

Figure 2. (a) ^1H NMR spectrum of EPSP ketal in D_2O at pD 9.0. (b) NOE difference spectrum resulting from irradiation of the methyl signal at 1.68 ppm showing the excitation of the H-5 protons selectively. Spectra were taken on a Varian XL 400 instrument.

the reaction mixture is allowed to stand with excess **3**, the ketal becomes the only detectable shikimate species separable from the mixture without denaturing EPSPS. Maximum production of **5** occurs while **4** is maintained by the enzyme. EPSPS catalytically converts **1** to **5** at $k = 0.2/\text{h}$ (pH = 6.3, 25 °C), a rate much slower than the reverse reaction.⁴ Figure 1 shows a ^{31}P NMR spectrum of an enzymatic synthesis of **5** with the equilibrium mixture containing S3P (2.49 ppm), EPSP (2.31 ppm), EPSP ketal (1.16 ppm), P_i (0.81 ppm), and PEP (-1.65 ppm).

The EPSP ketal is easily isolated from the reaction mixture in Figure 1 by anion-exchange chromatography.⁵ A number of corroborative experiments confirm the structure of **5**. Labeling with $[\text{U-}^{14}\text{C}]\text{S3P}$ and $[\text{1-}^{14}\text{C}]\text{PEP}$ indicates that all 10 carbon atoms must be present. Degradation of **5** in dilute acid produces **2** and pyruvate. The permethylated derivative of $[\text{2'-}^{13}\text{C}]\text{-5}$ displays a molecular ion at $m/z = 382$ compared to methylated **1** at $m/z = 381$ by CI mass spectrometry.⁶ The key structural features of **5** are readily observed by ^1H and ^{13}C NMR.⁷ The ^{13}C -2' carbon is quaternary by APT sequence, appears as a quartet in the ^1H -coupled ^{13}C spectrum, and is readily seen in the ^{13}C NMR spectrum of the internal equilibrium mixture at 110.6 ppm.^{3,12} The ^1H spectrum (Figure 2a) contains the C-3' methyl signal coupled (d, $J = 4.7$ Hz) to the C-2' carbon (99% ^{13}C). The stereochemistry at the C-2' position is *R* by 1-D NOE with transfer occurring between the C-3' (CH_3) signal at 1.68 ppm and the H-5 proton (Figure 2b). The EPSP ketal is stereochemically pure on the basis of this NOE result and the absence of a diastereomeric methyl ^1H NMR signal at 1 Hz line width.

The addition of **5** back to EPSPS with or without P_i does not result in conversion to **1** or **2**. A mixture of EPSPS (55 μM), $[\text{14C}]\text{S3P}$ (32 μM), and PEP (0.5 mM) formed and maintained **5** for 10 months at 4 °C. This nonreversibility suggests that EPSPS is not actually catalyzing the formation of **5** directly, since with time the equilibrium should favor the products with the least energy, S3P and pyruvate.^{2a} Formation of **5** is stopped in the presence of glyphosate [*N*-(phosphonomethyl)glycine], which sequesters enzyme with S3P in the herbicidal dead-end complex.⁸ Incubation of **1** (50 mM) at pD 4.8 does not produce **5** after 16

days at 25 °C; however, **2** (21%) is observed from hydrolysis.^{3,12} Incubation of $[\text{14C}]\text{S3P}$ (8 μM) with pyruvate (1.7 mM) with or without EPSPS (7 μM) at pH 7.0 for 18 days at 4 °C also does not produce **5**. Therefore, EPSP ketal formation is not an artifact of these incubations.

EPSPS has a cysteine reactive to DTNB at position 408 that is protected from modification by **2** and glyphosate or **1**,⁹ but **5** (2 mM) with or without P_i (100 mM) does not protect Cys-408 from modification by DTNB (60 μM). This suggests that productive association of **5** does not occur with the EPSPS active site. Taken together, all of these results preclude **5** from being an intermediate along the catalytic pathway and clearly demonstrate the need for corroborative information when enzyme intermediates are spectroscopically characterized.¹²

EPSPS catalyzes a direct addition-elimination reaction through **4**, which has been isolated and fully characterized.¹⁰ The internal equilibrium conditions maximize the concentration of **4**, facilitating optimum production of **5**. It is tempting to propose that **4** produces **5** from an $\text{S}_{\text{N}}2$ displacement of P_i by the shikimate 4-OH in the active site. However, direct formation at the active site seems unlikely from the protection and reversibility studies discussed above. Nevertheless, EPSPS catalytic activity is required, suggesting that **5** forms in solution from an enzymatically produced species. If the prolonged stabilization of enzyme-bound **4** permits its occasional release, then the solution degradation of **4** must account for the stereospecific formation of **5**. The stereochemistry of **4** and its relationship to **5** is not clear¹¹ and is the subject of a detailed investigation.¹²

Stereochemical Course of the Key Ring-Forming Reactions in Clavulanic Acid Biosynthesis

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Received October 10, 1989

Clavaminic synthase (CS) is an Fe(II)/ α -ketoglutarate (α -KG)-dependent oxygenase central to the clavulanic acid (**4**) biosynthetic pathway. It carries out a four-electron oxidative cyclization of proclavaminic acid (**1**) to clavaminic acid (**2**) with concomitant formation of 2 mol of CO_2 and succinic acid^{1,2} (Scheme I). An ^{18}O -labeling experiment has established that the 3-OH in **1** gives rise to the oxazolidine oxygen in **2** without detectable loss or exchange of heavy isotope, signaling a significant departure from conventional α -KG-dependent dioxygenase behavior.³ In this paper, the stereochemical course of this oxidative cyclization at C-4' of proclavaminic acid (**1**) is determined and a correlation is completed to an earlier configurational analysis.⁴ The stereochemical course of each clavulanic acid ring-forming reaction can now be defined and suggests possible mechanisms of β -lactam formation distinct from those proposed for nocardicin (**6**)⁵ and penicillin.⁶

Access to the stereospecifically 4'-deuteriated proclavaminates **1a** and **1b** was achieved through (4*R*)-(phenylthio)azetidinone

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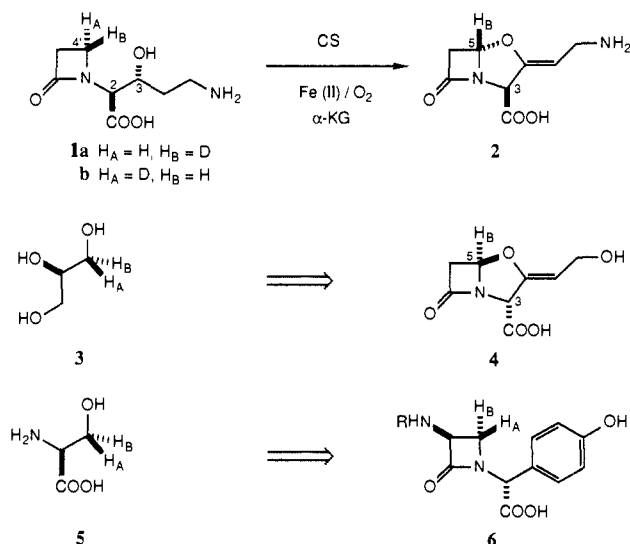
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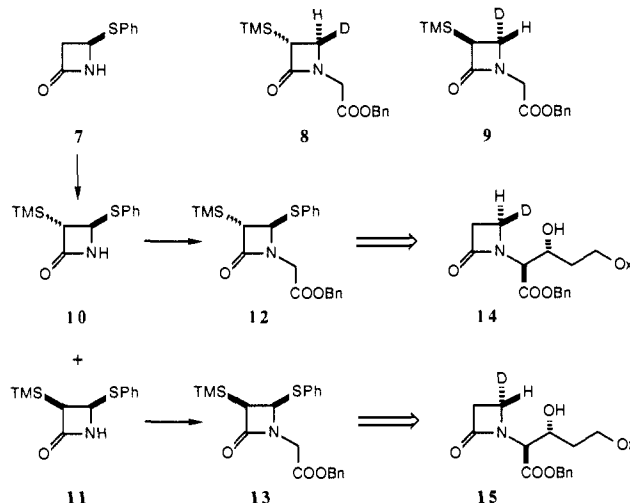
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Scheme I



Scheme II



(7, mp 68–69 °C, $[\alpha]_D = 137^\circ$; lit.⁷ mp 58–60 °C, $[\alpha]_D = 105^\circ$). To exploit the sensitivity of trialkyltin hydride reductions to steric effects,⁸ 7 was N-silylated and then treated with LDA and TMSCl to give a 2:1 mixture⁹ of 10 and 11, respectively, after mildly acidic workup (Scheme II). The trans- and cis-disubstituted β -lactams 10 and 11 were easily separated by silica gel chromatography (hexanes/EtOAc)¹⁰ and reacted with benzyl bromoacetate to give correspondingly 12 and 13. Reaction of 12 with 2 equiv of $n\text{Bu}_3\text{SnD}$ (cat. AIBN, PhH, reflux, 6 h, 70%) gave the 4'*R*-deuterated β -lactam 8, while analogous reaction of the cis isomer 13 proceeded considerably more slowly (4 equiv of $n\text{Bu}_3\text{SnD}$, 24 h, 50%) to give the enantiomeric 4'*S*-deuterated azetidinone 9. Mass spectral measurements revealed deuterium contents in 8 and 9 to be 97–98% d_1 ,¹² and careful ¹H NMR analyses established

that in both instances deuterium was oriented trans to the TMS group to an extent $17 \pm 1:1$ ($^3J_{\text{trans}} = 2.7$ Hz). Stereospecific introduction of label having been securely established, the TMS group was removed and the syntheses of the racemic N,O-protected (Ox = 4,5-diphenyl-4-oxazolin-2-one)¹³ proclavaminates 14 and 15 were completed as previously described.³ The success of this route and the potential broader applicability of intermediates as 12 and 13 derives from the facilitation by the trialkylsilyl group of reactions in which the thiophenyl is replaced in either a radical or cationic regime with substituents whose entry is simultaneously governed by the steric bulk of the silyl group.

(4'*R*)- and (4'*S*)-D,L-[4'-²H]proclavaminic acid, 1a and 1b, respectively, were incubated³ with CS² to give samples of clavaminic acid, which were purified, derivatized,³ and examined for their deuterium content at C-5 by ¹H NMR spectroscopy and CIMS. The β -deuterated substrate 1a was incubated to 65–70% conversion to afford a sample of clavamate where the vast majority of the label was retained, $94 \pm 1\%$ (MS). In the ¹H NMR spectrum, only a trace of hydrogen was detectable in the integral of H-5 (δ 5.70), and the multiplicity of the resonances for the H-6 hydrogens reduced to a simple AB quartet. The α -deuterated substrate 1b reacted significantly more slowly than its diastereomer 1a. The clavamate produced was isolated at approximately 50% conversion and contained $12 \pm 1\%$ (MS) deuterium at C-5 as revealed in the intensity of the resonance at δ 5.70 (H-5) and the appearance of a small upfield-shifted signal (ca. 0.005 ppm) at the base of the resonances for H-6 α (δ 3.08) owing to this minor vicinal deuterium substitution.¹⁴ Assuming that the enzymic cyclization is stereospecific and there exists no discrimination against labeled substrates at partial extents of reaction, i.e., no *V/K* isotope effect,¹⁵ the expected levels of deuterium in clavamate may be computed in these reactions to be 91–92% and 5–6%, respectively.¹⁶ It can be seen that the intervention of a *V/K* isotope effect would raise the level of deuterium in the product of both experiments. Nevertheless, while the data are insufficient to quantitatively address this issue, it can be seen that, even in the absence of such discrimination, the stereoselectivity of the oxidative cyclization is (conservatively) greater than 90%.

In conclusion, proclavaminates stereospecifically deuterated at C-4' have been prepared and incubated with purified CS. The 4'(*S*)-hydrogen was specifically lost (H_A in 1, Scheme I), accompanied by a significant kinetic isotope effect on the overall reaction rate, and the 4'(*R*)-hydrogen was correspondingly retained (H_B in 1). Therefore, CS, while unconventional in its utilization of molecular oxygen during catalysis,³ introduces a substrate oxygen intramolecularly at C-4' with retention of configuration as expected for hydroxylation.¹⁷ H_B in clavaminic acid (2, Scheme I) survives the subsequent configurational inversion at C-5 that occurs in the formation of clavulanic acid (4).¹⁸ It has been shown previously that H_B in 4 correlates to the *pro*-1(*R*)-hydrogen of glycerol (H_B in 3),⁴ whose absolute configuration remains unchanged through the intermediates of glycolysis to glyceric acid, the primary metabolic precursor of the clavulanate β -lactam

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carbons.¹⁹ Therefore, in the creation of the monocyclic β -lactam ring of proclavamate, the N-C-4' bond is formed with net retention of configuration, in keeping with either 0 or an even number of inversions at the carbon that becomes C-4'. In contrast, monocyclic β -lactam formation in nocardicin A (**6**, Scheme 1) from L-serine (**5**) occurs with inversion of configuration.⁵ Although no intermediates between glycerate and proclavamate have been unequivocally established,²⁰ the results of the present experiments suggest several possible mechanisms for β -lactam formation more complex than the simple S_N2 process apparent in nocardicin biosynthesis⁵ and distinct from the oxidative cyclization involved in isopenicillin N formation.⁶

Acknowledgment. We are grateful to Dr. J. L. Kachinski (JHU) for carrying out the mass spectral analyses essential to the work described, to W. J. Krol and D. Reuyl for informed discussion, and to the NIH (Research Grant AI 14937 and postdoctoral fellowship GM 12119 to S.P.S.) for financial support. The Government of West Bengal is thanked for a study leave to A. B. from Presidency College, Calcutta, India. Major analytical instrumentation used in this research was acquired with funds from the NIH and NSF (NMR, RR 01934 and PCM 83-03176; MS, RR 02318).

Registry No. **1a**, 124603-44-7; **1b**, 124603-45-8; **2**, 112296-12-5; **4**, 58001-44-8; **7**, 85270-00-4; **8**, 124603-41-4; **9**, 124649-51-0; **10**, 100188-51-0; **11**, 124649-49-6; **12**, 124603-40-3; **13**, 124649-50-9; **14**, 124603-42-5; **15**, 124603-43-6; CS, 111693-82-4; benzyl bromoacetate, 5437-45-6.

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Structural Effects on the Yields of Singlet Molecular Oxygen ($^1\Delta_gO_2$) from Alkylperoxyl Radical Recombination

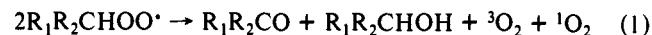
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Received October 27, 1989

Revised Manuscript Received December 20, 1989

Howard and Ingold,¹ following a suggestion of Russell, first reported singlet molecular oxygen from peroxyl terminations in 1968 (eq 1):



This reaction is important because it is a common termination step of the ubiquitous autoxidation process including many biological systems.² The reactions of the singlet oxygen formed must be taken into account in any comprehensive modeling scheme of these oxidation processes. Finally, we wondered whether reaction 1, possibly carried out under specialized conditions (e.g., combustion), might furnish singlet oxygen in synthetically useful yields.

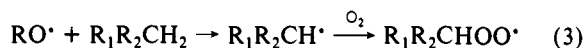
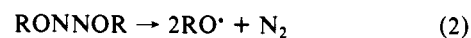
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Table I. Yields of 1O_2 from Radical-Initiated Autoxidation of Hydrocarbons^a

substrate, MBHT ^b	T, °C	% 1O_2	substrate, MBHT ^b	T, °C	% 1O_2
PhMe, 0.050	79.8	6.0 \pm 0.4	<i>n</i> -C ₁₂ H ₂₆ ^d	79.8	3.9 \pm 0.3
PhEt	69.9	11.5 \pm 1.2	<i>n</i> -Bu ₂ O	79.6	9.1 \pm 0.6
PhEt, 0.020	79.6	14.0 \pm 1.1	<i>c</i> -C ₃ H ₁₀ CO,	79.5	4.6 \pm 0.5
PhCMe ₃	79.8	3.4 \pm 0.3	0.042		
Ph ₂ CH ₂	69.4	11.3 \pm 0.6	Me ₂ NCHO	77.2	0.0 \pm 0.4
0.6 M fluorene	79.5	6.1 \pm 0.3	MeN(COC ₃ H ₆) ^e	79.5	0.0 \pm 0.4
Ph ₂ CH ₂ , 0.020	79.2	11.6 \pm 0.7	PhCH ₂ CN,	80.0	0.0 \pm 0.4
1-Me-naphthalene, 0.051	77.2	4.7 \pm 0.3	0.050		
<i>c</i> -C ₈ H ₁₆ ^c , 0.050	77.8	6.7 \pm 0.4	Me ₃ COOH ^f	79.8	0.0 \pm 0.3
<i>c</i> -C ₈ H ₁₄	78.5	6.4 \pm 1.3	TOOH ^g		7.8 \pm 0.5
			CH ₃ CN ^h	65.2	0.5 \pm 0.1

^aSolutions (5.0 mL) in Au-coated, water-jacketed cell; IR detected with North Coast Model E0817 instrument with phase-sensitive detection at 100 Hz. Average of three measurements relative to areas under decay curves of NO₂ under the same conditions. ^bInitial concentration of di-*tert*-butyl hyponitrite. Cage effect (f = escaped radical pairs) assumed 0.89, the value in PhCMe₃,³ unless noted otherwise. ^c f = 0.85 determined experimentally from induction period as described.³ ^d f = 0.84 estimated from relations derived by Kiefer and Traylor (Kiefer, H.; Traylor, T. G. *J. Am. Chem. Soc.* **1967**, *89*, 6667-6671) and published viscosity data (Stephen, K.; In-case, K. *Viscosity of Dense Fluids*; Plenum Press: New York, 1979). ^e*N*-Methylpyrrolidone. ^fInitially 0.25 M in PhCMe₃ solution. ^gInitially 0.10 M in PhCMe₃ solution. ^hInitiated with benzyl hyponitrite (0.060 M) with f = 0.65.¹⁷

In Table I we present yields of singlet oxygen from reaction 1, in which the peroxyl radicals were generated continuously from different oxygen-saturated solvents by free-radical initiation with hyponitrite esters³ (eqs 2 and 3) or directly from the hydroperoxide and initiators.



The yields were determined from the areas under the curves of chemiluminescence emission at 1.27 μ m vs time,⁴ relative to similar areas from the thermal decomposition of 1,4-dihydro-1,4-dimethylnaphthalene 1,4-endoperoxide (NO₂).⁵

For simple hydrocarbon substrates that are expected to terminate only by reaction 1, the yields of singlet oxygen are remarkably uniform. They range from 3.4 to 6.0% for primary and from 3.9 to 14.0% for secondary alkylperoxyl terminations. The values are in the same range as found by Kanofsky by oxidation in aqueous media² of several hydroperoxides with α -hydrogens. With additional functional groups present in the substrate, the yields either remain about the same (*n*-Bu₂O, cyclohexanone) or decrease (amides, nitriles).

We find a small but measurable quantity of 1O_2 from autoxidation of acetonitrile. This result is pertinent to some very interesting experiments reported recently by Sugimoto, Kanofsky, and Sawyer,⁶ who detected 1.27- μ m emission from the electrolytic reduction on Pt of O₂-saturated acetonitrile (but not from *N,N*-dimethylformamide, cf. Table I). The authors ascribed the result to singlet oxygen from termination of HOO \cdot radicals bound to the electrode surface:



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