A New Procedure for the One-Carbon Homologation of Ketones to α-Hydroxy Aldehydes

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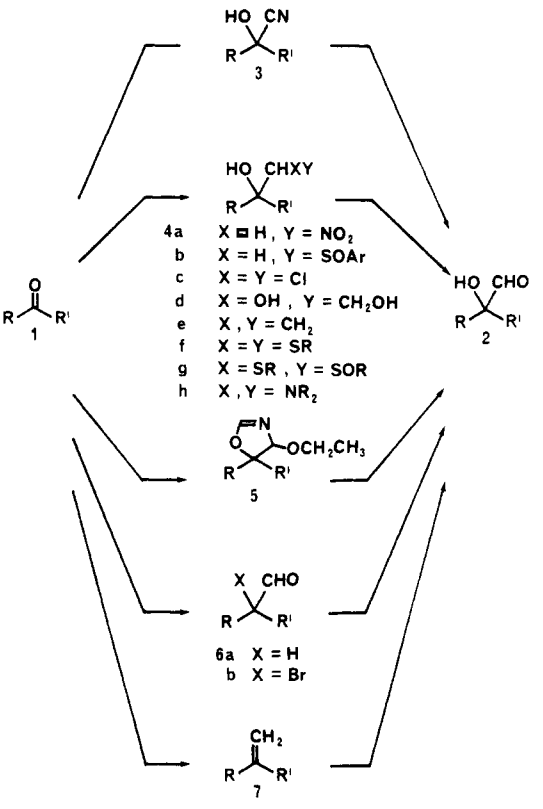
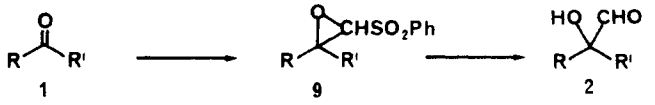
A new, one-carbon homologation procedure for the conversion of ketones to α-hydroxy aldehydes involves two steps: (1) Darzens condensation of ketones with chloromethyl phenyl sulfone; (2) ring opening of the intermediate α,β-epoxy sulfones with hydroxide ion generated by adding water to potassium *tert*-butoxide. This new sequence proceeds in good overall yields and with high stereoselectivity.

The conversion of carbonyl compounds **1** to α-hydroxy aldehydes **2** represents a useful transformation that was first addressed in the classic Kiliani–Fisher synthesis[1] via cyanohydrins[2] **3**. Other indirect procedures for the one-carbon homologation[3] of aldehydes or ketones **1** to α-hydroxy aldehydes **2** involve three general strategies summarized in Scheme I: (1) the conversion of **1** to carbinols[4-11] **4** or oxazolidines[12] **5** which possess masked aldehyde groups that are subsequently liberated; (2) the transformation of **1** to aldehydes **6** which are subsequently oxidized[13] or hydrolyzed;[14] (3) the preparation of olefins

Scheme I



Scheme II[a]



[a] a, $ClCH_2SO_2Ph$ (**8**), KOtBu or Ph_3CLi; b, H_2O, KOtBu followed by H_3O^+.

(1) (a) Pigman, W. "The Carbohydrates"; Academic Press: New York, 1957; p 106f. (b) Hudson, C. S. *Adv. Carbohydrate Chem.* **1945**, *1*, 1.

(2) For recent examples using cyanohydrins or the corresponding α-hydroxy acids for the synthesis of **2**, see: (a) Riehl, J. J.; Fougerousse, A. *Bull. Soc. Chim. Fr.* **1968**, 4083. (b) Tinapp, P. *Chem. Ber.* **1971**, *104*, 2266. (c) Schlosser, M.; Brich, Z. *Helv. Chim. Acta* **1978**, *61*, 1903. (d) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742.

(3) For a recent review on homologation reactions, see: Martin, S. F. *Synthesis* **1979**, 633.

(4) For the preparation of **2** from α-nitro alcohols **4a**, see: Sowden, J. C. *Adv. Carbohydr. Chem.* **1951**, *6*, 291.

(5) For the preparation of **2** from β-hydroxy sulfoxides **4b**, see: (a) Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1974**, *96*, 4280. (b) Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1976**, *40*, 2389.

(6) For the preparation of **2** from β,β-dichloro alcohols **4c**, see: (a) Blumbergs, P.; LaMontagne, M. P.; Stevens, J. I. *J. Org. Chem.* **1972**, *37*, 1248. (b) Shono, T.; Ohmizu, H.; Kise, N. *Tetrahedron Lett.* **1982**, *23*, 4801.

(7) For the preparation of **2** from triols $RCH(OR)CH(OH)CH_2OH$ **4d**, see: (a) von Euw, J.; Reichstein, T. *Helv. Chim. Acta* **1941**, *24*, 401. (b) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 2631.

(8) For the preparation of **2** from allylic alcohols or their derivatives $RCH(OR)CH{=}CH_2$ **4e**, see: (a) Levene, P. A.; Haller, H. L. *J. Biol. Chem.* **1929**, *83*, 579. (b) Levene, P. A.; Walti, A. *Ibid.* **1931**, *94*, 353. (c) Riehl, J.-J. *C. R. Acad. Sci.* **1962**, *255*, 725. (d) Just, G.; Luthe, C.; Potvin, P. *Tetrahedron Lett.* **1982**, *23*, 2285.

(9) For the preparation of **2** from α-hydroxy dithioacetals **4f**, see: (a) Weygand, F.; Bestmann, H. J.; Ziemann, H.; Klieger, E. *Chem. Ber.* **1958**, *91*, 1043. (b) Russell, G. A.; Ochrymowycz, L. A. *J. Org. Chem.* **1969**, *34*, 3618. (c) Sepulchre, A.-M.; Vass, G.; Gero, S. D. *C. R. Acad. Sci.* **1972**, *274*, 1077. (d) Paulsen, H.; Sinnwell, V.; Stadler, P. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 149. (e) Paulsen, H.; Sinnwell, V.; Stadler, P. *Chem. Ber.* **1972**, *105*, 1978. (f) Ross, W. J.; Harrison, R. G.; Jolley, M. R. J.; Neville, M. C.; Todd, A.; Verge, J. P. *J. Med. Chem.* **1979**, *22*, 412. (g) Takaishi, Y.; Yang, Y. L.; DuTullio, D.; Sih, C. J. *Tetrahedron Lett.* **1982**, *23*, 5489. (h) Walba, D. M.; Wand, M. D. *Ibid.* **1982**, *23*, 4995. (i) Jiang, J. B.; Urbanski, M. J.; Hajos, Z. G. *J. Org. Chem.* **1983**, *48*, 2001.

(10) For the preparation of **2** from **4g**, see: Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1972**, 2681.

(11) For the preparation of **2** from **4h**, see: (a) Sakito, Y.; Suzukamo, G. *Tetrahedron Lett.* **1982**, 4953. (b) Sakito, Y.; Suzukamo, G. *Chem. Lett.* **1979**, 705.

(12) For the preparation of **2** from oxazolidines **5**, see: (a) Oldenziel, O. H.; van Leusen, A. M. *Tetrahedron Lett.* **1974**, 167. (b) Gokel, G. W.; Gerdes, H. M. *Ibid.* **1979**, 3379.

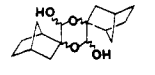
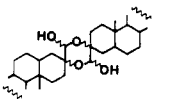
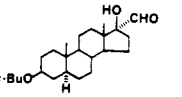
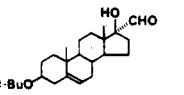
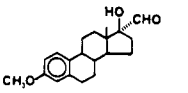
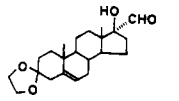
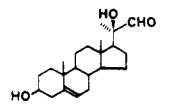
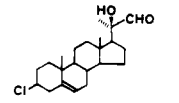
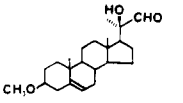
(13) For the preparation of **2** from aldehydes **6a**, see: (a) Riehl, J.-J. *C. R. Acad. Sci.* **1960**, *250*, 4174. (b) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427. (c) Rubottom, G. M.; Gruber, J. M.; Mong, G. M. *Ibid.* **1976**, *41*, 1673. (d) Cummins, C. H.; Coates, R. M. *Ibid.* **1983**, *48*, 2070. Also see ref 2a and 8c.

0022-3263/84/1949-1378$01.50/0

7 which are subsequently oxidized.[15] A direct procedure[16] for the reductive carbonylation of aldehydes employs carbon monoxide and diethylmethylsilane in the presence of dicobalt octacarbonyl and triphenylphosphine, but this method requires an excess of the initial aldehyde which clearly limits its synthetic utility. Many of these methods possess certain disadvantages which include limited scope, poor overall yields, numerous intermediates, competing rearrangement reactions, and the absence of stereoselectivity in generating the α-hydroxy aldehyde **2**. Several methods succeed in avoiding these problems by generating derivatives such as α-acetoxy aldehydes, but unmasking even these simple derivatives to obtain α-hydroxy aldehydes **2** entails certain difficulties with competing rearrangements.[9b,10] Finally, the tendency of certain α-hydroxy aldehydes **2** to dimerize[17] to 1,4-dioxanes and/or 1,3-dioxolanes presents another potential difficulty in the isolation and characterization of **2**.

In connection with our interest in the partial synthesis of ecdysone[18] side chains, we required a one-carbon homologation of pregnan-20-ones to (20*R*)-20-hydroxypregnane-20-carboxaldehydes[19] which proceeded with high efficiency and stereoselectivity. As shown in Scheme II, the Darzens condensation[20] of ketones **1** with chloromethyl phenyl sufone[21] (**8**) furnished α,β-epoxy sulfones[22] **9**. Although these α,β-epoxy sulfones **9** were known to intercept various nucleophiles[23] to furnish α-substituted aldehydes,

Table I. One-Carbon Homologation of Ketones 1 to α-Hydroxy Aldehydes 2

ketone 1	isolated yield of α,β-epoxy sulfone 9, %	α-hydroxy aldehyde 2	isolated yield of 2, %
a	97[b]		59
b	96		53
c	94		60
d	91		70
e	93		60
f	89		98[c]
g	60		92
h	62		95
i	74[a]		74

[a] Using $LiCPh_3$ rather than KOtBu as base. [b] Isolated as a mixture of *E*/*Z* isomers. [c] Isolated as dimer.

adaptation of this approach to the synthesis of α-hydroxy aldehydes **2** proved difficult. The exposure of α,β-epoxy sulfones to hydroxide ion under various conditions produced only intractable mixtures. The use of Gassman's procedure[24] for the generation of highly nucleophilic hydroxide ions[25] was, however, uniquely successful in converting **9** to α-hydroxy aldehydes **2**. We ascribe this success

(14) For the preparation of **2** from α-halo aldehydes **6b**, see: (a) Franke, A. *Monatsh. Chem.* **1900**, *21*, 213. (b) Franke A. *Ibid.* **1900**, *21*, 2127. (c) Dworzak, R.; Enenkel, A. *Ibid.* **1928**, *50*, 449. (d) Dworzak, R.; Pierri, J. *Ibid.* **1929**, *52*, 141. (e) Danilow, S.; Danilowa, E. V. *Chem. Ber.* **1934**, *67*, 24. (f) Danilow, S. *Ibid.* **1927**, *60*, 2390. (g) Danilow, S.; Danilowa, E. V. *Ibid.* **1930**, *63*, 2765. (h) Danilow, S.; Danilowa, E. V. *Ibid.* **1929**, *62*, 2653. (i) Kirrmann, A.; Chancel, P.; Vignalou, M.; Federlin, P. *Bull. Soc. Chim. Fr.* **1950**, 707. (j) Kirrmann, A.; Druesne, F. *C. R. Acad. Sci.* **1964**, *259*, 3285. (k) Gross, H.; Hilgetag, K.-P.; Gloede, J.; Geipel H. *Chem. Ber.* **1965**, *98*, 1673. (l) Padwa, A.; Dehm, D. *J. Org. Chem.* **1975**, *40*, 3139. (m) Sakai, T.; Seko, K.; Tsuji, A.; Utaka, M.; Takeda, A. *Ibid.* **1982**, *47*, 1101. Also see ref 2a and 13 a.

(15) For the preparation of **2** from olefins **7**, see: (a) Weisenborn, F. L.; Taub, D. *J. Am. Chem. Soc.* **1952**, *74*, 1329. (b) Curtin, D. Y.; Bradley, A. *Ibid.* **1954**, *76*, 5777. (c) Iriuchijima, S.; Maniwa, K.; Sakakibara, T.; Tsuchihashi, G. *J. Org. Chem.* **1974**, *39*, 1170.

(16) (a) Yukawa, T.; Kawasaki, K.; Wakamatsu, H. Ger. Pat. 2427934, 1975; *Chem. Abstr.* **1975**, *82*, 124761m. (b) Murai, S.; Kato, T.; Sonoda, N.; Seki, Y.; Kawamoto, K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 393.

(17) For examples of dimerizations to 1,4-dioxane-2,5-diols and 4-hydroxy-2-(hydroxymethyl)-1,3-dioxolanes, see: (a) Yanuka, Y.; Golander, Y. *J. Org. Chem.* **1972**, *37*, 2108. (b) Soerensen, P. E. *Acta Chem. Scand.* **1972**, *26*, 3357. (c) Nielsen, H.; Soerensen, P. E. *Acta Chem. Scand. Ser. A* **1977**, *A31*, 739. (d) Matsura, T.; Kunieda, T.; Takizawa, T. *Chem. Pharm. Bull.* **1977**, *25*, 239. (e) Jordan, S.; Markwell, R. E.; Woolcott, B. S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 928. (f) Bassignani, L.; Biancini, B.; Brandt, A.; Caciagli, V.; Bianchi, G. E.; Re, L.; Rossodivita, A.; Zappelli, P. *Chem. Ber.* **1979**, *112*, 148. (g) Gold, B.; Leuschen, T. *J. Org. Chem.* **1981**, *46*, 1372. (h) Griffiths, D. W.; Gutsche, C. D. *Ibid.* **1971**, *36*, 2184 and ref 2c and 9b.

(18) For recent reviews on ecdysones, see: (a) Berkoff, C. E. *Q. Rev Chem. Soc.* **1969**, *23*, 372. (b) Hikino, H.; Hikino, Y. *Prog. Chem. Org. Nat. Prod.* **1970**, *28*, 256.

(19) For an alternate synthetic solution to this problem, see: Huppi, G.; Sidall, J. B. *J. Am. Chem. Soc.* **1967**, *89*, 6790.

(20) For reviews on the Darzens condensation, see: (a) Newman, M. S.; Magerlein, B. J. *Org. React.* **1949**, *5*, 413. (b) Malinovskii, M. S. "Epoxides and Their Derivatives" Israel Program for Scientific Translations: Jerusalem, 1965; Chapter 3.

(21) (a) Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572. (b) Bordwell, F. G.; Cooper, G. D. *Ibid.* **1951**, *73*, 5184. We used *m*-chloroperoxybenzoic acid in place of peracetic acid.

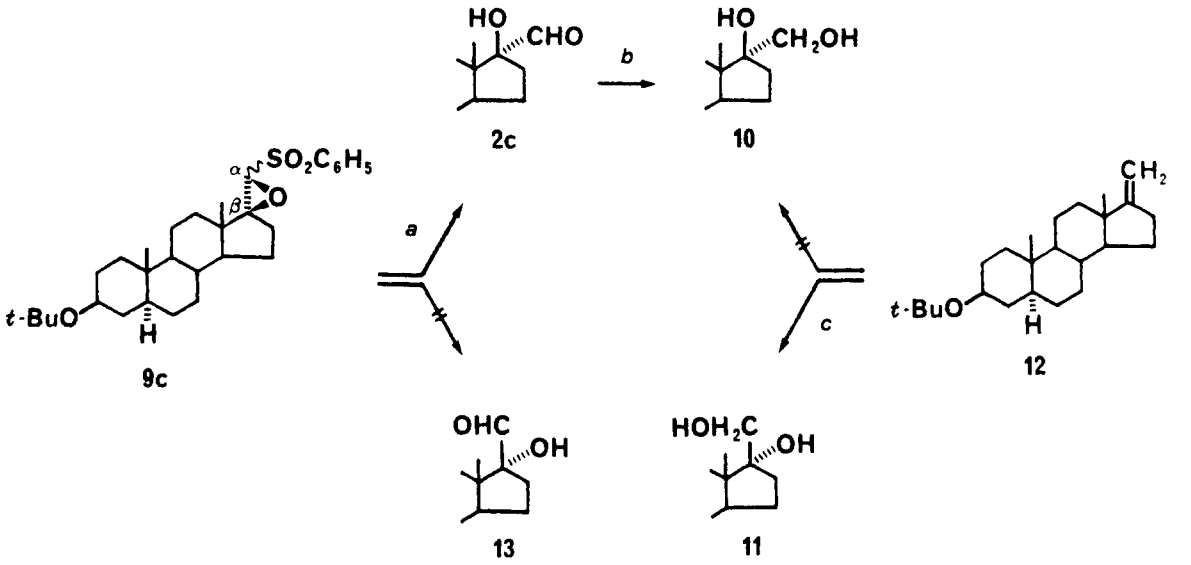
(22) For analogous Darzens condensations leading to α,β-epoxy sulfones, see: (a) Vogt, P. F.; Tavares, D. F. *Can. J. Chem.* **1969**, *47*, 2875. (b) Bohlmann, F.; Haffer, G. *Chem. Ber.* **1969**, *102*, 4017. (c) Tavares, D. F. *Tetrahedron Lett.* **1970**, 2373. (d) de Reinach-Hirtzbach, F.; Durst, T. *Ibid.* **1976**, 3677. (e) Durst, T.; Tin, K.-C.; de Reinach-Hirtzbach, F.; Decesare, J. M.; Ryan, M. D. *Can. J. Chem.* **1979**, *57*, 258. (f) Taber, D. F.; Gunn, B. P. *J. Org. Chem.* **1979**, *44*, 450. (g) Nkunya, M. H. H.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 461. (h) Houwen-Claassen, A. A. M.; McFarland, J. W.; Lammerink, B. H. M.; Thijs, L.; Zwanenburg, B. *Synthesis* **1983**, 628.

(23) (a) (α-azido aldehydes) Barone, A. D.; Snitman, D. L.; Watt, D. S. *J. Org. Chem.* **1978**, *43*, 2066. (b) (α-amino aldehydes as transitory intermediates) Taylor, E. C.; Maryanoff, C. A.; Skotnicki, J. S. *Ibid.* **1980**, *45*, 2512. (c) (α-Bromo aldehydes) Reference 22d,e.

(24) Gassman, P. G.; Hodgson, P. K. G.; Balchunes, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.

(25) The isolation of α,β-epoxy sulfones from a sodium hydroxide–hydrogen peroxide reaction medium testifies to the highly nucleophilic nature of Gassman's hydroxide reagent: Zwanenburg, B.; ter Wiel, J. *Tetrahedron Lett.* **1970**, 935.

Scheme III[a]



[a] a, H_2O, KOtBu; b, $LiAlH_4$; c, OsO_4.

to the rapid formation of base-stable dimers of the α-hydroxy aldehydes which, in most cases, revert to free α-hydroxy aldehydes on acidification at the end of the reaction.

As shown in Table I, the overall conversions of ketones **1** to α-hydroxy aldehydes **2** were acceptable for a variety of ketones. The yields in Table I represent material isolated by chromatography or direct crystallization, and the tabulated yields underestimate the actual yield of **2** in several cases. For example, the sodium borohydride reduction of a crude product containing α-hydroxy aldehyde **2c** furnished the corresponding diol in 93% yield whereas the α-hydroxy aldehyde **2c** itself was isolated by direct crystallization in only 60% yield. Extention of this methodology to aldehydes as well as ketones is possible, but in the case of benzaldehyde, which we examined in detail, product characterization is complicated by the diastereomeric mixture of 1,4-dioxane products.

The base-catalyzed ring opening of the α,β-epoxy sulfones **9** could proceed a priori by hydroxide attack at either the α or β positions. In the case of α,β-epoxy sulfones bearing other chiral centers, this mechanistic distinction is important since the different pathways lead to epimeric products. The most reasonable mechanism involves attack by hydroxide ion at the α-carbon, and evidence supporting this pathway was obtained by comparing the diols **10** and **11** obtained from the α-hydroxy aldehyde **9c** and the olefin **12**, respectively, as shown in Scheme III. Since the diol **10** obtained from **9c** was epimeric to the diol[26] **11** obtained from **12**, we inferred that the ring opening of the α,β-epoxy sulfone[26] **9c** obtained from an androstan-17-one proceeded via α-attack of hydroxide ion to give the α-hydroxy aldehyde **2c** and not **13**. In the case of pregnan-20-ones, we assumed that the Darzens condensation would follow Cram's rule to furnish the desired 20*R* configuration[27] in the α,β-epoxy sulfones **9**. Confirmation of this expectation was found in the X-ray crystallographic determination of α,β-epoxy sulfone **9i** which had 20*R*,22*R* stereochemistry (see supplementary material). Hydroxide ion attack at the α position (C-22) then secures the desired 20*R* product **2i** as shown in Table I.

Experimental Section

Infrared spectra were determined on a Beckman Microlab 600 spectrophotometer. The abbreviation TF denotes thin film. NMR spectra were determined on a Varian EM-360 or JEOL 270 MHz SC spectrometer. Mass spectra were determined on a Varian MAT CH5 or VG-ZAB-IF mass spectrometer. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

General Procedure for the Preparation of α,β-Epoxy Sulfones 9. 3β-*tert*-Butoxy-17β,20ξ-epoxy-20ξ-(phenylsulfonyl)-21-nor-5α-pregnane (9c). To 513 mg (1.5 mmol) of ketone **1c** and 550 mg (3 mmol, 2 equiv) of chloromethyl phenyl sulfone[21] (**8**) in 9 mL of 1:2 *tert*-butyl alcohol:THF at 10 °C was added 336 mg (3 mmol, 1.6 equiv) of 63.7% potassium *tert*-butoxide/*tert*-butyl alcohol[28] in 6 mL of 1:2 *tert*-butyl alcohol:THF over a 10-min period. The mixture was stirred at 10–15 °C for 8–14 h at which time thin-layer chromatography indicated the absence of ketone. The product was diluted with water and extracted with ether. The ether solution was washed with brine and dried over anhydrous magnesium sulfate. The product was chromatographed on Macherey Nagel silica gel in 1:80 ethyl acetate–dichloromethane to afford 701 mg (94%) of α,β-epoxy sulfone **9c**: mp 133–135 °C (from acetone); IR (KBr) 3066, 1576, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3, C-18 angular CH_3), 0.83 (s, 3, C-19 angular CH_3), 1.18 (s, 9, $C(CH_3)_3$), 3.3–3.4 (m, 1, C-3α H), 3.94 (s, 1, $CHSO_2C_6H_5$), 7.5–8.0 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 500 (M^+, 4), 427 (3), 329 (100), 273 (78), 255 (90), 161 (80), 147 (51); exact mass spectrum calcd for $C_{30}H_{44}O_4S$, 500.2962; found, 500.2960.

Spectral Data for α,β-Epoxy Sulfones 9. 9a (mixture of *E*/*Z* isomers): mp 89–92 °C (from 1:6 dichloromethane–hexane); IR (KBr) 3060, 1580, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91, 4.02 (two s, 3, $CHSO_2C_6H_5$); mass spectrum (70 eV), *m/e* (relative intensity) 264 (M^+, <1), 141 (7), 123 (100); exact mass spectrum calcd for $C_{14}H_{16}O_3S$, 264.0819; found, 264.0802.

9b (mixture of *E*/*Z* isomers): mp 139–141 °C (from CH_3OH); IR (KBr) 1582 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (two s, 1, $CHSO_2C_6H_5$), 7.5–8.0 (m, 5, aromatic H).

9d: mp 131.5–133 °C (from acetone); IR (KBr) 3060, 1582, 1149 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3, C-18 angular CH_3), 0.98 (s, 3, C-19 angular CH_3), 1.19 (s, 9, $C(CH_3)_3$), 3.1–3.5 (m, 1, C-3α H), 3.96 (s, 1, $CHSO_2C_6H_5$), 5.32 (m, 1, C-6 vinylic H), 7.5–8.1 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 498 (M^+, 5), 327 (95), 271 (100); exact mass spectrum calcd for C_{30}-

(26) We have assumed that the Darzens condensation of ketone **1c** and the hydroxylation of olefin **12** follow the usual steroid "rule" of α-attack to give the epoxy sulfone **9c** and diol **11**, respectively.
(27) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199.

(28) We prepared potassium *tert*-butoxide which was isolated as a solid 50–65% *t*-BuOK:*t*-BuOH solvate. The exact composition of the solvate was establihsed by simple titration using a phenolphthalein indicator.

$H_{42}O_4S$, 498.2818; found, 498.2811. Anal. ($C_{30}H_{42}O_4S$) C, H.

9e: mp 73–74 °C (from dichloromethane–hexane); IR (KBr) 3055, 1607, 1574, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (s, 3, C-18 angular CH_3), 3.75 (s, 3, OCH_3), 4.00 (s, 1, $CHSO_2C_6H_5$), 6.6–8.1 (m, 8, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 296 (23), 267 (62), 171 (100), 142 (20); exact mass spectrum calcd for $C_{26}H_{30}O_4S$, 444.1866; found, 444.1856. Anal. ($C_{26}H_{30}O_4S$) C, H.

9f: mp 140–142 °C (from acetone–hexane); IR (KBr) 3060, 1580, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3, C-18 angular CH_3), 1.02 (s, 3, C-19 angular CH_3), 3.8–4.05 (m, 5, OCH_2CH_2O and $CHSO_2C_6H_5$), 5.39 (m, 1, C-6 vinylic H), 7.5–8.0 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 484 (M^+, 3), 343 (53), 269 (100). Anal. ($C_{28}H_{36}O_5S$) C, H.

9g: mp 128–129 °C (from acetone); IR (KBr) 3060, 1582, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3, C-18 angular CH_3), 1.00 (s, 3, C-19 angular CH_3), 1.88 (s, 3, C-21 CH_3), 3.68 (s, 1, C-22 H), 5.30 (m, 1, C-6 vinylic H), 7.55–8.0 (m, 5, aromatic H). Anal. ($C_{33}H_{45}O_5S$) C, H.

9h: mp 78–81 °C (from acetone); IR (KBr) 3056, 1585, 1153 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (s, 3, C-18 angular CH_3), 1.02 (s, 3, C-19 angular CH_3), 1.87 (s, 3, C-21 CH_3), 2.76 (m, 1, C-6α H), 3.31 (s, 3, OCH_3), 3.68 (s, 1, C-22 H), 7.55–8.0 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 484 (M^+, 6), 469 (9), 452 (11), 429 (20), 311 (20), 77 (100); exact mass spectrum calcd for $C_{29}H_{40}O_4S$, 484.2647; found, 484.2638.

9i: mp 110–111 °C (from 1:2:10 methanol–ethyl acetate–hexane); IR (KBr) 3060, 1580, 1145 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3, C-18 angular CH_3), 0.99 (s, 3, C-19 angular CH_3), 1.87 (s, 3, C-21 CH_3), 3.34 (s, 3, OCH_3), 3.70 (s, 1, C-22 H), 5.30 (m, 1, C-6 vinylic H), 7.5–8.0 (m, 5, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity) 484 (M^+, 1), 335 (25), 310 (37), 110 (100); exact mass spectrum calcd for $C_{29}H_{40}O_4S$, 484.2646; found, 484.2646.

General Procedure for the Preparation of α-Hydroxy Aldehydes 2. 3β-*tert*-Butoxy-17α-hydroxy-5α-androstane-17β-carboxaldehyde (2c). To 95 mg (0.19 mmol) of α,β-epoxy sulfone **9c** in 3.5 mL of anhydrous THF was added 614 mg of a 63.7% potassium *tert*-butoxide/*tert*-butyl alcohol[28] solution followed by 19 μL of water. The mixture was stirred at 25 °C for 3–5 h at which time thin-layer chromatography indicated the absence of **9c**. The product was diluted with 1:9 dichloromethane–ether, washed successively with water and brine, and dried over anhydrous magnesium sulfate. The product was concentrated, dissolved in 25 mL of THF, and acidified with 2 mL of 1 M hydrochloric acid solution. After standing ca. 48 h at 25 °C, the solution deposited a crystalline product which was collected and recrystallized from acetone to afford 42 mg (60%) of α-hydroxy aldehyde **2c**: mp 205–208 °C (from acetone); ^1H NMR ($CDCl_3$) δ 0.80 (s, 3, C-18 angular CH_3), 0.93 (s, 3, C-19 angular CH_3), 1.18 (s, 9, $C(CH_3)_3$), 9.76 (s, 1, CHO); mass spectrum (70 eV), *m/e* (relative intensity) 376 (M^+, 41), 319 (12), 303 (20), 57 (100); exact mass spectrum calcd for $C_{24}H_{40}O_3$, 376.2976; found, 376.2955.

Spectral Data for α-Hydroxy Aldehydes 2. 2a: Reference 12a.

2b (predominantly dimer): mp 116–119 °C; (from acetone) (lit.[12a] mp 176–176.5 °C as a mixture of monomer and dimer).

2d: mp 183–185 °C (from acetone); IR (KBr) 3450, 1723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (s, 3, C-18 angular CH_3), 1.00 (s, 3, C-19 angular CH_3), 1.19 (s, 9, $C(CH_3)_3$), 3.2–3.4 (m, 1, C-3α H), 3.36 (s, 1, OH), 5.32 (m, 1, C-6 vinylic H), 9.75 (s, 1, CHO); mass spectrum (70 eV), *m/e* (relative intensity) 374 (M^+, 19), 318 (18), 301 (8), 262 (15), 56, (100); exact mass spectrum calcd for $C_{24}H_{38}O_3$, 374.2822; found, 374.2811.

2e: mp 168–170 °C (from acetone–hexane); IR (KBr) 3449, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (s, 3, C-18 angular CH_3), 3.78 (s, 3, OCH_3), 9.82 (s, 1, CHO); mass spectrum (70 eV), *m/e* (relative intensity) 314 (M^+, 100), 240 (35), 227 (94), 173 (25), 147 (23); exact mass spectrum calcd for $C_{20}H_{26}O_3$, 314.1882; found, 314.1882.

2f. This material was isolated by crystallization of the crude product without acid treatment to afford a dimer of **2f**: mp 188–192 °C (from ethyl acetate–hexane); IR (KBr) 3440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85, 1.04 (two s, 12, angular CH_3); mass spectrum (70 eV), *m/e* (relative intensity) 316 (100), 310 (12), 274 (12), 244 (37), 229 (21), 124 (35); exact mass spectrum calcd for $C_{20}H_{28}O_3$, 316.2029; found, 316.2028. Exposure of this dimeric product to the usual acid treatment led to hydrolysis of the ketal and unexpected rearrangement of α-hydroxy aldehyde to D-homosteroid as a tautomeric mixture of α-ketols (87%): mp 183–186 °C (from acetone–hexane); IR (KBr) 3420, 1716, 1656, 1613 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72, 1.18 (two s, 6, angular CH_3); mass spectrum (70 eV), *m/e* (relative intensity) 360 (2), 330 (1), 312 (10), 308 (9), 99 (70), 57 (100).

2g: mp 182–185 °C (from ethanol); IR (KBr) 3403 (br), 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3, C-18 angular CH_3), 1.01 (s, 3, C-19 angular CH_3), 1.35 (s, 3, C-21 CH_3), 3.54 (m, 1, C-3α H), 5.36 (m, 1, C-6 vinylic H), 9.56 (s, 1, CHO); mass spectrum (70 eV), *m/e* 346 (M^+, 6), 317 (100), 301 (64), 285 (30), 255 (58); exact mass spectrum calcd for $C_{22}H_{34}O_3$, 346.2534; found, 346.2532.

2h: mp 160–162 °C (from aqueous ethanol); IR (KBr) 3420, 1713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (s, 3, C-18 angular CH_3), 1.03 (s, 3, C-19 angular CH_3), 1.35 (s, 3, C-21 CH_3), 3.75 (m, 1, C-3α H), 5.36 (m, 1, C-6 vinylic H), 9.56 (s, 1, CHO); mass spectrum (70 eV), *m/e* (relative intensity) 366 (<1), 364 (<1), 337 (30), 335 (100), 319 (87), 317 (70), 291 (42); exact mass spectrum calcd for $C_{22}H_{33}O_2Cl$, 364.2217; found, 364.2209.

2i: mp 168–170 °C (from acetone); IR (KBr) 3437, 1719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3, C-18 angular CH_3), 1.00 (s, 3, C-19 angular CH_3), 1.35 (s, 3, C-21 CH_3), 3.36 (s, 3, OCH_3), 6.64 (m, 1, C-6 vinylic H), 9.56 (s, 1, CHO); mass spectrum (70 eV), *m/e* (relative intensity) 360 (M^+, 2), 342 (3), 331 (7), 315 (77), 255 (100); exact mass spectrum calcd for $C_{23}H_{36}O_3$, 360.2664; found, 360.2673.

3β-*tert*-Butoxy-21-nor-5α-pregnane-17β,20-diol (10). To 19 mg (0.05 mmol, 1 equiv) of lithium aluminum hydride in 3 mL of anhydrous ether under a nitrogen atmosphere was added 37.6 mg (0.1 mmol) of α-hydroxy aldehyde **2c** in 2 mL of ether. The mixture was refluxed for 45 min and quenched with ethyl acetate. The product was diluted with ether, washed successively with dilute hydrochloric acid and water, and dried over anhydrous magnesium sulfate. The product was chromatographed on Merck silica gel 60 using 1:1 ethyl acetate–hexane to afford 35.2 mg (93%) of **10**: mp 235–238 °C (from dichloromethane–hexane); IR (KBr) 3360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3, C-18 angular CH_3), 0.87 (s, 3, C-19 angular CH_3), 1.18 (s, 9, $C(CH_3)_3$), 3.28–3.79 (m, 3, C-3α H and CH_2OH); mass spectrum (70 eV), *m/e* (relative intensity) 378 (M^+, 20), 347 (20), 305 (22), 287 (65), 273 (100); exact mass spectrum calcd for $C_{24}H_{42}O_3$, 378.3133; found, 378.3121.

3β-*tert*-Butoxy-21-nor-5α-pregnane-17α,20-diol (11). To 310 mg (0.9 mmol) of **12** in 6 mL of anhydrous pyridine was added 250 mg (1 mmol) of osmium tetroxide in 2 mL of anhydrous pyridine. The mixture was stirred for 18 h at 25 °C and quenched with sodium bisulfite. The product was isolated in the usual fashion and purified on Merck silica gel 60 using 1:1 ethyl acetate–hexane to afford 315 mg (93%) of **11**: mp 156–157 °C (from dichloromethane–hexane); IR (KBr) 3350 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (s, 3, C-18 angular CH_3), 0.80 (s, 3, C-19 angular CH_3), 1.18 (s, 9, $C(CH_3)_3$), 3.35 (m, 1, C-3α H), 3.60, 3.68 (AB q, 2, J = 10.3 Hz, CH_2OH). Anal. ($C_{24}H_{42}O_3$) C, H.

3β-*tert*-Butoxy-21-nor-5α-pregn-17(20)-ene (12). The procedure of Sondheimer[29] was repeated using 1 g (2.89 mmol) of 3β-*tert*-butoxy-5α-androstan-17-one (**1c**), 3.57 g (10 mmol, 3.5 equiv) of methyltriphenylphosphonium bromide, and 5.6 mL of 1.6 M *n*-butyllithium in 1:10 hexane–THF to afford 800 mg (80%) of **12**: mp 144–146 °C (from ethanol); IR (KBr) 1652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3, C-18 angular CH_3), 0.81 (s, 3, C-19 angular CH_3), 1.18 (s, 3, $C(CH_3)_3$), 3.35 (m, 1, C-3α H), 4.61 (m, 2, C-20 vinylic H); mass spectrum (70 eV), *m/e* (relative intensity) 344 (10), 329 (6), 271 (100). Anal. ($C_{24}H_{40}O$) C, H.

X-ray Structure Determination for (20*R*,22*R*)-20,22-Epoxy-3β-methoxy-22-(phenylsulfonyl)-23,24-bisnorchol-5-ene (9i). A small crystal (0.40 × 0.24 × 0.18 mm^3) exhibited extinction conditions consistent with $P2_1$; the structure was solved and refined in $P2_1$. At 20 °C (1), a = 9.454 (3) Å, b = 8.223 (1) Å, c = 16.993 (3) Å, β = 100.43 (2), and Z = 2. Of 2486 reflections examined on the Nicolet R3m diffractometer (3.5° < 2θ <50° and $k, l > 0$), 2259 unique observed ($I > 1.2\sigma(I)$) reflections were used for structure refinement. Refinement of the structural parameters (anisotropic thermal parameters for all non-hydrogen atoms,

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hydrogen atoms at idealized positions) gave $R = 0.041$ and $R_w = 0.042$ and 1.12 for the standard deviation for an observation of unit weight. The highest peak in a final difference electron density map had a height of only 0.20 e Å^{-3}.

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Supplementary Material Available: Table 1, atomic coordinates for the non-hydrogen atoms; Table 2, bond lengths; Table 3, bond angles; Table 4, anisotropic thermal parameters; Table 5, hydrogen atom coordinates; a copy of Figure I (6 pages). Ordering information is given on any current masthead page.

Effect of Central Substituents on the Gas-Phase Acidities of Propenes

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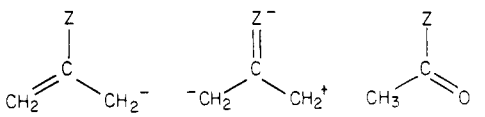
The gas-phase acidities of a number of 2-substituted propenes have been measured by using ICR spectrometry. The acidities are rationalized in terms of structural effects on both acid and anion forms. MNDO calculations reproduce the acidities to ±4.2 kcal/mol and provide information on the interaction of the π orbitals of substituent and acid.

Electron-acceptor groups such as the carbonyl and nitro functionalities are known to stabilize adjacent anions by a mixture of resonance (π acceptor) and polar (σ acceptor) properties.[1] When various structural frameworks are placed between the substituent and the reactive group, then the differing mixtures of π and σ interactions can operate, the classic case being the difference between para- and meta-substituted benzene systems. There have been numerous ingenious attempts to separate the π and σ contributions to such stabilization such as by sterically constraining the geometry of the π systems of the substituent and the reactive site to reduce overlap of the orbitals.[2] Recent efforts have focused on the use of linear free-energy relationships to separate σ and π effects, primarily through the use of dual substituent parameter equations.[3] There are now substituent constants that represent the polar and resonance properties of the more common substituent groups in both solution[4] and gas phase,[5] allowing mathematical separation of the two types of interactions.

One juxtaposition of π-interacting substituent and negatively charged group that has not been extensively investigated is that exemplified by the 2-substituted allyl-type anion 1. In formal valence bond terms, the negative charge cannot be delocalized into the substituent Z without involving charge-separated resonance structures



1a 1b 2

such as **1b**. This is, however, a "Y-delocalized" system[6] where any substituent, either π donating or π accepting, can result in stabilization of the anion.

The highest occupied molecular orbital (HOMO) of 1 involves little or no overlap between the π orbitals of the substituent and those of the allyl anion, due to the node at the central carbon. Thus, we might expect the acidities of the C2-substituted propenes to be largely determined by polar effects, although the lower orbitals should introduce some π interaction between the allyl moiety and the substituent.

Carboxylic acids provide anions analogous to 1, and a vast body of acidity data exists for such compounds.[7] Unfortunately, the substituents of most interest in this work, strong π donors such as NR_2 and OR, and π acceptors such as NO_2 and C≡N, result in compounds in this series that hydrolyze too readily in aqueous solution for the pK_as to be measured. In addition, the lone pairs on the carbonyl and hydroxy oxygens result in the Y-delocalized π system being present in both acid and anion forms, so any effect on acidity due to it will be attenuated. Substituted carbonyl compounds such as **2** do not have the Y-delocalized π system in the neutral and have acidities accessible in dimethyl sulfoxide as solvent.[8] Only a limited number have been measured, however, and none with the stronger π-acceptor groups such as NO_2 or C≡N. To avoid all problems with counterions, differential solvation, and solvolytic reactions, we have investigated the anionic reactions of a series of 2-substituted propenes in the gas phase using ion cyclotron resonance (ICR) mass spec-

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