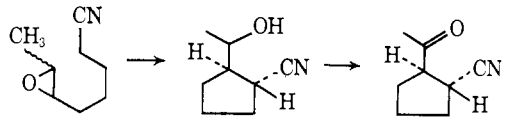
the known[9] methyl ketone XIX (90% yield, 94% pure;



XVII XVIII XIX

nmr $\delta(CDCl_3)$ 2.24 (3 H, s). The stereochemistry follows from the stability of the ketone to potassium *tert*-butoxide in *tert*-butyl alcohol.

It is clear that the oxirane ring imposes on the system a rigidity which makes it difficult to achieve the proper collinear arrangement for displacement at the oxirane carbon further from the nitrile. This point is considered more fully in the accompanying communication[10] which demonstrates that this geometric constraint can be used as the basis of a general method for the synthesis of four-membered rings.[11]

(9) R. Trave, L. Marlini, and L. Garanti, *Chim. Ind. (Milan)*, **40**, 887 (1958); I. N. Nazarov and N. V. Kuznetov, *Izv. Akad. Nauk SSSR*, 354 (1959). This experiment was performed by J. F. Cohen.

(10) G. Stork and J. F. Cohen, *J. Amer. Chem. Soc.*, **96**, 5270 (1974).

(11) We thank the National Science Foundation and the donors of the Petroleum Research Fund administered by the American Chemical Society for the support of this work.

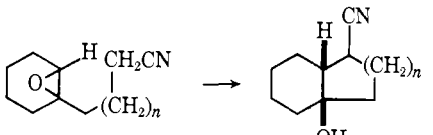
Gilbert Stork,* Lovji D. Cama, D. R. Coulson
Department of Chemistry, Columbia University
New York, New York 10027
Received March 25, 1974

Ring Size in Epoxynitrile Cyclization. A General Synthesis of Functionally Substituted Cyclobutanes. Application to (±)-Grandisol

Sir:

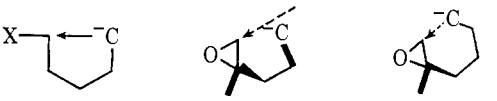
The cyclization of epoxynitriles of type I, which is described in the preceding communication, takes place more rapidly when $n = 2$ than when $n = 1$.[1] The easier formation of a cyclohexane compared to a cyclopentane ring was ascribed to geometric constraints imposed by the oxirane ring.

Examination of models suggests a simple explanation for this result. When the process leading to a five-membered ring involves displacement as illustrated by



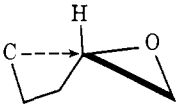
I II

III, there is no particular constraint in locating the carbanion (or indeed any other nucleophile such as oxygen, sulfur, nitrogen, etc.) in the proper position for backside collinear displacement. Reactions of this type generally lead to faster formation of the five- than of the six-membered ring. The situation is very different when the departing group is an epoxide of the type shown in IV. In such a case, the positioning of the carbanion along the dotted line representing collinear approach requires considerable bond distortion.[2] No such distortion is needed for the formation of a six-membered ring, as shown in V.



III IV V

While this analysis implies some difficulty in forming a five-membered ring, the fact that such a ring is formed in the particular case of I → II, $n = 1$, implies that the attendant strain in the transition state is not so great as to lead to alternatives such as intermolecular reaction or four-membered ring formation. On the other hand, the transition state for the formation of a four-membered ring seems to allow easy attainment of collinearity (*cf.* VI). It thus became an intriguing possibility that the



VI

formation of a cyclopentane rather than a cyclobutane ring in the previously studied case of I, $n = 1$, might actually be exceptional and merely reflect the special structural features of I which favor cyclization to a cyclopentane by not requiring displacement at a quaternary center.

We have now found that the epoxynitrile cyclization is unique, in that, *with equal substitution at both ends of the oxirane ring, cyclobutanes always form in preference to cyclopentanes, thus leading to a general, nonphotochemical synthesis of functionally substituted cyclobutanes.*[3] Obviously, this will also be the result when the oxirane carbon further from the nitrile is the more substituted.

Treatment of the cyanoepoxide VII[4] with 1.8 equiv of potassium hexamethyldisalazane in refluxing benzene for 1.25 hr gave (70% yield) the cyanocyclobutyl carbinol VIII, bp (bath) 95–115° (14 mm) (nmr $\delta(CDCl_3)$ 1.10 (3 H, s), 1.18 (3 H, s), 2.7 (O*H*)).[5] In further confirmation of the tertiary alcohol structure, VIII was completely recovered from attempted Jones

VII VIII

oxidation.

The stereochemistry shown in VIII follows from the much more informative case of the steric course of the cyclization of X, in which epimerization subsequent to cyclization is not possible. The nitrile IX, obtained from the corresponding secondary alcohol[6] (*via* displacement of the tosylate with sodium cyanide in dimethylformamide at 65°), was epoxidized to X which

(1) G. Stork, L. D. Cama, and D. R. Coulson, *J. Amer. Chem. Soc.*, **96**, 5268 (1974).

(2) *Cf.* L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970).

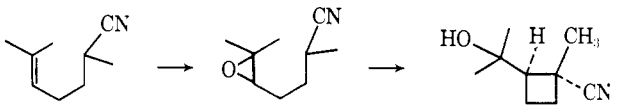
(3) For other nonphotochemical routes to cyclobutanes, see B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **95**, 5321 (1973), and references cited therein.

(4) The corresponding olefin was made by Wittig reaction. *Cf.* also C. Agami, M. Andrac-Taussig, and C. Prévost, *Bull. Soc. Chim. Fr.*, 173 (1966).

(5) This substance gave ir, nmr, and high resolution mass spectra in accord with the postulated structure. Reference is made in the text only to some of the more interesting spectral features.

(6) E. Cortes and F. Walls, *Boll. Inst. Quim. Univ. Nacl. Auton. Mex.*, **17**, 34 (1965).

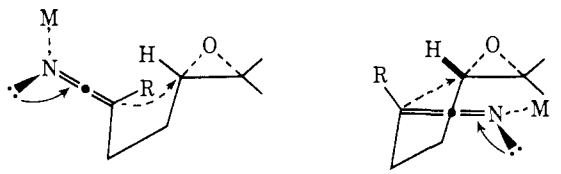
was then cyclized with 2.5 equiv of sodium hexamethyldisilazane in refluxing benzene to give, after 1 hr, a 58% yield of XI as a single isomer, bp 70–72° (0.08 mm), mp 40–40.5° (nmr $\delta(CDCl_3)$ 1.11 (3 H, s), 1.32 (3 H, s), 1.61 (3 H, s)).[5] The stereochemistry is established by the demonstration that the corresponding acid, mp 99.5–100°[5] (8 hr of heating with 30% aqueous potassium hydroxide), was entirely unchanged under a variety of conditions designed to produce the corresponding lactone. In particular, the acid was converted to an acetate mixed anhydride with acetic anhydride (120°, overnight). The aldehyde derived from XI



IX X XI

(diisobutylaluminum hydride) not only did not exist as a hemiacetal, it did not show any nuclear Overhauser enhancement of the aldehyde proton on irradiation of the tertiary alcohol methyls.

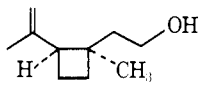
This stereospecificity is important not merely because it greatly enhances the value of the new cyclobutane synthesis but because it is not what would be expected if the transition state resembled the product, since a cyano group is smaller than a methyl. It allows us to refine our picture of the transition state to that shown in XII.



XII XIIA

It is clear that the effective steric hindrance of the cyano anion is in fact larger than that of a normal alkyl group as a consequence of the allenic structure of the metal salt.

In the two epoxides VII and X, the formation of a cyclobutane is favored since it involves displacement at the less substituted end of the epoxide. As was mentioned earlier, cyclobutanes still result when both ends of the epoxide are equally substituted. We illustrate this with a synthesis of (±)-grandisol (XIII), one of the

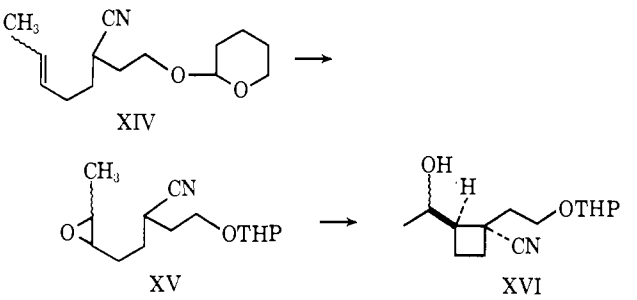


XIII

four components of the sex attractant released by the male boll weevil.[7,8]

Alkylation of 5-heptenenitrile[9] (lithium diisopropylamide in tetrahydrofuran containing 1.3 equiv of hexamethylphosphoramide) with 1 equiv of the tetrahydropyranyl ether of 2-bromoethanol gave (room temperature, overnight) XIV, bp 114–119 (0.05 mm), in *ca.* 50% yield. Epoxidation (*m*-chloroperbenzoic acid–methylene chloride, room temperature, overnight) gave the epoxide XV in 95% yield after chromatography on silica gel; nmr ($CDCl_3$) δ 1.28 (d, J = 5 Hz, CH_3).

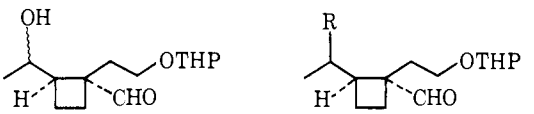
The most favorable stereochemical results were obtained when the cyclization of XV was carried out with lithium hexamethyldisilazane (4 equiv, benzene, 0°, 3.5 hr). The ratio of the desired cyclobutane XVI to



XIV XV XVI

its epimer (cyano cis to methylcarbinol) was ~95:5. The formation of the less stable isomer with the two larger groups cis to each other emphasizes again the lower energy of the transition state XII. The particular effectiveness of the *lithium* salt is presumably the result of magnifying interactions in a tight transition state.

Reduction of the cyano group (diisobutylaluminum hydride) then gave hydroxy aldehyde XVII[5] (52% from the epoxide XV) which was transformed to the methylcyclobutane XVIII[5] upon Wolff–Kishner reduction. It is obvious from the fact that the hydroxy aldehyde(s) XVII exists almost entirely as such, rather than as hemiacetal, that the stereochemistry corresponds largely to that shown in XVII. Oxidation of XVIII (Jones) led to the corresponding methyl ketone XIX[5] (60% from



XVII

XVIII, R = H, OH
XIX, R = O
XX, R = CH_2

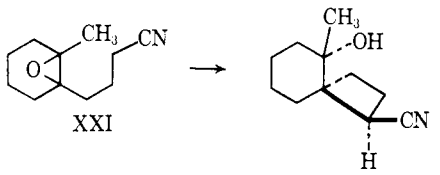
after silica gel chromatography) in which the ring methyls due to XIX and to its epimer (~95:5) can be easily distinguished by their singlet absorptions at δ 1.33 and 1.02, respectively. Conversion to the required isopropenyl group by Wittig reaction (butyl lithium as base, in tetrahydrofuran) gave the tetrahydropyranyl ether of XIII (77% after silica gel chromatography, ratio of the methyl groups at δ 1.19 and 0.93 = ~94:6) which, after considerable experimentation to define conditions which would not disturb the isopropenyl group, was converted (0.05 *N* aqueous perchloric acid–tetrahydrofuran 1:1, 3 days, room temperature) into (±)-grandisol (XIII),[5] isolated in 75% yield by preparative thin layer chromatography. The infrared, nmr and mass spectra corresponded to published values.[8] The ratio of the methyl absorptions at δ 1.17 and 0.92, due to grandisol and epigrandisol, respectively, was ~95:5. This ratio, as well as the identity of the material, was confirmed by careful gas chromatography.[10]

(7) J. H. Tumlinson, D. D. Hardee, R. C. Gueldner, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *Science*, **66**, 1010 (1969).

(8) For earlier syntheses, *cf.* J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin and J. P. Minyard, *J. Org. Chem.*, **36**, 2616 (1971); R. C. Gueldner, A. C. Thompson, and P. A. Hedin, *ibid.*, 37, 1854 (1972); R. Zurflüh, L. L. Dunham, V. L. Spain, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 425 (1970). A very elegant, nonphotochemical synthesis of grandisol which is, however, not readily adaptable to the synthesis of certain analogs, has recently been published by W. E. Billups, J. H. Cross, and C. V. Smith, *J. Amer. Chem. Soc.*, **95**, 3438 (1973).

(9) Made by the Wittig reaction of 5-bromovaleronitrile with acetaldehyde. See also N. A. LeBel, M. E. Post, and J. J. Wang, *J. Amer. Chem. Soc.*, **86**, 3759 (1964).

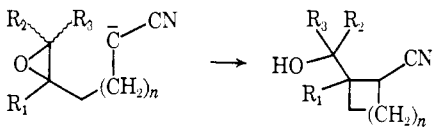
The high nucleophilicity of the nitrile anion permits ring formation even at a quaternary center. The epoxynitrile XXI undergoes cyclization after stirring overnight with potassium amide in liquid NH_3–glyme to give, in ~80% yield, the spirocyclononane XXII, bp 140° (bath,



XXI XXII

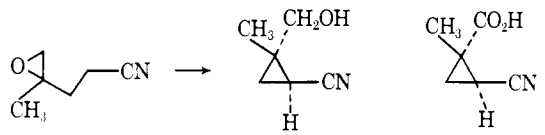
1 mm) (nmr $\delta(CCl_4)$ 1.05 (3 H, s), 2.9 (1 H, s), 3.4 (1 H, t)). The absorption of the hydrogen α to the nitrile is compatible with a cyanocyclobutane. The amide (mp 122.5–123.5°), also showed a 1 H triplet at δ 3.25 and so did the derived acid (nitric oxide on amide), mp 148.5–150°, obtained in 50% yield from the nitrile. The structure was further confirmed by dehydration of XXII with thionyl chloride–pyridine which gave the expected mixture of methylenecyclohexane and methylcyclohexene.[11]

The study of a number of other cases in this laboratory allows the conclusion that the epoxynitrile cyclization always yields the smaller ring, when both ends of the epoxide are equally substituted. This is true whether the smaller ring formed is three-, four-, five-, or six-membered.



$R_1, R_2 = H; R_3 = alkyl$ $n = 0, 1, 2, 3$
$R_1 = H; R_2, R_3 = alkyl$
$R_1, R_2, R_3 = alkyl$

In the special case of $n = 0$, the rate of cyclopropane formation is such that this ring is produced in preference to a cyclobutane, *regardless* of the relative degree of substitution of the oxirane ring. Thus, cyclization of the epoxynitrile XVII (potassium amide, liquid ammonia–glyme) gave the cyanocyclopropane XVIII, oxidized with Jones reagent to the acid XIX, mp 115–116°



XVII XVIII XIX

(nmr $\delta(CDCl_3)$ 1.54 (3 H, s), 1.26 (1 H, t, J ~5.3 Hz), 1.6–2.4 (2 H, m)).[5,12]

(10) We thank Zoëcon Corp., Palo Alto, Calif., for this gas chromatography comparison.

(11) Preliminary experiments on this cyclization were carried out at Columbia by D. R. Coulson, and a more thorough investigation was made by Lovji D. Cama. The cyclized nitrile XXII and the derived amide and acid gave satisfactory carbon and hydrogen analyses and spectral data.

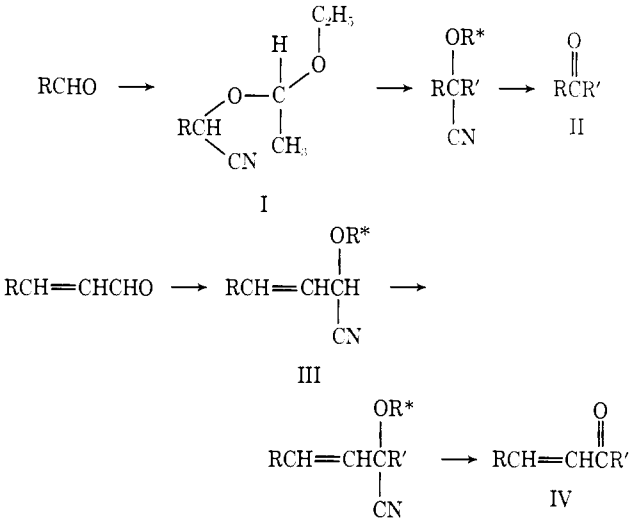
(12) This work was supported by the National Science Foundation and the National Institutes of Health.

Gilbert Stork,* Jonathan F. Cohen
Department of Chemistry, Columbia University
New York, New York 10027
Received March 25, 1974

Conjugate Addition of Acyl Carbanion Equivalents *via* the Protected Cyanohydrin Method

Sir:

The conjugate addition of acyl carbanion equivalents is a potentially important reaction. We now report that some of the protected cyanohydrins which we have employed as masked acyl carbanions in the synthesis of ketones[1] (I → II; III → IV) often readily undergo con-



I II III IV

jugate addition to enone systems. This is especially important as the widely used dithiane anions[2] generally undergo only 1,2-addition.[3]

We have examined the reaction of protected cyanohydrin anions with cyclohexenone, cyclopentenone, and benzalacetophenone. In all cases the additions were performed by addition at −78° of 1 equiv of the enone in dry tetrahydrofuran to a solution of the lithium salt of the protected cyanohydrin, prepared exactly as described previously.[1] After 5–10 min the solution was warmed to 0°, quenched with water, and extracted with ether and the product was purified by chromatography or alumina or Florisil. Under these conditions, the cyanohydrins derived from saturated aldehydes, *e.g.*, I, R = CH_3, gave considerable quantities of 1,2-adduct, in addition to the desired 1,4-product (V:VI = 60:40).[4]

This initial result was very encouraging and raised the question why the anions derived from protected

(1) G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971). In the formulas the symbol R* denotes the α-ethoxyethyl protecting group (*cf.* I).

(2) For an excellent review, see D. Seebach, *Synthesis*, 1, 17 (1969). Some more recent work has demonstrated the possibility of carrying out conjugate additions with copper reagents derived from phenyl thioacetals (T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Amer. Chem. Soc.*, **94**, 8641 (1972)), although additions to cyclic enones have not yet been reported with these reagents. Another very promising route to conjugate addition of acyl carbanion equivalents involves the anions of thioacetal monosulfoxides (J. E. Richman, J. L. Herrmann, and R. H. Schlessinger, *Tetrahedron Lett.*, 3271 (1973)).

(3) An intramolecular 1,4-addition of the protected cyanohydrin of an *aromatic* aldehyde has been reported in a case in which 1,2-addition could not compete (E. Aufderhaar, J. E. Baldwin, D. H. R. Barton, D. J. Faulkner, and M. Slaytor, *J. Chem. Soc.*, 2175 (1971)). See also G. Stork and R. Schultz, *J. Amer. Chem. Soc.*, **93**, 4074 (1971), for the 1,4-addition of the anion of a protected α-hydroxy ester to an unsaturated lactam. Stetter, *et al.* (H. Stetter and M. Schreckenberg, *Angew. Chem.* **85**, 89 (1973); *Tetrahedron Lett.*, 1461 (1973); *Chem. Ber.*, **107**, 210 (1974)), apparently unaware of previous work with anions derived from protected cyanohydrins (*vide supra* and ref 1), also report on the use of *aromatic* cyanohydrins in conjugate additions.

(4) Spectral data (ir, nmr) clearly established the proposed structure.