to the pseudoenantiomorphous counterparts (*R*)-**5a**-Sm and (*S*)-**5b**-Sm (the latter isolable as a 4/1 *S*/*R* mixture).[12] Absolute configurations follow from CD (pseudoenantiomers exhibit near-mirror-image spectra for $\lambda > 250$ nm)[12] and the crystal structure of (*R*)-**5a**-Sm.[14] Conversion of the diastereomeric chloro complexes to hydrocarbyl precatalysts proceeds with net retention of configuration as adduced from CD and X-ray diffraction (Scheme I).[12,15] The latter data reveal unexceptional metrical parameters[1,4] and unambiguously confirm that (*S*)-**6a**-Sm and (*R*)-**6b**-Sm are pseudoenantiomorphous. Alkylation[1,4] of the aforementioned (*R*)-**5a** and (*S*)/(*R*)-**5b** complexes similarly affords (*R*)-**6a**-Sm and a 70/30 (*S*)/(*R*)-**6b**-Sm mixture, respectively.[12]

In transformations doubtless mediated by the corresponding hydrides,[1,4,16] **6**-derived catalysts are capable of reducing traditionally challenging[7,17] unfunctionalized olefins such as 2-phenyl-1-butene (**7**)[18] and styrene (**8**)[19] with high activity (e.g., for **7**, N_t((*R*)-**6a**-Sm) = 20 000 h^{-1} at 25 °C)[20] and moderate to unprecedently high enantioselectivity (Table I). Enantioselection exhibits appreciable (but not identical) temperature dependence, with the pseudoenantiomorphous catalysts yielding products of *opposite* absolute configurations (and *inequivalent* ee's). For **7**, product configurations suggest a stereodifferentiating insertion process in which R = Ph and R′ = Et in A and B or, more likely, an olefin approach occurring along the ring centroid–Sm–ring centroid bisector,[17a,d,21] with Sm–H bent back and R = Ph oriented away from Cp″ and R*. Kinetic measurements[22] on all four catalysts under non-mass-transport-limited conditions in H_2[5b] yield rate law 1, compatible with rapid, operationally irreversible olefin

$$v = k[\mathrm{Sm}]^{1/2}[\mathrm{H_2}]^1[\mathbf{7}]^0 \qquad (1)$$

addition,[5b] a rapid preequilibrium involving a dialkyl or alkyl hydride dimer, and turnover-limiting Sm–C hydrogenolysis.[5b] Both k_{H_2}/k_{D_2} = 1.5–2.3 (25 °C)[23] and an increase in ee under non-mass-transport-limited conditions[24] (rapid hydrogenolytic interception of the Sm–alkyl intermediate) support this scenario.

In summary, these results demonstrate that organolanthanide coordination geometries can be constructed that effect, in a structurally understandable manner, asymmetric reductions of unfunctionalized olefins with high turnover frequencies and enantioselectivities. Extension to the organolanthanide-catalyzed hydroamination/cyclization of amino olefins[6] with high enantioselectivity is reported in a second communication.[25]

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Supplementary Material Available: Synthetic, spectroscopic, and analytical data, X-ray experimental details including tables of positional and anisotropic displacement parameters, and tables of bond lengths and angles (63 pages); listing of observed and calculated structure factor amplitudes for **6a**-Y and **6b**-Sm (70 pages). Ordering information is given on any current masthead page.

(14) Conticello, V. P.; Giardello, M. A.; Rheingold, A. L.; Stern, C. L.; Marks, T. J. Unpublished results.

(15) (*R*)-**6b**-Sm: $C_{66}H_{118}Si_6Sm_2$, space group *P*1; a = 8.993 (3) Å, b = 12.738 (2) Å, c = 16.549 (4) Å; α = 86.04 (2)°, β = 82.81 (2)°, γ = 72.91 (2)° (−120 °C); V = 1797 (2) Å^3, Z = 1. Structure solved by direct methods and refined to $R(F)$ = 0.026, $R_w(F)$ = 0.030 ($R_w(F)$ = 0.041 for the *S* configuration), for 8327 reflections having $I > 3\sigma(I)$. The two independent molecules differ slightly in orientation of the R* functionality. **6a**-Sm: diffraction-quality crystals only obtained for a 1/1 *R*/*S* mixed crystal; data collected on the isostructural Y analogue. $C_{33}H_{54}Si_3Y$, space group $P2_1$, a = 19.178 (4) Å, b = 8.736 (1) Å, c = 21.391 Å, β = 97.62 (2)° (−120 °C); V = 3552 (2) Å^3, Z = 4. Structure solved by direct methods and refined to $R(F)$ = 0.071, $R_w(F)$ = 0.083, for 3514 reflections having $I > 3\sigma(I)$.

(16) (a) Hydrides isolated after catalytic runs correspond spectroscopically to the independently prepared[16b] materials. (b) Conticello, V. P.; Brard, L.; Giardello, M. A.; Marks, T. J. Unpublished results.

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(20) [Catalyst] = 0.97 mM; [olefin] = 1.51 M; P_{H_2} = 755 Torr. Catalytic reactions were carried out under rigorously anhydrous anaerobic conditions.[1,4] Hydrogenation products were isolated by vacuum transfer followed by fractionation at reduced pressure, and purity was verified by ^{1}H NMR. Optical rotations were measured on an Optical Activity Ltd. AA-100 polarimeter using conditions identical to those reported in the literature.

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(22) [Catalyst] = 0.51–8.04 mM; P_{H_2} = 75–755 Torr; [olefin] = 0.75–3.4 M.

(23) Lin, Z.; Marks, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 7979–7985.

(24) For Table I entries 5 and 9, vortex mixing[5b] increases ee's to 80% and 16%, respectively.

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Common Origin of Clavulanic Acid and Other Clavam Metabolites in *Streptomyces*

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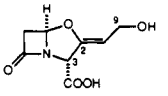
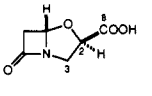
The potent β-lactamase inhibitor clavulanic acid (**1**)[1] co-occurs in *Streptomyces clavuligerus* with the clavam metabolites **2**–**5**.[2] The hydroxyethyl clavam **6** is known from an allied species, *S. antibioticus*.[3] These clavams share a common side chain configuration at C-2 and, importantly, lack the C-3 carboxyl and have the opposite ring fusion configuration to that in clavulanic acid.


1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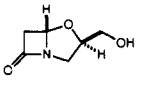
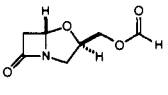

3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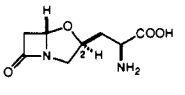
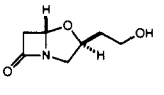
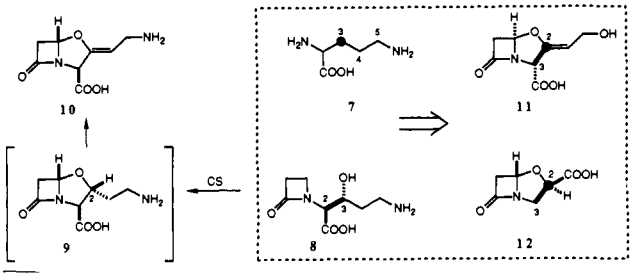

5


6

The structure of alanylclavam (**5**), from which the formation of **2**–**4**, **6**, and the dimeric clavamycins[4] could be easily rationalized, suggests that the biosynthetic origin of these clavams derives from utilization of L-ornithine (**7**) in the opposite regiochemical sense to that established for clavulanic acid (**1**),[5,6] i.e., such that the terminal nitrogen appears in the β-lactam ring rather than the α-amine. Moreover, a metabolic intermediate of **1**, dihydroclavaminic acid (**9**)[7,8] transiently involved in the oxidative cyclization/desaturation catalyzed by clavaminate synthase (CS),

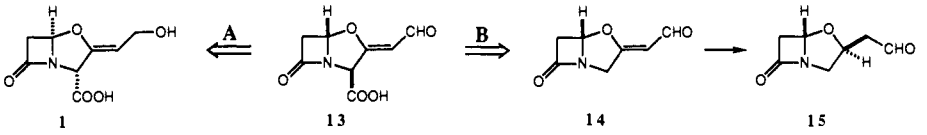
Scheme I



10 7 11 9 8 12

0002-7863/92/1514-2762$03.00/0

Scheme II



is of the opposite configuration at C-2 to all of the other known clavams [Scheme I; CS carries proclavaminic acid (**8**) to clavaminic acid (**10**)[9,10]]. Taken together these observations point to a related but separate pathway to the several clavams in *S. clavuligerus*. However, reported here are incorporation experiments with clavam-2-carboxylic acid (**2**) that imply extensive and unexpected biogenetic parallels between clavulanic acid (**1**) and the stereochemically divergent clavams (**2–6**).

A variant of *S. clavuligerus* (NCIB 11260) was used to produce both clavulanic acid (**1**) and clavam-2-carboxylic acid (**2**), the former serving as an internal control in incorporation experiments with the latter. Successive strain selection and considerable experimentation with several carbon sources resulted in a modified fermentation medium containing ground whole soy beans[11] to reproducibly obtain **2**. In an initial experiment with [U-^{14}C]-L-ornithine (0.5 mmol), **1** and **2** were isolated as their *p*-bromobenzyl (PBB)[5,12] and benzyl esters,[13] respectively. The specific incorporations of radioactivity were correspondingly 2.51% and 2.33%.[14] Similarly, a 1.0-mmol experiment gave a 4.60% specific incorporation of L-ornithine into **2**.

As L-ornithine gave roughly equivalent incorporations of radioactive label into clavulanic acid (**1**) and clavam-2-carboxylic acid (**2**), the nitrogen orientation and specificity of its utilization in the latter was examined using (2*S*,4*S*)-[4-^{2}H,5-^{13}C]ornithine (0.25 mmol).[15] With the expectation that the ^{13}C label would reside at C-3 in **2** and deuterium would be lost or retained, depending upon the stereochemistry and mechanism of oxygen incorporation at C-2 (detected as a β-isotope shift of the adjacent ^{13}C-enriched resonance[16]), we were suprised to find that no incorporation of *either* label was observed. On the other hand, the co-produced clavulanic acid showed a 2.6 ± 0.3% carbon enrichment at C-9, as expected.[5] While the absence of detected heavy isotope in **2** could be due to the operation of a large kinetic isotope effect in an oxidation/cyclization, such an outcome was thought less likely than L-ornithine incorporation in the same regiochemical sense as clavulanic acid (**1**); that is, the C-4/5 labels were lost in **2**. To examine this unanticipated possibility, [3-^{13}C]ornithine (**7**, 1.0 mmol) was prepared.[6] The incorporation of heavy isotope in **2** should either occur at the C-8 carboxylate or at C-2, depending upon whether the sense of ornithine utilization is correspondingly the opposite or the same as in clavulanic acid (**1**). Both clavam-2-carboxylate (**2**) and clavulanate (**1**) incorporated the precursor to equal extents to specifically label C-2 in each when analyzed by ^{13}C{^{1}H}NMR spectroscopy (3.5 ± 0.5% as their benzyl esters; see **7** → **11** and **12**, Scheme I). This unexpected parallel between clavam and clavulanate biosynthesis was pursued further by the synthesis[17] and incorporation of [2,3-$^{13}C_2$]-D,L-proclavaminic acid (**8**, 1.5 mmol; J_{CC} = 39.3 Hz), a later intermediate established in the biosynthesis of clavulanic acid. It gave intact incorporations of both labels into **1** (J_{CC} = 42.8 Hz) and **2** (J_{CC} = 30.7 Hz) as their corresponding benzyl esters at a specific efficiency of about 1% in each.[18]

These findings demonstrate the incorporation of L-ornithine in clavam-2-carboxylic acid (**2**) in the same regiochemical sense as clavulanic acid (**1**). Moreover, the relatively advanced biosynthetic intermediate to clavulanic acid, proclavaminic acid (**8**), is specifically and with equal efficiency utilized in clavamcarboxylate and clavulanate formation. It will be of interest to determine whether or not clavaminic acid (**10**), despite its overall oxidation state, is similarly used. That being so, the aldehyde **13**, proposed through oxidative deamination to be an intermediate in the striking "enantiomerization" of **10** to clavulanic acid (**1**; Scheme II, path A),[6] may also serve as an electron sink for decarboxylation to **14**. Reduction of **14** to **15** (Scheme II, path B) could account for the difficult inversion of carbinol stereochemistry from that at C-3 in **8** to that universally observed in the clavams, or pyridoxal phosphate-dependent reaction with clavaminate (**10**) could also give **15**. Moreover, the aldehyde **15**, through reduction to **6** or Baeyer–Villiger oxidation to **4**, provides entry into the remaining members of this series. However, exploration of these mechanistic possibilities must await further experimentation as does determination of either the net addition of a terminal carbon atom present in alanylclavam (**5**)[19] or uptake and subsequent decarboxylation of a C_6 or higher precursor.

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Registry No. **1**, 58001-44-8; **2**, 94425-20-4; **8**, 112240-59-2; L-ornithine, 70-26-8.

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(11) The fermentation medium was as described in ref 10 except 22.5 g/L of ground soy beans was used.
(12) The PBB esters were not used directly because of the difficulty in chromatographically separating *p*-bromobenzyl alcohol from the products. Therefore, the benzyl esters of both **1** and **2** were first prepared, and benzyl clavulanate was converted to its more readily crystallized *p*-bromobenzyl ester.
(13) Elson, S. W.; Oliver, R. S. *J. Antibiot.* **1978**, *31*, 586–592.
(14) The specific activity of clavam-2-carboxylic acid was approximated by dividing the product specific activity by three-fifths.
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(19) For example, see valclavam containing two additional carbons: Röhl, R.; Rabenhorst, J.; Zähner, H. *Arch. Microbiol.* **1987**, *147*, 315–320.