Pergamon

Tetrahedron Letters, Vol. 37, No. 41, pp. 7437-7440, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01605-X

A Novel Route to 2-Fluoromethyl- and 2-Hydroxymethyl-4-Alkyl Furans *via* Allene Oxides

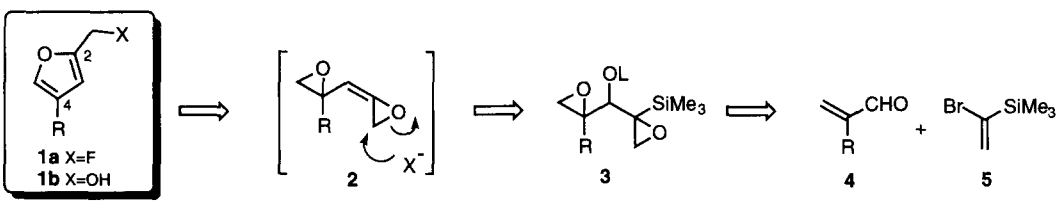
Marek M. Kabat#

Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warszawa, Poland

Abstract: A four-step protocol for the synthesis of 2-fluoromethyl and 2-hydroxymethyl 4-alkyl furans **1a** and **1b** from a-alkyl acroleins **4** and 1-bromo-1-trimethylsilylethylene (**5**) via allene oxides **2** is elaborated, and is applied to the preparation of steroid furans **10**, **11**, **14** and **15** from α,β–unsaturated aldehyde **8**. Copyright © 1996 Published by Elsevier Science Ltd

Substituted furans occur widely in nature, find application in a variety of commercial products, and play an important role in heterocyclic chemistry.[1] Numerous synthetic methods to obtain substituted furans have been developed,[2] however, 2,4-disubstituted furans are difficult to prepare and accessible starting materials are limited. Previously, 2,4-disubstituted furans were synthesized from acyclic precursors,[3] lactones[4] and by substitution of the furan ring.[5]

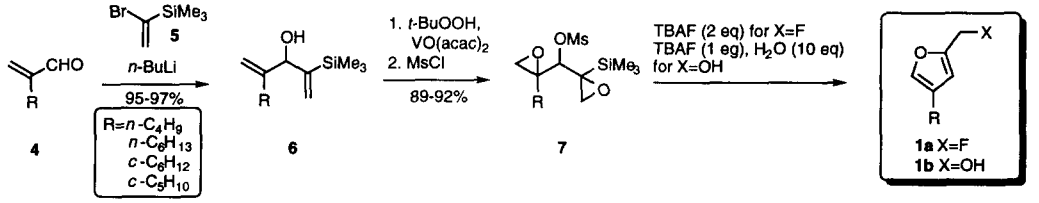
During the course of our investigations of the synthetic utility of allene oxides,[6] we anticipated that 2,4-disubstituted furans **1** with a hydroxymethyl or fluoromethyl substituent at the 2-position and an alkyl group at the 4-position of the aromatic ring should be available by opening of allene oxide **2** with an appropriate nucleophile (Scheme 1). The allene oxide precursors, diepoxysilane **3**, could be synthesized from the reaction of easily accessible α-substituted acroleins **4**[7] with vinylsilane **5** followed by epoxidation of double bond and elimination of the hydroxyl group.



Scheme 1

To verify our hypothesis, several α,β-unsaturated aliphatic aldehydes **4** (R=*n*-butyl, *n*-hexyl, cyclopentyl, cyclohexyl) were chosen for transformation into the corresponding furans. In addition, we wanted to synthesize 2-fluoromethyl and 2-hydroxymethyl furans connected at their 4-position to a steroid at C-17 to learn if these as yet unknown steroid furans with 3β-hydroxy-Δ^5 as well as 4-en-3-one functionalities will show interesting biological activity.

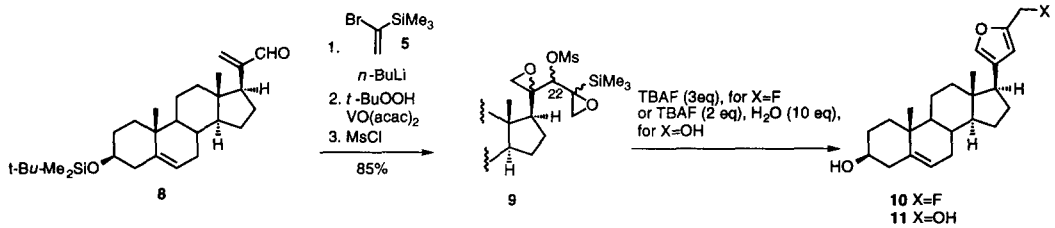
The reaction of 1-bromo-1-trimethylsilylethylene (**5**)/*n*-BuLi with α,β-unsaturated aldehydes **4** produced exclusively the allylic alcohols **6** (Scheme 2). Oxidation of both double bonds with *t*-BuOOH/VO(acac)$_2$[8] followed by reaction with MsCl provided the key diepoxymesylates **7** in 89-92% yields. In accordance with our plan, the structure of compounds **7** contained all necessary functionality for allene oxide formation and for the furan ring closure.



Scheme 2

For the preparation of fluorofurans, compounds **7** were treated with 2.5 eq of TBAF•3H$_2$O in THF (rt, 20 min) to produce the corresponding furan **1a** as the major product in 65-75% yield [^{1}H NMR, δ, 5.21 (2H, d, J_{HF} 49.8 Hz), 6.38 (1H, d, *J* 5.7 Hz), 7.23 (1H, d, *J* 4.2 Hz)] accompanied by the hydroxymethyl compound **1b** in 18-25% yield [^{1}H NMR, δ, 4.56 (2H, s), 6.18 (1H, s), 7.16 (1H, s)]. On the other hand, treatment of **7** with 1 eq of TBAF•3H$_2$O and an additional 10 eq of water afforded exclusively hydroxymethyl furan **1b** (65-80%). It is worth mentioning that the one-pot formation of furan derivatives **1a** and **1b** from acyclic precursors **7** is the result of several consecutive reactions: i) fluoride promoted formation of allene oxide, ii) opening of epoxide ring of allene oxide by fluoride (or water) with formation of an enol, iii) tautomerization into the keto form, iv) rearrangement of the α-methylene-β,γ-epoxy ketone to the α,β-unsaturated-γ-hydroxy ketone, v) attack of the hydroxyl group on the carbonyl group with ring closure to form the hemiacetal, vi) dehydration of the hemiacetal to the desired 2-fluoro- or 2-hydroxymethylfurans.

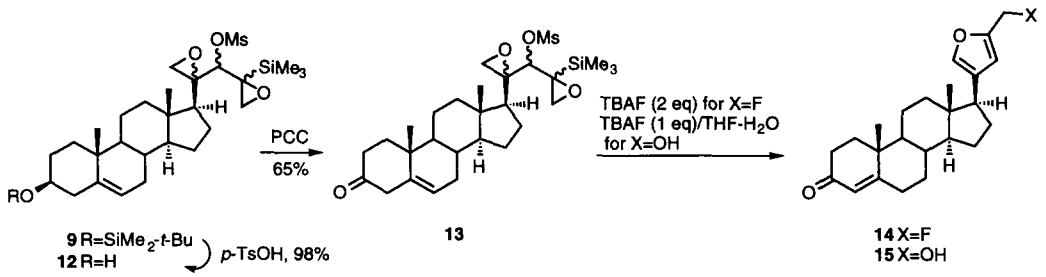
To synthesize steroidal fluoromethyl- and hydroxymethylfurans, the α,β-unsaturated aldehyde **8**[9] (Scheme 3) was treated, in an analogous manner to that described above, with 1-bromo-1-trimethylsilylethylene (**5**)/*n*-BuLi giving the allylic alcohols as a mixture of epimers at C-22.



Scheme 3

Epoxidation with *t*-BuOOH/VO(acac)$_2$ afforded the diastereomeric hydroxyepoxides which were esteryfied with MsCl producing epoxymesylates **9**. Since all newly created chiral centers will disappear in the final product, their diastereomeric ratios were not investigated. For the preparation of the steroid furan with a fluoromethyl substituent, compound **9** was treated with 3.5 eq of TBAF•3H$_2$O in THF (rt, 20 min) to produce, in 90% yield, an 85:15 mixture of fluoromethylfuran **10** and hydroxymethylfuran **11**, respectively. On the other hand, treatment of **9** with 2 eq of TBAF•3H$_2$O and additional 10 eq of water afforded **11** (78%).

To synthesize steroid furans with 4-en-3-one functionality, the silyl protective group in compound **9** was removed and alcohol **12** (Scheme 4) was oxidized with PCC in the presence of 4Å molecular sieves to the deconjugated ketone **13**. Then, treatment of **13** with 2.5 eq of TBAF•3H_2O gave fluoromethylfuran **14** (67%) and hydroxymethylfuran **15** (8%). Under the conditions for furan ring closure the migration of the 5,6-double bond to form the enone system occurred. On the other hand, compound **15** was obtained in good yield (71%) by treatment of **13** in THF solution at rt with 1 eq of TBAF and 10 eq of water.[10,11]



Scheme 4

The described work presents a novel, simple, four-step protocol for the synthesis of 2,4-substituted furans *via* allene oxides starting from easily accessible α-substituted acroleins and 1-bromo-1-trimethylsilylethylene. Because the application of a number of possible nucleophiles for allene oxide opening is described in the literature,[12] one should expect, that other nucleophiles would also react with **2** thus giving a variety of 2,4-disubstituted furans. With regard to the introduction of fluorine in the substituent at C-2 of the furan ring, which occurred relatively rapidly (ca 20-30 min) under very mild conditions and in the last stage of the synthesis, one can foresee the potential value of the present method in Positron Emission Tomography (PET)[13] for labeling molecules with isotope ^{18}F.

Acknowledgment: This work was supported by the Grant CPBP 01.13 of the Polish Academy of Sciences.

References and Notes

Permanent address: Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110, USA.

1. *Comprehensive Heterocyclic Chemistry*; Meth-Cohn, O., Ed.; Pergamon Press: New York, 1984; Vol 1.
2. For general reviews of the chemistry of furans, see: a) Bosshard, P.; Eugster, C. H. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Boulton, A. J., Eds; Academic Press: New York, 1966; Vol 7, pp 377-490. b) Dean, F. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1982; Vol 30, pp 167-238. c) Dean, F. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed; Academic Press: New York, 1982; Vol 31, pp 237-344. d) Dean, F. M.; Sargent, M. V. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press: New York, 1984; Vol. 4, Part 3, pp 531-589. e) Sargent, M. V.; Dean, F. M. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press, 1984; Vol. 4, Part 3, pp 599-659. f) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Bird, C. W.; Cheeseman, G. W. H., Eds.; Pergamon Press: New York, 1984; Vol 4, Part 3, pp 657-712.
3. a) Jung, J. H.; Lee, J. W.; Oh, D. Y. *Tetrahedron Lett.* **1995**, *36*, 923. b) Kang, K.-T.; Sun U, J.; Hwang, S. S.; Jyung, K. K. *Synth. Comm.* **1994**, *24*, 2915. c) Cormier, R. A.; Grosshans, C. A.; Skibbe, S. L. *Synth. Comm.* **1988**, *18*, 677. d) Igarashi, S.; Haruta, Y.; Nishide, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1989**, 737. e) Dean, F. M. *Adv. Hetero. Chem.* **1982**, *31*, 238. f) Dean, F. M. *Adv. Hetero. Chem.* **1982**, *30*, 168. g) Sargent, M. V.; Dean, F. M. Furans and their Benzo Derivatives: Reactivity, Synthesis and Applications. In *Comp. Hetero. Chem.* **1982**, *3*, 599. h) Hegde, S. G.; Wolinsky, J. *J. Org. Chem.* **1982**, *47*, 3148.

4. Grieco, P. A.; Pogonowski, C. S.; Burke, S. *J. Org. Chem.* **1975**, *40*, 542.
5. a) Nieman, J. A.; Keay, B. A. *Tetrahedron Lett.* **1994**, *35*, 5335. b) Lee, G. C. M.; Holmes, J. M.; Harcourt, D. A.; Garst, M. E. *J. Org. Chem.* **1992**, *57*, 3126. c) Bock, I.; Bornowski, H.; Ranft, A.; Theis, H. *Tetrahedron* **1990**, *46*, 1199. d) Obrecht, D.; *Helv. Chim. Acta* **1989**, *72*, 447. e) Chiarello, J.; Joullie, M. M. *Tetrahedron* **1988**, *44*, 41. f) Barnes, B. J.; Newcombe, P. J.; Norris, R. K.; Wilson, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1408. g) Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1984**, *25*, 4451. h) Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835. i) Nolan, S. M.; Cohen, T. *J. Org. Chem.*, **1981**, *46*, 2473. j) Florentin, D.; Roques, B. P.; Fournie-Zaluski, M. C. *Bull. Soc. Chim. Fr.* **1976**, 1999. k) Fournie-Zaluski, M. C.; Chatain-Cathaud, C. *Bull. Soc. Chim. Fr.* **1974**, 1571.
6. a) Kabat, M. M. *J. Org. Chem.* **1995**, *60*, 1823. b) Kabat, M. M. *Tetrahedron Lett.* **1993**, *34*, 8543. c) Kabat, M. M. *Tetrahedron: Asymm.* **1993**, *4*, 1417. d) Kabat, M. M. *J. Fluorine Chem.* **1989**, *43*, 435.
7. Selected methods. a) Parson, J. G.; Rizzacasa, M. A. *Tetrahedron Lett.* **1994**, *35*, 8263. b) Hon, Y.-S.; Chang, F. J.; Lu, L. *J. Chem. Soc., Chem. Comm.* **1994**, 2041. c) Matsuda, I.; Sakakibara, J.; Inoue, H.; Nagashima, H. *Tetrahedron Lett.* **1992**, *39*, 5799. d) Campi, E.; Fitzmaurice, N. J.; Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. *Synthesis* **1987**, 1031. e) Hayashi, M.; Mukayama, T. *Chem. Lett.* **1987**, 1283. f) Ochiai, M.; Fujita, E.; Arimoto, M.; Yamaguchi, H. *Tetrahedron Lett.* **1983**, *24*, 777. g) Tius, M. A.; Astrab, D. P.; Gu, X. *J. Org. Chem.* **1987**, *52*, 2625.
8. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
9. Compound **8** was synthesized from 3β-acetoxy-5-androsten-17-one *via* Knovenagel reaction with ethyl cyanoacetate according to ref. 9a; then, $NaBH_4$ reduction produced the 21-cyano-22-hydroxymethyl derivative which subsequently was acetylated then pyrolyzed to give the α,β-unsaturated nitrile according to ref. 9b. Reduction of this compound with Dibal-H followed by silylation of the 3-hydroxyl group afforded the unsaturated aldehyde **8**. a) Patel, D. K.; Petrow, V.; Royer, R.; Stuart-Webb, I. A. *J. Chem. Soc.* **1952**, 161. b) Kurek, A.; Kabat, M. M.; Gumulka, M.; Wicha, J. *Pol. J. Chem.* **1981**, *55*, 1369.
10. All new compounds provided analytical and spectroscopic data consistent with their structure. Selected analytical data for described steroid furan products:

    Compound **10**: mp 116-118 °C (hexanes-Et_2O), ^1H NMR ($CDCl_3$), δ: 0.53 (3H, s,18-H), 1.02 (3H, s, 19-H), 2.45 (1H, t, *J* 9.3 Hz, 17-H), 3.54 (1H, m, 3-H), 5.22 (2H, d, J_{HF} 49.8 Hz, CH_2F), 5.35 (1H, m, 6-H), 6.41 (1H, d, *J* 5.0 Hz, C=H), 7.24 (1H, d, *J* 5.0 Hz, C=H). ^{19}F NMR ($CDCl_3$), δ: -200.93 (tt, J_1 49.6 Hz, J_2 4.4 Hz). MS: LR(+) LSIMS: 372 (M+, 7), 355 (M-OH, 3), 353 (M-F, 3), 307 (100), 289 (60); HR: for $C_{24}H_{33}O_2F$ (M+) calcd 372.2464, found 372.2456.

    Compound **11**: mp 118-122 °C (acetone). UV λ_{max} (MeOH): 204 (ε 7 220), 218 (6 070), 249 (1 500), 280 (500). IR (KBr): 3300 (OH) cm^{-1}. ^1H NMR ($CHCl_3$), δ: 0.52 (3H, s, 18-H), 1.01 (3H, s, 19-H), 2.43 (1H, t, *J* 9.9 Hz, 17-H), 3.53 (1H, m, 3-H), 4.56 (2H, s, CH_2OH), 5.36 (1H, m, 6-H), 6.20 (1H, s, C=H), 7.16 (1H, s, C=H). MS: LR(+)LSIMS: 371 (M+H, 10), 369 (M-H, 12), 353 (M-OH, 23), 255 (10), 159 (50), 131 (56), 105 (100); MS: HR-EI. For $C_{24}H_{34}O_3$ (M+) calcd 370.2508, found 370.2509.

    Compound **14**: colorless crystals from Et_2O, mp not determined because of decomposition without melting. UV λ_{max} (MeOH): 237 (ε 15 180), 283 (1 100). ^1H NMR ($CDCl_3$), δ: 0.55 (3H, s, 18-H), 1.03 (3H, s, 19-H), 5.22 (2H, d, *J* 49.6 Hz, CH_2F), 5.74 (1H, s, 4-H), 6.40 (1H, d, *J* 6.0 Hz, C=H), 7.24 (1H, d, *J* 4.6 Hz, C=H). ^{19}F NMR ($CDCl_3$), δ: -201.08 (tt, J_1 49.9 HZ, J_2 4.9 Hz). MS: LR(+)LSIMS: 371 (M+H, 25), 219 (16), 154 (100), 136 (82). MS HR-EI. For $C_{24}H_{31}O_2F$ (M+) calcd 370.2308, found 370.2300.

    Compound **15**: mp 178-179 °C (Et_2O). IR ($CHCl_3$): 3609 (OH), 1663 (unsaturated ketone) cm^{-1}. UV λ_{max} (MeOH): 235 (ε 16 300), 283 (760). ^1H NMR ($CDCl_3$), δ: 0.56 (3H, s, 18-H), 1.19 (3H, s, 19-H), 4.58 (2H, s, CH_2-OH), 5.74 (1H, s, 4-H), 6.20 (1H, s, =CH), 7.17 (1H, s, =CH). MS: LR(+)LSIMS: 369 (M+H, 100), 351 (M+H-H_2O, 43), 219 (28), 154 (42), 136 (32). MS HR-EI. For $C_{24}H_{32}O_3$ (M+) calcd 368.2351, found 368.2343.
11. The biological activity of compounds **10**, **11**, **14**, and **15** will be disclosed elsewhere.
12. For review articles on allene oxides see: a) Smajda, W. *Chem. Rev.* **1983**, *83*, 263. b) Chan, T. H.; Ong, B. S. *Tetrahedron* **1980**, *36*, 2289. See also: c) Clemens, I. R.; Shipman, M.; Thorpe H. R. *Synlett* **1995**, 1065. d) Chan, T. H.; Ong, B. S. *J. Org. Chem.* **1978**, *43*, 2294.
13. a) Brennan, M. B. *C&E News* **1996**, *February 19*, 26. b) Satyamurthy, N.; Namavari, M.; Barrio, J. B. *Chemtech* **1994**, *March*, 25. c) Dagani, R. *C&E News* **1981**, *Nov. 9*, 30.

(*Received in UK* 23 *July* 1996; *revised* 12 *August* 1996; *accepted* 15 *August* 1996)