stereoselectivity and retention of configuration at all four olefinic centers is difficult to rationalize. Yet, application of the Sharpless proposals[3] allows a beautifully simple explanation as outlined in Scheme II.

Initial formation of the bis-π-complex **4** between diene and MnO_4^- is followed by two Sharpless type [2 + 2] additions giving the remarkably unstrained octahedral Mn(VII) intermediate **5**. Alkyl migration with retention to give **6**, followed by the key reductive elimination with retention, affords Mn(III) diester **7**. Oxidation of intermediate **7** and hydrolysis then yields MnO_2 and diol **2** with correct relative stereochemistry. Clearly, several reasonable variations of this mechanism involving differences in timing of the [2 + 2] additions, alkyl migrations, and oxidation of intermediate manganese species may be readily imagined. We feel that the crucial step involving migration of carbon from manganese to oxygen forming the THF ring with retention (**6** → **7**) elegantly explains the observed results. Indeed, we feel that the ease with which the Sharpless mechanism accounts for our results should be taken as a powerful argument in favor of Sharpless' basic proposals.

Further work on the mechanism of this reaction and its applications to the total synthesis of ionophorous natural products is in progress.

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(6) Diol **2a** had the following physical properties: ^{1}H NMR ($CHCl_3$) δ 1.13 (d, 6 H, J = 6.6 Hz, RCH_3), 1.68–2.00 (m, 4 H, RCH_2CH_2R), 3.59 (br s, 2 H, ROH), 3.86 (m, 2 H, R_2CHOR), 4.03 (q of ds, 2 H, J = 6.6, 3 Hz, R_2CHOH); ^{13}C NMR (proton decoupled, $CDCl_3$) δ 18.78, 24.12, 68.24, 83.43; IR (CCl_4) ν 3350 (s) cm^{-1}, concentration independent, OH; R_f (SiO_2, EtOAc), 0.20; bulb to bulb distillation at 75–80 °C (0.05 mm) gave analytically pure material. Anal. Calcd for $C_8H_{16}O_3$: C, 59.98, H, 10.07. Found: C, 59.92; H, 10.17. Diol **2b** had the following physical properties: ^{1}H NMR ($CDCl_3$) δ 1.15 (overlapping ds, 6 H, J = 6.0, 6.3 Hz, RCH_3), 1.6–2.0 (m, 4 H, RCH_2CH_2R), 3.5–4.2 (m, 6 H, R_2CHOR, OH); ^{13}C NMR (proton decoupled, $CDCl_3$) δ 18.59, 19.71, 24.32, 28.20, 67.95, 70.33, 85.78, 83.92; R_f (SiO_2, EtOAc), 0.18; purified as **2a** was. Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.75, H, 9.89. Diol **2c** had the following physical properties: ^{1}H NMR ($CDCl_3$) δ 1.16 (d, 6 H, J = 6.3 Hz, RCH_3), 1.47–2.16 (m, 4 H, RCH_2CH_2R), 3.4–3.8 (m, 6 H, R_2CHOR, ROH); ^{13}C NMR (proton decoupled, $CDCl_3$) δ 19.37, 28.10, 70.67, 84.45; IR (CCl_4) ν 3400 (s) cm^{-1}, concentration independent, OH; R_f (SiO_2, EtOAC), 0.16; purified as **2a** was. Anal. Calcd for $C_8H_{16}O_3$: C, 59.98; H, 10.07. Found: C, 59.75; H, 9.89. Ketal **3** had the following physical properties: mp 55–56 °C (vacuum); ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 6.5 Hz, R_2CHCH_3), 1.18 (s, 3 H, R_3CCH_3), 1.7–2.1 (m, 4 H, 12CH_2CH_2R), 3.31 (s, 3 H, ROCH_3), 4.01 (m, 2 H, R_2CHOR), 4.13 (partially obscured q of ds, 1 H, J_{vis} = 1.8, J_{CH_3} = 6.5 Hz, R_2CHCH(CH$_3$)(OR)). Ketal **3** crystallized in space group $p2_1/n$ with a = 6.896 (2) Å, b = 15.044 (3) Å, c = 8.860 (2) Å, β = 91.62 (2)°. The structure was solved using direct methods and refined using 637 observed reflections to a residual of 0.06. A discussion of the details of the structure and spectra of this compound will appear shortly.
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The Role of Substrate and Media Polarity on the Stereochemistries of the S_E2 Bromination of Trialkyl-*sec*-butyltin Compounds

Sir:

Although electrophilic substitution at saturated carbon has been studied in some detail,[1] little is known about the factors governing the stereochemical consequences of such reactions. The earliest stereochemical studies at carbon–tin centers examined the reaction of halogens with cyclopropyl derivatives; retention of configuration at carbon was uniformly observed,[2–5] but this was not unexpected because of the high inversion barrier.

Jensen and Davis[6] designed an organotin in accord with considerations that reaction (S_E2) by bromine might occur by an inversion process—*sec*-butyltrineopentyltin. Tetraalkyltin compounds, being coordinately saturated, would not allow a closed transition state which would force retention. The steric bulk of the neopentyl groups might serve to direct the approach of the electrophile away from the front side of the carbon–tin bond. A polar solvent, such as methanol, was utilized to support the charge-separated transition state. Indeed, the *sec*-butyltrineopentyltin was cleaved by bromine in methanol containing bromide ion to yield *sec*-butyl bromide with predominant inversion of configuration.[6,7] Although the bulk of the bromine was complexed with bromide ion to form Br_3^-, the kinetic results show conclusively that bromide ion in *any* form is *not* involved in the transition state; i.e., rate = $k[Br_2][R_4Sn]$ (eq 1, 2).

$$Br_3^- \rightleftharpoons Br_2 + Br^- \quad (1)$$

$$Br_2 + R_4Sn \rightarrow [\overset{\delta-}{Br}\text{-}Br\text{-}\overset{|}{\underset{|}{C}}\text{-}\overset{\delta+}{Sn}R_3]^{\ddagger} \rightarrow Br^- + BrR + \overset{+}{Sn}R_3 \quad (2)$$

Obviously, the next experiment to perform was to carry out the bromination in carbon tetrachloride wherein the separated ionic products of eq 2, Br^- and R_3Sn^+, would be of high energy. When this was done under conditions minimizing free-radical reactions, retention of configuration was observed.[8,9]

Recently, Rahm and Pereyre have criticized the stereochemical result in methanol claiming that retention, in the absence of front-side steric hindrance, is *general* for electrophilic substitution of *sec*-butyltrialkyltin compounds.[10] In support of this contention, these workers reported that *sec*-butyltriisopropyltin is brominated in methanol–cyclohexane with 45% retention of configuration. However, this result is not directly comparable with that of Jensen and Davis, since both the solvent system and structure of the organotin were changed.

In this report it is shown that the choice of leaving group (R_3Sn^+, eq 2) and of solvent can *independently* govern the stereochemical consequence of electrophilic substitution reactions of secondary alkyltin compounds. The only reasonable conclusion is that there is *no* preferred stereochemistry for this reaction and a delicate energy difference exists between inversion and retention pathways.

The steric bulk of the organotin compounds was varied, utilizing the four organotins *sec*-butyl(neopentyl)$_n$(isopropyl)$_{3-n}$. The requisite compounds were obtained from *sec*-butyltriphenyltin[11] of known optical purity and configuration.[12,13] The stereochemical results of the bromination of the four organotins in carbon tetrachloride, methanol (with and without added sodium bromide), and acetonitrile solvent systems are presented in Table I.

In carbon tetrachloride, in the presence of a free-radical inhibitor, a high degree of retention is uniformly observed, irrespective of the bulk of the R_3Sn– group. With methanol

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Table I. Stereochemistry[a] of the Bromination of R_3Sn-*sec*-butyl

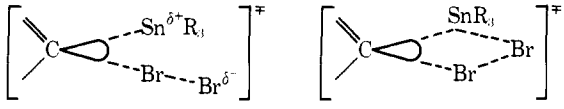
conditions[c]	observed stereochemistry, %			
	i-Pr_3Sn[b]	*i*-Pr_2NpSn[b]	*i*-$PrNp_2Sn$[b]	Np_3Sn[b,d]
CCl_4[e]	70 ret	74 ret	76 ret	89 ret
CH_3OH	22 ret	1 ret	35 inv	40–65 inv[f]
CH_3OH, 0.2 M NaBr	12 ret			~100 inv[g]
CH_3OH, 0.4 M NaBr	9 ret	4 inv		
CH_3OH, 0.91 M $NaClO_4$	10 ret			
CH_3CN	9 inv	60 inv	~100 inv	~100 inv

[a] Defined as optical purity of 2-bromobutane/optical purity of organotin; 15.8° used as maximum rotation of starting *sec*-butyltriphenyltin[13] and 34.2° for *sec*-butyl bromide.[10] ret = retention; inv = inversion. [b] R_3Sn: Np = neopentyl; *i*-Pr = isopropyl. [c] [organotin] = 0.22–0.25 M; reactions performed in dark, in air atmosphere, with dropwise addition of Br_2 over 1–5 h. Reactions not taken to completion. [d] Results from ref 8. [e] With appropriate inhibitor.[8] [f] See notes 9 and 14. [g] [NaBr] = 0.122 M.

as solvent, the amount of inversion increases with neopentyl substitution. If sodium bromide is added to the methanol, a greater amount of inversion is observed. Thus, *sec*-butyltrineopentyltin is brominated in methanol alone with 40% inversion, but the stereospecificity approaches 100% in the presence of bromide ion.[9,14] Similarly, the triisopropyl compound affords *sec*-butyl bromide with 22% retention of configuration in methanol alone; in the presence of 2 equiv of NaBr, 9% retention is realized. This reduction in observed retention is not simply the result of racemization of the product 2-bromobutane by bromide ion: *sec*-butyl bromide is not racemized by Br^- in 48 h in MeOH under reaction concentrations. Also, when *sec*-butyltriisopropyltin was brominated in methanol containing 4.6 equiv of $NaClO_4$, the stereochemistry of the reaction was 10% retention.

Inversion of configuration at carbon is uniformly observed for the bromination reactions in acetonitrile. The amount of inversion again increases with increasing neopentyl substitution at tin.

These results can be interpreted in terms of competing inversion (I) and retention (II or III) transition states.



II III

Carbon tetrachloride cannot support charged-separated species, so that reaction likely occurs via closed retention transition state III, but II may be possible if ions are formed as a close ion pair. In the more polar solvents, acetonitrile, methanol, or methanol-NaBr, competition between inversion transition state I and that for retention (II or III) is possible, and the net stereochemical results are largely governed by solvent polarity.

Acetonitrile favors inversion reactions more than methanol for these S_E2 brominations. The polarizability, dipole moment, and dielectric constant of acetonitrile are greater than the corresponding values for methanol, but methanol is a strong hydrogen bonding solvent and is expected to stabilize the developing bromide ion. Possibly, acetonitrile interacts more strongly than methanol with the leaving trialkylstannyl cation and this strong interaction more than offsets the stabilization (hydrogen bonding) of the leaving bromide ion by methanol. Stereochemical studies must be conducted in a broad range of solvents to understand the role of the solvent.

It is not clear why neopentyl substituents favor inversion more than isopropyl groups. In part, three neopentyl groups effectively block the front-side approach of the electrophile, thus favoring a back-face attack upon the carbon–tin bond. Yet, an examination of space-filling models reveals considerable crowding about the carbon–tin bond in triisopropyl-*sec*-butyltin which is brominated with predominant retention. The relative electron-donating capacities of neopentyl and 2-propyl groups may also govern the amount of inversion in these S_E2 reactions. Possibly, the immediate product of inversion, R_3Sn^+, is more stable when R = neopentyl than for isopropyl. Perhaps, also, assistance by relief of steric strain promotes inversion in the neopentyl compound, as is observed in solvolysis reactions on carbon.[15]

There are insufficient data presently available to answer these questions. Current efforts are directed toward elucidating the relative importance of these and other effects in determining the net S_E2 stereochemistry.

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Stereospecific Total Synthesis of (±)-Warburganal and Related Compounds

Sir:

Three new drimane sesquiterpenoids, warburganal (**1**), 3β-hydroxywarburganal, and muzigadial (**2**), were isolated

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