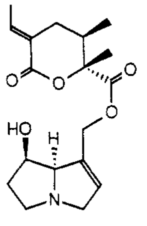

31

Finally, the silyl ether **30** was unmasked with hydrogen fluoride,[13] affording integerrimine which was identical by comparison of chromatographic behavior, spectral properties, and optical rotation[14] with the natural alkaloid.

Acknowledgment. We are indebted to Dr. C. C. J. Culvenor for a sample of natural integerrimine and to Dr. Koichi Narasaka, University of Tokyo, for IR and NMR spectra of **19**. Financial support was provided by the National Institute for Environmental Health Science (ES03334). Funds for the purchase of a Bruker AM 400 NMR spectrometer were provided by the National Science Foundation and the M. J. Murdock Charitable Trust.

Supplementary Material Available: Experimental details of **1**, **6**, **7**, **9**, **10**, **12–28**, and **30** (6 pages). Ordering information is given on any current masthead page.

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[13] Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

[14] Integerrimine has $[\alpha]_D$ −18.3° (c 0.12, $CHCl_3$) and $[\alpha]_D$ +2.7° (c 1.1, MeOH).

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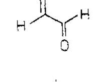
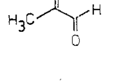
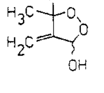
Diastereoselective Ene Reaction in the Photooxygenation of the Silyl Cyanohydrins of α,β-Unsaturated Aldehydes: Necessity for a Common Symmetrical Intermediate of the Perepoxide Type

Summary: The reaction of α,β-unsaturated aldehydes and their silyl cyanohydrin derivatives with singlet oxygen was studied. The latter showed a completely different pattern of reactivity and diastereoselectivity.

Sir: The present results (cf. Scheme I) on the photooxygenation of senecialdehyde (**1**) and tiglaldehyde (**2**) and their silyl cyanohydrins **1a,b** and **2a,b**, respectively, show that (i) while aldehyde **1** is inert toward $^1O_2$ even on prolonged exposure, aldehyde **2** affords exclusively the hydroxydioxolane **3**, the cyclic tautomer of the intermediary







allylic hydroperoxide [However, their silyl cyanohydrins **1a,b** and **2a,b**, respectively, react readily with singlet oxygen to give the ene-type products **4a,b** and **5a,b** from **1a,b** and **6a,b** and **7a,b** from **2a,b**], (ii) the regioselectivity is moderate (ca. 1:2) to low (ca. 1.3:1) for the conversions of **1a,b** into **4a,b** and **5a,b** and of **2a,b** into **6a,b** and **7a,b**, respectively [but for tiglaldehyde (**2**) the ene reaction takes place exclusively at the methyl group proximate to the carbonyl functionality[2]], and most importantly (iii) each regioisomer for a particular cyanohydrin is formed in the same diastereomeric ratio (dr), which is moderate (dr ~ 74:26) for **2a,b** and very high (dr > 96:4) for **1a,b**, i.e., E/Z ratios of **4a,b** are within experimental error equal to the threo/erythro ratios of **5a,b**.

A common symmetrical intermediate is essential in the formation of each of the pairs of regioisomers to account for these identical diastereoselectivities. We propose the perepoxide-like structures A and B as intermediates in the reaction of singlet oxygen with the silyl cyanohydrins **1a,b** and **2a,b**, respectively.

The required silyl cyanohydrins **1a,b** and **2a,b** were prepared from the aldehydes **1** and **2**, respectively, by treatment with the corresponding silyl chlorides (R = Me, t-Bu), KCN, and ZnI_2 in acetonitrile.[3] In the photooxygenations 0.2 M solutions of **1a,b** or **2a,b** in CCl_4 were irradiated externally with a 150-W sodium street lamp (Philips) at 0 °C and tetraphenylporphine (TPP) as sensitizer (5×10^{-4} M). The reaction progress was monitored by NMR and for 100% conversion ca. 6–8 h were necessary. The hydroperoxides **4–7** were isolated and purified by fractional distillation and/or silica gel chromatography and were characterized on the basis of their spectral (IR, ^1H and ^{13}C NMR) data. The proportion of regioisomers and for each the corresponding diastereomers were determined directly on the reaction mixture by means of 400-MHz ^1H NMR and 100-MHz ^{13}C NMR and are given in Scheme I (normalized to 100%). The silyl enol ethers **4a,b** proved to be sensitive toward photoisomerization during the photooxygenation. Thus, prolonged (ca. 24 h) irradiation resulted in a 6:1 photostationary mixture of E/Z isomers. A control experiment, employing a solution of K_2CrO_4 in methanol as UV filter, showed that immediately after complete conversion the E isomers of **4a,b** were produced predominantly (dr > 96:4) as the result of diastereomeric control.[4]

For such a high degree of diastereoselectivity to be observed, the enophilic attack of $^1O_2$ must be directed by intramolecular assistance through stereoelectronic effects and by diastereomeric differentiation through steric interaction. In regard to the stereoelectronic factor, it is significant to note that for the substrates **1a,b** the allylic hydrogen at the silyl cyanohydrin carbon suffers ene reaction, leading to enol ethers **4a,b**, while for the **5a,b** product a methyl hydrogen is abstracted by $^1O_2$. However, for substrates **2a,b** only methyl hydrogens participate in the ene reaction, affording the regioisomers **6a,b** and **7a,b** (Scheme I). Clearly the so-called cis effect[5] operates here, which for optimal intramolecular assistance directs the enophilic attack of $^1O_2$ preferentially to that side of the substrate which can align two allylic hydrogens perpendicular to the olefin plane and flanking the terminal oxygen atom. For substrate **1a,b** this stereoelectronic guidance

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[1] Humboldt, A. v. Postdoctoral Fellow, 1984–1986.

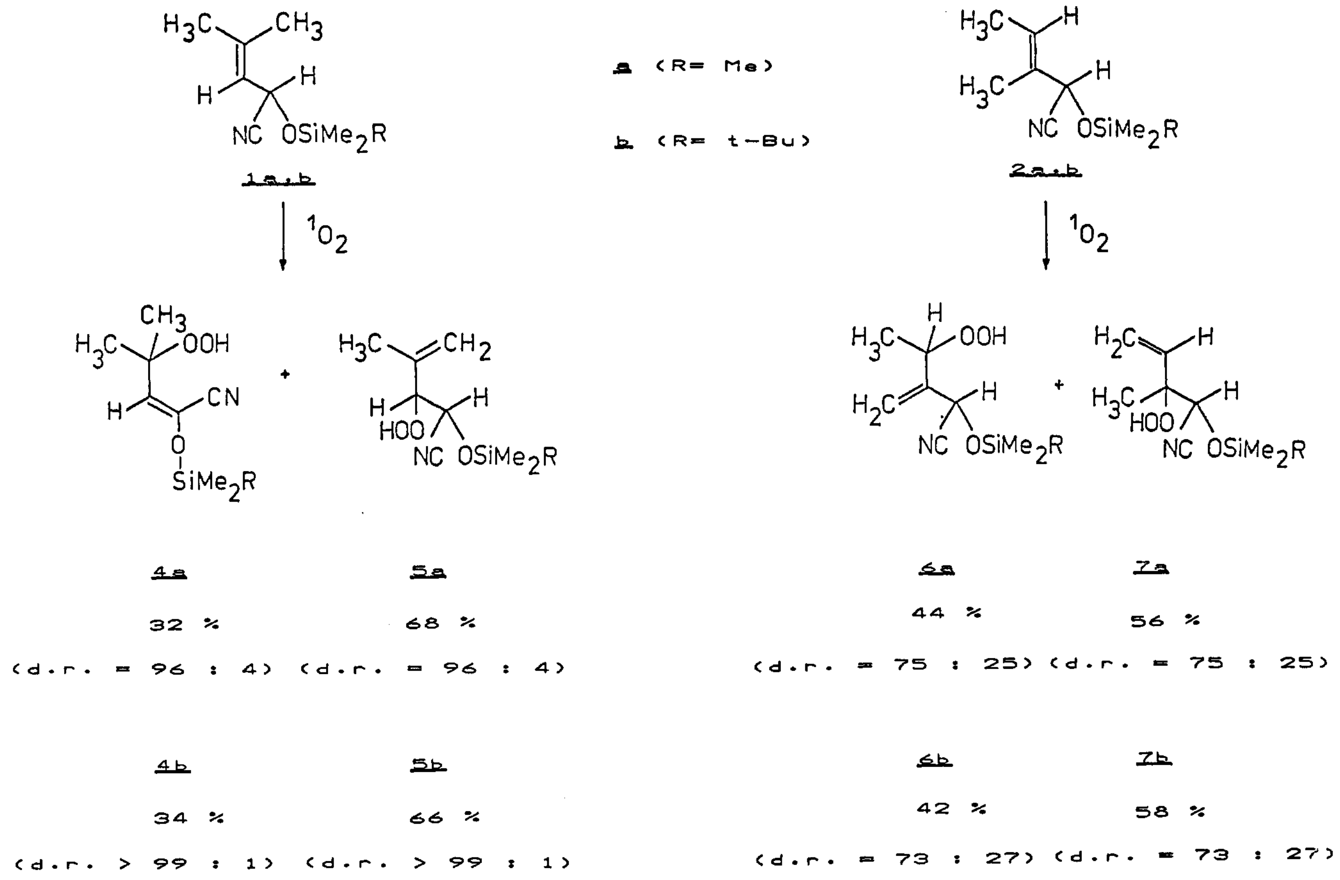
[2] (a) Ensley, H. E.; Carr, R. V. C.; Martin, R. S.; Pierce, T. E. *J. Am. Chem. Soc.* **1980**, *102*, 2838. (b) Orfanopoulos, M.; Foote, C. S. *Tetrahedron Lett.* **1985**, *26*, 5991. (c) Adam, W.; Griesbeck, A. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1070.

[3] (a) Rawai, V. H.; Rao, J. A.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 4275. (b) Albright, D. *Tetrahedron* **1983**, *39*, 3207.

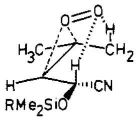
[4] The olefinic protons in **4a,b** are shifted for the E isomers ca. 0.13 ppm downfield relative to the Z isomers (cf. Hertenstein, U.; Hünig, S.; Reichelt, H.; Schaller, R. *Chem. Ber.* **1982**, *115*, 261), so that a rigorous stereochemical assignment of the E and Z pairs of **4a,b** was possible; the stereochemical assignment of the threo,erythro pairs **5a,b** was inferred from the E, Z pair **4a,b**, but a rigorous proof is in progress.

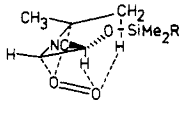
[5] (a) Orfanopoulos, M.; Grdina, M. B.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 275. (b) Schulte-Elte, K. H.; Muller, B. L.; Rautenstrauch, V. *J. Am. Chem. Soc.* **1980**, *102*, 1738.

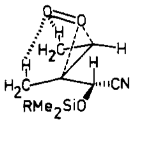
Scheme I

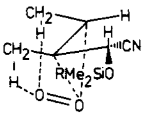


derives from the side bearing the cyanohydrin substituent (structures A), while for substrate **2a,b** it is the side away from that substituent (structures B).

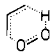

A

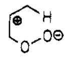

A′

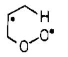

B


B′

The most convincing experimental support for structures A and B rests on the fact that identical diastereomeric ratios are observed for each regioisomer of a particular substrate, that is dr > 96:4 for (*E,Z*)-**4a,b** and *threo/erythro*-**5a,b** from substrate **1a,b** and dr ~74:26 for **6a,b** and **7a,b** from substrate **2a,b** (Scheme I). Both regioisomers of a given substrate must be formed from a common and symmetric precursor, symmetric in the sense that both olefinic carbons become simultaneously attached to the incoming singlet oxygen. As shown in structures A and B, the singlet oxygen molecule descends onto the double bond of the substrate along its perpendicular bisector, the proximate oxygen atom becoming simultaneously bonded with both olefinic carbons and the pendant oxygen atom interacting with the two flanking allylic hydrogen atoms (cis effect[5]) that are ultimately transposed in the ene reaction. In such a symmetric reaction mode, the extent of diastereoselectivity must be the same for each set of regioisomers since a common precursor figures as product branching point (cf. Scheme I). Therefore, the observed diastereomeric differentiation is dictated by the preferred conformational arrangement of the bulky silyloxy substituent, i.e., structure A preferred over A′ (symmetrical mode) and not by steric interactions of the approaching $^1O_2$ molecule with the chiral silyl cyanohydrin moiety (unsymmetrical mode). Since in the unsymmetrical binding of $^1O_2$ distinct diastereomeric ratios must be expected for a particular set of regioisomers, ene reaction via unsymmetrical pathways such as the concerted transition state (structure C)[6] or the dipolar (structure D)[7] and diradical (structure E)[8] intermediates cannot account for the present stereochemical results.


C


D


E

Thus, a common symmetric species is required to rationalize our unprecedented diastereoselectivities in the ene reaction of $^1O_2$ with the cyanohydrins **1a,b** and **2a,b**, and we postulate that the perepoxide-like structures A and B are engaged. Whether a bona fide perepoxide intermediate intervenes is debatable,[9] although during the last few years the existence of such elusive entities in photooxygenation reactions has been revived.[10]

This proposed model also readily accounts for the fact that the diastereoselectivity is much higher for **1a,b** than for **2a,b**. As structures A and A′ exhibit, the directing cyanohydrin chirality center is intimately involved in the

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(6) (a) Foote, C. S. *Pure Appl. Chem.* **1971**, *27*, 635. (b) Nickon, A.; Giorgio, L. B.; Daniels, P. J. L. *J. Org. Chem.* **1973**, *38*, 533. (c) Frimer, A. A. *Chem. Rev.* **1979**, *79*, 359.

(7) (a) Jefford, C. W.; Rimbault, C. G. *J. Am. Chem. Soc.* **1978**, *100*, 6437. (b) Clennan, E. L.; L'Esperance R. P. *J. Am. Chem. Soc.* **1985**, *107*, 5178. (c) Manring, L. E.; Foote, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 4710.

(8) Harding, L. B.; Goddard, W. A., III. *J. Am. Chem. Soc.* **1980**, *102*, 439.

(9) (a) Orfanopoulos, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1980**, *102*, 1417. (b) Stephenson, L. M.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419.

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enophilic attack, since the hydrogen atom at the cyanohydrin carbon in **1a**,**b** is being abstracted, affording (*E*)-**4** via structure A and (*Z*)-**4** via structure A′. Steric congestion is minimized by placing the bulky silyloxy substituent as far away from the reaction center as is feasible, so that structure A is preferred over A′ on the basis of energy. Consequently, for **1b** (R = *t*-Bu) the diastereomeric ratio is significantly higher than for **1a** (R = Me), i.e., dr > 99:1 vs. dr = 96:4 (Scheme I), as would be expected on steric grounds. However, in structure B the chiral cyanohydrin center is remote from singlet oxygen in the enophilic attack and conformational flexibility is responsible for the lower diastereoselectivity observed with **2a**,**b** (Cram-type stereocontrol). Indeed, whether **2a** (R = Me) or **2b** (R = *t*-Bu) are used, the dr values are within experimental error (Scheme I).

It is important to emphasize that the cis effect[5] is responsible for the observed diastereoselectivity in the photooxygenation of the silyl cyanohydrins **1a**,**b** and **2a**,**b**. Such stereoelectronic factors should prove useful in controlling the stereochemistry of singlet oxygen reactions, particularly in the synthetic application of diastereoselective oxygen functionalization.

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Cobalt-Mediated [2 + 2 + 2]Cycloadditions of Alkynes to the Pyrrole 2,3-Double Bond: A Novel Construction of Fused Dihydroindoles

Summary: Auxiliary η^5-CpCo mediates the [2 + 2 + 2]-cycloaddition of alkynes to the pyrrole 2,3-double bond, furnishing complexed fused dihydroindoles.

Sir: Pyrrole is a pivotal structural unit in nature, in synthetic organic chemistry, and in medicinally active compounds.[1] Its double bonds, particularly when vinyl-substituted, have been utilized in cycloaddition reactions leading to fused heterocycles.[1,2] We report that η^5-CpCo mediates a novel transformation of the pyrrole ring: the [2 + 2 + 2]cycloaddition of its 2,3-double bond to alkynes to generate the new 3a,7a-dihydroindole nucleus as incorporated in a variety of tri- and tetracyclic diene complexes. After those in indole,[3] our observations provide the second example of the incorporation of aromatic double bonds into cobalt-mediated cycloadditions,[4] involving a considerably more challenging substrate and pointing to a significantly larger scope of the reaction than previously anticipated.

The starting materials **1** were prepared in one step from pyrrole by adaptations of the literature procedures using known alkynoyl chlorides or iodoalkynes[3] (Table I).

The results presented in Table II were obtained under identical conditions to provide comparative data (unless noted otherwise): 1 equiv of **1**, 1.2 equiv of $CpCo(CO)_2$, 5 equiv of monoalkyne (added slowly by syringe pump at 23 °C). The solvent used was toluene, and the solution was irradiated with a Sylvania 300-W tungsten halogen slide projector lamp over the 10–15 h reaction time.

The cocyclizations of **1** shown in Table II give reproducible results; however, the reaction conditions are unoptimized. Thus, as shown in Table III, the chemo- and stereoselectivity of the reaction, as well as the yields of products can vary with changes in temperature, the nature of the cobalt auxiliary, and concentration of substrates. We have also noted temperature effects on the regioselectivity when unsymmetrically substituted cocyclization partners are used.[9] Because of the time-consuming nature of optimization, we have only carried it out for **1a** (92%). The results indicate that virtually quantitative yields might be attainable by fine-tuning conditions.

Some additional comments are in order concerning our results. (1) Stereochemical assignments were made by analogy to related systems utilizing the effects of the magnetic anisotropy of cobalt in ^{1}H NMR spectroscopy.[4] Further confirmation of regiochemistry was obtained by desilylation of some complexes with tetrabutylammonium fluoride and ^{1}H NMR analysis of the products. (2) The diastereomeric cobalt diene complexes shown in Table II were inseparable by chromatography or crystallization. However, their diastereomeric relationship was proven by oxidative demetalation to provide a single product. The product ratios appear to be of kinetic origin, equilibration being absent under the reaction conditions (110 °C). (3) Oxidative demetalation of the complexes in Table II can be accomplished either to the free diene or to the aromatized indole system, depending on conditions. The latter can be chosen to exactly meet the electronic requirements of the specific system by electrochemical methods. Thus, for example, **2a** and **3a** show an irreversible oxidation wave in cyclic voltammetry at +0.25V (vs. Ag/Ag^+, THF, 23 °C). In practical terms, complexes **2** and **3** will liberate their ligands as the diene by treatment with 1 equiv of Ce^{4+} (as ceric ammonium nitrate) or Hg^{2+} (as mercuric acetate) in CH_3CN and/or THF at temperatures ranging from −78 to

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(5) N-Alkynoylated pyrroles were prepared by treatment of the alkynoyl chloride with *N*-lithiopyrrole in THF at −78 °C.

(6) Formed by exposure of 5-iodopentyne to *N*-potassiopyrrole in Me_2SO at 23 °C.

(7) All new compounds gave satisfactory analytical and/or spectral data.

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