and to the feasibility of selectively manipulating the carboxyl and ester groups of the molecule. The absolute stereochemistry of the central core of 1 was established based on CD measurements on the bis(4-bromobenzoate) 8. The configuration of the methyl group in the C1 alkyl side chain was deduced by degrading 1 to (*R*)-(−)-2-methyl-3-phenylpropanoic acid, while the configuration of the adjacent acetoxy group was established from ^1H NMR considerations of the (*R*)- and (*S*)-*O*-methyl mandelates **14** and **15**. Single-crystal X-ray diffraction data on two crystalline derivatives (**16** and **17**) not only led to clarification of the asymmetric centers in the 4,6-dimethyl-2-octenoyl side chain but also afforded independent structural confirmation of the nature of the chemical and biological heart of zaragozic acid A.

Introduction

The screening of fermentation cultures for natural products that inhibit specific enzymatic steps in the synthesis of cholesterol has proven to be remarkably productive. Most significant were the codiscoveries of ML-236B and compactin from fermentations of *Penicillium* spp. and of monacolin K and mevinolin from fermentations of *Monascus ruber* and *Aspergillus terreus*, respectively.[1] These compounds and derivatives thereof are all potent inhibitors of the enzyme HMG-CoA reductase and have established themselves clinically as highly effective agents to reduce serum cholesterol in man. In addition to inhibitors of the reductase enzyme, screening activities by various research groups have resulted in the discovery of potent inhibitors to two earlier enzymes in the pathway from acetate to cholesterol, namely acetoacetyl-CoA thiolase[2] and HMG-CoA synthase.[3]

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(1) (a) Endo, A.; Kuroda, M.; Tanazawa, K. *FEBS Lett.* **1976**, *72*, 323–326. (b) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346–1348. (c) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165–1170. (d) Endo, A. *J. Antibiot.* **1979**, *32*, 852–854. (e) Alberts, A. W.; Chen, J.; Kuron, G.; Hunt, V.; Huff, J.; Hoffman, C.; Rothrock, J.; Lopez, M.; Joshua, H.; Harris, E.; Patchett, A.; Monaghan, R.; Currie, S.; Stapley, E.; Albers-Schonberg, G.; Hensens, O.; Hirschfield, J.; Hoogsteen, K.; Liesch, J.; Springer, J. *Proc. Nat. Acad. Sci. U.S.A.* **1980**, *77*, 3957–3961.

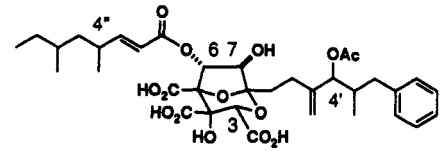
0022-3263/92/1957-7151$03.00/0

Recently, our screening efforts have concentrated on searching for inhibitors to squalene synthase (farnesyl diphosphate: farnesyl diphosphate transferase, EC 2.5.1.21), an enzyme which catalyzes the two-step conversion of two molecules of farnesyl pyrophosphate, first to presqualene pyrophosphate and subsequently to squalene.[4] As a result of our screening efforts along this line, three closely related fungal metabolites, zaragozic acids A (1), B (2), and C (3), were discovered as potent competitive inhibitors of squalene synthase.[5,6] The apparent K_i's for the three compounds range from 29 to 78 pM. The structures of the zaragozic acids are dramatically novel.[7] Common to all three compounds is the polar core unit, 2,8-dioxobicyclo[3.2.1]octane-4,6,7-trihydroxy-3,4,5-tricarboxylic acid. The distribution of functionality around the bicyclo[3.2.1]octane system resembles a conformationally restricted citric acid analog.

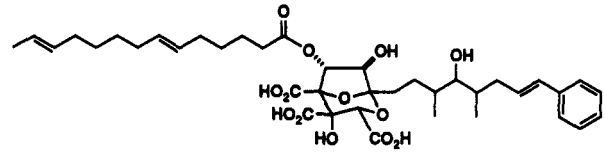
Zaragozic acids A, B, and C differ structurally from one another in terms of the alkyl appendage at C1 and the fatty acyl residue at C6-O. The relative stereochemistry of the substituents at C3, C4, C6, and C7 about the core of zaragozic acid A, B, and C has been defined based on NMR data and is as depicted in 1–3 but the absolute stereochemistry remained uncertain.[7,8] Because of the unprecedented nature of the structures, we felt that it was important not only to determine the absolute stereochemistry of the core but also to obtain independent confirmation of the core's relative stereochemistry.

We would like to report here results that permit the definition of the full absolute stereochemistry of zaragozic acid A and that also point out several selective chemical modifications of the functional groups within the molecule that will provide a basis on which to further develop the chemistry in the future.

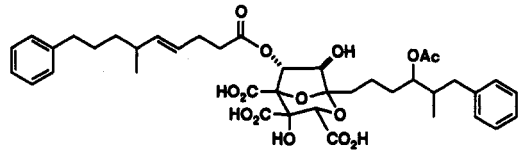
Selective Reactivity of Functional Groups in Zaragozic Acid A. Our initial attempts to get additional



1 zaragozic acid A



2 zaragozic acid B



3 zaragozic acid C

stereochemical evidence were directed at preparing crystalline salt and triester derivatives of zaragozic acid A, suitable for X-ray analysis. Unfortunately, perhaps partly due to the limited amount of compound initially available, neither approach led to any crystalline products. We then turned our attention to obtaining the information by alternative means.

The presence of the masked trans vicinal diol functionality of 1 seemed ideally suited for employing exciton coupled circular dichroism spectroscopy to establish the absolute stereochemistry of the core.[9] For this, the triol-trimethyl ester 5 was chosen as the starting material. Treatment of zaragozic acid A trimethyl ester (4) with 0.2% anhydrous K_2CO_3 in methanol at 30 °C for 80 min led to selective transesterification of the 4,6-dimethyl-2-octenoyl residue to give 5. Observation of a strong NOE signal between H3 and H6 in 5 established that no epimerization at C3 had occurred during the reaction. Interestingly, when transesterification was carried out under acid-catalyzed conditions (3% methanolic HCl at room temperature), selective removal of the 4'-*O*-acetyl moiety occurred, affording 6.

Worth comment is that the studies using methanolic K_2CO_3 also shed some light on the relative reactivities of the three methyl ester groups. When the transesterification of 4 was carried out with 0.2% K_2CO_3 in CD_3OD at 30 °C, 7 was obtained, in which the methyl esters at C3 and C5 of 6 had undergone exchange with the solvent. Monitoring of the exchange process by ^1H NMR showed that the methyl singlet at δ 3.71 ppm, corresponding to the ester at C3, was completely exchanged with CD_3 within 6 min.[10] By 75 min, the methyl on the C5 carboxyl at δ 3.68 ppm had fully exchanged while at least 80% of the C4-CO_2CH_3 signal at δ = 3.85 ppm remained intact. The results therefore indicate that the order of reactivity of the carbomethoxy residues of 4 is C3 > C5 > C4, at least with respect to attack by small nucleophiles at the carbonyl carbon. The differences in reactivity could

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(3) Greenspan, M. D.; Yodkovitz, J. B.; Chen, J. S.; Hanf, D. P.; Chang, M. N.; Chiang, P. Y. C.; Chabala, J. C.; Alberts, A. W. *Biochem. Biophys. Res. Commun.* **1989**, *163*, 548–553.

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(5) (a) Bergstrom, J. D.; Onishi, J. C.; Hensens, O. D.; Zink, D. L.; Huang, L.; Bills, G. F.; Nallin Omstead, M.; Rozdilsky, W.; Bartizal, K. F.; Dufresne, C.; Milligan, J. A.; Diez, M. T. Patent Appl. EP 448393 (publ. Sept. 25, 1991). (b) Bergstrom, J. D.; Liesch, J. M.; Hensens, O. D.; Onishi, J. C.; Huang, L.; VanMiddlesworth, F.; Diez, M. T.; Bartizal, K. F.; Nallin Omstead, M.; Rozdilsky, W.; Perez, F. P. Patent Appl. EP 450812 (publ. Oct. 9, 1991). (c) Bergstrom, J. D.; Onishi, J. C.; Huang, L.; Bills, G. F.; Nallin Omstead, M.; Bartizal, K. F.; Dufresne, C.; Diez, M. T. Patent Appl. EP 475,706 (publ. March 18, 1992). (d) Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Amend, A. M.; Karkas, J. D.; Bostedor, R. G.; Germershausen, J. I.; Bansan, V. S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O. D.; Liesch, J. M.; Zink, D. L.; Wilson, K. E.; Onishi, J.; Milligan, J. A.; Bills, G.; Bartizal, K. F.; Rozdilsky, W.; Abruzzo, G. K.; Kaplan, L.; Nallin Omstead, M.; Jenkins, R. G.; Huang, L.; Meinz, M. S.; Mojena, M.; Martin, I.; Palaez, F.; Diez, M.; Alberts, A. W. *Proc. Nat. Acad. Sci. U.S.A.*, in press.

(6) Subsequent to the initial submission of this paper for publication, scientists at Glaxo have announced the discovery of a compound identical to zaragozic acid A. (a) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neill, M. J.; Shuttleworth, A.; Stylli, C.; Tait, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. *J. Antibiot.* **1992**, *45*, 639–647. (b) Sidebottom, P. J.; Highcock, R. M.; Lane, S. J.; Procopiou, P. A.; Watson, N. S. *J. Antibiot.* **1992**, *45*, 648–658.

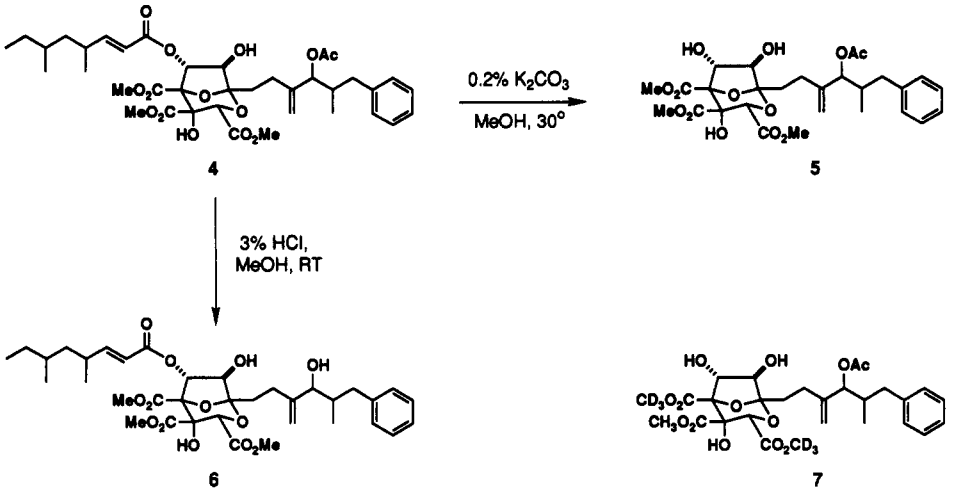
(7) (a) Bartizal, K. F.; Onishi, J. C. US Patent 5026554 (June 25, 1991). (b) Hensens, O. D.; Dufresne, C.; Liesch, J. M.; Zink, D. L.; Reamer, R. A.; VanMiddlesworth, F. Manuscript submitted to Tetrahedron Lett.

(8) Dufresne, C.; Wilson, K. E.; Zink, D. L.; Smith, J.; Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Nallin Omstead, M.; Jenkins, R. G.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J. C.; Milligan, J. A.; Mojena, M.; Pelaez, F. *Tetrahedron*, in press.

(9) Harada, H.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

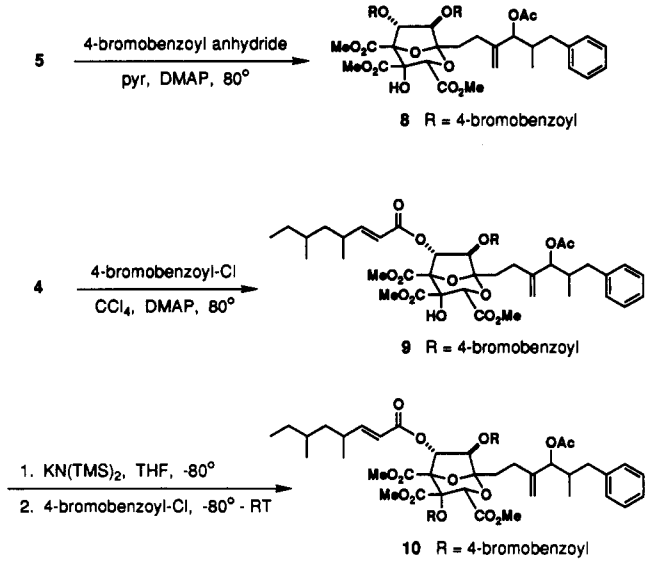
(10) Proton and carbon NMR assignments for 4 in CD_3OD are based on the results of one-bond proton–carbon correlation experiments (HETCOR, HMCQ) and multiple-bond proton–carbon correlation experiments (HETCOR, HMBC).

Scheme I



reasonably arise from a combination of steric factors and electronic assistance by the C4-OH through hydrogen bonding with the carbonyl oxygens of the esters at C3 and C5.

Absolute Stereochemistry of the Core. As a derivative suitable for exciton-coupled CD studies, the 6,7-bis(4-bromobenzoate) **8** of triol **5** was prepared. The trans relative stereochemistry of the benzoate residues is founded on the trans geometry ascribed to the C6,C7 substitutents of zaragozic acid A based on the observed H6–H7 coupling constant of 2.0 Hz.[11] The CD spectrum of **8** in dioxane exhibits a strong positive first Cotton effect at 255 nm ($\Delta\epsilon$ = +58) and a negative second Cotton effect at 238 nm ($\Delta\epsilon$ = −14), clearly arising from splitting of the two degenerate 4-bromobenzoate UV chromophores (λ_{max} = 252 nm). The results establish the absolute configuration at both C6 and C7 of zaragozic acid A to be *R*. From the relative core stereochemistry depicted in **1**, the configurations of C3 and C4 can then be assigned as *S* and *S*.



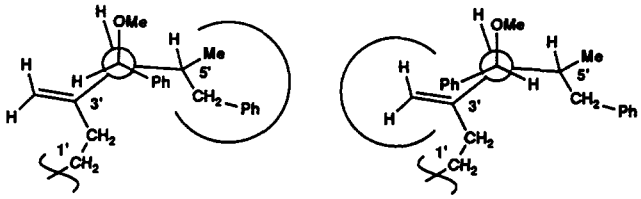
Although the absolute stereochemistry of the core had now been defined, our confidence in the C4 assignment was somewhat less than our confidence in the other asymmetric centers of the core due to the nature of the NMR arguments originally used to set its relative geometry.[7] To address this issue, the 4,7-bis(4-bromobenzoate) **10** of zaragozic acid trimethyl ester was prepared, which permitted independently defining by CD the C4 stereochemistry through correlation with the now-established C7(*R*). Treatment of **4** with excess 4-bromobenzoyl chloride and DMAP produced primarily the 7-(4-bromobenzoate) **9** and only a trace of **10**. Acylation of the C4-OH of **9** was successfully accomplished by preforming the C4 alkoxide with potassium bis(trimethylsilyl)amide, followed by quenching with 4-bromobenzoyl chloride. The CD spectrum of **10** displays a negative first Cotton effect at 258 nm ($\Delta\epsilon$ = −28) and a positive second Cotton effect at 240 nm ($\Delta\epsilon$ = +44). The benzoate at C7(*R*) is endo oriented. If the C4 benzoate is also endo, then a positive first Cotton effect would be predicted, irrespective of whether the 1,3-dioxane ring has a chair or boat conformation. If, on the other hand, the C4 benzoate is exo, then a negative first Cotton effect is predicted for a dioxane chair, while a weak ± first Cotton effect is predicted for a dioxane boat. Clearly, the observed CD data are only consistent with an exo orientation and therefore *S* configuration at C4, thereby confirming both the relative and absolute stereochemistry at this center.

Stereochemical Definition of the C1 Alkyl Side Chain. We next addressed the absolute stereochemistry of the 4′-acetoxy and 5′-methyl groups of the alkyl side chain appended at C1 of the core of zaragozic acid A. The configuration of the 5′-methyl appeared to be accessible by oxidatively degrading the side chain to 2-methyl-3-phenylpropanoic acid. At the outset of this phase of the project, no crystalline derivatives of zaragozic acid had yet been obtained. Because of this, we selected to degrade the bis(4-bromobenzoate) **8** with the idea that, besides affording the C5′ center in the desired form, the reaction would also produce a very compact core fragment. It was hoped that the compact core fragment might show a greater propensity to crystallize than had the previously examined derivatives with extended, conformationally flexible side chains.

Bis(4-bromobenzoate) **8** was first selectively deacetylated with 3% methanolic HCl to give the allylic alcohol **11** in 89% yield. Oxidation of **11** with ruthenium chloride and sodium periodate by the method of Sharpless[12] produced smoothly 2-methyl-3-phenylpropanoic acid (**12**) and the core derivative **13** in isolated yields of 67% and 72%, respectively. The isolated **12** was found to have a specific

(11) The trans geometry, in which the C7 hydroxy is endo, was strongly implied by (i) the observed NOE between H3 and H6 but not between H3 and H7 and (ii) the magnitude of the coupling constant $J_{H6,H7}$ = 2 Hz (ref 7).

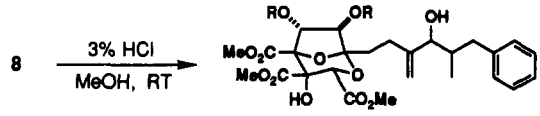
(12) Carlsen, Per H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.



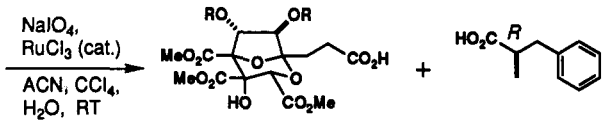
(R) - O-Me-mandelate (S) - O-Me-mandelate

Figure 1. Extended Newman projection of (S)-C4′-14 and (S)-C4′-15.

rotation of $[\alpha]_D = -16.7°$ (0.27 g/100 mL, MeOH), which establishes its absolute stereochemistry as (R)-2-methyl-3-phenylpropanoic acid and leads to an R configuration at C5′ of zaragozic acid.[13] Unfortunately, the core fragment 13 showed no greater willingness to crystallize than earlier derivatives.

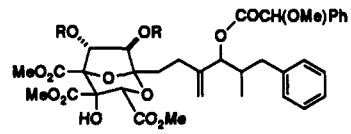


8 → 11 R = 4-bromobenzoyl



13 R = 4-bromobenzoyl 12

The configuration of the C4′ secondary hydroxyl of 11 was determined by employing the empirical O-methyl mandelate methodology of Trost et al.[14] The (R)- and (S)-O-methyl mandelate esters of 11 were prepared from the corresponding free acids using DCC and DMAP in 72% and 78% yields, respectively. A comparison of the proton NMR data for both compounds in $CDCl_3$ showed that the chemical shifts of the C5′ proton (δ = 1.90 ppm) and methyl group (δ = 0.54 ppm) and of the adjacent C6′ benzylic protons (δ = 2.32 and 1.87 ppm) in the zaragozic acid alkyl side chain of the (R)-O-methyl mandelate 14

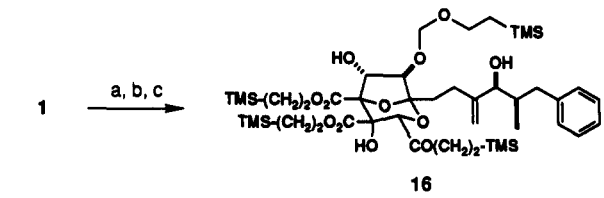


14 (R) - mandelate
15 (S) - mandelate

R = 4-bromobenzoyl

occur at higher field than the corresponding chemical shifts of the (S)-O-methyl mandelate 15 (δ: CH_3-C5′, 0.72 ppm; H-C5′, 2.03 ppm; H_2C6′, 2.60 and 2.24 ppm). In contrast, the protons of the exocylic methylene group at C4′ of the alkyl side chain appear at higher field in the S derivative 15 (δ = 4.72 and 4.49 ppm) than do those protons of the R derivative 14 (δ = 4.95 ppm, 2 H). The shift of proton resonances to higher field arises from the shielding effect of the eclipsed phenyl ring of the mandeloyl residue in extended Newman projection (Figure 1). The data are only consistent with this model if the configuration at C4′ of 14 and 15 is S.

Scheme II[a]



16

[a] (a) O-(2-TMSethyl)-N,N′-diisopropylisourea, PhH, 65 °C; (b) SEM-Cl, EtN(i-Pr)$_2$, CH_2Cl_2, reflux; (c) Ti(IV) ethoxide, 2-TMS-ethanol, 100 °C.

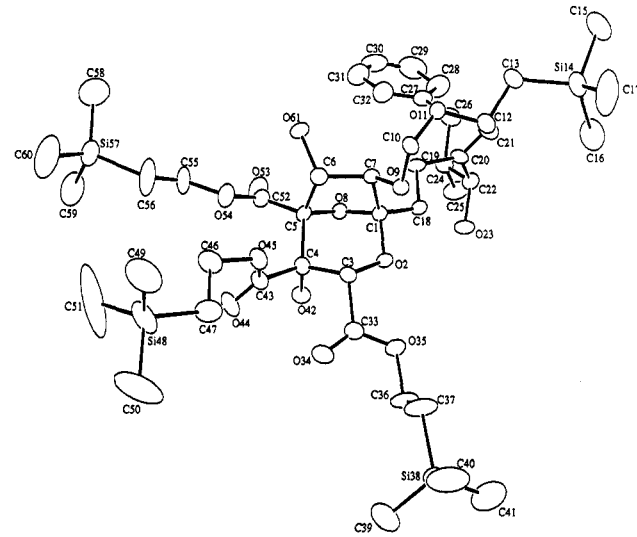


Figure 2. Perspective view (ORTEP) of 16, showing crystallographic numbering scheme. Ellipsoids represent 20% probability envelopes with hydrogens omitted for clarity.

In conclusion, the absolute stereochemistry of C4′ and C5′ in the alkyl side chain of zaragozic acid A is C4′(S) and C5′(R).

Crystallography. Subsequent to this work, the tetrakis(trimethylsilyl) derivative 16 was prepared and found to exist in a crystalline habit. The preparation of 16 proceeded smoothly from 1 in three steps—initial esterification using O-[2-(trimethylsilyl)ethyl]-N,N′-diisopropylisourea[15] followed by protection of the C7 alcohol as the SEM ether and finally transesterification of the C6-O acyl and C4′-O acetyl moieties.

Given the importance we placed on unambiguously determining the nature of the core structure, 16 was examined by single-crystal X-ray diffraction. The results of the structure determination are shown as a perspective drawing of the molecule in Figure 2. The core of the molecule is a 2,8-dioxobicyclo[3.2.1]octane unit which can be viewed as consisting of a six-membered ring (C1–O2–C3–C4–C5–O8) in a normal chair conformation with a two carbon bridge (C6 and C7) linking atoms C1 and C5. Each of the carbon atoms of this core is substituted with an additional group or groups. This dioxobicyclo core has also been observed in a series of furanose derivatives,[16] a shellfish toxin,[17] and a plant alkaloid.[18] However, this structure is the first example wherein such heavy substitution of the carbons of the bicyclic ring system has been observed. Bond distances and angles throughout the molecule are

(13) Schrecker, A. W. *J. Org. Chem.* **1957**, *22*, 33–35. (R)-2-Methyl-3-phenylpropanoic acid is reported to have $[\alpha]_D = -24.56°$ (neat).
(14) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370–2374.
(15) Mathias, L. J. *Synthesis* **1979**, 561–576.
(16) See, for example: Koll, P.; Saak, W.; Pohl, S. *Carbohydr. Res.* **1988**, *174*, 9–22.
(17) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019–1025.
(18) Sakabe, N.; Hirata, Y. *Tetrahedron Lett.* **1966**, 965–968.

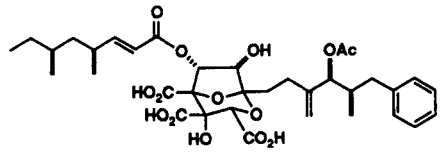
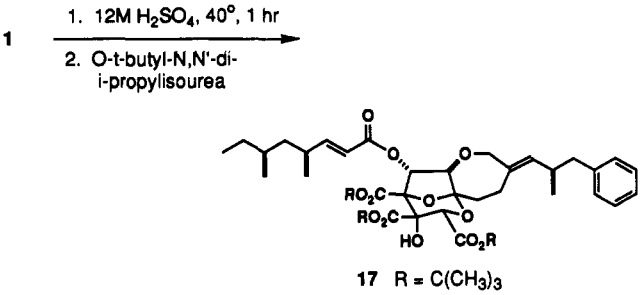


Figure 3. Absolute stereochemistry of zaragozic acid A.

reasonably representative of the various types given the inherent quality of the data. The molecules pack in a unit cell with few interactions other than generalized van der Waal forces, two exceptions being possible intermolecular hydrogen bonds between O11 and O23 (3.0 Å) and O42 and O61 (2.9 Å).

On the basis of the absolute configuration of C7 being *R* as determined by the CD work discussed above, the structural results determine that the other asymmetric centers of the core are C1(*S*), C3(*S*), C4(*S*), and C6(*R*). Thus, the original NMR stereochemical arguments used to deduce 1,[7] the CD work, and the crystallographic results are all in agreement on the relative configuration of the core substituents. In addition, the crystallographic results also support the stereochemical assignments of C4′(*S*) and C5′(*R*) made from the degradation and NMR studies described above.

At this point the only asymmetric centers of zaragozic acid A that remained undefined were C4″ and C6″ of the 4,6-dimethyl-2-octenoyl residue. The answer to this point came with the discovery that 1 rearranges under acidic conditions (aqueous H_2SO_4, 40 °C, 1 h) to a product which forms a crystalline tri-*tert*-butyl ester (17). With the stereochemistry at C7 fixed as *R* from the CD work, single-crystal X-ray diffraction studies of 17 established that both C4″ and C6″ have the *S* configuration.[19] The complete absolute stereochemistry of zaragozic acid A has therefore been determined as C1(*S*), C3(*S*), C4(*S*), C6(*R*), C7(*R*), C4′(*S*), C5′(*R*), C4″(*S*), and C6″(*S*) and is illustrated in Figure 3.



17 R = C(CH3)3

Conclusions

A knowledge of the absolute stereochemistry of a compound is a prerequisite before one can embark on studies to fully understand the influence of structure on biological activity. The unprecedented structural features of zaragozic acid A, particularly its central core, and our interest in understanding and developing its potent inhibitory activity on mammalian squalene synthase made the determination of absolute stereochemistry of critical importance. The full absolute stereochemistry of zaragozic acid A has now been defined, intentionally with some degree of redundancy. During this work selective removal of either the 4′-*O*-acetyl residue or the 4,6-dimethyl-2-octenoyl residue was accomplished. In addition, evidence was observed that selective manipulation of the individual carboxyl functions is also feasible. The chemist is now in a position to examine, in detail and with confidence, the fascinating structural similarity of the zaragozic acids with presqualene pyrophosphate, the intermediate in the enzyme step inhibited by the zaragozic acids and to investigate which functionality is critical for biological activity.

Experimental Section

General Methods. Proton NMR spectra were recorded either at 300 MHz on a Varian XL-300 spectrometer or at 400 or 500 MHz on a Varian VXR spectrometer. Carbon NMR spectra were recorded at 100 MHz on a Varian VXR spectrometer. Chemical shifts are reported in ppm downfield from TMS at 0 ppm, and spectra are referenced with respect to the solvent peak (δ_H = 7.24 ppm for $CDCl_3$; δ_H = 3.30 ppm and δ_C = 49.0 ppm for CD_3OD). Coupling constants are reported in Hz, and multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, and br = broadened. Infrared spectra were obtained on samples evaporated as films on a ZnSe multiple internal reflectance (MIR) crystal, using a Perkin-Elmer Model 1750 FTIR spectrometer. Band frequencies are reported in cm^{-1}. Bands are characterized as follows: s = strong, m = medium, w = weak, or br = broad. Ultraviolet spectra were recorded on a Beckmann DU70 spectrophotometer. The CD spectra were obtained on an AVIV Model 62DS circular dichroism spectrophotometer. Optical rotations were obtained on a Perkin-Elmer Model 241 polarimeter using a sodium lamp (589 nm, D line). Rotation data is reported as $[\alpha]^{temp}_D$ (concentration in g/100 mL, solvent). High-resolution liquid secondary ion mass spectrometry (HR LSIMS, Cs^+) data were acquired on a JEOL HX-110HF double-focusing mass spectrometer, operating at an accelerating voltage of 10 kV. Ultramark 1960F was used as the reference compound. The matrix was 3-nitrobenzyl alcohol, doped with LiOAc. High-resolution electron ionization mass spectrometry (HR EIMS, 90 eV) data were obtained on a MAT 212 double-focusing mass spectrometer. Perfluorokerosene was used as the internal reference compound.

Column chromatography employed E. Merck silica gel 60 (43–60 μm), and preparative thin-layer chromatography used E. Merck silica gel 60F glass plates (2.0-mm thickness).

Zaragozic Acid A, Trimethyl Ester (4). A solution of zaragozic acid A (243 mg, 80% pure, 0.281 mmol) in 15 mL of EtOAc was treated at −15 °C for 5 min with excess ethereal diazomethane. The excess diazomethane was neutralized with acetic acid, and the solution was concentrated to an oil that was chromatographed on silica gel (20 mL, 6:4 hexane/EtOAc). Concentration of the rich cut afforded 4 (151 mg, 73%) as a colorless oil: ^1H NMR (500 MHz, CD_3OD) δ 7.25 (m, 2 H, H9′, H11′), 7.18 (m, 2 H, H8′, H12′), 7.14 (m, 1 H, H10′), 6.79 (dd, *J* = 15.7, 8.8 Hz, 1 H, H3″), 6.29 (d, *J* = 2.0 Hz, 1 H, H6), 5.77 (dd, *J* = 15.7, 0.9 Hz, 1 H, H2″), 5.27 (s, 1 H, H3), 5.07 (br d, *J* = 4.8 Hz, 1 H, H4′), 5.01 (br s, 1 H, C3′=CHb), 4.97 (br s, 1 H, C3′=

(19) Colorless crystals of 17 were grown from *n*-butanol by evaporation. The crystal chosen for data collection (approximate dimensions 0.10 × 0.35 × 0.06 mm) was mounted in a nonspecific orientation on a Rigaku AFC5 diffractometer supplied with a rotating anode generator. The crystal data and experimental conditions are as follows: formula = $C_{45}H_{66}O_{12}$, M_r = 800.03, triclinic space group *P*1, *a* = 13.802 (2) Å, *b* = 14.545 (4) Å, *c* = 12.430 (3) Å, α = 92.79 (2)°, β = 96.42 (2)°, γ = 70.67 (2)°, *V* = 2339 Å^3, *Z* = 2, D_{calc} = 1.135 g cm^{-3}, μ(Cu K_α) = 0.63 mm^{-1}, *F*(000) = 866, *T* = 296 K. Data were collected[20] with Cu K_α monochromatized radiation (λ = 1.541 84 Å) to a 2θ limit of 140° yielding 8897 measured reflections. Scan type is ω − 2θ with a range of 0.79 + 0.14tan(θ)° and a variable speed of 0.5–16 deg min^{-1}. The data set was corrected for Lorentz, polarization, and background effects. Monitoring standard reflections (3 every 400 reflections) showed no decay correction necessary. Of the 8897 reflections measured there are 3916 observed data at the $I \geq 3\sigma(I)$ level. The data were corrected for absorption effects (maximum and minimum correction effects of 1.35 and 0.48).[23] The structure was solved using SHELXS-86[21] and refined[22] using full-matrix least-squares on *F* with a weighting scheme of $1/\sigma^2(F)$. Included in the refined parameters is a secondary extinction coefficient of 1.12 × 10^{-6}. The final agreement statistics, for 455 variables, are as follows: *R* = 0.080, *wR* = 0.070, *S* = 2.58, $(\Delta/\sigma)_{max}$ = 0.2. There is no structural significance to the maximum peak in a final difference Fourier (0.48 (6) e Å^{-3}). The refined structure model has all atoms assigned isotropic thermal parameters for both of the independent molecules. The H atoms are included at their calculated positions and constrained to ride with their attached atom. Tables of crystallographic coordinates, thermal parameters and geometrical quantities have been included in the supplementary material along with an ORTEP drawing of the molecule.

CHa), 4.04 (d, J = 2.2 Hz, 1 H, H7), 3.85 (s, 3 H, C4-CO_2CH_3), 3.71 (s, 3 H, C3-CO_2CH_3), 3.68 (s, 3 H, C5-CO_2CH_3), 2.67 (dd, J = 13.5, 6.4 Hz, 1 H, H6'b), ca. 2.44 (m, 1 H, H2'b), 2.32 (m, 1 H, H2'a), 2.43 (dd, J = 13.5, 8.6 Hz, 1 H, H6'a), 2.21 (m, 1 H, H5'), 2.10 (s, 3 H, C4'-$OCOCH_3$), ca. 2.00 (m, 2 H, H1'), 1.38 (m, 1 H, H5''b), ca. 1.31 (m, 1 H, H7''b), ca. 1.29 (m, 1 H, H6''), ca. 1.15 (m, 1 H, H7''a), ca. 1.13 (m, 1 H, H5''a), 1.03 (d, J = 6.7 Hz, 3 H, C4''-CH_3), 0.86 (t, J = 7.2 Hz, 3 H, H8''), 0.87 (d, J = 6.9 Hz, 3 H, C5'-CH_3), 0.85 (d, J = 6.7 Hz, 3 H, C6''-CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 11.6 (q, C8''), 14.3 (q, C5'-CH_3), 19.2 (q, C6''-CH_3), 20.8 (q, C4'-$OCOCH_3$), 21.0 (q, C4''-CH_3), 26.6 (t, C2'), 31.0 (t, C7''), 33.4 (d, C6''), 34.9 (t, C1'), 35.8 (d, C4''), 37.9 (d, C5'), 41.0 (t, C6'), 44.5 (t, C5''), 52.8 (q, C3-CO_2CH_3), 53.0 (q, C5-CO_2CH_3), 53.7 (q, C4-CO_2CH_3), 76.2 (s, C4), 76.9 (d, C3), 80.1 (d, C4'), 80.8 (d, C6), 82.2 (d, C7), 91.4 (s, C5), 107.2 (s, C1), 111.8 (t, C3'=CH_2), 119.8 (d, C2''), 127.0 (d, C10'), 129.4 (d, 2 ×, C9', C11'), 130.3 (d, 2 ×, C8', C12'), 141.7 (s, C7'), 147.7 (s, C3'), 157.9 (d, C3''), 166.1 (s, C1''), 167.2 (s, C5-CO_2CH_3), 168.7 (s, C3-CO_2CH_3), 171.2 (s, C4-CO_2CH_3), 172.2 (s, C4'-$OCOCH_3$); IR (film) 3481 (br, m), 2959 (m), 2929 (m), 1774 (m), 1738 (s), 1650 (w), 1439 (m), 1374 (m), 1241 (s), 1026 (m) cm^{-1}; HR EIMS calcd for $C_{38}H_{52}O_{14}$ 732.3357, found m/z 732.3373.

Triol 5. To zaragozic acid A, trimethyl ester (**4**, 1.6 g, 2.19 mmol), was added 200 mL of a freshly prepared methanolic solution of anhydrous potassium carbonate (0.2%). After being stirred for 80 min at room temperature, the reaction was neutralized with 6 mL of 0.1 N HCl and evaporated to an oil. Chromatography of the residue on silica gel (50 mL, 4:6 hexane/EtOAc) yielded triol **5** (0.86 g, 68%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.10–7.30 (m, 5 H), 5.14 (s, 1 H), 5.09 (d, J = 2 Hz, 1 H), 5.00 (br s, 1 H), 4.97 (br s, 1 H), 4.12 (d, J = 2 Hz, 1 H), 3.89 (s, 3 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 2.67 (dd, J = 13, 5.5 Hz, 1 H), 2.04–2.46 (m, 6 H), 2.09 (s, 3 H), 0.83 (d, J = 7 Hz, 3 H); IR (film) 3488 (br, s), 2956 (m), 1737 (s), 1650 (w), 1440 (m), 1374 (m), 1241 (s), 1031 (s) cm^{-1}; HR EIMS calcd for $C_{28}H_{36}O_{13}$ 580.2156, found m/z 580.2163.

4'-O-Desacetylzaragozic Acid A, Trimethyl Ester (6). Zaragozic acid A, trimethyl ester (**4**, 1.0 mg, 1.37 μmol), was dissolved in 0.15 mL of 3% methanolic HCl. After 16 h at room temperature, the solution was concentrated to dryness and the resulting residue was concentrated twice from fresh methanol. The ^1H NMR spectrum of the final oil (0.9 mg, 96%) indicated that the product was essentially pure **6**: ^1H NMR (300 MHz, CD_3OD) δ 7.30–7.09 (m, 5 H), 6.78 (dd, J = 15.5, 8.6 Hz, 1 H), 6.28 (d, J = 2.1 Hz, 1 H), 5.75 (dd, J = 15.6, 0.8 Hz, 1 H), 5.27 (s, 1 H), 5.09 (br s, 1 H), 4.98 (br s, 1 H), 4.08 (d, J = 2.0 Hz, 1 H), 3.90 (d, J = 5.0 Hz, 1 H), 3.85 (s, 3 H), 3.71 (s, 3 H), 3.67 (s, 3 H), 2.75 (dd, J = 13.3 Hz, 5.7 Hz, 1 H), 2.52–1.92 (m, 7 H), 1.44–1.08 (m, 5 H), 1.02 (d, J = 6.7 Hz, 3 H), 0.90–0.79 (m, 9 H); IR (film) 3431 (br, m), 2960 (m), 2928 (m), 1742 (s), 1649 (w), 1439 (m), 1253 (m), 1031 (m) cm^{-1}; HR EIMS calcd for $C_{36}H_{50}O_{13}$ 690.3251, found m/z 690.3256.

Bis(4-bromobenzoate) 8. To a solution of triol **5** (22 mg, 0.0379 mmol) in 0.5 mL of pyridine-d_5 was added 4-(N,N-dimethylamino)pyridine (20 mg, 0.164 mmol) and 4-bromobenzoyl anhydride (50 mg, 0.130 mmol). The solution was heated for 3 min at 80 °C and cooled to room temperature. ^1H NMR data indicated that the reaction was complete. The reaction was concentrated to a residue that was taken up in 10 mL of ether and washed successively with 0.1 N cold HCl (twice), water (twice), saturated aqueous $NaHCO_3$, water, and brine. After being dried over anhydrous Na_2SO_4, the ethereal solution was concentrated to an oil. The residue was chromatographed on silica gel (2.5 mL, 6:4 hexane/EtOAc) to yield **8** (32 mg, 89%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.79–7.89 (m, 4 H), 7.54–7.64 (m, 4 H), 7.07–7.24 (m, 5 H), 6.66 (d, J = 2.5 Hz, 1 H), 5.46 (d, J = 2.5 Hz, 1 H), 5.20 (s, 1 H), 5.08 (d, J = 5.1 Hz, 1 H), 4.99 (br s, 1 H), 4.97 (br s, 1 H), 3.95 (s, 3 H), 3.79 (s, 3 H), 3.66 (s, 3 H), 2.68 (dd, J = 13.2, 5.1 Hz, 1 H), 1.98–2.44 (m, 6 H), 2.04 (s, 3 H), 0.78 (d, J = 6.6 Hz, 3 H); UV (dioxane) λ_{max} 252 nm (ϵ = 35 300); CD (dioxane) λ_{max} 255 nm ($\Delta\epsilon$ = +58), 238 nm ($\Delta\epsilon$ = −14); IR (film) 3453 (br, w), 2954 (w), 1775 (m), 1734 (s), 1590 (m), 1439 (m), 1260 (s), 1097 (m), 1012 (m) cm^{-1}; HR LSIMS calcd for [$C_{42}H_{42}O_{15}{}^{79}Br_2$ + Li] 951.1050, found m/z 951.1044.

4-Bromobenzoate 9. To a solution of zaragozic acid A, trimethyl ester (**4**, 110 mg, 0.150 mmol), in 9 mL of CCl_4 was added 4-(N,N-dimethylamino)pyridine (110 mg, 0.902 mmol) and 4-bromobenzoyl chloride (300 mg, 1.47 mmol). The resulting white suspension was heated under nitrogen for 24 h at 80 °C. The reaction was cooled and diluted with 40 mL of ether and 10 mL of cold 0.1 N HCl. The ether layer was washed successively with cold 0.1 N HCl (twice), saturated aqueous $NaHCO_3$, water (twice), and brine and dried over $MgSO_4$. Evaporation of the solvent afforded a residue that was chromatographed on silica gel (7 mL, 6:4 hexane/EtOAc). Upon concentration, **9** (112 mg, 81%) was obtained as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (dt, J = 8.6, 2 Hz, 2 H), 7.59 (dt, J = 8.8, 2 Hz, 2 H), 7.25–7.06 (m, 5 H), 6.83 (dd, J = 15.8, 8.4 Hz, 1 H), 6.47 (d, J = 2.5 Hz, 1 H), 5.72 (dd, J = 15.6, 1 Hz, 1 H), 5.41 (d, J = 2.4 Hz, 1 H), 5.18 (s, 1 H), 5.08 (d, J = 5.0 Hz, 1 H), 4.98 (br s, 1 H), 4.96 (br s, 1 H), 3.95 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 2.67 (dd, J = 13, 4.6 Hz, 1 H), 2.46–1.98 (m, 7 H), 2.04 (s, 3 H), 1.39–1.00 (m, 5 H), 1.01 (d, J = 6.7 Hz, 3 H), 0.90–0.75 (m, 9 H); IR (film) 3465 (br, w), 2960 (m), 2927 (m), 1775 (m), 1734 (s), 1650 (m), 1590 (m), 1439 (m), 1241 (s), 1119 (s), 1013 (s) cm^{-1}; HR LSIMS calcd for [$C_{45}H_{55}O_{15}{}^{79}Br$ + Li] 921.2884, found m/z 921.2919.

Bis(4-bromobenzoate) 10. To a solution of **9** (5 mg, 5.46 μmol) in 0.4 mL of THF at −80 °C under nitrogen was added a 0.5 M solution of potassium bis(trimethylsilyl)amide (15 μL, 7.5 μmol) in toluene. After being stirred for 15 min, the reaction was treated at −80 °C with 4-bromobenzoyl chloride (3.7 mg, 18.2 μmol) dissolved in 25 μL of THF. The reaction was stirred for 15 min at −80 °C, allowed to warm to room temperature over 30 min, and stirred at room temperature for 2 h. The reaction was diluted with 5 mL of ether, washed successively with cold 1 N HCl, water (twice), and brine, and dried over $MgSO_4$. Following concentration, the residue was purified by preparative silica gel TLC (1:1 hexane/EtOAc) to afford the desired bis(4-bromobenzoate) **10** (3.5 mg, 58%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.7 Hz, 2 H), 7.82 (d, J = 8.7 Hz, 2 H), 7.60 (d, J = 8.7 Hz, 2 H), 7.49 (d, J = 8.7 Hz, 2 H), 7.24–7.10 (m, 3 H), 6.97 (br d, J = 6.7 Hz, 2 H), 6.87 (dd, J = 15.8, 8.3 Hz, 1 H), 6.68 (d, J = 2.8 Hz, 1 H), 5.75 (d, J = 15.8 Hz, 1 H), 5.42 (d, J = 2.8 Hz, 1 H), 5.27 (s, 1 H), 4.99 (d, J = 6.0 Hz, 1 H), 4.95 (br s, 1 H), 4.90 (br s, 1 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 2.56 (dd, J = 13.7, 4.6 Hz, 1 H), 2.08–2.49 (m, 6 H), 2.03 (s, 3 H), 1.77 (m, 1 H), 1.42–1.04 (m, 5 H), 1.02 (d, J = 6.6 Hz, 3 H), 0.88–0.78 (m, 6 H), 0.69 (d, J = 6.6 Hz, 3 H); UV (dioxane) λ_{max} 255 nm (ϵ = 36 000); CD (dioxane) λ_{max} 258 nm ($\Delta\epsilon$ = −28), 240 nm ($\Delta\epsilon$ = +44); IR (film) 2927 (m), 1775 (m), 1737 (s), 1650 (w), 1590 (m), 1262 (s), 1121 (m), 1012 (m) cm^{-1}; HR LSIMS calcd for [$C_{52}H_{58}O_{16}{}^{79}Br_2$ + Li] 1103.2252, found m/z 1103.2252.

4'-O-Desacetylbis(4-bromobenzoate) 11. A solution of bis(bromobenzoate) **8** (20 mg, 0.0211 mmol) in 2 mL of 3% methanolic HCl was stirred for 16 h at room temperature, concentrated to an oil, and evaporated twice from methanol. The residue was chromatographed on silica gel (1 mL, 6:4–4:6 hexane/EtOAc). Final concentration afforded **11** (17 mg, 89%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.3 Hz, 2 H), 7.79 (d, J = 8.5 Hz, 2 H), 7.61 (d, J = 8.5 Hz, 2 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.26–7.05 (m, 5 H), 6.63 (d, J = 2.1 Hz, 1 H), 5.49 (d, J = 2.1 Hz, 1 H), 5.19 (s, 1 H), 5.14 (br s, 1 H), 5.00 (br s, 1 H), 4.08 (br d, J = 4.4 Hz, 1 H), 3.93 (s, 3 H), 3.79 (s, 3 H), 3.66 (s, 3 H), 2.75 (dd, J = 13.4, 6.1 Hz, 1 H), 2.58–2.14 (m, 5 H), 1.91 (m, 1 H), 0.82 (d, J = 6.6 Hz, 3 H); IR (film) 3462 (br, w), 2957 (w), 1774 (m), 1733 (s), 1590 (m), 1439 (m), 1259 (s), 1097 (m), 1012 (m); HR LSIMS calcd for [$C_{40}H_{40}O_{14}{}^{79}Br_2$ + Li] 909.0945, found m/z 909.0920; calcd for [$C_{40}H_{40}O_{14}{}^{79}Br^{81}Br$ + Li] 911.0924, found m/z 911.0908; calcd for [$C_{40}H_{40}O_{14}{}^{81}Br_2$ + Li] 913.0904, found m/z 913.0920.

(R)-2-Methyl-3-phenylpropanoic Acid (12) and Core Fragment 13. To a solution of bis(4-bromobenzoate) **11** (90 mg, 0.0996 mmol) in a mixture of 1 mL of ACN and 1 mL of CCl_4 was added 1 mL of an aqueous solution of $NaIO_4$ (117 mg, 0.547 mmol). The mixture was stirred vigorously, and a solution of ruthenium(III) chloride trihydrate (1.46 mg, 0.005 58 mmol) in 0.5 mL of water was added. The mixture was stirred vigorously for 3.5 h at room temperature. Five mL of CH_2Cl_2 was added to the reaction. The upper organic layer was removed, and the lower aqueous layer was extracted three times with 5 mL of CH_2Cl_2. The combined organic solutions were diluted with 1.5 volumes of ether and filtered through Celite to remove insoluble ruthenium

salts. The filtrate was concentrated to an oil (98 mg), which was then purified by chromatography on silica gel (2 mL). **12** eluted with hexane/EtOAc/glacial HOAc (80:20:1), while the core fragment **13** eluted with hexane/EtOAc/glacial HOAc (55:45:1). Concentration of rich cuts afforded **12** (11 mg, 67%) and **13** (56 mg, 72%) as colorless oils.

12: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31–7.14 (m, 5 H), 3.06 (dd, J = 13.0, 6.0 Hz, 1 H), 2.75 (sextet, J = 6.3 Hz, 1 H), 2.67 (dd, J = 13.1, 7.9 Hz, 1 H); IR (film) 3400–2600 (br, s), 3029 (m), 2975 (m), 1703 (s), 1605 (w), 1496 (m), 1455 (m), 1289 (m), 1241 (m), 745 (m), 700 (m) cm^{-1}; $[\alpha]^{23}_D$ = −16.7° (0.27, MeOH); HR EIMS calcd for $C_{10}H_{12}O_2$ 164.0837, found m/z 164.0837.

13: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2 H), 7.80 (d, J = 8.4 Hz, 2 H), 7.61 (d, J = 8.5 Hz, 2 H), 7.57 (d, J = 8.4 Hz, 2 H), 6.66 (d, J = 2.3 Hz, 1 H), 5.43 (d, J = 2.4 Hz, 1 H), 5.17 (s, 1 H), 3.94 (s, 3 H), 3.78 (s, 3 H), 3.64 (s, 3 H), 2.87–2.65 (m, 2 H), 2.51–2.28 (m, 2 H); IR (film) 3600–2600 (br), 2957 (w), 1773 (m), 1733 (s), 1590 (m), 1485 (w), 1439 (m), 1400 (w), 1261 (s), 1098 (s), 1012 (s), 754 (s) cm^{-1}; HR LSIMS calcd for $[C_{29}H_{26}O_{15}{}^{79}Br_2$ + Li] 778.9798, found m/z 778.9753; calcd for $[C_{29}H_{26}O_{15}{}^{79}Br^{81}Br$ + Li] 780.9778, found m/z 780.9738; calcd for $[C_{29}H_{26}O_{15}{}^{81}Br_2$ + Li] 782.9758, found m/z 782.9729.

(*R*)-*O*-Methyl Mandelate 14. To a solution of bis(4-bromobenzoate) **11** (44 mg, 0.0487 mmol) in 1 mL of CH_2Cl_2 was added (*R*)-(−)-α-methoxyphenylacetic acid (24 mg, 0.144 mmol), dicyclohexylcarbodiimide (34 mg, 0.165 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (2 mg, 0.0164 mmol). The mixture was stirred at room temperature for 2.5 h, diluted with 5 mL of hexane, filtered, and evaporated in vacuo. The residue was taken up in 16 mL of hexane/CH_2Cl_2 (3:1) and washed successively with cold 1 N aqueous HCl, water, saturated aqueous sodium bicarbonate, and brine. After drying over $MgSO_4$, the solution was evaporated to a residue that was chromatographed on silica gel (1 mL, 7:3 hexane/EtOAc) to afford **14** (37 mg, 72%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H), 7.60 (d, J = 8.3 Hz, 2 H), 7.57 (d, J = 7.9 Hz, 2 H), 7.45 (br d, J = 7 Hz, 2 H), 7.41–7.26 (m, 3 H), 7.16–7.03 (m, 3 H), 6.79 (br d, J = 6 Hz, 2 H), 6.65 (d, J = 2.3 Hz, 1 H), 5.44 (d, J = 2.3 Hz, 1 H), 5.20 (s, 1 H), 5.07 (d, J = 3.4 Hz, 1 H), 4.95 (br s, 2 H), 4.78 (s, 1 H), 3.95 (s, 3 H), 3.79 (s, 3 H), 3.66 (s, 3 H), 3.38 (s, 3 H), 2.42–2.13 (m, 5 H), 2.02–1.84 (m, 2 H), 0.54 (d, J = 6.1 Hz, 3 H); IR (film) 3459 (br, w), 2953 (w), 1775 (m), 1733 (s), 1590 (m), 1265 (s), 1098 (m), 1012 (m) cm^{-1}; HR LSIMS calcd for $[C_{49}H_{48}O_{16}{}^{79}Br_2$ + Li] 1057.1469, found m/z 1057.1476.

(*S*)-*O*-Methyl Mandelate 15. The preparation of **15** from **11** (45 mg, 0.0496 mmol) and (*S*)-(+)-α-methoxyphenylacetic acid (24 mg, 0.144 mmol) was identical to that described above for the (*R*)-*O*-methyl mandelate **14** and afforded **15** (41 mg, 78%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.7 Hz, 2 H), 7.82 (d, J = 8.8 Hz, 2 H), 7.59 (d, J = 8.8 Hz, 2 H), 7.57 (d, J = 8.6 Hz, 2 H), 7.40 (br d, J = 7.4 Hz, 2 H), 7.35–7.08 (m, 6 H), 7.01 (br d, J = 7.0 Hz, 2 H), 6.64 (d, J = 2.3 Hz, 1 H), 5.38 (d, J = 2.4 Hz, 1 H), 5.17 (s, 1 H), 5.10 (d, J = 4.6 Hz, 1 H), 4.74 (s, 1 H), 4.72 (br s, 1 H), 4.49 (br s, 1 H), 3.94 (s, 3 H), 3.78 (s, 3 H), 3.65 (s, 3 H), 3.39 (s, 3 H), 2.60 (dd, J = 13.3 Hz, 5.4 Hz, 1 H), 2.37–1.95 (m, 6 H), 0.72 (d, J = 6.6 Hz, 3 H); IR (film) 3460 (br, w), 2953 (w), 1775 (m), 1733 (s), 1590 (m), 1261 (s), 1098 (m), 1012 (m) cm^{-1}; HR LSIMS calcd for $[C_{49}H_{48}O_{16}{}^{79}Br_2$ + Li] 1057.1469, found m/z 1057.1488.

Tetrakis-TMS Triol 16. A solution of **1** (0.75 g, 1.08 mmol) and *O*-[2-(trimethylsilyl)ethyl]-*N*,*N*′-diisopropylisourea (2.64 g, 14.5 mmol) in 40 mL of benzene was heated at 65 °C for 16 h. The reaction was allowed to cool and was concentrated in vacuo. The residue was purified by silica gel chromatography (3:1 hexane/EtOAc) to afford the tris-2-(trimethylsilyl)ethyl ester of **1** (0.89 g, 83%) as a greenish-yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.11 (m, 5 H), 6.85 (dd, J = 15.6 Hz, 8.5 Hz, 1 H), 5.84 (d, J = 1.8 Hz, 1 H), 5.73 (d, J = 15.6 Hz, 1 H), 5.17 (s, 1 H), 5.08 (d, J = 4.8 Hz, 1 H), 4.96 (br s, 1 H), 4.95 (br s, 1 H), 4.40–4.18 (m, 6 H), 4.01 (m, 1 H), 3.81 (s, 1 H), 3.11 (d, J = 2.4 Hz, 1 H), 2.67 (dd, J = 13.6, 5.2 Hz, 1 H), 2.41–2.07 (m, 7 H), 2.07 (s, 3 H), 1.35–0.91 (m, 11 H), 1.01 (d, J = 6.9 Hz, 3 H), 0.85–0.79 (m, 9 H), 0.046 (s, 9 H), 0.016 (s, 9 H), −0.005 (s, 9 H); IR (film) 3471 (br, m), 2955 (m), 1767 (m), 1737 (s), 1650 (w), 1250 (s), 1180 (m), 860 (s), 838 (s) cm^{-1}; HR LSIMS calcd for $[C_{50}H_{82}Si_3O_{14}$ + Li] 997.5173, found m/z 997.5200.

A solution of the above tris-2-(trimethylsilyl)ethyl ester (0.58 g, 0.586 mmol), *N*,*N*′-diisopropylethylamine (2.4 mL, 14.1 mmol), and [2-(trimethylsilyl)ethoxy]methyl chloride (2.0 mL, 11.73 mmol) in 16 mL of CH_2Cl_2 was refluxed for 24 h. After being cooled to room temperature, the reaction was washed successively with 1 N HCl, 5% aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by silica gel chromatography (4:1 hexane/EtOAc) to afford 7-*O*-[[(trimethylsilyl)ethoxy]methyl]zaragozic acid A, tris[2-(trimethylsilyl)ethyl ester] (0.61 g, 95%) as a clear yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.12 (m, 5 H), 6.84 (dd, J = 15.6, 8.0 Hz, 1 H), 6.41 (d, J = 1.6 Hz, 1 H), 5.70 (d, J = 15.6 Hz, 1 H), 5.13 (s, 1 H), 5.10 (d, J = 4.8 Hz, 1 H), 4.97 (br s, 1 H), 4.82 (d, J = 6.8 Hz, 1 H), 4.72 (d, J = 6.8 Hz, 1 H), 4.40–4.34 (m, 2 H), 4.22–4.11 (m, 4 H), 4.09 (d, J = 2.0 Hz, 1 H), 3.84 (s, 1 H), 3.65–3.56 (m, 2 H), 2.70 (dd, J = 13.6, 5.2 Hz, 1 H), 2.50–2.05 (m, 7 H), 2.07 (s, 3 H), 1.33–0.91 (m, 11 H), 0.99 (d, J = 6.4 Hz, 3 H), 0.90–0.78 (m, 11 H), 0.05 (s, 9 H), −0.01 (s, 9 H), −0.02 (s, 9 H), −0.05 (s, 9 H); IR (film) 3454 (br, w), 2957 (m), 1769 (m), 1738 (s), 1650 (w), 1250 (s), 861 (s), 838 (s) cm^{-1}; HR LSIMS calcd for $[C_{56}H_{96}Si_4O_{15}$ + Li] 1127.5986, found m/z 1127.6000.

A solution of the above 7-*O*-[(trimethylsilyl)ethoxy]methyl ether (0.56 g, 0.504 mmol) in 1.0 mL of 2-(trimethylsilyl)ethanol was treated with titanium(IV) ethoxide (100 μL, 0.476 mmol) and heated at 100 °C for 24 h. The reaction was cooled to room temperature, quenched with 1 N HCl, and stirred for 1 h. Following extraction with EtOAc (2×), the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by chromatography on silica gel (4:1 hexane/EtOAc) gave the triol **16** (0.31 g, 66%) as a white solid which was recrystallized from warm hexane: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.15 (m, 5 H), 5.18 (dd, J = 5.4 Hz, 1.8 Hz, 1 H), 5.15 (br s, 1 H), 5.03 (br s, 1 H), 4.98 (s, 1 H), 4.84 (d, J = 6.9 Hz, 1 H), 4.72 (d, J = 6.9 Hz, 1 H), 4.36–4.17 (m, 6 H), 4.11 (br m, 1 H), 3.96 (d, J = 1.8 Hz, 1 H), 3.75 (s, 1 H), 3.73–3.60 (m, 2 H), 2.85 (d, J = 3.0 Hz, 1 H), 2.78 (dd, J = 13.2, 5.6 Hz, 1 H), 2.52–1.86 (m, 8 H), 1.55–0.93 (m, 8 H), 0.83 (d, J = 6.6 Hz, 3 H), 0.05 (s, 9 H), 0.013 (s, 18 H), −0.004 (s, 9 H); IR (film) 3467 (br, m), 2954 (m), 2898 (w), 1761 (m), 1736 (m), 1250 (s), 1063 (m), 861 (s), 837 (s) cm^{-1}; HR LSIMS calcd for $[C_{44}H_{78}Si_4O_{13}$ + Li] 933.4680, found m/z 933.4663.

Acid Rearrangement Product 17. A solution of 1.0 g of zaragozic acid A (1.0 g, 1.45 mmol) in 5 mL of THF was treated with 5 mL of 12 M aqueous H_2SO_4 and stirred at 40 °C for 1 h. The reaction mixture was mixed with 10 mL of brine and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated to yield 906 mg of a gummy product. A portion of this product (500 mg) was dissolved in 5 mL of CH_2Cl_2, treated with *O*-*tert*-butyl-*N*,*N*′-diisopropylisourea (1.20 g, 6.00 mmol), and stirred for 15 h at 40 °C. The reaction was filtered. The filtrate was evaporated to an oil, reconstituted in 20 mL of EtOAc, washed with 1 N HCl (3 × 20 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. Purification by silica gel chromatography (EtOAc/hexane (3:7)) gave **17** (309 mg, 53%), which was recrystallized from EtOAc to yield 119 mg of **17** as needles: ^{1}H NMR (400 MHz, CD_3OD) δ 7.26–7.07 (m, 5 H), 6.94 (dd, J = 15.6, 8.5 Hz, 1 H), 6.35 (d, J = 2.4 Hz, 1 H), 5.88 (dd, J = 15.6, 0.9 Hz, 1 H), 5.33 (d, J = 10.1 Hz, 1 H), 4.91 (s, 1 H), 4.19 (d, J = 11.2 Hz, 1 H), 4.13 (d, J = 11.2 Hz, 1 H), 3.61 (d, J = 2.4 Hz, 1 H), 2.83–2.35 (m, 5 H), 1.97–1.70 (m, 2 H), 1.58 (s, 9 H), 1.49 (s, 9 H), 1.45 (s, 9 H), 1.40–1.10 (m, 4 H), 1.06 (m, 6 H), 0.88 (m, 3 H); IR (film) 3441 (br, w), 2960 (m), 2930 (m), 2869 (w), 1763 (w), 1736 (s), 1651 (w), 1455 (m), 1162 (s), 1120 (s), 1029 (m) cm^{-1}; HR LSIMS calcd for $[C_{45}H_{66}O_{12}$ + Li] 805.4714, found m/z 805.4733.

Crystallography. A crystal of the tetrakis(trimethylsilyl) derivative **16** was selected from a sample recrystallized from hexane and mounted on a Rigaku AFC5R diffractometer for data collection. The crystals were marginal with very broad diffraction peaks, and the resulting data set was not of high quality. Nevertheless, a direct methods solution was found and successfully refined to a final agreement factor of 6.5%. The crystal data and experimental conditions are as follows: formula = $C_{44}H_{78}O_{13}Si_4$, M_r = 927.45, space group = $P2_12_12_1$, a = 12.81 (3) Å, b = 67.0 (2) Å, c = 6.42 (1) Å, V = 5510 Å^3, Z = 4, D_x = 1.120 g cm^{-3}, Cu K_α monochromatized radiation, μ = 1.44 mm^{-1}, $F(000)$ = 2008, T =

296 K. One octant of data was collected[20] to a 2θ limit of 145° for 6268 measured reflections with 2708 observed with $I \geq 3\sigma(I)$. The structure was solved using SHELXS-86[21] and refined[22] using full-matrix least-squares on F with a weighting scheme of $1/\sigma^2(F)$. The final agreement statistics are as follows: $R = 0.065$, $wR = 0.065$, $S = 2.88$, $(\Delta/\sigma)_{max} = 0.07$ for 550 parameters. The maximum peak height in a final difference Fourier is 0.25(6) e Å^{-3}. The refined structure model has all non-H atoms refined with anisotropic thermal parameters and the H atoms included at their calculated positions and constrained to ride with their attached atom. The trimethylsilyl groups possibly suffer from rotational disorder, as indicated by the large thermal parameters for these atoms. However, examination of difference Fourier maps does not reveal obvious alternate positions, and it was decided to limit the model to anisotropic refinement without disorder positions.

Refinement of the enantiomeric structure, under identical conditions, gave R-factors which were not significantly different from the original model. Thus, the anomalous dispersion effects of the Si atoms do not, in this case, permit assignment of the absolute configuration based solely on the crystallography.

Tables of crystallographic coordinates, thermal parameters, and geometrical quantities have been included in the supplementary material.

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Supplementary Material Available: Proton NMR spectra of 4–6 and 8–15 and the ORTEP diagram of 17 (12 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(Z)- and (E)-γ-Silyloxy Allylic Stannanes. Highly Syn Selective Reagents for S_E' Additions to Aldehydes

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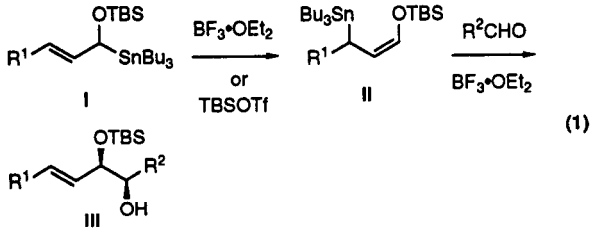
The (E)-γ-silyloxy allylic stannane **2E**, available in one step through addition of $Bu(Bu_3Sn)Cu(CN)Li_2$ to crotonaldehyde and subsequent in situ quenching of the enolate with t-$BuMe_2SiCl$, undergoes BF_3-promoted addition to representative aldehydes **3a–e**, affording syn adducts **4a–e** with >99:1 diastereoselectivity. The (Z)-γ-silyloxy allylic stannane **2Z** can be prepared by treatment of the adduct from Bu_3SnLi and crotonaldehyde with TBSOTf in the presence of i-Pr_2NEt. Stannane **2Z** also affords syn adducts upon BF_3-promoted addition to aldehydes **3a–e** but with somewhat lower diastereoselectivity (93:7–99:1).

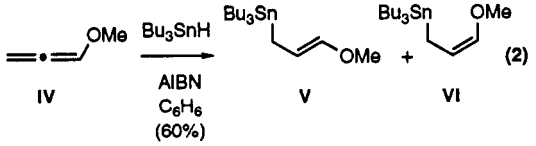
We recently described the synthesis of (Z)-γ-silyloxy allylic stannanes through 1,3-isomerization of the (E)-α-silyloxy isomers (eq 1).[1] At the time we noted that the



(1)

crotyl reagent (**II**, $R^1 = CH_3$) added to heptanal to give the adduct **III** ($R^1 = CH_3$, $R^2 = n$-C_6H_{13}) with 97:3 syn:anti selectivity. We subsequently employed the tridecenyl analogue of **II** ($R^1 = n$-$C_{10}H_{21}$) in a synthesis of the cytotoxic acetogenins (+)- and (−)-muricatacin.[2] In that application addition of **II** ($R^1 = n$-$C_{10}H_{21}$) to a conjugated aldehyde also proceeded with high syn stereoselectivity (95:5). The present report discloses a general route to (E)-γ-silyloxy allylic stannanes and summarizes our findings on additions of both Z and E isomers to representative aldehydes leading to syn 1,2-diol derivatives with >99:1 diastereoselectivity in the case of the latter reagents.

Prior to these studies (E)-γ-alkoxy allylic stannanes were not generally available. Koreeda prepared the (E)-(γ-methoxyallyl)stannane **V** as a 1:1 mixture with the Z isomer **VI**, through hydrostannation of methoxyallene (eq 2).[3]



(2)

We find that the higher order cyanocuprate $Bu(Bu_3Sn)Cu(CN)Li_2$[4] smoothly adds 1,4 to enals, and the resulting (E)-enolate can be trapped with TBSCl (eq 3).[5] In contrast, the 1,2-adduct of enal 1, secured through addition of Bu_3SnLi undergoes O-silylation and in situ isomerization

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(5) These enolates can also be trapped with reactive halides such as MOMCl and BOMCl. Additional studies to examine the scope of this method are in progress.

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