

antioconvergent transformation of an achiral substrate possessing σ -symmetry into a single enantiomer of a chiral lactone. Considering the broad substrate specificity of lipases, this approach is expected to be synthetically useful for asymmetric preparation of other optically pure γ - and δ -lactones from symmetrical hydroxy dicarboxylates and dihydroxy monocarboxylates. On a more general note, this

study shows that prochiral selectivity can be achieved by enzymes in organic solvents and used for reactions that are not feasible in aqueous solutions where hydrolysis is the dominant reaction.

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Reaction of Diphenylmethylene with Carbon Dioxide: Matrix Isolation of Diphenyloxiranone

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Summary: The thermal or photochemical reaction of matrix-isolated diphenylmethylene and CO₂ produces the highly unstable diphenyloxiranone, which was characterized by IR spectroscopy, isotopic labeling, and subsequent photochemistry.

Sir: The reactivity of carbenes depends largely on the spin state from which the carbene reacts. At room temperature carbenes with triplet ground state frequently yield products from both the excited singlet state and the triplet ground state. If the singlet-triplet gap (ΔG_{ST}) is small, as in diphenylmethylene (1) ($\Delta G_{ST} = 4.2$ kcal/mol),¹ singlet reactivity can arise from thermally equilibrated spin states. Griller explains the singlet reactivity of triplet carbenes by assuming an intersystem crossing (ISC) step during the course of the reaction.^{1b} Singlet products are thus formed directly in a "spin forbidden" reaction from triplet carbenes and singlet substrates. To elucidate the role of spin states on chemical reactivity we have studied both "spin allowed" and "spin forbidden" carbene reactions at low temperature (20–50 K), where electronically excited states are not thermally populated if ΔG_{ST} is larger than a few kilocalories/mole.²

Here we report on the direct observation of the "spin forbidden" reaction of carbene 1 and CO₂ to give diphenyloxiranone (2). Indirect evidence for the formation of the highly unstable α -lactone 2³ in the photoreaction of diphenyldiazomethane (3) and dry ice (fluorotrichloromethane as solvent) was given by Wheland and Bartlett.⁷ Alternative routes to 2 are the ozonolysis⁷ or autoxidation^{8,9} of diphenylketene.

Table I. IR Data of Diphenylmethylene (1), Matrix Isolated in Ar Matrices with Various Amounts of CO₂ at 10 K (Wavenumbers in cm⁻¹)

Ar	5% CO ₂	Δ^a	10% CO ₂	Δ^a	assignment ^b
3074.5 m	3074.9 m	+0.4	3074.5 m	+0.0	ν C-H
1479.6 m	1476.2 m	-3.4	1475.8 m	-3.8	
1466.6 w	1465.6 m	-1.0	1465.2 m	-1.4	ν C-C (19a)
1432.4 w	1433.3 w	-0.9	1433.3 w	-0.9	ν C-C (19b)
1066.9 w	1065.5 w	-1.4	1066.0 w	-0.9	β C-H (18a)
1020.2 m	1019.2 m	-1.0	1019.2 m	-1.0	ring (12)
891.4 w	892.4 w	+1.0	893.4 w	+2.0	τ C-H (17b)
743.4 s	747.8 s	+4.4	748.2 s	+4.8	τ C-H (11)
673.5 s	676.4 s	+2.9	- ^c		ϕ C-C (4)
565.0 w	565.0 m	+0.0	565.0 m	+0.0	

^a Frequency shift in CO₂-doped matrices. ^b Approximate description, Wilson notation for vibrations of phenyl rings in brackets (see ref 2d). The band at 1282 cm⁻¹ (ν_{as} C(Ph)-C(1)-C(Ph), ref 2d) is too weak to be observed in CO₂ doped matrices. ^c Not to be observed due to the very strong and broad CO₂ absorption at 652 cm⁻¹.

Photolysis of diazomethane 3 ($\lambda = 543$ nm, 10 K) in 0–10% CO₂-doped Ar or Xe matrices produces carbene 1 in high yields.^{2d} As long as the matrix is kept at 10 K, no thermal reaction of 1 and CO₂ is observed even at high O₂ concentrations (10%). At these high CO₂ concentrations carbene 1 and CO₂ molecules are in direct contact, which causes a perturbation of the IR spectrum of 1 (Table I). Compared to the spectrum of 1 in pure Ar bands are shifted up to 4.8 cm⁻¹ to higher or 3.8 cm⁻¹ to lower frequencies. Perturbation of the relative band intensities is also observed for several bands.

When a CO₂-doped matrix is warmed to 35 K, IR bands¹⁰ assigned to 1 slowly decrease and new bands appear. After 5-h annealing (10% CO₂ in Ar) at 35 K about 40% of 1 is converted to a new species, which is characterized by strong absorptions at 1890.4, 1877.8, and 699.1 cm⁻¹ (Table II). In Xe matrices (5% O₂) 90% conversion is observed after 12-h annealing at 70 K. UV irradiation ($\lambda > 220$ nm) of the new species slowly produces carbon monoxide (2140.6 cm⁻¹) and benzophenone (4) (1663.8 cm⁻¹).

(9) Hess, T. C. Ph.D. Thesis, University of California at Los Angeles, 1978.

(10) IR spectra were recorded by using a Bruker IFS66 FT-IR spectrometer. The resolution was generally 1 cm⁻¹, spectra were recorded in the range 4000–500 cm⁻¹. The set up for matrix isolation is described in ref 2a and b.

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(2) (a) Sander, W. *Spectrochim. Acta* 1987, 43A, 637. (b) Sander, W. *J. Org. Chem.* 1988, 53, 121. (c) Sander, W. *J. Org. Chem.* 1988, 53, 2091. (d) Sander, W. *J. Org. Chem.* 1989, 54, 333.

(3) α -Lactones in general polymerize at low temperatures, and only two species with electron-attracting (ref 4) and additionally bulky (ref 5) substituents have some stability at room temperature. Several alkyl-substituted α -lactones, generated at 77 K by irradiation of peroxy malonates, have been shown to give polyesters at temperatures as low as -100 °C (ref 6).

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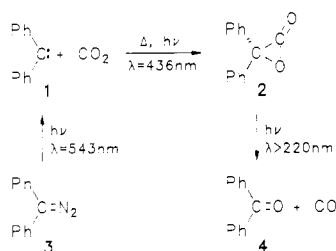
(8) Bartlett, P. D.; McCluney, R. E. *J. Org. Chem.* 1983, 48, 4165.

Table II. IR Frequencies of Four Isotopomers of Diphenyloxiranone (2a-d) (Wavenumbers in cm^{-1})

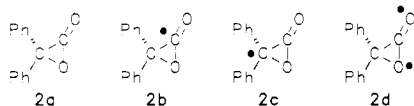
2a	2b ^a	Δ^b	2c ^c	Δ^b	2d ^d	Δ^b	assignment ^e
1910.1 m	1848 sh	0.967	1904.8 m	0.997	≈1879 w		ν C=O
1890.4 vs	1837.3 vs	0.972	1887.5 vs	0.998	1860.0 vs	0.984	
1877.8 s	1818 sh	0.968	1874.0 vs	0.998	1848.0 s	0.984	
1501.8 w	1501.3 w	0.9997	1500.8 w	0.9993	1501.3 w	0.9997	Ph (19a)
1456.5 m	1456.5 m	1.0	1455.5 m	0.9993	1456.5 m	1.0	Ph
1450.2 m	1449.7 m	0.9997	1449.7 m	0.9997	1449.2 m	0.9993	Ph (19b?)
1322.9 w	1323.4 w	1.0004	≈1322 vw		1323.4 w	1.0004	Ph (3)
1299.3 w	1278.6 w	0.9841	≈1285 w		1278.1 w	0.9837	
1227.0 w	1225.5 w	0.9988	1213.5 w	0.9890	1227.5 w	1.0004	ν _{as} C-C(2)-C
912.7 w	892.4 w	0.9778	903.5 w	0.9899	912.7 w	1.0	
777.7 m	776.7 m	0.9987	775.2 m	0.9968	776.7 m	0.9987	Ph (11?)
762.7 w	766.1 w	1.0045	≈769 w		765.6 w	1.0038	Ph (11?)
730.9 m	727.5 m	0.9953	730.4 m	0.9993	722.2 m	0.9881	
699.1 s	698.6 s	0.9993	697.6 m	0.9979	698.1 s	0.9986	Ph φ (4)
602.6 w	598.3 w	0.9929	589.1 w	0.9776	596.4 w	0.9897	
578.1 w	573.7 m	0.9924	574.2 w	0.9933	575.6 w	0.9957	Ph

^a [1-¹³C]-2. ^b Ratio of isotopic stretching frequencies ν^b/ν . ^c [2-¹³C]-2. ^d [¹⁸O₂]-2. ^e Approximate description, Wilson notation for vibrations of phenyl rings in parentheses. Tentative assignment on the basis of isotopic shifts and by comparison with spectra of benzophenone 4 (ref 13).

On the basis of IR spectra, isotopic labeling and the observed photochemistry the thermal reaction product has been assigned the structure of diphenyloxiranone (2).



The reaction of [1-¹²C]-1 and [1-¹³C]-1 with ¹²C¹⁶O₂ and the reaction of [1-¹²C]-1 with ¹³C¹⁶O₂ and ¹²C¹⁸O₂ produces four isotopomers 2a-d (Table II). Thus in 2a-d all atoms of the three-membered ring and the carbonyl group are labeled, which allows the identification of vibrations with contributions of these atoms.



In the carbonyl region of the IR spectrum of 2 three bands are observed (Table II), the strongest being at 1890.4 cm^{-1} . The position of this band is characteristic for carbonyl bands in α -lactones.¹¹ The splitting of the C=O stretching mode can be explained either by the presence of different matrix sites or conformations of 2, by Fermi resonance, or by both.

The frequencies and relative intensities of the IR bands in the carbonyl region depend on isotopic substitution. Labeling of the carbonyl group with ¹³C or ¹⁸O causes the IR bands in the carbonyl region to be shifted to lower frequencies (Table II). The ¹⁸O isotopic shift of 30.4 cm^{-1} for the strong band at 1890.4 cm^{-1} is similar to the shifts found in other carbonyl groups¹² whereas the ¹³C isotopic shift of 53.1 cm^{-1} is larger than expected. The calculated

$\nu(^{12}\text{C})/\nu(^{13}\text{C})$ ratio of stretching frequencies is 0.976 for a diatomic C-O vibrator¹² while the observed ratio is 0.972. The large observed shift can only be rationalized if the splitting of this mode into several components is caused by Fermi resonance and therefore the exact position of the C=O stretching mode is not directly observed. ¹³C labeling of the second ring carbon atom (C(2)) has only minor influence on the C=O stretching vibration (Table II).

The IR spectrum of 2 in the carbonyl region is complicated by the fact that the components behave differently on short wavelength irradiation ($\lambda > 220$ nm). The medium-intensity band at 1910.1 cm^{-1} increases and the band at 1877.8 cm^{-1} decreases in intensity after short-time irradiation at 10 K while the band at 1890.4 cm^{-1} remains unchanged. Annealing at 40 K causes reversion of the changes in band intensities. This behavior can be explained by the assumption of two conformers (presumably due to rotation of the phenyl groups), one with IR bands at 1910.1 and 1890.4 cm^{-1} and the other with bands at 1890.4 and 1877.8 cm^{-1} . Prolonged irradiation leads slowly to decarbonylation and formation of ketone 4.

Other bands which are identified are the asymmetrical C(Ph)-C(2)-C(Ph) stretching vibration at 1227.0 cm^{-1} and several vibrations of the phenyl groups. In benzophenone the C(Ph)-C(2)-C(Ph) stretching vibration is located at 1276 cm^{-1} .¹³ Bands which show only small isotopic shifts on labeling of any of the ring atoms are assigned to vibrations of the phenyl groups (Table II).

While carbene 1 is not carboxylated thermally at 10 K, and only slowly at elevated temperatures, irradiation into the long wavelength $\pi \rightarrow \pi^*$ absorption (triplet-triplet) of 1 ($\lambda_{\text{max}} = 454$ nm)^{14,15} gives 2 in a rapid reaction even at 10 K. With 5-10% CO₂-doped Ar matrices the initially fast photoreaction stops after several hours, and prolonged irradiation does not lead to complete conversion. If the matrix is irradiated at 30 K, where the mobility of trapped species (CO₂) in solid Ar is higher, the reaction is complete after several hours.

Although it is difficult to separate effects of diffusion and thermal barriers in bimolecular reactions in solids, the absence of thermal reaction in Ar matrices doped with high concentrations of CO₂ at 10 K suggests that there is a thermal barrier in this "spin forbidden" reaction. The

(11) Carbonyl absorptions at these high frequencies are characteristic for the oxiranone ring system. In alkyl-substituted α -lactones strong absorptions are observed between 1895 and 1935 cm^{-1} (ref 6) while electron-withdrawing groups (perfluorinated alkyl groups) shift the carbonyl band to 1945-1990 cm^{-1} (ref 4 and 5). Isomeric open chain structures are expected to exhibit absorptions at much lower frequencies. The formation of open chain structures as minor byproducts cannot be ruled out completely.

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(15) Irradiation with $\lambda = 436$ -nm light. A 500-W high-pressure mercury arc lamp and an interference filter was used.

perturbation of the IR spectrum of 1 indicates the direct interaction of 1 and CO₂, and thus diffusion cannot be the rate-limiting factor. The observed photochemical reactivity is in accordance with the photochemistry of excited 1 in polycrystalline alcohols at 77 K.¹⁶ Under these conditions O-H insertion (typical reaction of singlet carbenes)

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is faster than C-H insertion (triplet reaction), and thus electronically excited triplet carbene 1 reacts like a singlet carbene. An alternative explanation, the reaction of "hot" ground states produced by irradiation, cannot be ruled out by the present experiments.

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Studies of the Immunosuppressive Agent FK-506: Synthesis of an Advanced Intermediate

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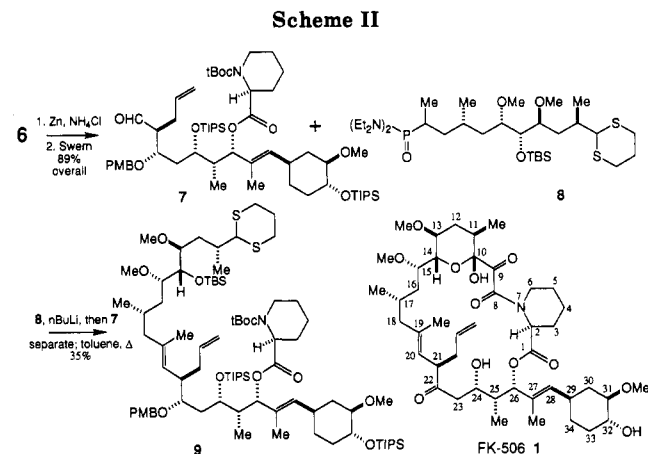
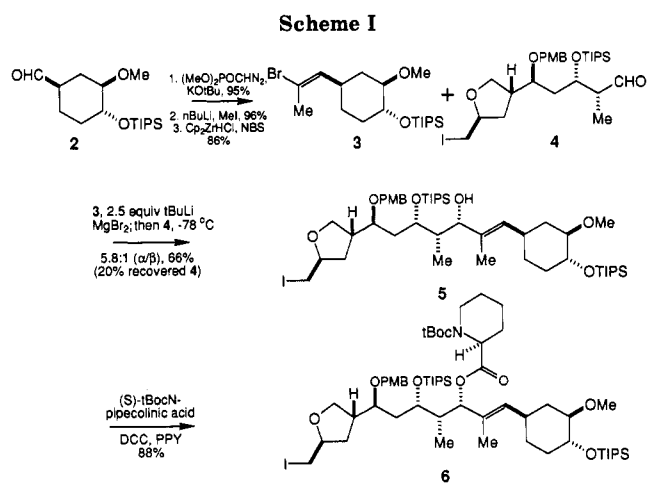
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Summary: The addition of a vinyl anion that corresponds to C₂₇ of the immunosuppressant FK-506 to an aldehyde that corresponds to C₂₆ results in a coupling process that is stereoselective and convergent and allows for the direct attachment of the C₂₆-pipercolinate moiety. The pipercolinate is shown to be compatible with conditions required to achieve a subsequent coupling reaction.

Sir: Several recent reports have described synthetic efforts¹ relating to the immunosuppressive and antiautoimmune agent, FK-506 (1),^{2,3} including the first total synthesis.⁴ Synthetic procedures such as these have the potential for helping to define the topographical relationship between this unusual ligand and its receptor(s). Our recent isolation and characterization of an FK-506 binding protein, termed fujiphilin, and an FK-506 associated cyclophilin⁵ variant, termed mimphilin, provide hope that this goal may soon be realized.⁶⁻⁸

The target molecules of our research program in the FK-506 area require an efficient method to couple the cyclohexyl moiety of the natural product to a carbon chain through the C₂₇-C₂₈ trisubstituted olefin spacer found in FK-506. Reported methods to achieve this objective utilized a Peterson olefination^{1b,c} and a Burgess reagent mediated elimination of a tertiary alcohol.^{1k} Herein we report an alternative coupling sequence that is convergent



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and stereoselective and allows for the attachment of the C₂₆-pipercolinate moiety without recourse to protecting-group chemistry at C₂₆.

The aldehyde 2 (Scheme I) was prepared by Swern oxidation of the corresponding alcohol whose synthesis (TIPS = H) was described in an earlier report.¹⁶ Homologation to the vinyl bromide proceeded in three steps. The direct conversion of the aldehyde function in 2 into a terminal acetylene was achieved according to the procedure of Gilbert⁹ ((MeO)₂POCHN₂, KOtBu, 95% yield). Methylation of the acetylene (nBuLi, MeI, 96% yield) was fol-

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