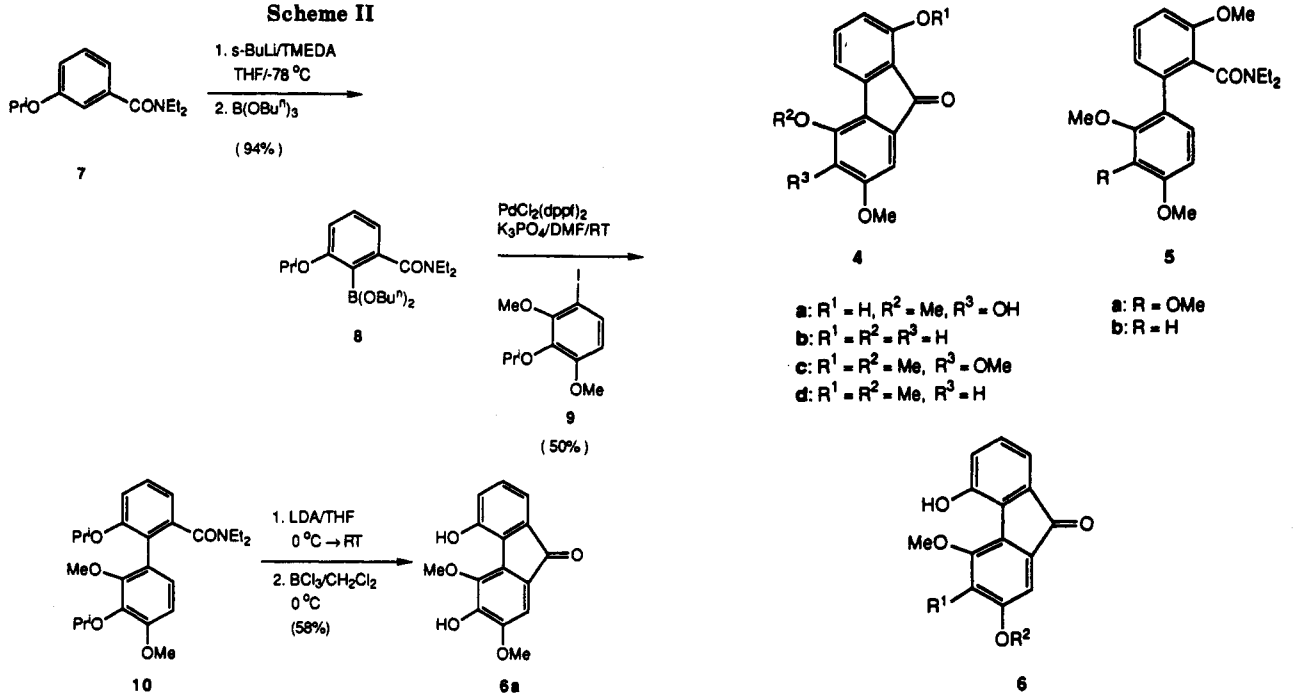
Scheme II



the structures were revised to **6a** and **6b**, respectively, on the basis of additional spectroscopic data[7c] and the synthesis of the misassigned **4a**, **4b**, their respectively dimethyl ethers **4c** and **4d**, and the natural products **6a** and **6b**.[7b] Concurrently, we applied our remote metalation process (2.5 equiv of LDA) on the readily accessible amides **5a** and **5b** to give **4c** (82%) and **4d** (72%), respectively, whose physical and spectra data were in agreement with those of the synthetic materials **4c** and **4d**[7b] but not with those of dengibsinin dimethyl ether and dengibsin dimethyl ether.[7a,14] The synthesis of dengibsinin **6a** (Scheme II) begins by standard metalation/$B(OBu^n)_3$ quench of the *m*-isopropoxybenzamide **7** to give the stable borate **8** in high yield. After considerable experimentation, the cross coupling of **8** with the alkoxylated iodobenzene **9**, constituting a case of high steric hindrance and propensity for protodeboronation, was achieved under anhydrous Suzuki conditions[15] to give **10**. Sequential LDA-induced cyclization and selective deisopropylation[16] furnished dengibsinin (**6a**, 24% overall yield) whose physical and spectral properties were identical with those reported for the natural product.[7a,b]

In summary, a new and general anionic equivalent of the Friedel-Crafts reaction for the construction of substituted and condensed fluorenones, including aza analogues and the natural product dengibsinin (**6a**), from readily available biaryls and *m*-teraryls has been developed. The established connection of this method to the evolving directed ortho metalation[1] and aryl boronic acid cross coupling[2] strategies as well as the potential[17] of fluorenones in Haller-Bauer,[18] Beckmann,[19] and Baeyer-Villiger[20] reactions augur well for its synthetic utility in aromatic and heteroaromatic chemistry.[21,22]

(14) Compound **4d** was also prepared by a route which begins by cross-coupling chemistry and ends similarly to that executed by Sargent.[7b] See: Sharp, M. J. M.Sc. Thesis, University of Waterloo, 1986.
(15) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221.
(16) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans 1* **1979**, 2593.
(17) Zhao, B.-p.; Snieckus, V., work in progress.
(18) Gilday, J. P.; Paquette, L. A. *Org. Prep. Proc. Int.* **1990**, *22*, 167.
(19) Esteban, S.; Marinas, J. M. *An. Quim.* **1978**, *74*, 1413; *Chem. Abstr.* **1979**, *91*, 19537f.
(20) Andrievskii, A. M.; Poplavskii, A. N.; Dyumaev, K. M. *Khim. Geterotsikl. Soedin.* **1982**, 703; *Chem. Abstr.* **1982**, *97*, 92088p.
(21) All new compounds show analytical and spectral (IR, ^1H and ^{13}C NMR, MS) data consistent with the assigned structures.
(22) We are grateful to NSERC Canada and Merck Frosst for financial support of our synthetic programs.

A Novel Synthesis of Furans by Base-Catalyzed Isomerization of Alkynyloxiranes

James A. Marshall* and William J. DuBay

Department of Chemistry, The University of South Carolina, Columbia, South Carolina 29208

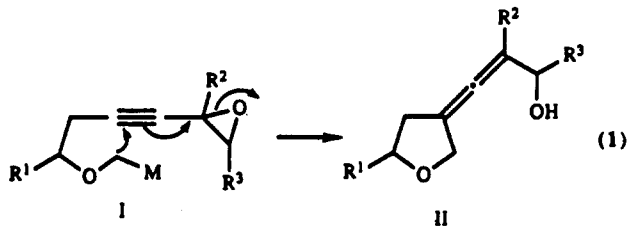
Received December 3, 1990

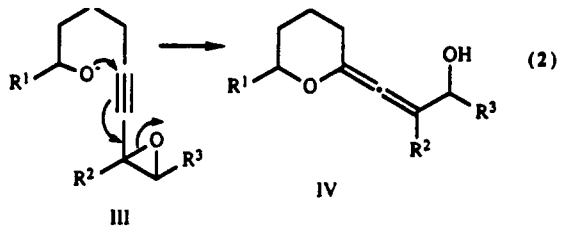
Summary: Treatment of alkynyloxiranes **3** with KO-*t*-Bu in *t*-BuOH causes isomerization to the furans **4**. A pathway involving a cumulene alkoxide is proposed.

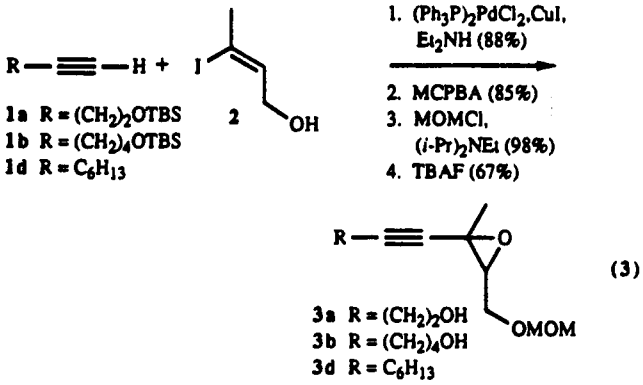
Persuant to studies on the synthesis of hydrofuran and hydropyran natural products we were interested in examining intramolecular S_N2' additions to alkynyloxiranes as exemplified in eqs 1 and 2. To determine the feasibility of these transformations, epoxy alcohols **3a** and **3b** were prepared as model systems (eq 3).[1] With the aim of ef-

(1) The coupling method of Sonogashiro et al. was employed. Sonogashiro, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. Vinyl iodide **2** was prepared from 2-butyn-1-ol by treatment with Red-Al (Aldrich) followed by I_2 in THF. Cf: Marshall, J. A.; DeHoff, B. S. *J. Org. Chem.* **1986**, *51*, 863.

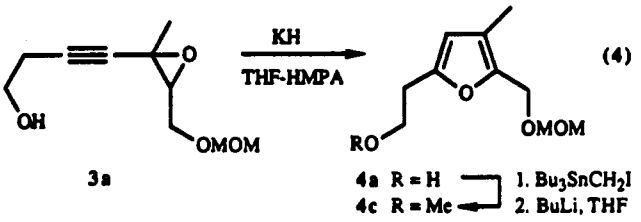
0022-3263/91/1956-1685$02.50/0







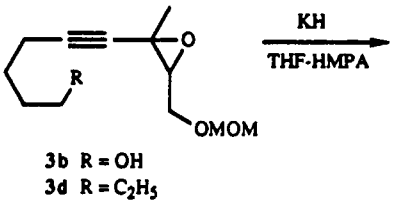
fecting the cyclization depicted in eq 1, we treated alcohol **3a** sequentially with KH in THF–HMPA followed by Bu_3SnCH_2I and *n*-BuLi in THF.[2] A single product resulted. However, it was not the expected hydrofuran II but rather the isomeric furan **4c** (eq 4). When steps 2 and

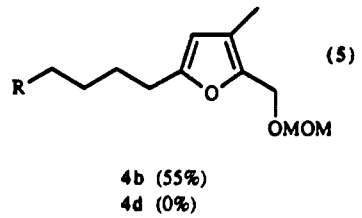


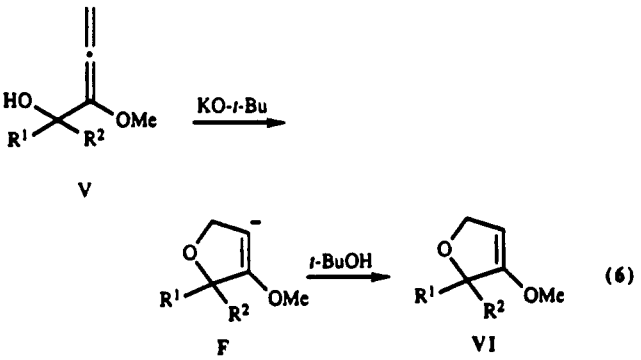
3 of the foregoing sequence were omitted, the furan **4a** was produced in high yield. Epoxy alcohol **3b** was likewise converted to furan **4b** upon base treatment (eq 5). Surprisingly epoxide **3d**, lacking the side chain hydroxyl, was recovered unchanged upon treatment with KH.

As a possible pathway for this remarkable isomerization we offer the sequence depicted in Figure 1. Accordingly, base initiated 1,4-elimination of the alkynyloxirane A would give rise to the cumulene alkoxide B. Cyclization via the vinylic anion C followed by proton transfer leads to the furanoid system (D ↔ E). Protonolysis of E may occur on workup or possibly E could function as a base in step 1. The failure of **3d** to afford the furan product suggests that an alkoxide base is most effective in the 1,4-elimination step.

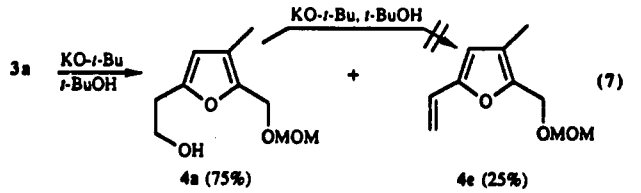
Precedent for the novel cyclization of B can be found in some early work of Magnus, illustrated in eq 6.[3] In



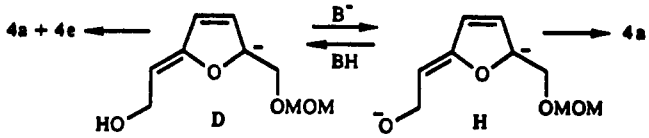




those examples vinylic anion F, possibly stabilized by the adjacent OMe substituent, was proposed as an intermediate. When subjected to KO-*t*-Bu in *t*-BuOH, the conditions employed by Magnus, all four of the alkynyloxiranes **3a**, **3b**, **3d**, and **3f** (R = CH_2OBn) yielded furans (Table I). Interestingly, with **3a** these conditions led to a reproducible 3:1 mixture of alcohol **4a** and the vinylfuran **4e** (eq 7). In a control experiment alcohol **4a** was not



converted to vinylfuran **4e** by KO-*t*-Bu in *t*-BuOH. Furthermore, the vinylfuran **4e** was not observed in reactions employing KH as the base. We propose that the elimination leading to **4e** occurs from intermediate D (Figure 1). In *t*-BuOH the leaving group is OH and the formation of **4a** vs **4e** reflects competing protonolysis and elimination pathways. With KH as the base, the primary OH grouping is present as the alkoxide H and elimination is thus disfavored.



Additional evidence for the proposed pathway comes from experiments with the alkynyloxirane **5**.[4] In this case the methyl substituent prevents formation of a furan ring. Upon treatment with KO-*t*-Bu, epoxide **5** was converted

(2) Analogous cyclizations of allylic methyl ethers have been reported. Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336.
(3) Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746.
(4) Prepared from the TBS ether of 3-butyn-1-ol (**1a**) and (*E*)-4-iodo-3-methyl-3-buten-1-ol[5] by the sequence shown in eq 3.
(5) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093.

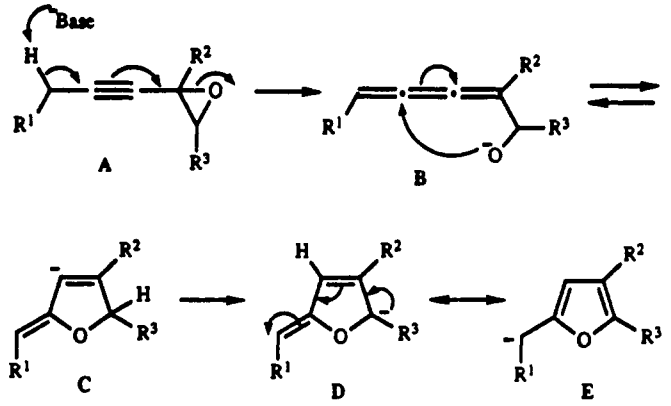
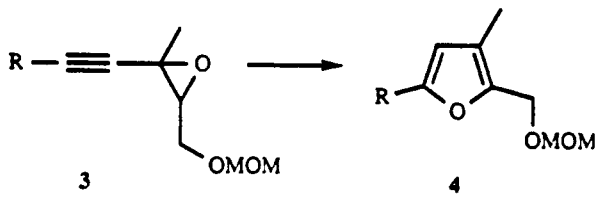


Figure 1.

Table I. Conversion of Alkynyloxiranes 3 to Furans 4

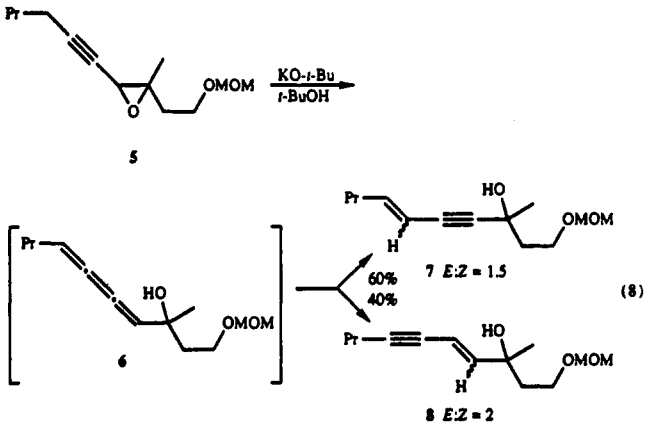


3 4

entry	series	R	conditions[a]	yield (%)[b]
1	a	CH_2CH_2OH	A	60
2	a	CH_2CH_2OH	B	86[c]
3	b	$(CH_2)_3CH_2OH$	A	55
4	b	$(CH_2)_3CH_2OH$	B	75
5	d	n-C_6H_{13}	A	0[d]
6	d	n-C_6H_{13}	B	70
7	f	CH_2OBn	B	70

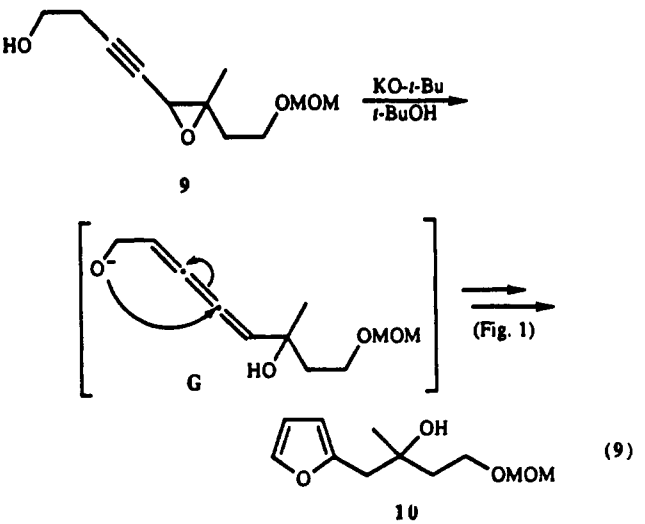
[a] A = KH, THF-HMPA; B = KO-*t*-Bu, *t*-BuOH. [b] Yield of chromatographed and/or distilled product. [c] A 3:1 mixture of **4a** and the vinylfuran **4e**. [d] Starting material was recovered.

to a complex mixture from which vinylacetylenes **7** and **8** were the sole isolable products (eq 8). Cumulene **6** is a logical precursor of **7** and **8**.[6]



Of further interest, base treatment of alkynyloxirane **9**, a close analog of **5**, led not to vinylacetylene analogues of **7** and **8**, but to furan **10** in 55% yield (eq 9). In this case the side chain alcohol initiates cyclization via G leading eventually to the furan as detailed in Figure 1. This result suggests that the cyclization B → C is reversible with proton transfer providing the ultimate driving force for these reactions.

(6) Sargsyan, M. S.; Badanyan, Sh. O. *Arm. Khim. Zh.* **1977**, *30*, 1000.



The present findings establish the base promoted isomerization of alkynyloxiranes as a viable new route to furans. The method is noteworthy as most existing furan syntheses employ strong acid.[7] Furthermore, the reaction is amenable to 3-methyl-2,5-disubstituted furans **4**, an important structural component of several marine natural products of current interest.[8] As illustrated by eq 9, monosubstituted furans can also be prepared. We have not yet examined other substitution patterns but plan to do so in due course.

Typical Experimental Procedure for Furan Synthesis: 2-[(Methoxymethoxy)methyl]-3-methyl-5-(2-hydroxyethyl)furan (4a). To a solution of 0.10 g (0.50 mmol) of epoxyalkyne **3a** in 2 mL of *tert*-butyl alcohol was added 0.29 g (1.10 mmol) of 18-crown-6 and 0.12 g (1.10 mmol) of potassium *tert*-butoxide. The yellow solution was allowed to stir at ~60 °C for 20 h, and then it was cooled to room temperature. The reaction mixture was diluted with ether and quenched with water. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (50% EtOAc–hexane) afforded 86 mg (86%) of a 3:1 mixture of furans **4a** and **4e** as a clear faint yellow oil. **4a**: IR (cm^{-1}, film) 3412, 2932, 2889, 1147, 1098, 1033, 924; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (s, 1 H, furan H), 4.64 (s, 2 H, CH_2OMe), 4.45 (s, 2 H, CH_2OMOM), 3.84 (dt, 2 H, J = 6.1, 6.1 Hz, CH_2OH), 3.37 (s, 3 H, OCH_3), 2.82 (t, 2 H, J = 6.1 Hz, CH_2CH_2OH), 2.00 (s, 3 H, CH_3), 1.66 (t, 1 H, J = 6.1 Hz, OH); HRMS calcd for $C_{10}H_{16}O_4$ (M^+) 200.1049, found 200.1048. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06. Found: C, 59.93; H, 8.10.

Acknowledgment. This research was supported by research grants from the National Science Foundation (CHE-8912745) and the NIH (GM-29475) to whom we are grateful.

Supplementary Material Available: Experimental procedures for **1a** → **3a** and ^1H NMR spectra for **3a,b,d,f, 4a,b,d–f, 9,** and **10** (20 pages). Ordering information is given on any current masthead page.

(7) For an exception, see: Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450. For leading references to furan synthesis and furanoid natural products, see: Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.

(8) Cf.: Bandunaga, M. M.; Fenical, W.; Donovan, S. F.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6463. Wright, A. E.; Burres, N. S.; Schulte, G. K. *Tetrahedron Lett.* **1989**, *30*, 3491.