Stereorational Total Synthesis of (±)-Porantherine[1]

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Abstract: An efficient stereorational total synthesis of (±)-porantherine (**1**), the major alkaloid isolated from *Poranthera corymbosa*, is described. The synthesis features two stereospecific Mannich-type condensations. Novel dialkylpiperidine **20** is prepared by the addition of 2 equiv of 5-lithio-2-pentanone 2′,2′-dimethylpropylene ketal (**19**) to *O*-methylvalerolactim. Porantherine is obtained in 31% overall yield.

Composed of herbs, shrubs, and trees, the *Euphorbiacea* family accounts for 220 genera and 4000 species distributed worldwide.[2] Most of the species are poisonous and are characterized by an irritating milky sap. Cyanogenetic glycosides have been detected in members of the *Poranthera* genus.[3] In particular, *Poranthera microphylla* Brogn. (small-leaved poranthera) has been implicated in a number of cases of livestock poisoning in New South Wales and Queensland, Australia.[4] A closely related species, *Poranthera corymbosa* Brogn. (clustered poranthera), in addition to being cyanogenetic, is rich in alkaloids. From a crude extract (0.4% based on dry plant weight, at Torrington, N.S.W.), Lamberton and co-workers at CSIRO Chemical Research Laboratories in Melbourne have isolated six alkaloids from this woody shrub.

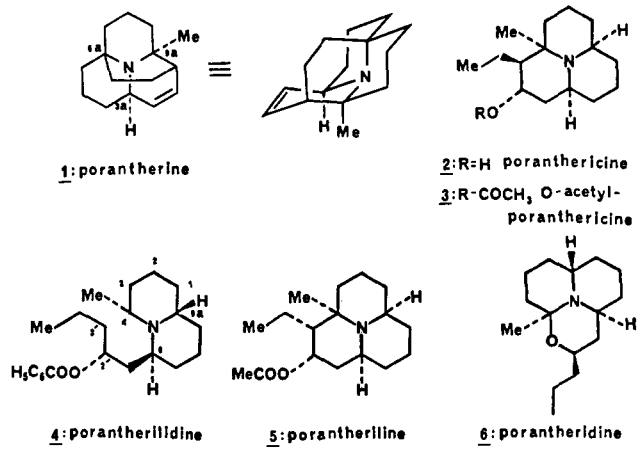
The structures of porantherine (**1**),[5-7] porantheticine (**2**),[8,9] porantherilidine (**4**), 6-(2′-(benzoyloxy)pentyl)-4-methylquinolizidine,[10] and porantheridine (**6**)[8,11] have been determined by X-ray crystallographic studies on derivatives of these four alkaloids. The structures of *O*-acetylporantheticine (**3**) and porantheriline (**5**) have been determined by chemical correlation to the antecedent alkaloid[12] (Scheme I). Several minor bases have been observed in the crude extracts but were not fully characterized due to insufficient quantities of material.

The Poranthera alkaloids are unusual since they are the first known natural products from a plant possessing a reduced 9b-azaphenalene ring skeleton. Related alkaloids are found in the defensive secretions (reflex bleeding) of insects. European ladybugs produce coccinelline, precoccinelline, (sp *Coccinelline septempuncta*)[13,14] and propylein (sp *Propoylaea quatuordecimpunctata*).[15] Hippodamine, convergine, and myrine have been isolated from the North American ladybug, *Hippodamia convergens*.[16] Feeding studies with labeled sodium acetate have established that seven such subunits serve as a precursor to a C_{14}-polyketide chain. Condensation with ammonia, or its equivalent, appropriate Mannich condensations, and loss of the terminal carboxyl group can account for the entire group of ladybug alkaloids.[17] Analogously, a route involving a C_{16}-polyketide chain has been proposed for the *P. corymbosa* alkaloids.[5,18] In fact, biosynthetic intermediates for all of these alkaloids are reminiscent of pinidine derivatives,[19] the Lobelia alkaloids,[20] and the fire ant venoms.[21]

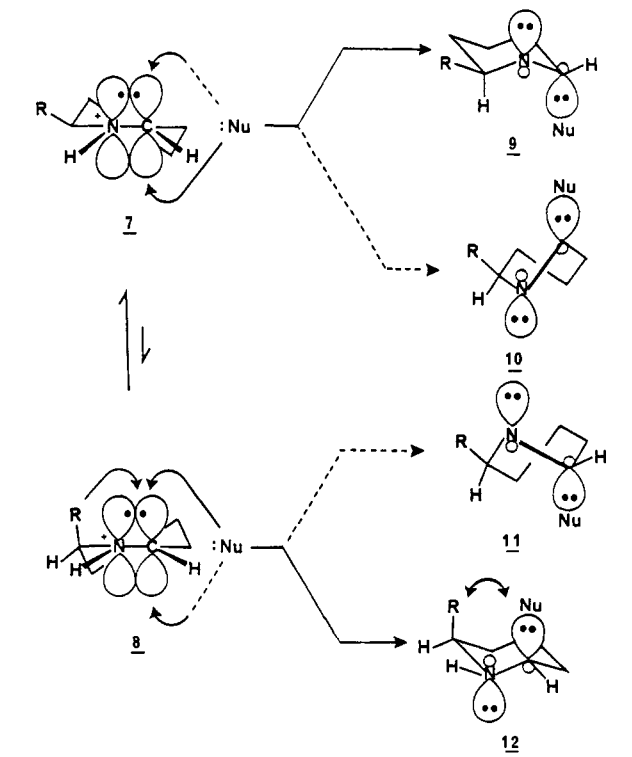
Shortly after the initial reports by the Australian group, Corey and Balanson at Harvard achieved a computer-aided, biomimetic synthesis of (±)-porantherine (**1**)[22] in 2.5% overall yield. More recently, the related alkaloids, porantherilidine (**4**) and porantheridine (**6**), have been synthesized by a route featuring a stereoselective 1,3-dipolar addition of an olefin to a nitrile oxide.[23]

Our interest in these molecules arises from a consideration of the steric and/or stereoelectronic arguments[24] developed in order to explain the remarkable stereoselectivity observed for the Robinson–Schöpf reaction[25] as applied to the total synthesis of the ladybug defense alkaloids, coccinelline and precoccinelline.[26] In the conformationally mobile system investigated, nucleophilic addition to tetrahydropyridinium conformers **7** and **8** can proceed through four possible transition states (**9**–**12**) wherein maximum orbital overlap is preserved between the incoming nucleophile (Nu) and the developing unshared electron pair on the nitrogen atom

Scheme I



Scheme II



† Deceased March 9, 1984.

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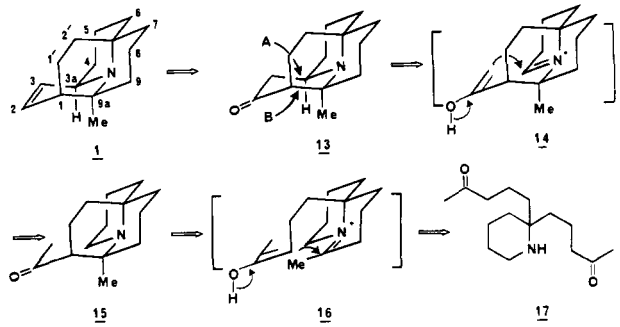
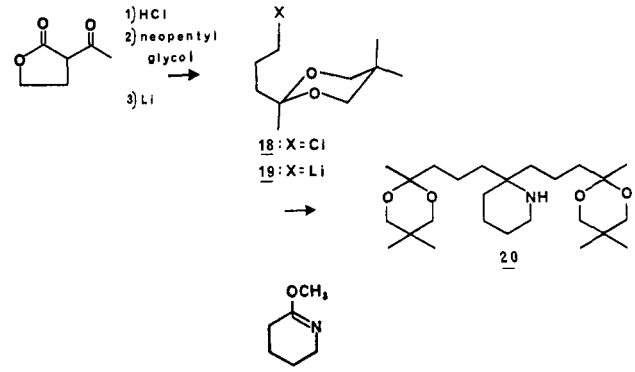
Scheme III



Scheme IV



(Scheme II). This results in products where the sp^3-hybridized orbitals are generated in an anticoplanar fashion. Resulting from parallel addition, twist boat like representations **10** and **11** are kinetically disfavored. Of the remaining chair-like transition states, **12** suffers from a 1,3-interaction between R and the incoming nucleophile, therefore; **9** is the most favored energetically. This explains the stereochemistry found in the product. Application of these principles had lead to total syntheses of monomorine I,[27] gephyrotoxin 223,[28] makomakine, aristoteline, hobartine,[29] and karachine.[30] In the case of an attempted synthesis of lycopodine, failure to heed these principles thwarted an otherwise reasonable plan.[31] More recently we realized that incorporation of the nucleophile into the R group of tetrahydropyridinium conformers **7** and **8** may provide, via the lower transition-state manifold, products having stereochemistry defined by **12**. To test these implications in a conformationally rigid or biased system, we designed a stereorational synthesis of the major alkaloidal constituent of *P. corymbosa*, (±)-porantherine (**1**).

Results and Discussion

The retrosynthetic analysis, involving two key Mannich condensations, is shown in Scheme III. We envisioned porantherine arising from reductive elimination of tetracyclic ketoamine **13** in an aprotic Bamford–Stevens reaction.[32] In this manner we expected to achieve high regioselectivity and suppress competing retro-Mannich reactions. On appraisal of stereoelectronic factors, one notes bonds marked A and B (in structure **13**) are anti to the lone pair of electrons on the nitrogen atom. In principle, these two bonds may be formed stereospecifically by addition of the respective thermodynamic and kinetic enols to the appropriate imminium salts (vide infra). Thus, bond A may be closed to give only the requisite stereochemistry at C_{3a} in (±)-porantherine. According to our synthetic plan, oxidation of tricyclic ketoamine **15** must give the necessary imminium ion (**14**). Formation of the bond marked B, again in an antiparallel sense as depicted in **16**, is constrained to give the required stereochemistry at carbon atom 9a. Finally, gem-disubstituted piperidine **17** is expected to serve as precursor to the substituted endocyclic imminium ion (**16**).

Our point of departure is the addition of 2 equiv of an or-

(2) The family name is derived from the African species *E. resinifera*. This species was so named by Juba, king of Mauretania, after his Greek physician Euphorbos, who used the plant as an emetic and a cathartic in the first century A.D. Since that time many useful substances have been obtained from these plants. For example, *Hevea* and *Manihut* yield rubber, while *Croton* and *Ricinus* afford medicinal products. *E. clutiodes* and *E. hibernia* have been used, respectively, by the Australian aborigines and the peasantry of South Ireland as fish and arrow poisons. A familiar example is the Christmas poinsettia (*E. pulcherrimia*) from Mexico and Central America.

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(7) The incorrect stereoformulation given in ref 5, 6, and 8 has been corrected. See the erratum in: *Tetrahedron Lett.* **1973**, 794.

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(18) (a) A polyketide progenitor has been postulated for (+)-9-aza-1-methylbicyclo[3.3.1]nonan-3-one, an alkaloid isolated from the Australian costal plant *Euphorbia atoto* Forst. See: Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1967**, *20*, 561. (b) Curiously, ladybugs belonging to the species *Adalia bipunctata* contain adaline, 9-aza-1-*n*-pentylbicyclo-[3.3.1]tridecan-3-one, a homologue of the *E. atoto* alkaloid. See: Tursch, B.; Braekman, S. C.; Daloze, D. Hootele, C.; Losman, D.; Karlsson, R.; Pasteels, J. M. *Tetrahedron Lett.* **1973**, 201. (c) Both of these alkaloids closely resemble pseudo-pelletierine, an alkaloid from *Punica granatum*. See: Pelletier, S. W. *Chemistry of the Alkaloids*; Van Norstrand Reinhold: New York, 1970; p 399. (d) Demonstrating how it may be dangerous to draw conclusions about structurally similar compounds arising from the same biochemical pathway, lysine is noted as the precursor to pseudopelletierine. See: Geissman, T. A.; Crout, D. H. G. *Organic Chemistry of Secondary Palnt Metabolism*; Freeman, Cooper: San Francisco, 1969; p 445. Plants of the genus Lycopodium have yielded three related alkaloids, lycocernuine, anhydrolycocernuine, carlinianine, and the triterpine α-onocerine. See: Miller, N.; Hootele, C.; Braekman-Danheur, C.; Braekman, J. C. *Bull. Soc. Chim. Belg.* **1971**, *80*, 629. (e) Crepidine, isolated from *Dendrobium crepidatum*, may have evolved along similar lines. Kierkegaard, P.; Pilotti, A.; Leander, K. *Acta Chem. Scand.* **1970**, *24*, 3757.

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ganometallic reagent to *O*-methylvalerolactim[33] (Scheme IV). Perusal of the literature[34] indicated Grignard reagents were marginally effective for the preparation of gem-disubstituted bases of this type. Generally the monosubstituted product is obtained, frequently in low yield (40%). This is particularly true for the less reactive alkyl Gringnard reagents having four or more carbon atoms. In addition, we wished to introduce the carbonyl functionality as a cyclic ketal. Previous investigations[35] indicate that this sensitive functionality would not survive the harsh reaction conditions required (refluxing dibutyl ether). For this reason we examined the addition of organolithium reagents to the lactim ether.[36] When *n*-butyllithium or 4-pentenyllithium[22] was added in excess to *O*-methylvalerolactim, the anticipated disubstituted amines, 2,2-dibutylpiperidine and 2,2-di-4-pentenylpiperidine, were obtained in 72% and 85% yield, respectively. Satisfied with these model studies we turned our attention to the introduction of the protected carbonyl appendages. Although we prepared the lithium reagent from 5-chloro-2-pentanone ethylene ketal, the yield (35%) of organometallic reagent was inferior to that observed from 5-chloro-2-pentanone 2′,2′-dimethylpropylene ketal (**18**). Chloro ketal **18** was readily synthesized in 80% yield by azeotropic distillation of neopentyl glycol with 5-chloro-2-pentanone in benzene.[37]

The yield of 5-lithio-2-pentanone 2′,2′-dimethylpropylene ketal (**19**) is quite sensitive to the reaction conditions, being optimum (85%) for ether solutions containing 10–15% THF at −25 °C. Also, the amount of sodium in the lithium has a pronounced effect; highest yields are obtained with 1%+ sodium–lithium alloy. Routinely, chloro ketal **18** is added dropwise to a cold, stirring, ether suspension of lithium sand.[38] The solvent is removed in vacuo and replaced with pentane or benzene. The resultant suspension is filtered under argon and then titrated.[39] When stored under an argon atmosphere, the solution prepared in this manner was stable for weeks in the freezer. If the original ether solution is simply filtered and not replaced with hydrocarbon solvent, the titer gradually decreases over the course of several days. For example, titration of a 0.425 M solution after 72 h at 0 °C indicated a 0.32 M solution. The addition of tetramethylethylenediamine (TMEDA) (1 equiv, distilled from *n*-butyllithium and stored with 4-Å molecular sieves under nitrogen) to this organolithium solution accelerated the decomposition process at 0 °C. A solution originally 0.474 M titrated 0.23 M after 24 h and 0.15 M after 48 h. Additionally, a large amount of 2,2-dimethyl-1,3-propanediol crystallized from the quenched reaction mixture on cooling in the freezer.

It is interesting to note that the organometallic reagent extracted into hydrocarbon solvent contains exactly $^1/_2$ of 1 equiv of lithium chloride, as determined by simple gravimetric analysis of precipitated silver chloride. If required, halide-free material may be obtained by reacting the halide-containing solution with mercuric chloride in THF to generate, in excellent yield after purification, bis(4-oxopentyl 2′,2′-dimethylpropylene ketal)mercury. Reaction with excess lithium metal gives the halide-free material in a high overall yield process.[40]

Yields of disubstituted amine **20** were disappointing (15%) when excess amounts of organolithium reagent were used in the addition. Additives such as TMEDA, or attempts to activate the imino ether and/or the organometallic reagent with $AlCl_3$, $TiCl_4$, and BF_3 etherate,[41] as well as reactions with the corresponding organocerium (prepared from CeI_3[42] in THF) and dialkylmercurial reagents, did not improve the yield of amine **20**. Infrared and TLC analyses of the crude reaction mixture obtained after workup indicated that a significant amount of starting lactim was present, but none was recovered after chromatography due to volatility. Inverse addition, longer reaction times (up to 3 days), variation of temperatures (−78, −40, −25, 0, 25, 65, 78 °C), variation of the solvent polarity (pentane, benzene, mixtures of ether–benzene, THF–benzene, ether, THF), and combinations thereof did not increase the amount of product. In similar experiments with the addition of tetramethytlethylenediamine (TMEDA, 1 equiv) to the lithium reagent prior to the addition of the lactim, no improvement of the yield (3–7%) of the diketal amine **20** was observed. Furthermore, the chromatography was complicated by the presence of TMEDA. In the experiments described above the organolithium reagent was generally still present when the reaction was quenched. When the reaction was conducted in refluxing THF or benzene in the presence of TMEDA, no lithium reagent was detected after 48 h. Control experiments without lactim also behaved in this manner.

Treatment of the lactim with the halide-free organometallic reagent produced slightly higher yields of the desired amine. However, in light of the extra purification step and the toxic nature of dialkylmercurial compounds, the increase in yield did not justify the extra effort. We suspected that deprotonation was the problem here. Therefore, an addition–neutralization sequence, in which one cycle constitutes addition of 2.5 equiv of organolithium to 1 equiv of lactim ether, followed by neutralization with 1 equiv of THF-diluted water, was employed. Although a yield of 70% was obtained after six cycles, this procedure consumed large quantities of our valuable lithium reagent. As such, it was not suitable for our synthetic purposes. It may be noted a similar addition–neutralization sequence was successfully employed by Corey and Balanson with a less valuable organolithium reagent in effecting the addition of 1-lithio-4-pentene to an imine.[22]

Accordingly, we found it more efficient to prepare **20** by using an excess of the imino ether. Unlike the lithium reagent, the unreacted (or deprotonated) lactim may be recovered after aqueous workup and distillation. With the use of a fivefold excess of *O*-methylvalerolactim, disubstituted piperidine **20** was obtained as a colorless oil in 80% yield (based on limiting organolithium reagent). These observations strongly suggest that deprotonation of the imino ether may be responsible for the low yields. The organometallic reagent itself, or the lithium 2,2-dialkylamide, can serve as the possible base. Such deprotonation has been observed for *O*-methylvalerolactim when reacted with lithium dialkylamides at −78 °C.[43]

Two additional comments regarding the addition of lithium reagent **19** to *O*-methylvalerolactim are appropriate at this point. First, in contrast to alkyl- and alkenyllithium reagents the overall rate of addition to *O*-methylvalerolactim is qualitatively slower (days vs. hours) with the lithio ketal derivative. It may be that the oxygen atoms of the ketal moiety render the oligomeric lithium complex more stable, and hence, more sluggish toward nucleophilic

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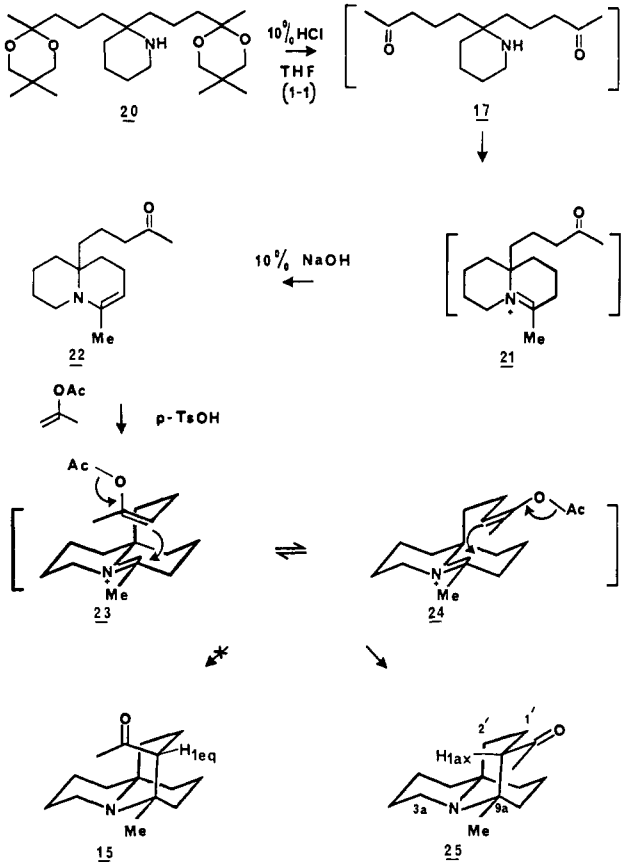
Scheme V



addition of this sort. The presence of ethereal solvents or additives such as TMEDA disrupts this association, and the reagent decomposes at a rate faster than addition. Second, with respect to the mechanism of addition of the lithioketal reagent to the imino ether, we suggest the second equivalent of organometallic reagent adds much faster than the first. This is reasonable since the gem-disubstituted amine **20** is obtained and the corresponding imine derivative is not isolated or detected in the reaction mixture by infrared spectroscopy when excess *O*-methylvalerolactim is used. On comparison with ketones, the less reactive nature of esters prallels this behavior toward organometallic reagents.[44]

Attempts to induce crystallization of amine **20** were unsuccessful. However, on treatment with anhydrous oxalic acid, oxalate derivative **20a** was obtained in 91% yield after recrystallization from ethyl acetate (Scheme II). Conversion to the oxalate derivative provided a means of storing and easily manipulating the oily free base. With adequate supplies of amine **20** in hand, we turned our efforts toward procuring methyl-substituted endocyclic enamine **22** via the intermediacy of **17** and **21** (Scheme V). Hydrolysis of the cyclic ketals in **20** (or **20a**) with 10% aqueous hydrochloric acid for 1 h followed by basic workup, extraction, and column chromatography furnished the desired enamine (**22**) as a somewhat unstable colorless oil in greater than 90% yield. In this step, it may be noted that removal of the ketal protecting group is accompanied by subsequent carbon–nitrogen bond formation and, in part, compensates for its use.

We were now in a position to form bond B to give a tricyclic ring system. Ketoenamine **22** was refluxed with 5 equiv of isopropenyl acetate and 2 equiv of *p*-toluenesulfonic acid in benzene for 48 h. Neutralization with 10% sodium hydroxide, extraction with ether, and column chromatography afforded tricyclic amino ketone **25** as a colorless oil in 95% yield. Thermodynamic enol acetate **24** is the reactive species.[22,45] In this reaction, ring closure can only occur to give the desired stereochemistry at C_{9a}. However, there exists the possibility of forming epimers **15** and **25**, placing the acetyl group at C_1 in an axial or equatorial position (Scheme V).

The 200-MHz ^1H NMR spectrum indicated, by the presence of singlets at 0.92 and 2.00 ppm corresponding to the C_{9a} methyl group and the acetyl moiety protons, respectively, that only a single isomer was obtained. One would predict that isomer **25** would be formed in preference to isomer **15**, which places the acetyl function in an unfavorable axial position. Moreover, models suggest a strong steric interaction occurs between the axial acetyl group of **15** and the C_{3a} axial proton; this crowding is not present in **25**. Molecular mechanics calculations (MM2) performed on epimers **15** and **25** indicate a large difference in relative strain energy (3.75 kcal/mol) for these rigid systems. This difference in energy readily accounts for the presence of only one isomer observed under our equilibrating reaction conditions. This difference in strain energy is largely attributable to the interaction between the acetyl moiety and the C_{3a} axial proton.

As convincing as these arguments seemed they are experimentally unsupported. This question of stereochemistry could be settled in a straightforward unambiguous manner by use of ^1H NMR spectrometry. The methine proton at C_1 will be coupled to the vicinal axial and equatorial protons. This interaction will give rise to a characteristic doublet signal with coupling constants indicative of relative orientation.[46] Therefore the problem was reduced to one of identifying the resonance resulting from the C_1 proton. Previous reports on spin systems in which protons are separated by four single bonds with intervening sp^2-hybridized carbon atoms describe long-range coupling.[47] Two distinct mechanisms have been reported. In rigid cyclohexanone fragments, the familiar planar zig-zag or "W"-type coupling similar to that observed in fully saturated rigid systems is displayed by the α-equatorial protons. The second interaction mechanism involves the central π-bond. Here, maximum $\sigma-\pi$ overlap is favored when the α-protons are constrained to a diaxial configuration. So, regardless of the C_1 proton orientation (axial or equatorial), a mechanism is available by which coupling to the acetyl methyl protons may be observed. In unstrained rigid systems reported, long-range coupling constants are typically 1–3 Hz for both types of interaction. However, in freely rotating systems as is ours, values of 0.3–0.6 Hz have been measured.[48] For this reason we performed a 500-MHz 2D shift-correlated ^1H NMR experiment.[49] We decided a COSY-45 experiment with N-type selection would give the detailed, long-range-coupling information required. As such, we can firmly establish the resonance resulting from the C_1 methine proton.

The one-dimensional projection and two-dimensional spectrum are shown in Figure 1. The contour map shows that the methine proton exhibiting long-range coupling to the acetyl methyl moiety resonates at 2.85 ppm (labeled H_1) and as expected gives rise to the most downfield resonance. The COSY-45 experiment also shows this proton is coupled to three other protons. They are the vicinal bowsprit protons marked $H_{1'ax}$ and $H_{1'eq}$ (J = 13 and 6 Hz) and the axial proton marked H_{9ax} (not fully resolved at 500 MHz) through a planar W-type coupling. Stereochemical assigment is based on the observed coupling pattern. As shown, a large (J = 13 Hz) and a small (J = 6 Hz) coupling associated with the adjacent axial and equatorial protons is consistent with

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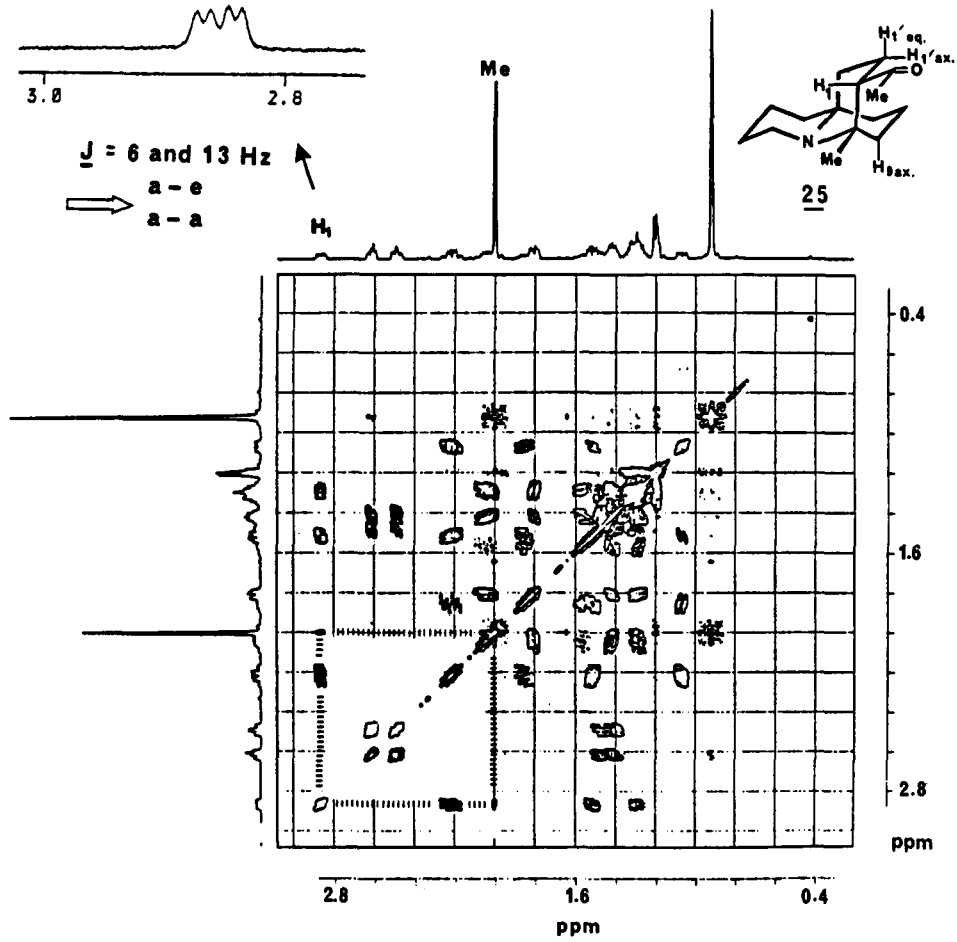
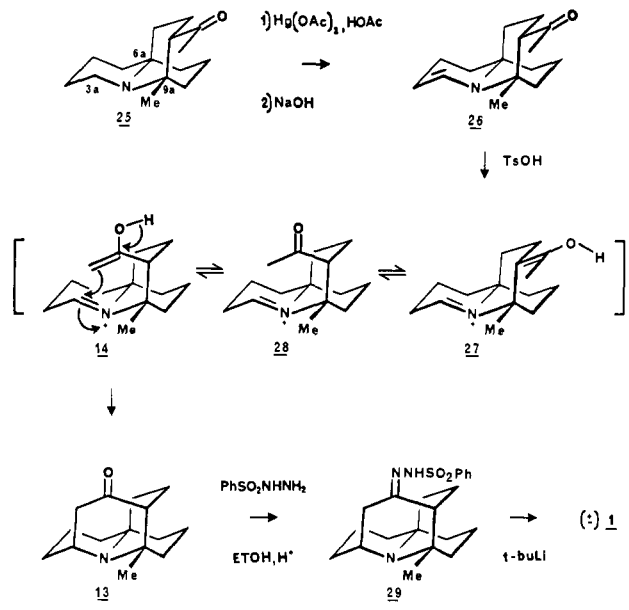


Figure 1. A 500-MHz COSY-45 experiment has been performed on tricyclic ketoamine **25** in the region 0.2–3.0 ppm. The one-dimensional projections are at the sides. Dashed lines highlight coupling between H_1 and the acetyl group protons. An expanded plot showing resonance from H_1 is shown at top left.

an axial stereochemical formulation as in **25**. The epimeric proton is structure **15**, with an equatorial orientation of H_1, should have two small couplings and appear as four similarly spaced lines. In accordance with these arguments isomer **15** was ruled out. From this assignment, we may conclude that the $\sigma-\pi$ coupling mechanism is operating. Although this stereochemical result was not unexpected, especially under our equilibrating reaction conditions, we still had a good chance[50] to complete our synthesis.

Oxidation of tricyclic ketoamine **25** with a fivefold excess of mercuric acetate in refluxing 5% acetic acid[51] removed the offending axial proton at the C_{3a} site to give a planar, sp^2-hybridized, carbon atom. After basic workup and extraction, unsubstituted enamine **26** was obtained in 65% or 57% yield after purification by column chromatography (Scheme VI). A single isomer was indicated by the presence of singlets at 2.19 and 1.18 ppm in the 500-MHz ^1H NMR spectrum. If our MM2 calculations were correct, on treatment with acid we should now be able to obtain, via the exocyclic enol **27**, reasonable concentrations of both epimers. Once established, the equilibrium may be shifted toward product formation since imminium ion **14** is ideally suited to effect irreversibly, with formation of bond A, the final ring closure. Much to our delight, an 85% yield of desired tetracyclic ketoamine **13** was isolated after refluxing enamine **21** with *p*-toluenesulfonic acid in benzene for 24 h followed by basic extractive workup and chromatography. The ketoamine **13** may be obtained directly from ketoamine **25** without purification of the unstable enamine **26** in 56% overall yield for the three steps. The crystalline product so obtained was identical in physical and spectroscopic properties to the material prepared earlier.[52]

Scheme VI



(50) Chance favors the prepared mind. Louis Pasteur.

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(52) We thank Professor Corey for providing spectra of tetracyclic ketoamine **13** as well as synthetic (+)-porantherine.

Previously, this tetracyclic amino ketone was reduced with sodium borohydride and then treated with thionyl chloride in pyridine to effect reductive elimination. We noted the modest yield obtained for the last step in the Corey and Balanson synthesis and therefore examined the highly regioselective aprotic Bamford–Stevens reaction. The requisite hydrazone hydrochloride (**29a**) began to crystallize from an acidified, refluxing, ethanolic solution of tetracyclic ketoamine **13** and benzenesulfonyl hydrazide after 2 h. The product, obtained in 89% from the cooled solution on filtration, proved to be analytically pure.

Treatment of hydrazone hydrochloride **29a** with excess *tert*-butyllithium for 8 h in ether–hexane solution gave (±)-porantherine (**1**) in 87% after workup and chromatography. The spectral and physical properties of our synthetic product were in satisfactory agreement with data recorded by the Australian and Harvard groups. Also, the 200-MHz ^{1}H NMR and mass spectra of natural and synthetic porantherine hydrochloride were in agreement.[53]

Conclusions

In a manner similar to the previous effort, our analysis takes advantage of the latent symmetry in ketoamine **13** to simplify the synthesis. However, we begin with *O*-methylvalerlactim that has one piperidine ring intact. This is in contrast to the Corey and Balanson approach that closes this ring after formation of the [3.3.1] bicyclic skeleton. As a consequence, several additional steps are required. Also, the mixture of C_1 epimers obtained in the earlier synthesis has been avoided by our analysis of steric factors.

Although there is a great deal of creative "art and imagination" within the realm of synthetic endeavor, success is rooted in sound synthetic planning. Both economic (requiring eight steps) and efficient (31% overall yield) our synthesis of (±)-porantherine underscores the importance of stereoelectronic effects when devising a plan. The organolithium compound **19** is a useful new reagent. The more reactive nature of lithium reagents and the increased stability of the cyclic ketal are distinct advantages over the widely used Grignard reagent prepared from 5-chloro-2-pentanone ethylene ketal. Forthcoming results from these laboratories will define more fully the scope and limitations, as well as present additional applications of this lithium regent in natural product syntheses.

Experimental Section

General Comments. Melting and boiling points are uncorrected. Infrared spectra were recorded on a Beckman 4210 spectrophotometer. Proton nuclear magnetic resonance (NMR) spectra were obtained by using a Bruker WP 200 FT or a AM 500 FT instrument operating at 200.133 and 500.138 MHz, respectively. Chemical shifts are reported as parts per million (ppm) downfield from tetramethylsilane in δ units. Coupling constants (J) are in hertz (Hz). NMR data are reported in the following order: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), numbers of protons, coupling constants. Except as indicated, either deuteriochloroform or carbon tetrachloride with 5% added deuteriobenzene were used as solvents. Carbon NMR spectra were recorded on the Bruker instruments operating at 50.320 and 125.759 MHz. Peak positions are in ppm with deuteriochloroform, carbon tetrachloride, or deuteriobenzene with assigned values of 77.0, 96.0, or 128.0 ppm, respectively, as internal standards. The 500-MHz ^{1}H shift-correlated 2D NMR data (AM-500) were collected on a 0.2 M $CDCl_3$ solution of tricyclic ketoamine **26**, at 303 K. A COSY-45 experiment has been performed with N-type selection (parameters: $X1$ = 256, $X2$ = 1024, NS = 4, N = 512, $N2$ = 1024, $W1$ = ±720 Hz, $W2$ = 1440 Hz, recyle delay = 2 s, Δt_1 = 0.694 ms). The digital resolution was 1.4 Hz/pt in both domains. Data acquisition and transformation with sine-bell in both domains required ca. 1 h. High-resolution mass spectral (MS) data were collected on an AEI-MS9 instrument. Fragmentation data are reported as m/e (%; relative intensity). Elemental analyses were performed by Spang Microanalytical Laboratories, Eagle Harbor, MI.

All solvents were of, at least, reagent grade quality. Further purification and drying employed standard methods.[54] Thus, diethyl ether, tetrahydrofuran (THF), and benzene were distilled from sodium benzophenone ketyl. Triethylamine was distilled and stored with 4-Å molecular sieves under nitrogen. Ethyl acetate and hexane were distilled in glass before use.

Reaction of δ-valerolactam with dimethyl sulfate afforded the *O*-methylvalerolactim.[35] 5-Chloro-2-pentanone was prepared from 2-acetylbutyrolactone (Fluka).[55] 2,2-Dimethyl-1,3-propanediol was supplied by Fluka and used without further purification. Although several sources of lithium were surveyed (Aldrich, wire, 3.2-mm diameter, 99.9%; Alfa, 30% dispersion in mineral oil; Lithium corporation of America, 30% dispersion in mineral oil), the highest yield of organolithium reagent was obtained with lithium wire, 3.2-mm diameter 98+%, high sodium, from Aldrich.

All reactions were routinely conducted in glassware which was flame-dried under a positive nitrogen pressure. For the manipulation of reaction mixtures involving air-sensitive compounds,[56] standard Schlenkware was flame-dried in vacuo and filled with argon. Anhydrous solvents were transferred via oven-dried cannula or syringe.

Thin-layer chromatography (TLC) was carried out on EM 60 PF 254 silica gel plates or EM 150 F-254 precoated aluminum oxide plates. Silica gel for flash chromatography[57] was EM kieselgel 60 (230–400 mesh ASTM). For medium-pressure liquid chromatography (MPLC), columns were packed with activity grade IV neutral aluminum oxide (Merck) and then eluted at pressures of 20–25 psi with a Fluid Metering Inc. lab pump. Fractions obtained by chromatography were monitored by TLC. Components were visualized by UV light, iodine vapor, and molybdophosphoric acid. Nitrogenous bases were distinguished by spraying with aqueous cobalt(II) chloride–ammonium thiocyanate solution.[58] For chromatography involving triethylamine, analytical TLC plates were warmed with a heat gun and then cooled to room temperature in vacuo before visualization.

Model Studies on Organolithium Additions to *O*-Methylvalerolactim. 2,2-Di-4-pentenylpiperidine. A 0.32 M benzene solution of 5-lithio-1-pentene[22] (80 mL, 25.0 mmol) was cooled to 0 °C in a 200-mL round-bottom flask equipped for magnetic stirring. The imino ether (0.56 g, 5.0 mmol) was added by syringe over 5 min. The reaction mixture was stirred for 72 h at 0 °C under argon. After this time the reaction was quenched with water (50 mL). The aqueous layer was extracted with ether (3 × 50 mL). The combined ether layers were extracted with 7% HCl (4 × 50 mL). The aqueous layer containing the ammonium salt was washed with a small amount of ether, basified with 40% NaOH, and then extracted with ether (3 × 100 mL). The combined ether extracts were dried (K_2CO_3), filtered, and then concentrated in vacuo to give 1.15 g of a slightly yellow oil. Medium-pressure chromatography (alumina, 5% ethanol–hexane) gave 2,2-di-4-pentenylpiperidine (1.00 g, 4.52 mmol) in 91.4% yield (judged by NMR to contain 20% of a double bond isomer): IR (neat liquid) 3170, 2950, 2850, 1835, 1635, 1460, 1375, 990, 910 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 5.75 (m), 5.39 (m), 2.78 (m), 2.60 (br), 2.06–1.91 (m), 1.60–1.28 (m); ^{13}C NMR (50 MHz, $CDCl_3$) 138.6, 114.5, 53.6, 40.5, 35.4, 35.9, 34.2, 26.1, 19.9 (one C not resolved); additional resonances were noted at 130.5, 123.4, 34.9, 26.1, 20.5, 12.5, attributable to another double bond isomer; high-resolution mass spectrum, calcd. for $C_{15}H_{27}N$ 221.2145, found 221.2148; mass spectrum, (M^+) 221 (0.7), 196 (1.2), 180 (3.4), 153 (11.1), 152 (100), 110 (18.6), 96 (5.9), 55 (9.3), 43 (9.4), 41 (14.1).

2,2-Dibutylpiperidine. In a similar experiment using 1.7 M *n*-butyllithium, the disubstituted amine was obtained in 65% yield: IR (neat liquid) 3250, 2890, 2830, 1440, 1360 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 2.5 (m, 2 H), 1.61–0.85 (m, 25 H); high-resolution mass spectrum (M^+ − 1) calcd for $C_{13}H_{26}N$ 196.2067, found 196.2068; mass spectrum, (M^+) 197 (13.9), 196 (100), 152 (4.3), 96 (5.4), 69 (4.7), 57 (6.4), 56 (4.9), 55 (12.3), 43 (9.3), 41 (12.9).

5-Chloro-2-pentanone 2′,2′-Dimethylpropylene Ketal (18). Freshly distilled 5-chloro-2-pentanone (47.36 g, 0.392 mol, bp 75–76 °C at 25 mmHg) was placed in a 250-mL round-bottom flask equipped with a water separator. Benzene (100 mL), 2,2-dimethyl-1,3-propanediol (40.90 g, 0.392 mol), and a catalytic amount of *p*-toluenesulfonic acid were added. The resultant solution was refluxed for 6 h, while the reaction was monitored by infrared spectroscopy. At the end of this time the

(53) We also thank Dr. J. A. Lamberton of CSIRO, Australia, for kindly providing a reference sample of natural porantherine hydrochloride.

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extruded water was drained from the trap and 4-Å molecular sieves were added. Refluxing was continued another 2 h, then the pale-yellow solution was cooled to room temperature. The reaction mixture was washed with 10% NaOH (100 mL) and water (3 × 30 mL). The organic layer was dried (Na_2CO_3), filtered, and concentrated with a rotary evaporator. After the addition of a small amount of Na_2CO_3, the resultant oil was carefully fractionated at reduced pressure. The major portion of the ketal was collected as a colorless oil (63.53 g, 0.308 mmol, 78.5%). The distillation proves to be troublesome if significant amounts of diol are present. Alternatively, purification may be achieved by simple (7:1, silica:crude reaction mixture) chromatography eluting with 5% ethyl acetate–hexane at a slightly positive pressure. Yields are slightly higher (80–83%) than those observed for distillation. The material so obtained is suitable for most synthetic purposes: bp 133–134 °C at 30 mmHg (92.0–92.2 °C at 0.21 mmHg; IR (liquid film) 2975, 2950, 2860, 1392, 1370, 1119, 1182, 1055, 695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 3.56 (t, 2 H, J = 5.9 Hz, CH_2Cl), 3.55 ($^1/_2$ ABq, 2 H, J = 11.2 Hz, OCH_2), 3.40 ($^1/_2$ ABq, 2 H, J = 11.2 Hz, OCH_2), 1.92 (m, 2 H, CH_2), 1.83 (m, 2 H, CH_2), 1.36 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 0.86 (s, 3 H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 98.23, 70.01 (double intensity), 45.17, 35.85, 29.64, 26.55, 22.21, 19.84; high-resolution mass spectrum, calcd for $C_9H_{16}{}^{[37]}ClO_2$ ($M^+ - CH_3$) 193.0810, found 193.0809; mass spectrum, ($M^+ - CH_3$) 193 (19.2), 191 (62.8), 129 (100), 123 (16.4), 121 (57.4), 105 (24.7), 69 (58.1), 56 (37.5). Anal. Calcd for $C_{10}H_{19}ClO_2$: C, 58.07; H, 9.27; Cl, 17.18. Found: C, 57.90; H, 9.06; Cl, 17.27.

5-Lithio-2-pentanone 2′,2′-Dimethylpropylene Ketal (19). While flushing with argon, lithium (6.94 g, 1 mol) and specially treated mineral oil[47] were added to a dry 250-mL three-neck round-bottom flask equipped with a pressure-equalizing addition funnel and a Hershberg stirrer. The lithium and oil were heated and stirred until a fine dispersion was obtained. After the mixture cooled, the lithium was washed several times with anhydrous diethyl ether. Finally, a solution of 15% THF–diethyl ether (200 mL) was added to the flask. When the mixture cooled to −25 °C, cold (0 °C) chloro ketal **18** (20.6 g, 99.7 mmol) was added dropwise with vigorous stirring over the course of 30 min. Stirring was continued another 45 min. After that time a significant amount of white precipitate had formed. The mixture was filtered through a sintered glass frit with the aid of positive argon pressure. The colorless filtrate was collected at −25 °C and then warmed to 0 °C as the solvent was removed in vacuo. Hydrocarbon solvent (benzene or pentane, 10 mL) was added and the solvent removed again. The white residue was taken up in cold (0 °C) pentane or benzene (200 mL). An aliquot of the solution was titrated (0.43 M, 85.4 mmol, 85.6%). When the active organometallic solution was immediately quenched with water, dried, concentrated in vacuo, and subjected to flash chromatography (silica, 10% ethyl acetate–hexane), two compounds were obtained in approximately 95:5 relative ratio. **2-Pentanone 2′,2′-dimethylpropylene ketal**: IR (neat liquid) 2960, 2930, 2880, 1470, 1385, 1375, 1105, 1045 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 3.46 ($^1/_2$ ABq, 2 H, J = 11 Hz, OCH_2), 3.34 ($^1/_2$ ABq, 2 H, J = 11 Hz, OCH_2) 1.54 (m, 2 H), 1.35 (m, 2 H), 1.26 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 0.85 (m, 3 H, CH_3), 0.81 (s, 3 H, CH_3); ^{13}C NMR (50 MHz, CCl_4) 98.3, 69.9 (double intensity), 40.7, 29.7, 22.7, 22.4, 19.7, 16.4, 14.3; high-resolution mass spectrum, calcd for $C_9H_{17}O_2$ ($M^+ - CH_3$) 157.1229, found 157.1221; mass spectrum, ($M^+ - CH_3$) 157 (61.5), 129 (94.9), 87 (100), 71 (59.2), 69 (86.7), 57 (8.9), 56 (51.7), 55 (13.1) 45 (29.1), 43 (96.0). From reaction with molecular oxygen, a small amount of the corresponding alcohol was obtained. **2-Oxo-5-pentanol 2′,2′-dimethylpropylene ketal**: IR (neat liquid) 3400, 2920, 2840, 1450, 1360, 1085 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 3.51 (m, 2 H, CH_2OH), 3.46 ($^1/_2$ ABq, 2 H, J = 11 Hz, OCH_2), 3.35 ($^1/_2$ ABq, 2 H, J = 11 Hz, 2 H, OCH_2), 2.83 (br s, 1 H, OH), 1.65–1.54 (m, 4 H), 1.24 (s, 3 H, CH_3), 0.89 (s, 3 H, CH_3), 0.73 (s, 3 H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 98.7, 70.1 (double intensity), 62.6, 35.0, 29.7, 26.4, 22.6, 22.2, 19.8; high-resolution mass spectrum, calcd for $C_9H_{17}O_3$ ($M^+ - CH_3$) 173.1178, found 173.1176; mass spectrum, ($M^+ - CH_3$) 173 (72.7), 129 (100), 103 (29.6), 87 (19.3), 85 (46.9), 84 (12.2), 69 (15.9), 56 (15.4), 43 (16.7).

Bis(4-oxopentyl 2′,2′-dimethylpropylene ketal)mercury. To a −25 °C pentane solution of 5-lithio-2-pentanone 2′,2′-dimethylpropylene ketal (0.35 M, 200.0 mL, 73.5 mmol), contained in a 250-mL round-bottom flask under a nitrogen atmosphere, was added dropwise over 90 min a THF solution (50 mL) of mercury(II) chloride (9.96 g, 36.75 mmol). The solution was stirred an additional 1 h at 0 °C and then allowed to warm to room temperature overnight. Subsequently, water (50 mL) was added, and the layers were separated. The organic layer was washed with water (3 × 50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to give the dialkylmercurial compound as a colorless oil (18.94 g, 34.9 mmol, 95.1%): bp 180 °C at 0.15mmHg; IR (neat liquid) 2950, 2875, 1475, 1455, 1395, 1380, 1370, 1005, 855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 3.53 ($^1/_2$ ABq, 4 H, J = 11 Hz, OCH_2), 3.43 ($^1/_2$ ABq, 4 H, J = 11 Hz, OCH_2), 1.94 (m, 4 H), 1.72 (m, 4 H), 1.13 (s, 6 H, CH_3), 1.04 (t, 4 H, J = 7.6 Hz, $HgCH_2$), 1.01 (s, 6 H, CH_3), 0.89 (s, 6 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 99.03 (double intensity), 70.35 (quadruple intensity), 44.22 (double intensity), 43.69 (double intensity), 29.99 (double intensity), 22.86 (double intensity), 22.61 (double intensity), 22.55 (double intensity), 20.41 (double intensity); fast atom bombardment mass spectrum, (glycerol matrix) calcd for $C_{20}H_{37}{}^{[202]}HgO_4$ 542, found 542; mass spectrum, 324 (0.2), 202 (7.1), 200 (5.2), 199 (3.3), 157 (3.8), 130 (5.8), 129 (100), 85 (11.0), 69 (32.4). Anal. Calcd for $C_{20}H_{38}HgO_4$: C, 44.23; H, 7.00. Found: C, 44.18; H, 6.83.

Halide-Free 5-Lithio-2-pentanone 2′,2′-Dimethylpropylene Ketal (19a). Lithium metal (1.0 g, 144 mmol), contained in a 25-mL round-bottom flask, was suspended in 4:1 ether–THF solution (5 mL) at −25 °C by a magnetic stirring bar. Bis(4-oxopentyl 2′,2′-dimethylpropylene ketal)-mercury (1.99 g, 3.68 mmole) dissolved in 4:1 ether–THF (5 mL) was added by means of a pressure-equalizing addition funnel over 30 min as the solution was magnetically stirred under a nitrogen atmosphere. After the addition was complete, the solution was warmed to 0 °C for 2.5 h. During this time the solution became dark as mercury metal precipitated. The solution was diluted with an equal volume (10 mL) of 4:1 ether–THF and then an aliquot (2 mL) was titrated with 1 M *sec*-butyl alcohol in xylene with 1,10-phenanthroline as an indicator (0.33 M, 6.67 mmol, 90.6%).

2,2-Bis(4-oxopentyl 2′,2′-dimethylpropylene ketal)piperidine (20). Method I. To a 0 °C solution of lithio ketal **19** in ethereal benzene 0.42M, 38.2 mmol) was added by syringe *O*-methylvalerolactim (791 mg, 7.0 mmol) in a small amount of diethyl ether (12 mL). The resultant yellow solution was stirred for 24 h at 0 °C, and the excess organolithium reagent was quenched with 10% sodium hydroxide (20 mL). The aqueous layer was extracted with ether (2 × 10 mL). The combined organic extracts were dried (Na_2CO_3), filtered, and concentrated on a rotary evaporator. The reaction volatiles were removed by bulb-to-bulb distillation to give a viscous yellow oil. The resultant oil was subjected to flash chromatography (silica, 5% triethylamine–ethyl acetate). Diketal amine **20** was obtained as a yellow oil (430 mg, 1.01 mmol, 14.4%). A large amount of 2-pentanone 2′,2′-dimethylpropylene ketal was isolated (5.12 g, 29.8 mmol) in addition to some 2-oxo-5-pentanol 2′,2′-dimethylpropylene ketal (0.377 g, 2.05 mmol).

Method II. In an attempt to increase the amount of the dialkyl-substituted amine, an addition–neutralization procedure was employed. In one cycle, a benzene solution containing 2.5 equiv of lithium reagent **19** (0.42 M, 30.0 mL, 12.6 mmol) was added to a diethyl ether solution of *O*-methylvalerolactim (0.565 mg, 5.00 mmol) at 0 °C under argon. The solution was stirred for 1 h, and then the reaction was neutralized with water (1 equiv diluted with THF), dried, filtered, and concentrated. This procedure was repeated 5 times, and the reaction was worked-up in the usual manner. After flash chromatography, diketal amine **20** was isolated in 70.2% yield (1.49 g, 3.51 mmol).

Method III. Since the above method consumed large amounts of the unrecoverable alkyllithium reagent, **19** was used as the limiting reagent in this procedure. To a 0 °C pentane solution of lithium reagent **19** (0.32 M, 31.25 mL, 10.0 mmol) was added *O*-methylvalerolactim (5.65 g, 50.0 mmol) via syringe. The reaction mixture was stirred at 0 °C overnight under argon. After warming to room temperature, the reaction mixture was stirred an additional 5 days. At the end of this time the solution gave only a faintly positive test for organometallic reagent.[39] The reaction was quenched with a small amount of water and treated as described in method I. After the usual chromatography, disubstituted piperidine **20** was obtained as a colorless oil (1.70 g, 4.00 mmol, 80.0%): IR (liquid film) 3350, 2990, 2950, 2940, 2875, 1480, 1460, 1395, 1382, 1372, 1350, 1095, 955, 905 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 3.60 (br s, 1 H, NH), 3.43 ($^1/_2$ ABq, 4 H, J = 11.2 Hz, OCH_2), 3.31 ($^1/_2$ ABq, 4 H, J = 11.2 Hz, OCH_2), 2.70 (br m, 2 H, NCH_2), 1.61–1.33 (m, 18 H), 1.31 (s, 6 H, CH_3), 1.27 (s, 6 H, CH_3), 0.85 (s, 6 H, CH_3); ^{13}C NMR (50 MHz, CCl_4), 99.12 (double intensity), 70.44 (quadruple intensity), 53.78, 41.25, 39.31 (double intensity), 37.40 (double intensity), 35.27, 30.36 (double intensity), 27.27, 23.46 (double intensity), 23.20 (double intensity), 21.03, 20.63 (double intensity), 17.33 (double intensity); high-resolution mass spectrum, calcd for $C_{25}H_{47}NO_4$ 425.3493, found 425.3470; mass spectrum, ($M^+ - CH_3$) 410 (32.4), 255 (27.1), 254 (100), 168 (26.8), 150 (12.7), 129 (28.0), 110 (12.2), 69 (8.9), 63 (18.9), 43 (13.5). A small sample was subjected to Kugelrohr distillation (oven temp 165 °C at 0.12 mm Hg) before the elemental analysis was obtained. Anal. Calcd for $C_{25}H_{47}NO_4$: C, 70.54; H, 11.13; N, 3.29. Found: C, 70.27; H, 10.91; N, 3.30.

2,2-Bis(4-oxopentyl 2′,2′-dimethylpropylene ketal)piperidinium Oxalate (20a). To an ether solution (0.5 mL) of ketal amine **20** (111 mg, 0.261 mmol) was added anhydrous oxalic acid (23.5 mg, 0.261 mmol) dissolved in ether (0.5 mL). Oxalate derivative **20a** formed immediately. The salt was collected on a sintered glass filter funnel, washed with a small amount of anhydrous diethyl ether, and then recrystallized from ethyl

acetate (123 mg, 0.239 mmol, 91.5%): mp 147–150 °C; IR ($CHCl_3$) 3685, 3300, 2960, 2875, 2250, 1790, 1760, 1655, 1605, 1395, 1375, 1312, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.31 (br s, 1 H, CO_2H), 3.51 ($^1/_2$ ABq, 4 H, J = 11.3 Hz, OCH_2), 3.39 ($^1/_2$ ABq, 4 H, J = 11.3 Hz, OCH_2), 3.12 (br m, 2 H, NH_2^+), 1.80–1.60 (m, 12 H), 1.44–1.35 (m, 8 H), 1.33 (s, 6 H, CH_3), 0.99 (s, 6 H, CH_3), 0.87 (s, 6 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 164.51 (double intensity), 98.64, 70.23 (quadruple intensity), 59.12, 39.43, 38.21 (double intensity), 33.72, 30.97, 29.86 (double intensity), 22.78, 22.47 (double intensity), 21.69, 20.29 (double intensity), 18.36, 16.39 (double intensity); mass spectrum, loss of $C_2H_2O_4$ ($M^+ - CH_3$) 410 (44.3), 255 (26.5), 254 (100), 168 (25.6), 150 (41.7), 129 (60.9), 71 (39.5), 69 (22.9), 43 (38.8), 41 (15.5). Anal. Calcd for $C_{27}H_{49}NO_8$: C, 62.91; H, 9.51; N, 2.72. Found: C, 62.80; H, 9.41; N, 2.81.

Ketoenamine 22. Amino diketal **20** (1.20 g, 2.82 mmol) was stirred with a 1:1 10% HCl–THF solution (3 mL) in a 10-mL round-bottom flask. After the mixture stirred for 1 h under nitrogen, diethyl ether was added. A 15% sodium hydroxide solution was used to adjust the pH of the solution to >10. The basic solution was extracted with more diethyl ether (3 × 2 mL). The combined organic extracts were washed with 10% NaOH, dried (Na_2CO_3), and filtered. The solvent was removed in vacuo to give a solidified yelllow oil. Flash chromatography (silica gel, 1:1 hexane–ethyl acetate with 5% triethylamine added) of the mixture gave 2,2-dimethyl-1,3-propanediol (0.563 g, 5.42 mmol, 96.2%) and ketoenamine **22** as an unstable colorless oil (0.625 g, 2.66 mmol, 94.3%): IR (liquid film) 2910, 1705, 1635, 1430, 1738, 1360, 1248, 1142 cm^{-1}; ^1H NMR (200 MHz, CCl_4) 4.08 (br m, 1 H, $NC(CCH_3)CH$), 3.21 (br m, 1 H, NCH), 3.15 (br m, 1 H, NCH), 2.83 (br m, 2 H, $C(CH_3)CHCH_2$), 2.30 (t, 2 H, J = 6.0 Hz, $COCH_2$), 2.00 (s, 3 H, $COCH_3$), 1.88 (m, 2 H), 1.64 (s, 3 H, $NCCH_3$), 1.56–1.25 (m, 10 H); ^{13}C NMR (50 MHz, CCl_4) 204.41, 139.40, 95.15, 54.00, 43.69, 41.24, 33.29, 32.80, 29.28, 26.77, 25.90, 21.05, 20.01, 19.51, 17.29; high-resolution mass spectrum, calcd for $C_{15}H_{25}NO$ 235.1930, found 235.1924; mass spectrum (M^+) 235 (85.7), 192 (74.7), 169 (59.3), 164 (56.2), 151 (91.4), 150 (100), 135 (45.7), 78 (49.5), 71 (31.9), 57 (27.5).

Tricyclic Ketoamine 25. Bicyclic ketoenamine **22** (0.520 g, 2.23 mmol) was placed in a 100-mL round-bottom flask. Benzene (75 mL), isopropenyl acetate (1.12 g, 2.90 mmol), and *p*-toluenesulfonic acid (0.551 g, 2.90 mmol) were added. The solution was refluxed under an inert atmosphere for 48 h with a water separator containing 3-Å molecular seives. After this time the amber reaction mixture was cooled. Sodium hydroxide (5 mL, 6 N) was used to wash the benzene solution. The pale-yellow organic layer was dried (Na_2CO_3), filtered, and concentrated in vacuo. The residual oil was subjected to flash chromatography (silica, 9:1 hexane–ethyl acetate with triethylamine added). Tricyclic ketoamine **25** (0.495 g, 2.11 mmol, 94.6%) was obtained as a colorless oil: IR (liquid film) 2950, 2920, 2875, 1702, 1448, 1358, 1230, 1215, 1158, 1142 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 2.85 (bdd, 1 H, J = 13.5, 5.6 Hz, CH_3COCH), 2.62 (ddd, 1 H, J = 11.1, 5.9, 4.5 Hz, NCH_{eq}), 2.49 (ddd, 1 H, J = 14.4, 11.6, 2.7 Hz, NCH_{ax}), 2.23 (ddd, 1 H, J = 20.0, 13.0, 6.3 Hz, $COCHCH_{2ax}$), 2.06 (m, 1 H), 2.0 (s, 3 H, CH_3), 1.90 (m, 1 H), 1.83 (m, 1 H), 1.57 (m, 1 H), 1.52 (dd, 1 H, J = 13.8, 6.7 Hz, $NC(CH_3)CH_{2ax}$), 1.50–1.40 (m, 4 H), 1.38–1.25 (m, 3 H), 1.24–1.17 (m, 2 H), 1.07 (dd, 1 H, J = 13.7, 6.5 Hz), 0.93 (s, 3 H, $NCCH_3$); ^{13}C NMR (50 MHz, CCl_4) 210.25, 55.50, 52.51, 52.03, 40.89, 40.16, 37.04, 33.00, 32.30, 29.49, 28.36, 27.38, 25.03, 21.36, 20.98; high-resolution mass spectrum, calcd for $C_{15}H_{25}NO$ 235.1930, found 235.1919; mass spectrum, (M^+) 235 (19.4), 192 (32.2), 164 (38.2), 151 (54.3), 150 (100), 136 (12.7), 97 (10.4), 55 (15.1), 43 (28.6), 41 (17.3). A sample was sealed for elemental analysis after bulb-to-bulb distillation (oven temp 100 °C at 0.05 mmHg). Anal. Calcd for $C_{15}H_{25}NO$: C, 76.60; H, 10.64; N, 5.96. Found: C, 76.51; H, 10.55; N, 5.83.

Tricyclic Ketoenamine 26. A 25-mL round-bottom flask equipped for magnetic stirring was charged with tricyclic ketoamine **25** (410 mg, 1.74 mmol). The sample was dissolved in 5% acetic acid (10 mL), and mercuric acetate was added (2.77 g, 8.69 mmol). The contents were heated under a nitrogen atmosphere for 4 h wth a water-cooled condenser in place. After the reaction mixture was cooled to room temperature the precipitated mercury(I) acetate was removed by filtration. The excess mercury(II) ions were precipitated as mercury(II) sulfide by saturating the yellow solution with H_2S. After a short digestion period (5 min) on a steam bath, the mixture was centrifuged. The centrifugate was carefully basified with 40% NaOH, then extracted with ether (3 × 50 mL). The combined extracts were dried (K_2CO_3), filtered, and concentrated. Flash chromatography (silica, 9:1 hexane–ethyl acetate containing 5% by volume triethylamine) gave enamine **26** as an unstable oil (230 mg, 0.987 mmol, 56.7%): IR (liquid film) 2915, 1705, 1635, 1355 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.16 (d, 1 H, J = 8.4 Hz, NCH), 4.48 (m, 1 H), 3.37 (m, 1 H), 2.83 (m, 1 H), 2.41–2.35 (m, 2 H), 2.19 (s, 3H, CH_3), 2.19–1.18 (m, 10 h), 1.18 (s, 3 H, CH_3), 0.65 (m, 1 H); high-resolution mass spectrum, calcd for $C_{15}H_{23}NO$ 233.1774, found 233.1778; mass spectrum, (M^+) 233 (29.3), 190 (55.1), 176 (14.4), 162 (14.5), 150 (22.2), 148 (51.9), 138 (33.5), 55 (31.8), 43 (100), 41 (68.6). Additionally, some unreacted tricyclic ketoamine **25** was obtained (28 mg, 0.12 mmol, 7.1%).

2,3-Dihydroporantherin-2-one (13). Tetracyclic ketoamine **13** may be obtained direclty from tricyclic ketoamine **25**. In the procedure described, the intermediate unsubstituted enamine **26** was carried on immediately without extensive purification. Thus, tricyclic ketoamine **25** (0.454 g, 1.93 mmol) was heated just below reflux in a 25-mL round-bottom flask with mercuric acetone (3.19 g, 10 mmol) and 5% aqueous acetic acid (15 mL). During the heating period, mercurous acetate (301 mg, 1.07 mmol, 55.6% of the theoretical) precipitated. Additionally, a small amount of metallic mercury was observed but not isolated. A redistribution reaction of the mercury(I) compound may account for a low recovery of mercurous acetate and formation of metallic mercury. After 4 h of heating under argon, the reaction mixture was cooled to room temperature. Working rapidly now, the mercurous salt was removed by filtration. Excess mercury(II) ions were precipitated as mercuric sulfide by saturating the amber filtrate with hydrogen sulfide. The resultant suspension was digested on a steam bath for 5 min under argon and then centrifuged. The supernatant was transferred to a separatory funnel while being flushed with argon. The residual mercuric sulfide was washed with a small amount of water. The washings were combined with the original supernatant. Diethyl ether (25 mL) was added to the separatory funnel. The pH of the aqueous layer was adjusted to 12 with 15% NaOH, and the layers were separated. Extraction of the basic aqueous layer with ether was repeated (3 × 25 mL). The combined ether layers were dried briefly (Na_2CO_3) and filtered. Removal of the ether with a rotary evaporator was accomplished as rapidly as possible with a minimum of heating. Crude enamine **26** (292 mg, 1.25 mmol, 65%) was taken up in benzene (50 mL), *p*-toluenesulfonic acid (1.90 g, 10 mmol) was added, and the mixture was refluxed for 24 h under an atmosphere of argon with a water separator containing 3-Å molecular sieves. After this period, the cooled solution was washed with aqueous 15% NaOH (5 mL) and the layers were separated. The organic layer was dried (Na_2CO_3), filtered, and concentrated with a rotary evaporator to give a solidified oil. Flash chromatography (silica, 3:1 hexane–ethyl acetate containing 5% by volume triethylamine) of the mixture gave tetracyclic ketoamine **13** as a crystalline solid (253 mg, 1.08 mmol, 56.3% for three steps). The infrared spectrum and the TLC characteristics of this material were identical with those reported by Corey and Balanson: mp 114–116 °C; IR ($CHCl_3$) 2940, 1705, 1462, 1270, 1157, 1138, 1045 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 3.58 (dddd, 1 H, J = 11.3, 7.0, 5.2, 1.8 Hz, NCH), 2.50 (m, 1 H), 2.39 (dd, 1 H, J = 16.8, 11.4 Hz), 2.14 (bd, 1 H, J = 6.5 Hz), 2.11 (dd, 1 H, J = 17.0, 5.2 Hz), 2.01 (m, 1 H), 1.84–1.39 (m, 13 H), 1.26 (dd, 1 H, J = 14.9, 8.4 Hz), 0.99 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $cDCl_3$) 214.56, 55.52, 52.13, 52.07, 48.93, 43.82, 43.29, 39.26, 38.85, 30.02, 29.22, 25.70, 24.16, 21.34, 15.16; high-resolution mass spectrum, calcd for $C_{15}H_{23}NO$ 233.1774, found 233.1773; mass spectrum, (M^+) 233 (100), 218 (21.1), 205 (54.1), 190 (88.8), 176 (60.8), 162 (52.8), 148 (46.2), 135 (14.4), 55 (29.2), 43 (15.5), 41 (35.4). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.25; H, 9.87; N, 6.01. Found: C, 77.38; H, 9.84; N, 6.14. In addition to some unreacted tricyclic ketoamine **25** (60.2 mg, 0.256 mmol, 13.3%), a small amount of the unstable endocyclic enamine **26** was isolated (22.4 mg, 0.96 mmol, 5.0%).

2,3-Dihydroporantherin-2-one (Phenylsulfonyl)hydrazone Hydrochloride (29a). An ethanolic solution (2 ml) of tetracyclic ketoamine **13** (100 mg, 0.429 mmol) was refluxed in a 5-mL round-bottom flask with benzenesulfonyl hydrazide (73.9 mg, 0.429 mmol) and a slight excess of concentrated HCl. After 30 min a white precipitate began to form. Refluxing was continued for 4 h. After this time the reaction mixture was cooled to room temperature and then stored in the freezer overnight. The precipitate was collected by filtration, washed with a small amount of ether, and allowed to dry in high vacuum. The hydrazone hydrochloride (**29a**) prepared in this manner was analytically pure (150 mg, 0.354 mmol, 82.6%): mp 245–247 °C; IR (KBr pellet) 3440, 3000, 2960, 2595, 1655, 1455, 1342, 1185, 1172, 1032, 924, 748 cm^{-1}; ^1H NMR (500 MHz, Me_2SO-d_6–D_2O, referenced to trimethylsilyl propionate) 7.89 (d, 2 H, J = 7.6 Hz, *o*-ArH), 7.73 (t, 1 H, J = 7.5 Hz, *p*-ArH), 7.64 (unresolved dd, 2 H, *m*-ArH), 3.82 (m, 1 H, NCH), 2.90 (dd, 1 H, J = 18.1, 6.5 H), 2.62–2.51 (m, 4 H), 2.11–1.34 (m, 15 H), 1.36 (dd, 1 H, J = 14.4, 8.2 Hz), 1.12 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, Me_2SO-d_6–D_2O, referenced to Me_2SO_4-d_6, 39.6) 140.41, 139.19, 135.02, 130.70, 128.64, 61.36, 60.97, 50.65, 45.11, 40.35, 37.67, 36.39, 28.42, 28.19, 26.62, 26.49, 25.62, 19.93, 13.83; high-resolution mass spectrum, calcd for $C_{21}H_{29}N_3O_2S$ 387.1974, found 387.1974; mass spectrum, (M^+ – HCl) 387 (1.3), 247 (26.8), 246 (100), 218 (5.5), 217 (11.6), 174 (8.7), 148 (10.9), 78 (10.5), 77 (19.6), 41 (8.5). Anal. Calcd for $C_{21}H_{30}ClN_3O_2S$:

C, 59.50; H, 7.08; N, 9.92. Found: C, 59.47; H, 6.99; N, 9.90.

(±)-Porantherine (1). (Phenylsulfonyl)hydrazone hydrochloride **29a** (110.0 mg, 0260 mmol) was suspended in 5 mL of diethyl ether contained in a 25-mL round-bottom flask equipped with a magnetic stirring bar. When the mixture cooled to −78 °C, *tert*-butyllithium (1.45 M, 1.21 mL, 1.76 mmol) was added by syringe in small portions over 5 min. After 1 h of stirring at 0 °C all the solid had dissolved, giving a yellow solution. Stirring was continued for 10 h as the solution was slowly warmed to room temperature. Over this period the solution gradually turned red. Subsequently, the reaction mixture was diluted with ether (10 mL) and quenched with a small amount of water (2.0 mL). The aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were dried (Na_2CO_3), filtered, and concentrated under reduced pressure to give a yellow oil. After flash chromatography (silica, 9:1 hexane–ethyl acetate with 5% added triethylamine), (±)-porantherine (**1**) was obtained as a waxy solid (52.5 mg, 0.241 mmol, 93.0%): IR (CCl_4) 2950, 2890, 1605, 1490, 1458, 1123, 1048, 1001, 992, 952, 855 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 5.69 (m, 2 H), 3.72 (br, 1 H) 2.39 (m, 1 h), 1.92–1.18 (m, 15 H), 1.14 (s, 3 H, CH_3), 0.98–0.85 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 131.94, 131.62, 53.33, 52.93, 50.72, 43.32, 39.62, 37.64, 35.76, 31.07, 28.18, 25.46, 23.51, 21.75, 16.94; high-resolution mass spectrum, calcd for $C_{15}H_{23}N$ 217.1830, found 217.1841; mass spectrum, (M^+) 217 (61.7), 202 (21.4), 189 (58.1), 174 (81.7), 167 (32.2), 165 (31.4), 83 (28.5), 69 (35.4), 67 (32.2), 57 (61.7), 43 (69.3), 41 (100).

Synthetic porantherine hydrochloride (1a) precipitated from an ether solution of the free base on acidification with ethereal HCl (~5 N): mp >200 °C dec; IR ($CHCl_3$) 3700, 2960, 2440, 1605, 1460, 1120 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 11.2 (br, 1 H NH), 5.72–5.80 (m, 2 H, CH=CH), 4.30 (m, 1 H, NC*H*), 2.73–1.73 (m, 16 H), 1.56 (s, 3 H CH_3), 1.40 (m, 1 H); mass spectrum, (M^+ − Cl) 218 (23.0), 217 (93.3), 202 (69.2), 189 (86.6), 188 (62.5), 175 (36.3), 174 (100), 148 (31.3), 109 (44.5), 41 (44.1), 36 (63.1).

Synthetic porantherine picrate (1b) precipitated slowly from an alcoholic solution of the free base after the addition of a saturated solution (ethanol) of picric acid. The picrate so obtained was dried in vacuo at 105 °C for 12 h. Anal. Calcd for $C_{21}H_{26}N_4O_7$: C, 56.50; H, 5.83; N, 12.55. Found: C, 56.34; H, 5.75; N, 12.33.

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Registry No. (±)-**1**, 54382-19-3; (±)-**1a**, 108818-56-0; (±)-**1b**, 108818-57-1; (±)-**13**, 54312-69-5; **18**, 88128-57-8; **18** (X = H), 5421-99-8; **18** (X = OH), 108818-49-1; **18** (Hg derivative), 108818-58-2; **19a**, 108818-50-4; **20**, 108818-51-5; **20a**, 108818-52-6; (±)-**22**, 108818-53-7; (±)-**25**, 108818-54-8; (±)-**26**, 54312-76-4; (±)-**29a**, 108818-55-9; CH_2=$CH(CH_2)_3Li$, 54313-25-6; $CH_3CO(CH_2)_3Cl$, 5891-21-4; $HOCH_2CMe_2CH_2OH$, 126-30-7; CH_2=$C(OAc)CH_3$, 108-22-5; *o*-methylvalerolactim, 5693-62-9; 2,2-di(4-pentenyl)piperidine, 108818-48-0; 2,2-dibutylpiperidine, 92144-58-6.

Structure and Conformation of Two Coprogen-Type Siderophores: Neocoprogen I and Neocoprogen II

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Abstract: Two coprogen-type siderophores, neocoprogen I (**4**), $C_{31}H_{47}N_6O_{12}Fe$, and neocoprogen II (**5**), $C_{27}H_{41}N_6O_{11}Fe$, have been isolated from the fungus *Curvularia lunata*, and their structures and conformations have been elucidated. The coprogens have a linear trimeric skeleton made from three N^δ-hydroxy-N^δ-acylated ornithines, two of which form a diketopiperazine ring while the third forms an ester linkage to the dimer. In **4**, one of the terminal N^δ-acyl groups is an acetyl group, while in **5**, both of these are acetyl groups. The structure of neocoprogen I (**4**) [identified as the ferric complex of isotriornicin (**7**)] has been determined by single-crystal X-ray diffraction at 138 K with crystals grown from ethanol/acetonitrile. The crystals are orthorhombic: $P22_12_1$, a = 8.683 (13) Å, b = 28.33 (4) Å, c = 36.84 (4) Å, V = 9062.2 Å^3, Z = 8. The structure has been determined from 2756 diffractometer data and refined to a final R = 0.114. The distinct feature of neocoprogen I (**4**) structure is the Δ-trans geometry of its iron coordination. This is the first example of a trans isomer of an iron trihydroxamate siderophore in the solid state. The structure of neocoprogen II (**5**), a novel siderophore, has been elucidated on the basis of chemical degradation and spectroscopic studies including ^1H and ^{13}C NMR spectroscopy. CD spectra show that both neocoprogen I (**4**) and neocoprogen II (**5**), like coprogen (**1**), exist predominantly as Δ optical isomers in aqueous solutions at neutral pH. Stereoisomeric possibilities of the ferric complexes of the linear trihydroxamates are discussed, and their structural features are related to their role in microbial iron transport.

Under iron-deficient growth conditions most microorganisms produce low molecular weight iron chelating agents called siderophores. It is now generally accepted that these siderophores are responsible for microbial iron transport. Several families of siderophores have been identified, including ferrichromes, ferrioxamines, fusarinines, coprogens, catecholamides, pseudobactins, and mycobactins.[1-3] Two types of ligating groups are prevalent among these families, the hydroxamates and the catecholates, both of which form stable octahedral complexes with iron.

Among the hydroxamate siderophores, the coprogen family is structurally characterized by the presence of a diketopiperazine ring. Although they are built up of typical units (δ-*N*-hydroxyornithine, *trans*-anhydromevalonic acid, and acetic acid) as in other fungal hydroxamate siderophores, the manner in which these building blocks are arranged in the coprogen family is completely different. Two of the amino acid components are linked together, head-to-head through a diketopiperazine ring, and the third component is linked to the rest of the molecule via an ester linkage. As a result, in the coprogen family the hydroxamate groups become parts of a long chain. The trihydroxamate members of the coprogen family are shown in Chart I. Dimerum acid[4] and

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