Supplementary Material Available: Experimental procedures and elemental analyses, NMR and mass spectral data for compounds 1–14, and crystallographic data for compounds **14a** and **14b** (24 pages). Ordering information is given on any current masthead page.

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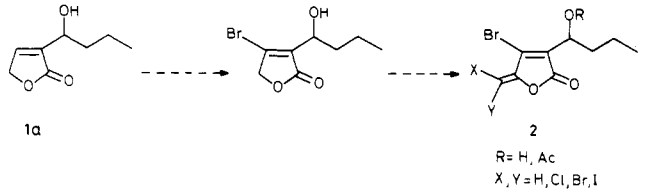
Synthesis of 3-(1-Hydroxyalkyl)furan-2(5*H*)-ones: Unexpected Substitution Reaction in Allylic Alcohols by Bromine

Summary: Substitution of an allylic hydroxyl group in α,β-butenolide derivatives by bromine under typical ionic bromination conditions is reported.

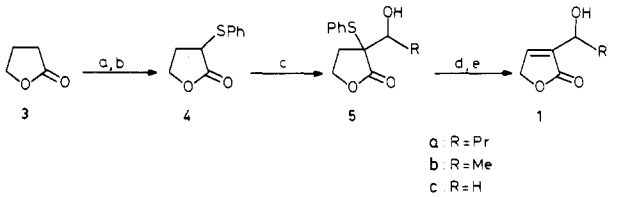
Sir: In relation to our research on structurally simple α,β-butenolides[1] we have prepared 3-(1-hydroxybutyl)-furan-2(5*H*)-one (**1a**) in order to study its bromination–dehydrobromination reactions, since the formed products could be possible intermediates for the synthesis of fimbrolides **2**.[2]



Product **1a** was already described,[3] but when the reported synthetic sequence was repeated, we found **1a** highly contaminated by the isomeric lactone 3-(1-hydroxybutyl)furan-2(3*H*)-one and by the dehydrated product, 3-(1-butenyl)furan-2(5*H*)-one. Therefore, we conceived a new synthesis starting from commerical butyrolactone **3** (Scheme I).

B. M. Trost et al. had synthesized **1b** by another route since they found that the anion generation of **4** followed by quenching with aldehydes led to equivocal results.[4] On the other hand, Hoye and co-workers[5] described better results for these condensations when performed in the presence of $ZnCl_2$. We allowed the reaction of the anion of 3-(phenylthio)-4,5-dihydrofuran-2(3*H*)-one[6] (**4**) with butyraldehyde to proceed in the absence of Lewis catalysts. Thus, **5a** was isolated as a 1:1 diastereoisomeric mixture in 84% yield;[7] both isomers were separated by column chromatography (mp 66–68 and 81–82 °C). Oxidation of

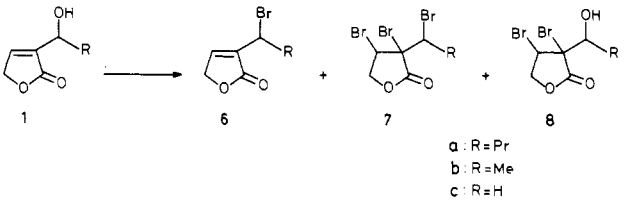
Scheme I



(a) Br_2; (b) PhSNa, THF; (c) LDA, RCHO; (d) *m*-CPBA or $NaIO_4$; (e) pyrolysis.

crude **5a** with *m*-chloroperbenzoic acid in methylene chloride at 0 °C for 1 h or with sodium periodate in methanol/water (1:1) at room temperature for 17 h, followed by pyrolysis of the corresponding sulfoxides, afforded **1a** in 65–80% yield.

When **1a** was submitted to the conventional ionic bromination conditions (1 equiv of puriss. bromine, purchased from Fluka AG, in CCl_4), to our surprise, we isolated the new 3-(1-bromobutyl)furan-2(5*H*)-one (**6a**), which results from the substitution of the hydroxyl group by the bromine atom leaving the double bond unmodified. Changing the conditions of the reaction (solvent, time; entries 1–4 of Table I) never did give rise to an addition reaction on **1a**.



The structural assignment of **6a** was unambiguous since the IR spectrum presented no absorption in the 3600–3050 cm^{-1} (OH region), the ^1H NMR spectrum showed a broad singlet at δ 7.47 (vinylic proton), and the chemical ionization (NH_3) mass spectrum indicated molecular ions at *m/e* 238, 236 $(C_8H_{11}BrO_2 + 18)^+$.

Note from Table I that starting material **1a** was always recovered in fair yields and that when the reaction time was highly prolonged the tribromo derivative **7a** (correct mass spectrum) was isolated in 14% yield, indicating its formation from **6a**. This was confirmed by independent bromination of **6a** (entries 7 and 8).

Due to this unexpected reaction behavior we decided to study in more detail this bromination process. The only described substitution reactions of the OH group for bromine are, to the best of our knowledge, the cases of 3-phenyl-2-propen-1-ol and 1-phenyl-2-propen-1-ol, in which the tribromo derivatives were obtained in poor yields.[8,9] No explanation for these results was given. Moreover, the mechanism of molecular bromine addition to olefines[10] and the halogenation of α,β-unsaturated acyclic esters[11] have received much attention during recent years. In addition, the bromination of the **6a** analogous compound, 3-butylfuran-2(5*H*)-one, takes place under standard reaction conditions yielding the normal addition product.[12]

In order to study the influence of the alkyl chain we synthesized **1b**[4] and **1c** (IR ($CHCl_3$) 3650–3300 cm^{-1}; ^1H

(1) Bigorra, J.; Font, J.; Jaime, C.; Ortuño, R. M.; Sánchez-Ferrando, F. *Tetrahedron* **1985**, *41*, 5577 and references cited therein.
(2) (a) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Tetrahedron Lett.* **1977**, 37. (b) Pettus, J. A., Jr.; Wing, R. M.; Sims, J. J. *Tetrahedron Lett.* **1977**, 41.
(3) Watanabe, M.; Shirai, K.; Kumamoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3318.
(4) Trost, B. M.; Mao, M. K. T. *Tetrahedron Lett.* **1980**, *21*, 3523.
(5) Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1980**, *45*, 3549.
(6) Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242.
(7) All new compounds gave satisfactory elemental analysis, except the di- and tribromo derivatives.
(8) Klages, A.; Klenk, K. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 2552.
(9) Arcus, C. L.; Strauss, H. E. *J. Chem. Soc.* **1952**, 2669.
(10) Bellucci, G.; Chiappe, C.; Marioni, F. *J. Am. Chem. Soc.* **1987**, *109*, 515 and references cited therein.
(11) Pitkanen, M.; Korhonen, I. O. O. *Tetrahedron* **1985**, *41*, 4707 and previous papers in the series.
(12) (a) Gryff-Keller, A.; Kolodziejck, W.; Prejzner, J. *Org. Magn. Reson.* **1983**, *21*, 157. (b) Prejzner, J. *J. Pol. Chem.* **1979**, *53*, 785; *Chem. Abstr.* **1979**, *91*, 175096s.

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Table I. Bromination Reactions of 3-Alkylfuran-2(5*H*)-one Derivatives

entry	compd	solv	time, h	starting matrl (%)[a]	6 (%)[a]	7 (%)[a]	bromine addtn (%)[a]
1	**1a**	CCl_4	19	**1a** (21)	**6a** (52)		
2	**1a**	CCl_4	48	**1a** (7)	**6a** (50)	**7a** (14)	
3	**1a**	CH_2Cl_2	80	**1a** (trace)	**6a** (44)		
4	**1a**	benzene	19	**1a** (30)	**6a** (46)		
5	**1b**	CH_2Cl_2	19		**6b** (42)		
6	**1c**	CH_2Cl_2	19	**1c** (2)	**6c** (12)	**7c** (24)	**8c** (38)
7	**6a**	CCl_4	80	**6a** (18)		**7a** (53)	
8	**6a**	CH_2Cl_2	80	**6a** (20)		**7a** (12)	
9	**9**	CCl_4	120	**9** (10)	**6a** (25)	**7a** (19)	**11** (25)
10	**10**	CCl_4	74	**10** (6)	**6a** (30)		**12** (20)

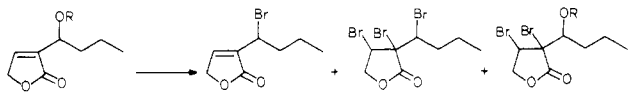
[a] Isolated yields.

NMR ($CDCl_3$) δ 2.78 (br s, OH), 4.47 (br s, 2 H), 4.87 (br s, 2 H), 7.42 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 56.2, 70.7, 133.1, 146.6, 173.3) using the sequence indicated in Scheme I. Compound **1c** was the only (hydroxymethyl)butenolide not yet synthesized, since the 5-hydroxymethyl isomer was already known,[13] and the 4-hydroxymethyl isomer has been described very recently.[14]

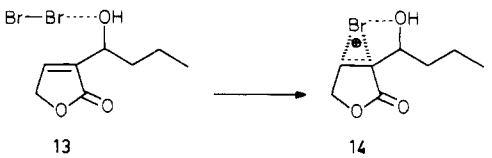
When **1b** was brominated in CH_2Cl_2 (entry 5) the only isolated product was again the bromine-substituted derivative **6b**. The structural assignment of **6b** was based on the same features as exposed for **6a**. However, the bromination of **1c** gave a mixture of compounds from which **1c**, **6c**,[15] **7c**,[16] and **8c** (entry 6) could be isolated and identified. Compound **8c** presented IR absorption at 3600–3100 cm^{-1}, and the mass spectrum (CI, NH_3) presented molecular ions at m/e 294, 292, and 290 corresponding to the formula $C_5H_6Br_2O_3$.

The results that **1a** and **1b** undergo substitution, while **1c** partially undergoes bromine addition and substitution, point to the fact that bromine addition to the double bond of 3-(1-hydroxyalkyl)furan-2(5*H*)-ones suffers at least from steric hindrance.

Two new alcohol protected derivatives from **1a** were also synthesized, the acetate **9** (80% yield) and the methyl ether[17] **10** (50% yield), and we submitted them to bromination (entries 9 and 10). In all cases the compounds derived from O-substitution (**6a** + **7a**) were again the main isolated products, but the normal addition compound was formed now to some extent.



The rate of electrophilic attack of bromine to a double bond decreases with the presence of an electron-withdrawing substituent at the allylic position,[18] and our molecules have three of these substituents. For this reason the reaction progress should be very slow, as is indeed experimentally observed, and the nonpolar reagent Br_2 should attack the double bond only after having been polarized. Following Bellucci's studies[19] we postulate also the formation of a complex between bromine and the hydroxyl group, **13**, and the intramolecular transfer of Br_2 to the carbon–carbon double bond with the final formation of the intermediate **14**. Such bromine–oxygen interaction has been as well proposed to account for halolactonizations of γ,δ-unsaturated β-hydroxy acids.[20] The nucleophilic step in the mechanism will be influenced now by several effects: (i) the hydroxyl group will direct the attack by the nucleophile at the β-position of the carbonyl group;[19] (ii) the lactone oxygen will favor reaction at the α-position;[19] and (iii) on the other hand, the effect of the carbonyl group is not clear as shown by the work of Heasley[21] on α,β-bromonium ester ions and by Johnson et al.,[22] Chong and Sharpless,[23] and our own work[24] on α,β-epoxy carboxylic compounds, although a predominance of attack at the α-position is observed. As a consequence, we think that the nucleophilic opening of the bromonium ion **14** by the bromide is strongly decelerated, and if it is produced it should occur at the α-position. This reaction inhibition



seems to be more important when bulky alkyl chains are present at the α-position (**1a** and **1b**). Then, in these cases the reaction proceeds, although slowly, through the substitution of the hydroxyl group by the bromide anion. The results obtained for compounds **9** and **10** are interpretable on the basis of the oxygen–bromine interaction intensity and the leaving group ability of the OR substituent.

In order to elucidate in more detail the factors governing this unexpected bromination reaction some experiments (addition of bromine to acyclic analogous derivatives and addition of bromine chloride to **1**) are in progress in our laboratory.

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Registry No. **1a**, 72876-43-8; **1b**, 76643-90-8; **1c**, 109765-92-6; **3**, 96-48-0; **4**, 35998-30-2; **5a** (isomer 1), 109765-89-1; **5a** (isomer

(13) (a) Font, J. *An. Quim., Ser. B* **1966**, *62*, 477. (b) Camps, P.; Font, J.; Ponsati, O. *Tetrahedron Lett.* **1981**, *22*, 1471.
(14) Gadir, S. A.; Smith, Y.; Taha, A. A.; Thaller, V. *J. Chem. Res., Synop.* **1986**, 222.
(15) Chapleo, C. B.; Svanholt, K. L.; Martin, R.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 100.
(16) The IR spectrum of **7c** (as a diatereoisomeric mixture) presented no absorption in the hydroxylic region, its ^1H NMR spectrum lacked an absorption in the olefinic region and the mass spectrum (CI, NH_3) showed molecular ions at m/e 358, 356, 354, and 352 [$(M + 18)^+$].
(17) Hough, L.; Jones, J. K. N.; Mitchell, D. L. *Can. J. Chem.* **1958**, *36*, 1720.
(18) Dubois, J. E.; Goetz, E. *Tetrahedron Lett.* **1963**, 303.
(19) (a) Barili, P. L.; Bellucci, G.; Berti, G.; Golfarini, M.; Marioni, F.; Scartoni, V. *Gazz. Chim. Ital.* **1974**, *104*, 107. (b) Bellucci, G.; Berti, G.; Bianchini, R.; Ingrosso, G.; Mastrorilli, E. *Gazz. Chim. Ital.* **1976**, *106*, 955.
(20) Snider, B. B.; Johnston, M. I. *Tetrahedron Lett.* **1985**, *26*, 5497.
(21) Heasley, V. L.; Spaite, D. W.; Shellhamer, D. F. *J. Org. Chem.* **1979**, *44*, 2608.
(22) Herr, R. W.; Wieland, D. M.; Johnson, C. R. *J. Am. Chem. Soc.* **1970**, *92*, 3813.
(23) Chong, J. M.; Sharpless, K. B. *Tetrahedron Lett.* **1985**, *39*, 4683.
(24) Ortuño, M. R.; Cardellach, J.; Font, J. *J. Heterocycl. Chem.* **1987**, *24*, 79.

2), 109765-90-4; **5b**, 82111-61-3; **5c**, 109765-91-5; **6a**, 109765-93-7; **6b**, 109765-95-9; **6c**, 58588-90-2; **7a**, 109765-94-8; **7c**, 109765-96-0; **8c**, 109765-97-1; **9**, 109765-98-2; **10**, 109765-99-3; **11**, 109766-00-9; **12**, 109766-01-0; PrCHO, 123-72-8; MeCHO, 75-07-0; CH_2O, 50-00-0.

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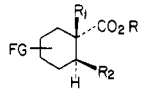
Stereoselective Construction of Functionalized *cis*-1,2-Dialkylcyclohexanecarboxylates: A Novel Synthesis of (±)-Geijerone and γ-Elemene

Summary: General applicability of our intramolecular ester enolate alkylation method to the stereoselective construction of functionalized *cis*-1,2-dialkylcyclohexanecarboxylates is illustrated in the context of a novel synthesis of (±)-geijerone and a formal synthesis of γ-elemene.

Sir: Functionalized *cis*-1,2-dialkylcyclohexanecarboxylates **1** are very important and frequently encountered structural features in the synthesis of natural products.[1] We recently reported a novel approach based upon intramolecular ester enolate alkylation in an unfunctionalized model system.[2]



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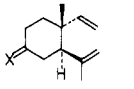
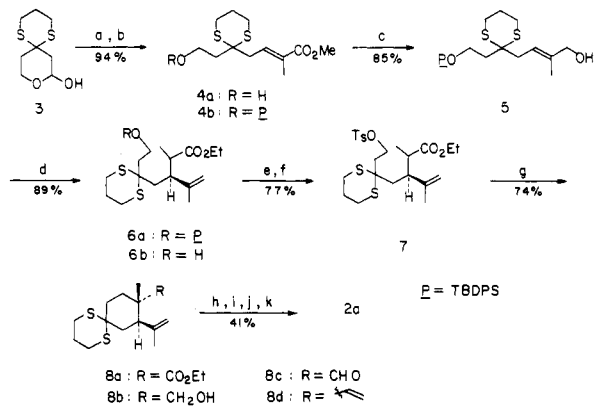


2a: X = O
2b: X =

In this communication we describe a novel synthesis of (±)-geijerone[3] (**2a**) and a formal synthesis of γ-elemene[4] (**2b**), a member of elemanoid sesquiterpenes, in order to demonstrate that our intramolecular alkylation strategy should be applicable to the synthesis of a variety of functionalized *cis*-1,2-dialkylcyclohexanecarboxylates as summarized in Scheme I.

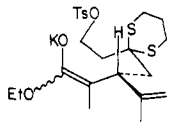
Condensation of lactol[5] **3** with methyl (triphenylphosphoranylidene)propionate followed by protection of the hydroxyl group with *tert*-butylchlorodiphenylsilane[6] afforded ester **4b** in 94% yield. Reduction of unsaturated ester **4b** with LAH in THF gave the corresponding allylic alcohol **5**, which was subjected to Johnson's ortho ester Claisen rearrangement[7] to produce ester **6a** as a 1:1 mixture of stereoisomers in 78% yield for two steps. Deprotection of the silyl group with fluoride and tosylation yielded key intramolecular alkylation substrate **7** in 77% overall yield.

Scheme I[a]

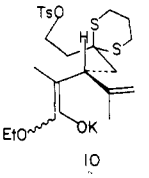


[a] (a) $Ph_3{=}C(CH_3)CO_2Me$, CH_2Cl_2, reflux, 4 h; (b) TBDPS-Cl, imidazole, DMF, room temperature, 13 h; (c) LAH, THF, 0 °C, 2 h; (d) $CH_3CH_2C(OEt)_3$, phenol, 165 °C, 15 h; (e) $(n\text{-Bu})_4NF$, THF, room temperature, 2 h; (f) TsCl, DMAP, CH_2Cl_2, 0 °C, 3 h; (g) KHMDS, THF, −78 to 0 °C, 3 h; (h) DIBAL, toluene, −20 °C, 15 min; (i) DCC, pyridinium trifluoroacetate, DMSO–PhH (1:3), room temperature, 2 h; (j) Ph_3PCH_3I, *n*-BuLi, Et_2O, reflux, 1 h; (k) excess CH_3I, CH_3CN–H_2O (9:1), room temperature, 24 h.

Treatment of ester **7** with KHMDS[8] in THF at −78 °C followed by warming to 0 °C for 3 h produced the desired cyclohexanecarboxylate **8a** with greater than 96% stereoselectivity[9] in 74% yield, probably through eclipsed transition state **9** rather than bisected **10**.[10]



9



10

Reduction with DIBAL, Moffatt oxidation, Wittig reaction, and hydrolysis of thioketal group proceeded uneventfully to give (±)-geijerone with spectral data fully consistent with those reported.[11] Since (±)-geijerone was converted to γ-elemene by Yoshikoshi, the present synthesis also constitutes a formal synthesis of the sesquiterpene.[4]

In summary synthesis of (±)-geijerone was achieved in a stereoselective manner in 11 steps and 16.6% overall yield from lactol **3**, suggesting a broad potential of our intramolecular ester enolate alkylation method. Work is in progress to apply this methodology to more elaborate systems.

(1) For an extremely elegant use of intramolecular alkylation to six-membered rings, see: Stork, G. *Heterocycles Special Issue* **1987**, *25*.
(2) Ahn, S. H.; Kim, D.; Chun, M. W.; Chung, W. *Tetrahedron Lett.* **1986**, *27*, 943.
(3) Isolation and structure of geijerone: (a) Thomas, A. F. *Helv. Chim. Acta* **1972**, *55*, 815. (b) Thomas, A. F. *Ibid.* **1972**, *55*, 2429. Synthesis of (±)-geijerone: Kato, M.; Kurihara, H.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2470.
(4) Isolation and structure of γ-elemene: (a) Gough, J. H.; Sutherland, M. D. *Aust. J. Chem.* **1964**, *17*, 1270. (b) Bernardi, R.; Cardani, C.; Ghiringhelli, D.; Selva, A. *Chim. Ind. (Milan)* **1970**, *52*, 581. (c) Ganter, C.; Keller-Wojtkiewicz, F. B. *Helv. Chim. Acta* **1971**, *54*, 183. Synthesis of γ-elemene: ref 3b.
(5) Lactol **3** was prepared by a conventional four-step sequence from diethyl acetone-1,3-dicarboxylate (1,3-propanedithiol, $BF_3{\cdot}Et_2O$; 1.1 equiv of KOH, EtOH; $ClCO_2CH_3$, TEA, $NaBH_4$; DIBAL, toluene).
(6) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(7) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(8) The more highly aggregated and less reactive lithium enolate, generated by LDA, gave much less satisfactory yield (18%) of the cyclized product under similar condition with a slightly better stereoselectivity (97:3).
(9) Capillary GC analysis (0.2 mm i.d. × 50 m long CBP-1 column, 260 °C) revealed the presence of less than 4% of a minor isomer.
(10) Compound **8a**: IR (film) ν 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 1.12 (s, 3 H), 1.23 (t, J = 7 Hz, 3 H), 1.63 (s, 3 H), 1.45–3.14 (m, 13 H), 4.09 (q, J = 7 Hz, 2 H), 4.68 (br s, 1 H), 4.83 (m, 1 H); ^{13}C NMR ($CDCl_3$, 20.15 MHz) δ 14.24, 15.17, 23.20, 26.02, 26.14, 26.44, 30.03, 33.18, 38.29, 43.86, 46.59, 49.98, 60.55, 113.47, 145.66, 177.51; HRMS calcd for $C_{16}H_{26}O_2S_2$ 314.1374, found 314.1375.
(11) We thank Professor Yoshikoshi (Tohoku University) for kindly providing us with reference spectra of racemic geijerone.

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