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

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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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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.

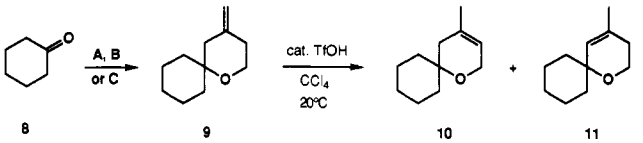
Although an enormous amount of synthetic effort has been invested over the past 10 years into the preparation of these subunits,[9] most of the available methodologies suffer from either lengthy sequence of steps and/or poor overall yields. In this paper, we report on some of our results toward the successful 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

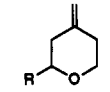
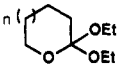
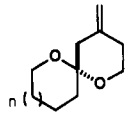
Table I. Control of the ISMS Reaction



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.

0022-3263/92/1957-2211$03.00/0

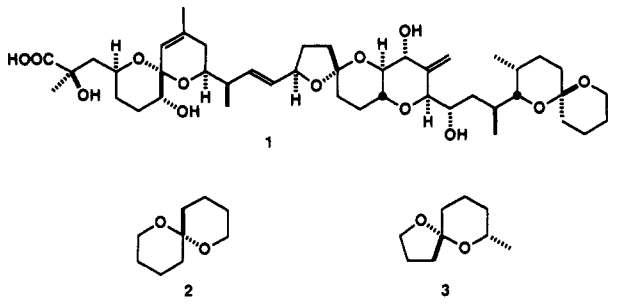


Figure 1.

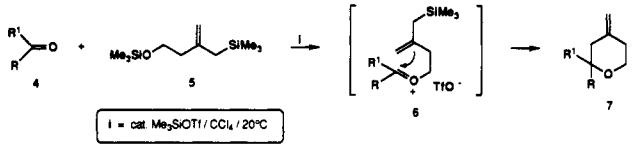


Figure 2.

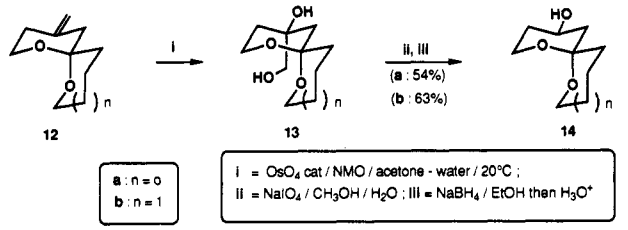


Figure 3.

°C the exocyclic isomer **9** predominated only by a factor of 6:1 (Table I, entry 2). Although this initial success opened up exciting prospects, the formation of a mixture of regioisomers in these proportions is synthetically intolerable. We reasoned that triflic acid, generated in trace amount by the hydrolysis of TMSOTf, was responsible for the formation of this mixture of isomers. Indeed, when a catalytic amount of triflic acid is added to the exo isomer **9**, rapid equilibration takes place and a 1:1 mixture of the endo isomers **10** and **11** is again produced.

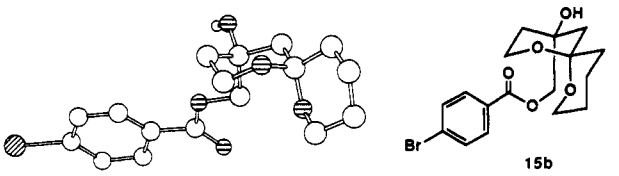


Figure 4.

Much to our surprise, *ISMS annelation of cyclohexanone, in the presence of another silyl ether such as $C_6H_{13}OTMS$ or C_2H_5OTMS, gives almost exclusively the exo isomer* **9**, *in excellent yield* (Table I, entry 3). The results of the condensation of **5** with a few representative carbonyl derivatives are displayed in Table II.

In all the cases studied so far, the exo isomer of the tetrahydropyran is obtained in high yield. The workup involved is trivial, and the crude product is usually sufficiently pure to be engaged in another reaction without further purification. It is important to realize that some of these exocyclic systems isomerize readily to their endocyclic isomers and that purification can sometimes be a real problem. Interestingly, the reaction is also successful with acetals and ketals (Table II, entry 2). *Much more importantly, ISMS annelation using ortholactones*[18] *as substrates affords spiroketals in a single step and in high yield* (Table II, entry 3). In these latter cases, no silyl ether other than **5** is required.

The power of the ISMS reaction is further illustrated by the short synthesis[19,20] of **14b**—a minor component of the rectal gland secretion of the female *D. oleae* fruit fly—and of its lower homologue **14a** (Figure 3).

Catalytic osmylation[21] of spiroketal **12b** (OsO_4/NMO/aqueous acetone/20 °C) gives a single diol **13b**, the

(3) (a) Schmid, G.; Fukuyama, T.; Akasaka, Y.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259, 260, 262. (b) Collum, D. B.; McDonald, J. H., III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2117. (c) Urry, D. W.; Goodall, M. C.; Glickson, J. D.; Mayers, D. F. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1907.

(4) (a) Tsukube, H.; Sohmiya, H. *J. Org. Chem.* **1991**, *56*, 875. (b) Pramanik, B. N.; Das, P. R.; Bose, A. K. *J. Nat. Prod.* **1989**, *52*, 534.

(5) (a) Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiot.* **1980**, *33*, 1120. (b) Mishima, H.; Kurabayashi, M.; Tamura, C.; Sato, S.; Kuwano, H.; Saito, A.; Aoki, A. *Tetrahedron Lett.* **1975**, 711. For a review of synthetic approaches, see: Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87.

(6) (a) Iwata, C.; Moritani, Y.; Sugiyama, M.; Fujita, M.; Imanishi, T. *Tetrahedron Lett.* **1987**, *28*, 2255. (b) Francke, W.; Reith, W.; Bergström, G.; Tengö, J. *Naturwissenschaften* **1980**, *67*, 149.

(7) (a) Birnecker, W.; Wallnöfer, B.; Hofer, O.; Greger, H. *Tetrahedron* **1988**, *44*, 267. (b) Mori, K.; Ikunaka, M. *Tetrahedron* **1987**, *43*, 45.

(8) (a) Ichikawa, Y.; Isobe, M.; Bai, D.-L.; Goto, T. *Tetrahedron* **1987**, *43*, 4737. (b) Isobe, M.; Ichikawa, Y.; Goto, T. *Tetrahedron Lett.* **1986**, *27*, 963.

(9) (a) Perron, F.; Albizati, K. M. *Chem. Rev.* **1989**, *89*, 1617. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.

(10) These two compounds have also been choosen as models to test the methodology toward the preparation of [4,5] and [5,5] spiroketals, both units being key-fragments of okadaic acid **1**.

(11) Mekhalfia, A.; Markó, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779.

(12) These conditions are similar to those employed in Noyori's ketalization procedure: (a) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259. (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. Although this method of ketalization was reported more than 10 years ago, it is remarkable that the enormous potential of this approach for the synthesis of oxygen-containing heterocycles has not been recognized before our studies.

(13) Perst, H. *Oxonium Ions in Organic Chemistry*; Verlag-Chemie: Weinheim, 1971.

(14) For some selected references on the generation and synthetic use of oxonium cations, see: (a) Wilson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Campbell, S. F.; Bordner, J. *Tetrahedron* **1990**, *46*, 1757. (b) Castaneda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695. (c) Nussbaumer, C.; Fråter, G. *J. Org. Chem.* **1987**, *52*, 2096. (d) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857. (e) Cockerill, G.; Kocienski, P.; Treadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093. (f) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496. (g) Schulte-Elte, K. H.; Hawer, A.; Ohloff, G. *Helv. Chim. Acta* **1979**, *62*, 2673. (h) Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9.

(15) For the formation of tetrahydropyrans and oxepanes from allyltrimethylsilane and aldehydes, see: (a) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911. (b) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973. (c) Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441.

(16) We are aware of only two other approaches—based on the direct condensation of allylsilanes, carbonyl compounds, and alcohols—that lead to the one-step preparation of homoallylic ethers: (a) Sakurai, H.; Sasaki, K.; Hayashi, J.; Hosomi, A. *J. Org. Chem.* **1984**, *49*, 2808. (b) Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, 765. All the other ones require prior acetalization or ketalization of the aldehyde/ketone substrate.

(17) Trost, B. M.; Chan, D. M. T.; Nanninga, N. *Org. Synth.* **1984**, *62*, 58.

(18) The ortholactones are readily prepared by treating the lactones with Meerwein salt followed by sodium ethoxide: Kocienski, P. J.; Street, S. D. A.; Yeates, C.; Campbell, S. F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2171. The ISMS reaction can be performed on the lactones themselves, but the yields are, so far, lower.

(19) (a) Kocienski, P.; Yeates, C. *Tetrahedron Lett.* **1983**, *24*, 3905. (b) Kay, T. I.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915. (c) Baker, R.; Herbert, R.; Parton, A. H. *J. Chem. Soc., Chem. Commun.* **1982**, 601. (d) Baker, R.; Herbert, R.; House, P. E.; Jones, O. T.; Francke, W.; Reith, W. *J. Chem. Soc., Chem. Commun.* **1980**, 52. (e) Baker, R.; Herbert, R. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1123. (f) Mori, K.; Uematsu, T.; Watanabe, H.; Yanagi, K.; Minobe, M. *Tetrahedron Lett.* **1984**, *25*, 3875. (g) For a recent synthesis of another *D. oleae* pheromone, see: DeShong, P.; Rybczynski, P. J. *J. Org. Chem.* **1991**, *56*, 3207.

(20) The stereochemistry of the reduction of ketones analogous to the ones derived from **13a** and **13b** has been documented previously (refs 19a, 19c, 19f, and 19g).

(21) VanRheenen, V.; Kelly, R. C.; Cha, D. F. *Tetrahedron Lett.* **1976**, 1973.

structure of which was unambiguously established by X-ray diffraction analysis of the derived *p*-bromobenzoate **15b** (Figure 4). As expected, osmylation took place from the less hindered face. Oxidative cleavage using sodium periodate followed by sodium borohydride reduction and acidic workup produces the desired spiroketal **14b**, accompanied by ~5% of the axial isomer. The overall yield for the synthesis of **14b**, starting from the ortholactone, is 63%. An identical route was followed to prepare the lower homologue **14a** in a respectable 54% overall yield.

In summary, we have shown that the ISMS reaction is a powerful tool for the production of tetrahydropyrans, spiroethers, and spiroketals. These are important subunits in a variety of natural products. By using the ISMS annelation, the spiroketals **14a** and **14b** were synthesized readily and in high overall yields. Further work on expanding the scope of this novel methodology as well as on its application to the total synthesis of milbemycin β3 and okadaic acid is being actively pursued in this laboratory and will be reported in due course.

Acknowledgment. Financial support for this work by the Algerian Ministry for Higher Education is gratefully acknowledged. Awards from the Science and Engineering Research Council, The Nuffield Foundation, and The Royal Society are highly appreciated. We are grateful to P. R. Ashton and I. R. Johnstone (MS), S. J. Thorpe (GC), and Dr. B. F. Taylor (NMR) for their enthusiastic contribution.

Supplementary Material Available: Experimental details for obtained compounds (13 pages). Ordering information is given on any current masthead page.

Intramolecular Oxypalladation and Cross-Coupling of Acetylenic Alkoxides

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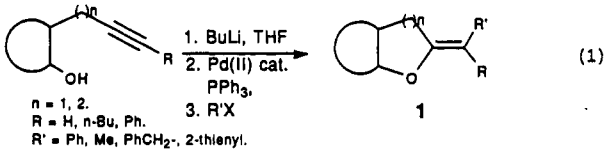
Summary: Stereodefined 2-alkylidenetetrahydrofurans and pyrans were synthesized by treatment of alkyl or aryl acetylenic alcohols with *n*-BuLi in THF at 0 °C followed by addition of a solution of 10 mol % of $Pd(OAc)_2$ or $PdCl_2$ and PPh_3 in THF and 1 equiv of an organic halide.

The construction of acid-sensitive exocyclic alkenes 1 with ≥98% stereoselectivity is a synthetic challenge.[1] Our interest in the palladium-catalyzed cyclization and cross-coupling of acetylenic aryl halides[2] or triflates[3] encouraged us to examine analogous acetylenic alcohols for the synthesis of such alkenes. The palladium-catalyzed cyclization of acetylenic alcohols has been shown to be an efficient route to the synthesis of various heterocycles.[4] However, the stereoselective synthesis of alkenes 1 from acetylenic alcohols via palladium catalysis is still essentially unexplored.[5] We now report a new strategy for the stereoselective construction of alkenes 1 via the palladium-catalyzed cyclization and cross-coupling of acetylenic alcohols with organic halides (eq 1).



(1)

Our results (Table I) demonstrate that a wide range of stereodefined α-alkylidene cyclic ethers can be formed through this cyclization and coupling reaction. A typical procedure is as follows. A solution of *n*-BuLi (1.4 mL of 1.6 M in benzene, 2.2 mmol) was added dropwise to a solution of 2-(2-propynyl)phenol[6] (0.26 g, 2 mmol) in 2 mL of THF at 0 °C under a nitrogen atmosphere. To the reaction mixture was added a solution of $Pd(OAc)_2$ (45 mg, 0.2 mmol) and Ph_3P (53 mg, 0.2 mmol) in 1 mL of THF and then benzyl bromide (0.38 g, 2.2 mmol). The reaction mixture was stirred at room temperature for 4 h and then quenched with water (10 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a pale yellow solid, which was purified by HPLC (Chemcosorb 5-ODS-H, MeOH) to give (*E*)-2,3-dihydro-2-(2-phenylethylidene)-benzofuran[7] (0.29 g, 65%) as a white solid (mp 35–37 °C). The stereoisomeric purity was ≥98% as determined by GC and by ^1H NMR and ^{13}C NMR spectra. The relative stereochemistry of the vinyl proton and the benzylic protons was determined by ^1H-2D NOESY NMR spectrometry (entry 4).

Both acetylenic alkyl and aryl alkoxides undergo the cyclization and cross-coupling reaction to form five- or six-membered rings with high regio- and stereoselectivities. The palladium catalyst, Ph_3P, and *n*-BuLi are all essential to make the reaction take place.[8] Use of chloroform, dimethylformamide, toluene, or benzene as solvent gave only trace (<3%) or undetectable amounts of desired product. Using zinc alkoxide, prepared by treating a lithium alkoxide with 1 equiv of zinc chloride in THF, or coupling the acetylenic alkoxide with phenylzinc chloride in the reaction also gave no desired product. Both $Pd(OAc)_2$ and $PdCl_2$ were effective catalysts. Other palladium

(1) (a) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842. (b) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 1187. (c) Luo, F. T.; Negishi, E. I. *J. Org. Chem.* **1983**, *48*, 5144. (d) Ley, S. V.; Lygo, B.; Organ, H. M.; Wonnacott, A. *Tetrahedron* **1985**, *41*, 3825.

(2) (a) Wang, R. T.; Chou, F. L.; Luo, F. T. *J. Org. Chem.* **1990**, *55*, 4846. (b) Luo, F. T.; Wang, R. T. *Heterocycles* **1990**, *31*, 1543 and 2181. (c) Luo, F. T.; Wang, R. T. *Heterocycles* **1991**, *32*, 2365.

(3) Luo, F. T.; Wang, R. T. *Tetrahedron Lett.* **1991**, *32*, 7703.

(4) (a) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845. (b) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323. (c) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655. (d) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277.

(5) The palladium-catalyzed cyclization of acetylenic carboxylates with allyl halides has been reported: Yanagihara, N.; Lambert, C.; Iritani, K.; Uitmoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 2753.

(6) Kall, T.; Sossi, Kh. *Uchenye Zapinski Tartusk. Gosudarst. Univ.* **1960**, *95*, 179; *Chem. Abstr.* **1962**, *56*, 5868d.

(7) All new compounds have been fully characterized by ^1H- and ^{13}C-NMR, MS or IR spectroscopy, and either elemental analysis or high-resolution mass spectroscopy. Although (*E*)-2-(phenylmethylene)tetrahydrofuran has been reported,[1d] we found that the reported NMR spectral data are different from ours (entry 6).

(8) The use of other bases, e.g., $NaHCO_3$, MeONa, in running the reaction gave no detectable amount of the desired product.

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