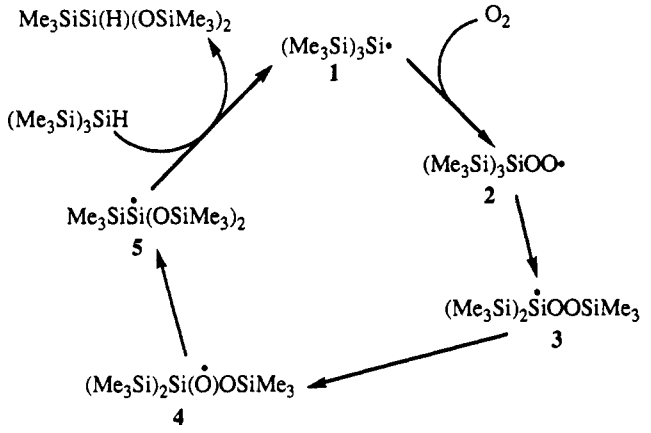
Scheme I. Intramolecular Mechanism



a free-radical mechanism rather than by direct insertion of any oxygen molecule to the Si–Si bond followed by a molecular rearrangement. When the SiH function in TTMSS is replaced by SiD,[8] $(Me_3SiO)_2Si(D)SiMe_3$ is formed exclusively.

The mechanisms that we conceive for reaction 1, following the fundamental concepts of free-radical chemistry, are two and are called *intermolecular* and *intramolecular*, respectively. By intermolecular mechanism we intend that the two oxygen atoms in the final product arise from two different oxygen molecules whereas in the intramolecular mechanism the two oxygen atoms arise from the same oxygen molecule.

Oxygen-labeling experiments were carried out to distinguish between intramolecular and intermolecular mechanisms. The tris(trimethylsilyl)silane was treated with a mixture of $^{16}O_2$ and $^{18}O_2$ (ca. 60/40 ratio).[10] The crude products were analyzed by mass spectrometry to determine the isotopic distribution. From the EI mass spectrum recorded by GC/MS analysis of the reaction mixture,[11] the relative amounts of the coeluting isotopomers $(Me_3Si^{16}O)_2Si(H)SiMe_3$, $(Me_3Si^{16}O)(Me_3Si^{18}O)Si(H)SiMe_3$, and $(Me_3Si^{18}O)_2Si(H)SiMe_3$ could be determined by measuring the relative abundance of the corresponding $[M - 15]^+$ (and $[M - 17]^+$) ions. A completely intramolecular mechanism would result in the same label distribution in the products as in the reactants whereas an intermolecular mechanism would lead to a statistical distribution of the labels in the products. The mass spectrometric results are reported in the following equation:

$$(Me_3Si)_3SiH + (\text{ca. } 60\%\ ^{16}O\text{–}^{16}O/40\%\ ^{18}O\text{–}^{18}O) \longrightarrow (Me_3Si^{16}O)_2Si(H)SiMe_3 + (Me_3Si^{18}O)_2Si(H)SiMe_3 \quad (2)$$

64:36

Therefore, an intramolecular free-radical chain process is responsible for such behavior.

The reaction sequence shown in Scheme I would agree with the above experimental data. That is, silyl radical 1 adds to molecular oxygen to form the peroxyl 2 which may rearrange to 3 by means of an unusual 1,3-shift of the Me_3Si group which then undergoes a homolytic internal substitution to form the silyloxyl radical 4. The latter could rearrange to 5 by a 1,2-shift of the Me_3Si group.[12,13] Hydrogen abstraction from the silane by radical 5 gives the desired product and the $(Me_3Si)_3Si^•$ radical, thus completing the cycle of this chain reaction.[14] To our knowledge the unimolecular steps 2 → 3 (1,3-shift), 3 → 4 (S_Hi), and 4 → 5 (1,2-shift) in Scheme I are unknown reactions.[15] We believe that the strength of the silicon–oxygen bond is a potent driving force in these novel rearrangements. Further work on the mechanism of reaction 1 as well as on the autoxidation of other silanes is in progress.[17]

Acknowledgment. Financial support from the Progetto Finalizzato Chimica Fine II (CNR-Rome) is gratefully acknowledged.

Registry No. TTMSS, 1873-77-4; $(Me_3SiO)_2Si(H)SiMe_3$, 139347-50-5.

Supplementary Material Available: Spectra and details of the mass spectroscopic studies (3 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.

(10) The molar ratio of the $^{16}O_2/^{18}O_2$ gas mixture was determined from the intensities of $^{16}O_2^{•+}$ and $^{18}O_2^{•+}$ molecular ion peaks, recorded by electron impact ionization of the gas mixture.

(11) GC/MS was performed by using a Varian 3600 GC linked to a Finnigan MAT 8400 double-focusing instrument. The mass spectrometer was operated in EI ionization (70 eV) and at resolution of 1000, while the magnet was scanned from m/z 33 to 500 in 0.8 s.

(12) For 1,2-migration of the trimethylsilyl group in free radicals, see: Harris, J. M.; MacInnes, I.; Walton, J. C.; Maillard, B. *J. Organomet. Chem.* **1991**, *403*, C25 and references cited therein.

(13) A similar 1,2-migration of the Me_3Si group from Si to O has recently been observed: Ballestri, M.; Chatgilialoglu, C.; Lucarini, M.; Pedulli, G. F. *J. Org. Chem.* **1992**, *57*, 948.

(14) The initiation step remains in doubt.

(15) The reactions 2 → 3 (1,3-shift) and 4 → 5 (1,2-shift) in Scheme I are predicted to be exoergonic by at least 40 kcal mol^{-1}, on the basis of the known values of the bond dissociation energies[16] for Me_3Si–$SiMe_3$, 84.5 kcal mol^{-1}, and for Me_3Si–OH, 128 kcal mol^{-1}.

(16) Walsh, R. *Acc. Chem. Res.* **1981**, *14*, 246. Walsh, R. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1989; pp 371–391.

(17) The oxygen-induced production of radicals from $(Me_3Si)_3SiH$ could be used to initiate some important reactions, such as the reduction of organic halides: Chatgilialoglu, C. Unpublished results.

Stereoselective Synthesis of (*E*)- and (*Z*)-1-Azabicyclo[3.1.0]hex-2-ylidene Dehydroamino Acid Derivatives

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Summary: Bromination of dehydroamino acid derivatives with NBS or Br_2/2,6-lutidine yields (*E*)- or (*Z*)-β-bromodehydroamino acid derivatives selectively. Subsequent intramolecular Michael addition–elimination of an aziridine proceeds with complete retention of olefin geometry to provide the 1-azabicyclo[3.1.0]hex-2-ylidene ring system

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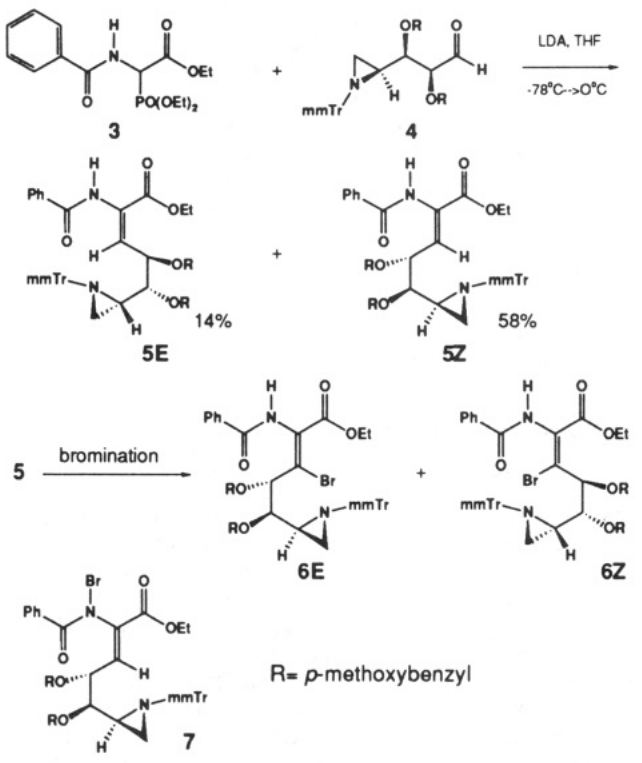
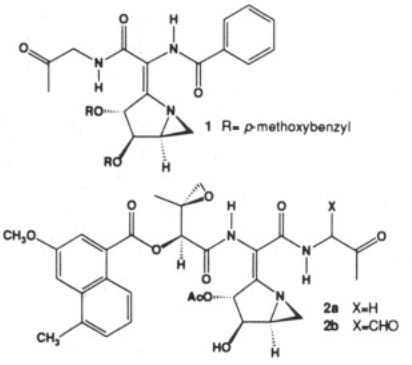
Scheme I



proposed for the azinomycin series of antitumor antibiotics.

We recently reported on the synthesis of **1**,[1] the first compound to contain the 1-azabicyclo[3.1.0]hex-2-ylidene dehydroamino acid partial structure proposed for the antitumor antibiotics azinomycins A (**2a**) and B (**2b**).[2,3]

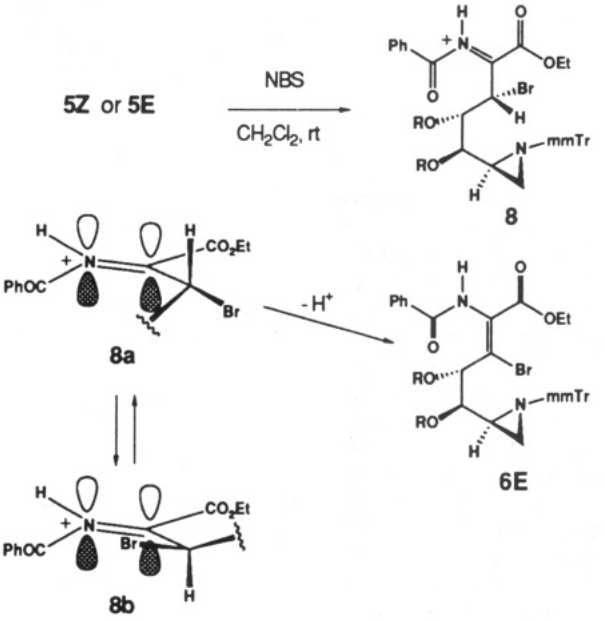


(1) Armstrong, R. W.; Moran, E. J. *J. Am. Chem. Soc.* **1992**, *114*, 372.
(2) The spectral properties of carzinophilin and azinomycin B are identical (Moran, E. J. Ph.D. Thesis, 1992, University of California at Los Angeles). For isolation and proposed structures of carzinophilin: (a) Hata, T.; Koga, F.; Sano, Y.; Kanamori, K.; Matsumae, A.; Sugawara, R.; Shima, T.; Ito, S.; Tomizawa, S. *J. Antibiot. Ser. A (Tokyo)* **1954**, *107*, 7. (b) Lown, J. W.; Hanstock, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 3212. (c) Onda, M.; Konda, Y.; Hatano, A.; Hata, T.; Omura, S. *J. Am. Chem. Soc.* **1983**, *105*, 1995. (d) Onda, M.; Konda, Y.; Hatano, A.; Hata, T.; Omura, S. *Chem. Pharm. Bull.* **1984**, *32*, 2995. For isolation and proposed structures of azinomycins A and B: (e) Yokoi, K.; Nagaoka, T.; Nakashima, T. *Chem. Pharm. Bull.* **1986**, *34*, 4554. (f) Nagaoka, K.; Matsumoto, M.; Oono, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 1527.
(3) Synthetic studies related to carzinophilin and azinomycins: (a) Shibuya, M. *Tetrahedron Lett.* **1983**, *24*, 1175. (b) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855. (c) Garner, P.; Park, J. M.; Rotello, V. *Tetrahedron Lett.* **1985**, *26*, 3299. (d) Shibuya, M.; Terauchi, H. *Tetrahedron Lett.* **1987**, *28*, 2619. (e) Ando, K.; Yamada, T.; Shibuya, M. *Heterocycles* **1989**, *29*, 2209. (f) England, P.; Chun, K-H.; Moran, E. J.; Armstrong, R. W. *Tetrahedron Lett.* **1990**, *31*, 2669. (g) Moran, E. J.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 3807. (h) Miller, S. C. Ph.D. Thesis, University of Rochester, 1991.

Table I. Bromination of Enamides 5

	condns	6E/6Z	isolated yield (%)
5Z	NBS, CH_2Cl_2, rt	>95:<5	71
5E	NBS, CH_2Cl_2, rt	>95:<5	34
5Z	Br_2, 2,6-lutidine (10 equiv), CH_2Cl_2, −10 °C, DABCO	1:2	77
5Z	Br_2, 2,6-lutidine (cosolvent), CH_2Cl_2, 40 °C, DABCO	1.5:1	57
5E	Br_2, 2,6-lutidine (10 equiv), CH_2Cl_2, −10 °C, DABCO	1:2.5	60

Scheme II

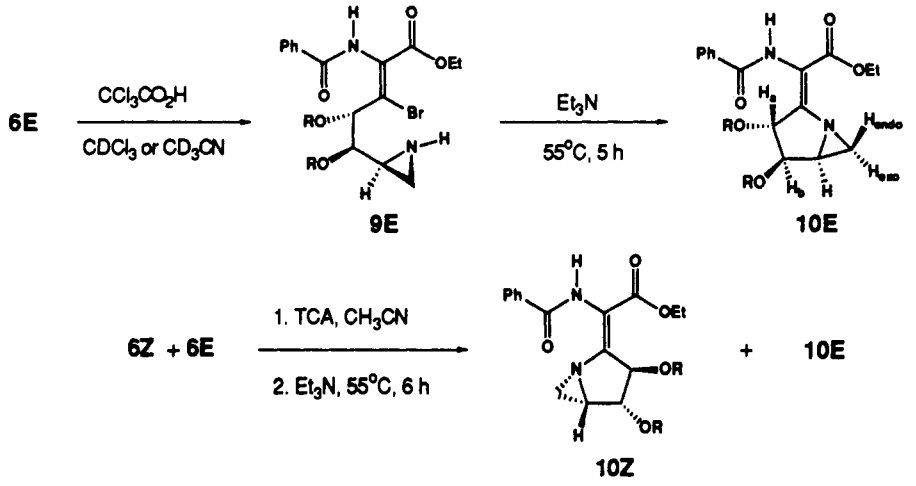


Compound **1** was prepared by stereoselective intramolecular addition–elimination of an aziridine to a (*Z*)-β-bromodehydroamino acid derivative. Comparison of the NMR spectra of **1** and **2b** provided strong evidence for the *E* stereochemistry of the tetrasubstituted olefin in the natural products. A method was thus sought for the synthesis of an (*E*)-vinyl bromide precursor with the expectation that the cyclization would afford the desired olefin geometry. We now wish to report the development of bromination conditions that provide access to either (*Z*)- or (*E*)-β-bromodehydroamino acid derivatives. These can be cyclized with retention of olefin configuration to provide the corresponding (*Z*)- or (*E*)-1-azabicyclo[3.1.0]hex-2-ylidene isomers **10*Z*** and **10*E***.

Condensation of glycine phosphonate **3**[4] with aldehyde **4**[5] afforded a 4:1 *Z*/*E* mixture of isomers **5** which were readily separable (Scheme I). Subsequent bromination afforded the desired bromides **6*E*** and **6*Z*** in good yields and moderate to high stereoselectivity depending on starting olefin geometry and bromination conditions (Table I). Reaction of **5*Z*** with 2–3 equiv of NBS[6] in methylene chloride at room temperature afforded vinyl bromide **6*E***[7] (25% yield) and the unstable *N*-bromo derivative **7** (46%), which upon sitting converted quantitatively to **6*E*** (71%

(4) Kober, R.; Steglich, W. *Liebigs Ann. Chem.* **1983**, 599.
(5) Full details for the synthesis of **4** and **5** will be forthcoming.
(6) Nunami, K.-I.; Hiramatsu, K.; Hayashi, K.; Matsumoto, K. *Tetrahedron* **1988**, *44*, 5467.
(7) The assignments of olefin geometry for **6*E*** and **6*Z*** are based on their stereospecific conversion to **10*E*** and **10*Z***, respectively (vide infra). The assumption of complete retention of geometry, rather than complete inversion, is supported by NOE difference experiments on **1** and its *Z* vinyl bromide precursor (ref 1).

Scheme III



total yield).[8] The structure of 7 was tentatively assigned by ^1H NMR. The absence of an amide hydrogen resonance indicated N-bromination, while the chemical shift of the vinyl hydrogen was consistent with *Z* olefin geometry. Under similar conditions, bromination of **5*E*** furnished **6*E*** with high diastereoselectivity (>95%) but low yield (34%). No *N*-bromo derivatives were observed in the latter case. The reaction of NBS with either **5*E*** or **5*Z*** probably involves a common intermediate such as 8, which would result from addition of Br^+ directed by the allylic ether in a Felkin–Anh[9] fashion (Scheme II). Deprotonation of the β-carbon in 8 would thus occur via rotamer **8a**, affording vinyl bromide **6E** exclusively.

In contrast to the NBS reaction, bromination of either **5*E*** or **5*Z*** with Br_2 in methylene chloride in the presence of 2,6-lutidine, followed by DABCO[10] addition, afforded an inseparable mixture of **6*E*** and **6*Z***. The best *Z* selectivity (2.5:1 as analyzed by ^1H NMR) was achieved using low temperature (−10 °C) and limited amounts (10 equiv) of 2,6-lutidine with **5*E*** as substrate. Addition of 2,6-lutidine to the dehydroamino acid prior to addition of Br_2 proved to be crucial, since in the absence of base the only reaction observed was decomposition of the substrate. The Br_2 reaction may proceed by way of a dibromide intermediate (supported by ^1H NMR and TLC analysis) which eliminates HBr upon treatment with DABCO. This process would generate intermediates which are related to the conjugate base of 8. The production of isomeric mixtures at the β-carbon with Br_2 may reflect a lower selectivity in the initial electrophilic addition than is observed with NBS.

With the desired vinyl bromides in hand, we next turned our attention to the cyclization reactions.[11] A solution of **6*E*** in CD_3CN was treated with 1.2 equiv of trichloroacetic acid at room temperature resulting in the deprotection of the monomethoxytrityl group and formation of the free aziridine intermediate **9*E*** (Scheme III). This reaction was monitored by ^1H NMR to prevent hydrolysis of the aziridine. Addition of Et_3N followed by warming at 55 °C over a 6-h period resulted in exclusive formation of **10*E*** in 90% isolated yield. Thus, cyclization of the *E* isomer proceeds with complete retention with respect to initial olefin geometry.[12] The rates of monomethoxytrityl deprotection and cyclization are slower in $CDCl_3$, but yields are similar to those obtained in CD_3CN. Since vinyl bromides **6*E*/6*Z*** obtained from the Br_2 reaction were inseparable, cyclization studies were undertaken on the mixture. Deprotection followed by cyclization of a 1.5:1 mixture of **6*E*/6*Z*** afforded bicyclic aziridines **10** which were readily separable by chromatography. Formation of the *Z* isomer (**10*Z***) proceeded in >95% chemical yield based on the amount of **6*Z*** in the starting mixture, indicating that cyclization is effected with complete retention for **6*Z*** as well as for **6*E***. These results are consistent with the observed retention of configuration in the intermolecular reaction of aziridines with β-bromo acrylates and nitriles.[13]

The stereochemistry about the olefin in compound **10*E*** was established by observation of a nuclear Overhauser enhancement between the amide hydrogen and the allylic methine (H_a), suggesting a syn relationship of these two atoms and thus *E* geometry. Similar enhancements between the same hydrogens were observed for the trisubstituted olefin **5*Z***. The bicyclic nature of **10*E*** (and **10*Z***) was supported by a strong enhancement between the allylic methine and the endo hydrogen (H_{endo}) of the aziridine methylene. Analysis of the ^1H NMR spectra of **10*Z*** and **10*E*** reveals subtle differences in their ring conformations. The allylic methine in **10*E*** shows a 5.0-Hz spin–spin coupling to the homoallylic hydrogen (H_b). This value is in line with that observed for the identical atom pairs in azinomycin B (4.0 Hz). In contrast, this value is only 1.5 Hz for **10*Z*** and is similar to that observed for **1** (1.0 Hz). These spin–spin couplings appear to have some predictive value for olefin geometry in the 1-azabicyclo[3.1.0]hex-2-ylidene systems.

A protocol has been developed for the stereoselective synthesis of either *Z* or *E* derivatives of the unusual dehydroamino acid proposed for the azinomycin antitumor antibiotics. This protocol involves formation of β-bromodehydroamino acid derivatives followed by intramolecular Michael addition–elimination which proceeds with complete retention of the starting olefin geometry. This methodology provides the first synthesis of the (*E*)-1-azabicyclo[3.1.0]hex-2-ylidene ring system (**10*E***) found in the natural product. Application of this approach to the

(8) Compound 7 could simply act as a brominating agent in an intermolecular fashion. *N*-Bromoacetamide converts **5*Z*** to **6*E*** (>95%) in yields similar to the NBS reaction.

(9) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. Anh, N. T. *Fortschr. Chem. Forschung* **1980**, *88*, 145.

(10) Olsen, R. K.; Hennen, W. J.; Wardle, R. B. *J. Org. Chem.* **1982**, *47*, 4605.

(11) The intermolecular Michael addition of sulfur and nitrogen nucleophiles to β-bromodehydroamino acid derivatives proceeds only at high temperature and with moderate stereoselectivity about the olefin (ref 6).

(12) The mechanistic aspects of nucleophilic vinylic substitutions have been thoroughly addressed: Rappaport, Z. *Acc. Chem. Res.* **1981**, *14*, 7.

(13) De Ancos, B.; Maestro, M. C.; Martin, M. R.; Farinza, F. *Synthesis* **1988**, 136.

synthesis of the azinomycins is currently under investigation in these laboratories.

Acknowledgment. Support from NSF (CHE 88-58059) and Bristol Myers-Squibb (Dr. T. Doyle) is gratefully acknowledged.

Supplementary Material Available: ^1H and ^{13}C NMR data for compounds $5E/Z$, $6E/Z$ mixture, and $10E/Z$ (13 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.

The Intramolecular Silyl Modified Sakurai (ISMS) Reaction. A Simple and Versatile Synthesis of Tetrahydropyrans, Spiroethers, and Spiroketals†

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Received November 13, 1991

Summary: The Intramolecular Silyl Modified Sakurai (ISMS) reaction is a powerful tool for the construction of tetrahydropyrans, spiroethers, and spiroketals. The ISMS methodology was applied to a short and stereocontrolled synthesis of a minor component of the rectal gland secretion of the female *Dacus oleae* fruit fly.

Tetrahydropyrans, spiroethers, and spiroketals are important subunits of a plethora of biologically active natural products. These include polyethers,[2] such as monensin[3] and nigericin,[4] antiparasitic agents of the milbemycin and avermectin families,[5] and insect pheromones,[6] e.g., **2** and **3**. Other important natural products include neurotoxins,[7] such as okadaic acid **1**.[8] In order to develop efficient synthetic routes toward these challenging targets, a practical and high-yielding synthesis of tetrahydropyrans, spiroethers, and spiroketals[9] is required.

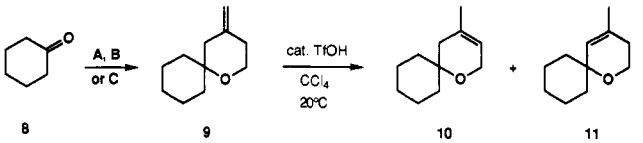
Although an enormous amount of synthetic effort has been invested over the past 10 years into the preparation of these subunits,[9] most of the available methodologies suffer from either lengthy sequence of steps and/or poor overall yields. In this paper, we report on some of our results toward the successful realization of a general strategy that overcomes these limitations. The simplicity and efficiency of this approach is further illustrated by the expedient total synthesis of the two pheromones **14a** and **14b**.[10]

We have recently reported[11] a three-component condensation—the Silyl Modified Sakurai (SMS) reaction—which produces homoallylic ethers *in one step*, directly from carbonyl compounds, allylsilanes, and trimethylsilyl ethers. The SMS reaction is catalyzed[12] by trimethylsilyl triflate (TMSOTf) and probably involves the in situ generation of an oxonium cation[13-15] analogous to **6**. We envisioned that by using the intramolecular version of this reaction—the ISMS reaction—tetrahydropyrans, such as **7**, would be produced *in a single step* (Figure 2).

Thus, the required bis-silylated reagent **5** was prepared from the commercially available alcohol, following the procedure of Trost, Chan, and Nanninga,[17] and reacted initially with cyclohexanone (Table I).

As can be seen from Table I, direct condensation of **5** with cyclohexanone **8**, under TMSOTf catalysis, proved only partially successful. Indeed, although the heterocycle was produced in good overall yields, a mixture of double-bond isomers was obtained. At room temperature, a roughly equal proportion of the $\Delta^{2,3}$ and $\Delta^{3,4}$ endo isomers **10** and **11** (Table I, entry 1) was produced, whereas at −15

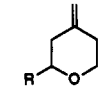
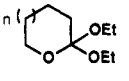
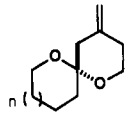
Table I. Control of the ISMS Reaction



entry	condn[a]	ratio (9:10:11)	yield (%)
1	A	−:1:1	84
2	B	12:1:1	87
3	C	50:<1:<1	83

[a] A = 5/cat. TMSOTf/CCl_4/20 °C; B = 5/cat. TMSOTf/CCl_4/−15 °C; C = 5/cat. TMSOTf/CCl_4/10–15 mol % $C_6H_{13}OSiMe_3$/20 °C.

Table II. ISMS Reaction with Carbonyls and Derivatives

entry	substrate	product	yield
1			
		R = C_6H_{13}	83%[a]
		R = Ph	85%[a]
2			88%
3			
		12a: n = 0	80%
		12b: n = 1	83%

[a] Reaction carried out in the presence of 200 mol % C_3H_5OTMS. [b] Reaction carried out in the absence of added C_2H_5OTMS.

† Dedicated fondly to Dr. Claude Lambert.

(1) University of Sheffield, X-ray Crystallographic Analysis.

(2) (a) Westley, J. W. *Polyether Antibiotics: Naturally Occuring Acid Ionophores*; Marcel Decker: New York, 1982; Vols. 1 and 2. (b) Wierenga, W. The Total Synthesis of Ionophores. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4, p 263.

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