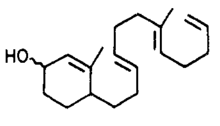

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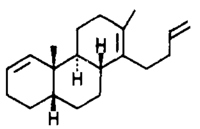

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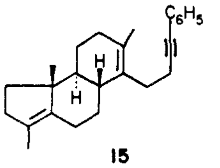

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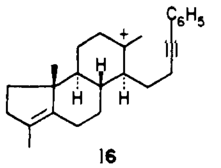

16

(C/D trans) isomers.[12] To test whether an intermediary tricyclic hydrocarbon, namely **15**, was similarly involved in the formation of the 13α (C/D cis) isomers produced in the cyclization of the substrate **1**, the substance **2**, with a deuterium label at *pro* C-14, was prepared.[13] The tetracyclic products **3** and **5** from the cyclization of the substrate **2** were separated and analyzed by mass spectrometry which showed that both isomers had retained >97% of their deuterium label. This result precludes the possibility of the intermediacy of **15** in the formation of the 13α (C/D cis) isomer.

In attempting to rationalize the fact that the phenylacetylenic terminator favors formation of 13α (C/D cis) isomers relative to the styryl terminator, we have entertained the possibility that the lower steric requirement of the former facilitates axial approach to the tricyclic cation **16**. A difference in the angle of attack on the sp^1 vs. the sp^2 carbon by the cationic center may also be a factor.[14]

Conclusions. In polyene cyclization of the type under consideration here, we feel that high stereoselectivity to form 13β (C/D trans) products having natural configuration will be realized with olefinic terminators, provided that these bonds are sufficiently nucleophilic to react with the incipient cationic center of the tricyclic species (cf. formula **16**) faster than deprotonation occurs to form a tricyclic olefin (which, as shown above in the case of **14**, leads to 13α isomers by a reprotonation mechanism).[15] In addition to the styryl group, a number of other olefinic terminators appear to give highly stereoselective cyclizations and we plan to report on these subsequently.

Acknowledgement. We thank the National Institutes of Health and the National Science Foundation for support of this research.

References and Notes

(1) For recent papers in this series, see (a) W. S. Johnson, L. R. Hughes, J. A. Kloek, T. Niem, and A. Shenvi, *J. Am. Chem. Soc.*, preceding paper in this issue; (b) W. S. Johnson, R. S. Brinkmeyer, V. M. Kapoor, and T. M. Yarnell, *ibid.*, **99**, 8341 (1977).

(2) In work to be described later, substrates 1 with a *p*-methoxyl and with a *p*-fluoro substituent in the phenyl group have been synthesized. These on cyclization gave tetracyclic products with isomer distributions almost identical with those found for the unsubstituted case.

(3) (a) W. S. Johnson and L. A. Bunes, *J. Am. Chem. Soc.*, **98**, 5597 (1976); (b) W. S. Johnson, *Bioorg. Chem.*, **5**, 72 (1976).

(4) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Am. Chem. Soc.*, **93**, 4332 (1971).

(5) Modification of a previously reported procedure (W. S. Johnson and G. E. DuBois, *J. Am. Chem. Soc.*, **98**, 1038 (1976), note 12) was employed. Thus, after the addition of the anhydrous ether, the solution was warmed slowly to 0 °C and stirred at this temperature for 3 h. Finally the mixture was quenched with excess methanol prior to isolation of the product.

(6) This substance was purified by column chromatography on Florisil.

(7) This substance was evaporatively distilled using a Büchi Kugelrohrofen at a temperature ranging from 200 to 210 °C at pressures in the range 0.02–0.1 mmHg.

(8) The NMR and IR spectra were consistent with the assigned structure; a satisfactory combustion analysis was obtained for this specimen.

(9) Cf. A. J. Fatiadi, *Synthesis*, 65 (1976).

(10) To ensure that the ratio of 13β (C/D trans) to 13α (C/D cis) isomers shown by analyzing the ketonic mixture was an accurate representation of the proportions in the initial cyclized product, the following control experiments were performed. Each of the pure phenyl ketones **3**, **4**, **5**, and **6** was reduced with lithium aluminum hydride to give the corresponding alcohols. These alcohols were then individually oxidized with activated manganese dioxide[9] in hexane to regenerate the starting ketones in virtually quantitative yield.

(11) Indeed the process may be 100% stereoselective as the small amount of 13α product may have arisen from an isomeric contaminant in the cyclization substrate **7** having the *Z* configuration of the trisubstituted olefinic bond.

(12) K. E. Harding, E. J. Leopold, A. M. Hudrlik, and W. S. Johnson, *J. Am. Chem. Soc.*, **96**, 2540 (1974).

(13) The allylic alcohol $CH_2{=}C(CH_3)CH(OH)(CH_2)_2C{\equiv}CC_6H_5$, which is an intermediate in the preparation of **10** (see ref 1a), was oxidized with Jones reagent and the resulting α,β-unsaturated ketone was then reduced with lithium aluminum deuteride. The product was converted (via the orthoacetate Claisen reaction) into deuterio-**10** which was then employed in a sequence analogous to that shown in Scheme I.

(14) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).

(15) Examples of inadequately nucleophilic sp^2 terminators that lead to cis-fused products are the terminal vinyl group (as in **13**) and probably the chlorovinyl group. The latter was involved in a cyclization (to form one new ring) which yielded trans- to cis-fused products in a ratio of 3:2 as shown by P. T. Lansbury, T. R. Demmin, G. E. DuBois, and V. R. Haddon, *J. Am. Chem. Soc.*, **97**, 394 (1975).

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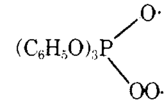
Epoxidation of Olefins with Carbonyl Oxides

Sir:

We report that carbonyl oxides, e.g., **1**, produced via singlet oxygen oxidation of diazo compounds, can epoxidize olefins. The oxidation of the diazo compound can be carried out by both photosensitized and triphenyl phosphite ozonide methods.

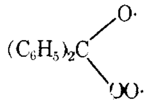
$(C_6H_5)_2\dot{C}OO\cdot$

1



$(C_6H_5O)_3P(O\cdot)(OO\cdot)$

2



$(C_6H_5)_2C(O\cdot)(OO\cdot)$

3

This method of producing carbonyl oxides and studying their reactions with olefins avoids many of the complicating factors of olefin ozonolysis, including the strong competition of aldehydes for carbonyl oxides. These results confirm the earlier suggestion of Kwart and Hoffman[1] that carbonyl oxides obtained under nonozonolysis conditions will act as epoxidizing agents.

Hamilton has suggested[2] that certain reactions catalyzed by the monooxygenase enzymes (MOX) occur via an oxygen atom transfer mechanism which he termed an oxenoid mechanism. Hamilton and co-workers subsequently showed[3] that carbonyl oxides, produced by oxidizing 9-diazofluorene and diphenyldiazomethane, serve as models for MOX in that they are capable of oxidizing hydrocarbons to alcohols and carbonyl compounds. In addition, there have now been several reports[1,4-11] of olefin epoxidation with carbonyl oxides. In all of these cases, the carbonyl oxides were produced under ozonolysis conditions. Wasserman and Miller[12] have invoked epoxidation via a carbonyl oxide in order to explain an epoxide product in the photosensitized oxygenation of a pyrrole. Use of the nonozonolysis source of carbonyl oxides has permitted us to show that such epoxidations are a general reaction. This observation and our earlier report[13] that carbonyl oxides, similarly produced, can oxidize an aromatic hydrocarbon add further support to the suggestion of Hamilton[3-5] that these intermediates serve as useful chemical models for the MOX.

The suggestion that photooxidation of diazo compounds could produce carbonyl oxides was first made by Kirmse et al.[14] The possibility was subsequently confirmed by Bartlett and Traylor[15] and Hamilton and Giacin.[3] We earlier had shown[16,17] that carbonyl oxides so produced can be trapped

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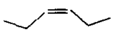
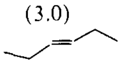
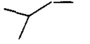
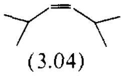
Table I. Results of Olefin Epoxidations

olefin (mmol)	reaction conditions	olefin consumed, mmol	epoxide yield, %	epoxide stereochemistry (cis/trans)
				
(2.91)	A[a]	0.28	10.4	84/16
(3.12)	B[b]	0.38	5.9	88/12
(3.01)	C[c]	1.36	3.2	55/45
(3.0)	D[d]	1.12	0.9	18/82
(3.0)	E[e]		0	
(3.0)	F[f]		0	
				
(3.0)[g]	A[a]	0.19	2.6	0/100
(3.0)[g]	C[c]	0.65	7.8	12/88
				
(2.51)	A	0.17	24	0/100
(2.51)	B	0.23	12.8	0/100
(3.0)	C	0.73	4.2	0/100
(3.0)	D	0.6	2.2	0/100
(3.0)	E		0	
(2.51)	F	0.24	3.4	0/100
(3.0)	G[h]		0	
				
(3.04)	A	0.15	26.7	96/4
(3.04)	B	0.10	15	93/7
(3.04)	C	0.54	4.3	69/31
(3.05)	D	0.25	1.2	54/46
(2.98)	F	0.24	4.2	75/25

[a] Reaction was performed by adding a CH_2Cl_2 solution of olefin and diphenyldiazomethane at −90 °C to a solution of triphenyl phosphite ozonide at −96 °C and then allowing the mixture to warm up to room temperature. [b] Reaction was performed by adding a cold (−50 °C) solution of triphenyl phosphite ozonide to a 0 °C CH_2Cl_2 solution of olefin and diphenyldiazomethane. [c] Reaction was performed by photooxidizing diphenyldiazomethane in CH_2Cl_2 solution in the presence of the olefin and using Ⓟ-Rose Bengal as sensitizer. [d] Photolysis control reaction using benzophenone and no diazo compound. [e] Photolysis control reaction using only light, oxygen, and sensitizer. [f] Phosphite ozonide control reaction was conducted the same as A except no diazo compound was present. [g] Starting olefin gives a cis/trans epoxide ratio of 3.4/96.6 when treated with *m*-chloroperbenzoic acid. [h] Phosphite ozonide control reaction was the same as B except no diazo compound was present.

by aldehydes to give ozonides, and that the efficiency of carbonyl oxide production can be greatly improved by using singlet oxygen to oxidize the diazo compounds.[18]

In a typical epoxidation experiment diphenyldiazomethane (1.17 g, 6 mmol) was photooxidized[19] in the presence of *cis*-3-hexene (252 mg, 3 mmol) in methylene chloride solution using Ⓟ-Rose Bengal[21] (50 mg) as sensitizer. The diazo compound was added to the photolysis vessel in six aliquots with each aliquot added only after the red color of the preceding addition had disappeared.[22] After the sensitizer beads were filtered off, the volatile material was pumped into a liquid nitrogen trap and analyzed by GLC. The results of this and similar experiments are shown in Table I.

The oxidations were also accomplished using triphenyl phosphite ozonide as a source of singlet oxygen.[23] These experiments were carried out in two different sets. In one set the diazo compound was added to a cold (−70 °C) solution of the triphenyl phosphite ozonide (direct addition). In the second set (reverse addition) the cooled (−50 °C) ozonide solution was added to a solution of the diazo compound maintained at 0 °C. The results of these experiments are also shown in Table I.

The epoxidation via the carbonyl oxide is partially stereospecific; trans olefins give trans epoxides while cis olefins give mainly cis epoxides. This stereochemistry is the same as that observed by Hamilton and Keay[4,5] when the carbonyl oxide used was derived from alkyne ozonization.

Since benzophenone is a product of the diazo compound oxidations and some of our reactions were run under photolysis conditions, it became necessary to run additional control reactions. Shimizu and Bartlett[24] have shown that olefins can be epoxidized by intermediates produced from excited carbonyl compounds (including benzophenone) and oxygen. When photochemical reactions, using only benzophenone,[25] are run on some of the olefins used in this study, then small amounts of epoxide are formed.

That such reactions are not responsible for the major portion of epoxide formed in the diazo compound oxidation reactions can be seen from examining the data in Table I. In addition to the fact that the control reactions using only benzophenone give much lower epoxide yields, the stereochemistry of the epoxidation is different. Thus, for example, *cis*-3-hexene gives an 84/16 (cis/trans) epoxide ratio when epoxide is produced using phosphite ozonide and diazo compound, but gives a ratio of 18/82 when benzophenone alone and photolysis conditions are used.

The epoxide cis/trans ratio obtained (55/45) from *cis*-3-hexene when singlet oxygen is produced photochemically is different from that obtained (84/16) using phosphite ozonide.[26] A contribution from the benzophenone-mediated epoxidation would be expected to alter the cis/trans epoxide ratio in favor of trans epoxide, but the expected extent of this reaction (Table I) indicates that it cannot be solely responsible for the observed ratio. Recent theoretical calculations[27,28] indicate that the carbonyl oxide should exist as a planar singlet diradical, **1**, in its lowest energy state. The calculations also indicate the availability of several other low-lying states. We have shown that use of the phosphite ozonide oxidation method *plus irradiation* alters the epoxide cis/trans ratio toward that obtained in the photosensitization experiments. These results could indicate that more than one state of the carbonyl oxide is involved in the epoxidation reaction under some conditions. The possible intervention of several states of the carbonyl oxide, which states lead to different chemical outcomes, has a potentially dramatic implication for reactions involving carbonyl oxides, including the ozonolysis reaction. We are presently investigating such possibilities.

We have also obtained some data which indicate that triphenyl phosphite ozonide itself may act as an epoxidizing reagent. In the case of *trans*-2,5-dimethyl-3-hexene a small amount of epoxide is obtained in the absence of diazo compound.[29] Hamilton and Keay[5] have reported a similar result when cyclohexene is treated with the triphenyl phosphite ozonide. These latter reactions could be occurring via an intermediate, **2**, which is somewhat analogous to that (**3**) which Shimizu and Bartlett have suggested for the benzophenone-oxygen epoxidation reactions.

At this time it is not clear why epoxidations occurring with the carbonyl oxide are more stereospecific than those apparently occurring via **1** or **2**.

It should also be noted that stereospecific production of epoxides which has been observed to accompany some ozonolysis reactions may be due to reactions of carbonyl oxides with olefins and not to reactions of ozone with the olefin as previously suggested.[17]

Acknowledgment. We are grateful to the National Science Foundation for support of this work.

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(2) G. A. Hamilton, *J. Am. Chem. Soc.*, **86**, 3391 (1964).
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(4) R. E. Keay and G. A. Hamilton, *J. Am. Chem. Soc.*, **97**, 6876 (1975).

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(17) R. W. Murray and A. Suzui, *J. Am. Chem. Soc.*, **95**, 3343 (1973).
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(19) The photooxidation apparatus used was similar to that described in the literature.[20] A General Electric DWY 650-W lamp was used without filter. Epoxide products were identified by comparing their properties with those of authentic materials obtained by treating the olefins with *m*-chloroperbenzoic acid.
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(21) E. C. Blossey, D. C. Neckers, A. L. Thayer, and A. P. Schaap, *J. Am. Chem. Soc.*, **95**, 5820 (1973).
(22) This method minimizes reactions of the diphenyldiazomethane giving azine.
(23) R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **91**, 5358 (1969).
(24) N. Shimizu and P. D. Bartlett, *J. Am. Chem. Soc.*, **98**, 4193 (1976).
(25) The amount of benzophenone used in these controls was equal to 50% of the maximum possible from the diazo compound.
(26) Control reactions have shown that neither olefin nor epoxide is isomerized under any of the reaction conditions. Also no epoxide is formed when only sensitizer, oxygen, and olefin are used. The epoxide cis/trans ratio was also found to be independent of temperature within experimental error.
(27) W. R. Wadt and W. A. Goddard, *J. Am. Chem. Soc.*, **97**, 3004 (1975).
(28) P. C. Hiberty, *J. Am. Chem. Soc.*, **98**, 6088 (1976).
(29) The yield[30] obtained (3.4%) under these conditions is considerably less than that obtained (24%) when diazo compound is present. Also *cis*-3-hexene gave no epoxide in a similar control reaction with phosphite ozonide.
(30) Epoxide yields are based on olefin consumed. These reactions are also accompanied by the competing singlet oxygen ene reaction. We have shown that allylic hydroperoxide cannot epoxidize olefins under our reaction conditions. The higher yields obtained in the phosphite ozonide direct addition cases probably indicates that a bimolecular reaction between the ozonide and diazo compound occurs to give the carbonyl oxide. To the extent that this is true there is less opportunity for the competing ene reaction to occur.

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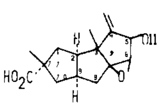
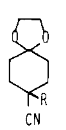
A Stereocontrolled Total Synthesis of (±)-Hirsutic Acid C

Sir:

We report the first fully stereocontrolled synthesis of (±)-hirsutic acid C (**1**), a representative of a novel tricyclic sesquiterpene class whose members possess antibiotic and antitumor activity.[1,2] The key structural problem is the creation of four of the seven chiral centers (C(2), C(3), C(9), and C(11)) since it has been shown these four centers allow ultimate control of the remaining three.[2a] Using a rigid bridged bicyclic template, these four centers are introduced with the correct relative stereochemistry and then the polycycle is unraveled to reveal the skeleton of hirsutic acid. Two intramolecular Michael reactions create the key polycycle **13**. Adaptability of this route toward a chiral synthesis is also illustrated.

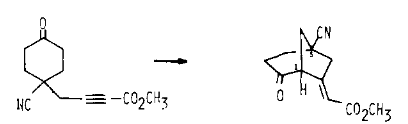


1



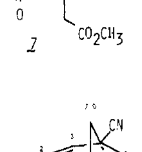
2, R = H
3, R = $CH_2C{\equiv}CH$
4, R = $CH_2C{\equiv}CCO_2CH_3$

4-Cyanocyclohexanone ketal (**2**) is smoothly alkylated with 1-trimethylsilylpropargyl bromide ($LiN(C_3H_7\text{-}i)_2$, THF, −30 °C) to give after desilylation (KOH, CH_3OH) crystalline cyano ketal **3**,[3] mp 75–76 °C, in 88% yield. Conversion of **3** to the acetylide ion (LDA, TMEDA, THF, −78 °C) must be done with careful maintenance of the low temperature to avoid elimination of cyanide. The acetylide is smoothly carboxylated (CO_2 and then CH_2N_2) to give **4**[3] and the ketal hydrolyzed (PhH, 2.5% aqueous HCl, H_2O, reflux, 6 h) to give cyclohexanone **5**,[3,4] mp 99–101 °C, in 88% yield. While use of acetylenes as Michael acceptors has been rather restricted, they are in fact excellent substrates.[5] Thus, subjection of **5** to triethylamine (4–8 equiv) in refluxing toluene for 12 h gives keto enoate **6**,[3,4] mp 115–116 °C, in 65–70% yield. The stereochemistry of the double bond is proposed as *E* on the basis of the proton at C(1) appearing at δ 3.46, whereas in the very minor *Z* isomer (<5%) this proton appears at δ 4.39—the difference reflecting the additional deshielding by the ester carbonyl group. This reaction establishes the stereochemistry of C(2) and C(11) of hirsutic acid C since C(1) and C(5) of **6** become these carbons in **1**. Hydrogenation (5% Pd/$BaCO_3$, 1 atm, C_2H_5OH-C_2H_5OAc, 80%) of enoate **6** from the exo face establishes the stereochemistry of C(7) in the saturated keto ester **7**,[3] mp 90–92 °C, as shown; this stereochemistry translates into C(9) of hirsutic acid C. Subjecting the keto ester **7** to the Reformatsky reaction ($BrZnCH_2CO_2C_2H_5$, PhH-ether, reflux, 15 min) confirms the stereochemistry of **7** since only the lactone **8**[3] is observed. Subjection of lactone **8** to 0.5 M methanolic sodium methoxide at room temperature for 3 h effects ring opening and transesterification to give acid **9**,[3,4,6] mp 141–146 °C, in 77% overall yield from **7** in which the chemical differentiation of the three functional groups is maintained. Selective reduction of the acid (BH_3-THF, 0 °C, 75%) and acetylation (Ac_2O, pyridine, RT, 89%) generates acetate **10**[3] which is subjected to bromination (NBS, CCl_4, reflux, 30 min), dehydrobromination (LiBr, Li_2CO_3, DMF, 130 °C, 20 min) and hydrolysis (K_2CO_3, CH_3OH, 0 °C, 2 h) without isolating any intermediates to give the dienoate **11**[3,4,6] in 79% yield from enoate **10**. Oxidation of the alcohol **11** to the aldehyde **12**[3] ($C_5H_5N^+HCrO_3Cl^-$, CH_2Cl_2, RT, 60–80%) sets the system up for the second critical Michael reaction.



5 6

In situ formation of an acyl anion equivalent for an intramolecular Michael reaction was achieved with 2.3 equiv of 3,4-dimethyl-5-(2′-hydroxyethyl)thiazolium iodide[7] and 50 equiv of triethylamine in refluxing 2-propanol for 5 h to give directly the critical tricyclic ketone **13**,[3,4] mp 118–119 °C, in 67% yield. At this point, the four centers (C(2), C(3), C(9), and C(11)) of hirsutic acid which correspond to C(9), C(1), C(6), and C(4), respectively, of ketone **13** have been established with correct relative stereochemistry. With the problem of stereochemistry solved, the polycycle must now be unfolded to reveal the hirsutic acid system.



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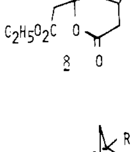

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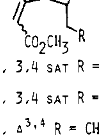
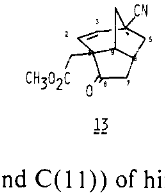
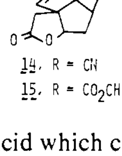


9, 3,4 SAT R = CO_2H
10, 3,4 SAT R = CH_2OAc
11, $\Delta^{3,4}$ R = CH_2OH
12, $\Delta^{3,4}$ R = CHO



13



14, R = CN
15, R = CO_2CH_3

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