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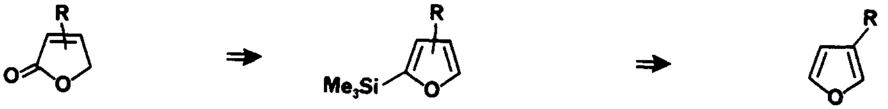
3-ALKYLFURANS AS USEFUL SYNTHETIC EQUIVALENTS FOR SUBSTITUTED Δ^2-BUTENOLIDES

David Goldsmith[*1], Dennis Liotta[*1,2], Manohar Saindane, Liladhar Waykole and Phillip Bowen
Department of Chemistry, Emory University, Atlanta, Georgia 30322

Abstract: Substituted Δ^2-butenolides may be prepared from furan equivalents by regiospecific metallation, sulfenylation and/or silylation, removal of the sulfur group and peracid oxidation.

Unsaturated five-membered lactones commonly occur as structural elements of natural products. Strategies for the preparation of the α-methylene lactones have emerged from many laboratories[3]. Δ^2-Butenolides have received less attention[4]. Recently, however, the discovery of a variety of bio-active butenolide substituted compounds[5] has piqued interest in these lactones, and a number of new methods have been developed and used for their construction[6,7].

In our work on the synthesis of butenolide containing diterpenoids we sought a convenient, accessible, and easily transformable synthon for a Δ^2-butenolide. The most likely candidate appeared to be a furan unit. Our strategy (shown in the retrosynthetic scheme) for the conversion of furans to Δ^2-butenolides 1a and 1b was based on the recent work of Kuwajima and Urabe[8,9]. These authors showed that Δ^3-butenolides are produced by the action of peracetic acid on 5-alkyl-2-trimethylsilylfurans. If this process were applicable to the corresponding 3- and 4-alkyl-2-trimethylsilylfurans 2a and 2b, and if the latter compounds could be readily prepared then a general solution to the problem of constructing the Δ^2-compounds was at hand.

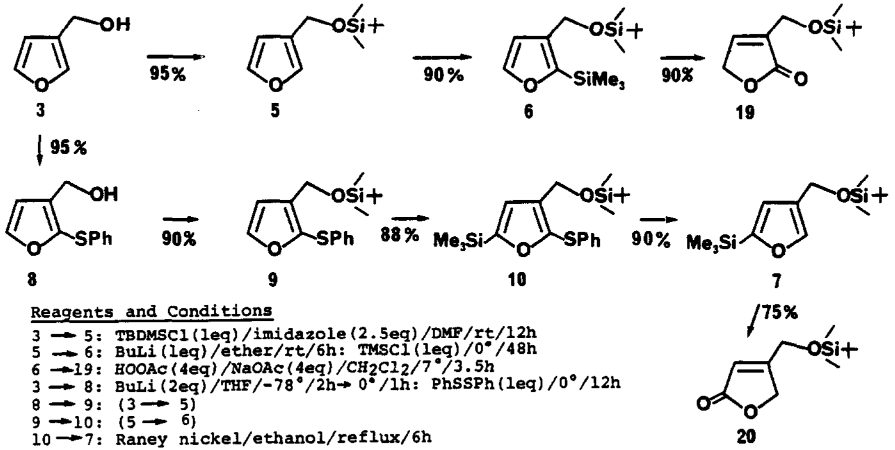


1a, 2R
b, 3R

2a, 3R
b, 4R

The requisite furans, for the projected sequence, alcohols 3 and 4, were prepared by the method of Graf and König[10a] as recently modified by Liotta et al[10b]. As indicated in Scheme I, either furan-3-methanol, 3, or its tert-butyldimethylsilyl ether 5 may be regiospecifically lithiated[11] and substituted at the α-position ortho to the oxyalkyl group. Thus 5 on lithiation and silylation yields 6 in 86% yield. The isomeric α-trimethylsilyl compound 7 was also obtained by application of the protection/deprotection sequence of Cohen and Nolan[12]. Sulfenylation of the dilithio- derivative of 3 yielded 8, and the latter was converted into its silyl derivative 9. A

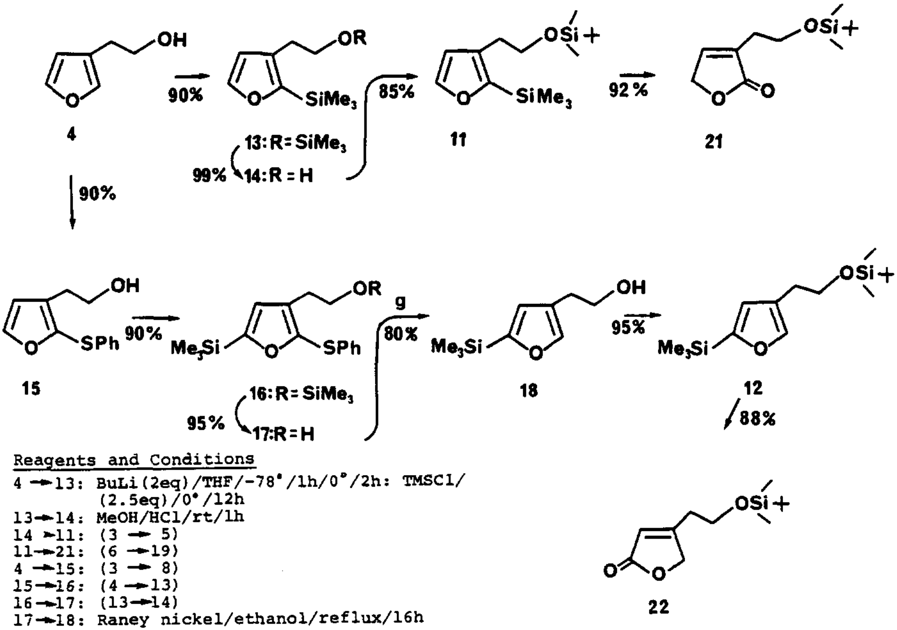
Scheme I



Reagents and Conditions

3 → 5: TBDMSCl(1eq)/imidazole(2.5eq)/DMF/rt/12h
5 → 6: BuLi(1eq)/ether/rt/6h: TMSCl(1eq)/0°/48h
6 → 19: HOOAc(4eq)/NaOAc(4eq)/CH_2Cl_2/7°/3.5h
3 → 8: BuLi(2eq)/THF/-78°/2h→ 0°/1h: PhSSPh(1eq)/0°/12h
8 → 9: (3 → 5)
9 → 10: (5 → 6)
10 → 7: Raney nickel/ethanol/reflux/6h
7 → 20: (6 → 19)

Scheme II



Reagents and Conditions

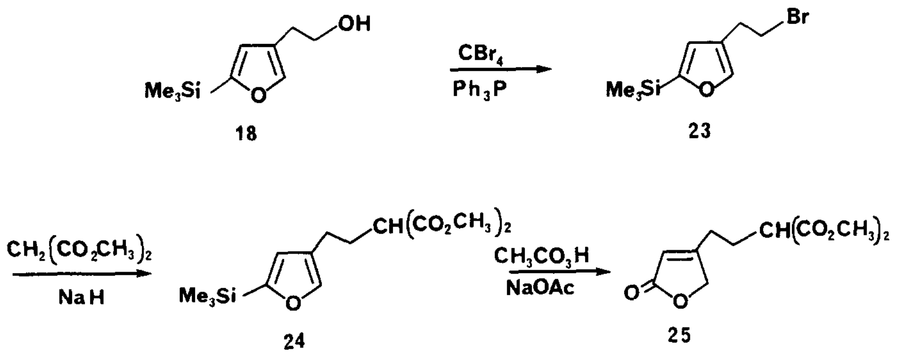
4 → 13: BuLi(2eq)/THF/-78°/1h/0°/2h: TMSCl/
(2.5eq)/0°/12h
13 → 14: MeOH/HCl/rt/1h
14 → 11: (3 → 5)
11 → 21: (6 → 19)
4 → 15: (3 → 8)
15 → 16: (4 → 13)
16 → 17: (13 → 14)
17 → 18: Raney nickel/ethanol/reflux/16h
18 → 12: (3 → 5)
12 → 22: (6 → 19)

second lithiation, C-silylation, and Raney-nickel induced desulfurization afforded 10 and 7 in turn.

The *tert*-butyldimethylsilyl ether of 4 could not be metallated regiospecifically. Treatment of this ether with butyl lithium/trimethylsilyl chloride gave an approximately 1:1 mixture of 11 and 12. These isomers though separable were then prepared individually by the lengthier but specific routes shown in Scheme II. Thus 4 gave silyl furan 13 with butyl lithium/TMSCl, and to parallel the Scheme I series we converted 13 into alcohol 14, thence to silyl ether 11. Application of the sulfenylation route to 4 gave, *via* intermediates 15, 16, 17, and 18, the isomeric 2-trimethylsilylfuran 12.

The preparation of the four silylfurans 6, 7, 11, and 12 are efficient processes. Yields exceeding 85% were obtained for all steps. High yields of the desired butenolides were also obtained when the peracetic acid oxidation procedure[8] was applied to their furan equivalents. Thus treatment of 6, 7, 11, and 12 with peracetic acid at 7° C for 3.5 h gave butenolides 19, 20, 21, and 22, respectively; only 20 being obtained in less than 88% yield.

We have also shown that a functionally substituted furan may be prepared and utilized for carbon-chain extension. Thus, we prepared bromide 23 [13] from 18 (80%) and reacted it with malonic ester to afford furyl diester 24 (70%). Oxidation of 24 gave Δ^2-butenolide 25 (78%)[14].



These results in conjunction with earlier developments in the synthesis of 3-alkylfurans demonstrate that substituted furan rings may serve as useful synthetic equivalents of *both* 2- and 3-alkyl Δ^2-butenolides. The application of these results to the synthesis of representative natural products will be described in forthcoming publications.

References and Notes

(1) This work was supported by grants from the National Institutes of Health.

(2) Fellow of the Alfred P. Sloan Foundation, 1980-84. Recipient of a Camille and Henry Dreyfus Teacher-Scholar Fellowship, 1981-86.

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(14) All yields are of isolated purified products. Infrared, ^{1}H NMR (60, 90, and 200 MHz), precise mass measurement spectral data and combustion analysis results are fully consistent with the assigned structures. Following are ^{1}H NMR and IR values for representative compounds:

6: δ (CDCl$_3$) 7.5(d,1H, J=1Hz), 6.38(d, 1H, J=1Hz), 4.63(s,2H), 0.95(s, 9H), 0.1(s, 15H).

9: δ 7.5(d, 1H, J=3Hz), 7.2(m,5H), 6.55(d, 1H, J=3Hz), 4.68(s,2H), 0.95(s,9H), 0.0 (s,6H).

7: δ 7.52(s,1H), 6.57(s,1H), 4.60(s,2H), 0.95(s,9H), 0.10(s,6H).

19: δ 7.33(m,1H), 4.28(m,2H), 4.45(m,2H), 0.95(s,9H), 0.10(s,6H): υ_{max} 1760 cm^{-1}(CHCl$_3$).

20: δ 5.92(m,1H), 4.88(d,2H,J=1Hz), 4.63(d,2H,J=1Hz), 0.95(s,9H), 0.10(s,6H): υ_{max} 1770 cm^{-1}(CHCl$_3$).

11: δ 7.50(d,1H,J=Hz), 6.25(d,1H,J=1Hz), 3.75(t,2H,J=7Hz), 2.70(t,2H,J=7Hz), 0.90(s,9H), 0.30(s,9H), 0.00(s,6H).

17: δ 7.20(m,5H), 6.68(s,1H), 3.80(t,2H,J=7Hz), 2.74(t,2H,J=7Hz), 2.25(br.s.,1H), δ 0.30 (s,9H).

12: δ 7.50(s,1H), 6.55(s,1H), 3.78(t,2H,J=7Hz), 2.70(t,2H,J=7Hz), 0.90(s,9H), 0.30(s,9H), 0.10(s,6H).

21: δ 7.27(m,1H), 4.80(m,2H), 3.8(t,2H,J=6Hz), 2.4(t,d,2H,J=6Hz,1Hz), 0.95(s,9H), 0.10 (s,6H): υ_{max} 1750 cm^{-1} (CHCl)$_3$.

22: δ 5.90(m,1H), 4.82(m,2H), 3.85(t,d,2H,J=6Hz,1Hz), 2.6(t,2H,J=6Hz), 0.95(s,9H), 0.10 (s,6H): υ_{max} 1750 cm^{-1}(CHCl$_3$).

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