(dd, J = 17.5, 6 Hz, H-6β and H-8β), 2.56 (apparent br. sext, J = 6.5 Hz, H-5a and H-8a), 2.71 (ddd, J = 11.0, 6.5, 6.5 Hz, H-2α and H-4α), 3.11 (ddd, J = 11.0, 6.0, 5.5 Hz, H-2β and H-4β), 3.75 (t, J = 6.8, H-8b); ^{13}C NMR, Table II; MS (m/z, relative intensity) 166 (M^+ + 1, 10), 165 (M^+, 61), 164 (41), 106 (28), 96 (100), 82 (84). Anal. Calcd for $C_{10}H_{15}NO \cdot {}^1/_2H_2O$: C, 68.92; H, 9.18; N, 8.04. Found: C, 68.86; H, 9.23; N, 8.02.

Acknowledgment. This work was supported by the DGICYT (project PB88-0316), Spain. We thank Mr. Joaquim Nolla and Mrs. Asunción Marín for experimental contributions.

Erythro Selective Additions of Tetra-*n*-butylammonium Enolates of 2-Oxetanones to Aldehydes: Application to Tetrahydrofuran Synthesis

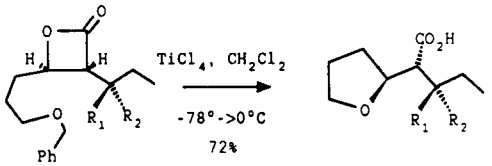
Keith T. Mead* and Minnie Park

Department of Chemistry, Mississippi State University, Mississippi State, Mississippi 39762

Received October 25, 1991

We have shown that 2-oxetanones bearing a 3-(benzyloxy)propyl substituent at the 4-position rearrange upon Lewis acid treatment to give α-substituted tetrahydrofuranacetic acids.[1,2] These intramolecular β cleavage reactions have been shown to proceed with complete inversion of stereochemistry,[1] giving highest product yields with titanium tetrachloride mediation.

With the intention of broadening the scope of this finding, we wanted to know if these ring-opening reactions could be applied to structures such as 1 (see Scheme I) in which a secondary alcohol group is β to the carbonyl moiety. We envisioned a two-step sequence from the enolate 3 of aldol reaction followed by intramolecular lactone ring opening as a means of targeting the derivatives 2. With appropriate choice of aldehyde, application of this strategy to the construction of tetrahydrofuran rings bearing multiple side-chain asymmetry, a feature common to a number of biologically active natural products,[3] might be possible.



1a R_1=OH, R_2=H
1b R_1=H, R_2=OH

2a R_1=OH, R_2=H
2b R_1=H, R_2=OH

Given the stereospecific nature of the intramolecular ring-opening step, it follows that all three stereocenters in the tetrahydrofurans 2 would ultimately be decided by the stereochemistry of the aldol addition, which in turn should be controlled by the enolate counterion.[4] Earlier work[1] had shown that enolate 3 could be generated as a stable tetraalkylammonium salt by fluoride treatment of the α-silyl species 4.[5] Aldol additions of tetraalkylammonium enolates, typically generated from silyl enol ethers,[6] have been documented.[7] However, studies to date have largely been limited to the use of acyclic analogues and ring systems larger than four.[8] Our first priority, therefore, was to demonstrate the feasibility of the proposed aldol reaction.

Scheme I

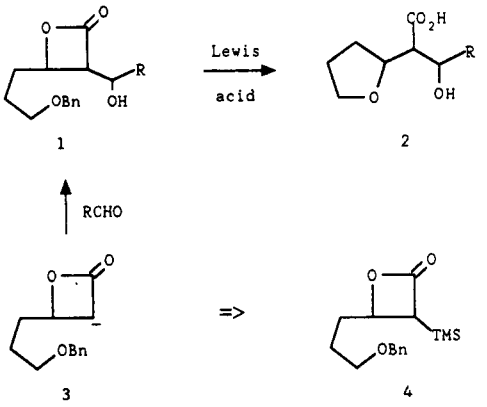


Table I. Results of Fluoride-Initiated Aldol Reactions of Lactones 4-6

entry	lactone	R^2	A/B[a]	no.	yield[b] (%)
1	5	Ph	88:12	7/8	79
2	6	Ph	85:15	9/10	81
3	5	Et	63:37	11/12	88[c]
4	5	^{i}Pr	96:4	13/14	85
5	5	^{i}Pr	62:38[d]	13/14	57
6	5	furyl	77:23	15/16	71
7	4	Et	55:45	1a/1b	72

[a] The ratio of erythro to threo isomer for each reaction was determined by ^{1}H NMR integration of the β-H signals of the crude product mixture. [b] Values refer to combined isolated yields of both stereoisomers. [c] Estimated yield. See Experimental Section. [d] Reaction carried out by rapid addition of 5 to the aldehyde/Bu_4NF mixture.

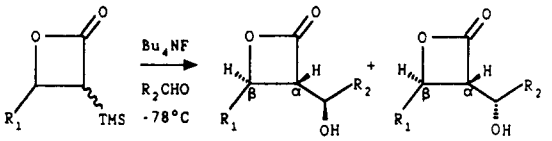
Results and Discussion

For this study, the structurally simpler silyl lactones 5 and 6 were prepared,[9] in addition to the required lactone 4,[10] and reacted with a series of aldehydes in the presence of Bu_4NF (see Table I). Although initial attempts proved disappointing, optimum yields were eventually obtained by slow addition of the silyl lactone to a mixture of aldehyde and stoichiometric fluoride in THF at −78 °C. Under these conditions, proton exchange between the generated enolate and its silyl precursor, which had plagued us in an earlier study,[1] could be avoided. Rapid addition of the lactone resulted in the formation of complex byproducts as well as decreased stereoselectivity (see entry 5).

(1) Mead, K. T.; Yang, H.-L. *Tetrahedron Lett.* **1989**, *30*, 6829.
(2) Mead, K. T.; Yang, H.-L. *J. Org. Chem.* **1990**, *55*, 2991.
(3) For examples, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Kondo, S.; Yasui, K.; Katayama, M.; Marumo, S.; Kondo, T.; Hattori, K. *Tetrahedron Lett.* **1987**, *28*, 5861.
(4) For recent review articles on this topic, see: (a) Yamago, S.; Machii, D.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2098. (b) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177.
(5) For a related use of this strategy, see: Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372.
(6) For exceptions to this generalization, see ref 5 and: Kuwajima, I.; Inoue, T.; Sato, T. *Tetrahedron Lett.* **1978**, 4887.
(7) (a) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (b) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265. (c) Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932.
(8) For the one exception to this, see ref 7c.
(9) For the preparation of 5 and 6, see: Brady, W. T.; Saidi, K. *J. Org. Chem.* **1979**, *44*, 733.
(10) For the preparation of this lactone, see: Mead, K. T.; Samuel, B. *Tetrahedron Lett.* **1988**, *29*, 6573.

0022-3263/92/1957-2511$03.00/0

In all cases, reaction gave a mixture of two products, both of which were identified from proton NMR as the expected trans isomers by the coupling constant (4 Hz) between the two remaining ring hydrogens (H-α and H-β). The two products were thus assigned trans-erythro (A) and trans-threo (B), with the erythro stereoisomer initially

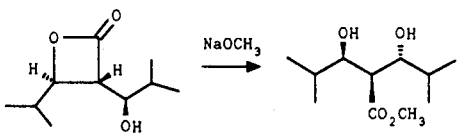


4 R_1=$(CH_2)_3OBn$
5 R_1=i-Pr
6 R_1=Et

being assigned as the predominant product based on prior reports of related aldol reactions.[7] As expected, the degree of stereoselectivity in these reactions was found to be heavily dependent on the nature of both R_1 and R_2, being highest when both of these substituents were branched chained and thus exhibited significant steric bulk (compare entries 4 and 7).

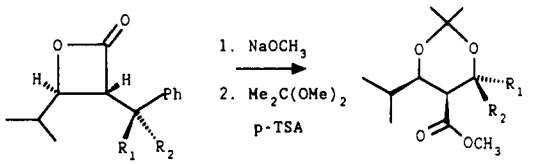
The ^1H NMR signals for the β-hydrogens of the individual aldol products were well separated, with the signals for the erythro diastereomers appearing downfield relative to those of the corresponding threo derivatives. The integration of these expanded signals provided a convenient method for measuring diastereomeric product ratios (see supplementary material).

To confirm the erythro stereochemistry of the major product, use was made of the fact that lactone ring cleavage would yield an *anti*-1,3-diol. Owing to symmetry elements, this was most easily applied to the aldol derivative **13** which was treated with sodium methoxide.[11] Proton NMR of the product showed one methyl ester singlet and four methyl doublets, indicative of a single compound possessing nonequivalent isopropyl groups, consistent with structure **17**.



13 17

We were further able to show that this selectivity is general to both aliphatic and aromatic aldehydes[12] by converting the mixture of lactones **7** and **8** to the aceto-

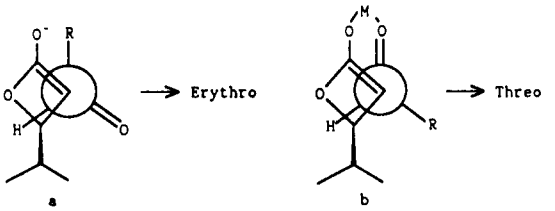


7 R_1=OH, R_2=H
8 R_1=H, R_2=OH

18 R_1=Ph, R_2=H
19 R_1=H, R_2=Ph

nides **18** and **19**. The twist-chair nature of the major product **18**, the preferred conformer for an acetonide of an *anti*-1,3-diol,[13] was confirmed by ^{13}C NMR which showed two signals at approximately 24 ppm for each of the acetonide methyl groups.[14]

The propensity for tetraalkylammonium enolates to add to aldehydes with erythro selectivity has been well documented[7] and can be ascribed to an open extended TS geometry.[4,7a] For reactions involving the enolate derived from lactone **5**, this may be depicted by projection a. By contrast, the presence of a chelating metal would be expected to reverse this selectivity by favoring TS b, as



evidenced by Mulzer's findings with lithium enolates.[15] Unfortunately, the formation of such enolates by low-temperature deprotonation appears to be restricted to α-substituted 2-oxetanones.[16] Ion exchange appeared to us to offer an alternative route to these intermediates. However, fluoride reactions of lactones **4–6** conducted in the presence of metal salts ($LiClO_4$, LiBr, $ZnBr_2$) resulted in the recovery of starting material each time. Presumably, additions of these salts to the Bu_4NF/aldehyde mixture at −78 °C precipitated the corresponding metal fluoride, thereby rendering it inactive.

Despite this setback, we were pleased to find that the proposed rearrangement proceeded without incident. Cyclization of each of the separated stereoisomers **1a** and **1b** to the tetrahydrofurans **2a** and **2b**, respectively, took place cleanly on exposure to $TiCl_4$. A convenient alternative was to react a 55:45 mixture of **1a** and **1b** (see Table I, entry 7) with this Lewis acid and then separate the products **2a** and **2b**, formed in an identical ratio, by column chromatography.

Our strategy for preparing 2-substituted tetrahydrofurans bearing both α- and β-side-chain asymmetry has been realized. The ability to prepare a variety of metal enolates of 2-oxetanones would, by influencing the course of the aldol addition, significantly extend the scope of this approach. Aldolate equilibration[17] is one method we will explore in our ongoing efforts to achieve this.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR were recorded at 300 and 75.5 MHz, respectively, on a QE-300 instrument. Tetramethylsilane was used as the internal standard, and, unless otherwise stated, $CDCl_3$ was used as the solvent. IR spectra were recorded on a Midac-FT spectrometer. The Bu_4NF used for reactions was purchased as a 1 M solution in THF from Aldrich Chemical Co. and dried for 12 h over activated 4-Å molecular sieves before use. Propionaldehyde and isobutyraldehyde were purchased from Aldrich Chemical Co. and distilled immediately before use. THF was distilled from benzophenone ketyl. Aldol reactions were carried out under a dry N_2 atmosphere in flame-dried glassware. Additions of silyl lactones to Bu_4NF/aldehyde mixtures were made using a syringe pump. Methylene chloride used for ring-opening reactions was purified by distillation from

(11) A procedure reported by Vederaz and co-workers was adopted for this reaction. For details, see: Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105.
(12) Although aldol additions of tetraalkylammonium enolates have generally been shown to proceed with erythro selectivity, threo selectivity has been reported in cases when benzaldehyde was used. For examples, see refs 7b and 7c.
(13) Anteunis, M. J. O.; Tavernier, D.; Borremans, F. *Heterocycles* **1976**, *4*, 293.
(14) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.
(15) Mulzer, J.; Chucholowski, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 777.
(16) When an α-substituent is absent, as in **3**, self-condensation between the enolate and its lactone precursor prevails. For examples, see ref 1 and Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620.
(17) Swiss, K. A.; Choi, W.-B.; Liotta, D. C. *J. Org. Chem.* **1991**, *56*, 5978.

CaH_2. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Product purity was established using TLC and high-field ^1H NMR. In most cases this purity was shown to be ≥95% (see supplementary material).

General Procedure for Aldol Reactions. A 1.2-mL sample of Bu_4NF (1.2 mmol) was diluted to 3.0 mL with dry THF and cooled with the aid of a dry ice/acetone bath. When a precipitate began to appear, homogeneity was immediately restored by the addition of aldehyde (2.4 mmol). To this mixture at −78 °C was then added a solution of the silyl lactone (1.1 mmol) in 1.2 mL of THF over a 30–45-min period. Following this addition, the reaction mixture was treated with a few drops of aqueous NH_4Cl, diluted with 10 mL of ether, warmed to room temperature, and washed with 10 mL of water. The aqueous phase was extracted with 10 mL of ether, and the combined organic phases were washed with saturated brine, dried over anhydrous Na_2SO_4, and concentrated to an oil for purification by flash chromatography.

3-(Hydroxyphenylmethyl)-4-(1-methylethyl)-2-oxetanones (7 and 8). Elution of the crude oil with hexane–ether (10:1 increased to 5:1) gave the products as a mixture of diastereomers: IR (neat) 3370, 1817 cm^{-1}. **7**: ^1H NMR δ 7.37 (5 H, m), 5.28 (1 H, d, J = 3.8 Hz), 4.40 (1 H, dd, J = 8.4, 4.0 Hz), 3.51 (1 H, t, J = 4.0 Hz), 3.35 (1 H, bs), 1.76 (1 H, m), 0.85 (3 H, d, J = 6.6 Hz), 0.43 (3 H, d, J = 6.9 Hz); ^{13}C NMR δ 169.80, 140.90, 128.67, 128.08, 125.26, 78.26, 68,88, 61.99, 31.83, 17.87, 16.32. **8**: ^1H NMR δ 5.01 (1 H, d, J = 6.5 Hz), 4.10 (1 H, dd, J = 8.3, 4.1 Hz), 3.56 (1 H, dd, J = 6.5, 4.1 Hz).

4-Ethyl-3-(hydroxyphenylmethyl)-2-oxetanones (9 and 10). Elution of the crude oil with hexane–ether (10:1 increased to 5:1) provided partial separation of the diastereomers: IR (neat) 3474, 1816 cm^{-1}. **9**: ^1H NMR δ 7.34 (5 H, s), 5.28 (1 H, d, J = 4.0 Hz), 4.72 (1 H, pseudo dt, J = 6.7, 4.0 Hz), 3.53 (1 H, pseudo t, J = 4.0 Hz), 2.38 (1 H, bs), 1.80 (1 H, m), 1.56 (1 H, m), 0.68 (3 H, t, J = 7.5 Hz); ^{13}C NMR δ 169.74, 140.84, 128.68, 128.11, 125.25, 78.26, 68.93, 61.95, 31.82, 17.87. **10**: ^1H NMR δ 5.06 (1 H, d, J = 6.4 Hz).

3-(Ethylhydroxymethyl)-4-(1-methylethyl)-2-oxetanones (11 and 12). Elution of the crude oil with 10:1 hexane–ether gave the products as a mixture of diastereomers. Unfortunately, for this product volatiles (i.e., trace Et_2O, excess aldehyde) could not be completely removed by high vacuum without significant loss of the aldol product (see supplementary material): IR (neat) 3402, 1816 cm^{-1}. **11**: ^1H NMR δ 4.33 (1 H, dd, J = 8.2, 4.0 Hz), 3.97 (1 H, m), 3.33 (1 H, dd, J = 8.5, 4.1 Hz), 3.06 (1 H, bs), 1.96 (1 H, m), 1.53 (2 H, m), 0.91–1.03 (9 H, m); ^1H NMR signals separately assigned to minor isomer (**12**): δ 4.23 (1 H, dd, J = 8.1, 4.1 Hz), 3.79 (1 H, m).

3-(1-Hydroxy-2-methylpropyl)-4-(1-methylethyl)-2-oxetanones (13 and 14). Elution of the crude oil with 10:1 hexane–ether separated the major product **13** from the minor component **14**: IR ($CHCl_3$) 3490, 1815 cm^{-1}. **13**: ^1H NMR δ 4.38 (1 H, dd, J = 7.4, 4.0 Hz), 3.76 (1 H, dd, J = 7.0, 4.8 Hz), 3.47 (1 H, dd, J = 4.8, 4.0 Hz), 2.60 (1 H, bs), 1.98 (1 H, m), 1.76 (1 H, m), 0.89–1.07 (12 H, m); ^{13}C NMR δ 171.19, 79.26, 72.84, 57.68, 31.97, 31.68, 19.19, 18.68, 18.29, 17.42.

Rapid addition of lactone **5** to the aldehyde/Bu_4NF mixture resulted in the formation of **13** and **14** in a 60:40 ratio. This allowed the ^1H NMR assignment of the β-H of the minor isomer **14**: δ 4.23 (1 H, dd, J = 8.3, 4.0 Hz). See supplementary material.

3-(Furylhydroxymethyl)-4-(1-methylethyl)-2-oxetanones (15 and 16). Elution of the crude oil with 5:1 hexane–ether provided complete separation of the major product **15** from the minor component **16** along with a second fraction containing both isomers: IR (neat) 3370, 1826 cm^{-1}. **15**: ^1H NMR δ 7.36 (1 H, s), 6.34 (2 H, s), 5.20 (1 H, d, 3.8 Hz), 4.44 (1 H, dd, J = 8.1, 4.0 Hz), 3.66 (1 H, dd, J = 4.0, 3.8 Hz), 1.90 (1 H, m), 0.95 (3 H, d, J = 6.6 Hz), 0.69 (3 H, d, J = 6.8 Hz), O*H* signal hidden; ^{13}C NMR δ 169.6, 153.4, 142.2, 110.5, 107.2, 78.49, 67.01, 59.18, 31.9, 17.74, 16.41. **16**: ^1H NMR δ 7.40 (1 H, s), 6.47 (1 H, m), 6.37 (1 H, m), 5.04 (1 H, d, J = 6.2 Hz), 4.18 (1 H, dd, J = 8.2, 4.1 Hz), 3.73 (1 H, dd, J = 6.2, 4.1 Hz), 3.67 (1 H, bs), 1.94 (1 H, m), 0.99 (3 H, d, J = 6.6 Hz), 0.82 (3 H, d, J = 6.8 Hz).

4-[3-(Benzyloxy)propyl]-3-(ethylhydroxymethyl)-2-oxetanones (1a and 1b). Elution of the crude oil with 1:1 hexane–ether provided complete separation of both diastereomers: IR ($CHCl_3$) 3427, 1814 cm^{-1}. **1a**: ^1H NMR δ 7.33 (5 H, s), 4.66 (1 H, m), 4.51 (2 H, s), 3.89 (1 H, app. bs), 3.47 (2 H, t, J = 7.0 Hz), 3.28 (1 H, dd, J = 5.7, 4.3 Hz), 2.47 (1 H, bs), 1.41–2.00 (6 H, m), 0.96 (3 H, t, J = 7.3 Hz); ^{13}C NMR δ 169.52, 137.71, 128.48, 128.34, 127.90, 74.86, 73.25, 69.83, 69.57, 62.12, 31.93, 27.87, 25.27, 15.24. **1b**: ^1H NMR δ 7.33 (5 H, s), 4.54 (1 H, m), 4.50 (2 H, s), 3.76 (1 H, m), 3.54 (2 H, t, J = 6.0 Hz), 3.33 (1 H, dd, J = 4.4, 4.2 Hz), 2.22 (1 H, bs), 1.56–1.99 (6 H, m), 0.96 (3 H, t, J = 7.3 Hz); ^{13}C NMR δ 169.58, 137.93, 128.40, 127.77, 127.74, 74.21, 73.08, 69.59, 69.49, 61.58, 31.27, 27.77, 25.27, 15.20.

2,6-Dimethyl-4-(methoxycarbonyl)-3,5-heptanediol (17). To a suspension of 13 mg of NaH (50% oil, 0.27 mmol) in 2 mL of dry THF cooled to ice-bath temperature was carefully added 2 mL of methanol. When a clear solution was observed (5 min) the mixture was warmed to room temperature and a solution of 50 mg of lactone **13** (0.27 mmol) in 2 mL of THF was added over a 5-min period. This mixture was stirred for 1 h, treated with 0.03 mL of acetic acid, and concentrated in vacuo. Chromatography on silica gel (5:1 hexane–ether) gave 31 mg of the diol product: IR (neat) 3467, 1717 cm^{-1}; ^1H NMR δ 3.82 (1 H, t, J = 6.5 Hz), 3.73 (3 H, s), 3.56 (1 H, dd, J = 9.4, 2.1 Hz), 3.28 (2 H, bs), 2.84 (1 H, dd, J = 6.5, 2.1 Hz), 1.68 (2 H, m), 1.04 (3 H, d, J = 6.6 Hz), 1.01 (3 H, d, J = 6.7 Hz), 0.93 (3 H, d, J = 6.8 Hz), 0.89 (3 H, d, J = 6.7 Hz); ^{13}C NMR (DMSO) δ 173.08 74.24, 72.02, 52.84, 51.31, 32.35, 31.28, 20.97, 19.93, 19.38, 15.22.

1,3-Dioxanes 18 and 19. A 95-mg sample of the lactone mixture **7** and **8** (0.43 mmol) was reacted with sodium methoxide exactly as described above for the lactone **13**. The crude diol product was then dissolved in 2 mL of acetone to which was added 0.5 mL (4.1 mmol) of 2,2-dimethoxypropane and 19 mg (0.1 mmol) of *p*-toluenesulfonic acid. After the mixture was allowed to stir overnight, 20 mL of ether was added and the mixture was washed with saturated aqueous $NaHCO_3$. The separated organic phase was then dried over anhydrous Na_2SO_2 and concentrated to an oil. Chromatography on silica gel (15:1 hexane–ether) gave 68 mg (54%) of a colorless oil which became a white semisolid on cooling: IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 7.32 (5 H, m), 5.16 (1 H, d, J = 8.5 Hz), 3.70 (3 H, s), 3.63 (1 H, dd, J = 10.2, 5.4 Hz), 3.04 (1 H, dd, J = 8.5, 5.4 Hz), 1.70 (1 H, m), 1.55 (3 H, s), 1.43 (3 H, s), 0.99 (3 H, d, J = 6.5 Hz), 0.93 (3 H, d, J = 6.6 Hz); ^{13}C NMR δ 172.76, 141.19, 128.62, 127.84, 125.86, 101.77, 74.29, 72.32, 54.69, 51.68, 29.76, 24.29, 23.74, 19.81, 18.69.

α-(Ethylhydroxymethyl)tetrahydrofuran-2-acetic Acid (2a). A solution of lactone **1a** (54 mg, 0.19 mmol) in 3.4 mL of dry CH_2Cl_2 was cooled to −78 °C and treated dropwise with 42 μL (38 mmol) of $TiCl_4$. When the addition was complete, the reaction mixture was warmed to ice-bath temperature and stirred for 1.5 h. The reaction was quenched by the addition of a few drops of water, and the resulting mixture was dried over anhydrous Na_2SO_4. Evaporation of CH_2Cl_2 at reduced pressure gave an oil which was purified by column chromatography (1:1 hexane/ethyl acetate elution) to give 26 mg (72%) of a clear viscous oil: IR (neat) 3400, 1719 cm^{-1}; ^1H NMR δ 4.70 (2 H, bs), 4.24 (1 H, m), 4.02 (1 H, m), 3.95–3.79 (2 H, m), 2.58 (1 H, dd, J = 8.1, 7.9 Hz), 2.16–1.47 (6 H, m), 1.01 (3 H, t, J = 7.3 Hz); ^{13}C NMR δ 175.61, 79.85, 73.48, 68.28, 55.53, 30.58, 27.45, 25.14, 9.56.

α-(Ethylhydroxymethyl)tetrahydrofuran-2-acetic Acid (2b). An identical procedure carried out on lactone **1b** provided product **2b**: IR (neat) 3400, 1719 cm^{-1}; ^1H NMR δ 5.80 (2 H, bs), 4.28 (1 H, m), 3.95–3.77 (3 H, m), 2.64 (1 H, dd, J = 8.2, 2.9 Hz), 2.17–1.59 (6 H, m), 1.00 (3 H, t, J = 7.3 Hz); ^{13}C NMR δ 176.79, 79.72, 71.64, 68.09, 54.24, 29.89, 27.88, 25.07, 10.34.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Support from the National Institute of General Medical Sciences through Research Grant No. 1 R15 GM46141-01 is gratefully acknowledged. A National Science Foundation EPSCoR award (Research Grant No. RII-8902064), for the support of general instrumentation, is also greatly appreciated.

Supplementary Material Available: ^1H NMR spectra for **1a**, **1b**, **2a**, **2b**, **7/8**, **9/10**, **11/12**, **13/14**, **15**, **17**, and **18/19**; ^{13}C NMR spectra for **1b**, **2a**, and **17**; NOESY spectrum for **18/19**; and an expanded region of the ^1H NMR spectrum for **11/12** showing the

β-H dd splitting pattern for both stereoisomers (16 pages). This material is contained in many 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.

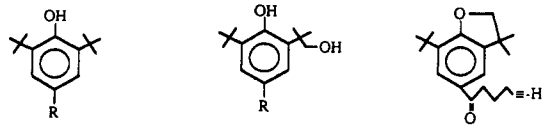
A Short, Efficient Synthesis of *tert*-Butyl-Hydroxylated Di-*tert*-butylphenols

Joseph A. Miller*[,1] and Randall S. Matthews

The Procter & Gamble Co., Miami Valley Laboratories, P.O. Box 398707, Cincinnati, Ohio 45239-8707

Received October 16, 1991

The enzymatic hydroxylation of a *tert*-butyl group in the food antioxidant BHT (butylated hydroxytoluene, **1**) to produce the diol **2** occurs in hepatic and pulmonary microsomes of rats and mice and has been found to be an important step both in BHT bioactivation and the resulting toxicity in these species.[2] Not surprisingly, a similar hydroxylation reaction has also been found to be a significant biliary metabolic pathway in rats for the new di-*tert*-butylphenolic antiinflammatory drug tebufelone **3**. Upon requiring samples of the two tebufelone derivatives **4** and **5** derived from hydroxylation of a *tert*-butyl group, we realized that synthetic methods to allow construction of this functionality had not been previously reported.[3] This paper describes an expedient method for the synthesis of the hydroxylated di-*tert*-butylphenol building block **6**, and its elaboration into both tebufelone derivatives **4** and **5**.



1: R = Me
3: R = -C(=O)(CH$_2$)$_3$C≡CH

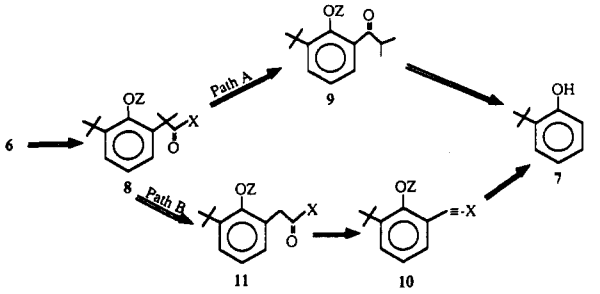
2: R = Me
4: R = -C(=O)(CH$_2$)$_3$C≡CH

5

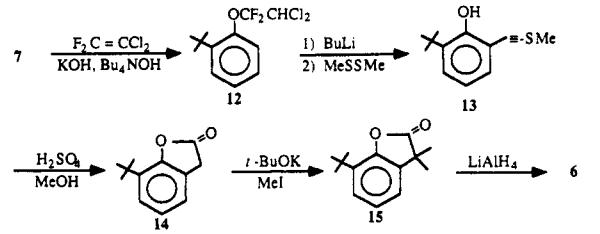
6: R = H

Two approaches were considered initially for the conversion of the commercially available 2-*tert*-butylphenol (**7**) into **6**, with both routes proceeding through the dimethylated arylacetyl derivative **8** (Scheme I). The more direct pathway (A) utilized the Tl-mediated rearrangement[4] of the aryl ketone **9** into the corresponding geminal dimethylated methyl ester **8** (X = OMe). Although the conversion of the model system isobutyrophenone → methyl α,α-dimethylphenylacetate[5] was straightforward [Tl(NO$_3$)$_3$, CH(OMe)$_3$–MeOH, 50 °C, 4 h; 74% yield], the application of this chemistry to the *tert*-butylphenolic system **9**[6] led to the formation of complex product mixtures under a variety of reaction conditions. The feasibility of the alternate pathway (B) hinged on two steps: introduction of the ortho acetylenic group, followed by its conversion into the corresponding arylacetyl derivative. Whereas the ortho acetylenic moiety in **10** (X = TMS, Z = H) could indeed be successfully introduced via Pd-catalyzed coupling[8] of (trimethylsilyl)ethynylzinc chloride with the corresponding aryl iodide, the overall sequence from **7** contained several steps and produced **10** in a low combined yield.[9] As an attractive alternative, Johnson has recently described a procedure whereby haloethyl aryl ethers are converted in a single step into (2-hydroxyaryl)acetylenes by means of BuLi.[11] Furthermore, since this reaction affords the respective lithium acetylide prior to hydrolysis, addition of an electrophile other than water can directly provide the corresponding derivatized alkyne. Using this approach, **7** was first converted into the requisite phenolic 1,1-difluoro-2,2-dichloroethyl ether **12** (93%; Scheme II) via reaction with 1,1-dichloro-2,2-difluoroethylene under phase-transfer conditions.[11] The ether **12** was then transformed into the corresponding *o*-silyloxy silylacetylene **10** (X, Z = TMS) by treatment with BuLi and subsequent silylation. Interestingly, hydroboration–oxidation of this silylated alkyne did not afford the desired substituted acetic acid analogue **11** (Z = H, X = OH) cleanly.[12]

Scheme I



Scheme II



(1) Present address: Exxon Chemical Co., Basic Chemicals Technology, P.O. Box 4900, Baytown, TX 77522-4900.

(2) Thompson, J. A.; Malkinson, A. M.; Wand, M. D.; Mastovich, S. L.; Mead, E. W.; Schullek, K. M.; Laudenschlager, W. G. *Drug Metab. Dispos.* **1987**, *15*, 833 and references cited therein. Thompson, J. A.; Schullek, K. M.; Fernandez, C. A.; Malkinson, A. M. *Carcinogenesis* **1989**, *10*, 773. Malkinson, A. M.; Thaete, L. G.; Blumenthal, E. J.; Thompson, J. A. *Toxicol. Appl. Pharmacol.* **1989**, *101*, 196. Bolton, J. L.; Sevestre, H.; Ibe, B. O.; Thompson, J. A. *Chem. Res. Toxicol.* **1990**, *3*, 65. Bolton, J. L.; Thompson, J. A. *Drug Metab. Dispos.* **1991**, *19*, 467.

(3) Two other studies appeared after completion of this work that also describe the synthesis of phenolic compounds containing a hydroxylated *tert*-butyl group: Ikuta, H.; Yamagishi, Y.; Akasaka, K.; Yamaysu, I.; Kobayashi, S.; Shirota, H.; Katayama, K. *Japanese Patent* JP 63115860 (1988). Goto, K.; Hashimoto, K.; Kanai, K. *World Patent* WO 9009985 (1990).

(4) McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3340. Taylor, E. C.; Robey, R. L.; Liu, K.-T.; Favre, B.; Bozimo, H. T.; Conley, R. A.; Chiang, C.-S.; McKillop, A.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 3037. Taylor, E. C.; Chaing, C.-S.; McKillop, A.; White, J. F. *J. Am. Chem. Soc.* **1976**, *98*, 6750.

(5) The conversion of isobutyrophenone → methyl α,α-dimethylphenylacetate has been accomplished in low yield (17%) previously using I$_2$/AgNO$_3$: Higgins, S. D.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 235.

(6) Compound **9** (Z = H) was prepared (59% yield) via metal-promoted Fries rearrangement[7] of the corresponding *o*-bromoaryl isobutyrate.

(7) Miller, J. A. *J. Org. Chem.* **1987**, *52*, 322.

(8) King, A. O.; Negishi, E.; Villani, Jr., F. J.; Silveira, A., Jr. *J. Org. Chem.* **1978**, *43*, 358.

(9) For example, the reaction of 2-iodo-6-*tert*-butylphenol with (trimethylsilyl)ethynylzinc chloride [2.2 equiv, 5 mol % Pd(Ph$_3$P)$_4$, THF, 25 °C] afforded the arylalkyne **11** (Z = H, X = TMS) in 80% yield. The starting aryl iodide was prepared in two steps from **7** via ortho bromination[10] (Br$_2$; Zn/NaOH, 100 °C; 50% yield) and then lithiation/iodination of the resulting bromide (*t*-BuLi, THF, −78 °C; I$_2$, −78 → 0 °C; 31% yield).

(10) Tashiro, M.; Fukata, G. *J. Org. Chem.* **1977**, *42*, 835.

(11) Subramanian, R.; Johnson, F. *J. Org. Chem.* **1985**, *50*, 5430.

0022-3263/92/1957-2514$03.00/0