Synthesis of Rosefuran. A New Route to Furans through Base-Catalyzed Cyclization of Hydroxy Alkynoates and Alkynones

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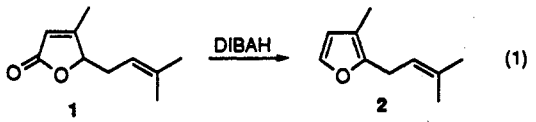
Summary: A new synthesis of furans involving intramolecular 1,4-addition of (*Z*)-6-hydroxy 4-en-2-ynoates and ynones has been developed and applied to a total synthesis of rosefuran.

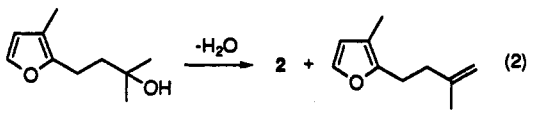
Of all the natural fragrance extracts in use today, perhaps none is more prized than oil of rose. The olfactive properties of this valued commodity stem in large part from trace components of which rosefuran (**2**) is one.[1] This relatively simple natural product has been the target of numerous synthetic efforts.[2-5] Because of its acute acid lability, the classic furan synthesis through acid catalyzed cyclization of a prenylated γ-keto aldehyde would undoubtedly fail.[2] For that reason, synthetic efforts to date have mainly employed furans as starting materials to which the pentenyl chain is appended as a unit or in part.[4] An alternative strategy utilizes the prenylated butenolide **1** as the penultimate intermediate.[5] In several syntheses,



(1)

1 **2**

the tertiary alcohol **3** is employed with dehydration being effected under thermal or very weakly acidic conditions.[3b,4d] However, these approaches afford mixtures of rosefuran and its isopentenyl isomer **4**. We recently found that basic

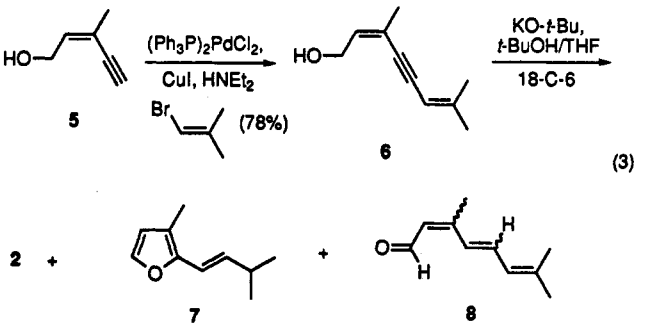


(2)

3 **4**

treatment of γ-alkynyl allylic alcohols leads to furans directly.[6] This novel methodology seemed ideally suited to an acid-sensitive substance such as rosefuran. Accordingly, we initiated studies toward that end.

Our first approach, treatment of the dienynol **6** with KO-*t*-Bu, led to a mixture of rosefuran **2**, the conjugated isomer **7**, and several acyclic aldehyde isomers **8** in varying amounts, depending on reaction conditions and times (eq 3). In no case was rosefuran formed as a major product.

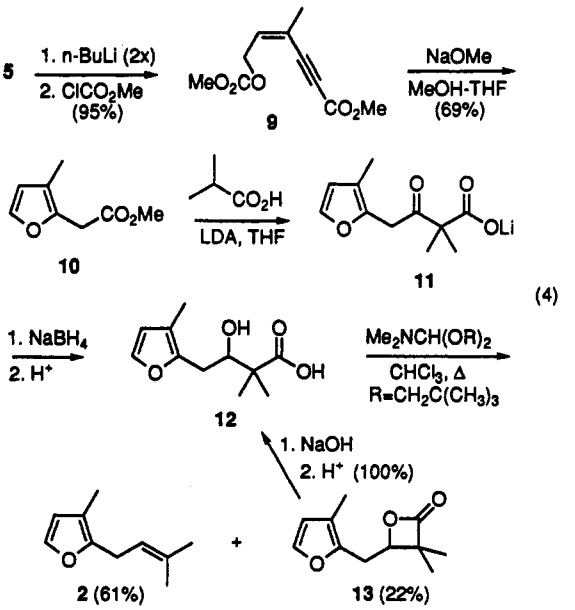


(3)

5 **6** **7** **8**

Aldehydes **8**, which comprised *ca.* 50% of the product mixture, must arise by 1,5 hydrogen transfer. Control experiments established that rosefuran is converted to the conjugated isomer **7** under the reaction conditions.

A more satisfactory synthesis was eventually formulated along the lines shown in eq 4. This route features a novel



(4)

9 **10** **11** **12** **2** (61%) **13** (22%)

furan-forming step in which the alkynoate **9a** is converted to the 2-furylacetate **10a** through intramolecular 1,4-addition of the derived alkoxide.[7] The isopropylidene moiety was introduced by addition of dilithio isobutyrate and direct *in situ* reduction of the adduct **11** with $NaBH_4$ in water. The crude hydroxy acid was treated with DMF dineopentyl acetal in refluxing $CHCl_3$ affording a *ca.* 3:1 mixture of rosefuran **2** and β-lactone **13** in 83% overall

(1) Guenther, E. *The Essential Oils*; D. Van Norstrand Inc.; New York, 1949, Vol. 5, p 1.

(2) Iriye, R; Uno, T.; Ohwa, I.; Konishi, A. *Agric. Biol. Chem.* **1990**, *54*, 1841 describe a nonconventional acyclic approach in which 4-hydroxy citral was treated with 2% PPTS in CH_2Cl_2 affording rosefuran in 32% yield. It was also reported that 4-ketogeranial was quantitatively converted to rosefuran (^1H NMR analysis) upon warming at 55 °C in 0.8% HCO_2H in $CDCl_3$ for 1 week. However, the product was not actually isolated.

(3) (a) Okazaki, R.; Negishi, Y., Inanoto, N. *J. Org. Chem.* **1984**, *49*, 3819. (b) Tsukasa, H. *Agric. Biol. Chem.* **1989**, *53*, 3091.

(4) (a) Buchi, G.; Kovata, E.; Enggist, P.; Uhde, G. *J. Org. Chem.* **1968**, 1227. (b) Vig, O. P.; Vig, A. K.; Hanala, K.; Sharma, S. D. *J. Ind. Chem. Soc.* **1974**, *51*, 900. (c) Berch, A. J.; Stobbe, J. *Tetrahedron Lett.* **1976**, 2079. (d) Meier, L.; Scharf, H. D. *Liebigs. Ann. Chem.* **1986**, 731.

(5) (a) Gedge, D. R.; Pattenden, G. *Tetrahedron Lett.* **1977**, 4443. (b) Takano, S.; Morimoto, M.; Satoh, S.; Ogasawara, K. *Chem. Lett.* **1984**, 1261.

(6) Marshall, J. A.; DuBay, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1450. Marshall, J. A.; DuBay, W. J. *J. Org. Chem.*, in press.

(7) Yields in excess of 85% were generally realized from small scale (<1 g) reactions in which furan ester **10a** was purified by chromatography. The yield noted in eq 4 was taken from a run in which 11 g of **10a** was obtained after distillation.

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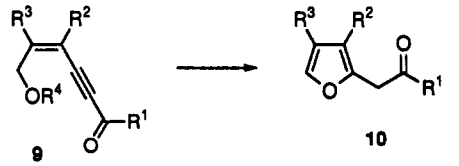
Table I. Cyclization of Alkynyl Carbonyls to Furans



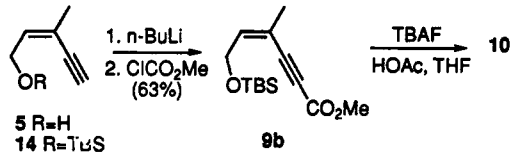
9 10

series	R^1	R^2	R^3	R^4	condns[a]	yield, %	series
9a	OMe	Me	H	CO_2Me	A	69[b]	**10a**
9b	OMe	Me	H	TBS	B	72	**10a**
9c	OMe	H	Me	CO_2Me	A	70[b]	**10b**
9b	n-C_6H_{13}	Me	H	TBS	B	92	**10c**
9e	n-C_6H_{13}	H	Me	TBS	B	89	**10d**

[a] A = NaOMe, MeOH, THF. B = TBAF, HOAc, THF. [b] Yield based on two steps from the corresponding enynol precursor.

yield.[8] The later was quantitatively converted to hydroxy acid **12** which could be recycled to **2** and **13**.

Ester **10a** could also be prepared by treatment of the TBS-protected hydroxy alkynoate **9b** with TBAF (eq 5).

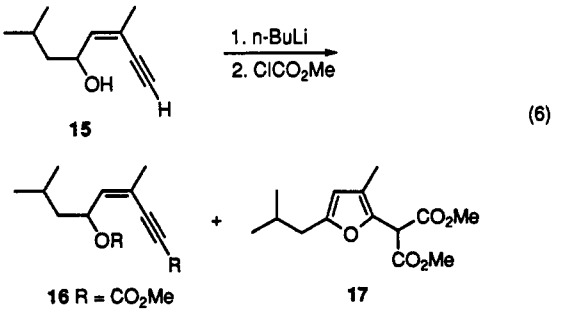


5 R=H
14 R=TBS

9b (5)

The ease of this reaction prompted our investigation of other γ-alkynyl allylic alcohols possessing alkynyl carbonyl substituents. Our findings are summarized in Table I.

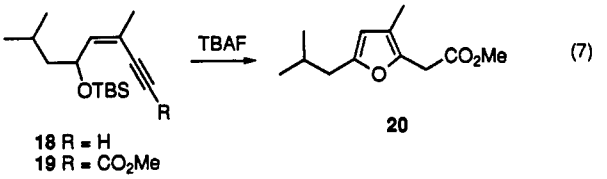
Interestingly, carbomethoxylation of the secondary alkynyl alcohol **15** led to a mixture of the expected diester **16** and the furylmalonate **17**, the product of sequential cyclization and enolate acylation (eq 6). In this case the



15 (6)

16 R = CO_2Me **17**

use of the TBS ether **18** as the carbomethoxylation substrate followed by cleavage with TBAF afforded the desired furan **20** in 77% yield (eq 7).



18 R = H
19 R = CO_2Me **20** (7)

In summary, we have developed a new route to furans through internal alkoxide addition to alkynoates and alkynones that shows excellent potential for the synthesis of heretofore difficultly accessible systems.[9]

Acknowledgment. This work was supported by Research Grant RO1 GM29475 from the National Institute of General Medical Sciences for which we are grateful. Followup studies on the cyclization of dienynol **6** to furans **2** and **7** were conducted by Chad Bennett as part of an undergraduate research project.

Supplementary Material Available: Selected ^1H NMR spectra and experimental procedures for all new compounds (29 pages). This material is contained in 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.

(8) Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, 1545.

(9) For an alternative route to the previously unknown 4-methylfuran-2-acetic acid (**10b**, R^1 = OH) see: Carling, R. W.; Leeson, P. D. *Synlett* **1993**, 40.