Direct Oxygenation of Enolates Generated by Anionic Oxy-Cope Rearrangement. Expedient Preparation of Polycyclic α-Hydroxy Ketones

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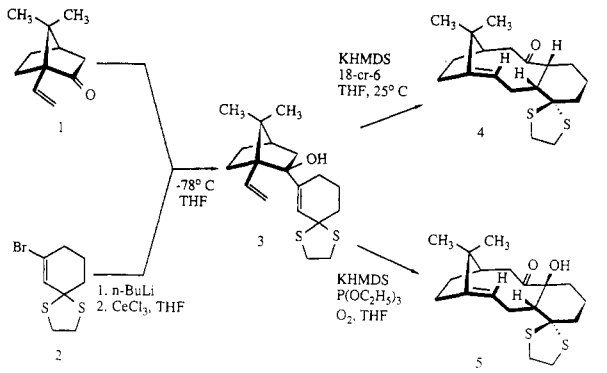
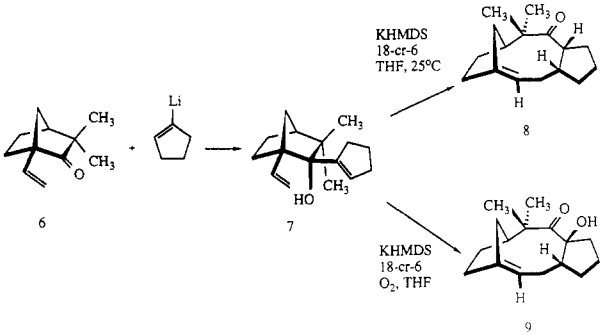
α-Hydroxy ketones are prepared by anionic oxy-Cope rearrangement of allyl homoallyl alcohols followed by direct exposure of the product to oxygen with or without triethyl phosphite present. Of particular importance is the regiochemistry of enolate anion formation, since this dictates the locus of the newly added hydroxyl group. An example is given where ring strain effects induce rapid 1,3-prototropic shift prior to oxygen uptake. The protocol serves additionally as a tool for establishing the course of reaction. The entire sequence can usually be executed over a very short time span in a single flask, thereby providing a notable level of convenience.

That formation of the potassium alkoxides of 1,5-dien-3-ols can greatly accelerate [3.3]-sigmatropic rearrangement was first described in 1975.[2] This finding has provided for electronic reorganization to occur in the vicinity of 25 °C instead of the substantially more elevated temperatures required for the neutral systems.[3] As a consequence, the oxyanionic Cope process can be applied to natural product synthesis.[4-27] Although an appreciation of the powerful capacity of this transformation for stereoselective molecular construction has burgeoned recently,[28-33] few reports have appeared that describe the direct linking of this isomerization to a sequential reaction.[24,26,34,35] Herein we demonstrate that execution of the oxy-Cope reaction in the presence of oxygen is capable of providing vicinally dioxygenated polycyclic molecules regiospecifically and in good yield.

Scheme I



Scheme II



Enolate hydroxylation has been extensively studied in the past. The classical Barton work in the steroid series[36]

(1) On sabbatical leave during 1986-1987 from Miami University, Oxford, OH.

(2) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.
(3) Berson, J. A.; Jones, M., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5017, 5019.
(4) Evans, D. A.; Golob, A. M.; Mandel, N. S.; Mandel, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 8170.
(5) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.
(6) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 2463.
(7) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 4309.
(8) Jung, M. E.; Light, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 7614.
(9) Jung, M. E.; Hatfield, G. L. *Tetrahedron Lett.* **1983**, 2931.
(10) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4186.
(11) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493.
(12) Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625.
(13) Kozikowski, A.; Shmiesing, R. *J. Chem. Soc., Chem. Commun.* **1979**, 106.
(14) Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1984**, 5103.
(15) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172.
(16) Tice, C. M.; Heathcock, C. H. *J. Org. Chem.* **1981**, *46*, 9.
(17) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190.
(18) Schreiber, S. L.; Santini, C. *Tetrahedron Lett.* **1981**, 4651.
(19) (a) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972. (b) Paquette, L. A.; Crouse, G. D. *Tetrahedron* **1981**, Suppl. 1, 281.
(20) (a) Kuroda, C.; Nakamura, T.; Hirota, H.; Enomoto, K.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 146. (b) Utagawa, A.; Hirota, H.; Ohno, S.; Takahashi, T. *Ibid.* **1988**, *61*, 1207.
(21) Rigby, J. H.; Denis, J.-P. *Synth. Commun.* **1986**, *16*, 1789.
(22) Ohmuna, T.; Hata, N.; Miyachi, N.; Wakamatsu, T.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 219.
(23) Early, W. G.; Jacobson, E. J.; Meier, G. P.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3781.
(24) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31.
(25) Paquette, L. A.; DeRussy, D. T.; Cottrell, C. E. *J. Am. Chem. Soc.* **1988**, *110*, 890.
(26) (a) Oplinger, J. A.; Paquette, L. A. *Tetrahedron Lett.* **1987**, *28*, 5441. (b) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1989**, *45*, 107.
(27) Paquette, L. A.; Poupart, M.-A. *Tetrahedron Lett.* **1988**, *29*, 273.
(28) Wender, P. A.; Sieburth, S. McN.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967.
(29) (a) Crouse, G. D.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 3167. (b) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 4411.
(30) Uma, R.; Rajogopalan, K.; Swaminathan, S. *Tetrahedron* **1986**, *42*, 2757 and earlier references cited therein.
(31) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879.
(32) Paquette, L. A.; DeRussy, D. T.; Gallucci, J. C. *J. Org. Chem.* **1989**, *54*, 2278.
(33) Paquette, L. A.; He, W.; Rogers, R. D. *J. Org. Chem.* **1989**, *54*, 2291.
(34) Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038.
(35) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.*, in press.

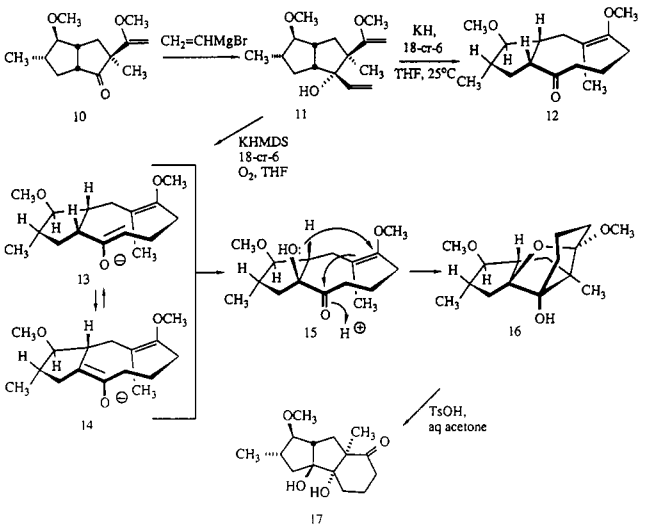
0022-3263/89/1954-4576$01.50/0

has been modified,[37] extended,[38] and improved upon by the introduction of MoO_5·pyridine·HMPA[39] and other reagent combinations.[40] For our purposes, the Gardner modification that employs in situ triethyl phosphite to reduce the hydroperoxidic intermediates[37a,b] produced from reaction with elemental oxygen proved quite satisfactory. The one limitation brought on by this oxidation procedure is the need to avoid primary or secondary reaction sites because of the facility with which the resulting products in such situations experience fragmentation under the operating conditions.[39,41]

Results and Discussion

Ketone 1 is readily available in optically pure condition by dehydrochlorination of D-camphor-10-sulfonyl chloride with triethylamine in the presence of diazomethane, followed by thermal extrusion of sulfur dioxide from the resulting episulfone.[42] The condensation of 1 with bromide 2[43] is preferably mediated by anhydrous cerium trichloride in order to take advantage of the greatly decreased basicity of the dichlorocerate.[44] Under these circumstances, carbon–carbon bond formation occurs exclusively from the endo surface to deliver 3 in 77% yield (Scheme I). Despite the fact that this crystalline alcohol has four diastereomeric [3.3]-sigmatropic transition states open to it, only a single pathway is followed when 3 is stirred with potassium hexamethyldisilazide in tetrahydrofuran containing 18-crown-6 under argon for 30 min at room temperature.[45] Quenching of the reaction mixture with saturated ammonium chloride solution delivered 4, whose double bond geometry was elucidated on the basis of an intense nuclear Overhauser interaction (18%) between the olefinic proton and proximate apical methyl substituent. The ring juncture stereochemistry was deduced by comparative NMR analysis with the product formed by comparable condensation with the parent cyclohexenyl organometallic for which series an X-ray crystallographic analysis is available.[46]

Scheme III



When 3 was alternatively stirred with 5 equiv of potassium hexamethyldisilazide in tetrahydrofuran for 10 min, immediately treated with 1.2 equiv of triethyl phosphite, and exposed to a stream of oxygen for 2 min, 5 resulted. Following chromatographic purification, the isolated yield of 5 was 44%. Omission of the phosphite did not arrest the formation of 5, which, however, was now obtained with reduced efficiency (20%). The configuration of the hydroxyl-bearing carbon in 5 is assumed to be that resulting from capture of oxygen from the less hindered π surface of the enolate anion. This stereochemical course is uniformly followed during the formation of 4 and alkylation products of the same enolate (X-ray analysis).[47a]

The method of choice for preparing 6 consists of sulfonating fenchone with acetic anhydride and sulfuric acid,[48] conversion to the sulfonyl chloride, and homologation of the derived sulfene as described above.[42] Reaction of 6 with cyclopentenyllithium occurs with exclusive exo nucleophile capture[47b] to give 7 (79%, Scheme II). Following the conversion of 7 to its potassium salt under an inert atmosphere as before, two products were isolated in yields of 91 and 4%, respectively. The major constituent was conclusively identified as the isomeric ketone 8 by three-dimensional X-ray crystallography.[46] Consequently, the 7 → 8 rearrangement also proceeds via a transition state having a unique, clearly defined spatial orientation of the vinyl and cyclopentenyl double bonds.[45] The oxygenated nature of 9, clearly apparent from its infrared, NMR, and mass spectral properties, was confirmed by combustion

(36) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578.

(37) (a) Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. (b) Gardner, J. N.; Poppen, T. L.; Carlon, F. E.; Gnoj, O.; Herzog, H. *Ibid.* **1968**, *33*, 3695. (c) Büchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. *J. Am. Chem. Soc.* **1970**, *92*, 999. (d) Enslin, P. R. *Tetrahedron* **1971**, *27*, 1909. (e) Plattner, J. J.; Gless, R. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 8613. (f) Ohnuma, T.; Seki, K.; Oishi, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1974**, 296.

(38) (a) Hanna, R.; Ourisson, G. *Bull. Soc. Chim. Fr.* **1967**, 3742. (b) Muxfeldt, H.; Hardtmann, G.; Kathawala, F.; Vedejs, E.; Mooberry, J. B. *J. Am. Chem. Soc.* **1968**, *90*, 6534. (c) Büchi, G.; Kulsa, P.; Rosati, R. L. *Ibid.* **1968**, *90*, 2448. (d) Büchi, G.; Pickenhagen, W.; Wuest, H. *J. Org. Chem.* **1972**, *37*, 4192. (e) Avramoff, M.; Spinzak, Y. *J. Am. Chem. Soc.* **1963**, *85*, 1655. (f) Gersmann, H. R.; Nieuwenhuis, H. J. W.; Bickel, A. F. *Proc. Chem. Soc., London* **1962**, 279. (g) Siddall, J. B.; Baddeley, G. V.; Edwards, J. A. *Chem. Ind. (London)* **1966**, 25. (h) Doering, W. v. E.; Haines, R. M. *J. Am. Chem. Soc.* **1954**, *76*, 482. (i) Bordwell, F. G.; Knipe, A. C. *Ibid.* **1971**, *93*, 3416. (j) Barton, D. H. R.; Werstiuk, N. H. *J. Chem. Soc. C.* **1968**, 148. (k) Cocker, W.; Crowley, K. J.; Srinivasan, K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1971. (l) Richardson, W. H.; Smith, R. S. *J. Am. Chem. Soc.* **1967**, *89*, 2230. (m) Adam, W.; Liu, J.-C. *Ibid.* **1972**, *94*, 2894. (n) Richardson, W. H.; Hodge, V. F.; Stigall, D. L.; Yelvington, M. B.; Montgomery, F. C. *Ibid.* **1974**, *96*, 6652. (o) Sawaki, Y.; Ogata, Y. *Ibid.* **1975**, *97*, 6983. (p) Sawaki, Y.; Ogata, Y. *J. Org. Chem.* **1976**, *41*, 2340.

(39) (a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. (b) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

(40) For example: (a) Keitsema, R. H. *J. Am. Chem. Soc.* **1957**, *79*, 4465. (b) Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839. (c) Oppolzer, W.; Mahelanabis, K. K. *Ibid.* **1975**, *16*, 3411. (d) Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wellach, R. H. *J. Org. Chem.* **1982**, *47*, 2487. (e) Lodaya, J. S.; Koser, G. F. *Ibid.* **1988**, *53*, 210. (f) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *Ibid.* **1975**, *40*, 3427. (g) McCormick, J.-C.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607. (h) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083. (i) Brown, H. C.; Pai, G. G.; Jadhav, P. K. *J. Am. Chem. Soc.* **1984**, *106*, 1531. (j) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *Ibid.* **1985**, *107*, 4346. (k) Masui, M.; Ando, A.; Shiori, T. *Tetrahedron Lett.* **1988**, *29*, 2835.

(41) (a) Kohler, E. P.; Thompson, R. B. *J. Am. Chem. Soc.* **1937**, *59*, 887. (b) Barton, D. H. R.; Pradha, S. K.; Sternhell, S.; Templeton, J. F. *J. Chem. Soc.* **1961**, 255. (c) Biellman, J. F.; Raji, M. *Bull. Soc. Chim. Fr.* **1962**, 441. (d) Laundon, B.; Morrison, G. A. *J. Chem. Soc. C* **1971**, 1694. (e) Lack, R. E.; Ridley, A. B. *Ibid.* **1968**, 3017.

(42) Fischer, N.; Opitz, G. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 877.

(43) Shih, C.; Swenton, J. S. *J. Org. Chem.* **1982**, *47*, 2825.

(44) (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233. (b) Imamoto, T.; Sugiura, Y. *J. Organomet. Chem.* **1985**, *285*, C21. (c) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763. (d) See also ref 24–26, 31–33, 35, and 45.

(45) A detailed analysis of these mechanistic pathways is to be made elsewhere: Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P. *J. Am. Chem. Soc.*, in press.

(46) We thank Prof. Robin Rogers (Northern Illinois University) for carrying out this crystallographic study, the details of which will be published elsewhere (ref 35 and 45).

(47) (a) Pegg, N. A., unpublished results. (b) This configurational question has been resolved by X-ray analysis of a higher homologue: DeRussy, D. T., unpublished results. (c) Zydowsky, T. M.; Cleary, D. G., unpublished results.

(48) Kuusinen, T.; Lampinen, M. *Suom. Kemi* **1958**, *31B*, 381.

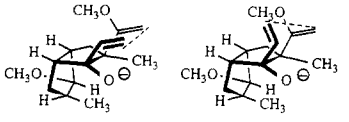
analysis. The coformation of **9** under the anaerobic conditions employed suggested the possibility that the enolate precursor of the tricyclic ketones is exceptionally reactive toward oxygen. This is indeed the case.

Treatment of **7** with potassium hexamethyldisilazide/18-crown-6 in the presence of oxygen but in the absence of triethyl phosphite provided **9** in 87% yield. Realization of a comparably efficient transformation when potassium hydride or potassium *tert*-butoxide was used as base required that triethyl phosphite be present as an additive. We have not seriously pursued the question of how hydroperoxide reduction occurs during this conversion. Suffice it to say that hexamethyldisilazane probably plays a role, since the utilization of other non-amide bases does not eventuate in the formation of **9** with efficiencies at all approaching that specified above.[49] The greatly imbalanced steric shielding in existence above and below the π plane of the enolate anion should strongly favor introduction of the hydroxyl group from the β face.

Encouraged by the facility with which the preceding transformations take place, we next proceeded to consider the manner in which alcohol **11** would respond to sequential rearrangement and oxidation. Ketone **10**[47c] served as the starting point for the preparation of **11**. The condensation of **10** with vinylmagnesium bromide proceeded quantitatively (Scheme III). Because **11** proved sensitive to chromatography, purification in this manner returned only 55–60% of the original sample.

The addition of potassium hydride and 18-crown-6 to tetrahydrofuran solutions of **11** in the absence of air resulted in oxy-Cope rearrangement with the production of **12** (56%). The structure of **12** is of more than passing interest. The appearance of its vinyl methyl signal at δ 1.63 is not especially diagnostic of double bond geometry since there is no indication of an exceptional level of anisotropic shielding that would require this substituent to be positioned alongside the carbonyl oxygen.[50] Molecular models convincingly show that a proximal methyl–carbonyl relationship cannot at all be attained when the medium ring π-bond possesses *E* geometry. On the other hand, the illustrated *Z* arrangement nicely positions the methyl substituent directly alongside the carbonyl group at an angle suitable for advantage to be taken of transannular interaction (see below).

Electronic reorganization within the potassium salt of **11** probably takes place with its vinyl ether double bond oriented away from the adjacent cyclopentane ring as shown in **18**. Because the second double bond in **18** is an unadorned vinyl group, the question of whether the boat (**18A**) or chair (**18B**) transition state is adopted during



18A 18B

[3.3]-sigmatropic change is now less obvious. However, isomerization via the boat geometry necessarily leads from **18A** to the *trans,trans*-1,5-cyclononadiene **13** initially (Scheme III). Rearrangement by means of **18B** would, on the other hand, eventuate in formation of the less strained cis,trans diastereomer. This distinction is lost on simple protonation to give **12** since the stereochemically relevant enolate geometry is lost on ketonization.

That adoption of **18A** is actually preferred kinetically is suggested from oxygenation studies on the intermediate enolate anion. Exposure of the reaction mixture to O_2 (with or without triethyl phosphite present) afforded on workup a product containing an added oxygen atom but lacking the anticipated cyclononene double bond. Analysis of the ^1H and ^{13}C NMR spectra of this product indicated it to have the structural features present in **16**. Thus, in C_6D_6 solution both methoxyl groups are in evidence, but only one methine proton geminal to oxygen is apparent. Furthermore, the vinylic methyl group in **12** now finds itself attached to a fully substituted tetrahedral carbon. The existence of a ^{13}C signal at 108.58 ppm indicated a ketal to be present. In addition, five more carbons were bonded to oxygen; of these, two were tertiary centers.

The formation of **16** can be rationalized in terms of the rapid conversion of **13** to the isomeric enolate **14**. Although prototropic shifts of this type are precedented,[25,26,32,51] we

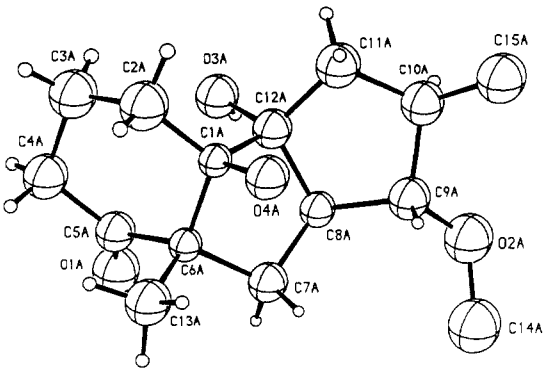


Figure 1. Final ORTEP drawing for molecule A of **17**. Molecule B looks essentially the same and has an identical numbering scheme, so it is not drawn here. Non-hydrogen atoms are drawn with 50% probability thermal ellipsoids, and the hydrogen atoms are drawn with an artificial radius.

Table I. Crystallographic Details for 17

formula wt, amu	268.36
space group	$P2_1/c$
a, Å	9.628 (2)
b, Å	14.319 (4)
c, Å	21.118 (4)
β, deg	97.98 (2)
volume, Å^3	2883
Z	8
density (calc), g/cm^3	1.24
crystal size	0.18 mm × 0.20 mm × 0.38 mm
radiation	Mo Kα with graphite monochromator
linear abs coeff, cm^{-1}	0.82
temperature	19 °C
2θ limits	$4° \le 2\theta \le 44°$
scan speed	4.0–24.0 deg/min in 2θ
background time/scan time	0.5
scan range	(Kα_1 − 1.0)° to (Kα_2 + 1.0)°
data collected	$+h,+k,\pm l$
unique data	3553
unique data, with $F_o^2 > 0$	2891
final number of variables	153
$R(F)^a$	0.199
$R_w(F)^b$	0.110
error in observation of unit weight, e	2.72
R (on F for $F_o^2 > 3\sigma(F_o^2)$)	0.102

$^a R(F) = \sum||F_o| - |F_c||/\sum|F_o|$. $^b R_w(F) = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]1/2$ with $w = 1/\sigma^2(F_o)$.

(49) (a) Capp, C. W.; Hawkins, E. G. E. *J. Chem. Soc.* **1953**, 4106. (b) Büchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. *Ibid.* **1970**, 999.

(50) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: New York, 1969; pp 88ff.

(51) Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331.

are led to surmise that the **13** → **14** step is rapid and unidirectional because the trans → cis inversion in double bond geometry is accompanied by reasonable levels of strain release.[52] The driving force would be much less impelling if the enolate geometry were originally cis.

The structural assignment to **16** was substantiated by aqueous acidic hydrolysis to **17** and three-dimensional X-ray analysis of this colorless crystalline solid (Figure 1, Table I). Since unmasking of the carbonyl group in **17** is unaccompanied by other structural changes, the relative configurations of its six stereogenic centers must already be present as such in **16**. As a result, it is seen that oxygen attacks **14** cleanly from that direction syn to the ring juncture hydrogen. Once **15** is produced, the hydroxyl group finds itself positioned in close proximity to the trans-annular methoxyl-substituted trigonal center. Since the other terminus of this double bond is compressed against the carbonyl group (see above) and is undoubtedly influenced by this close approach, a simple push–pull electronic drift can be set in motion to elaborate two σ bonds at the cost of two π bonds. The combined effects of proximity and thermodynamics contribute to rapid closure of **15**, a process perhaps amenable to base and acid catalysis, and have precluded our ability to isolate this intermediate.

Conclusions

Sigmatropic rearrangements are well recognized to have the capacity for formation of σ bonds with establishment of new reactive functionality.[53] For anionic oxy-Cope reactions, enolate anions are generated, almost always in regioselective fashion.[4-35] Herein we demonstrate the feasibility of linking the structural isomerization directly to an oxygenation step, thereby further enhancing the level of substrate functionalization. The general methodology developed herein results in convenient conversion of allylic homoallylic alcohols to structurally embellished α-hydroxy ketones (or in the case of **15** a product equivalent). When prototropic shift does occur prior to oxygenation as it is apt to do in certain circumstances, this methodology can serve as a tool for unequivocally elucidating operation of the added step. In every example, the α-hydroxy ketone that results may be utilized in a host of subsequent synthetic transformations as desired.

Experimental Section[54]

Alcohol 3. Cerium trichloride heptahydrate (750 mg, 2.0 mmol) was dried at 145 °C and 0.1 Torr for 3.5 h and blanketed with argon while being allowed to cool. Dry tetrahydrofuran (3 mL) was introduced, and the slurry was stirred magnetically for 3 h. A solution of bromide **2**[43] (400 mg, 1.6 mmol) in dry tetrahydrofuran (10 mL) was cooled to −78 °C and treated with *n*-butyllithium (1.1 mL of 1.5 M in hexanes, 1.7 mmol). The yellow solution was stirred for 30 min at −78 °C and then transferred via cannula onto the above slurry also at −78 °C. Following stirring of this mixture at −78 °C for 6.5 h, a solution of **1**[42] (164 mg, 1.0 mmol) in dry tetrahydrofuran (1 mL) was introduced. The reaction mixture was stirred for 1 h at −78 °C and overnight at −30 °C before being quenched with saturated ammonium chloride solution (10 mL) and extracted with ethyl acetate (2 × 20 mL).

The combined extracts were dried and evaporated, and the residue was purified by column chromatography on silica gel to give **3** (260 mg, 77%) as a colorless crystalline solid, mp 89–90 °C; IR ($CHCl_3$, cm^{-1}) 3600, 3200–2800, 1635, 1460, 1390, 1375, 1330, 1280, 1250–1200, 1090, 1055, 1015, 925, 860; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (dd, J = 11.0, 17.8 Hz, 1 H), 5.94 (s, 1 H), 5.19 (dd, J = 2.0, 11.0 Hz, 1 H), 5.02 (dd, J = 2.0, 17.8 Hz, 1 H), 3.45–3.25 (m, 4 H), 2.25–1.60 (series of m, 11 H), 1.20 (s, 3 H), 1.30–1.10 (m, 2 H), 0.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 142.78, 137.35, 126.71, 115.38, 84.77, 66.05, 58.90, 51.34, 45.75, 42.14, 41.16, 39.97, 39.88, 26.03, 25.54, 25.50, 23.05, 21.63, 21.00; MS m/z (M^+) calcd 336.1582, obsd 336.1566; $[\alpha]^{20}_D$ −6.2 ° (c 0.47, $CHCl_3$).

Anal. Calcd for $C_{19}H_{28}OS_2$: C, 67.83; H, 8.39. Found: C, 67.51; H, 8.41.

Anionic Oxy-Cope Rearrangement of 3. A solution of **3** (100 mg, 0.30 mmol) in dry tetrahydrofuran (2 mL) was added to a solution of potassium hexamethyldisilazide (0.65 mL of 0.5 M in toluene, 1.1 equiv) in dry tetrahydrofuran (2 mL) containing 18-crown-6 (86 mg, 1.1 equiv). The mixture was stirred at room temperature under argon for 30 min and quenched with saturated ammonium chloride solution (3 mL). The product was extracted into ether (3 × 10 mL), and the combined organic phases were washed with 2 M hydrochloric acid (5 mL), dried, and evaporated. Purification of the residue by column chromatography on silica gel afforded 43 mg (43%) of **4** as a colorless solid: mp 126–128 °C; IR (KBr, cm^{-1}) 2940, 1690, 1450, 1385, 1280, 1160, 1085, 935, 830; ^1H NMR (300 MHz, $CDCl_3$) δ 5.18 (br dd, 1 H), 3.35–3.20 (m, 4 H), 2.99 (t, J = 6.3 Hz, 1 H), 2.80–2.52 (m, 3 H), 2.50–2.35 (m, 2 H), 2.30–2.15 (m, 1 H), 2.10–1.55 (m, 8 H), 1.50–1.35 (m, 2 H), 1.25 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 211.70, 147.87, 122.17, 72.87, 52.01, 50.68, 49.34, 47.25, 45.33, 42.56, 40.89, 38.93, 27.73, 26.89, 25.03, 24.53, 22.31, 22.17, 20.42; MS m/z (M^+) calcd 336.1581, obsd 336.1553; $[\alpha]^{20}_D$ −77.6° (c 0.33, $CHCl_3$).

Anal. Calcd for $C_{19}H_{28}OS_2$: C, 67.83; H, 8.39. Found: C, 67.75; H, 8.38.

Tandem Oxy-Cope Rearrangement/Oxygenation of 3. A solution of **3** (50 mg, 0.149 mmol) in dry tetrahydrofuran (1 mL) was added to a solution of potassium hexamethyldisilazide (1.5 mL of 0.5 M in toluene, 5 equiv) in dry tetrahydrofuran (3 mL). The mixture was stirred at room temperature under argon for 10 min prior to the introduction of triethyl phosphite (31 μL, 1.2 equiv). A stream of oxygen was bubbled through the mixture for 2 min with the yellow solution immediately becoming orange. Saturated ammonium chloride solution (3 mL) was added, and the product was extracted into ether (3 × 10 mL). The combined ethereal extracts were washed with 2 M hydrochloric acid (5 mL), dried, and concentrated. Purification of the residue by silica gel chromatography furnished 33 mg (44%) of **5** as a white solid: mp 193–196 °C; IR ($CHCl_3$, cm^{-1}) 3690, 3610, 3600–2800, 1685, 1450, 1220, 1085, 1045; ^1H NMR (300 MHz, $CDCl_3$ δ 5.65–5.55 (m, 1 H), 3.35–3.20 (m, 2 H), 3.06 (d, J = 12.0 Hz, 1 H), 2.85–2.75 (m, 2 H), 2.55–2.35 (m, 2 H), 2.20–2.10 (m, 2 H), 2.00–1.80 (m, 6 H), 1.60–1.45 (m, 4 H), 1.30 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 212.76, 148.87, 120.43, 80.07, 74.85, 60.52, 51.51, 46.37, 44.94, 40.95, 38.88, 38.75, 35.38, 28.26, 25.57, 24.97, 22.38, 20.84, 20.46; MS m/z (M^+) calcd 352.1531, obsd 352.1534; $[\alpha]^{20}_D$ −90.8° (c 0.24, $CHCl_3$).

Anal. Calcd for $C_{19}H_{28}O_2S_2$: C, 64.73; H, 8.01. Found: C, 64.85; H, 8.00.

Alcohol 7. Into a 100-mL oven-dried flask flushed with argon was placed 4.07 g (21.0 mmol) of 1-iodocyclopentene and 20 mL of anhydrous tetrahydrofuran. After being cooled to −78 °C, this solution was treated dropwise with *tert*-butyllithium (24.7 mL of 1.7 M in pentane, 42.0 mmol), and a white precipitate formed. This mixture was stirred for 30 min prior to the addition of **6** (1.71 g, 10.5 mmol) dissolved in 10 mL of dry tetrahydrofuran. After

(52) (a) Cope, A. C.; Banholzer, K.; Keller, H.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644. (b) Cope, A. C.; Hecht, J. K.; Johnson, H. W., Jr.; Keller, H.; Winkler, H. J. S. *Ibid.* **1966**, *88*, 761. (c) Cope, A. C.; Howell, C. F.; Bowers, J.; Lord, R. C.; Whitesides, G. M. *Ibid.* **1967**, *89*, 4024.

(53) (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (c) Bennett, G. B. *Synthesis* **1977**, 589. (d) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (e) Gajewski, J. *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981. (f) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 503. (g) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(54) Melting points were taken on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1320 spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Bruker WP 300 instrument, while carbon-13 spectra were recorded at 75 MHz (Bruker WP 300) or at 200 MHz (Bruker NR/80). Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Exact mass determinations were obtained at the Ohio State University Chemical Instrument Center (Kratos MS-30). MPLC purifications were carried out on Lobar Lichroprep Si60 glass columns, while HPLC separations made use of a Waters Prep 500 instrument.

2.5 h of stirring at −78 °C, saturated aqueous ammonium chloride solution was added, and the product was extracted into ether (3 × 75 mL). The combined organic phases were washed with brine (2 × 100 mL), dried, and evaporated. HPLC purification (silica gel, elution with 2% ether in petroleum ether) gave 1.93 g (79%) of **7** as a pale yellow oil: IR (neat, cm^{-1}) 3585, 3405, 3075, 2935, 1735, 1635, 1465, 1388, 1195, 1045, 1000, 955, 915; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (dd, J = 16.8, 10.5 Hz, 1 H), 5.66 (t, J = 2.0 Hz, 1 H), 5.02 (dd, J = 16.9, 2.1 Hz, 1 H), 4.97 (dd, J = 10.5, 2.1 Hz, 1 H), 2.41–2.35 (m, 2 H), 2.31–2.24 (m, 3 H), 2.01 (dd, J = 10.4, 8.4 Hz, 1 H), 1.90–1.65 (m, 4 H), 1.50–1.35 (m, 3 H), 1.16 (dt, J = 12.5, 4.2 Hz, 1 H), 0.98 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 148.35, 141.24, 126.52, 112.24, 83.08, 59.32, 48.90, 45.01, 38.15, 35.60, 31.76, 30.91, 28.13, 24.40, 23.73, 22.01; MS m/z (M^+) calcd 232.1821, obsd 232.1821; $[\alpha]^{23}_D$ −5.9° (c 4.35, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.69; H, 10.42. Found: C, 82.53; H, 10.53.

Anionic Oxy-Cope Rearrangement of 7. In an oven-dried 25-mL flask flushed with argon was placed **7** (158 mg, 0.681 mmol), 18-crown-6 (216 mg, 0.817 mmol), and 5 mL of dry tetrahydrofuran. Potassium hexamethyldisilazide (1.6 mL of 0.5 M in toluene, 0.817 mmol) was introduced at room temperature, and the reaction mixture was stirred for 30 min, cooled to 0 °C, and quenched with saturated ammonium chloride solution. Following the usual workup, but excluding an acid wash, the product was purified by MPLC on silica gel (elution with 2% ether in petroleum ether) to give 144 mg (91%) of **8** as a white solid, mp 117–118 °C (from ethanol). Flushing the column with 20% ether–petroleum ether gave 7 mg (4%) of **9** (see below for characterization). For **8**: IR ($CHCl_3$, cm^{-1}) 3020, 3000, 2960, 2930, 2860, 1680, 1450, 1375, 1265, 1045, 997, 870; ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 (dd, J = 10.1, 6.2 Hz, 1 H), 3.32 (br t, J = 5.7 Hz, 1 H), 2.75 (br d, J = 12 Hz, 1 H), 2.58 (m, 1 H), 2.25 (m, 1 H), 2.15–1.50 (series of m, 13 H), 1.36 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 222.22, 143.60, 118.78, 49.63, 48.82, 48.42, 48.16, 31.77, 31.57, 30.60, 28.68, 27.90, 27.58, 25.33, 23.31, 22.44; MS m/z (M^+) calcd 232.1827, obsd 232.1803; $[\alpha]^{23}_D$ −66.5° (c 1.0, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.69; H, 10.42. Found: C, 82.48; H, 10.47.

Tandem Oxy-Cope Rearrangement/Oxygenation of 7. Method A. A solution of **7** (164 mg, 0.707 mmol) and 18-crown-6 (224 mg, 0.848 mmol) in dry tetrahydrofuran (5 mL) was treated with potassium hexamethyldisilazide (1.7 mL of 0.5 M in toluene, 0.848 mmol) and stirred at room temperature for 30 min. At this point, dry oxygen was bubbled through the mixture for 10 min prior to the addition of saturated ammonium chloride solution. The usual workup (no acid wash) followed by MPLC purification (silica gel, elution with 10% ether in petroleum ether) afforded 153 mg (87%) of **9** as colorless crystals: mp 163–167 °C (from aqueous ethanol); IR ($CHCl_3$, cm^{-1}) 3600, 3020, 3000, 2930, 2860, 1672, 1450, 1390, 1365, 1190, 870; ^1H NMR (300 MHz, $CDCl_3$) δ 5.11 (t, J = 8.0 Hz, 1 H), 2.94 (d, J = 11.6 Hz, 1 H), 2.67 (m, 1 H), 2.30 (m, 1 H), 2.20–1.35 (series of m, 14 H), 1.57 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 217.98, 144.79, 118.24, 90.36, 54.89, 51.14, 49.48, 41.45, 31.96, 31.17, 28.14, 27.74, 27.64, 26.73, 23.72, 20.12; MS m/z (M^+) calcd 248.1777, obsd 248.1800; $[\alpha]^{22}_D$ −19.25° (c 1.03, $CHCl_3$).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.33; H, 9.74. Found: C, 77.00, H, 9.71.

Method B. Into an oven-dried 25-mL two-necked flask flushed with argon was placed 0.212 mL of 25% potassium hydride in mineral oil (53 mg, 1.32 mmol). The solid was washed three times with dried pentane and suspended in 2 mL of anhydrous tetrahydrofuran. A solution of **7** (153 mg, 0.659 mmol) and 18-crown-6 (349 mg, 1.32 mmol) in the same solvent (2 mL) was introduced in one portion, and the mixture was stirred for 30 min at room temperature. Triethyl phosphite (131 mg, 0.791 mmol) was added, and oxygen was bubbled through the mixture for 10 min. Saturated ammonium chloride solution was added after argon purging and cooling to 0 °C. The usual workup (no acid wash) followed by MPLC purification as before gave 97 mg (59%) of **9**.

Method C. A mixture of **7** (153 mg, 0.659 mmol), 18-crown-6 (209 mg 0.791 mmol), and potassium *tert*-butoxide (89 mg, 0.791 mmol) in dry tetrahydrofuran (4 mL) was stirred under argon for 10 min, treated with triethyl phosphite (131 mg, 0.791 mmol), and spurged with oxygen for 5 min. Saturated ammonium chloride solution was introduced, and the products were purified as before. There was isolated 128 mg (78%) of **9**.

Alcohol 11. Vinylmagnesium bromide (1.05 mL of 0.92 M in tetrahydrofuran, 0.970 mmol) was diluted with dry tetrahydrofuran (8 mL) and cooled to 0 °C. A solution of **10** (154 mg, 0.647 mmol) in the same solvent (6 mL) was added dropwise during 10 min, and the reaction mixture was stirred for 30 min prior to the addition of saturated aqueous ammonium chloride solution. The product was extracted into ether (3×), washed with brine, dried, and evaporated. There was obtained 175 mg (100%) of **11** as an off-white solid that was judged to be pure by TLC analysis. MPLC of this product (Florisil, elution with 5% ether in petroleum ether) resulted in considerable loss of material. There was recovered 100 mg (58%) of pure colorless solid: mp 76–77 °C; IR (film, cm^{-1}) 3450, 2950, 1630, 1570, 1450; ^1H NMR (300 MHz, C_6D_6) δ 5.84 (dd, J = 17.4, 10.7 Hz, 1 H), 5.04 (dd, J = 17.3, 1.4 Hz, 1 H), 4.97 (dd, J = 10.7, 1.4 Hz, 1 H), 4.07 (d, J = 2.7 Hz, 1 H), 3.81 (d, J = 2.6 Hz, 1 H), 3.28 (s, 3 H), 3.31–3.19 (m, 1 H), 3.07 (s, 3 H), 2.87–2.80 (m, 1 H), 2.65–2.53 (m, 1 H), 2.31 (dd, J = 13.0, 8.9 Hz, 1 H), 2.19–2.04 (m, 1 H), 1.87 (dd, J = 13.1, 6.8 Hz, 1 H), 1.65–1.55 (m, 1 H), 1.45–1.28 (m, 2 H), 1.24 (s, 3 H), 1.19 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 168.34, 142.31, 111.71, 95.78, 83.68, 81.40, 59.63, 57.70, 54.21, 50.02, 49.45, 43.58, 43.28, 29.06, 20.05, 18.05; MS m/z (M^+) calcd 266.1882, obsd 266.1920.

Anionic Oxy-Cope Rearrangement of 11. In an oven-dried 25-mL two-necked flask flushed with argon was placed 25% potassium hydride in mineral oil (6 mg, 0.15 mmol). After three washings with dried pentane, 2 mL of dry tetrahydrofuran was added, and the solution of **11** (19.7 mg, 0.074 mmol) and 18-crown-6 (39 mg, 0.15 mmol) in dry tetrahydrofuran (2 mL) was introduced in one portion. After being stirred for 30 min, the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ether (3×). The combined organic phases were dried and evaporated to give 23 mg of crude product. Purification by MPLC on silica gel (elution with 30% ether in petroleum ether) afforded 11 mg (56%) of **12** as a very light yellowish oil: IR (neat, cm^{-1}) 2950, 1690, 1450, 1370, 1340, 1200; ^1H NMR (300 MHz, C_6D_6) δ 3.39–3.05 (m, 2 H), 3.24 (s, 3 H), 3.13 (s, 3 H), 2.84 (dd, J = 7.7, 6.4 Hz, 1 H), 2.57 (ddd, J = 10.2, 8.8, 8.7 Hz, 1 H), 2.36–2.10 (m, 3 H), 1.97–1.81 (m, 4 H), 1.63 (s, 3 H), 1.63–1.54 (m, 1 H), 1.37–1.29 (m, 1 H), 1.21–1.11 (m, 1 H), 0.91 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, CD_3CN, ppm) 214.33, 151.77, 121.27, 96.30, 57.51, 55.83, 55.28, 53.68, 41.62, 40.30, 36.11, 35.79, 28.38, 25.13, 23.81, 19.38; MS m/z (M^+) calcd 266.1882, obsd 266.1878.

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.93; H, 10.04.

Tandem Oxy-Cope Rearrangement/Oxygenation of 11. A. Inclusion of Triethyl Phosphite. A solution of **11** (30 mg, 0.113 mmol) and 18-crown-6 (45 mg, 0.170 mmol) in 3 mL of dry tetrahydrofuran was blanketed with argon and treated with potassium hexamethyldisilazide (0.340 mL of 0.5 M in toluene, 0.170 mmol) in one portion. The reaction mixture was stirred at room temperature for 30 min, triethyl phosphite (23 mg, 0.136 mmol) was added, and dry oxygen was bubbled in for 10 min. The solution was poured into saturated ammonium chloride solution and extracted with ether. The usual workup (no acid wash) was followed by MPLC on Florisil (elution with 20% ether in petroleum ether) to give 12 mg (38%) of **16** as a white solid: mp 118–119 °C; IR (CCl_4, cm^{-1}) 3618, 2968, 2936, 1466, 1115; ^1H NMR (300 MHz, C_6D_6) δ 3.53 (dd, J = 8.8, 8.2 Hz, 1 H), 3.27 (s, 3 H), 3.24 (s, 3 H), 2.64 (dd, J = 11.4, 9.3 Hz, 1 H), 2.55–2.44 (m, 2 H), 2.15 (dd, J = 14.4, 11.2 Hz, 1 H), 1.83–1.59 (m, 3 H), 1.45–1.04 (m, 5 H), 1.18 (d, J = 6.8 Hz, 3 H), 0.86 (s, 3 H), 0.61 (s, 1 H); ^{13}C NMR (75 MHz, C_6D_6, ppm) 108.58, 95.46, 90.70, 81.35, 57.35, 55.60, 54.69, 49.47, 42.00, 34.33, 30.73, 27.95, 25.08, 19.26, 18.85, 11.99; MS m/z ($M^+ - OCH_3$) calcd 251.1648, obsd 251.1599.

B. Exclusion of Triethyl Phosphite. Processing of 20 mg (0.075 mmol) of **11**, 30 mg (0.113 mmol) of 18-crown-6, and 0.113 mmol of potassium hexamethyldisilazide as above but with the exclusion of triethyl phosphite furnished 18 mg (85%) of **16**.

Acid-Catalyzed Hydrolysis of 16. Method A. The unpurified sample of **16** from the above reaction was dissolved in 3

mL of acetone and treated with 0.5 mL of water and a crystal of *p*-toluenesulfonic acid. Following 3 h of stirring at room temperature, the reaction mixture was concentrated in vacuo, and the residual oil was taken up in ether, washed with saturated sodium bicarbonate solution and brine, dried, and evaporated. MPLC purification (silica gel, elution with 75% ethyl acetate in petroleum ether) gave **17** (4 mg, 23%) as a colorless crystalline solid, mp 152–153 °C (from chloroform–petroleum ether); IR ($CDCl_3$, cm^{-1}) 3597, 3340, 2952, 2925, 1694, 1452; ^1H NMR (300 MHz, $CDCl_3$) δ 3.35 (s, 3 H), 3.01 (dd, J = 9.1, 7.5 Hz, 1 H), 2.90 (dd, J = 13.0, 9.4 Hz, 1 H), 2.62–2.44 (m, 1 H), 2.29–2.11 (m, 3 H), 2.06–1.18 (series of m, 9 H), 1.24 (s, 3 H), 1.05 (dd, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 213.73, 94.44, 93.95, 83.59, 62.41, 58.56, 57.81, 40.75, 39.37, 36.00, 35.25, 30.40, 21.07, 20.30, 17.55; MS m/z ($M^+ - CH_3$) calcd 237.1491, obsd 237.1518.

Method B. In a dry 25-mL flask flushed with nitrogen was placed 25% potassium hydride in oil (20 mg, 0.50 mmol). Following washing of the solid with petroleum ether (3 × 5 mL), it was suspended in 5 mL of anhydrous tetrahydrofuran and treated with a solution of iodine in tetrahydrofuran until the yellow color persisted for 5 min.[55] Alcohol **11** (26.6 mg, 0.100 momol) dissolved in 5 mL of dry tetrahydrofuran was added dropwise at −10 °C, and the reaction mixture was warmed to 0 °C during 1 h. 18-Crown-6 (13 mg, 0.050 mmol) was introduced, the cooling bath was removed, and stirring was maintained for 48 h before a saturated ammonium chloride quench was implemented. The usual workup (no acid wash) provided unpurified **16**, which was directly hydrolyzed as described earlier. MPLC purification led to the isolation of 10 mg (37%) of **17**, identical in all respects with the solid obtained in part A.

X-ray Crystallographic Analysis of 17. Crystals of **17** are colorless, but contain many striations. Preliminary examination of the diffraction pattern indicated that the chosen crystal was weakly diffracting with broad reflection profiles. Data was collected on this crystal since visual examination of the rest of the sample did not reveal any other suitable crystals in terms of size and/or clarity. The crystal system is monoclinic with space group $P2_1/c$. The cell constants are a = 9.628 (2) Å, b = 14.319 (4) Å, c = 21.118 (4) Å, and β = 97.98 (2)°, as determined at 19 °C by a least-squares fit of the diffractometer setting angles for 22 reflections with 2θ in the range of 15–28° with Mo Kα radiation (Kα = 0.710 69 Å). There are two independent molecules in the asymmetric unit.

Intensities were measured by the θ–2θ scan method at ambient temperature. Six standard reflections were measured after every 100 reflections and gave no indication of crystal decomposition. The data were corrected for Lorentz and polarization effects and put onto an absolute scale by means of a Wilson plot.[56]

The structure was solved with MULTAN 80,[57] with the majority of the atoms of each molecule in the asymmetric unit appearing on the electron density map. The positions of missing atoms were located by standard structure factor and Fourier procedures. The SHELX-76 package[58] was used for all full-matrix least-squares refinements. Because of the poor quality of the data set, the refinement was only carried to the isotropic stage. Those hydrogen atoms whose positions could be calculated in terms of a known geometry were added to the model as fixed contributions with C–H = 0.98 Å and $B_H = B_{C(iso)} + 1.0$ Å^2. The methyl group hydrogen atoms which could be located on an electron density map were idealized to sp^3 geometry and included in the model also. One hydroxyl hydrogen atom bonded to O3A was also located and included in the model.

Not all of the methyl hydrogen atoms and hydroxyl hydrogen atoms are included in the model. It should be mentioned that anisotropic refinement was attempted but the results were not satisfactory. Some of the atoms of each molecule developed peculiar anisotropic thermal parameters while other atoms developed thermal parameters which were nonpositive definite. In addition, the estimated standard deviations of the bond lengths and angles did not improve. So it was thought best to keep this structure at the isotropic level. The final refinement cycle gave agreement indices of R = 0.199 and R_w = 0.110 for the 2891 intensities with $F_o^2 > 0$ and the 153 variables (isotropic nonhydrogen atoms and hydrogen atoms fixed). The final difference electron density map has maximum and minimum peak heights of 0.73 and −0.69 e/Å^3, respectively.

The two independent molecules in the asymmetric unit are labeled A and B. A superposition of these two molecules shows that they have essentially the same conformation. In cases such as this, there is the possibility that these two independent molecules are actually related by some "missing" symmetry element so that the true space group is of higher symmetry than the one actually found. A search for a higher symmetry space group revealed that none were possible. A set of precession photographs was taken of the data collection crystal and confirmed the same space group and unit cell constants as found on the diffractometer. An examination of the packing of these molecules in the unit cell indicates that the intermolecular constants for molecule A are different from those for molecule B. The hydrogen bonding network shows this very clearly. Molecules A and B are linked together by hydrogen bonds into a dimer unit with O1A...O3B = 2.74 Å and O3A...O1B = 2.86 Å. Two dimer units are further joined together by a hydrogen bonding interaction: O.4A...O3B = 2.95 Å. If molecules A and B were identical, then the analogous contact O4B...O3A would also be short, but it is not. Since the environments of these two molecules are different, they cannot be related by a missing symmetry element, so that the current model with two molecules in the asymmetric unit appears to be correct.

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Supplementary Material Available: Figure illustrating the superpositioning of molecules A and B of **17** and tables of final bond lengths, bond angles, intermolecular distances, and final positional and thermal parameters (6 pages); structure factors for **17** (13 pages). Ordering information is given on any current masthead page.

(55) Macdonald, T. L.; Natalie, K. J., Jr.; Prasad, G.; Sawyer, J. S. *J. Org. Chem.* **1986**, *51*, 1124.

(56) Programs used for data reduction are from the CRYM Crystallographic Computing package: Duchamp, D. J.; Trus, B. L.; Westphal, B. J. (1964), California Institute of Technology, Pasadena, CA, and modified by G. G. Christoph at The Ohio State University, Columbus, OH.

(57) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. M. MULTAN 80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data; Universities of York, England and Louvain, Belgium, 1980.

(58) Sheldrick, G. M. SHELX-76. Program for Crystal Structure Determination; University Chemical Laboratory: Cambridge, England, 1976.