Experimental Section

Nuclear magnetic resonance spectra were recorded on a Hitachi Perkin-Elmer R-24B 60-MHz ^1H NMR spectrometer.

Radioactivity measurements were performed on a Beckmann LS-100 liquid scintillation system.

Materials. The starting material silica gel was Merck Kieselgel 60 (Art. No. 7734), 70–230 mesh, pore diameter 60 Å, specific surface area = 500 m^2/g.

Catalysts **1–4** supported on silica gel were synthesized and analyzed as described previously.[4b] They were then sifted to give mesh intervals of 70–100, 100–140, and 170–230, respectively. Catalysts **1–4** had titers of 0.68, 0.94, 1.24, and 0.66 mequiv of Br^-/g, respectively.

Hexadecyltributylphosphonium bromide **5** was prepared according to Starks,[18] mp 54 °C.

n-Butyl bromide and inorganic reagents were ACS reagent grade. $Na^{131}I$ was supplied by New England Nuclear, Massachusetts, U.S.A.

Kinetic Methods. All the kinetic experiments were run at the desired temperature (70, 80, 90 ± 0.5 °C) in a 10-mL flask with a Teflon top connected with a circulating paraffin thermostat (Colora K-5 Ultrathermostat).

In a typical experiment without stirring, the flask was charged with water (3.25 mL), potassium iodide (5.0 g, 30.0 mmol), and catalyst (0.05 molar equivalents, corresponding to 0.74, 0.53, 0.40, and 0.76 g of **1**, **2**, **3**, and **4**, respectively) and equilibrated for 0.5 h. 1-Bromobutane (1.74 mL, 10.0 mmol) was then added. The interfacial area between organic and aqueous phase was 3.0 cm^2.

The reaction procedure was to take samples of the upper organic layer at suitable time intervals and to follow with NMR the disappearance of reagent and appearance of 1-iodobutane. The relative concentrations of the two were determined from the areas (a_{Br} and a_I) of the central peaks of the partially overlapping triplets centrated at 3.38 and 3.18 ppm, respectively (CCl_4; internal Me_4Si), after calibration with known mixtures of authentic samples. The pseudo-first-order rate constants were obtained from the slope of the plots of ln $(a_{Br}/a_{Br} + a_I)$ vs. time, after the rapid first period was rejected, by the least-squares method (correlation coefficient > 0.98). All the kinetic runs were followed to more than 70% conversion.

Experiments with stirring were conducted under the same conditions by using a Teflon-coated stirring bar (2.0 cm × 0.7 cm) placed in the reaction vessel first. Its length was selected as slightly less than the diameter of the bottom of the flask so that the type of stirring would be the same in all experiments. The magnetic stirrer was connected with a mechanical revolution counter in order to determine the precise stirring speed. All the kinetic runs were performed at least twice and gave good reproducibility of the observed kinetic constants (approximately ±5% for the unstirred and ±10% for the stirred experiments).

Iodine contents of **1** and **3** were evaluated before and after catalysis; the catalyst was previously converted into I^- form by treatment with KI(aq)/heptane, according to the results of the radioactivity measurements, and then placed in the reaction with stirring. After usual washing the dried catalyst was analyzed according to Volhard. Results: catalyst **1**, 0.61 before and 0.63 mequiv of I^-/g after the catalysis; catalyst **3**, 1.15 before and 1.15 mequiv I^-/g after the catalysis.

Radioactivity Measurements. The stock solution was prepared from 0.1 mL of a solution of $Na^{131}I$ in 0.1 N NaOH (5 mCi) with 100 g of KI, bringing the volume to 150 mL with water. The flask was charged with 0.50 mol equiv of immobilized phosphonium salts (catalysts **1–4**), 0.8 mL of heptane, and 1.0 mL of water. The resulting mixture was stirred for approximately 5 min and 5.0 mL of radioactive solution was added. Concentration gradients in the aqueous phase were eliminated with a few rotations of the suspension.

In the experiments without stirring, the flask was left to rest away from vibrations. At suitable intervals samples were drawn from the solid phase, washed with water until radioactivity disappeared in the aqueous phase and with acetone, and allowed to air-dry. In experiments with stirring, rate of 1000 rpm was ensured.

The 20–60-mg samples of radioactive silica in strips were placed in scintillation flasks with 10.0 mL of a 0.05 M solution of 2,5-diphenyloxazole (PPO, Beckmann) in toluene and analyzed.

Since catalysts **1–4** and nonfunctionalized silica gel differ in radiation quenching properties (**1** > **2** ≥ **3**, **4**), a common reference could not be taken.

It was therefore assumed that Br^-–I^- exchange was complete after 15 h with stirring for each catalyst. The different values of observed radioactivity were thus referred to this.

(18) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.

Acknowledgment. The authors are grateful to Professor J. H. Fendler for making possible the radioactivity measurements at Texas A&M University and to the Italian CNR for financial support.

Supplementary Material Available: A listing of additional equations (1 page). Ordering information is given on any current masthead page.

Synthesis of Crobarbatine Acetate. A Macrocyclic Pyrrolizidine Alkaloid Ester

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Received August 1, 1980

Abstract: A synthesis of the 11-membered lactonic pyrrolizidine alkaloid ester, crobarbatine acetate, and a diastereomer (**26** and **27**) has been achieved, starting from (+)-retronecine (**1**) and (±)-*trans*-β-methyl-γ-carboxy-γ-valerolactone (**3**). The highly functionalized intermediate **22** was coupled with **1** to give the allylic ester **23** in 62% yield. Cyclization to give lactones **26** and **27** was brought about by treating **23** with copper(I) triflate in toluene–THF.

The pyrrolizidine alkaloids have attracted the attention of organic chemists with increasing frequency in recent years.[1-10] The large number of these alkaloids and their wide range of biological activities have made them particularly attractive syn-

(1) Culvenor, C. C. J.; Bull, L. B.; Dick, A. T. "The Pyrrolizidine Alkaloids"; North Holland Publishing Co.: Amsterdam, 1968.
(2) Leonard, N. J. In "The Alkaloids"; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, 1950; Vol. 1 pp 107–164.
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(4) Warren, F. L. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. 12, pp 245–331.
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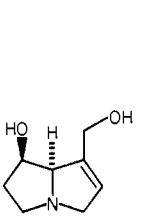
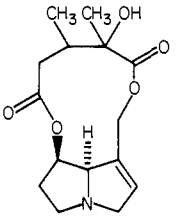
thetic targets. More than 20 naturally occurring 11-membered ring pyrrolizidine alkaloids have been characterized, and although many of these show marked, acute hepatotoxicity as well as some potentially useful physiological properties, no representative of this group has been synthesized. The large ring in these compounds incorporates two lactonic functions, in which a pyrrolizidine diol [the "necine base", most commonly retronecine (**1**)] is doubly esterified by an unsymmetrical diacid.[11]



1

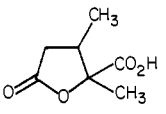


2

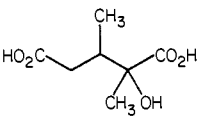
We undertook a study of the synthesis of these alkaloids both because of their intrinsic interest and because of our interest in their role as biosynthetic precursors of certain lepidopteran pheromones.[12] We chose crobarbatine (**2**)[13] as our target because it serves as a prototype for the study of directed large-ring bis lactone formation from a necine base and a relatively simple, unsymmetrical diacid. We now report the joining of two appropriate moieties in a directed fashion which affords crobarbatine as its acetate ester, as well as a diastereomer (**26** and **27**).

The two hydrolysis products of **2** are retronecine (**1**) and "crobarbatic acid" (**3**, stereochemistry unknown), the spontaneous lactonization product of 2-hydroxy-2,3-dimethylglutaric acid (**4**).[13] We hoped to couple these two components to form a primary, allylic ester, followed by lactonization to afford **2** itself.

Retronecine (**1**) has been synthesized by Geissman et al.[14] in 1962 and by Tufariello et al.[15] and by Keck et al.[16] in 1980. It can also be obtained by hydrolysis of the readily available alkaloid monocrotaline (**5**).[17]



3



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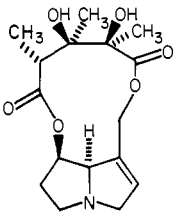
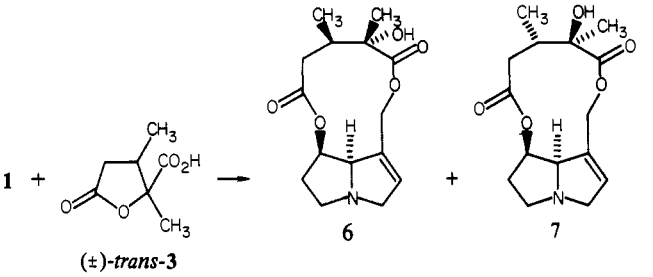


5

Our strategy required a convenient route to diacid **4** or the related lactonic acid **3**. We also needed to ascertain the stereochemistry of natural **3**. Both the cis and trans isomers of this lactone had been prepared by Bradbury and Masamune via the addition of hydrogen cyanide to ethyl 2-methylacetoacetate, followed by acidic hydrolysis.[18,19] We found that the Nagata reagent, diethylaluminum cyanide,[20] provided excellent yields (~90%) of the desired product. In contrast to hydrogen cyanide,

Scheme I



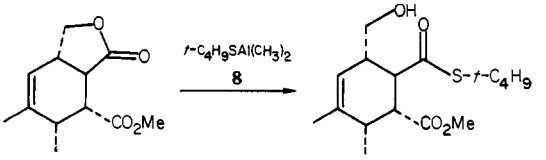
(±)-*trans*-**3** **6** **7**

the Nagata reagent also provided a high degree of stereoselectivity, with the *trans*-lactone predominating over the cis in a 10:1 ratio. These isomers could be separated by fractional crystallization.[19,21] The trans and cis acids could then be resolved with cinchonidine and brucine, respectively.[19,21]

It remained to be determined whether the cis or trans isomer of **3** corresponds to crobarbatic acid. A comparison of the reported melting point of crobarbatic acid (177–178 °C)[13] with those of optically active *cis*-**3** (55–57 °C) and *trans*-**3** (181–182 °C) suffices to establish that the methyl groups in crobarbatic acid and in crobarbatine itself are trans. Since the absolute configuration of crobarbatic acid could not be established (the optical rotation is not reported[13]), we planned to condense racemic *trans*-**3** with (+)-retronecine (**1**) as outlined in Scheme I. Retronecine would then serve as a key intermediate and as a resolving agent, giving rise to diastereomeric diesters **6** and **7**, one of which should prove identical with crobarbatine. Hydrolysis of the correct synthetic diastereomer would then reveal which enantiomer of *trans*-**3** was the correct one. If desired, the synthesis could then be repeated, starting from the appropriate enantiomer of *trans*-**3**.

To implement this scheme, we needed a reaction sequence for opening the lactonic ring of *trans*-**3**, protecting the resulting tertiary alcohol, and discriminating between the two carboxyl groups. We hoped to open the lactone with dimethylaluminum *tert*-butyl sulfide (**8**), forming a *tert*-butyl thioester.[22] Thioesters have demonstrated considerable utility in the activation of carboxyl groups for the syntheses of macrocyclic lactones.[23–26] After the tertiary hydroxyl group was protected, the first carboxyl group would be deprotected and another activating group introduced. This new activating group might then allow a selective coupling with the allylic hydroxyl group of **1**. The stage would then be set for macrocyclic lactonization involving the thioester and the remaining secondary hydroxyl group.

Before a protecting group for the free carboxylic acid was chosen, the reactivity of the dimethylaluminum *tert*-butyl sulfide (**8**) had to be considered. We hoped to esterify the free carboxyl group in *trans*-**3** before opening the lactone ring with **8**. A case involving such selectivity had already been reported: lactonic ester **9** was found to afford a 90% yield of thioester **10** on treatment with **8**.[22] This result looked promising, since it suggested that a γ-lactone could be opened in the presence of a methyl ester.



9 **10**

Accordingly, we treated *trans*-**3** with ethereal diazomethane to obtain methyl ester **11** in quantitative yield. Reaction with 1

(9) Robins, D. J. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, San Francisco, London, 1979; Vol. 24, pp 247–291.
(10) Fodor, G. In "Recent Development in the Chemistry of Natural Carbon Compounds"; Akadémiai Kiadó: Budapest, 1965; Vol. 1, pp 53–68.
(11) For a recent synthesis of an unnatural macrocyclic lactone from **1** and a symmetrical diacid, see: Robins, D. J.; Sakdarat, S. *J. Chem. Soc., Chem. Commun.* **1980**, 282–283.
(12) Schneider, D.; Boppre, M.; Schneider, H.; Thompson, W. R.; Boriack, C. J.; Petty, R. L.; Meinwald, J. *J. Comp. Physiol.* **1975**, *97*, 245–256.
(13) Puri, S. C.; Sawhney, R. S.; Atal, C. K. *Experientia* **1973**, *29*, 390.
(14) Geissman, T. A.; Waiss, A. C. *J. Org. Chem.* **1962**, *27*, 139–142.
(15) Tufariello, J. J.; Lee, G. E. *J. Am. Chem. Soc.* **1980**, *102*, 373–374.
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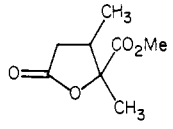
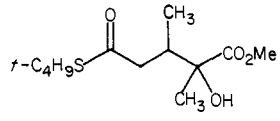
(17) Adams, R.; Rogers, E. F. *J. Am. Chem. Soc.* **1939**, *61*, 2815–2819.
(18) Bradbury, R. B.; Masamune, S. *J. Am. Chem. Soc.* **1959**, *81*, 5201–5209.
(19) Masamune, S. *J. Am. Chem. Soc.* **1960**, *82*, 5253–5255.
(20) Nagata, W.; Yoshioka, M. *Org. React.* **1977**, *25*, 255–476.
(21) Private communication with Professor S. Masamune.
(22) Weinreb. S. M.; Hatch, R. P. *J. Org. Chem.* **1977**, *42*, 3960–3961.
(23) Back, T. G. *Tetrahedron* **1977**, 3041–3059.
(24) Nicolaou, K. C. *Tetrahedron* **1977**, 683–710.
(25) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585–607.
(26) Masamune, S. *Aldrichimica Acta* **1978**, *11*, 23–32.
(27) Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1957**, *10* 474–479; **1958**, *11*, 97.

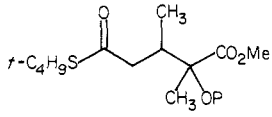
equiv of **8** in refluxing methylene chloride afforded the expected hydroxy thioester **12**. Unfortunately, **12** was found to relactonize readily under either weakly acidic or basic conditions, as well as upon silica gel chromatography. Further problems were encountered with this route. Several protecting groups for the sterically hindered tertiary hydroxyl group **12** were examined, but none provided satisfactory yields of protected alcohol **13** (acetate, 77%; methoxyethoxymethyl ether, 46%). Furthermore, it proved exceedingly difficult to hydrolyze the methyl ester of **14** specifically. For these reasons, the methyl ester was abandoned, and other protecting groups were considered.



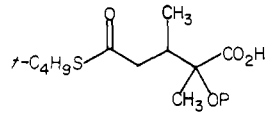
11



12

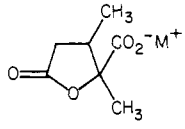


13

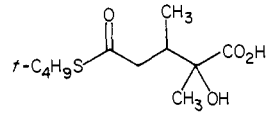


14

Protection of *trans*-**3** as its carboxylate salt seemed an attractive possibility because of the trivial nature of the protection and deprotection sequence required. Lithium salt **15a**, prepared from *trans*-**3** and 1 equiv of lithium carbonate, afforded only a 40% yield of thioester **16** after a 2-day reaction with **8** in refluxing methylene chloride. It was suspected that the low solubility of

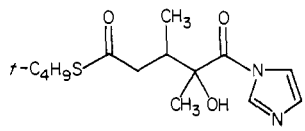


15a, $M^+ = Li^+$
15b, $M^+ = Al(CH_3)_2^+$

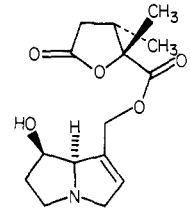


16

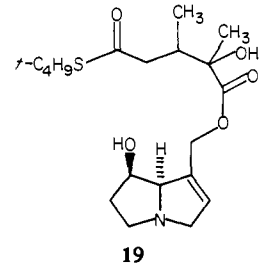
15a in methylene chloride was responsible for the sluggishness of this transformation. Since many aluminum salts are soluble in methylene chloride, the dimethylaluminum salt **15b** was prepared by treatment of *trans*-**3** with 1 equiv of trimethylaluminum in methylene chloride at 0 °C. Treatment of this soluble salt with **8** in methylene chloride at reflux for 2 days afforded thioester **16** in quantitative yield. Unlike the corresponding methyl ester **12**, acid **16** was quite stable. Initially, activation of the carboxyl group of **16** without protection of the alcohol was explored. However, the imidazolide **17**, prepared from **16** and 1 equiv of *N,N'*-carbonyldiimidazole, proved to be unstable and polymerized readily during storage. When the mixture was treated with 1 equiv of retronocine in THF, lactonic ester **18**, rather than the desired thioester **19**, was isolated in 32% yield.



17

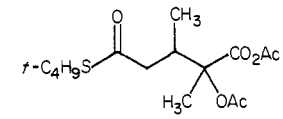


18

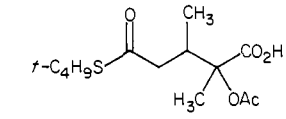


19

The tertiary hydroxyl of **16** was therefore protected as its acetate. Acetylation of **16** was accomplished by treatment with acetic anhydride, triethylamine, and 4-(dimethylamino)pyridine[28] in methylene chloride at room temperature, which gave the acetate anhydride **20**. Addition of **20** to a stirred suspension of silica gel in ether at room temperature, followed by filtration after 5 h, provided nearly pure acid **21** in quantitative yield.



20



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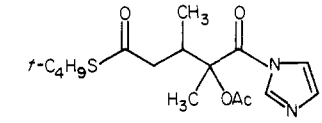

22

Our attention then turned to activation of the carboxyl group for coupling to the allylic hydroxyl group of retronecine (**1**). Several activating groups for this purpose have been reported. Culvenor and his co-workers have prepared several allylic pyrrolizidine monoesters by displacement of chloride from the corresponding allylic chloride derived from retronecine.[29-31] Semisynthetic diesters of retronecine have been prepared by Mattocks from retronecine and various acid chlorides.[32] Methods have also been devised by Crout et al. for the selective esterification of retronecine to give analogues of pyrrolizidine alkaloids.[33] These workers found that the allylic hydroxyl group of retronecine could be selectively esterified with simple acids by using *N,N'*-dicyclohexylcarbodiimide. With α,β-unsaturated and α-hydroxy-α,α-dialkyl acids, an *N*-acylimidazole-activated intermediate resulted in increased yield and selectivity.[33] Consideration of these results led us to choose an *N*-acylimidazole-activating group for **21**. The imidazolide **22** was prepared quantitatively by treating 1 equiv of *N,N'*-carbonyldiimidazole with **21** in THF at room temperature. This preparation of **22** achieved our goal of opening *trans*-**3**, differentiating between the two carboxylic groups, and protecting the resulting tertiary alcohol.

Imidazolide **22** failed to react with **1** even when it was stirred for a long period[34,35] or refluxed in THF,[36] and we therefore employed a base catalyst as described by Staab[34] and Crout.[33] The use of a catalytic amount of imidazolyl sodium gave rise to a complex mixture. 1,5-Diazabicyclo[4.3.0]non-5-ene[37] gave the allylic ester **23** but only in variable yields. Purification of **23** proved to be a problem; it hydrolyzed readily even under mildly basic conditions. Attempted chromatography on alumina with methanol-containing solvents led to rapid transesterification, resulting in the isolation of methyl ester **24** instead of the desired *tert*-butyl thioester **23**. At this point, we reasoned that purification of allylic ester **23** could be simplified if the alkoxide of retronecine itself were used as the catalyst for esterification. A catalytic amount of sodium hydride was added to a solution of retronecine in THF, and imidazolide **22** was then added. After stirring at room temperature for 3 h, the reaction was quenched by the addition of aqueous ammonium chloride, and the solution was evaporated to dryness in vacuo. The residue was taken up in acetonitrile and

(28) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569–583.
(29) Culvenor, C. C. J.; Dann, A. T.; Smith, L. W. *Chem. Ind. (London)* **1959**, 20.
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(35) Staab, H. A.; Lüking, M.; Dürr, F. H. *Chem. Ber.* **1962**, *95*, 1275–1283.
(36) Staab, H. A. *Angew. Chem.* **1959**, *71*, 194–195.
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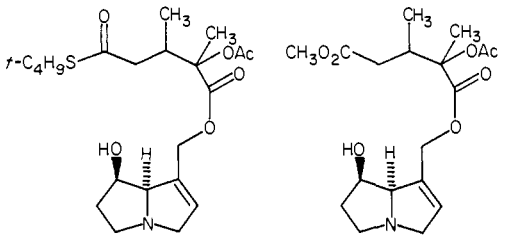
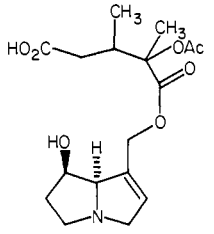
chromatographed on Sephadex LH-20.[38] Allylic monoester **23** (62%, as the expected mixture of diastereomers) eluted well ahead of both the imidazole and recovered retronecine.



23 **24**

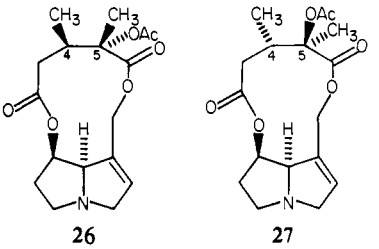
Medium- and large-ring lactonizations are well-known to be disfavored entropically. Classically, high-dilution techniques have been applied to prevent polymerization of hydroxy acids during lactonization. These procedures, however, are inconvenient on a preparative scale and often result in low yields. For these reasons, several research groups have sought new methods for macrocyclic lactonization.[23-26] Although these techniques had only rarely been applied to alkaloid synthesis,[12,39] it was anticipated that, with minor modifications, this methodology could be useful in the synthesis of our target alkaloid. Since mercuric trifluoroacetate had demonstrated considerable utility in the lactonization of *tert*-butyl thioesters for syntheses of methymycin,[40] zearalenone,[41] and pikromycin[26] by Masamune and his co-workers, we employed this reagent first in an attempt to cyclize thioester **23**. However, only starting material was recovered if less than 6 equiv of the mercuric salt was employed. In the presence of large excesses of Hg(II), only carboxylic acid **25** was obtained.



25

A mixture of mercuric chloride and cadmium carbonate has also been used by Masamune to effect lactonizations.[41] In our case, no reaction was observed in refluxing acetonitrile; **23** was recovered quantitatively. Similarly, copper(I) trifluoroacetate[42-44] failed to lactonize **23** and gave only carboxylic acid **25**.

Finally, copper(I) trifluoromethanesulfonate–benzene complex[42,45] was found to effect the crucial lactonization in good yield. A mixture of **23** and the copper(I) complex [about 5 equiv of Cu(I)] in THF–toluene was stirred at room temperature under argon for one day. After workup, a mixture of diastereomeric cyclic diesters **26** and **27** was obtained in 62% yield. Careful column chromatography on activity grade III alumina, eluting with benzene and gradually increasing solvent polarity with chloroform, separated two components, designated A and B in order of increasing polarity. One of these two acetates should be the acetate of crobarbatine, but since the acetate ester of **2** has not been described, no comparison is possible at this point.



26 **27**

The configurations of A and B were determined by acid hydrolysis, which afforded the enantiomers of *trans*-**3**. Cervinka et al.[46] have correlated the sign of the Cotton effect of five- and six-membered lactonic acids with their absolute configurations. This analysis applies to lactonic acids in which the carboxyl group is attached to the carbon bearing the heterocyclic oxygen and is independent of configuration at the other carbon atoms. They demonstrated that lactonic acids with the *S* configuration at this carbon atom exhibit a positive Cotton effect, while the *R* configuration gives rise to a negative Cotton effect. The lactonic acid isolated from hydrolysis of A, identical with (−)-*trans*-lactonic acid **3** obtained by cinchonine resolution, showed a positive Cotton effect at 237 nm. Similarly, the lactonic acid from B corresponded to (+)-*trans*-**3** and exhibited a negative Cotton effect. Therefore, the stereochemistry shown in expression **26** (5*S*),(4*R*) could be assigned to A, and that shown in **27** (5*R*),(4*S*) could be assigned to B.

We attempted to deacetylate both **26** and **27** by base-catalyzed hydrolysis, hoping to obtain the free alkaloid from one of these esters and a diastereomer from the other. Disappointingly, even under mildly basic conditions, to which the closely related monocrotaline (**5**) is inert, **26** and **27** were overhydrolyzed to give retronecine itself. We turned then to acid-catalzyed hydrolysis, since Culvenor et al. have shown that both monocrotaline monoacetate (spectabiline) and diacetate can be hydrolyzed with 10% HCl to afford monocrotaline itself.[27] In the case of our acetates, **27** furnished the deacetylated product **7** in low yield, but under no conditions could **6** be isolated from the hydrolysis of **26**.

Unfortunately, our attempts to obtain either an authentic sample of crobarbatine or the seeds of *Crotalaria barbata* were unsuccessful, due to the scarcity of this plant.[47] We were, therefore, unable to compare **7** directly with an authentic sample of crobarbatine or to compare the synthetic acetates **26** and **27** with crobarbatine acetate. The problem was compounded by our inability to crystallize our hydrolysis product on a small scale without decomposition. Only limited published data for **2** (melting point, mass spectrum, infrared spectrum (KBr), and a 60-MHz ^{1}H NMR spectrum in D_2O) therefore served as our basis for deciding whether **7** corresponds to naturally occurring crobarbatine or its diastereomer.

The electron-impact mass spectrum of **7** agrees well with the literature data for the alkaloid,[13] but these spectra cannot be expected to be sensitive to stereochemical differences. The published infrared spectrum (KBr) of crobarbatine exhibits the expected peaks attributable to the ester carbonyls (1735 cm^{-1}) and a hydroxyl group (3300 cm^{-1})[13,47] The infrared spectrum (KBr) of **7** also shows 1735- and 3400-cm^{-1} absorptions; more importantly, the fingerprint regions of the two spectra show good correspondence, although the quality of these spectra was not as high as one would like.

Similarly, the 60-MHz NMR spectrum of **7** does not provide an absolutely unambiguous comparison with the crobarbatine spectrum provided to us by Sawhney.[47,48]

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(39) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S. *J. Am. Chem. Soc.* **1975**, *97*, 654–655.
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(42) Masamune, S.; Hayase, T.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756–6758.
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(46) Cervinka, O.; Hub, L.; Klásek, A.; Santavy, F. *Chem. Commun.* **1968**, 261–263.
(47) Private communication with Dr. Rajinder S. Sawhney (cf. ref 13).
(48) It is intriguing that the configuration shown for crobarbatine in Glasby, J. S., Ed. "Encyclopedia of the Alkaloids"; Plenum Press: New York and London, 1975; Vol. 1(A-H), pp 351–352, is that given in expression **7**. Unfortunately, there is no indication of the basis for this stereochemical assignment.

All of these difficulties would vanish if we had found a protecting group for the tertiary hydroxyl function of our crobarbatine precursors which could be removed under conditions where crobarbatine itself is stable. We plan to study this problem further and also to apply the synthetic strategy described in this paper to the synthesis of some of the more important pyrrolizidine alkaloids.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover melting point apparatus or Kofler hot-stage melting point unit and are uncorrected. Unless otherwise noted, all reactions were conducted in an atmosphere of argon. In most cases, liquids were introduced into the reaction vessel via a hypodermic syringe inserted through a rubber serum cap located on a sidearm of the vessel.

Other general procedures include, unless otherwise specified, stirring of solutions magnetically and removal of solvents under reduced pressure using a rotary evaporator and vacuum pump.

Anhydrous tetrahydrofuran (THF) was freshly distilled from commercial THF containing sodium benzophenone ketyl. Toluene was distilled from calcium hydride and then stored over sodium. Methylene chloride was either distilled from calcium hydride or filtered through alumina Woelm (activity grade I). Acetonitrile was predried over 4-Å molecular sieves, distilled from calcium hydride, and stored with 0.5% (w/v) P_2O_5.

Infrared (IR) spectra were obtained on a Perkin-Elmer Model 257 spectrometer and calibrated by using the 1601.4-cm^{-1} band of polystyrene. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 90 MHz with a Varian Associates EM-390 spectrometer or at 60 MHz with a Varian Associates A60-A spectrometer using tetramethylsilane (Me_4Si) as an internal standard. Chemical shifts were reported in parts per million (ppm) downfield from Me_4Si. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 20 MHz with a Varian Associates CFT-20 spectrometer. Mass spectra were recorded on either an Associated Electronic Industries MS-902 spectrometer equipped with a VG Micromass 2040 data reduction system or a Finnigan Model 3300 gas chromatograph/mass spectrometer equipped with a System Industries Model 150 data reduction system. Electron-impact mass spectra (EIMS) were obtained at 70 eV, and chemical ionization mass spectra (CIMS) utilized methane as the ionizing gas. Only characteristic peaks in the EIMS and CIMS are reported. Gas–liquid chromatographic (GLC) analyses were carried out on a Hewlett-Packard Model 5720A instrument. Medium-pressure liquid chromatography was carried out on a system constructed of Altex columns and fittings, using ICN silica gel (0.032 – 0.063 mm) as absorbent and a FMI Model RP pump operating at 30–100 psi as the pressure source. Optical rotatory dispersion (ORD) spectra were obtained on a Cary 60 spectrometer. Optical rotations were measured on a Perkin-Elmer Model 141 Polarimeter.

Analtech precoated silica gel and alumina plates with fluorescent indicator 0.25, 1, and 2 mm were used for preparative thin-layer chromatography (TLC). Machery Nagel and Co. Polygram Sil-G/UV-254 silica gel plates (0.25 mm thickness) and Alox N/UV-254 alumina plates (0.2 mm thickness) were used for analytical TLC. Compounds were visualized in both analytical and preparative TLC by ultraviolet light, iodine vapor, phosphomolybdic acid spray, or treatment with a solution containing vanillin (3%) dissolved in 200:1 ethanol–sulfuric acid. Column chromatography was performed with Grace silica gel (Grade 950, 60–200 mesh), Woelm neutral alumina (activity grade I), or Sephadex LH-20.

***trans*-β-Methyl-γ-carboxy-γ-valerolactone (3).** A solution of diethylaluminum cyanide (a 2 M solution in benzene, 100 mL, 0.2 mol) was added dropwise to a solution of ethyl β-methyllevulinate (17.7 g, 0.112 mol)[18] in dry toluene (400 mL) at −23 °C under argon. The mixture was stirred at −23 °C for 80 min, then transferred to a solution of methanol (800 mL) and concentrated HCl (480 mL), and stirred at −80 °C for 1.5 h. The foamy solution with a white precipitate was poured into a solution of concentrated HCl (150 mL) and water (100 mL) and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated in vacuo to leave a liquid residue (lactonic nitrile; IR ($CHCl_3$): 2300, 1805 cm^{-1}) to which was added a few *p*-toluenesulfonic acid crystals as a stabilizer.

A mixture of this residue, water (100 mL), and concentrated HCl (200 mL) was refluxed for 1.5 days and continuously extracted with diethyl ether to afford 16 g (90%) of lactonic acids (**3**) as a mixture of stereoisomers. The ratio of the corresponding trans and cis methyl esters (obtained upon treatment of a small sample of **3** with ethereal diazomethane) was found to be 10:1 by GLC (3% OV-1, isothermal, 100 °C). Fractional crystallization from either $CHCl_3$ or ethyl acetate–cyclohexane, as described by Bradbury and Masamune,[18,19,21] gave *trans*-**3**: mp 149–150 °C (lit.[21] 151–152 °C), mp (*p*-bromophenacyl derivative) 87–88 °C (lit.[21] 86–88 °C); ^1H NMR (D_2O) 1.08 (d, 3 H, J = 7 Hz), 1.63 (s, 3 H), 2.4–3.1 (m, 3 H) ppm; IR (KBr) 3300–2500 (br), 1756, 1735 cm^{-1}; ^{13}C NMR (D_2O): 179.42, 173.51, 88.75, 40.00, 35.47, 20.73, 13.51 ppm; CIMS, *m/e* (relative intensity) 159 (M^+ + 1, 3), 113 ($M^+ - CO_2H$, 100).

Resolution of *trans*-β-Methyl-γ-carboxy-γ-valerolactone (3).[19,21] The trans acid (**3**).[19,21] was resolved via its cinchonidine salt to afford the (+)-enantiomorph: mp 181–182 °C (lit. 181.5–183 °C); $[\alpha]^{rt}_D$ +3.05° (H_2O, *c* 0.013) [lit. $[\alpha]^{25.5}_D$ +3.93° (H_2O, *c* 2.72)] as described by Masamune.[19,21]

Methyl *trans*-β-Methyl-γ-carboxy-γ-valerolactone (11). Ethereal diazomethane was added to a suspension of trans acid **3** (1.0 g, 6.33 mmol) in diethyl ether (40 mL) until a light yellow color persisted. The desired methyl ester **11** (1.09 g, 100%) was obtained after removal of the solvent: ^1H NMR ($CDCl_3$) 1.08 (d, 3 H, J = 7 Hz), 1.60 (s, 3 H), 2.28–2.78 (m, 3 H), 3.77 (s, 3 H) ppm; IR ($CHCl_3$) 1785, 1740 cm^{-1}; EIMS, *m/e* (relative intensity) 113 ($M^+ - CO_2CH_3$, 100).

***S*-*tert*-Butyl *O*-Methyl 4-Hydroxy-3,4-dimethyl-1-thioglutarate (12).** A solution of methyl ester **11** (53 mg, 0.31 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise to a cooled (0 °C) solution of dimethylaluminum *tert*-butyl sulfide (**8**)[22] in dry CH_2Cl_2 [prepared from *tert*-butyl mercaptan (35 μL, 0.31 mmol) and 2.5 M trimethylaluminum in hexane (130 μL, 0.325 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C] and then refluxed for 21 h under argon. The mixture was quenched by the slow addition of 0.5% HCl (20 mL) and CH_2Cl_2 (10 mL), stirred at room temperature for a short time, and extracted with four portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried over Na_2SO_4, filtered through celite, and concentrated in vacuo to give 62 mg of viscous oil, shown by NMR analysis to be predominantly the desired produce **12**: ^1H NMR ($CDCl_3$) 0.86 (d, 3 H, J = 7 Hz), 1.36 (s, 3 H), 1.43 (s, 9 H), 2.2-2.9 (m, 3 H), 3.2 (s, 1 H, –OH), 3.78 (s, 3 H) ppm; IR ($CHCl_3$) 3520, 1730, 1675 cm^{-1} (1790 cm^{-1}, due to **11**). Preparative silica gel TLC (elution with diethyl ether and pentane (1:1)) gave one UV-active band. This band contained 57 mg of material, which was shown by NMR analysis to be a mixture of the desired product **12** and methyl ester **11** in the 64:36 ratio. Two dimensional TLC development showed that the desired product **12** suffered relactonization to form methyl ester **11** on silica gel.

***S*-*tert*-Butyl Hydrogen 4-Hydroxy-3,4-dimethyl-1-thioglutarate (16).** To a cooled (0 °C) suspension of *trans*-lactonic acid **3** (6 g, 38 mmol) in dry CH_2Cl_2 (150 mL) was added trimethylaluminum in hexane (15.1 mL of a 2.5 M solution, 38 mmol). The mixture was stirred at 0 °C for 20 min under argon. To this mixture was added a cooled (0 °C) solution of dimethylaluminum *tert*-butyl sulfide (**8**)[22] in dry CH_2Cl_2 [prepared from *tert*-butyl mercaptan (17.8 mL, 160 mmol) and trimethylaluminum in hexane (64.2 mL of a 2.5 M solution, 160 mmol) in CH_2Cl_2 (200 mL) at 0 °C]. The mixture was allowed to warm to room temperature and was refluxed for 2 days under argon. It was then quenched by the cautious addition of 3% HCl (250 mL), stirred at room temperature for 20 min, and extracted with five portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield 9.42 g (100%) of **16**: mp (CH_2Cl_2) 125–126.5 °C; ^1H NMR ($CDCl_3$) 0.98 (d, 3 H, J = 6.5 Hz), 1.44 (s, 12 H), 2.33–2.90 (m, 3 H), 6.30 (br, 2 H) ppm; IR (CH_2Cl_2) 3400–2500 (br), 1714, 1680 cm^{-1}; EIMS, *m/e* (relative intensity) 159 ($M^+ - C_4H_9S$, 38), 113 ($M^+ - C_4H_9S - CO_2H_2$, 100); CIMS, *m/e* (relative intensity) 249 (M^+ + 1, 20), 159 ($M^+ - C_4H_9S$, 100), 113 ($M^+ - C_4H_9S - CO_2H_2$, 43).

***S*-*tert*-Butyl γ-Hydroxy-β,γ-dimethyl-δ-oxoimidazole-1-thiovalerate (17).** A solution of acid **16** (69.5 mg, 0.28 mmol) in THF (5 mL) was added to a solution of *N,N'*-carbonyldiimidazole (45.4 mg, 0.28 mmol) in THF (2 mL) and stirred at room temperature for 3.5 h under argon, after which the mixture was concentrated in vacuo. The solid residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to yield the corresponding imidazolide **17** (80 mg, 96%). ^1H NMR ($CDCl_3$): 1.03 (d, 3 H, J = 7 Hz), 1.43 (s, 9 H), 1.57 (s, 3 H), 2.3–2.9 (m, 3 H), 6.2 (br, 1 H), 6.98 (br s, 1 H), 7.76 (br s, 1 H), 8.70 (br s, 1 H).

Monocrotaline 5. Monocrotaline was isolated from seeds of *Crotalaria spectabilis* by a modification of the procedure described by Adams.[17] The crushed seeds (12.1 g) were extracted with methanol in a Soxhlet apparatus for 3 days. The resulting solution was concentrated in vacuo, and to the residue was added 60 mL of 0.5 N H_2SO_4 (then adjusted to 2 N by addition of concentrated H_2SO_4) and Zn dust (4 g). The acidic mixture was stirred for 4 h, extracted with three portions of diethyl ether, basified with Na_2CO_3, and then extracted with four portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried over Na_2SO_4 and filtered to afford 0.9 g of crude solid. Recrystallization from absolute ethanol afforded 721 mg (6% of dry seed weight) of white crystals: mp 201–202

°C (lit.[17] 197–198 °C), ^{1}H NMR ($CDCl_3$) characteristic peaks, 1.21 (d, 3 H, J = 7 Hz), 1.34 (s, 3 H), 1.53 (s, 3 H), 4.5–5.2 (m, 3 H), 6.05 (br s, 1 H).

Retronecine (1).[17] A mixture of 6 g of monocrotaline and 15 g of barium hydroxide octahydrate in 125 mL of water was refluxed for 5 h. After being cooled, the solution was saturated with CO_2 by addition of dry ice and the barium carbonate filtered off. The filtrate was concentrated to 25 mL, basified with Na_2CO_3, and continuously extracted with diethyl ether for 2 days. The ethereal extract was dried over Na_2SO_4 and concentrated in vacuo. The solid residue was recrystallized from acetone to give 2.4 g of **1**, mp 119–120 °C (lit.[17] 121 °C).

Reaction of Imidazolide 17 and Retronecine (1). A suspension of retronecine (**1**) (23.4 mg, 0.15 mmol) and freshly prepared imidazolide **17** (36.4 mg, 0.122 mmol) in dry THF (4 mL) was stirred at room temperature for 1 day under argon. The solution was concentrated in vacuo, then dissolved with CH_2Cl_2, and washed with water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford 11.6 mg (32%) of **18**: ^{1}H NMR ($CDCl_3$) characteristic peaks, 1.07 (d, 3 H, J = 7 Hz), 1.64 (s, 3 H), 4.80 (br s, 2 H), 5.87 (br s, 1 H) ppm; IR ($CHCl_3$) 3400, 1790, 1740 cm^{-1}; EIMS, m/e (relative intensity) 295 (M^+, 2), 138 (43), 137 (16), 136 (9), 95 (7), 94 (44), 93 (100); CIMS; m/e (relative intensity) 296 (M^+ + 1,100) 138 (33).

***S-tert*-Butyl Hydrogen 4-Hydroxy-3,4-dimethyl-1-thioglutarate Acetate Anhydride with Acetic Acid (20).** A solution of acid **16** (1.64 g, 6.6 mmol), 4-(dimethylamino)pyridine (0.614 g, 5.03 mmol), triethylamine (6 mL, 43 mmol), and acetic anhydride (12 mL, 127 mmol) in CH_2Cl_2 (125 mL) was stirred at room temperature for 18 h. The solution was then poured into a mixture of ice and 10% aqueous HCl (75 mL) and extracted with three portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to yield (2.20 g, 99%) of **20**: ^{1}H NMR ($CDCl_3$) 1.04 (d, 3 H, J = 7 Hz), 1.46 (s, 9 H), 1.58 (s, 3 H), 2.08 (s, 3 H), 2.27 (s, 3 H), 2.3–2.9 (m, 3 H) ppm; IR ($CHCl_3$) 1740, 1679 cm^{-1}.

***S-tert*-Butyl Hydrogen 4-Hydroxy-3,4-dimethyl-1-thioglutarate Acetate (21).** A suspension of anhydride **20** (2.2 g, 6.63 mmol), silica gel (15 g), and water (5 mL) in diethyl ether (150 mL) was stirred at room temperature for 5 h and filtered. The filtrate was concentrated in vacuo to afford 1.92 g (100%) of **21**: ^{1}H NMR ($CDCl_3$) 1.01 (d, 3 H, J = 7 Hz), 1.45 (s, 9 H), 1.58 (s, 3 H), 2.04 (s, 3 H), 2.2–2.9 (m, 3 H), 10.2 (s, 1 H) ppm; IR ($CHCl_3$) 3300–2700 (br), 1740, 1720, 1678 cm^{-1}; EIMS, m/e (relative intensity) 201 ($M^+ - C_4H_9S$, 10), 159 ($M^+ - C_4H_9S - C_2H_2O$, 35), 113 ($M^+ - C_4H_9S - C_2H_2O - CO_2H_2$, 45); CIMS, m/e (relative intensity) 291 (M^+ + 1, 7), 201 ($M^+ - C_4H_9S$, 42), 159 ($M^+ - C_4H_9S - C_2H_2O$, 95), 113 ($M^+ - C_4H_9S - C_2H_2O - CO_2H_2$, 100).

***S*-tert-Butyl γ-Hydroxy-β,γ-dimethyl-δ-oxoimidazole-1-thiovalerate Acetate (Ester) (22).** A solution of acid **21** (1.9 g, 6.55 mmol) in THF (50 mL) was added to a solution of *N,N'*-carbonyldiimidazole (1.28 g, 7.89 mmol) in THF (60 mL). The mixture was stirred at room temperature for 3.5 h under argon, after which it was concentrated in vacuo. The solid residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with two portions of diethyl ether. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to yield the corresponding imidazolide **22** (2.22 g, 100%): mp (pentane) 112–114 °C; ^{1}H NMR ($CDCl_3$) 1.17 (d, 3 H, J = 7 Hz), 1.38 (s, 9 H), 1.60 (s, 3 H), 2.07 (s, 3 H), 2.2–2.8 (m, 3 H), 7.03 (br s, 1 H), 7.52 (br s, 1 H), 8.26 (br s, 1 H) ppm; IR ($CHCl_3$) 1760–1740 (br), 1678 cm^{-1}; EIMS, m/e (relative intensity) 273 ($M^+ - C_3H_3N_2$, 20), 217 (33), 113 ($M^+ - C_3H_3N_2 - C_4H_9S - C_3H_3O_2$, 97); CIMS, m/e (relative intensity) 341 (M^+ + 1, 17), 273 ($M^+ - C_3H_3N_2$, 31), 231 ($M^+ - C_3H_3N_2 - C_2H_2O$, 20), 217 (100).

***S-tert*-Butyl *O*-[[(1*R*,7a*R*)-2,3,5,7a-Tetrahydro-1-hydroxy-1*H*-pyrrolizin-7-yl]methyl] 4-Hydroxy-3,4-dimethyl-1-thioglutarate 4-Acetate (23).** To a suspension of NaH (85 mg, 1.77 mmol, 0.22 equiv, 50% oil dispersion, washed twice with pentane) in dry THF (80 mL) was added retronecine (1.41 g, 9.10 mmol) at room temperature under argon. Hydrogen was evolved rapidly. The suspension was stirred at room temperature for 5 min, and a solution of **22** (2.75 g, 8.09 mmol) in dry THF (70 mL) was dropped in rapdily. The reaction mixture was stirred at room temperature for 3 h, aqueous NH_4Cl (95 mg, 1.77 mmol, in 3 mL of water) was added, and the mixture was stirred at room temperature for 5 min. The solution was concentrated in vacuo, and residue was chromatographed on Sephadex LH-20 (ca. 60 g) with acetonitrile as the eluting solvent. The allylic ester **23** (564 mg, 62%) was the first component to elute, after about 80 mL of solvent. This was followed by imidazole and then unreacted retronecine (**1**) in much later fractions. **23**: ^{1}H NMR ($CDCl_3$) characteristic peaks, 0.99 (d, 3 H, J = 7 Hz), 1.46 (s, 9 H), 1.57 (s, 3 H), 2.04, 2.06 (2 s, 3 H), 4.6–5.0 (br m, 2 H), 5.88 (br s, 1 H) ppm; IR ($CHCl_3$) 1740, 1678 cm^{-1}.

Reaction of 23 with Mercuric Trifluoroacetate. The general procedure was as follows. A solution of thioester **23** in dry acetonitrile was added dropwise to a colorless solution of excess (greater than 6 equiv) mercuric trifluoroacetate in acetonitrile at room temperature under argon (reaction concentration ca. 0.003–004 M). The mixture became clear red-brown immediately, then light brown, golden yellow, and finally clear light yellow-brown. The mixture was stirred at room temperature for one day and H_2S was bubbled in until no further black precipitate appeared. The mixture was filtered through celite, and solvent was removed in vacuo leaving the acid **25** quantitatively. This reaction was carried out under various conditions. With greater than 6 equiv of mercuric trifluoroacetate, regardless of the reaction time and temperature, the reaction gave the acid **25** consistently. No reaction occurred when only 2 equiv of mercuric trifluoroacetate were used: ^{1}H NMR ($CDCl_3$): characteristic peaks, 1.07 (d, 3 H, J = 7 Hz), 1.53 (s, 3 H), 2.06 (s, 3 H), 5.83 (br s, 1 H) ppm; IR ($CHCl_3$) 3500–2500 (b), 1735, 1664 cm^{-1}; EIMS, m/e (relative intensity) 355 (M^+, 1), 338 (M^+ - OH, 3), 138 (16); CIMS, m/e (relative intensity) 356 (M^+ + 1,2), 338 (M^+ - OH, 25), 159 (100).

Reaction of 23 with Cuprous Trifluoroacetate. A solution of thioester **23** (67.1 mg, 0.157 mmol) in CH_2Cl_2 (30 mL) was added to a mixture of cuprous trifluoracetate[43] [prepared by refluxing copper(I) oxide (510 mg) and trifluoroacetic anhydride (3 mL) in dry toluene (45 mL) for 3.5 h, then filtering and drying in vacuo] in CH_2Cl_2 (90 mL) and stirred at room temperature for 1 day under argon. H_2S was then bubbled into this green solution containing black solid until no further black precipitate formed. Filtration through celite and concentration in vacuo afforded 49.4 mg of residue. This was dissolved in water and extracted with 3 portions of $CHCl_3$. The aqueous layer was concentrated in vacuo to afford 41.5 mg of acid **25**.

Reaction of 23 with Mercuric Chloride. A suspension of **23** (95.4 mg, 0.223 mmol), mercuric chloride (426 mg, 1.57 mmol), and cadmium carbonate (576 mg, 3.34 mmol) in acetonitrile (110 mL) was refluxed under argon for 1 day. The suspension was allowed to cool to room temperature, and H_2S was bubbled in until no further black precipitate appeared. The mixture was filtered through celite, concentrated in vacuo, and chromatographed on Sephadex LH-20 (CH_3CN as eluting solvent) to obtain **23** (89 mg, 94% recovery).

Lactonization of 23 with Copper(I) Trifluoromethanesulfonate (Benzene Complex). A solution of thioester **23** (146 mg, 0.34 mmol) in dry toluene (45 mL) was added dropwise (ca. 1 H) to a dark black-green mixture of copper(I) trifluoromethanesulfonate (benzene complex) [450 mg, ca. 5 equiv of Cu(I)] and dry toluene (50 mL) at room temperature under argon. The dark black-green solution became brownish black and deposited some dark brown solid after the addition. Upon addition of 30 mL of dry THF, everything dissolved. The mixture was stirred at room temperature for 22 h, and H_2S was bubbled in until no further black precipitate appeared. About 500 mg of Na_2CO_3 was added, the mixture was stirred for 5 min and filtered through celite. The solvents were removed under reduced pressure, leaving 125 mg of residue. This was taken up in a small volume of 0.5 N HCl and continuously extracted with diethyl ether for 4 h. The aqueous phase was then made basic and continuously extracted with diethyl ether to give 72 mg (63%) of cyclization products **26** and **27** as a mixture of diastereomers: ^{1}H NMR ($CDCl_3$) characteristic peaks, 1.10 (d, 3 H, J = 7 Hz), 1.13 (d, 3 H, J = 7 Hz), 1.51 (s, 3 H), 1.56 (s, 3 H), 2.06 (s, 6 H, acetate), 4.3–4.5 (br m, 2 H), 4.56 (br s, 2 H), AB quartet (4.35, 4.93; 2 H, J = 12.5 Hz), 5.08–5.24 (br m, 1 H), 5.34–5.59 (br m, 1 H), 5.96–6.06 (br s, 2 H) ppm; IR ($CHCl_3$) 1740 (br) cm^{-1}; EIMS, m/e (relative intensity) 337 (M^+, 8), 251 (M^+ - 86, 15), 250 ($M^+ - CO_2 - C_2H_3O$, 85), 136 (82), 137 (18), 138 (8), 119 (61), 120 (55), 121 (10), 93 (100), 94 (34), 95 (11); CIMS, m/e (relative intensity) 366 (M^+ + 29, 5), 338 (M^+ + 1, 55), 278 (36), 250 (40), 120 (100).

Separation of (4*R*,5*S*,13a*R*,13b*R*)-4,5,8,10,12,13,13a,13b-Octahydro-5-hydroxy-4,5-dimethyl-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]-pyrrolizidine-2,6(3*H*)-dione 5-Acetate (26) and (4*S*,5*R*,13a*R*,13b*R*)-4,5,8,10,12,13,13a,13b-Octahydro-5-hydroxy-4,5-dimethyl-2*H*-[1,6]dioxacycloundecino[2,3,4-*gh*]pyrrolizidine-2,6(3*H*)-dione 5-Acetate (27). A mixture of **26** and **27** (529 mg) was carefully chromatographed on alumina (175 g, deactivated with 10 mL water) utilizing a benzene–chloroform increasing polarity gradient. The first component to elute (114 mg, designated A) was characterized as pure diastereomer **26**. This was followed by a mixture of diastereomers (340 mg, A + B) and finally pure component B (68 mg) which was characterized as diastereomer **27**. Component A, **26**: ^{1}H NMR ($CDCl_3$) characteristic peaks, 1.10 (d, 3 H, J = 7 Hz), 1.56 (s, 3 H), 2.06 (s, 3 H), 4.4–4.5 (br m, 1 H), 4.56 (br s, 2 H), 5.34–5.59 (br m, 1 H), 5.96–6.06 (br s, 1 H) ppm; IR ($CHCl_3$) 1740 (br) cm^{-1}; ^{13}C NMR ($CDCl_3$) 171.34, 170.27, 169.60, 134.90, 132.52, 82.17, 78.23, 73.24, 61.17, 59.40, 53.91, 37.31, 37.11, 33.19, 21.25, 15.91, 15.73 ppm; High-resolution MS, molecular ion at m/e 337. 337.1502 (calcd for $C_{17}H_{23}O_6N$, 337.1525). Component **B**, **27**: ^{1}H NMR ($CDCl_3$) characteristic peaks, 1.13 (d, 3 H, J = 7 Hz), 1.51 (s,

3 H), 2.06 (s, 3 H), 4.3-4.4 (br m, 1 H), AB quartet (4.35, 4.93; 2 H, J = 12.5 Hz), 5.08-5.24 (br m, 1 H), 5.96-6.06 (br s, 1 H) ppm; IR ($CHCl_3$) 1740 (br) cm^{-1}; ^{13}C NMR ($CDCl_3$) 170.54, 169.82, 169.53, 134.41, 133.10, 81.74, 76.98, 74.37, 61.42, 58.00, 53.66, 38.18, 35.93, 33.48, 21.05, 15.37, 14.82 ppm; High-resolution MS, molecular ion at m/e 337, 337.1506 (calcd for $C_{17}H_{23}O_6N$, 337.1525).

Determination of Absolute Configuration of 26 and 27. The acetate **26** (12 mg) in 10% HCl (3 mL) was refluxed for 4 h, followed by continuous extraction with diethyl ether to afford *trans*-**3** (5.3 mg). The ORD spectrum of this sample showed a positive Cotton effect at 237 nm, identical with that of (-)-*trans*-**3** (obtained by resolution of (±)-**3** by using cinchonine). It was assigned a 4*R*,5*S* configuration based on the work of Cervinka and co-workers.[46] Similarly, acetate **27** (13 mg) afforded *trans*-**3** (5.5 mg), which was assigned the 4*S*,5*R* configuration based on its negative Cotton effect at 235 nm,[46] identical with that of (+)-*trans*-**3**.

Attempted Deacetylation of 26 by 10% HCl. A solution of acetate **26** (15.2 mg) in 10% HCl (0.5 mL) was refluxed for 25 min and then basified to pH 9 by the addition of sodium carbonate. Acetonitrile (15 mL) was added, and the mixture was concentrated in vacuo. The solid residue was filtered through celite with acetonitrile and methylene chloride. Removal of solvents in vacuo provided 14.8 mg of residue which contained retronecine and lactonic ester **18** in a ratio 3:1, based on NMR analysis.

Attempted Deacetylation of 27 by 10% HCl. A solution of acetate **27** (99 mg) in 10% HCl (0.9 mL) was refluxed for 20 min and then basified to pH 9 by the addition of sodium carbonate. Acetonitrile (15 mL) was added, and the mixture was concentrated in vacuo. The solid residue was filtered through celite with acetonitrile and methylene chloride. Removal of solvents in vacuo provided 54 mg of residue which was chromatographed on alumina (activity I) with methylene chloride-methanol (50:1) as the eluting solvent. Deacetylated **7** (18 mg, 21%) was the first component to elute, followed immediately by lactonic ester **18**, and then retronecine in later fractions. The hydrolysis product, **7**, gave the following spectral data: ^1H NMR ($CDCl_3$) characteristic peaks only, 1.11 (d, 3 H, J = 6.5 Hz), 1.33 (s, 3 H), 4.30-4.45 (br m, 1 H), 4.58 and 4.75 (AB quartet, 2H, J = 12 Hz), 5.15-5.35 (br m, 1 H), 5.99 (br s, 1 H) ppm; ^1H NMR (D_2O) 1.08 (d, 3 H, J = 6.5 Hz), 1.33 (s, 3 H), 4.92 (s, 1 H), 5.15 (br m, 2 H), 6.22 (br s, 1 H) ppm [lit.:[13] characteristic peaks, 1.07 (d, 3 H, J = 6.5 Hz), 1.32 (s, 3 H), 4.81 and 5.28 (AB quartet, J = 16 Hz), 6.27 (m) ppm; a spectrum obtained directly from the authors,[47] however, showed the 4.8-5.5 ppm region much obscured]; IR (KBr) 3400, 1735 cm^{-1} [lit.:[13,47] 3300, 1735 cm^{-1}]; EIMS, m/e (relative intensity) 295 (M^+, 18), 251 ($M^+ - CO_2$, 5), 208 ($M^+ - CO_2 - C_2H_3O$, 3) 138 (40), 136 (38), 121 (13), 120 (37), 119 (37), 95 (31), 93 (98), 80 (40); [lit.:[13] 295 (83), 251 (29), 208 (14), 138, 136, 121, 120, 119, 95, 93, 80]; CIMS, m/e (relative intensity) 296 ($M^+ + 1$, 100), 251 ($M^+ - CO_2$, 5), 138 (26), 120 (94); High-resolution MS, molecular ion at m/e 295.1439 (calcd for $C_{15}H_{21}O_5N$, 295.141 96).

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Preparation of Tribenzo[21]aneN$_6$: A Metal Template Synthesis

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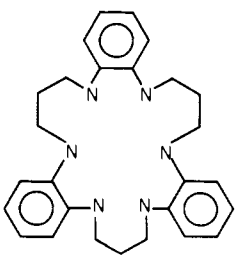
Abstract: The nitrogen-containing macrocycle tribenzo[*b*,*i*,*p*]-1,4,8,11,15,18-hexaazacycloheneicosane (**1**) was synthesized by a series of reactions involving the alkylation of doubly deprotonated aromatic amine complexes of cobalt(III). The synthesis was successful starting with either (1,2-diaminobenzene)[1,3-bis[(*o*-aminophenyl)amino]propane]cobalt(III) (**2**) or tris(1,2-diaminobenzene)cobalt(III) (**4**) but the yield was considerably better with **2** (67%) than with **4** (25%). The electronic spectrum of the cobalt(III) complex of **1** shows a charge-transfer band in the visible region and a transition localized on the aromatic rings of the ligand in the UV region. The UV and CD spectra give some information about the configuration of the complex. The free macrocycle **1** was recovered from its cobalt(III) complex and characterized.

The synthesis of polyheteroatom-containing macrocycles and their interactions with cations have been subjects of considerable interest.[1] Many of the more successful synthetic procedures for the preparation of these materials involve so-called template reactions in which the macrocycle is assembled around a metal ion. We report the preparation of the nitrogen-containing macrocycle tribenzo[*b*,*i*,*p*]-1,4,8,11,15,18-hexaazacycloheneicosane (**1**) (tribenzo[21]aneN$_6$) in reasonable yield by means of a series of reactions involving the alkylation of deprotonated aromatic amine moieties coordinated to cobalt(III).

It would seem as though the general synthetic procedure outlined here might be useful for the introduction of short chains into a variety of coordinated ligands.

Results and Discussion

[1,3-Bis[(*o*-aminophenyl)amino]propane](1,2-diaminobenzene)cobalt(III) (**2**) was prepared by a modified Bauer and Drinkard procedure.[2] Sodium tris(carbonato)cobaltate(III) was reacted with 1 equiv of the hydrochloride salt of 1,3-bis[(*o*-aminophenyl)amino]propane,[3] followed by 1 equiv of 1,2-diaminobenzene (eq 1).



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2 is quite acidic ($pK_1 \simeq 2.0$, $pK_2 \simeq 4.7$, $pK_3 \simeq 5.7$), and the reasonably stable doubly deprotonated species proved to be suf-

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