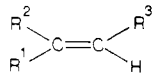
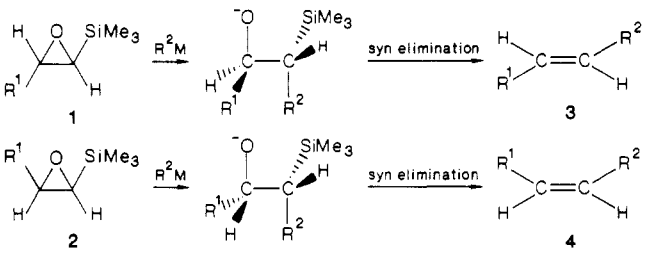
Table I. Reaction of Epoxysilanes with Organometals[a]

R^1	R^2	R^3M	yield,[b] % of 	stereoselectivity, %	others
n-C_5H_{11}	H	Li_2CuPh_2CN	94 (>95)	>95	
H	n-C_5H_{11}	Li_2CuPh_2CN	77 (82)	>95	
H	n-C_4H_9	PhLi	- (50)	>95	$PhSiMe_3$ (50%)
n-C_4H_9	H		82	>95	
H	n-C_4H_9		80	>95	
n-C_4H_{11}	H	$Li_2Cu(CH{=}CH_2)CN$	80	>95	
n-C_4H_9	H	n-$C_4H_9C{\equiv}CLi$	95	>95	
H	n-C_5H_{11}	n-$C_4H_9C{\equiv}CLi$	92	≥98	
H	n-C_4H_9	$LiAlClEt_2(C{\equiv}C_4H_9$-$n)$	0		n-$C_4H_9CH(OH)CHClSiMe_3$ (96%)
H	n-C_5H_{11}	$LiCH_2CONEt_2$	95[c]		
H	n-C_6H_{13}		83	≥98	

[a] Organolithium reactions were run at -78 to 25 °C by gradually warming the reaction mixture, while organocopper reactions were run at -50 to -20 °C followed by warming to 25 °C. [b] Isolated yield. The number in parentheses is a GLC yield. [c] Yield of *N,N*-diethyl-4-hydroxy-3-(trimethylsilyl)nonanamide.

Scheme I[a]



[a] R^1 and R^2 = carbon groups. M = Li and Cu.

The following two procedures are representative. **2-[(*Z*)-1-Octenyl]-1,3-dithiane.** To a solution of 1,3-dithiane (0.255 g, 2.12 mmol) in 6 mL of THF at -25 °C was added *n*-BuLi (2.7 M in hexane, 0.82 mL, 2.22 mmol). The reaction mixture was stirred at 25 °C for 1-2 h, followed by addition of (*Z*)-1-(trimethylsilyl)-1-octene oxide (0.425 g, 2.12 mmol) in 2 mL of THF. The resulting mixture was stirred overnight at 25 °C, quenched with 3 N HCl, extracted with ether, washed with $NaHCO_3$, dried over $MgSO_4$, and distilled to give 0.41 g (83%) of the title compound as an isomerically >98% pure material: bp 105-108 °C (0.05 mmHg); IR (neat) 785 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, J = 7 Hz, 3 H), 1.0-1.7 (m, 8 H), 1.7-2.4 (m, 4 H), 2.6-3.0 (m, 4 H), 4.90 (d, J = 9 Hz, 1 H), 5.2-5.7 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.30, 22.79, 25.22, 28.00, 29.10, 29.58, 30.55, 31.88, 43.46, 126.01, 134.75. Anal. Calcd for $C_{12}H_{22}S_2$: C, 62.55; H, 9.62. Found: C, 62.36; H, 9.71. **(*E*)-1,3-Nonadiene.** To a suspension of CuCN (0.43 g, 4.8 mmol) in 4 mL of THF at -78 °C was added vinyllithium (1.85 M in ether, 5.2 mL, 9.6 mmol).[9] The reaction mixture was warmed to 0 °C, and the resulting clear solution was cooled to -20 °C. To this was added (*Z*)-1-trimethyl-1-heptene oxide (0.74 g, 4 mmol) in 4 mL of THF. The mixture was gradually warmed to 25 °C and stirred for 2-3 h. Quenching with aqueous NH_4Cl, extractive workup, and distillation gave 0.40 g (80%) of the title compound[10] as an isomerically >96% pure substance: IR (neat) 1650 (w), 1010 (m), 910 (s), 750 (s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.90 (t, J = 6 Hz, 3 H), 1.0-1.7 (m, 6 H), 2.0-2.4 (m, 2 H), 4.7-5.2 (m, 2 H), 5.5-6.6 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 14.15, 22.69, 29.07, 31.60, 32.67, 114.62, 131.11, 135.72, 137.60.

Acknowledgment. We thank the National Institutes of Health (Grant GM 36792) for support. We also thank Kurt J. Mouis for running the epoxysilane opening reaction with phenyllithium.

Supplementary Material Available: Experimental data for synthesized compounds (5 pages). Ordering information is given on any current masthead page.

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Synthesis of Oxidized Spiroketals via 2-Furyl Ketone Oxidation-Rearrangement

Summary: A new method for the synthesis of highly oxidized spiroketals has been developed via the oxidation-rearrangement of 2-furyl ketones, readily available by the reaction of furyllithium reagents with lactones. Spiroketals hydroxylated in the 2-position are produced as slowly equilibrating mixtures of diastereomers in good yield. The method has been applied to the synthesis of trioxadispiroketals modeling those present in the polyether antibiotics salinomycin, narasin, and their analogues.

Sir: Spiroketals are important subunits of a growing variety of naturally occurring compounds of considerable current importance and interest. Although simple derivatives of both the 1,7-dioxaspiro[5.5]undecane (1) and

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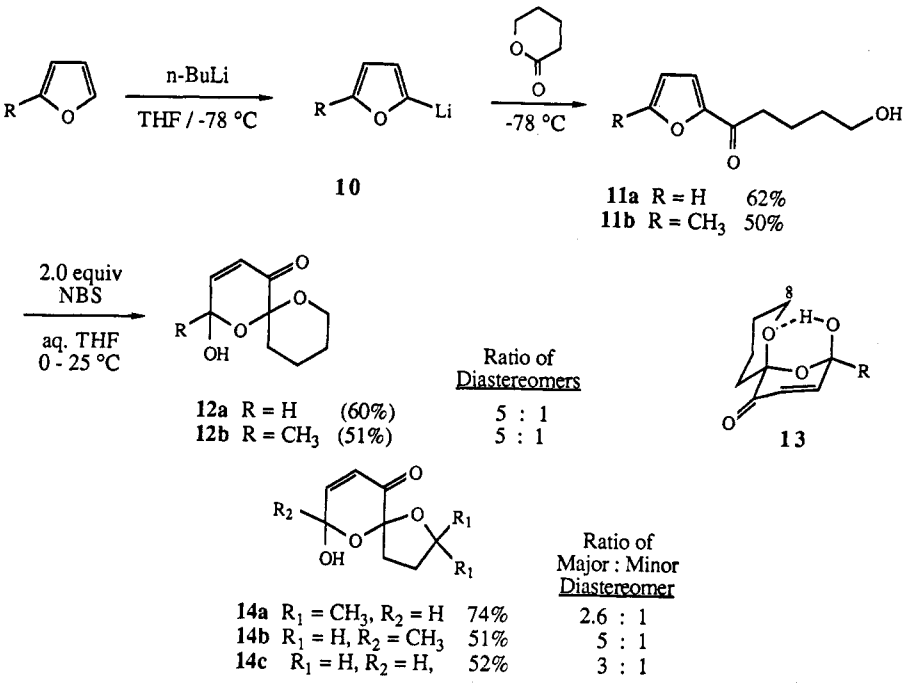
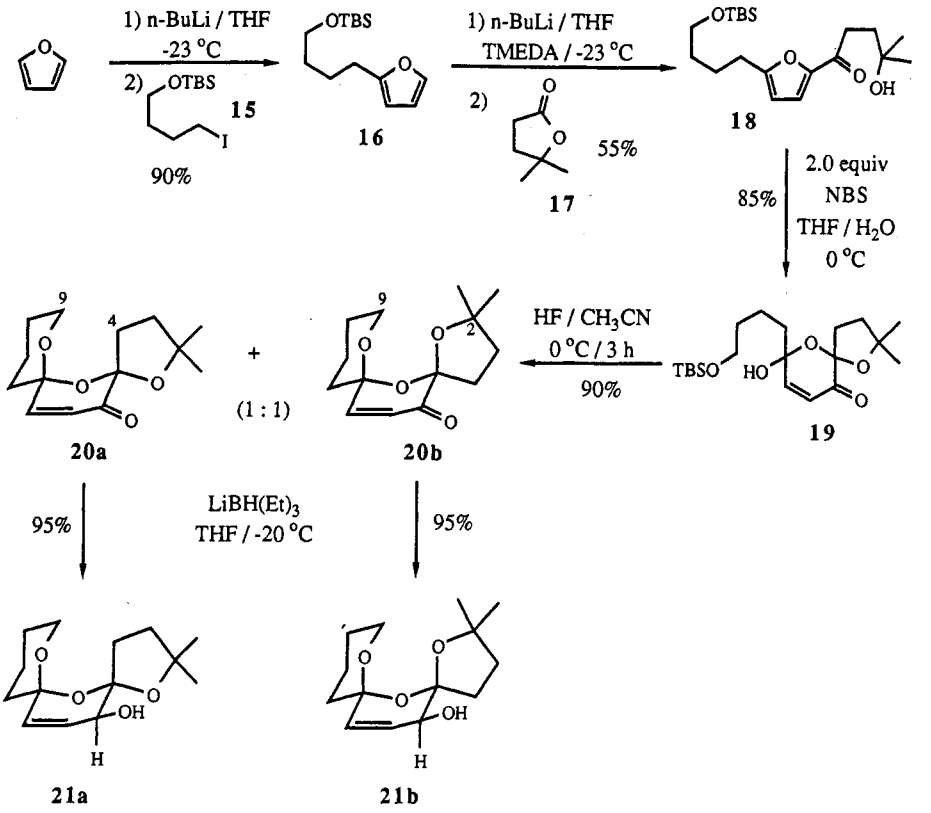
Scheme I



Scheme II



1,6-dioxaspiro[4.5]decane (**2**) ring systems are known in nature,[1] more frequently the spiroketal is more highly oxidized, as exemplified by the milbemycin–avermectins,[2] polyether ionophores in general,[3] and phyllanthocin and related metabolites.[4] While the literature abounds with methods for the synthesis of spiroketals,[5] most of these

(1) Compounds in this category consist primarily of insect pheromones. For a review, see: Baker, R.; Herbert, R. H. *Nat. Prod. Rep.* **1984**, *1*, 299. Also see: Kitching, W. M.; Lewis, J. A.; Fletcher, M. T.; Drew, R. A. I.; Moore, C. J.; Francke, W. *J. Chem. Soc., Chem. Commun.* **1986**, 853 and listed citations.

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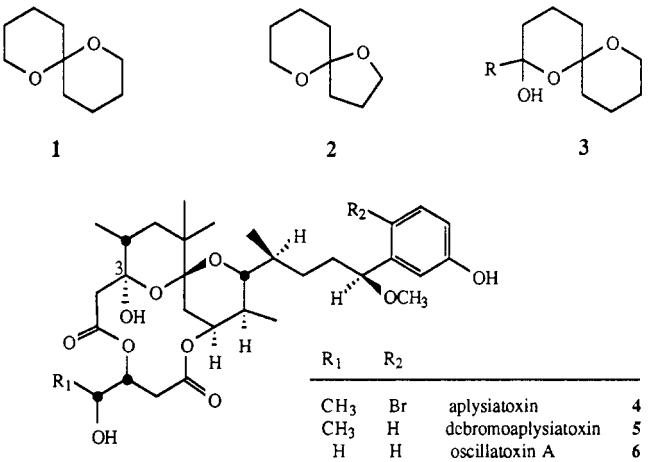
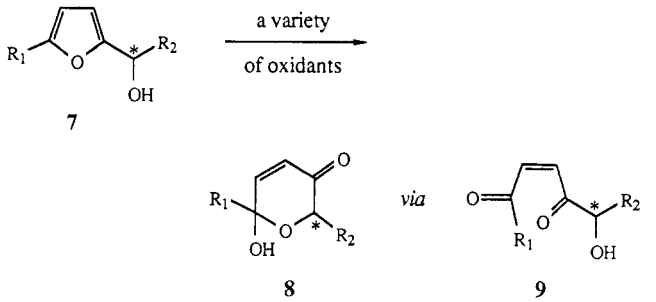
involve the assembly of fully functionalized dihydroxy ketone precursors (or an equivalent) prior to spirocyclization. To our knowledge, no general methods have been described for the efficient formation of spiroketals oxidized at the 2-position (as in 3).[6] Important compounds containing this functional arrangement are the aplysiatoxin–oscillatoxin metabolites of marine blue-green algae[7] and the trioxadispiroketal-containing polyethers salinomycin,[8a] narasin,[8b] and their analogues.[9] Indeed, the Achille's heel of a recent attempt[10] at aplysiatoxin synthesis was the inability to generate the key hydroxyl group at C3 (aplysiatoxin numbering). We wish to describe the oxidation–rearrangement of 2-furyl ketones leading to oxidized spiroketals of three structural types.

It is well known that when 2-furyl carbinols of general structure 7 are treated with any of several oxidizing agents[11a] including peracids,[11b] PCC,[11c] and Br_2,[11d] the



R_1	R_2		
CH_3	Br	aplysiatoxin	4
CH_3	H	debromoaplysiatoxin	5
H	H	oscillatoxin A	6

furan nucleus undergoes an oxidation–rearrangement sequence producing the pyranone derivatives 8, presumably involving ring closure of ene–dione intermediates such as 9 or an equivalent thereof. Our approach involves the oxidation of 2-furyl ketones allowing a convergent, two-step construction of functionalized spiroketals (related to 3) such as those present in 4–6.[12] It should be noted that DeShong has developed a complementary[13] oxidation of 2-furyl carbinols leading to spiroketals related to 1 and 2.



Treatment of a solution of 2-furyllithium in THF at −78 °C with δ-valerolactone (Scheme I) produces predominantly the monoaddition product 11 along with varying amounts of the product of double addition to the carbonyl, which can be removed easily by chromatography on silica. No trace of the ring-closed hemiketal form of the hydroxy ketone 11 could be observed by ^1H or ^{13}C NMR spectroscopy. When 11 is treated with 2 equiv of *N*-bromosuccinimide in aqueous THF the hemispiroketals 12 result in good yield as a slowly equilibrating mixture of diastereomers. The conformation of the major isomers was found to be as shown in 13 and is supported by the observation of a nuclear Overhauser enhancement between the hydroxyl hydrogen and the C-8 hydrogens using 2-dimensional NOE spectroscopy. This was confirmed by infrared spectroscopy by the presence of both a free OH band (3610 cm^{-1}, CCl_4) and a band for an intramolecularly hydrogen-bonded OH at ca. 3590 cm^{-1}. This conformation is consistent with the strong preference of alkoxy groups

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(12) All yields refer to >95% pure isolated products. The structures of all new compounds were consistent with their routine 300-MHz ^1H and ^{13}C NMR, IR, and their low- and high-resolution mass spectral data, including peak matching of the parent molecular ions. Additional spectroscopic experiments, including NMR ^1H and ^{13}C decoupling and correlation spectroscopy, were required in most cases. Complete data will be reported in a full account of this work.

(13) The two processes are complementary in that the carbons in the furyl substrates translate into entirely different positions on the spiroketal rings. See: DeShong, P. L.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901.

to attain an axial orientation on six-membered rings when flanked by an oxygen atom and a carbonyl group.[14]

In addition, oxidized forms of 1,6-dioxaspiro[4.5]decanes can be synthesized by an analogous sequence starting with γ-lactones. The hemispiroketals **14a–c** were synthesized in good overall yield and again isolated as mobile mixtures of diastereomers containing one predominant species, which has been tentatively assigned conformations analogous to the six-membered ring cases.

The method has been applied to the synthesis of trioxadispiroketals, key structural units of the narasin–salinomycin polyether antibiotics.[15] Sequential alkylation (Scheme II) of furan with the iodide **15** followed by the lactone **17** results in the 2-furyl ketone **18**. Oxidation–rearrangement of **18** with 2 equiv of NBS in THF/H_2O (2:1) at 0 °C gives an equilibrium mixture of hemispiroketals **19**, which were not further purified. Desilylation and spiroketalization with 5% HF in CH_3CN provided a 1:1 mixture of the two diastereomeric trioxadispiroketals **20a** and **20b**, which were readily separated by chromatography on silica. Isomer **20a** was assigned the stereochemistry and conformation shown on the basis of weak (1–5%) inter-annular nuclear Overhauser enhancement of one of the hydrogens on C-4 when the C-9 axial hydrogen is irradiated. Isomer **20b** was assigned the structure and conformation shown on the basis of a 6% enhancement of a methyl group attached to C-2 when the C-9 axial hydrogen was irradiated. Although isomer **20b** possesses what appears to be the maximum anomeric effect stabilization, it does not greatly predominate in the product mixture. This may be due to unfavorable dipole–dipole interaction at the two spiro carbons.[16]

Reduction of each isomer with $LiBH(Et)_3$ in THF gave rise to a single allylic alcohol in each case. Isomer **21b** possesses the configuration of the trioxadispiroketal present in salinomycin[8a] and narasin[8b] while **21a** matches that of deoxy (O-8)-epi-17-salinomycin.[17]

In summary, efficient syntheses of hemispiroketals and trioxadispiroketals have been accomplished. The route is convergent, utilizing sequential alkylation of 2-lithiofuran derivatives as the key C–C bond forming steps. Oxidation–rearrangement of the 2-furylketones followed by thermodynamic cyclization leads to highly oxidized spiroketals modeling those present in **4–6**, as well as the narasin–salinomycin polyether antibiotics. Further studies involving the application of this method are in progress.

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(15) Other methods of trioxadispiroketal synthesis: (a) Baker, R.; Brimble, M. A. *J. Chem. Soc., Perkin Trans. 1* **1988**, 125. (b) Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 3253. (c) Cottier, L.; Descotes, G. *Tetrahedron* **1985**, *41*, 409.
(16) Kishi, Y.; Hatakeyama, S.; Lewis, M. D. *Front. Chem. Plenary, Keynote Lect. IUPAC Congr. 28th, 1981*; Laidler, K. J., Ed.; Pergamon Press: Oxford, 1982; pp 287–304. For general discussions and examples see ref 3, Vol. 2, Chapters 3, 5, and 6.
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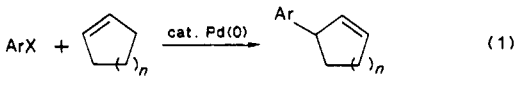
Palladium-Catalyzed Intermolecular Vinylation of Cyclic Alkenes

Summary: Vinylic halides or triflates and cyclic alkenes undergo facile, palladium-catalyzed, intermolecular, allylic cross-coupling under mild reaction conditions to afford excellent yields of 1,4-dienes.

Sir: There are a number of examples of the *intermolecular*, palladium-catalyzed, allylic cross-coupling of aryl halides and cyclic alkenes (eq 1).[1–6] We recently reported



(1)

three convenient procedures to effect such reactions. The use of 0.5 mmol of organic halide, 2.5 mmol of cyclic alkene, 2.5% $Pd(OAc)_2$ (3 mg), 3 equiv of KOAc (1.5 mmol), and 1 equiv of n-Bu_4NCl (0.5 mmol) in DMF (1.0 mL) under nitrogen at room temperature or 80 °C (procedure A) generally gives excellent yields,[7] but subsequent work revealed that certain cyclic alkenes afforded mixtures of regioisomers under these conditions and a number of important organic functional groups in the aryl halide could not be accommodated by this procedure.[8] Consequently, we developed two alternative procedures [Procedure B:[9] organic halide (0.5 mmol), cycloalkene (2.5 mmol), 3% $Pd(OAc)_2$ (3.5 mg), 9% PPh_3 (12 mg), 2 equiv of Ag_2CO_3 (1.0 mmol), CH_3CN (6 mL). Procedure C: same as procedure A, plus 2.5% PPh_3]. The former procedure effectively inhibited isomerization and the latter proved particularly useful for functionally substituted aryl halides. These and related arylation procedures have recently proven quite valuable for *intramolecular* cyclizations.[9–15]

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