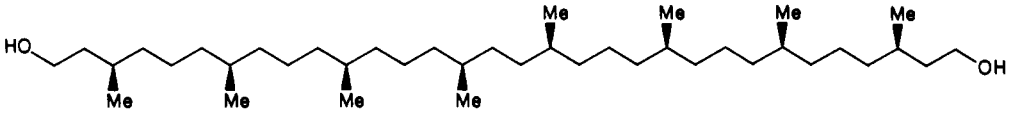
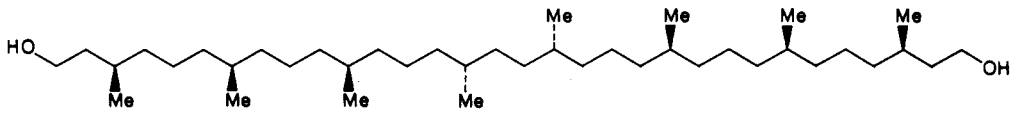
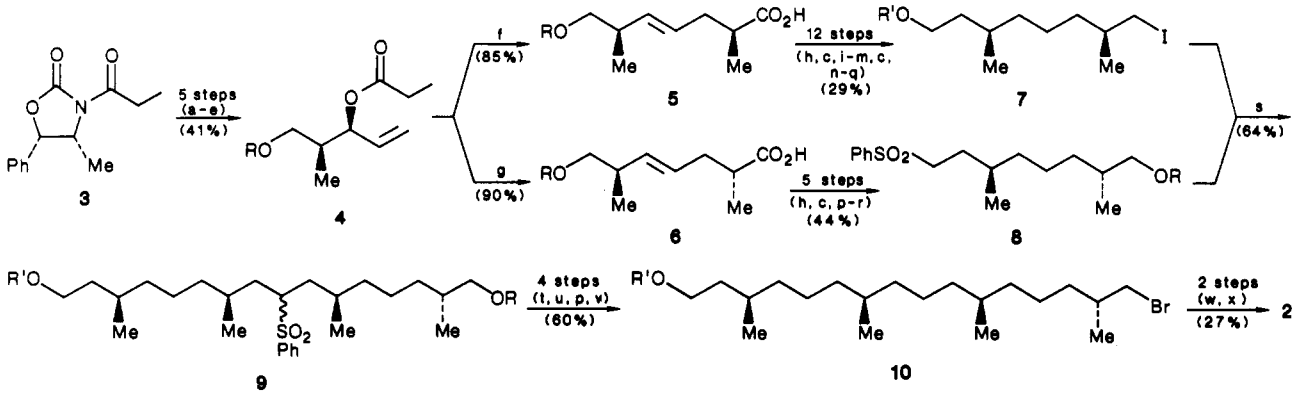


1



2

Scheme I[a]



[a] (a) (1) $(n\text{-Bu})_2$BOTf, Hunig's base, CH_2Cl_2, 0 °C; (2) acrolein, −78 °C; (b) KOH, MeOH, 0 °C; (c) $LiAlH_4$, THF; (d) 1.1 equiv of *t*-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2; (e) propionyl chloride, pyridine, CH_2Cl_2; (f) (1) LDA, THF, −78 °C; (2) *t*-$BuMe_2SiCl$, HMPA, THF, −78 °C to room temperature; (3) reflux, 2 h; (4) K_2CO_3, MeOH, 0 °C; (g) (1) LDA, 23% HMPA in THF, −78 °C; (2) *t*-$BuMe_2SiCl$, THF, −78 °C to room temperature; (3) reflux, 2 h; (4) K_2CO_3, MeOH, 0 °C; (h) 1 atm H_2, PtO_2, EtOH; (i) $MeOCH_2CH_2OCH_2Cl$, Hunig's base, DMAP, CH_2Cl_2, 0 °C to room temperature; (j) HF, CH_3CN, 0 °C; (k) *p*-TsCl, pyridine, DMAP, CH_2Cl_2; (l) KCN, 18-crown-6, CH_3CN, reflux 48 h; (m) 1.2 equiv of diisobutylaluminum hydride, hexane, CH_2Cl_2, −78 °C; (n) *t*-$BuPh_2SiCl$, Et_3N, CH_2Cl_2, 0 °C to room temperature; (o) Me_3SiCl, NaI, CH_3CN, CH_2Cl_2, −40 °C; (p) $MeSO_2Cl$, pyridine, CH_2Cl_2; (q) *n*-$Bu_4N^+I^-$, THF, reflux 5 h; (r) 2 equiv of $LiCH_2SO_2Ph$, 30% HMPA in THF, −30 °C to room temperature; (s) (1) addition of 1.0 equiv of *n*-BuLi to **7**, 40% HMPA in THF, −78 °C to 30 °C; (2) addition of **8** at −25 °C; (3) warm to room temperature; (t) 6% Na(Hg), MeOH; (u) 1% HCl, ether, THF, 0 °C; (v) *n*-$Bu_4N^+Br^-$, THF, reflux; (w) (1) Mg, THF, reflux; (2) $AgNO_3$; (x) HCl, EtOH, THF.

from *Methanobacterium thermoautotrophicum*.[8] At 125.76 MHz, a $CDCl_3$ solution of diol **2** showed 17 resonances,[9] of which 7 differ by at least 0.05 ppm from corresponding resonances in the naturally derived diol. The greatest differences are seen in the resonances from C-2 ($\Delta\delta$ = −0.05), C-8 ($\Delta\delta$ = −0.06), C-12 ($\Delta\delta$ = −0.05), C-16 ($\Delta\delta$ = −0.14), the C-11 methyl group ($\Delta\delta$ = +0.06), and the C-15 methyl group ($\Delta\delta$ = +0.06) ($\Delta\delta = \delta_1 - \delta_2$). The spectrum of a 1:1 mixture of **2** and the naturally derived diol confirmed the conclusion that the two compounds are different.

In addition to providing confirmation for the previously assigned stereochemistry of the archaebacterial C_{40} diol, the present synthesis further demonstrates the versatility of the aldol-Claisen sequence for establishing remote stereochemical relationships. It is worthy of note that only one act of asymmetric synthesis is used in the synthesis of diol **2** (the aldol reaction of imide **3** with acrolein). By controlling the stereochemistry of enolate formation, the relative stereochemistry of **4** is parlayed into the syn and anti relationships of **5** and **6**. These substances are both "pseudosymmetrical", in that the two ends of the seven-carbon chain are differentiated by their oxidation state. Whereas in the present synthesis we convert **5** into **7** and **6** into **8**, we could have used **5** and **6** to prepare the enantiomers of **7** and **8**, simply by rearranging the sequence of transformations so as to homologate the other end of the chain. *In principle, compound 4 (or, for that matter, any of its stereoisomers) can be converted into any of the 132 stereoisomers of diol 1*!

Acknowledgment. This research was supported by a research grant from the United States Public Health Service (AI-15027).

Registry No. **2**, 104486-21-7; **3**, 77877-20-4; **4**, 104486-22-8; **5**, 104486-23-9; **6**, 104486-24-0; **7**, 104423-51-0; **8**, 104423-52-1; **9**, 104423-53-2; **10**, 104423-50-9.

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(8) The authentic sample was kindly supplied by Dr. Tadashi Aoki and Prof. C. Dale Poulter, of the University of Utah.

(9) Diol **2** showed resonances at δ 19.688, 19.737, 19.775, 24.377, 24.486, 29.548, 32.792, 32.813, 33.054, 34.433, 37.325, 37.365, 37.392, 37.459, 37.500, 39.993, and 61.280. Line shape and peak height suggests that the 19.688, 24.486, and 37.500 ppm resonances are each due to two carbons. The ^{13}C NMR spectrum of **1** has been reported elsewhere.[2]

Total Synthesis of (±)-Cortisone. Double Hydroxylation Reaction for the Construction of Corticoid Side Chain

Summary: An 18-step synthesis of (±)-cortisone has been achieved with the aid of silicon-based new synthetic sequences, in particular, homoenolate chemistry.

Sir: Owing to their remarkable physiological properties coupled with the structural complexity,[1] cortisone (1) and

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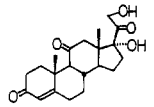
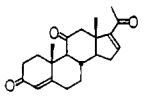
its congeners have been the subject of extensive chemical and pharmacological investigations and continuously served as an attractive target for synthetic chemists both in academia and in industry. Following the early successful syntheses of cortisone itself,[2] recent interests have been focused on the preparation of 11-keto steroidal nuclei,[3] into which the dihydroxyacetone side chain may be installed by using established several-step routes.[4]

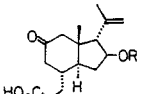
Several years ago we initiated an investigation which was directed toward the design of a synthetic route to a hydrindanone (i.e., pro-CD ring such as **3**)[3g] that has the structural elements necessary for the elaboration of the AB ring as well as the highly oxygenated side chain. In particular, we directed our effort for the efficient construction of the side chain. The successful outcome of such an endeavor, a total synthesis of (±)-cortisone (**1**) is the subject of the present paper.



Cortisone 1



2

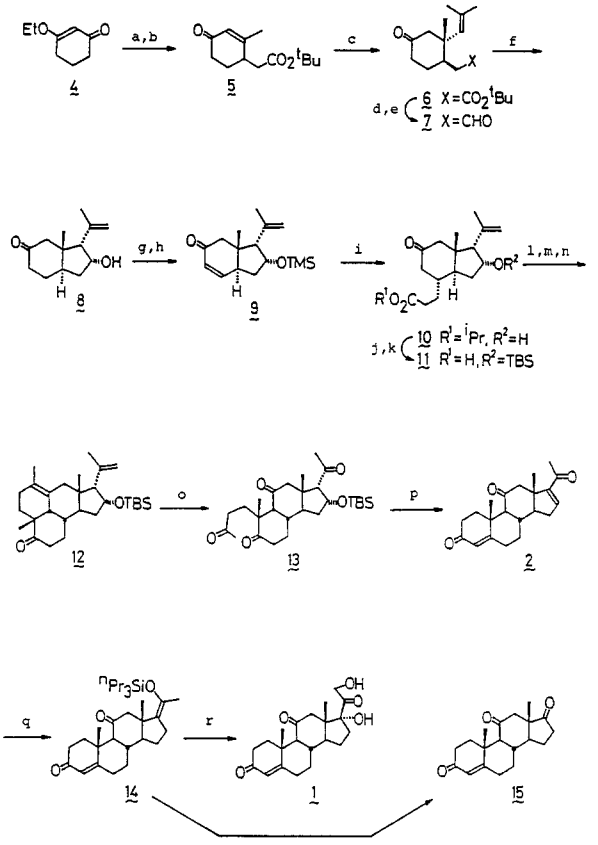


3

The overall strategy required the initial preparation of the crucial hydrindanone **3**, which is then to be elaborated into triketone **2**. Conversion of **2** to cortisone is a type of process employed for the commercial production of corticosteroids, which usually requires several steps.[4] We have accomplished this conversion in only two steps to finish the 18-step total synthesis of (±)-cortisone (Scheme I).

The 6-keto acid structure in **3** suggested the use of conjugate addition of a propionate homoenolate[5] onto an enone such as **9**, which would be synthesized from the keto ester **5**. To this end, **5** (two steps, 81% from enone **4**)[3g] was treated with a variety of organocopper reagents derived from (2-methyl-1-propenyl)magnesium bromide. A satisfactory conjugate addition onto this hindered enone was realized only by the use of a large excess (>3-fold excess) of the R_2Cu-type reagent (78% yield of **6**[6]). We

Scheme I[a]



[a] (a) LDA; $BrCH_2COO$-*t*-Bu/THF; (b) MeMgBr (1.2 equiv)/ether; 2 N HCl; (c) $(CH_3)_2C{=}CHMgBr$ (1.5 equiv), Me_3SiCl (5 equiv), CuBr·Me_2S (5 mol %)/THF, −78 °C, 30 min; 1 N HCl; (d) $LiAlH_4$/ether; (e) $(COCl)_2$, Me_2SO/CH_2Cl_2; Et_3N; (f) Me_2AlCl (1 equiv)/CH_2Cl_2, 0 °C, 15 min; (g) NaI, Me_3SiCl, Et_3N/CH_3CN; (h) $Pd(OAc)_2/CH_3CN$; (i) $Zn(CH_2CH_2COO$-*i*-$Pr)_2$ (2.6 equiv), CuBr·Me_2S (15 mol %), HMPA (2.6 equiv), $BF_3{\cdot}Et_2O$ (4.8 equiv)/THF; (j) *t*-$BuMe_2SiCl$, Et_3N, DMAP (20 mol %)/DMF; (k) KOH/aqueous EtOH; (l) $CH_2{=}C(CH_3)Li$ (4 equiv)/THF; (n) TFA (1 equiv)/CH_2Cl_2, 0 °C, 30 min; (o) O_3; Me_2S/MeOH/CH_2Cl_2; (p) DBU (10 equiv)/PhH (0.03 M), 230 °C, 3 h; (q) *n*-Pr_3SiH (1 equiv), RhCl $(PPh_3)_3$ (6.5 mol %)/THF, 65 °C, 38 h; (r) *m*-CPBA (3 equiv), $KHCO_3$ (20 equiv)/CH_2Cl_2, 0 °C, 1.5 h; 1 N HCl/THF.

were pleased to find, however, that by performing the reaction in the presence of Me_3SiCl,[7] copper-catalyzed (5% CuBr·Me_2S) reaction of only 1.5 equiv of the Grignard reagent afforded the same yield.

The keto ester **6** obtained as a single isomer was converted to the olefinic aldehyde **7** ($LiAlH_4$, Swern oxidation, 78%). Me_2AlCl mediated cyclization[8] of **7** then afforded the desired hydrindanone in 85% yield as a mixture of isomers, in which an 17-isopropenyl isomer (**8**)[6] predominated (85% of the total).[9] The homoallylic alcohol moiety thus created serves as a masked form of an enone, which will be generated at a later stage of the synthesis (i.e., from

(1) Cf. Fieser, L. F.; Fieserm M. *Steroids*; Reinhold Publishing: New York, 1959; p 600.

(2) (a) Review: *Natural Products Chemistry*; Nakanishi, K., Goto, T., Ito, S., Natori, S., Nozoe, S., Eds. Kodansha/Academic: New York; 1974; Vol. 1, p 421. (b) Woodward, R. B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W. M. *J. Am. Chem.* **1952**, *74*, 4223. (c) Sarett, L. H.; Arth, G. E.; Lukes, R. M.; Beyler, R. E.; Poos, G. I.; Johns, W. F.; Constantin, J. M. *J. Am. Chem. Soc.* **1952**, *74*, 4974. (d) Velluz, 1.; Nomine, G.; Mathieu, J. *Angew. Chem.* **1960**, *72*, 725, 1293.

(3) (a) Johnson, W. S.; Escher, S.; Metcalf, B. W. *J. Am. Chem. Soc.* **1976**, *98*, 1039. (b) Stork. G.; Logusch, E. W. *J. Am. Chem. Soc.* **1980**, *102*, 1219. Stork. G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767. Stork, G.; Clark, G.; Shiner, C. S. *J. Am. Chem. Soc.* **1981**, *103*, 4948. Stork, G.; Sherman, D. H. *J. Am. Chem. Soc.* **1982**, *104*, 3758. (c) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron Lett.* **1983**, *24*, 3145. (d) Snider, B. B.; Kirk. T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364. (e) Ziegler, F. E.; Wang, T. F. *J. Am. Chem. Soc.* **1984**, *106*, 718. Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1984**, *49*, 3278. (f) Denmark, S. E.; Germanas, J. P. *Tetrahedron Lett.* **1984**, *25*, 1231. (g) Fukuzaki, K.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1984**, *25*, 3591. (h) Narula, A. S.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 685.

(4) (a) Review: *Organic Reactions in Steroid Chemistry*; Fried, J.; Edwards, J. A.; Eds.; Van Nostrand-Reinhold: New York, 1972; Vol. 2, p 127 and references therin. (b) Van Rheenen, V.; Shephard, K. P. *J. Org. Chem.* **1979**, *44*, 1582. (c) Biollaz, M.; Haefliger, W.; Velarde, E.; Crabbé, P.; Fried, J. F. *Chem. Commun.* **1971**, 1322. (d) Neef, G.; Eder, U.; Seeger, A.; Wiechert, R. *Chem. Ber.* **1980**, *113*, 1184. (e) Moriarty, R. M.; John, L. S.; Du, P. C. *J. Chem. Soc., Chem. Commun.* **1981**, 641. (f) Barton, D. H. R.; Motherwell, W. B.; Zard, S. Z. *J. Chem. Soc. Chem. Commun.* **1981**, 774. (g) Nédélec, L.; Torelli, V.; Hardy, M. J. *Chem. Soc., Chem. Commun.* **1981**, 775. (h) Gumułka, M.; Kurek, A.; Wicha, J. *Pol. J. Chem.* **1982**, *56*, 741. (i) Daniewski, A. R.; Wojciechowska, W. *J. Org. Chem.* **1982**, *47*, 2993; *Synthesis* **1984**, 132. (j) Heinemann, H. A. F.; Kreiser, W. Ger. Offen. 2 655 104; *Chem. Abstr.* **1978**, *89*, 129802e. (k) Walker, J. A.; Hessler, E. J. U.S. Patent *S* 4 357 279; *Chem. Abstr.* **1983**, *98*, 72566k.

(5) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368.

(6) This compound was characterized by 200-MHz ^1H NMR (and 50-MHz ^{13}C NMR), IR, and elemental analysis. All yields are based on purified material.

(7) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029.

(8) (a) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron*, **1981**, *37*, 3927. (b) The reaction with 1 equiv of the aluminum reagent at 0 °C proceeded cleanly while the use of excess reagent invariably gave a tertiary chloride as a major product.

(9) The stereochemistry at C-17 in **8** was determined by chemical correlation to a 17α-acetyl compound, and that of 16-OH was assigned as α by 500-MHz ^1HNMR analysis. The major isomer **8** was generally separated at this stage from three other isomers (ca. 5% each) for the sake of experimental simplicity, whereas the sterochemistry of C-16 and C-17 is erased at a later stage.

12 to 2). Further conversion to 9 was achieved straightforwardly by a standard silylation/dehydrogenation procedure.[10]

Now the stage is set for the crucial (Me_3SiCl/Cu(I)-μmediated) conjugate addition of the zinc homoenolate of propionate onto the enone 9. We fully anticipated very selective formation of the desired adduct 10 via the sterically favorable approach of the organocopper reagent.[3d] Surprisingly, a nearly quantitative reaction yielded an inseparable 1:1 mixture of stereoisomers (δ 0.92 and 1.12 for the 18-methyl group). This unexpected result necessitated extensive search of the conditions that produce the desired 8α-compound. The work along this line, however, was greatly hampered by the very low reactivity of the (copper) homoenolate.[5] To our great satisfaction, $BF_3 \cdot Et_2O$[11] was found not only to promote the addition but to direct it to the desired α-side attack (>80% yield, >95% α).[12] To our knowledge, this is a rare example of the additive dependence of the stereochemistry of the conjugate addition.[13]

Conversion of 10[6] to the steroid nucleus (2) was then achieved via an internal Diels–Alder route.[3b] The 16-hydroxyl group was protected, the ester hydrolyzed, and the keto acid 11 (35% from 8) subjected to Stork's three-step protocol to obtain the tetracyclic ketone 12 in 68% overall yield, together with two structural isomers (20%).[14] Ozonolysis (13,[6] 80%) followed by treatment with DBU (2,[6] 75%) not only completed the AB ring synthesis but also set the D ring ready for the final hydroxylation of the side chain.

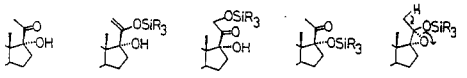
The last stage of the synthesis was initiated by functionalizing the C-17 position. Thus, the less hindered Δ^{16}-double bond in 2 was selectively reduced by Rh-catalyzed hydrosilylation[15] to obtain the enol silyl ether 14[6] (89% on 74% conversion), which was then to be subjected to *m*-CPBA oxidation.[16] The whole synthetic scheme afterward, which would amount to a very complicated one by conventional routes, was greatly simplified by development of a novel double hydroxylation reaction. Thus, treatment of a mixture of enol silyl ether 14 and finely powdered $KHCO_3$ in methylene chloride with *m*-CPBA (3 equiv added slowly as a methylene chloride solution at 0 °C) resulted in highly chemoselective hydroxylation of *both C-17 and C-21 positions*[17] to give, after aqueous acidic workup, (±)-cortisone in 83% isolated yield. The synthetic material was identical with an authentic sample by 200-MHz ^1H NMR, 50-MHz ^{13}C NMR, and TLC mobility under several different conditions.

A very slight modification of the final oxidation step converts the enol silyl ether 14 directly into (±)-adrenosterone. Thus, treatment of 14 with a mixture of excess *m*-CPBA and $KHCO_3$ at room temperature produced 15 in about 50% yield.

The above-mentioned double hydroxylation precedure with its considerable generality,[16b] has obvious importance for the synthesis of various other pharmaceutically important compounds, and further studies are under way.[18]

Supplementary Material Available: Physical properties of several key synthetic intermediates [compounds 2, 6–8, 10–14] (4 pages). Ordering information is given on any current masthead page.

(10) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(11) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* *1982*, *47*, 119.
(12) The stereochemistry at *pro*-C-8, -13, and -14 was confirmed by correlating to a Stork's intermediate.[3b] We thank Prof. Stork for generous provision of an authentic ^1H NMR spectrum.
(13) After completion of this work, a similar observation has been reported: Corey, E. J.; Boaz, N. W. *Tetrahedon Lett.* **1985**, *26*, 6015.
(14) These involve both an olefinic regioisomer (12% yield) due to the dehydration reaction (inert to the Diels–Alder conditions) and a stereoisomer (8%) due to the cycloaddition reaction. Attempted isomerization ($RhCl_3$) of the regioisomer resulted in destruction of the homoallylic alcohol moietry.
(15) Ojima, I.; Kogure, T.; Nagai, Y. *Tetrahedron Lett.* **1972**, 5035.
(16) (a) Brook, A. G.; Macrae, D. M. *J. Organomet. Chem.* **1974**, *77*, C19. (b) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, 4319. (c) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.
(17) (a) Some comments on the mechanism may be due. Unoptimized reactions produced varying amounts of compounds i–iii and none of the "normal" product iv. Since the siloxy ketone iv produces neither of these



i ii iii iv v

three products upon exposure to the reaction conditions, we consider that a presumed[16] epoxide v directly rearranges to ii, which is then further oxidized to iii. (b) For example, this reaction applies to preparations of 16α-methylcorticoids and to derivatization of 1-acetylcyclohexene.
(18) Financial support from the Ministry of Education, Science, and Culture (Grant-in-Aid for Special Research) is gratefully acknowledged.

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Additions and Corrections

Vol. 49, 1984

Emmanuel Y. Osei-Twum, Doug McCallion, Avtar S. Nazran, Rick Panicucci, Prabhakar A. Risbood, and John Warkentin*. Hydroxyalkylation with α-Hydroperoxydiazenes. Alcohols from Olefins and Carbonyl Compounds from Enol Ethers.

Page 341. The symbol I should appear in the blank space under $CH_2{=}C(CH_3)OCH_3$ in the second column. The last part of footnote r (2,4-DNP mp 95–95.5 °C[15]) should appear instead as the last part of footnote s.

David A. Jaeger,* Craig A. Martin, and Timothy G. Golich. "Destructible" Surfactants Based on a Ketal Group.

Page 4546. Line 12 of column 2 should read: 5-cm column of neutral Al_2O_3 (pH 7.4) using 1:9....