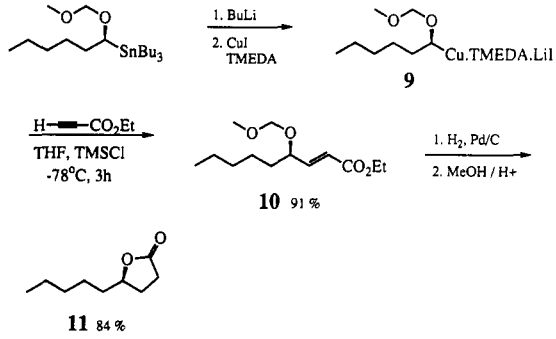
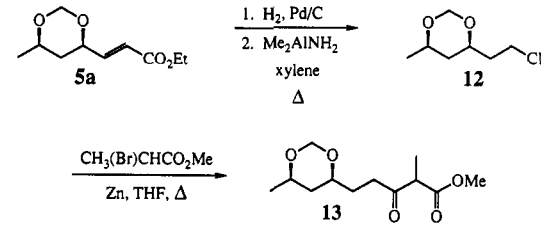
Since the cyclic α-alkoxy TMEDA–organocopper reagent was shown to give the 1,4-addition product **5** with complete retention of configuration, the acyclic α-alkoxy TMEDA organocopper reagent **9** was also investigated. The organocopper reagent was prepared from the corresponding stannane of 98% ee. Addition to ethyl propiolate provided heptenoate **10** in 98% yield. Hydrogenation and acidic methanolysis directly produced pelargono lactone.[3] Unfortunately, the lactone was obtained in only 18% ee.[16] Therefore, generation of acyclic α-alkoxyorganocopper reagents in lieu of the higher order cuprate[3] does not circumvent the problem of racemization.



The racemization of enantiopure higher order acyclic α-alkoxyorganocuprates was related to the formation of byproducts arising from oxidative dimerization.[3] Interestingly, the organocopper reagents derived from **1a** and **1b** showed no tendency toward dimerization. One other example of a 1,4-addition reaction of an enantiopure organocopper reagent with retention of configuration has been reported.[18] These data indicate that cyclic higher order cuprates and organocopper species are chemically distinct.[19] The mechanistic details of 1,4-addition reactions of organocopper and cuprate reagents remain unclear.[20] One can only speculate that racemization processes for charged cyclic cuprate species are unavailable for cyclic neutral copper(I) reagents in 1,4-addition reactions.[21] The racemization of acyclic copper(I) reagents may be related to a lower energy barrier toward pyramidal inversion; however, the actual mechanism is unknown.

Asymmetric synthesis using the organocopper reagents can be realized. For example, β-keto ester **13** is similar to a known intermediate in the synthesis of (−)-methyl nonactate.[22] Hydrogenation of **5a** and direct conversion of the ester to nitrile **12**[23] was accomplished in 95% overall yield. A modified Blaise reaction[24] then provided **13** in 85% yield (54% overall yield from methyl 3-hydroxybutyrate). An analogous gem-dimethylketal derivative has been converted to (−)-methyl nonactate in two steps.[22]



Acknowledgment. B.D.G. thanks the Burroughs Wellcome Fund for fellowship support. R.J.L. thanks American Cyanamid for an American Cyanamid Academic Award (1989).

Supplementary Material Available: Complete spectral and analytical data for all new compounds (3 pages). Ordering information is given on any current masthead page.

(16) **11** $[\alpha]_D$ observed +8.3°, c = 2.4(CH_2Cl_2) [lit[17] +44.6°, c = 2.4 (CH_2Cl_2)].
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(18) Fuchs, P. L.; Hutchinson, D. K. *J. Am. Chem. Soc.* **1987**, *109*, 4930–4939.
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(20) For lead references to mechanistic studies see refs 3 and 18.
(21) The addition of cyclic higher order cyano α-alkoxyorganocuprates derived from glycosyl stannanes to epoxides with retention of configuration has recently been reported: Prandi, J.; Audin, C.; Beau, J.-M. *Tetrahedron Lett.* **1991**, *32*, 769–771.
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(23) Weinreb, S. M.; Wood, J. L.; Khatani, N. A. *Tetrahedron Lett.* **1979**, 4907–4910.
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Highly Stereoselective S_E' Additions of α-Alkoxy Allylstannanes to Chiral Aldehydes. Synthesis of a C-1–C-9 Subunit of Tylonolide

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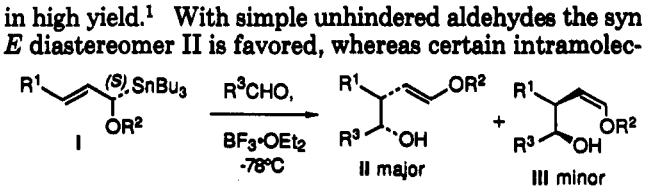
Received June 24, 1991

Summary: The racemic α-alkoxy allylic stannane **RS4** adds to the 2*S* aldehyde **24** to afford the homoaldol adduct **25** (45%) derived exclusively from the *S* enantiomer **S4** along with isomerized (*R*)-γ-alkoxy allylstannane **26** of >80% ee (50%) and unreacted aldehyde (40%). Use of the nonracemic α-alkoxy allylstannane **28** (1:1 mixture of diastereomers) in excess leads to the homoaldol adduct **29**, which is transformed in two steps to lactol ether **31**, an intermediate in Nicolaou's synthesis of *O*-micinosyl tylonolide.

We have shown that enantioenriched α-alkoxy allylic stannanes undergo stereospecific anti S_E' additions to achiral aldehydes to afford homoaldol products II and III in high yield.[1] With simple unhindered aldehydes the syn *E* diastereomer II is favored, whereas certain intramolecular applications lead to the syn *Z* isomer III as the major product.[2] The present report describes preliminary



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(2) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 1657. Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 3899. Marshall, J. A.; Markwalder, J. A. *Tetrahedron Lett.* **1988**, *29*, 4811.

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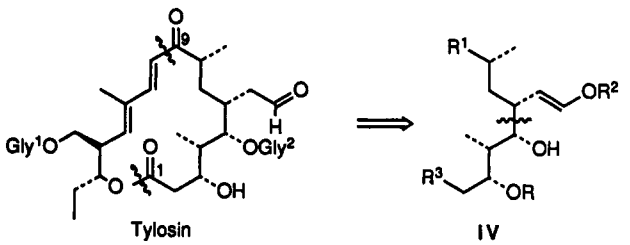
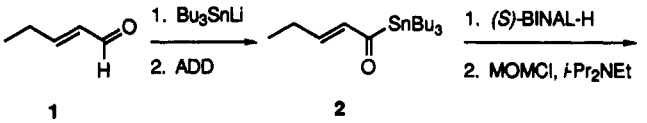
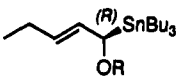
studies on additions of chiral α-alkoxy allylic stannanes to chiral nonracemic aldehydes leading to homoaldol products related to IV. Such compounds are of interest as precursors to macrolide natural products such as tylosin.[3]



We began our studies by examining additions of the (*R*)- and (*S*)-α-alkoxy stannanes **R4** and **S4** to aldehyde **6**. The stannanes were readily prepared in ca. 90% ee through reduction of the acylstannane **2** with (*S*)- or (*R*)-BINAL-H as previously described.[1] The ee of each was determined by ^{1}H NMR analysis of the *O*-methylmandelate derivative **R5** or **S5**.[4] Aldehyde **6** was prepared by reduction of the

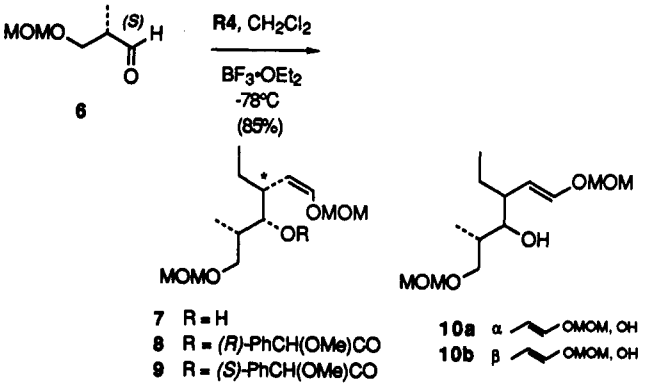


1 **2**



R3 R = H
R4 R = MOM
R5 R = (*R*)-PhCH(OMe)CO

MOM ether of (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate (SMHP)[5] with DIBAH in CH_2Cl_2 (89% yield). Reaction of aldehyde **6** with **R4** proceeded readily at −78 °C in the presence of BF_3·OEt_2 to afford a ca. 11:1 mixture of (*Z*)- and (*E*)-enol ethers **7** and **10** in 85% yield. The

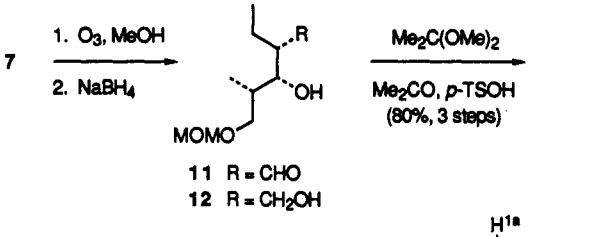


7 R = H
8 R = (*R*)-PhCH(OMe)CO
9 R = (*S*)-PhCH(OMe)CO

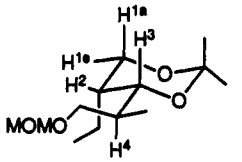
10a α OMOM, OH
10b β OMOM, OH

E product **10a** is presumed to arise from the small amount of **S4** present in the alkoxy stannane employed for the addition.[6] It should be noted that the reaction is unusual in that (*E*)-enol ethers (cf. **II**) are generally formed as major products in additions of alkoxy stannanes to simple achiral aldehydes.[1]

The stereochemistry of the adduct **7** at C* can be assigned on mechanistic grounds.[6] Confirmatory experimental support for the carbinyl configuration comes from the ^{1}H NMR spectrum of the (*R*)- and (*S*)-*O*-methylmandelates **8** and **9**.[4] The relative OH/vinyl ether stereochemistry was established by conversion to the acetonide **13** after ozonolysis and reduction.[7]



11 R = CHO
12 R = CH_2OH

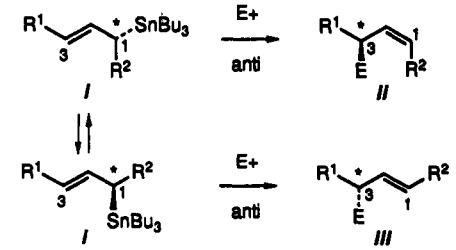


13 ($J_{1e,2}$ = 1.7 Hz; $J_{1a,2}$ = 2.6 Hz; $J_{2,3}$ = 2.2 Hz; $J_{3,4}$ = 9.7 Hz)

Addition of stannane **S4** to aldehyde **6** proceeded sluggishly and produced a mixture of five products of which **10a** was the major adduct. Thus, **6**/**R4** represents the matched and **6**/**S4** the mismatched pairing in these reactions.

With a view toward the synthesis of possible macrolide precursors such as IV, we next examined the addition of alkoxy stannanes **4** to aldehyde **24**. This, aldehyde was prepared from the THP ether of (*R*)-(−)-methyl 3-hydroxy-2-methylpropionate (RHMP)[5] via aldehyde **14** as outlined in (Scheme I).

Addition of *racemic* alkoxy stannane **RS4** to the 2*S* aldehyde **24** (1:1) yielded a mixture comprised of the adduct **25** (45%), recovered aldehyde **24** (40%), and the *optically active* γ-alkoxy allylic stannane **26** (50%). The latter was shown to possess the *R* configuration by independent synthesis through BF_3-promoted 1,3-isomerization



(3) For previous synthetic work in this area, see: (a) Tatsuta, K.; Amemiya, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 3997. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2030. (c) Grieco, P. A.; Inanaga, J.; Liss, N. H.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 5781. (d) Masamune, S.; Lu, L. D-L.; Jackson, W. P.; Kaiko, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, *104*, 5523. (e) Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonsmitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2219. (f) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

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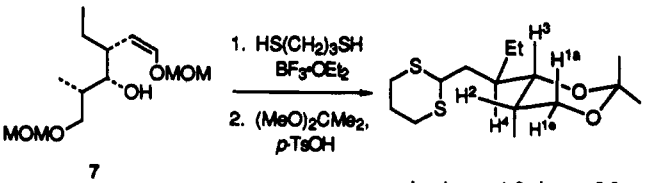
(5) This ester was purchased from Aldrich Chemical Company, Milwaukee, WI.

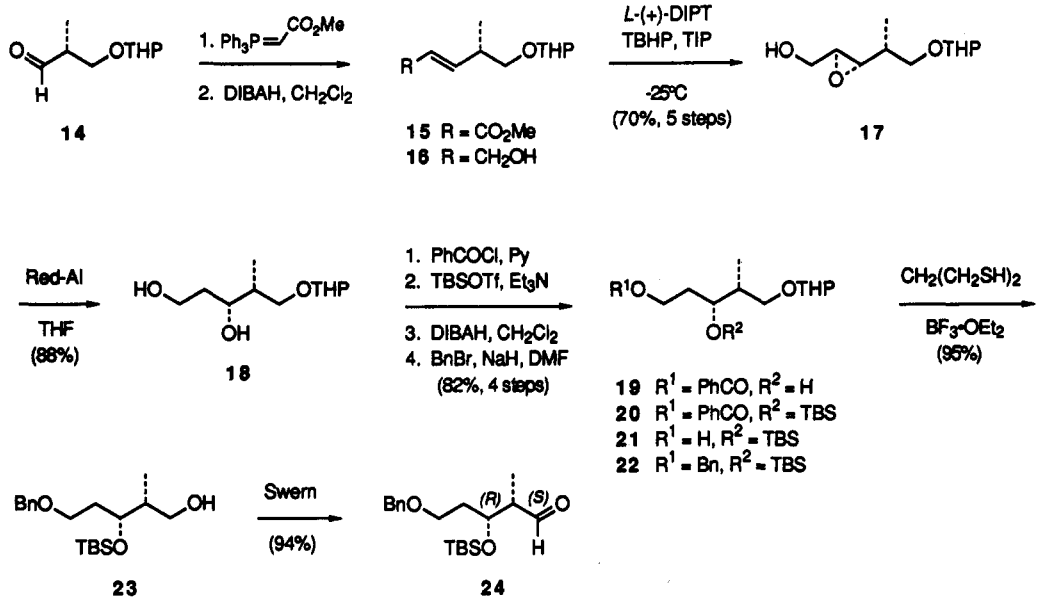
(6) In all cases examined to date we have found that electrophilic additions to chiral allylic stannanes such as **4** proceed by an exclusive anti S_E' pathway.[1,2] Thus, the geometry of the double bond in the final product(s) can be used to assign the absolute stereochemistry at C3 of the product if the configuration at C1 of the stannane is known. Because the ee of allylstannane **R4** was ca. 90%, it is estimated that no more than 5% of **10a** could have arisen from **S4**. Thus, the diastereoselectivity favoring **7** is >20:1 and **10** is a ca. 1:1 mixture of the two syn adducts **10a** and **10b**.

(7) To assuage the concerns of a referee that the Trost *O*-methylmandelate method may not be applicable to alcohols such as **7**, we performed the following conversion:

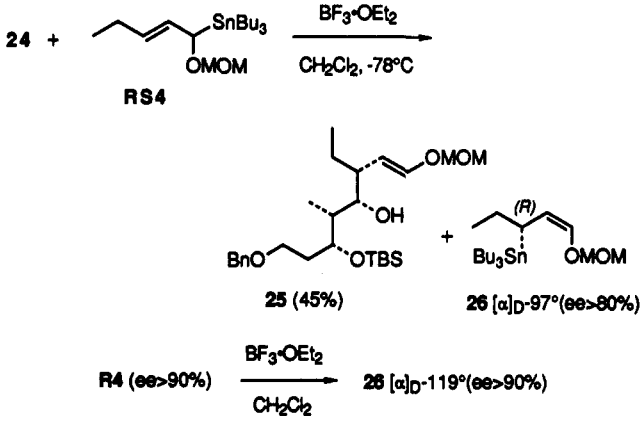


IV $J_{1e,2}$ = 1.6, $J_{1a,2}$ = 2.6, $J_{2,3}$ = 2.2, $J_{3,4}$ = 10.1 Hz

Scheme I

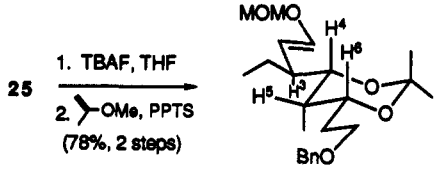


14 **15** R = CO_2Me, **16** R = CH_2OH **17** **18** **19** R^1 = PhCO, R^2 = H **20** R^1 = PhCO, R^2 = TBS **21** R^1 = H, R^2 = TBS **22** R^1 = Bn, R^2 = TBS **23** **24**



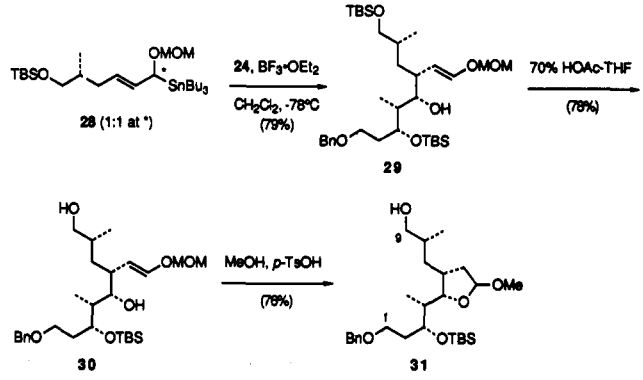
of authentic (*R*)-α-alkoxy stannane **R4** of ~90% ee.[8] Thus, the α-(*S*) aldehyde **24** shows a remarkable affinity for the (*S*)-stannane **S4** to the virtual exclusion of **R4**. Recalling that the α-(*S*) aldehyde **6** is matched with the (*R*)-stannane **R4**, it must be concluded that the β-silyloxy substituent of aldehyde **24** plays a major role in controlling the enantiomeric pairing of the reactants.

The stereochemistry of adduct **25** was confirmed by ^1H NMR analysis of the cyclic acetonide **27**.



27 ($J_{5,6}$ = 2.2 Hz; $J_{4,5}$ = 1.7 Hz; $J_{3,4}$ = 9.8 Hz)

Additional confirmation of the foregoing stereochemical assignments was secured by the synthesis of lactol ether **31**, a C-1 to C-9 subunit that was employed by Nicolaou in his synthesis of *O*-micinosyl tylonolide.[3b] Alkoxy stannane **28**, a 1:1 mixture of diastereoisomers, was prepared in a nine-step sequence from the TBS ether of SHMP.[5] Addition of 2.5 equiv of this stannane to aldehyde **24** afforded the adduct **29** in 79% yield and recovered stannane **28** enriched in the *R* enantiomer. Selective hydrolysis of the primary TBS ether followed by treatment with methanolic *p*-TsOH gave the lactol methyl ether **31**, identified by comparison of the ^1H NMR and infrared spectra with those of Nicolaou.



These findings show that S_E' additions of chiral α-alkoxy allylstannanes to chiral aldehydes represent a workable new convergent approach to precursors of important 16-membered macrolides. The contrasting stereomatching of the α-(*S*) aldehydes **6** and **24** with the (*R*)- and (*S*)-stannanes **R4** and **S4**, respectively, would not be expected from simple transition-state models.[1] However, both adducts **7** and **25** result from anti S_E' addition in line with prior examples and both derive from addition in the Cram–Felkin–Ahn sense, as has previously been observed with achiral allylstannanes.[9] Additional studies are in progress to probe the effect of β-alkoxy stereocenters on the double diastereodifferentiation of such additions.

Acknowledgment. Support for this work was provided by research grant CHE-8912745 from the National Science Foundation. We are grateful to Professor K. C. Nicolaou for providing spectral data for compound **31**.

Supplementary Material Available: Experimental details and ^1H NMR for prepared compounds (40 pages). Ordering information is given on any current masthead page.

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(9) Cf. Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883.