Table I. Rates of Hydration of CO_2 Catalyzed by Imidazole Derivatives[a] (pH 7.50 at 25 °C)

catalyst	10^{-3} M	buffer factor, 10^{-3} [b]	apparent k_{cat}, $M^{-1}\,s^{-1}$ [c]
imidazole	4.0	1.59	*d*
histamine	4.0	1.02	14.9
$(imidazole)_2Zn^{II}$ [e]	2.0	1.60	2.0
3-Zn^{II} [e]	2.0	0.60	16.2
$(histamine)_2Zn^{II}$ [e]	2.0	1.82	57.9
6-Zn^{II} [e]	2.0	1.95	166
human carbonic anhydrase B		k_{cat}/K_m, 1×10^7 [f]	
human carbonic anhydrase C		$k_{cat}K_m$, 8×10^7 [f]	

[a] The initial concentration of CO_2 was 1.25×1^{-2} M; see ref 15. [b] Determined by the direct titration and defined by equivalents of H^+ formed/absorbance increase of *p*-nitrophenol. [c] $[\Delta(HCO_3^-)_{formed}^{catalytic} - \Delta(HCO_3^-)_{formed}^{spontaneous}]/(CO_2)_0 \times (catalyst)_0 \times \Delta t$. This value is practically the same as k_{cat}/K_m. [d] Negligibly small. [e] Zinc chloride was used. [f] Reference 15.

bonate was followed with assistance of an indicator, *p*-nitrophenol.[15] The results obtained are summarized in Table I.

Although the catalytic activities of the present models are considerably lower than that of the native carbonic anhydrase (k_{cat}/K_m, $10^7\ M^{-1}\ min^{-1}$), it is significant and interesting to note that both the hydrophobic environment provided by cyclodextrin and the Zn^{2+} bound to the imidazoles[16] contribute to the carbonic anhydrase activity. Thus, as is seen from the Table I, each Zn^{2+} complex is more effective than the corresponding uncomplexed imidazole derivative and each cyclodextrin derivative is more effective than the corresponding catalyst without cyclodextrin. Another interesting finding is that the introduction of an additional base enhances the activity as is seen for the bis(histamino)cyclodextrin-Zn^{2+} (**6**-Zn^{2+}) compared with **3**-Zn^{2+}. Therefore, with regard to the present models, all three factors, Zn^{2+}-imidazole, hydrophobic environment, and base seem to help to generate the carbonic anhydrase activity.

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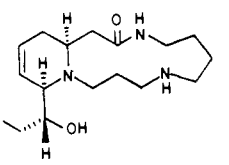
Stereochemistry of the Intramolecular Imino Diels–Alder Reaction

Sir:

The intramolecular version of the Diels–Alder reaction has recently been applied to synthesis of a wide variety of natural products and structurally interesting polycyclic molecules.[1,2] The stereochemistry of this process is now generally understood, and is predictable in most cases.[1-3] Recently, we demonstrated that the intramolecular imino Diels–Alder cyclization is a useful method for alkaloid synthesis.[4] Unlike the "all-carbon" case, the stereochemistry of the intramolecular imino cyclization has never been investigated.[5-7] We now report that this cyclization is, in fact, highly stereoselective but gives results *opposite* those usually found in closely analogous "all-carbon" systems.

As an initial target molecule for this study, we chose methyl dihydropalustramate (**2**), a degradation product of the *Equisetum* spermidine alkaloid palustrine (**1**).[8] This particular



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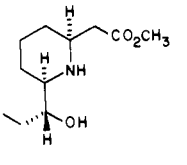

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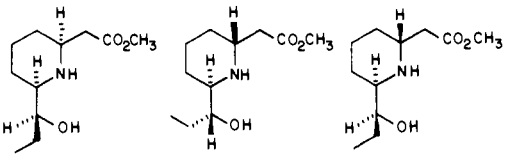
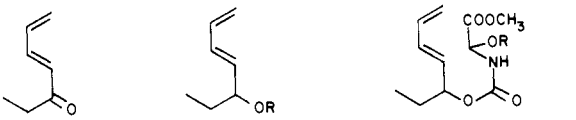
structure was chosen since all four possible diastereomers (**2–5**) have been prepared and fully characterized by Eugster and co-workers,[8] thus giving us the opportunity of making an unambiguous chemical correlation of relative stereochemistry.



3 **4** **5**

Treatment of butadiene with propionyl chloride in the presence of anhydrous stannic chloride (−42 °C, CH_2Cl_2), followed by treatment of the crude product with $CaCO_3$ (80 °C, 30 h), gave dienone **6** in 42% yield. Reduction of **6** with $LiAlH_4$ in ether gave diene alcohol **7** (92%; bp 26–30 °C (0.08) Torr; IR (film) 3360, 902 cm^{-1}) and this alcohol was converted into the carbamate **8** using sodium cyanate–trifluoroacetic acid in ether[9] (55%; mp 60–61.5 °C; IR (film) 1720, 1605, 908 cm^{-1}). Carbamate **8** condensed nicely with methyl glyoxylate[10] in refluxing acetone, giving the crystalline adduct **9** (83%; mp 65–67 °C; IR ($CHCl_3$) 3430, 3340, 1750, 1705 cm^{-1}).



6 **7** R = H; **8** R = $CONH_2$; **9** R = H; **10** R = $COCH_3$; **11** R = CONHPh

The hydroxyl group of **9** could be acetylated (acetic anhydride–pyridine–CH_2Cl_2, reflux) to afford the oily ester **10** (89%; IR (film) 3350, 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.10 (3 H, s), 3.81 (3 H, s)). Similarly, bis carbamate **11** was prepared by treating alcohol **9** with phenyl isocyanate in refluxing methylene chloride and was used without purification.

Pyrolysis of acetate **10** (PhBr, 230–240 °C, 2.5 h, sealed tube) gave an inseparable 45:55 mixture of what proved to be

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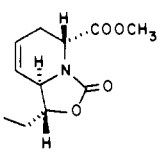
epimeric cycloadducts **12** and **13**, respectively, in 46% yield (NMR ($CDCl_3$) δ 1.1 (3 H, two overlapping t), 3.85 (3 H, s),



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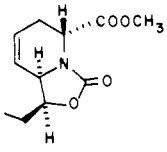
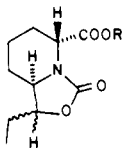


13

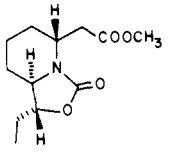
5.7 (2 H, m)) (vide infra).[11] None of *cis*-tetrahydropyridine ring-substituted adducts were detected. The total yield of these cycloaddition products could be increased to 59% if bis carbamate **11** was pyrolyzed under identical conditions.[12]

The structures of adducts **12** and **13** were established as follows. Hydrogenation of the mixture of **12** and **13** (5% Pd/C, ethyl acetate, atmospheric pressure, room temperature) gave dihydro esters **14** (99%) which on gentle hydrolysis (5% NaOH, MeOH, room temperature, 2.5 h) gave a mixture of epimeric acids **15** in 95% yield. This material was homologated



14 R=CH_3

15 R=H



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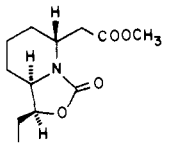
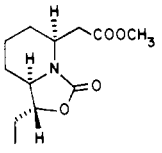


17

by an Arndt–Eistert sequence. Thus, treatment of the mixture of acids **15** with (1) PCl_5–ether, reflux, (2) CH_2N_2–ether, and (3) Ag_2O–CH_3OH gave an inseparable mixture of esters **16** and **17** in 40% overall yield (IR (film) 1745, 1730 cm^{-1}).

Authentic samples of racemic synthetic methyl dihydropalustramate (**2**) and isomers **3** and **4** obtained from Professor C. H. Eugster[13] were converted with carbonyldiimidazole (THF, reflux)[14] into cyclic carbamates **18**, **19**, and **16**, respectively. The authentic *cis*-piperidine isomers **18** and **19** had



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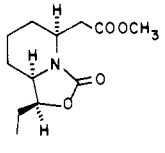

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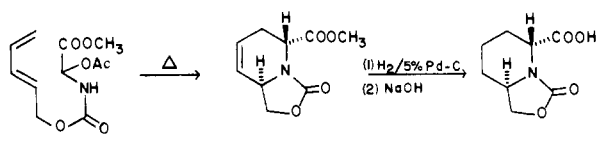
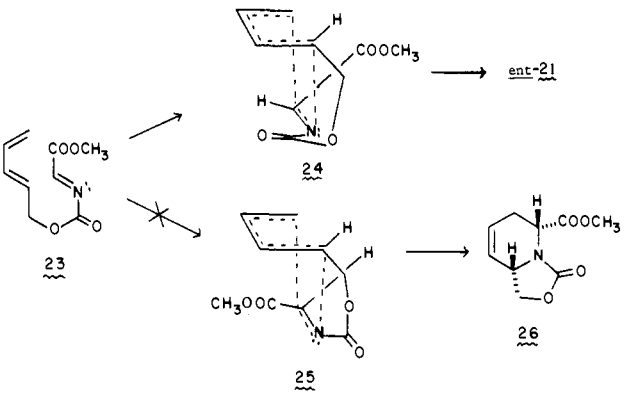
TLC properties identical with those of each other but clearly different from those of the authentic trans isomer **16** (R_f 0.30 and 0.22, respectively; silica gel PF_{254} plates, 1:1 hexane–EtOAc) which was inseparable from our synthetic mixture of **16** and **17**. Examination of the ^1H NMR spectra (200 MHz) of these compounds also indicated that our synthetic material belonged to the trans series of isomers. In addition, it was apparent from the spectra that isomer **17** is the major component of the synthetic mixture, indicating that Diels–Alder adduct **13** is the one formed in slight excess in the [4 + 2] cycloaddition step.

To confirm these stereochemical conclusions, diene **20** was prepared using the chemistry described above: NMR ($CDCl_3$) δ 2.10 (3 H, s), 3.79 (3 H, s), 4.62 (2 H, d, J = 6.5 Hz), 5.02–6.40 (6 H, m). Pyrolysis of **20** ($PhCH_3$, 215 °C, 2 h, sealed tube) gave a *single* cycloadduct proven to be **21**: 30%; NMR ($CDCl_3$) δ 3.78 (3 H, s), 5.8 (2 H, m) (vide infra). Hydrogenation of **21** (5% Pd/C–ethyl acetate, atmospheric pressure), followed by mild basic hydrolysis (5% NaOH, CH_3OH, room temperature, 2.5 h),[15] gave crystalline acid **22** (93% from **21**; mp 122.5–124 °C). A single-crystal X-ray diffraction analysis was carried out on this acid, firmly establishing its relative stereochemistry as shown in **22**.[16]



20 21 22

We speculate that these cyclizations may go through an initially formed, but unisolable, (*E*)-acylimine such as **23**.[19] Cyclization of **23** can occur via a transition state such as **24**,



23 24 25 26

having the *N-acyl* group endo, which would lead to the observed trans product **21**. Also possible is transition state **25**, having the *carbomethoxyl* group endo, leading to the cis adduct **26**. As pointed out by Oppolzer,[1a] in analogous "all carbon" intramolecular Diels–Alder reactions (i.e., N: = C–H),[20] one expects the terminal unsaturated group to be endo, thus leading via a transition state like **25** to the cis series of adducts. Just why this stereochemical outcome occurs in the carbon case is not at present completely clear, although an explanation has been suggested by Roush.[2r] Clearly, in the (*E*)-imino cases, the observed products would have to be derived from transition state **24** rather than **25**.[19] Work by Krow[6] on the acid catalyzed *inter*molecular imino Diels–Alder cycloaddition has indicated that π substituents on nitrogen invariably have a stronger endo-directing effect than identical substituents on carbon. This result may possibly be due to secondary orbital interactions, although no MO calculations have been reported on these acyl imine systems to date. This propensity for acyl substituents on nitrogen to direct endo thus carries over into the intramolecular case, and is apparently strong enough to overcome the usual situation where the terminal unsaturated group is the endo director.

We are currently studying the stereochemistry of some other intramolecular imino Diels–Alder cyclizations and will report this work shortly.

Acknowledgment. This work was generously supported by grants from the National Science Foundation (MPS75-01558 and CHE 78-19916). We thank Mr. Alan Freyer (PSU) for 200-MHz NMR spectra taken on a Bruker WP-200. Partial support for purchase of this instrument from the National Science Foundation Chemical Instrumentation Program is acknowledged. We thank Dr. William Roush (MIT) for helpful discussions.

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(11) We have been unable to separate isomers **12** and **13.** The isomeric *p*-nitrobenzyl esters prepared from acid **15** could be separated by analytical LC on a 1-ft μ-Bondapak C_{18} reverse-phase column (70:30 H_2O–CH_3CN, five recycles). Exact isomer ratios were determined at this stage.

(12) A detailed description of pyrolysis experiments with various leaving groups will be given in the full paper.

(13) We are extremely grateful to Professor Eugster for supplying us with these valuable samples.

(14) Cf. Kutney, J. P.; Ratcliffe, A. H. *Synth. Commun.* **1975,** *5,* 47.

(15) Reesterification of this acid with ethereal diazomethane established that no epimerization had occurred in the hydrolysis step.

(16) Single crystals of acid **22** (5:1 from benzene–ethyl acetate) belonged to space group $Pna2_1$, with a = 10.421 (2), b = 13.220 (4), and c = 6.270 (5) Å. A total of 2175 independent reflections were collected out to 2θ = 70° using a fully automated four-circle diffractometer (Enraf-Nonius) and monochromated Mo Kα (0.70930 Å) X-rays. After Lorentz, polarization, and background corrections, 571 reflections were judged observed [$I \geq 3\sigma(I)$]. Full-matrix, least-squares refinement with anisotropic temperature factors for C, N, and O and isotropic temperature factors for H converged to R = 0.039.[17] Complete data will be published in the full paper.[18]

(17) All programs used for this study were part of the "Structure Determination Package", Enraf-Nonius, Delft, Holland, 1975, revised 1977, and were implemented on a PDP 11/34 computer.

(18) We are grateful to Marguerite Bernheim (PSU) for carrying out this determination.

(19) If a (*Z*)-acylimine were an intermediate, these cyclizations would have to go through a transition state having *both* carbonyl groups exo. Although secondary orbital effects would not be significant in this transition state, such a possibility cannot be ruled out, based upon work by Roush[2r] and by White.[2a] It is conceivable that a *Z*-exo transition state might be favored over **24** based upon conformational and steric factors.[21] However, we have no way of proving whether the actual reacting acyl imine has the *E* or *Z* configuration.

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(22) Fellow of the A. P. Sloan Foundation, 1975–1979; Recipient of a Research Career Development Award from NIH (HL-00176 and HL-00541). To whom correspondence should be addressed at The Pennsylvania State University.

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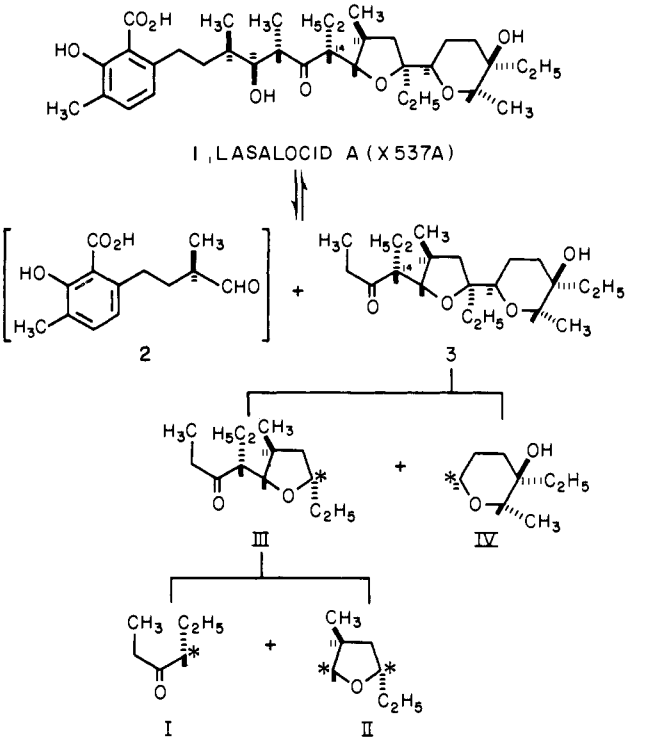
Total Synthesis of Lasalocid A (X537A)

Sir:

The polyether antibiotics[1] represent a class of structurally fascinating, complex organic molecules that possess potent physiological activity by virtue of their ionophoric character. While several members of this class have yielded to chemical total synthesis,[2] the biological importance of these molecules justifies continued excursions into their synthesis. In that vein, we report here a highly convergent, "building block" approach from carbohydrate precursors that has led to a total synthesis of lasalocid A (X537A)[3] and has broad potential as a strategy for the synthesis of other natural polyether ionophores, as well as many structural analogues.

Scheme I



Degradative work by Westley[4] showed that lasalocid A (**1**) underwent reverse aldol-type cleavage on either heat or base treatment, and, while the aldehyde **2** was unstable and underwent further degradation, the polyether ketone **3** was readily available. A key feature of both the present synthesis and that described by Kishi[2a] is the ability to affect an aldol-type condensation between these two degradation products. This point, as well as a synthesis of the benzyl ester of the acid aldehyde **2,** has been demonstrated by Kishi,[2a,5] and a synthesis of the stereochemically more demanding polyether ketone **3** then constitutes the requirements for a total synthesis. In addition, the similarity between this ketone **3** and the components of the other polyether antibiotics[1] meant knowledge gained in this effort might be applied to the other even more complex systems.

For this work, the ketone **3** was schematically envisaged as arising from the three subunits I, II, and IV (Scheme I). The plan called for the initial union of parts I and II, and then subsequent joining of that product III with the remaining subunit IV. This approach has the advantage of not only being highly convergent, but also amenable to extensive variation of the subunits used.

The starting point for the synthesis of the furanoid equivalent III was "α"-D-glucosaccharino-1,4-lactone (**4**)[6] (Scheme II). After appropriate blocking, this lactone was converted into the furanoid glycal **5**[7] (subunit equivalent II) by the procedure[8] developed in these laboratories. The ketone equivalent I was then added in the form of the α-butyryl side chain by enolate Claisen rearrangement of the glycalyl butyrate. Stereocontrol of the α-ethyl group in the ester **6** was made possible by control of the *E*/*Z* ratio of enolates formed[9] prior to Claisen rearrangement, and the diastereomer **6**[7] is the principal product (ratio 75:25) under the conditions shown. After purification

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