Kinetically Controlled Total Syntheses of *dl*-Trachelanthamidine and *dl*-Isoretronecanol

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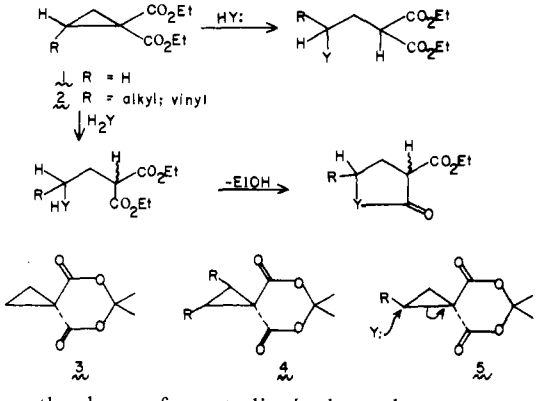
Abstract: The syntheses of the necine bases trachelanthamidine and isoretronecanol have been achieved in a stereospecific fashion. The stereochemistry was controlled via acyclic precursors **9** and **10.** Exploiting the well-known tendency of syn addition of carbenoids into double bonds, these were converted into activated phthalimido cyclopropanes **11** and **12,** respectively. The amines released upon treatment with hydrazine opened the cyclopropane rings in the spiro sense with complete inversion of stereochemistry to give, eventually, lactams **25** and **26.** These were converted to isoretronecanol and trachelanthamidine by reduction with lithium aluminum hydride.

Background

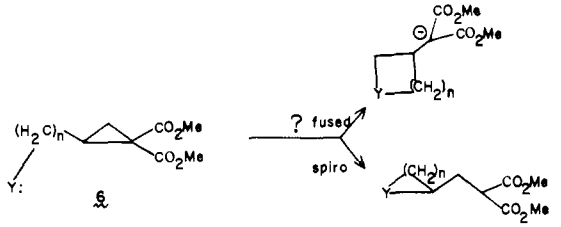
The tendency of doubly activated cyclopropanes, exemplified by compound **1,** to suffer ring opening under nucleophilic assault, was first recognized by Perkin[2] and clarified by Linstead and co-workers.[3] The meager utilization of this homo-Michael process in serious synthetic investigations[4] was, no doubt, largely due to the requirement of rather harsh reaction conditions (attended by mediocre yields) for such reactions, even in the presence of two geminal activating substituents.[5-8]

This already less than satisfactory situation in the parent compound, **1,** is further undermined with even modest monoalkyl substitution such as is found in system **2.**[9,10] The particular compound where R = ethyl reacts with amine nucleophiles to give a mixture of products, only with the greatest of reluctance.

We have felt that, in principle, the opening of systems such as **1** and **2** via nucleophiles of the type H_2Y constitutes a promising route for the synthesis of five-membered rings and have, accordingly, endeavored to render the process operationally useful. Our research has been directed at two levels. To facilitate intermolecular reactions, we have realized massive activation beyond that found in compound **1,** via recourse to the phenomenon of spiroactivation as exemplified in compound **3.**[11] Compound **3** reacts with a variety of weak nucleophiles under very mild conditions. Furthermore, as is already suggested in some published work, and will be more fully developed in future reports, spiroactivation allows for realization of ring opening reactions with symmetrically substituted cyclopropanes of the type **4**[12] and unidirectional ring opening (at the more hindered carbon) of monosubstituted systems such as **5,**[13] under mild conditions, in high yield.

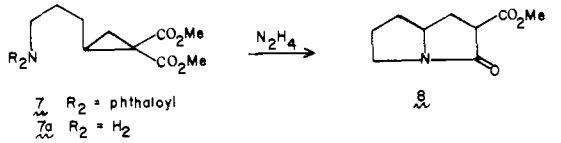


The other locus of our studies in the cyclopropane area has involved ring opening reactions via intramolecular nucleophiles. It was first necessary to define the ease and the sense (spiro vs. fused mode) of ring opening of systems such as **6.** We have not yet probed, in detail, the effects of additional substitution on the cyclopropane, beyond that represented in **6.** However, for the simple trisubstituted system, it was found that ring opening occurs under mild conditions, and that it occurs exclusively in the spiro sense for carbon,[14,15] oxygen,[16] and nitrogen[17] nucleophiles, when the resultant primary product of this process is a three-, five-, or six-membered ring. In the one case which was examined, wherein the product of spiro attack is a cyclobutane, this process is still kinetically preferred (2:1)[15] relative to the fused mode which produces a cyclopentane. In the cases shown below, the reactions are quite clean and occur under reasonable reaction conditions. *Thus, intramolecularity is also a massive activating influence on the ring opening of substituted cyclopropanes.*



Y	n	mode
C	1	spiro [14]
C	3	spiro [15]
N	3	spiro [17]
O	3	spiro [16]
C	4	spiro [15]
N	4	spiro [17]

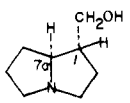
Among the cases studied to establish this data base was that of compound **7.**[17] Dephthaloylation of compound **7** with 1.2 equiv of hydrazine gave rise to an amine (**7a**) which, under the conditions of its formation (methanol–reflux), underwent two smooth cyclizations to yield **8** in nearly quantitative yield. In addition to providing powerful testimony for the enormous activating influence of the intramolecular circumstance, and for the predominance of the spiro mode, the transformation of **7** → **8** was provocative of the possibilities of using this new methodology for the total synthesis of the necine bases. These alkaloids have wide phytochemical distribution both in the free form and, more commonly, as esters of the necic acids in the context of Senecio alkaloids.



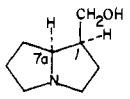
The structure, syntheses, and physiological properties of these alkaloids have been continuously and amply re-

viewed.[18-20] In this report, we focus on the two simplest bases, i.e., the diastereomers derived from 1-hydroxymethylpyrrolizidine.

Interestingly, all four optical permutants of 1-hydroxymethylpyrrolizidine are naturally occurring. The two diastereometric families are most commonly described in terms of the specific antipodes, trachelanthamidine and isoretronecanol, both of which have the 7aα H configurations. The strategy which has been used to control the stereochemistry at C(1) relative to C(7a) has developed along the following lines. Using synthetic intermediates wherein C(1) is subject to thermodynamic suasion, the substituent at this carbon may be induced, by equilibration, to assume an exo disposition.[21] This corresponds to the α configuration for the substituent (if C(7aH) is α), and provides a route to the trachelanthamidine series. Alternatively, catalytic hydrogenation of various derivatives with unsaturation at C(1) has been used[22,23] to provide an entry to the isoretronecanol series by reduction from the exo (B) face. This approach has recently been used in a clever way by Albonico to achieve syntheses of trachelanthamidine and isoretronecanol.[24a] A conceptually different route, due to Stevens[24b], recently afforded isoretronecanol.



trachelanthamidine
laburnine = $H_{7a}\beta$; $H_1\alpha$



isoretronecanol
lindelofidine = $H_{7a}\beta$; $H_1\beta$

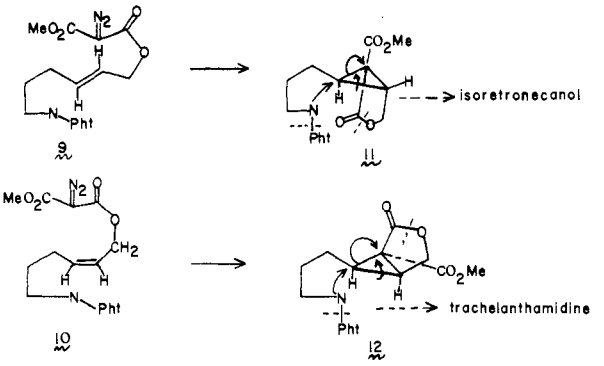
Our approach to this problem was conditioned by several considerations. First, we wished to demonstrate experimentally, what we intuitively believed to be the case, i.e., *that the intramolecular opening of activated cyclopropanes occurs with inversion of configuration*[25a] *without complication from any detectable S_N1 process.* Our previous studies in the intermolecular series[25b], addressed to this point, suggested that the intercession of unimolecular ionization (or radical) processes, of a type which might tend to randomize the stereochemical result,[26] would not be expected under the mild conditions which suffice for the intramolecular reaction.

Given the expectation of clean inversion of configuration in the spiro mode it follows that one should be able to achieve either the isoretronecanol or trachelanthamidine stereochemistry under strictly kinetic influences by recourse to cyclopropanes **11** and **12**.[27] These cyclopropanes would be the expected products of intramolecular insertion of diazo esters **9** and **10,** respectively.

It will be recognized that this strategy does not rely, at any point, on debatable postulates of steric accessibility, or on thermodynamic equilibration. We found the logical rigor of this kinetically based approach to be intrinsically attractive. Of greater practical import was the possibility of its extension to other schemes which would embrace the more complex pyrrolizidine bases bearing additional oxygen substituents (cf. platynecine, turneforcidine, hastanecine, and dihydroxyheliotridane)[18-20] at C(7). In such cases, the recourse to thermodynamic equilibration or to steric approach control in catalytic reduction may well be complicated. The successful application of this cyclopropane based strategy to the stereospecific total synthesis of (±)-trachelanthamidine and (±)-isoretronecanol is described below.

Results

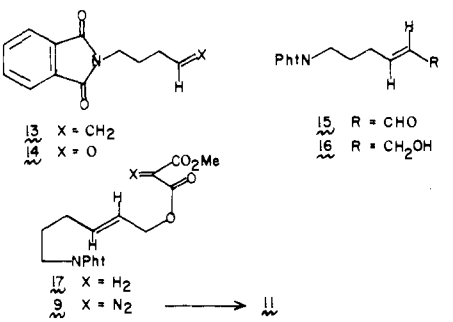
(i) Preparation of the Required Cyclopropanes. The synthesis of isoretronecanol began with the alkylation of potassium phthalimide with 5-bromo-1-pentene using phase-transfer conditions first developed in our laboratory by J. Dynak.[28] Compound **13,** mp 34–35 °C, was thus obtained in 95% yield. Subsequent to Dynak's work, there recently appeared a description of the value of such catalysis on Gabriel type alkyl-



ations.[29] Ozonolysis of **13** gave 4-phthalimidobutyraldehyde (**14**), mp 79–80 °C, in 67% yield. Reaction of **14** with triphenylformylmethylenephosphorane[30a] gave (85%) trans enal **15,** mp 90–91 °C, δ ($CDCl_3$) 6.1 (RCH=C*H*CHO), 6.9 (RC*H*=CHCHO, $J_{CH=CHCHO}$ = 16 Hz).

Reduction to the trans allylic alcohol, **16,** was achieved with sodium borohydride in ethanol at 0 °C. Crude **16** was acylated with carbomethoxyacetyl chloride to afford **17** (72% from **15**). The desired **9** was obtained (93%) by diazo transfer using tosyl azide.[30b] Diazomalonate **9** was converted to cyclopropane **11** in 65% yield by heating with copper bronze in toluene under reflux.[30c]

THE SYNTHESIS OF CYCLOPROPANE 11

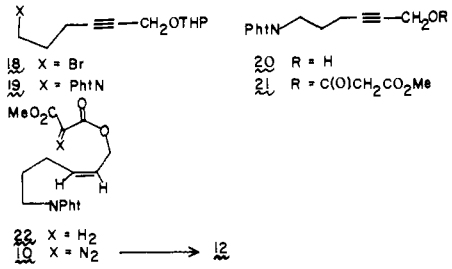


The *Z* diazomalonate, **10,** was synthesized through a different methodology. The lithium salt of propargyl alcohol tetrahydropyranyl ether was alkylated by 1,3-dibromopropane to give the bromo-OTHP system **18.** This was now used to alkylate potassium phthalimide under phase-transfer catalysis to afford **19** (76%). The phthalimido-yne-ol, **20,** was obtained from **19** upon treatment with tosyl acid in methanol. Acylation of **20** with carbomethoxyacetyl chloride gave **21,** which was submitted to catalytic reduction with hydrogen on 5% palladium–barium sulfate in the presence of methanol containing traces of quinoline. The crude dihydro product, **22,** was directly converted to **10** (63% from **19**) by the action of tosyl azide. Examination of the 250-MHz NMR spectrum of the olefinic diazo ester thus obtained indicated it to be largely *Z* isomer **10** contaminated with variable amounts (5–10%) of the *E* isomer **9.** Thus the semihydrogenation of the alkyne linkage in **21** gave some trans olefin **17,** in addition to desired cis product **22.**[31] Fortunately, diazo compound **10** could be rendered homogeneous by several recrystallizations from ether at low temperatures.

Given the nature of our study, we accepted a serious attrition in yield for the advantage of operating with a homogeneous diazo cis olefin. Thermolysis of pure **10** under copper catalysis gave an 81% yield of the desired cyclopropane **12.** The NMR spectra of **11** and **12** are analytically easily distinguishable at 250 MHz and one can deduce that they each emerged free of one another from the cyclopropanation reactions of their precursor *Z* and *E* olefins. Thus, the carbenoid insertions of **9** and **10** are, indeed, stereospecific within the limits of our detection (ca. 2%).

The success of the venture now rested on the regio- and stereospecificity of the intramolecular homoconjugate addition process.

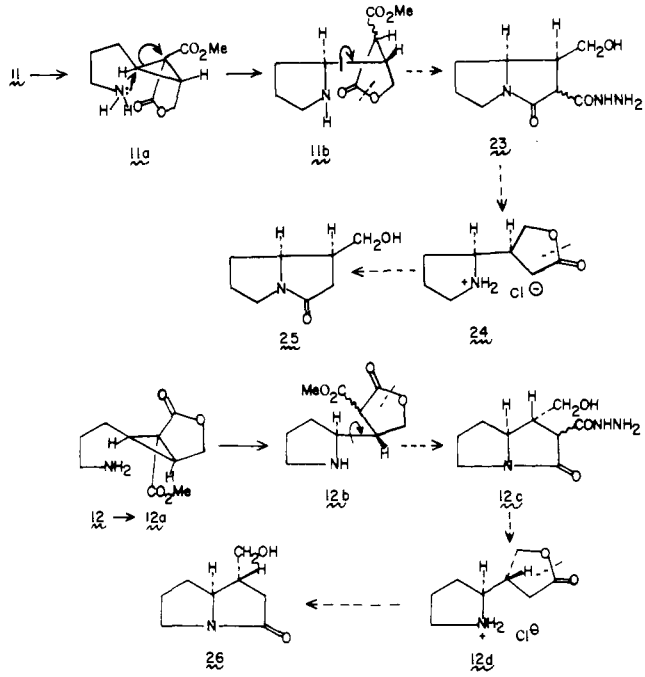
THE SYNTHESIS OF CYCLOPROPANE 12



(ii) Synthesis of *dl*-Isoretronecanol and *dl*-Trachelanthamidine. Several attempts to execute the dephthaloylation of **11** with nearly stoichiometric amounts of hydrazine hydrate in hot methanol (cf. **7** → **8**) were not rewarding and led to rather substantial recovery of starting material and complex mixtures of products. We surmised, but did not prove, that hydrazinolysis of the strained lactone may be competitive with dephthaloylation of the imide linkage. This stands in contrast to the methyl esters of **7**, whose slow reactions with hydrazine are not competitive with dephthaloylation. Thus, one might have attempted to deal with this problem by modifying the lactone in the direction of, for instance, a hydroxy methyl ester. However, we chose to attack with an excess of hydrazine. Not surprisingly then, treatment of **11** with 3 equiv of hydrazine hydrate in methanol under reflux for **4** h afforded a nearly quantitative yield of a crude product whose molecular weight (*m/e* 213) and spectral properties ($\lambda_{max}^{CHCl_3}$ 3.02, 3.40, 5.93 μm; δ $CDCl_3$, absence of CO_2CH_3 resonance) indicated it to be largely a lactam hydrazide. Assuming the occurrence of inversion in the intramolecular opening of **11a**, the relative chirality of the product C(7a) and C(1) in the product would be formulated as shown in **23** (vide infra). Rather than deal extensively with a system with extraneous (and difficulty interpretable) chirality at C(2), crude **23** was subjected to the action of hot aqueous HCl. Evaporation of the volatiles left a salt whose infrared spectrum contained a broad envelope (2.8–4.2 μm) and a "carbonyl" maximum at 5.62 μm, which is suggestive of a γ-lactone. Accordingly, we formulate the salt in terms of structure **24**. Of course, whether the alcohol has been acylated by the original lactam or hydrazide carbonyl function is neither known nor of any significant consequence. The required deacylation of the β-dicarbonyl system had been achieved.

Treatment of the presumed **24** with sodium methoxide–methanol afforded homogeneous **25** in 80% yield from **11**. The gross structure of **25** as a hydroxy γ-lactam is supported by its mass (*m/e* 155, parent) and infrared ($\lambda_{max}^{CHCl_3}$ 2.85, 6.00 μm) spectra. Its composition purity is further vouchsafed by its C, H, and N combustion analysis. Its stereochemical purity could not be guaranteed at this point, since even its richly detailed 250-MHz NMR spectrum was not fully resolved. This point was only established when its epimer became available, and the two high-field ^1H NMR spectra could be evaluated in conjunction with one another (vide infra).

Having achieved a satisfactory command over the experimental details of the required type of conversion, we performed the same operations on cyclopropane **12**. Reaction of **12** with excess hydrazine hydrate followed by treatment of the resultant product with hot aqueous HCl followed by neutralization with sodium methoxide–methanol gave an 85% yield of hydroxymethyllactam **26**. The proton NMR spectra of both compounds, which were measured at 250 MHz, unambiguously showed them to be uncontaminated with one another. The chromatographic mobilities of the two epimers are sufficiently close that we were confident that we did not, through inadvertence, separate small amounts of **25** from the process which gave **26** or small amounts of **26** from the process which gave **25**. That this is, in fact, the case was further demonstrated by starting with diazo compound **10**, which was contaminated with ca. 7% of the *E* isomer **9**. This mixture gave a very comparable mixture of cyclopropanes **11** and **12**, which was transformed to a mixture of ca. 93% **26**/7% **25**. *We have thus demonstrated that the intramolecular homoconjugate openings are occurring with complete stereospecificity. There is no detectable crossing of the pathways starting with pure* **9** *and* **10**.



There remained only the verification (the 250-MHz NMR spectra are not decisive in this regard) of the logically anticipatable result, i.e., that **25** has the isoretronecanol stereochemistry and **26** has the relative chirality of trachelanthamidine. This result would be the one expected from inversion of configuration in the ring mutation step. It will be recognized this stereochemical outcome is not contingent on the particular sequence **11** → **11a** → **11b** → **23**. The same overall result would arise from hydrazide intermediates derivable from either **11a** or **11b**. The precise stage of acyl hydrazide formation is of no consequence with respect to the relative chirality of C(7a) and C(1).

Reduction of lactam alcohol **25** with lithium aluminum hydride in tetrahydrofuran afforded *dl*-isoretronecanol in 95% yield. The melting point of the picrate, 189.5–191 °C, was undepressed upon admixture with an authentic sample provided by Professor Leonard.

Similarly, $LiAlH_4$ reduction of **26** afforded a 94% yield of *dl*-trachelanthamidine. The melting point of its picrate, 174–175.5 °C, corresponds closely with that reported in the literature (174–175 °C). In view of the difficulties of obtaining pure authentic samples of these alkaloids, their 250-MHz NMR spectra are provided in the microfilm edition of the journal.

25 —LAH→ isoretronecanol

26 —LAH→ trachelanthamidine

The objectives formulated for this study were thus completed. The additional substitution present in cyclopropanes

11 and **12** relative to model system **7** proved to be of no discernible complication to the ring opening process. The principle of spiro opening, given this set of ring forming options (spiro → **5** vs. fused → **6**), has again been sustained, now in a stereochemical situation where clean inversion has been rigorously demonstrated. The groundwork for a systematic attack on the more complex necine bases would appear to be secure. Attempts to realize these strategies in the realm of laboratory practice will be described in future reports.

Experimental Section[33]

Preparation of *N*-(4-pentenyl)phthalimide (13).[34] A mixture prepared from 5-bromo-1-pentene (10.0 g, 0.067 mol) potassium phthalimide (13.5 g, 0.073 mol) and tetrabutylammonium bromide (0.550 g, 0.0017 mol) and 600 mL of benzene was heated under reflux for 6 h. The mixture was diluted with 500 mL of ether and filtered through Celite. Evaporation of the volatiles in vacuo left a residue which was chromatographed on 100 g of silica gel. Elution with 3:1 hexane–ethyl acetate afforded compound **13** (13.65 g, 95%), mp 34–35 °C, lit.[35] 34–35 °C.

Preparation of 4-Phthalimidobutyraldehyde (14). Ozone was bubbled through a solution of compound **13** (227 mg, 1.06 mmol) in 10 mL of 1:1 methanol–methylene chloride at −60 °C. When a blue color persisted, the reaction was stopped. Excess ozone was blown off with a stream of nitrogen. To the solution at −60 °C was added by syringe 0.25 mL of dimethyl sulfide. Stirring was continued at −20 °C to room temperature over 3 h. Evaporation of the volatiles left a residue which was chromatographed on 23 g of silica gel. Elution with 9:1 hexane–ethyl acetate afforded **14** (151 mg, 66%) as colorless crystals, mp 79–80 °C (hexane): $\lambda_{max}^{CHCl_3}$ 3.32, 3.41, 3.55, 3.68, 5.63, 5.80, 5.85 μm; δ ($CDCl_3$) 3.5–3.9 (t, J = 6 Hz, 2), 9.65 (m, 1); *m/e* 217 (parent).

Anal. ($C_{12}H_{11}O_3N$) C, H, N.

Preparation of (*E*)-6-Phthalimidohex-2-enal (15). A solution of compound **1** (217 mg, 1.0 mmol) and triphenylformylmethylenephosphorane (6.08 mg, 2.0 mmol)[30a] in 10 mL of benzene was heated under reflux for 22 h. Evaporation of the volatiles left a residue which was chromatographed on 16 g of silica gel. Elution with 4:1 hexane–ethyl acetate afforded **15** (210 mg, 85%) as colorless crystals, mp 90–91 °C (hexane–benzene): $\lambda_{max}^{CHCl_3}$ 3.35, 3.44, 3.58, 3.68, 5.65, 5.86 5.93 μm; δ ($CDCl_3$) 3.6–3.9 (t, J = 6 Hz, 2), 5.9–6.4 (d,t, J_d = 16, J_d = 9, J_t = 1 Hz, 2), 6.6–7.2 (d,t, J_d = 16, J_t = 6 Hz, 2), 9.3–9.6 (d, J = 8 Hz, 1); *m/e* 243 (parent).

Anal. ($C_{14}H_{13}O_3N$) C, H, N.

Direct Conversion of 15 to (*E*)-6-Phthalimidohex-2-ene-1-ol Carbomethoxyacetate (17). To a solution of compound **15** (243 mg, 1.0 mmol) in 3 mL of chloroform cooled to 0 °C was added a solution of sodium borohydride (19 mg, 0.5 mmol) in 3 mL of anhydrous ethanol. After being stirred for 8 min at 0 °C, the reaction mixture was quenched by the addition of 2 mL of 10% HCl. Extraction with three 15-mL portions of chloroform and evaporation gave crude alcohol **16.** To this residue, dissolved in 5 mL of anhydrous ether, was added 0.13 mL of pyridine and carbomethoxyacetyl chloride (151 mg, 1 mmol). The system was stirred for 2 h at 0 °C, after which the reaction was quenched with 5 mL of water. The aqueous phase was reextracted with three 15-mL portions of ether. The organic layers were dried over magnesium sulfate. The residue left upon evaporation of the volatiles in vacuo was chromatographed on 60 g of silica gel. Elution with 4:1 hexane–ethyl acetate gave 250 mg (72%) of **17** as a colorless oil: $\lambda_{max}^{CHCl_3}$ 3.24, 3.35, 5.71, 5.85 μm; δ ($CDCl_3$) 3.33 (s, 2), 3.5–3.8 (m, containing a singlet, ca. 3 H at 3.65 ppm, 2), 4.85 (d, J = 5 Hz, 2), 5.6–5.8 (m, 2); *m/e* 345.

Preparation of (*E*)-Diazo Ester 9. To a solution of compound **3** (180 mg, 0.52 mmol) in 2 mL of acetonitrile was added triethylamine (0.073 mL, 0.52 mmol) followed by tosyl azide (103 mg, 0.52 mmol). The resultant system was stirred for 24 h at room temperature. The volatiles were evaporated in vacuo and the residue was taken up in 8 mL of ether. The ether solution was extracted successively with dilute aqueous KOH then dried over magnesium sulfate. The residue left after evaporation of the volatiles in vacuo was chromatographed on 8 g of silica gel. Elution with 85:15 hexane–ethyl acetate afforded compound **9** (180 mg, 93%) as a yellow oil: $\lambda_{max}^{CHCl_3}$ 3.25, 3.33, 4.63, 5.71, 5.86 μm; δ ($CDCl_3$) 1.5–2.3 (m, 4), 3.6–3.9 (m, containing a singlet, ca. 3 H at 3.85), 4.65 (d, J = 5 Hz, 2), 5.6–5.9 (m, 2), 7.6–8.0 (m, 2); *m/e* 343 (parent − 28).

Preparation of *exo*-Phthalimidopropylcyclopropane (11). A solution of compound **17** (349 mg, 0.94 mmol) in 12 mL of toluene was heated under reflux in the presence of 512 mg copper–bronze for 19 h. After filtration and evaporation of the solvent in vacuo, the residue was chromatographed on 20 g of silica gel. Elution with 7:3 hexane–ethyl acetate gave 208 mg (65%) of **11** as colorless crystals, mp 124–126 (benzene–hexane): $\lambda_{max}^{CHCl_3}$ 3.25, 3.33. 5.64, 5.86 μm; δ ($CDCl_3$) 1.6–1.9 (m, 5), 2.55–2.65 (m, 1), 3.6–3.8 (t, J = 6 Hz, 2), 3.85 (s, 3), 4.15–4.35 (m, 2), 7.6–7.9 (m, 4); *m/e* 343 (parent).

Anal. ($C_{18}H_{17}O_6N$) C, H, N.

Preparation of *dl*-3-Oxoisoretronecanol (25). A solution of compound **11** (200 mg, 0.583 mmol) in 8 mL of methanol was heated under reflux in the presence of hydrazine hydrate (87.5 mg, 1.748 mmol) for 4 h. The volatiles were evaporated in vacuo. The residue (**23**) was heated under reflux in 8 mL of 10% HCl for 13 h. Evaporation of the volatiles afforded a water-soluble residue (**24**). This was suspended in 8 mL of methanol. To this was added 4 mL of 25% sodium methoxide–methanol and the resulting system was heated under reflux for 2 h. After neutralization with aqueous ammonium chloride, the system was extracted with five 10-mL portions of chloroform. The combined organic phases were dried over anhydrous magnesium sulfate and the residue left upon evaporation of the volatiles was chromatographed on 20 g of Florisil. Elution with 3:1 benzene–acetone afforded **25** (72 mg, 80%) as a yellow oil: $\lambda_{max}^{CHCl_3}$ 2.85, 6.00 μm δ ($CDCl_3$) (250 MHz) ref 32.

Anal. ($C_8H_{13}O_2N$) C, H, N.

Preparation of *dl*-Isoretronecanol. To a solution of compound **25** (30 mg, 0.193 mmol) in 2 mL of THF was added lithium aluminum hydride (18 mg, 0.482 mmol) and the system was heated under reflux for 14 h. To this was added successively 20 μL of water, 20 μL of 15% aqueous sodium hydroxide, and 60 μL of water. Evaporation of the volatiles left a residue which was leached with ether. The ether solution was dried over magnesium sulfate. Evaporation of the volatiles afforded *dl*-isoretronecanol (26 mg, 95%) as a yellow oil: $\lambda_{max}^{CHCl_3}$ 2.93, 3.34 μm; δ ($CDCl_3$) ref 32; *m/e* 141 (parent); picrate mp 189.5–191 °C (lit.[22] 189–190 °C); mmp 189–192 °C.

Preparation of 6-Bromohex-2-yn-1-ol OTHP Ether (18). To a solution of propargyl alcohol OTHP (9.8 g, 0.07 mol) in 100 mL of dry THF and 12.6 g (0.07 mol) of dry hexamethylphosphoramide cooled to −30 °C and maintained under an inert atmosphere was added dropwise a solution of 1.5 M *n*-butyllithium in hexane (47 mL = 0.07 mol). The resultant reaction mixture was stirred at −30 °C and to it was added dropwise a solution of 1,3-dibromopropane (28.3 g, 0.14 mol) in 70 mL of THF. The resultant system was stirred at room temperature for 22 h. Most of the THF was evaporated in vacuo and the residual contents were poured into 500 mL of water. Extraction with ether followed by evaporation of the volatiles, first at the water pump and then at the oil pump, left a residue of 19.5 g, which was chromatographed on 75 g of silica gel. Elution with hexane gave 6.5 g of a mixture of **18** and 1,3-dibromopropane. Elution with chloroform gave 5.5 g of pure **18.** Rechromatography of the impure fractions gave an additional 3.1 g (total = 47%) of **18:** $\lambda_{max}^{CHCl_3}$ 3.32, 4.42 μm; *m/e* 261 (parent); δ ($CDCl_3$) 1.4–2.7 (m, 10), 3.4–4.1 (m, 4), 4.12 (t, J = 2 Hz, 2), 4.80 (br s, 1).

Preparation of 6-Phthalimidohex-2-yn-1-ol OTHP Ether (19). A system prepared from potassium phthalimide (4.62 g, 0.025 mol), bromide **18** (5.62 g, 0.0218 mol), tetra-*n*-butylammonium chloride (0.11 g), and 50 mL of benzene was heated under reflux for 6 h. After dilution with ether, the mixture was filtered through Celite. Evaporation of the volatiles at the water pump left a residue of 7.7 g. Chromatography on silica gel gave, upon elution with 1:1 chloroform–hexane, compound **19** (5.33 g, 76%) as a pure oil: $\lambda_{max}^{CHCl_3}$ 3.30, 4.42, 5.61, 5.81 μm; δ ($CDCl_3$) 1.3–2.4 (m, 10), 3.4–4.0 (m, 4), 4.1 (t, J = 2 Hz, 2), 4.8 (br s, 1), 7.8 (m, 4).

Anal. ($C_{19}H_{21}O_4N$) C, H, N.

Preparation of 6-Phthalimidohex-2-yn-1-ol (20). A solution of compound **19** (1.8 g, 5.5 mmol) in 120 mL of methanol containing 0.05 g of *p*-toluenesulfonic acid was stirred at room temperature for 48 h. Evaporation of the volatiles at the water pump left a residue which was taken up with 200 mL of 1:1 chloroform–ether. The organic layer was extracted with water and dried over anhydrous $MgSO_4$. Evaporation of the volatiles left a residue (1.46 g) which was chromatographed on 60 g of silica gel. Elution with 2:3 hexane–chloroform gave compound **20** (1.23 g, 93%): $\lambda_{max}^{CHCl_3}$ 2.86, 4.46, 5.62, 5.82 μm; *m/e* calcd for $C_{14}H_{13}NO_3$, 243.0895, found, 243.0891 (parent); δ ($CDCl_3$) 1.6–2.6 (m, 4), 2.74 (br, s, 1), 3.78 (t, J = 7 Hz, 2), 4.14 (t, J = 2 Hz,

2), 7.76 (m, 4).

Preparation of 6-Phthalimidohex-2-yn-1-ol Carbomethoxyacetate (21). To a solution of alcohol **20** (1.50 g, 6.17 mmol) in 50 mL of ether containing pyridine (0.630 g, 8 mmol) was added dropwise a solution of carbomethoxyacetyl chloride (0.950 g, 7 mmol) in 30 mL of ether. The reaction mixture was stirred for 1.5 h at 0 °C. After dilution with ether, the system was extracted with water. The ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the volatiles left a residue (2.0 g) of **21** suitable for the next step: $\lambda_{max}^{CHCl_3}$ 3.30, 4.50, 5.75, 5.82 μm; *m/e* calcd for $C_{18}H_{17}O_6N$, 343.1055, found, 343.1051 (parent); δ ($CDCl_3$) 1.8–2.5 (m, 4), 3.41 (s, 2), 3.73 (s, 3), 3.80 (t, J = 6 Hz, 2), 4.62 (t, J = 2 Hz, 2), 7.60–8.00 (m, 4).

Semihydrogenation of 21. Formation of 22 and 17. A solution of crude **21** (2.0 g) as prepared above in 20 mL of methanol containing quinoline (0.2 g) was stirred with 0.2 g of 5% palladium on barium sulfate under an atmosphere of hydrogen. After filtration of the catalyst, the volatiles were removed in vacuo and the residue was taken up in 2:1 ether–chloroform. The solution was extracted with 1% aqueous HCl followed by water and brine and the organic layers were dried over anhydrous magnesium sulfate. Evaporation of the volatiles left a residue of 1.82 g, which was used in the next step.

Formation of (*Z*)-Diazo Ester 10. To a solution of the crude olefinic malonate mixture (1.82 g) prepared as above in 35 mL of acetonitrile containing 1.11 g of triethylamine was added tosyl azide (1.2 g). The reaction mixture was stirred at room temperature for 39 h. The volatiles were removed in vacuo and the residue was dissolved in 200 mL of ether. The ether solution was extracted with cold 5% aqueous sodium hydroxide solution followed by water and brine. The organic phase was dried over anhydrous magnesium sulfate. Evaporation of the volatiles in vacuo left a residue (1.8 g) which was chromatographed on 70 g of silica gel. Elution with 3:2 hexane–chloroform gave 1.33 g (58% from **20**) of diazo compounds **10** and **9.** Analysis of the 250-MHz NMR spectrum of the mixture in conjunction with the spectrum of pure **9** (see above) and pure **10** (vide infra) showed this to be a 93:7 mixture of **10**/**9.** Four recrystallizations from ether afforded 500 mg of pure **10**, mp 60–61 °C: $\lambda_{max}^{CHCl_3}$ 3.30, 4.65, 5.68, 5.82 μm; δ ($CDCl_3$) 1.8–2.5 (m, 4), 3.72 (t, J = 7 Hz, 2), 3.82 (s, 3), 4.80 (d, J = 6 Hz, 2), 5.55–5.80 (m, 2), 7.60–8.01 (m, 4).

Anal. ($C_{18}H_{17}N_3O_6$) C, H, N.

Preparation of Cyclopropane 12. A solution of homogeneous diazo compound **10** (234 mg, 0.63 mmol) in 7.5 mL of toluene was heated under reflux in the presence of 343 mg of copper–bronze for 22 h. After filtration of the catalyst and removal of the volatiles in vacuo, the residue was chromatographed on 15 g of silica gel. Elution with 7:3 hexane–ethyl acetate gave cyclopropane **12** (176 mg, 81%) as a crystalline solid, mp 110–112 °C (benzene–hexane): $\lambda_{max}^{CHCl_3}$ 3.27; 3.36, 5.64, 5.84 μm; *m/e* 343 (parent); δ ($CDCl_3$) 1.5–1.6 (m, 2), 1.7–2.0 (m, 2), 2.2–2.5 (m, 1), 2.7–2.9 (m, 1), 3.6–3.9 (m, 5), 4.1–4.3 (m, 1), 4.4–4.5 (m, 1), 7.6–8.0 (m, 4).

Anal. ($C_{18}H_{17}O_6N$) C, H, N.

Preparation of *dl*-3-Oxotrachelanthamidine (26). A solution of cyclopropane **12** (167 mg, 0.487 mmol) in 7 mL of methanol containing 95% hydrazine hydrate (73.0 mg, 1.461 mmol) was heated under reflux for 5 h. Evaporation of the volatiles first at the water pump and finally at the oil pump left a residue (**12a**) which was heated under reflux in 7 mL of 10% aqueous HCl for 18 h. Evaporation to dryness left a salt (**12b**) which was suspended in 9 mL of methanol. To this was added 2.5 mL of 25% sodium methoxide–methanol. The resultant system was heated under reflux for 2 h. The reaction was neutralized with saturated aqueous ammonium chloride. Most of the methanol was evaporated at the water pump and the aqueous system was extracted with five 10-mL portions of chloroform. The organic layers were dried over anhydrous magnesium sulfate. Evaporation of the volatiles left a residue which was chromatographed on 13 g of Florisil. Elution with 3:1 benzene–acetone afforded 64 mg of lactam alcohol **26** as an oil: $\lambda_{max}^{CHCl_3}$ 2.84, 3.29, 5.98 μm; δ ($CDCl_3$) ref 32; *m/e* 155 (parent).

Anal. ($C_{18}H_{13}O_2N$) C, H, N.

Preparation of *dl*-Trachelanthamidine. A solution of compound **26** (67 mg, 0.432 mmol) in 5 mL of tetrahydrofuran containing lithium aluminum hydride (41 mg, 1.08 mmol) was heated under reflux for 15 h. The reaction was worked up by successive addition of 40 μL of water, 40 μL of 15% aqueous sodium hydroxide, and 120 μL of water. Evaporation of the volatiles left a residue which was leached with ether. The ether solution after filtration of the salts was dried over anhydrous magnesium sulfate. Evaporation of the volatiles afforded *dl*-trachelanthamidine (57 mg, 94%) as a yellow oil: $\lambda_{max}^{CHCl_3}$ 2.91, 3.37 μm; *m/e* 141 (parent); δ ($CDCl_3$) ref 32, picrate mp 174–175.5 °C (lit.[21] 174–175 °C).

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Supplementary Material Available: the 250-MHz spectra of lactam alcohols **25** and **26** and of trachelanthamidine and isoretronecanol (2 pages). Ordering information is given on any current masthead page.

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Cyclic Peptides. 17. Metal and Amino Acid Complexes of *cyclo*(Pro-Gly)$_4$ and Analogues Studied by Nuclear Magnetic Resonance and Circular Dichroism[1]

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Abstract: The ion-binding and conformational properties of the synthetic cyclic octapeptide, *cyclo*(L-prolylglycyl)$_4$ [*cyclo*-(Pro-Gly)$_4$], have been investigated via ^{13}C nuclear magnetic resonance (NMR) and circular dichroism (CD) spectroscopy. *cyclo*(Pro-Gly)$_4$ forms complexes of 1:2 and 1:1 cation–peptide stoichiometries with a variety of alkali and alkaline earth cations. Among the metal cations *cyclo*(Pro-Gly)$_4$ selectively binds the larger cations, such as Cs^+ and Ba^{2+}, with binding constants comparable to those of naturally occurring cyclic peptides. The cyclic peptide also forms complexes with ammonium salts of amino acids in which 1:1 and 2:1 cation–peptide stoichiometries are observed. In addition, the cyclic peptide recognizes whether the D or L enantiomer of the amino acid salt is bound. In water solution ca. 75% of the *cyclo*(Pro-Gly)$_4$ conformers contain cis peptide bonds. By contrast, in chloroform solution the cyclic peptide adopts a C_4-symmetric conformer containing all trans peptide bonds and is stabilized by four 1 ← 3 hydrogen bonds (γ turns). The cyclic peptide–cation complexes are also C_4-symmetric on the NMR time scale and contain all trans peptide bonds but do not contain 1 ← 3 hydrogen bonds. The conformational type inferred for the cyclic peptide–cation complexes in solution agrees well with the solid-state structure determined by x-ray crystallography. Initial results indicate that the octapeptide, *cyclo*(D-Phe-L-Pro-Gly-L-Pro)$_2$, and the decapeptide, *cyclo*(Pro-Gly)$_5$, also bind cations strongly forming complexes having the highest symmetry allowed by the sequence and all peptide bonds trans in chloroform solution.

Cyclic peptides possess potent biological activities as antibiotics, toxins, hormones, and ion-transport agents. Progress in relating the activity of these peptides to their conformational states has been summarized in recent comprehensive reviews.[2] The role of particular intermolecular and intramolecular forces in producing a functional conformation can be explored through synthesis and study of selected cyclic peptides following a rationale which we have indicated.[3] This rationale pools the information from spectroscopic measurements and theoretical calculations to deduce solution conformers which are consistent with all of the experimental data. In this way salient features of the conformations are determined, but the detail and precision of x-ray crystallographic results on solid samples cannot be matched in solution studies.

Cyclic hexa-, octa-, and decapeptides of the *cyclo*(Pro-Gly)$_n$ series have shown a wide range of complexing powers in their binding of many alkali and alkaline earth cations, ammonium groups, and substituted alkylammonium groups in the form of amino acid ester salts.[4] Further, the demonstrated ability of the *cyclo*(Pro-Gly)$_n$ peptides to distinguish D from L enantiomers of amino acids[4] suggests that related cyclic peptides could be employed to resolve racemic mixtures of amino compounds.

This report focuses mainly on *cyclo*(Pro-Gly)$_4$ which has been shown to transport cations across lipid bilayers[5] and which has a cation complex whose crystal structure is reported in an accompanying paper.[6] Herein, the conformational and cation-binding properties of *cyclo*(Pro-Gly)$_4$ in solution will be compared to those of its cyclic hexapeptide homologue,[7] as well as to those of an octapeptide analogue and the decapeptide homologue. In addition, the structures of *cyclo*(Pro-Gly)$_4$ complexes in solution will be compared to the crystal structure.

It is noteworthy that *cyclo*(Pro-Gly)$_4$ and related peptides form "sandwich" complexes in solution. These include the following (with cation–peptide stoichiometries indicated in parentheses): "peptide sandwich" (1:2), "double-decker sandwich" (2:2), and "cation sandwich" (2:1). It has been suggested that the biological activity of naturally occurring ionophores (such as valinomycin, antamanide, and enniatin B) may be related to their ability to form sandwich complexes.[2a,b] For instance, it has been proposed that an ionophore sandwich (1 cation:2 ionophores) could be an intermediate in a relay mechanism of cation transport.[2c]

Experimental Section

The synthesis and characterization of *cyclo*(Pro-Gly)$_3$ and *cyclo*-(Pro-Gly)$_4$ have been reported.[8] During the syntheses of *cyclo*(Pro-Gly)$_5$ and *cyclo*(D-Phe-L-Pro-Gly-L-Pro)$_2$, intermediate peptides were identified by their infrared and NMR spectra and were monitored by