γ-butyro- or δ-valerlactone can be recovered essentially unchanged. Under the same conditions, *n*-Bu_2SnO was found to be more condescending to lactone stability (20% cleavage of hexadecanolide), hence its selection as the reagent of choice in the macrolide-forming reactions.

It is reported[7c] that when treated with alcohols, stannylated carboxylic acids *trans*-stannylate to produce the acid and the alkoxy stannyl ether. This process does not readily occur with amines,[9] nor are esters or amides formed under these reaction conditions. Thus, when a hydroxy carboxylic acid is treated with a catalytic amount of organotin oxide, a reactive stannylated intermediate (A or C in Scheme I) is formed in low concentrations and subsequently releases the tin reagent possibly by a template-driven extrusion process (Scheme I) to give the lactone. Hence, the method enjoys the intrinsic advantages of high dilution without resorting to the technique itself, since the tin reagent is continuously regenerated essentially under conditions of microscopic reversibility. The same scheme is operable with ω-amino carboxylic acids.

The ability of tin to enhance the nucleophilicity of heteroatoms bound to it and its capacity to expand its valency from four to five and six through coordination are well expressed in the literature[10a] and in some instances documented by X-ray structural analyses.[11] Thus, as a consequence of intramolecular coordination, a bis-stannylated complex (expression A in Scheme I) could form and, in effect, assume the geometry or template requirements for the extrusion[12] of the tin oxide to yield the macrolide. Some evidence in support of this proposal was obtained by reducing the ability of the tin substrates to coordinate through substitutent modification on tin.[10] Thus, considerably longer periods of time (~5 times) were required for reactions in which cyclohexyltin oxides were used over those of *n*-butyltin analogues, presumably due to the larger steric requirements of the cyclohexyl group and the weaker coordinating ability[10b] of the corresponding bis-stannylated intermediates.

Macrolide formation mediated by *n*-Bu_2SnO can be envisioned to take place through the intermediacy of structures B and C in Scheme I. Structure B could actually be favored due to the additional ionic interaction[13] by way of hydrogen bonding, although we have no experimental evidence in support of this argument.

We are currently investigating this reaction in greater detail to determine the effect of ring size and whether or not this approach can be extended to include ω-halo and ω-mercapto carboxylic acids for the preparation of lactones and thiolactones, respectively.

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(14) (a) Holder of UNIDO, CIDA fellowship; (b) Summer undergraduate research participant.

Kosta Steliou,* A. Szczygielska-Nowosielska,[14a] A. Favre[14b]
M. A. Poupart,[14b] Stephen Hanessian*

Department of Chemistry
l'Université de Montréal
Montreal, Quebec, Canada H3C 3V1

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Stereoelectronic Control in the Breakdown of Hemiorthothiol Esters, RC(OR′)$_2$SH[1]

Sir:

The generation and breakdown of transient tetrahedral intermediates of the type RC(OR′)(OH)$_2$, RC(OR′)$_2$(OH), and RC(OR′)(NR$_2$″)(OH) are subject to stereoelectronic control as evidenced by Deslongchamps' elegant studies on the ozonolysis of acetals,[2] carbonyl exchange reactions,[3] hydrolyses of cyclic ortho esters[4] and imidate salts,[5] and oxidative cleavages of vinyl ortho esters.[6] Sulfhydrolytic studies of imidates also have suggested the possible involvement of stereoelectronic effects in the breakdown of hemiorthothioamide intermediates, RC(OR′)(NR$_2$″)SH.[7] We hereby report on the role of the stereoelectronic factor in the breakdown of hemiorthothiol esters—RC(OR′)$_2$SH—under kinetic control. The model tetrahedral intermediates in question, *viz.*, [**1**]–[**4**] (Figure 1),[8] were generated *directly* by the ion–ion combination of dialkoxycarbonium cations **5**–**8** with hydrosulfide anion, under aprotic conditions, at zero or subzero temperatures.

According to the stereoelectronic theory,[9] a carbon–heteroatom bond, C–Y, in a tetrahedral intermediate RC(X)(Y)(Z), is severed relatively easily if there are *two* nonbonded electron pairs (one on X, one on Z) antiperiplanar to C–Y; other things being equal, the cleavage of C–Y is appreciably less facile if *one* or *no* antiperiplanar electron pair is present. Thus, for hemiorthothiol esters one predicts that (i) in tetrahedral intermediate [**1**] either C–O bond ought to cleave easily (each C–O is antiperiplanar to two electron pairs), (ii) neither C–O bond in model intermediate [**2**] would be severed with ease (each C–O is antiperiplanar to only one electron pair), and (iii) in each of the tetrahedral intermediates [**3**] and [**4**], the *endocyclic* C–O bond should break in preference to the exocyclic one (the former C–O bond is antiperiplanar to two nonbonded electron pairs, while the latter, to only one).

Intermediate [**1**], generated by the reaction of compound **5**[10] with anhydrous NaSH[11] in dry acetonitrile at 0 °C, under a nitrogen atmosphere, led to a mixture of two rather labile isomeric hydroxythionacetates—**9** and **10** (50.5% isolated yield; ~1.5:1 by integration of the respective –*C*HOC(=S) ^{1}H NMR (CDCl$_3$) signals at δ 4.54 and 5.36; IR (neat) 3400, 1460, 1275, 1220, 1030 cm^{-1}; R_f 0.47 (CHCl$_3$–CH$_3$CN 5:1 v/v)).[12]

Treatment of **6**[13] with anhydrous NaSH under conditions identical with those for the generation of [**1**] gave no trace of compound **11a**;[14] the principal sulfur-containing (positive PdCl$_2$

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(8) All tetrahedral intermediates in the sequel, regardless of lifetime, are indicated with square brackets.

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(10) Prepared from BF$_3$·Et$_2$O and the ortho ester derived from *trans*-2-(hydroxymethyl)cyclohexanol and triethyl orthoacetate (95% yield).

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(12) No attempts were made to separate the labile thionacetates **9** + **10**. Treatment of this mixture with NaH/CH$_3$CN (0 °C) gave **16** (35% isolated yield) which was quantitatively methylated (CH$_3$I) to yield ortho ester **17**; the latter proved to be identical (IR, ^{1}H NMR) with the product of the reaction of **5** with CH$_3$SLi.

(13) Synthesized from δ-valerolactone by sequential treatment with (i) LDA/THF (−78 °C, 30 min), (ii) 3-chloroiodopropane/HMPT (−78 °C; 15 h), (iii) AgBF$_4$/Et$_2$O (27 °C, 3 h), (iv) MeONa/MeOH–*i*-PrOH (−78 °C, 2 h), (v) BF$_3$·Et$_2$O (−78 °C, 20 min); overall yield 20.2%. The last two steps were carried out in order to obtain silver-free, crystalline **6**.

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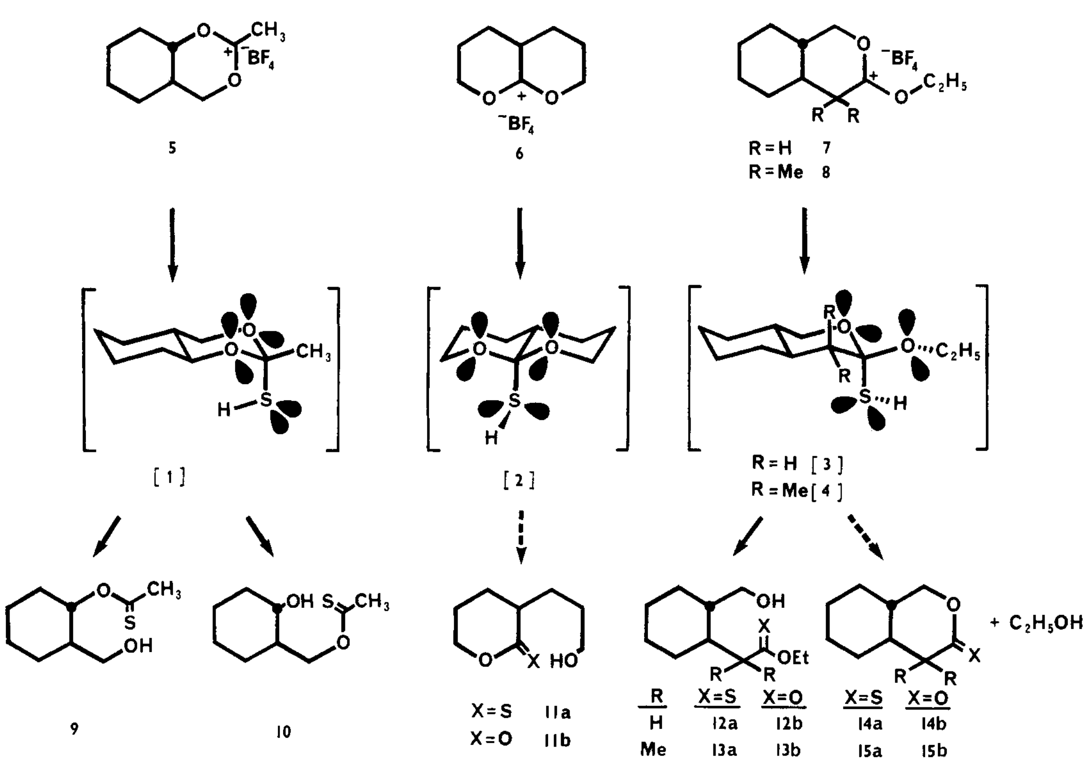
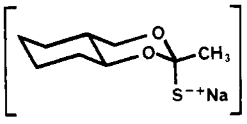
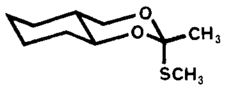


Figure 1. Generation and breakdown of hemiorthothiol ester tetrahedral intermediates [1]-[4].

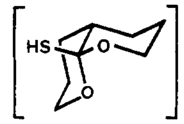
stain) products consisted of a mixture of two interconvertible substances, [2] and [18] (20.2% isolated yield);[15] NMR($CDCl_3$)



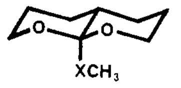
[16]



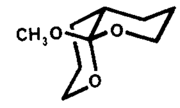
17



[18]



X=S 19a
X=O 19b



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δ 1.20–2.20 (10 H, m, ring CCH_2C, CCHC, and SH), 3.50–3.90 (4 H, m, OCH_2); IR (neat) 1240, 1210, 1165, 1140, 1080, 1025, 995 cm^{-1}; m/e 140 (M^+ - 34).[16] Treatment of the isolated mixture above with moist ethereal HBF_4 gave **11b** quantitatively with evolution of hydrogen sulfide; each component in the mixture, after chromatographic separation[17] and subsequent exposure to moist air, also rapidly yielded hydroxylactone **11b**. In the light of these results, we propose diastereomeric structures [2] and [18] for the interconverting compounds.[18] Interestingly, two hemiorthothiols, *viz.*, [21] and [22], have been reported in the literature.[19]

Finally, the breakdown of [3][20] and [4][21] (NaSH, acetone,

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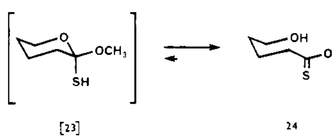
(14) Thiono compounds on silica gel chromatograms, upon spraying with 0.5% $PdCl_2$ solution, develop into dark brown spots.

(15) Quite possibly, [2] and [18] interconvert by dissociation and recombination of hydrosulfide ion. The labile nature of the C–S bond in [2] and/or [18] is further substantiated by the absence of the ordinarily weak CS–H stretching band in the infrared spectra and our failure to synthesize **19a** by the addition of CH_3SLi to **6** under a wide variety of conditions, including those for the successful synthesis of **17**. In contrast, addition of NaOMe to **6** did yield **19b** (60% yield); however, the latter underwent thermal isomerization during distillation at 60 °C (0.25 torr) to give an ~1:1 mixture of **19b** and the diastereomeric ortho ester **20**.

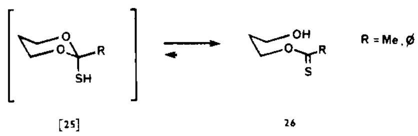
(16) The loss of 34 mass units corresponds to the elimination of H_2S as is generally observed for thiols.

(17) The [2] + [18] mixture was isolated by preparative TLC on silica gel at room temperature under an argon atmosphere by eluting with $CHCl_3$–CH_3CN (5:1 v/v), R_f 0.64. Further, [2] and [18] were separated from each other by preparative TLC by eluting with ether (R_f's 0.36 and 0.48); the faster component, following isolation at room temperature (10 min), consisted of a rearranged mixture (~1:1 by TLC) of the two components, but the slower component rearranged more slowly (2 h) to give an identical 1:1 mixture.

(18) The reluctance of [18] to transform to **11a**, despite stereoelectronic assistance by two antiperiplanar nonbonded electron pairs, may be explained on kinetic and/or thermodynamic grounds. The kinetic explanation stems from a vector analysis (see: Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738) for the C(=S)OR function and the principle of microscopic reversibility. Models indicate that the locus of points to be traced by the departing hydroxyl group should be *along* the axis of the C–S bond and that such a motion is possible only through the straining of already-energetic boat-type conformations. Hence the barrier for cleavage may be unusually high because of the demands of the leaving group. The breakdown of [2] would also engender a similar strain. The thermodynamic explanation, on the other hand, would require that the equilibrium ([2] + [18]) ⇌ **11a** lie to the left. We presently favor the kinetic explanation because (i) each of the following three equilibria, [1] ⇌ (**9** + **10**), [23] ⇌ **24**, [25] ⇌ **26**, favors the hydroxythion ester component, *viz.*, **9** + **10**, **24**, **26**, respectively, rather than the tetrahedral intermediates [1], [23], and [25], and (ii) heating of a mixture of [2] + [18] in xylene (130 °C) under nitrogen for 30 min generated minute amounts of a much more polar $PdCl_2$-positive[14] spot, most probably **11a**, the R_f of which (0.31) was reminiscent of that of the known hydroxylactone **11b** (R_f 0.20, $CHCl_3$–CH_3CN 5:1 v/v). Continued heating of the xylene solution resulted in complete decomposition of **11a**. Attempted independent synthesis of **11a**, unfortunately, was unsuccessful.



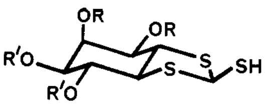
[23] 24



[25] 26

(19) McCasland, G. E.; Furuta, S.; Furst, A.; Johnson, L. F.; Shoolery, J. N. *J. Org. Chem.* **1963**, *28*, 456.

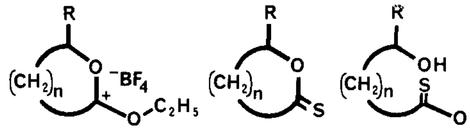
(20) Precursor lactonium salt **7** was prepared from *trans*-hydrindanone by treatment with (i) *m*-CPBA/CH_2Cl_2 (27 °C, 30 h), (ii) $Et_3O^{+-}BF_4/CH_2Cl_2$ (27 °C, 3 h), (iii) NaOMe/MeOH-*i*-PrOH (-78 °C, 1 h), (iv) BF_3·Et_2O (-78 °C, 15 min); overall yield 59%.



[21] $R = R' = Ac$

[22] $R_2 = R'_2 = Me_2C$

18-crown-6, −78 °C) led to the exclusive cleavage of the endocyclic C–O bonds to give **12a** and **13a**, respectively.[22-24]



R	n			
Me	2	27	28	29
Et	3	30	31	32
H	4	33	34	35

These results clearly prove that the breakdown of hemiorthothiol intermediates [**3**] and [**4**], in each of which there are two leaving (alkoxy) groups of identical intrinsic leaving group abilities (except for orientation of nonbonded electron pairs), is subject to stereoelectronic control (Deslongchamps effect), despite a counteracting entropy term.[25] It is highly probable that, under aprotic conditions, a similar stereoelectronic effect is operative in the cleavage of hemiortho esters of the type $RC(OH)(OR)_2$. We are currently pursuing our studies in that direction.

Acknowledgment. We thank the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Biomedical Research Support Program (BRS 6 Grant RR 7150), Division of Research Resources, National Institutes of Health, for financial support. We are also grateful to Professors G. Posner and R. H. Schlessinger for the details of their lactone α-alkylation procedures.

Moses K. Kaloustian,* Farid Khouri
Department of Chemistry, Fordham University
Bronx, New York 10458

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(21) Lactonium salt **8** was prepared from *trans*-2,3-tetramethylene-δ-valerolactone (**14b**) by treatment with (i) LDA/THF (−78 °C, 0.5 h), (ii) MeI/HMPT (−42 °C, 3 h), (iii) LDA/THF (−78 °C, 0.5 h), (iv) MeI/HMPT (−42 °C, 3 h), (v) $Et_3O^{+-}BF_4/CH_2Cl_2$ (27 °C, 3 h), (vi) NaOMe/MeOH–*i*-PrOH (−78 °C, 1 h), (vii) $BF_3\cdot Et_2O/Et_2O$ (−78 °C, 15 min); overall yield 17.5%.

(22) In view of the minute amounts of the kinetic products formed at −78 °C (**12a** and **13a**) and their marked propensity to undergo cyclization (**12a** → **14a**; **13a** → **15a**), we could not isolate and characterize them directly. But, when a sample of **7** was treated with NaSH in CD_3CN, rapid scanning in the δ 4.0–5.0 range revealed a characteristic quartet ($-C(=S)OCH_2CH_3$) at 4.50 ppm, *at the same time* that an aliquot of the NMR sample showed an intense $PdCl_2$-positive spot on TLC (R_f 0.55). Subsequent TLC analysis showed this spot to grow fainter in favor of another thiono compound (R_f 0.75). Correlation of the R_f values of fully characterized compounds **29**, **32**, **35** (R_f's 0.53 ± 0.02) and **28**, **31**, **34** (R_f's 0.76 ± 0.02) from the sulfhydrolysis of **27**, **30**, and **33** further substantiate the structural assignments of **12a** and **13a** (R_f's 0.53 and 0.55, respectively) and **14a** and **15a** (R_f's 0.78 and 0.77, respectively). As the temperature was raised, the spots with R_f's 0.53 and 0.55 gradually grew fainter while those with R_f's 0.78 and 0.77 intensified. All the R_f's above were determined on Merck precoated TLC silica gel 60 F-254 by eluting with $CHCl_3$–CH_3CN 5:1 v/v. Further, **15a** was isolated and its ^1H NMR spectrum revealed characteristically shifted signals ($CDCl_3$) for the diastereotopic geminal methyl groups (δ 1.28, 1.48) as compared with those of **15b** (δ 1.16, 1.28).

(23) On the TLC plates, minute amounts of thionolactones **14a** and **15a** were observed in the respective mixtures. However, control experiments with chromatographically pure **32** indicated that upon rechromatography on silica gel, a small amount of thionolactone **31** was formed. If anything, the cyclizations of **12a** and **13a** to give **14a** and **15a**, respectively, ought to be more facile than that of **32** to **31**; hence, the minute amounts of **14a** and **15a** in the original mixtures are, in all likelihood, artifacts of the TLC experiment.

(24) Interestingly, the sulfhydrolysis of **30** at −78 °C, under conditions identical with those for **7** and **8**, also revealed *exclusive* cleavage of the endocyclic C–O bond to give **32**; the latter gradually rearranged to give a mixture of **31** and **32**. The sulfhydrolysis of **30**, at −40 °C, on the other hand, gave an 80:20 (**32**/**31**) mixture; at 0 °C, the ratio was 53:47.

(25) At a standard state of 1 M, $\Delta S°$ for a typical reaction in which one molecule of reactant fragments into two species would be +35 gibbs and the corresponding $\Delta G°$ would be −10.5 kcal/mol (see: Jencks, W. P. *Adv. Enzymol.* **1975**, *43*, 276). Hence, the cleavage of the *exocyclic* C–O bond in each of [**3**] and [**4**] should be favored entropically by part of the 10.5 kcal/mol depending on the relative extent of cleavage in the respective transition states. If one disregards this entropy term completely and assumes a ratio of rate constants of 100:1 ($k_{[3]\to\mathbf{12a}}/k_{[3]\to\mathbf{14a}}$ or $k_{[4]\to\mathbf{13a}}/k_{[4]\to\mathbf{15a}}$), the *lower* limit for the stereoelectronic factor is conservatively estimated at 2.7 kcal/mol at −78 °C.

[20.10]-, [22.10]-, and [26.10]Betweenanenes, Conformationally Flexible Bicyclic Alkenes: Synthesis, Chemistry, and Optical Resolution

Sir:

In 1977 we described the synthesis of [10.10]betweenanene (**13**, n = 12), a novel fused-ring trans bicyclic alkene.[1] The bridging arrangement of the two rings was found to block additions to the buried double bond, resulting in dramatic reactivity differences between the trans (**13**, n = 12) and cis (**12**, n = 12) isomers.[1-3] We now wish to record the synthesis of [20.10]-, [22.10]-, and [26.10]betweenanenes (**13a–c**) by a new route of general applicability and some preliminary chemical studies on these conformationally flexible olefins, including the optical resolution and absolute configuration of the [26.10] and [22.10] homologues.

Our interest in the aforementioned betweenanenes was stimulated by the possibility that the larger ring might be capable of rotation, jump rope fashion, around the smaller ring, thereby exposing the double bond to external reagents (see Scheme I, structure **13**). An examination of space-filling models led us to believe that the [24.10] system (**13**, n = 26) could undergo such isomerism. The synthesis of the relevant olefins is outlined in Scheme I.[4]

Diketones **2** and **3**, obtained via cuprous iodide promoted addition[5] of ω-undecenylmagnesium bromide and ω-tridecenylmagnesium bromide,[6] respectively, to dodecandioyl chloride (**1**), yielded trienes **4** and **5** upon McMurry cyclization with the $TiCl_3$/Li reagent.[7] Hydroboration–oxidation[8] gave the diols **6** and **9** whose further conversion to dialdehydes **7** and **10** was effected with the Corey–Suggs reagent.[9] Dialdehyde **8** was secured via oxidation of triene **4** with osmium tetroxide to the bis(glycol) which was cleaved with periodic acid.[10] Cyclization of the foregoing dialdehydes with $TiCl_3$/Li[7] led to the dienes **11a–c** as mixtures (cis–trans) of disubstituted double bond isomers (mainly the trans isomer, ν = 965 cm^{-1}).[11] Selective hydrogenation over Pt cleanly afforded the cis bicyclic olefins **12a–c**. Photolysis in xylene–cyclohexane (1:6) with a 450-W medium-pressure mercury lamp effected partial conversion to the trans isomers (**13a**/**12a** = 1.1, **13b**/**12b** = 1.6, **13c**/**12c** = 1.3)[3,12] which

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(4) Satisfactory spectral and analytical data were obtained for all new compounds.

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(6) The bromide was prepared by addition of ω-undecenylmagnesium bromide to ethylene oxide and subsequent treatment of the resulting alcohol with *N*-bromosuccinimide and triphenylphosphine in benzene according to Schweizer et al. (*J. Org. Chem.* **1969**, *34*, 212–215).

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