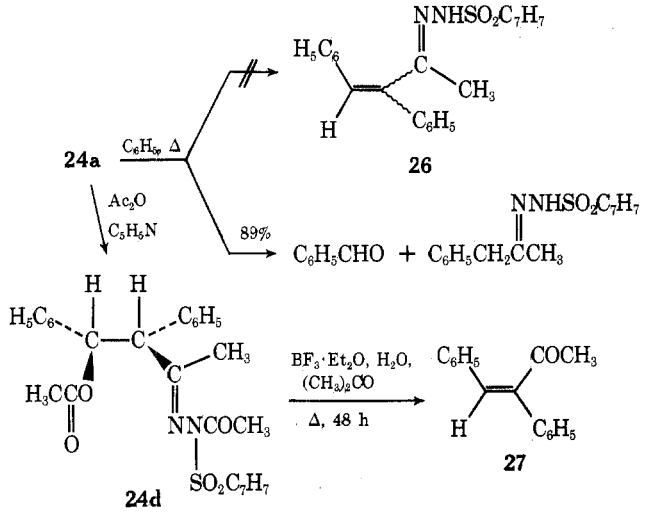
(85%). Sequential reaction of **23** with *n*-butyllithium and phenylcopper provides *erythro*-α-phenyl-β-hydroxytosylhydrazone (**24a**,[8] 60%). Hydrolysis[12] of **24a** provides *erythro*-β-hydroxy ketone **24b**[8,15] (60%), which can be converted to acetate **24c**[8] [$(CH_3CO)_2O/C_5H_5N$, 98%] for the purpose of spectral assignment.[16] The isomeric *threo*-tosylhydrazone **25a** has not been directly isolated from this reaction, but its presence (~10%[17]) has been inferred by isolation of *threo*-β-hydroxy ketone **25b**[8] (6%) by hydrolysis[12] and chromatography of the **24a** reaction residues (7% **24b** also isolated). This places the value of the **24a:25a** ratio for the phenylation reaction at ~7:1.

An additional complication exists with the acyclic example. Attempted dehydration of **24a** (C_6H_6, reflux, 6 h) produces no unsaturated tosylhydrazone (**26**), but, instead, **24a**



undergoes retro-aldol reaction. This difficulty is overcome by conversion of **24a** to the bisacetyl derivative **27d**[7] ($(CH_3CO)_2O/C_5H_5N$, 98%) which, in turn, can be converted to the thermodynamically more stable enone **27** by a single-step hydrolysis–elimination reaction (80%).[18]

Although the primary goal of this investigation was to provide methodology for the α-arylation of α,β-unsaturated ketones, the α-aryl-β-hydroxytosylhydrazones and α,β-unsaturated tosylhydrazones produced via the azoene route should serve equally well as precursors for previously established tosylhydrazone transformations.[19]

Acknowledgment. I wish to thank Eli Lilly and Co. for a Young Faculty Grant.

Supplementary Material Available. General experimental, characterization information, and spectral data (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) A recent paper details a method for the α-alkylation of α,β-unsaturated ketones via the reaction of lithium dialkylcuprates (5 equiv) with α-epoxy oximes: E. J. Corey, L. S. Melvin, Jr., and M. F. Haslanger, *Tetrahedron Lett.*, 3117 (1975).
(2) (a) Another method for the α-arylation (and alkylation) of enones is based on the reaction of Grignard reagents with α-epoxydimethylhydrazones: G. Stork and A. Ponaras, *J. Org. Chem.*, following paper in this issue. (b) See also A. Ponaras, *Diss. Abstr.*, **34**, 145 (1973). (c) We are very grateful to Dr. Stork and Dr. Ponaras for providing us these results prior to publication.
(3) C. E. Sacks and P. L. Fuchs, *J. Am. Chem. Soc.*, **97**, 7372 (1975).
(4) (a) A. Eschenmoser, D. Felix, and G. Ohloff, *Helv. Chim. Acta*, **50**, 708 (1967); (b) J. Schreiber, D. Felix, A. Eschenmoser, M. Winter, F. Gautschi, K. H. Schulte-Elte, E. Sundt, G. Ohloff, J. Kalvoda, M. Kaufmann, P. Wieland, and G. Anner, *ibid.*, **50**, 2101 (1967); (c) P Wieland, H. Kaufmann, and A. Eschenmoser, *ibid.*, **50**, 2108 (1967); (d) M. Tanabe, D. F. Crowe, R. L. Dehn, and G. Detre, *Tetrahedron Lett.*, 3739 (1967); (e) M. Tanabe, D. F. Crowe, and R. L. Dehn, *ibid.*, 3943 (1967); (f) D. Felix, J. Schreiber, G. Ohloff, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 2896 (1971); (g) E. J. Corey and H. S. Sachdev, *J. Org. Chem.*, **40**, 579 (1975).
(5) Addition (and base-catalyzed) reactions of lithium reagents with azoenes generated from *N,N*-ditosylhydrazones have been previously reported: J. F. W. Keana, D. P. Dolata, and J. Ollerenshaw, *J. Org. Chem.*, **38**, 3815 (1973).
(6) Prepared from the corresponding enone by the method of R. L. Wasson and H. O. House, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 552.
(7) (a) This mild procedure appears to be generally applicable for the preparation of high-purity α-epoxytosylhydrazones in excellent yields. Difficulties associated with preparation of this compound class in polar solvents or in the presence of acid catalysts are well documented.[4,7b] α-Epoxytosylhydrazones are best kept in the freezer for extended storage. (b) A. Padwa, *J. Org. Chem.*, **30**, 1274 (1965). (c) Melting points (°C, all with decomposition, $-N_2$): **5**, 90–91; **12**, 86–87; **17a**, 117–118.5; **17b**, 89–90; **23**, 123–125.
(8) (a) This material exhibits spectra (ir, NMR) and analysis (CHNS or CH) in accord with its assigned structure. (b) Melting point and TLC R_f values for these compounds can be found in the microfilm version.
(9) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).
(10) The solution of anion **11** appears to be stable at temperatures below *ca.* −30 °C (TLC analysis). The temperature (−20 °C) at which the phenylation reaction proceeds appears to be the same temperature at which epoxide fragmentation occurs *in the absence of phenylcopper*. This observation is consistent with the epoxide fragmentation being the rate-determining step for the overall process. (Simpler azoenes are phenylated within 1 min at −65 °C[3].)
(11) (a) This material exhibits spectra (ir, NMR, mass) and analysis (exact mass) in accord with its assigned structure. (b) Melting points (°C): **2**, 86–87; **16**, 77–78; **21a**, 94–95 (lit.[11c] 94–95); **21b**, oil (lit.[11c] oil); **27**, 54–55 (lit.[11d] 55–556). (c) H. Born, R. Pappo, and J. Szmuszkovicz, *J. Chem. Soc.*, 1779 (1953). (d) H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959).
(12) C. E. Sacks and P. L. Fuchs, *Synthesis*, in press.
(13) Direct hydrolysis[12] of **8** is less satisfactory. Several other minor uncharacterized products contaminate a mixture of β-hydroxy ketone and enone **10**.
(14) The Corey[1] and Stork[2] procedures give products of trans stereochemistry. The synthetic and mechanistic consequences of this observation are under further investigation.
(15) Benzaldehyde and phenylacetone (20–25% each) are also produced in this reaction.
(16) See supplimentary material for the spectral assignments.
(17) This estimation is based on the assumption that the hydrolysis reaction[12] is equally efficient (~60%) for both isomers.
(18) If this reaction is conducted for shorter periods of time or at a lower temperature, significant amounts (40–50%) of acetate **24c** may be isolated in addition to enone **27**.
(19) (a) For example, tosylhydrazones **9** and **15** serve as excellent substrates for the Dauben–Shapiro diene synthesis.[19b] Treatment of **9** and **15** (in THF, −78 °C) with lithium diisopropylamide[19c,d] (2.5 equv), followed by warming to room temperature (1.5 h), produces 2-phenyl-1,5,5-trimethyl-1,3-cyclohexadiene (90%) and 1-phenyl-4,4a,5,6,7,8-hexahydronaphthalene (85%), respectively. (b) W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Am. Chem. Soc.*, **90**, 4762 (1968). (c) G. E. Gream, L. R. Smith, and J. Meinwald, *J. Org. Chem.*, **39**, 3461 (1974). (d) E. Vedejs and R. A. Shepherd, *J. Org. Chem.*, **41**, 742 (1976).

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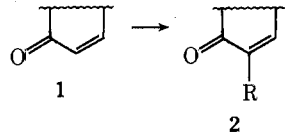
α-Alkylation and Arylation of α,β-Unsaturated Ketones

Summary: The *N,N*-dimethylhydrazones of α,β-epoxy ketones react with aryl and alkyl Gringnard reagents to produce intermediates β-hydroxyhydrazones which are dehydrated to α-aryl or α-alkyl enones; the scheme represents a method for the introduction of alkyl and aryl groups on the α carbon of an α,β-unsaturated ketone.

Sir: The introduction of carbon substituents on the α carbon of an α,β-unsaturated ketone, with preservation of the α,β unsaturation (**1** → **2**), can often be carried out by formation

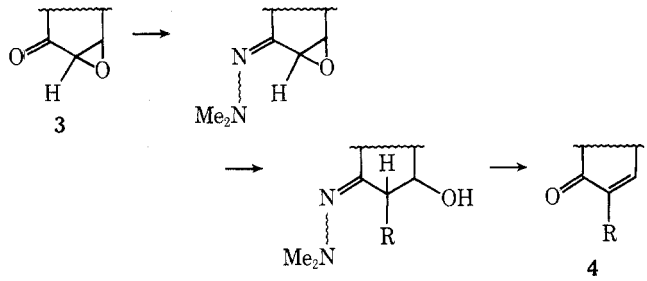


1 **2**

of the thermodynamic enolate ion, followed by treatment with an alkyl halide.[1] The method is not applicable, however, inter alia, (a) when the α,β-unsaturated ketone is incapable of

enolization toward the γ carbon, (b) when the equilibration conditions are incompatible with sensitive functions in the molecule, and (c) when the desired α substituent is an aryl group.[2]

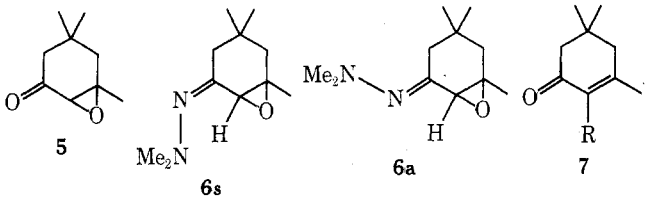
We now describe a solution to this problem.[3] Treatment of the *N,N*-dimethylhydrazone of the epoxy ketone corresponding to the initial α,β-unsaturated ketone with a primary alkyl or aryl Grignard reagent leads, after hydrolysis, to the desired α-alkylated or arylated enone. The sequence is shown in **3** → **4**.[4]



3 **4**

We illustrate tlhe process in detail with isophorone oxide[5] **5**: treatment of **5** with 2 equiv of *N,N*-dimethylhydrazine and 0.5 equiv of propionic acid (ethyl acetate, 0 °C, 40 min)[6] and work-up (10% aqueous sodium carbonate) gave the *N,N*-dimethylhydrazone **6** in 95% yield, as a 1:1 mixture of syn and anti isomers [δ 0.84 (s, 3 H), 0.93, 0.95 (2 s, ratio 45:55, 3 H), 1.32 (s, 3 H), 1.4–2.2 (m, 4 H), 2.38, 2.44 (2 s, ratio 1:1, 6 H), 3.14, 3.89 (2 s, ratio 1:1, 1 H);[7] mass spectrum *m/e* 196.1561]. Assignment of the δ 3.89 resonance to the syn isomer **6s** was made by irradiation at δ 2.41 which produced nuclear Overhauser effect enhancement of the δ 3.89, but not the 3.14, resonance.

Reaction of the epoxyhydrazone **6** with 1.5 equiv of phenylmagnesium bromide (tetrahydrofuran, 0 °C → room temperature, 1.5 h), followed by hydrolysis of the crude product by refluxing with 3 M hydrochloric acid in 50% aqueous ethanol for 1 h, gave (77% yield)[8] 2-phenylisophorone **7** (R =



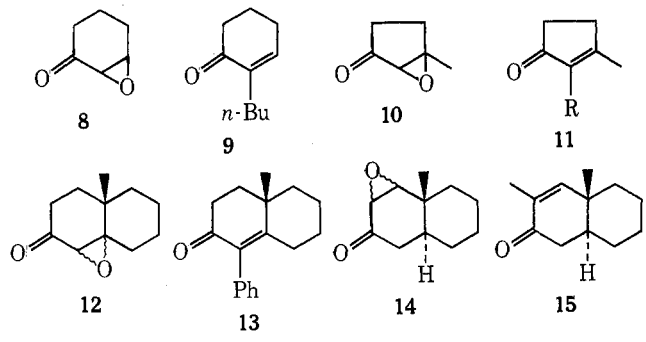
5 **6s** **6a** **7**

phenyl) [mp 85.5–87 °C, ir (film) 5.98, 6.11 μm; δ 1.09 (s, 6 H), 1.78 (s, 3 H), 2.26 (s, 2 H), 2.29 (br s, 2 H), 6.80–7.30 (m, 5 H); mass spectrum *m/e* 214.1353].

The dimethylhydrazone group can also be removed via ozonolysis (methylene chloride, 0 °C) and the resulting β-hydroxy ketone dehydrated with either acid or base. Alternatively, treatment of the crude Grignard reaction product with methyl iodide in acetonitrile at room temperature, followed by evaporation of solvent and hydrolysis of the residual quaternary salt in refluxing 90% aqueous 2-methoxyethanol containing a weak inorganic base (e.g., formate), gives the α,β-unsaturated ketone.[9] Yields via these procedures were comparable with those obtained using direct acid hydrolysis.

The synthesis of **7** (R = methyl,[10] butyl,[11] and 3-methoxyphenethyl) was carried out via the corresponding Grignard reagents to give **7** in yields of 63, 65, and 61%. respectively,[8] from the epoxy ketone **5**.

Cyclohexenone oxide (**8**) was transformed into 2-butylcyclohexenone (**9**) in 45% yield; there was no evidence of attack of the Grignard reagent on the epoxide at the β position. The epoxide **10** from 3-methylcyclopentenone was transformed

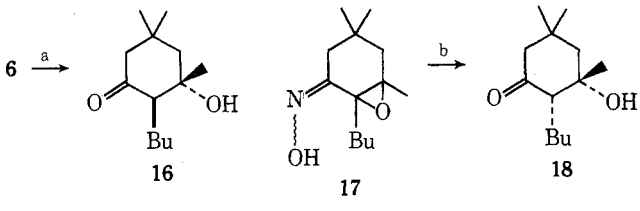


8 **9** **10** **11** **12** **13** **14** **15**

by the same process into 3-methyl-2-phenylcyclopentenone (**11**, R = phenyl) in 53% yield, and also into the known dihydrojasmone[12] (**11**, R = n-C_5H_{11}) in 51% yield.

The two epoxides, **12**, from 10-methyl-$\Delta^{1,9}$-2-octalone[13] were separately converted in a similar sequence to the 1-phenyl derivative **13**, mp 80–82 °C. The yield was higher (63%) from the dimethylhydrazone of the β-oxide than that from the more slowly reacting α-oxide (47%). The two epoxides, **14**, were separately converted to the known[14] *trans*-3,10-dimethyl-Δ^3-2-octalone (**15**), in 53% overall yield from the α-oxide[15] and 40% overall yield from the β-oxide.[19]

We have made some attempts to determine the mechanism of the reaction and have established that, at least in the isophorone series, the initial opening leads stereospecifically to inversion at the α carbon of the epoxyhydrazone. This was demonstrated by comparing the two (different) β-hydroxy ketones **16** and **18** obtained, respectively, by (a) ozonolysis of



16 **17** **18**

the reaction product of the dimethylhydrazone of isophorone oxide with butylmagnesium bromide and (b) by sodium borohydride reduction, followed by ceric ion cleavage,[21] of the oxime of 2-butylisophorone oxide (**17**).[22] The two substances were clearly isomeric [*m/e* 212 (M^+)],[23] and both gave 2-butylisophorone (**7**, R = butyl) on acid-catalyzed dehydration.

These facts are compatible with direct displacement on the epoxide although they do not rule out an a priori possible elimination–addition mechanism.[24]

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this work.

References and Notes

(1) Cf. J. M. Conia, *Rec. Chem. Prog.*, **24**, 43 (1963); H. O. House, "Modern Synthetic Reactions", second ed, W. A. Benjamin, New York, N.Y., 1972, Chapter 9.

(2) For an alternative sequence which, however, should have fairly strict conformational requirements, cf. S. Julia and C. Moutonnier, *Bull. Soc. Chim. Fr.*, 321 (1964). A different method which proceeds from α,β-epoxy ketones involves alkylation of the enolate from calcium–ammonia reduction: J. D. McChesney and H. F. Wycpalek, *J. Chem. Soc., Chem. Commun.*, 542 (1971). This method is obviously not readily applicable to α-arylation.

(3) A. A. Ponaras, *Diss. Abstr.*, **34**, 145 (1973); *Chem. Abstr.*, **79**, 105038 (1973).

(4) The reaction is not useful with secondary Grignard reagents or when the α carbon of the α,β-epoxy ketone bears no hydrogen. Enone is eventually recovered in these cases (elimination–dehydration?).

(5) H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957). In some cases, e.g., **10**, better yields were obtained using dipotassium hydrogen phosphate, rather than sodium hydroxide, for the epoxidation.

(6) The dimethylhydrazones of certain epoxy ketones, e.g., **14**, are unstable, and are best prepared at about −35 °C over several hours using only 0.1 equiv of propionic acid.
(7) NMR spectra were taken in carbon tetrachloride.
(8) Small amounts (usually <10%) of the unalkylated enone were also obtained in these reactions. The mechanism of this reduction is not clear; see A. A. Ponaras, Ph.D. Dissertation, Columbia University, New York, N.Y. 1972.
(9) Cf. M. Avaro, J. Levisalles, and H. Rudler, *J. Chem. Soc., Chem. Commun.*, 445 (1969). We were unable to effect hydrolysis of the dimethylhydrazone group using the published reaction conditions. For other possible cleavage methods, see J. R. Maynez, *J. Org. Chem.*, **40**, 3302 (1975); J. E. McMurry, *ibid.*, **40**, 1502 (1975); and, especially, E. J. Corey and D. Enders, *Tetrahedron Lett.*, 3 (1976).
(10) K. Eiter and H. Oediger, *Justus Liebigs Ann. Chem.*, **682**, 62 (1965).
(11) Identical with an authentic sample prepared by the method of G. Stork and J. Ben Aim, *J. Am. Chem. Soc.*, **93**, 5938 (1971).
(12) Identical with an authentic sample: G. Stork and R. Borch, *J. Am Chem. Soc.*, **86**, 935 (1964).
(13) J. T. Edward and J. M. Ferland, *Can. J. Chem.*, **44**, 1317 (1966).
(14) R. Futaki, *J. Org. Chem.*, **23**, 451 (1958).
(15) Prepared by reaction of *trans*-10-methyl-Δ^3-2-octalone[16] with alkaline hydrogen peroxide. The α configuration of the epoxide was confirmed via Wharton reaction[17] to give the allylic alcohol, mp 60.5–62.5 °C, followed by catalytic hydrogenation to *trans,trans*-1-hydroxy-9-methyldecalin, mp 59–61 °C (reported[18] mp 56–57 °C).
(16) C. Djerassi and D. Marshall, *J. Am. Chem. Soc.*, **80**, 3986 (1958).
(17) P. S. Wharton and D. S. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961).
(18) S. H. Grover and J. B. Stothers, *Can. J. Chem.*, **52**, 870 (1974).
(19) Obtained as a low-melting solid via (1) reduction of *trans*-10-methyl-Δ^3-2-octalone with aluminum hydride to the β-alcohol, (2) epoxidation[20] with 3-chloroperbenzoic acid in chloroform to give a 2:1 mixture of β and α epoxides, (3) Jones oxidation, (4) chromatography.
(20) Cf. H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957); J. W. Bird and D. G. M. Diaper, *Can. J. Chem.*, **47**, 145 (1969).
(21) This method of making β-hydroxy ketones appears to be quite general (A. A. Ponaras, unpublished observations). For another use of oximes of epoxy ketones in an alkylation sequence closely related to our own work, see E. J. Corey, L. S. Melvin, Jr., and M. F. Haslanger, *Tetrahedron Lett.*, 3117 (1975).
(22) The stereochemistry shown in **18** is based on the presence of two separated singlets for the *gem*-dimethyl group at δ 1.00 and 1.11, corresponding to the equatorial and axial methyls of (essentially) a single chair conformation. In contrast, the *gem*-dimethyls of **16** appear as a six-proton singlet at δ 1.05, representing the average of two conformations of very close energy.
(23) For instance, acid-catalyzed opening of certain epoxyhydrazones in protic media is clearly nonconcerted: inter alia, B. Ellis, S. P. Hall, and S. Waddington-Feather, *J. Chem. Soc.*, 4111 (1961).
(24) Introduction of a phenyl substituent on the α carbon of an α,β-unsaturated ketone can also be achieved via reaction of arylcopper reagents with the tosylhydrazones of α,β-epoxy ketones: P. L. Fuchs, *J. Org. Chem.*, preceding paper in this issue.

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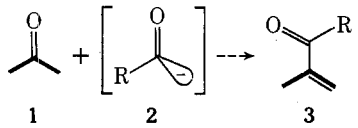
A Synthesis of α,β-Unsaturated Ketones from α,β-Unsaturated Nitriles

Summary: An effective sequence for the synthesis of α,β-unsaturated ketones involves (1) the Horner–Emmons modification of the Wittig reaction to synthesize α,β-unsaturated nitriles, $R_2CH_2(R_1)C{=}C(R_3)CN$, from carbonyl compounds, $R_2CH_2COR_1$, and (2) the oxidative decyanation of the α,β-unsaturated nitriles to afford α,β-unsaturated ketones, $R_2CH{=}C(R_1)COR_3$, by sequential treatment with lithium diisopropylamide, oxygen gas, sodium sulfite, and sodium hydroxide.

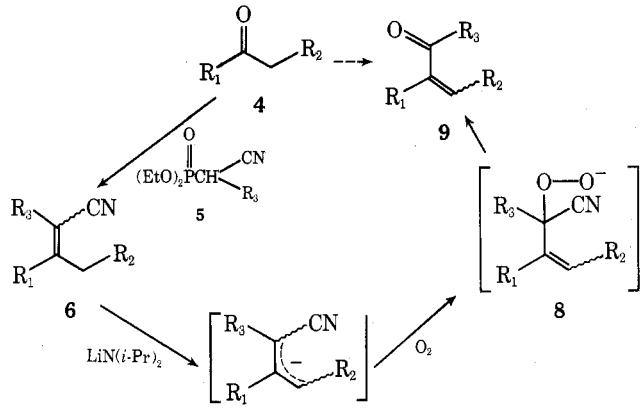
Sir: The condensation–dehydration reaction of a carbonyl compound **1** with an acyl carbanion equivalent **2** would provide an α,β-unsaturated ketone **3** in which the carbonyl carbon



1 2 3

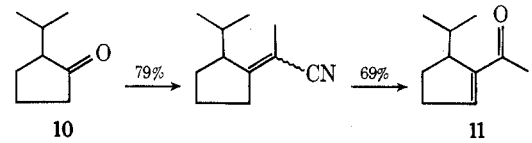
of **1** was incorporated as the α carbon of **3**. We required methodology of this type in order to effect the homologation of 17-keto steroids to 20-keto-Δ^{16} steroids.[1] Unfortunately, the classic Rupe rearrangement[2] of 17β-hydroxy-17α-ethynyl steroids derived from 17-keto steroids fails to effect the desired transformation.[3] We now wish to report that the oxidative decyanation[4] of α,β-unsaturated nitriles provides a convenient synthesis of certain α,β-unsaturated ketones including 20-keto-Δ^{16} steroids. In this case, the nitrile group serves as the masked carbonyl group in the acyl carbanion equivalent.[5]

The Horner–Emmons modification of the Wittig reaction[6] of aldehydes **4** (R_1 = H) and ketones **4** with the anions of substituted diethyl phosphonoacetonitriles **5** furnishes α,β-unsaturated nitriles **6** in excellent yield. The reaction of **6** with lithium diisopropylamide in 20% HMPA–THF[7] results in the



abstraction of a γ hydrogen from a methylene site to afford the delocalized anion **7**. The introduction of dry oxygen gas results in the regioselective trapping of **7** at the α carbon to produce the hydroperoxide **8**. Reduction of **8** with aqueous sodium sulfite and exposure of the cyanohydrin to sodium hydroxide affords the α,β-unsaturated ketone **9** in good yield (Table I).

In exploring the scope of this oxidative decyanation procedure, we have found that the reaction is well suited for the synthesis of α,β-unsaturated ketones but not α,β-unsaturated aldehydes. In addition, the reaction is limited to the synthesis of α,β-unsaturated ketones **9** which possess only one nonhydrogen β substituent.[8] This apparent limitation can be turned to some advantage, however, in the synthesis of α,β-unsaturated ketones **9** derived from unsymmetrical ketones **4**. For example, 2-isopropylcyclopentanone (**10**) furnished **11** which



10 11

is not otherwise readily accessible. In cases where the yields of **9** were disappointing, we found that a fraction of **6** had been diverted to the production of γ-hydroxy-α,β-unsaturated nitriles. Although the regioselectivity of oxygen trapping at the α or γ sites in **7** varies with structure in a way that is not clearly understood, the oxidative decyanation of α,β-unsaturated nitriles **6** provides a viable solution to the synthesis of an array of α,β-unsaturated ketones **9**.[9]

The following is a typical experimental procedure. To 131 mg (1.3 mmol, 1.3 equiv) of diisopropylamine in 2.0 ml of anhydrous THF under a nitrogen atmosphere at −78 °C was added 0.44 ml of 3.00 M *n*-butyllithium in hexane. To the lithium diisopropylamide solution was added 409 mg (1.0 mmol) of the tetrahydropyranyl ether of 3β-hydroxypregna-5,17(20)-diene-20-carbonitrile in 2.5 ml of 40% HMPA–THF. Oxygen gas was bubbled (250 ml/min) into the solution for 30 min. The reaction was quenched with 2 ml of 1 M sodium sulfite solution, stirred for 1 h at 25 °C, diluted with 25 ml of 20% dichloromethane–ether, washed with 25 ml of 1 M sodium hydroxide solution