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The Biogenetic-Type Total Synthesis of Methyl Adirubine

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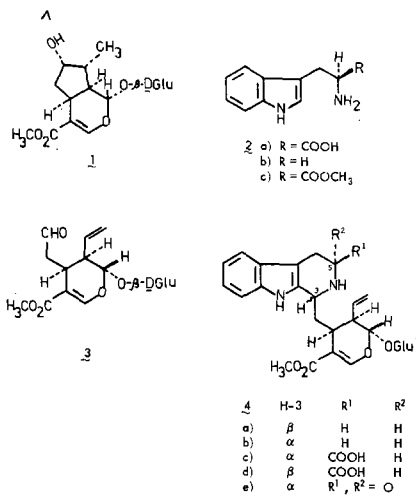
The first total synthesis of methyl adirubine (**11a**), representing the 5-carboxy-*Corynanthé* indole alkaloid group, has been completed. The biogenetic-type sequence, comprising new steps **27** → **28** → **29** → **16** → **17** → **33** → **18** → **34** → **35-IV** → methyl adirubine, also defines the stereochemistry of the latter as **11b**.

The familial relationship of monoterpenoid indole alkaloids derives from their biogenesis from two common precursors, the mevalonate-derived iridoid glycoside loganin (**1**) and the amino acid tryptophan (**2a**) (*1*, *2*), incorporation of which has been



well established in a variety of species (*3*). In noting that the carboxylate function of tryptophan is not retained in virtually all monoterpenoid indole alkaloids, Battersby suggested that tryptophan (**2a**) was decarboxylated to tryptamine (**2b**) prior to condensation with secologanin (**3**) to produce vincoside (**4a**) as the first intermediate in the biosynthetic sequence combining amine and terpene moieties (**4**). In support of this hypothesis Battersby demonstrated that labeled tryptamine (**2b**), secologanin (**3**), and a synthetic mixture of vincoside (**4a**) and isovincoside (≡ strictosidine) (**4b**) (stereochemistry (*5*)) were incorporated into several of the alkaloids of *Catheranthus roseus* (*Vinca rosea*) (*4*). The intermediacy of tryptamine in this species has been confirmed by the *in vivo* experiments of Kutney (*6a*) and more recently by the *in vitro*

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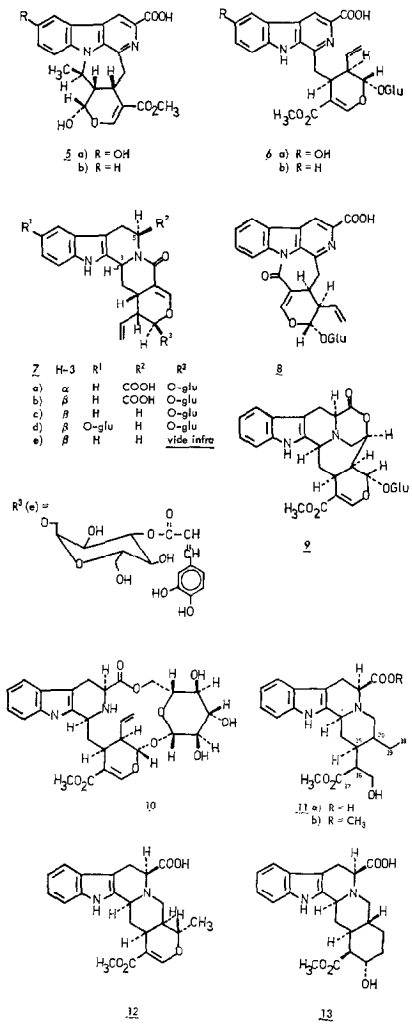
experiments of Scott (*6b*), in which levels of tryptamine incorporation into ajmalicine of up to 18% have been reported.

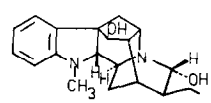
Since the appearance of Battersby's work, the view that the decarboxylation of tryptophan preceded condensation with secologanin was widely held. Beginning in 1968, however, a number of vincoside related compounds retaining the tryptophan carboxylate group were uncovered, thereby casting doubt on this assumption. Isolated from *Adina cordifola* and especially *A. rubescens*, tropical trees of the family Rubeaceae, these compounds include adifoline (**5a**) (*7*), cordifoline (**6a**) (*8*), their 10-desoxy analogs



5b and **6b** (*9*), 3α,5α- (**7a**) and 3β,5α-tetrahydrodesoxycordifoline lactam (**7b**) (*10*), desoxycordifoline lactam (**8**) (*11*), rubenine (**9**) (*12*), and macrolidine (**10**) (*13*). In addition the decarboxy glycosides vincoside lactam (**7c**) (5b), 10β-D-glucosyloxy-vincoside lactam (**7d**) (*14*), rubescine (**7e**) (*15*), and 5-oxostrictosidine (**4e**) (*16*) were

isolated from *A. rubescens*. Also worthy of note was the isolation from *Rhazya orientalis* of 5α-carboxystrictosidine (≡ 3α,5α-tetrahydrodesoxycordifoline) (**4c**) (*17*). Brown suggested (*18*) that the latter compound (or perhaps its H-3β epimer **4d**) served as a precursor to the above alkaloids and suggested further that "tetrahydrodesoxycordifoline could be (a) a biogenetic cul-de-sac, (b) an alternate intermediate to vincoside for some indole alkaloids, or (c) the progenitor of a novel range of acidic indole alkaloids in which the carboxy-group of tryptophan was retained." Much credibility was given to the latter point of view with the isolation and structure determination of adirubine (**11a**) (*18*), 5α-carboxytetrahydroalstonine (**12**) (*19*), and 5α-carboxycorynanthine (**13**) (*20*), and one cannot help but speculate that many more such alkaloids await isolation.

Our interest in these compounds was stimulated by the possibility that oxidative decarboxylation of a 5-carboxy-*Corynanthé* alkaloid could be involved in the biosynthesis of ajmaline (**14**) and related alkaloids, and a total synthesis of ajmaline was accomplished in our laboratory *via* the analogous decarbonylation of compound **15** (*21*). Adirubine (**11a**) was of particular interest, first because we believed that a total



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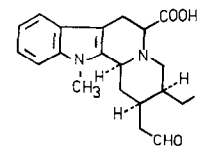

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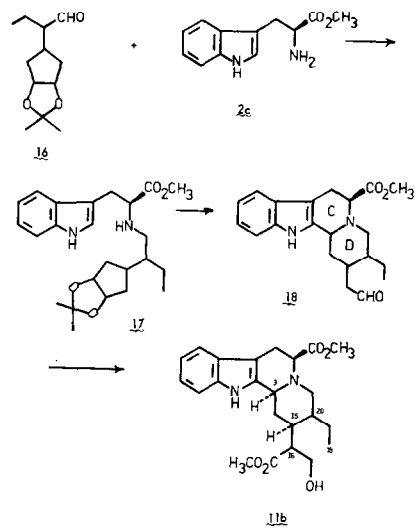
synthesis of this molecule could be achieved by means of a general method of *Corynanthé* alkaloid synthesis that has evolved in our laboratory and that such a total synthesis would be the first one of a 5-carboxyindole alkaloid; and, second, because we believed that as a consequence of our synthetic efforts we could assign the configuration at position 20, which had not been done at the time the overall structure was deduced. To avoid the difficulties of working with an amino acid, we chose as our goal methyl adirubine (**11b**) (*18*), the methyl ester of the parent compound. The only prior synthetic effort was the conversion by Brown and Chapple of 3β,5α-tetrahydrodesoxycordifoline (**4d**) to a stereoisomer of methyl adirubine, but not to methyl adirubine itself (*22*).

In accord with previous synthetic efforts, we envisioned a synthesis of methyl adirubine along the lines illustrated in Scheme 1.

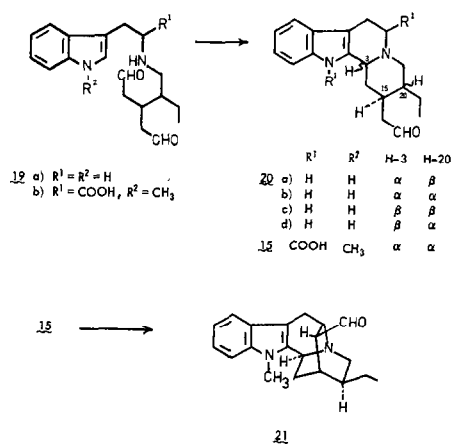
The first stage of the proposed synthesis involved preparation of the "C_9" fragment of **16**, which fulfills essentially the same function in this synthesis as does secologanin in biosynthesis. Preparation of a compound of this type is well precedented in the work of van Tamelen and Oliver (*21*) and others (*23*, *24*), and was not expected to present any difficulties. Also precedented (*21*) was the coupling of an aldehyde of type **16** to tryptophan (**2a**) by means of reductive alkylation. In this case we wished to take advantage of the readily available asymmetric starting material methyl-L-tryptophanate (**2c**) in order to obtain the desired optical isomer of methyl adirubine without any additional chemical resolutions.

The crucial part of the synthesis is the periodate cleavage of the diol derived from **17** followed by Pictet–Spengler cyclization of the resulting dialdehyde to give tetracyclic aldehydes having gross structure **18**. The use of the Pictet–Spengler reaction to construct



SCHEME 1

rings C and D mimics the biosynthesis of *Corynanthé* alkaloids in that similar cyclizations occur during biogenesis, although the rings are formed in two separate steps in nature. The proposed synthesis would thus be classified as a biogenetic-type synthesis of "type C, a chemical analog of a biosynthesis" (*25*), where the substrate is only approximately similar to the biogenetic substrate, but the reaction type corresponds to the natural process. Once again there were ample precedents (*21*, *23*, *24*). Van Tamelen *et al.* obtained racemic tetracyclic compounds of all four relative configurational families [*normal* (**20a**), *allo* (**20b**), *pseudo* (**20c**), and *epiallo* (**20d**)] upon cyclization of amine dialdehyde **19a**.



The nonstereospecificity of the cyclization is an important aspect, since in the present research it is necessary to obtain both 15,20 *cis* and 15,20 *trans* tetracycles in order to ensure that an actual precursor of methyl adirubine would be available. Van Tamelen

and Oliver carried out a similar cyclization on amino acid dialdehyde **19b**, but they did not fully characterize the resulting products. Instead, the entire reaction mixture was subjected to a decarbonylation procedure from which desoxyajmalal B (**21**) was obtained, thus only firmly establishing the presence of allo isomer **15** in the cyclization mixture.

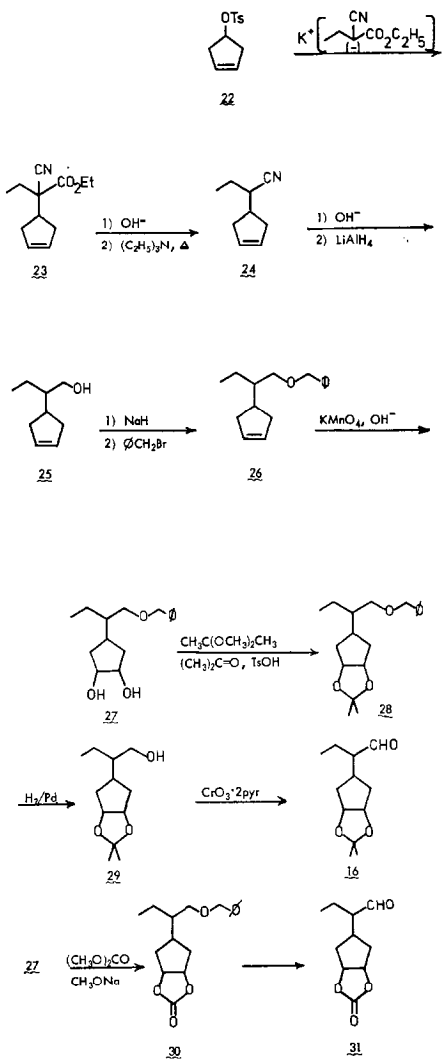
The steps in the final elaboration of the proper diastereomer of **18** to methyl adirubine are easily envisioned, viz, oxidation of the aldehyde to acid and subsequent esterification, α-formylation of the acetate ester side chain, and borohydride reduction of the resulting β-hydroxyacrylate. During the course of this work a synthesis of DL-geisschoschizine was published which followed a similar scheme (*26*), including the oxidation and formylation steps proposed here. Borohydride reduction of β-hydroxyacrylates to β-hydroxypropionates has been demonstrated in the work of Kutney (*27*) and Battersby (*28*).

A majority of the individual synthetic steps involved in the preparation of the "C_9" unit (**16**) (Scheme 2) were repetitions of previous work and will not be dealt with at length here, although recent refinements in the synthesis will be discussed in some detail. Cyclopentadiene was hydroborated/oxidized to give Δ^3-cyclopentenol, which in turn was converted to its *p*-toluenesulfonate ester (**22**). The potassium enolate of ethyl 2-cyanobutyrate was alkylated with tosylate **22** yielding cyanoester **23**, which was hydrolyzed and decarboxylated to give 2-(Δ^3-cyclopentenyl)-butyronitrile (**24**). Nitrile **24** was hydrolyzed, and the resulting acid was reduced with lithium aluminum hydride, giving 2-(Δ^3-cyclopentenyl)-1-butanol (**25**). The benzyl ether of the alcohol was prepared by a procedure slightly different from the one used earlier: The sodium alcoholate was made by refluxing the alcohol with sodium hydride in tetrahydrofuran (THF), after which the addition of benzyl bromide and further reflux gave the desired product. Oxidation of the double bond to a diol had been previously accomplished with osmium tetroxide; but since use of large quantities of this expensive and dangerous reagent is undesirable, a more suitable procedure for the oxidation was sought. It was found (*24a*) that by means of a carefully controlled permanganate oxidation (*29*) one could achieve the conversion of **26** to diol **27** in reasonable yield.

The newly formed diol must be protected before debenzylation and oxidation to the aldehyde, or else intramolecular acetal formation will occur in those stereoisomers where the butyl and diol functions are *cis* on the cyclopentyl ring (*21c*). (No attempt to separate diastereomers was made in the course of the synthesis of this fragment.) To this end van Tamelen and Oliver prepared cyclic carbonate **30** by treating diol **27** with dimethyl carbonate and sodium methoxide. When it was later determined that cyclic carbonate was an unsuitable protecting group for the present work, the acetone ketal (**28**) of diol **27** was prepared by treatment of the diol with an acetone, 2,2-dimethoxypropane solution, catalyzed by a small amount of *p*-toluenesulfonic acid. Acetonide **28** was readily debenzylated via palladium catalyzed hydrogenolysis, and the resulting alcohol (**29**) was oxidized to aldehyde **16** by the Collins method. Carbonate/ether **30** was converted to aldehyde **31** in the same manner.

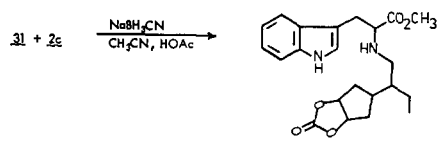
The first critical step in the synthesis was the reductive alkylation of methyl-L-tryptophanate with aldehyde **16** (or **31**). Van Tamelen and Oliver performed a reaction of this type by stirring tryptophan and aldehyde **31** in ethanol with palladium catalyst under hydrogen at atmospheric pressure, finding that in order to obtain a successful

reaction particular care had to be taken to avoid poisoning the catalyst (*21*). An excellent alternative procedure was devised by adapting a reductive alkylation method of Borch and Hassid (*30*). Thus, by addition of an appropriate quantity of acetic acid



SCHEME 2

to a stirred acetonitrile solution of methyl-L-tryptophanate (**2c**) (in 50% excess), aldehyde (**16** or **31**), and cyanoborohydride, diastereomeric reductive alkylation products (**32** or **17**) were obtained in yields comparable to the best yields obtained by the catalytic reduction method. By this method, then, aldehydes **31** and **16** were converted to alkylated methyl tryptophanates **32** and **17**, respectively.



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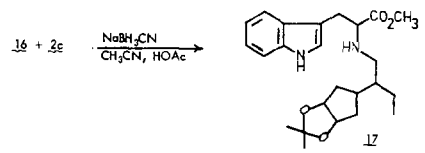

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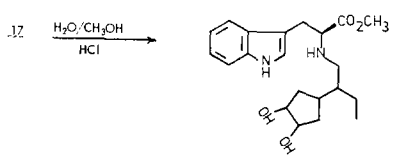
At this point the protecting group of the diol must be removed without disturbing the ester. However, the conditions used by van Tamelen and Oliver to saponify carbonate **32**—overnight reflux in sodium hydroxide/methanol—were found to effect saponification of the carbomethoxyl as well. The carbonate could be removed by prolonged reflux in sodium methoxide/methanol, but this method is unacceptable in that approximately half of the substrate is destroyed as a consequence, and the asymmetry at the amino acid α-position would surely be lost. It was necessary, therefore, to find an alternate diol protecting group that was labile under conditions that would affect neither the carbomethoxyl nor the α-position of the amino acid. Since methyl-L-tryptophanate of good optical purity may be prepared via Fisher esterification of L-tryptophan, a ketal, which may be hydrolyzed under milder acid conditions than those required for esterification, came to mind as an obvious substitute for the cyclic carbonate. Accordingly, tryptophan acetonide **17** was prepared from acetonide/aldehyde **16**, and it was found that the ketal could be cleaved in approx. 50% yield by allowing a solution of the ketal in 3:2 methanol/water (adjusted to pH ~ 1.5 with hydrochloric acid) to stand for 3 to 5 days. Unreacted ketal could be recovered from the reaction mixture and recycled, thereby improving the overall yield of diol **33**.



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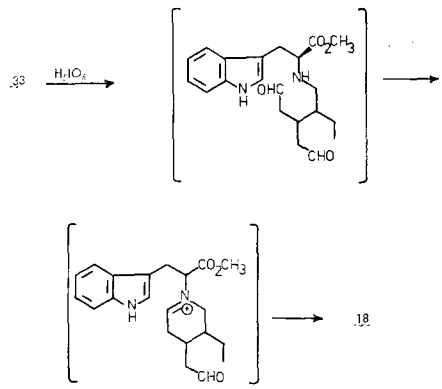
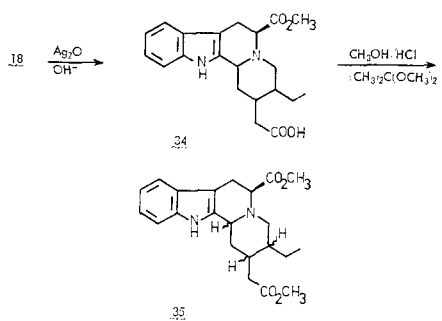
The periodate cleavage of diol **33** to dialdehyde **34** followed by intramolecular Pictet–Spengler cyclization of the diastereomers of **34** to diastereomeric tetracyclic aldehydes of structure **18** was then carried out (*23*, *31*). Diol **33** was dissolved in an acetic acid/sodium acetate buffer solution, a solution of an equivalent of periodic acid in the same buffer was added, and the mixture was then stirred in the dark for 24 hr. Since the resulting aldehydes (18) were expected to be unstable (as were related aldehydes), no attempt was made to isolate or characterize the products of the cleavage/cyclization.



The crude cyclization products were oxidized with silver oxide, and the resulting amino acids (**34**) were esterified by the Fisher method. The result of this sequence was an extraordinarily complex reaction mixture comprising the diastereomeric diesters of gross structure **35** and the accumulated byproducts of four reactions (cleavage, cyclization, oxidation, and esterification). The analysis of this reaction mixture took place in four stages: (1) The diesters (**35**) were separated *en masse* from the other



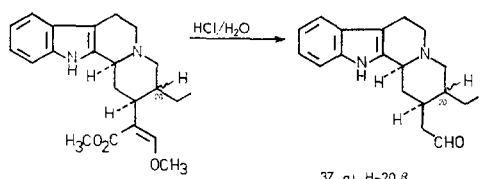
material, (2) the diastereomeric diesters were separated, (3) the correct precursor of methyl adirubine was identified, and (4) stereochemical assignments were made for the adirubine precursor. In a typical run mixed diesters were obtained in 40% overall yield for the sequence of reactions from **33** to **35**.

Analytical thin layer chromatography (tlc) of the mixture of diesters showed the presence of at least six compounds in widely varying amounts. Preparative separation of the diastereomers was chiefly accomplished by means of repeated multiple elution tlc. By such means five of the diastereomers were obtained in sufficient purity and quantity to permit nmr analysis, and four in sufficient quantity to permit ir spectra to be obtained. For convenience these compounds will be denoted "diesters **35-I**–**35-IV**," going from high to low R_f values. It is difficult to give a yield value for the individual diastereomers since they are obtained as glassy solids which darken slowly with exposure to air; thus with repeated chromatographies substantial quantities must have been lost because of aerial oxidation, as well as repeated manipulation.

With at least some of the diastereomers in hand it was possible to identify the potential

precursor of methyl adirubine. Fortunately, since the stereochemistry of the alkaloid was partially known (**11a**), it was possible to establish certain physical criteria which the precursor diester must meet. The stereochemistry of the C-5 hydrogen was established as α by Brown (*18*) on the basis of a positive Cotton effect in the 250–300 nm region of the circular dichroism (cd) spectrum. (The sign of the Cotton effect in this region has been well correlated with the absolute stereochemistry at C-3 in *Corynanthé*, *Yohimbé*, and quebrachamine alkaloids (*32*, *33b*).) The hydrogen at C-5 was assigned the α configuration on the assumption that adirubine is derived from L-tryptophan. The hydrogen at C-15 was also presumed to be α on biosynthetic grounds, assuming loganin is also a precursor. The observation of Bohlmann bands in the ir spectrum at 2800, 2760, and 2735 cm^{-1} and the lack of an nmr signal at lower field than δ 3.8 for H-3 established that H-3 is *trans* diaxial to the nitrogen lone pair and implies a *cis* relationship of H-3 and H-15 (*18*, *33a*). Clearly, any diastereomer of **35** to be considered a potential precursor of methyl adirubine must also display these spectral characteristics. Diesters **35-I**, **35-II**, and **35-V** were immediately withdrawn from consideration when Bohlmann bands were not observed in the ir spectra of these compounds. Compound **35-III** could be examined only by nmr, but the presence of signals in the δ 4.2–4.6 region cast doubt upon its being the desired diastereomer. Compound **35-IV**, on the other hand, displayed Bohlmann bands in the ir spectrum; and its nmr spectrum, in addition to manifesting no H-3 signal below δ 3.8, bore a striking resemblance to the spectrum of methyl adirubine itself (Fig. 1). The cd spectrum of **35-IV** had a strong positive Cotton effect in the 250–300 nm region, thereby, with the other evidence, establishing diester **35-IV** as the prime candidate for the required methyl adirubine precursor, a hypothesis which was borne out by experiment. **35-IV** could easily be obtained in a crystalline state (mp 253.5–255°C), thereby greatly improving its stability. Unfortunately, in the pure state it represented a minor product of the cyclization, and only a very small quantity was obtained.

The stage was now set for the final elaboration of diester **35-IV** to methyl adirubine. Formylation of esters has been frequently employed in alkaloid synthesis, such as in the synthesis of DL-corynantheine (*34*) and the recent synthesis of DL-geissoschizine, previously cited (*26*). Since this reaction was potentially troublesome (a diester had not previously been employed in this reaction in any previous alkaloid synthesis) and diester **35-IV** was scarce, it was desirable to prepare model compounds on which to



36 a) H-20 β
b) H-20 α

37 a) H-20 β
b) H-20 α

perfect this procedure. Dihydrocorynantheine (**36a**) and corynantheidine (**36b**) were degraded to dihydrocorynantheal (**37a**) and corynantheidal (**37b**), respectively, by acid hydrolysis/decarboxylation. The aldehydes were then converted respectively to methyl dihydrocorynantheate (**38a**) ("*trans* ester") and methyl corynantheidate (**38b**)

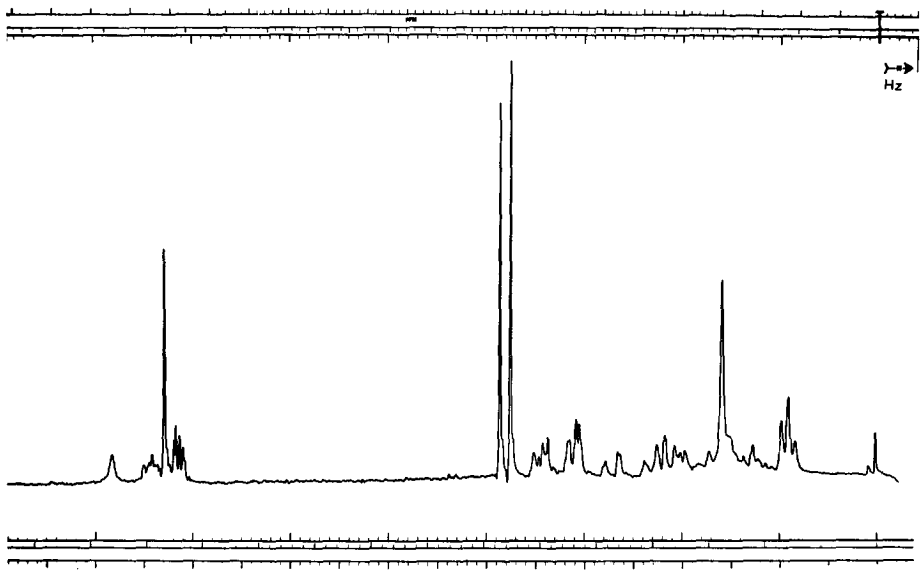
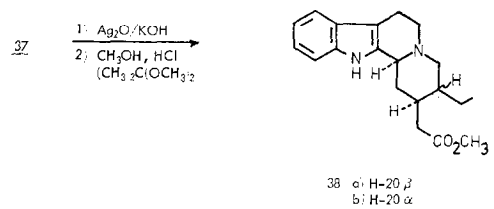


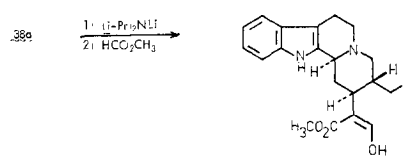
FIG. 1. Nmr spectrum (100 MHz) of diester **35-IV**.

("*cis* ester") via the same silver oxide oxidation and Fisher esterification procedures used to prepare the diesters (**35**).



38 a) H-20 β
b) H-20 α

Since the yield of formylated product reported by Yamada *et al.* (56%) (*26*) using lithium diisopropylamide as the base was much higher than typical yields in formylations employing triphenylmethyl sodium, this procedure was used as a model for formylation studies in this work. Accordingly, formylation of trans ester **38a** gave a 49% yield of desmethyldihydrocorynantheine (**39**), the nmr spectrum of which corre-



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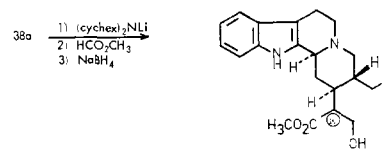
sponded to that of a sample of **39** prepared by mild acid hydrolysis of dihydrocorynantheine. In a second experiment the formylation of **38a** was repeated, but in this case the crude product mixture was treated with methanolic sodium borohydride. The yield of the two polar compounds, which were presumed to be the C-16 epimers of **40**,



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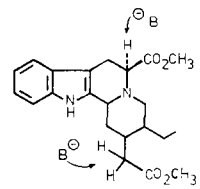
was 30% after chromatography. Of paramount importance was the appearance of a multiplet centered at δ 3.9 and assigned to the $-CH_2OH$ protons, which constituted evidence that the required formylation/reduction had been successfully carried out in this case.

In order to complete the synthesis of methyl adirubine this overall hydroxymethylation must be performed on a diastereomer of diester **35**. Since the C-5 hydrogen in **35** is at least as acidic as the C-16 hydrogen, generation of the desired C-16 anion was considerably more problematical than the case of monoester **38a** owing to the difficulty



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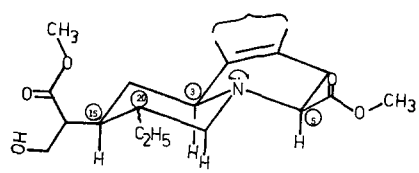
of forming two negative charges in the same molecule. In fact yields of hydroxymethylated products were uniformly lower in the diester series than in the monoester series. Also, deprotonation at C-5 could lead to loss of stereochemical integrity at that center if the desired *S* configuration of the anion is not conformationally much more favorable than the *R* configuration. Given the known stereochemistry of methyl adirubine and its expected equilibrium conformation (below), one would presume that the 5-carbomethoxy group is equatorial in the natural *S* configuration and thus the configuration should be retained through a deprotonation/reprotonation cycle.

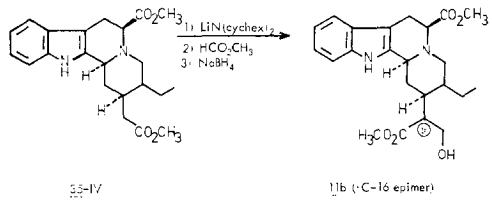
Initial studies of the formylation/reduction sequence were carried out with diester **35-II**, the most abundant diastereomer of **35**. A solution of the anion in THF/HMPTA was treated with methyl formate, and the crude formylation mixture was reduced with



sodium borohydride. Analysis and separation of the reaction mixture was carried out by tlc, and nmr spectra suggested that all three diester products were hydroxymethylated.

Armed with the knowledge that a **35** diastereomer could be successfully hydroxymethylated, we could now attempt the completion of the synthesis of methyl adirubine.

Diester **35-IV** was subjected to formylation and reduction, producing, in this case, only two compounds (A and B) of appropriate polarity in 9.3 and 3.9% yield, respectively. These products, along with authentic methyl adirubine, were analyzed by tlc. Compound A, methyl adirubine, and a mixture of the two gave single spots at $R_f = 0.369$, while compound B gave a spot at $R_f = 0.295$, suggesting that synthetic compound



A was in fact methyl adirubine and that compound B was the C-16 epimer. Compound A was confirmed as methyl adirubine by comparison of its physical data with those of the authentic material. The nmr spectrum (Fig. 2) of the synthetic material is superimposable on that of the natural product (**35**). The mass spectra of natural and synthetic methyl adirubine (obtained by Dr. James Trudell at Stanford) were identical (M^+ at *m/e* 414), and the requisite Bohlmann bands were observed in the ir spectrum of the synthetic product. It can be assumed that the synthetic product is the correct enantiomer, since the absolute configuration at C-3 of **35-IV** was found by cd to be correct for methyl adirubine. Finally the synthetic and authentic samples display virtually identical melting point behavior.

With the completion of the synthesis of methyl adirubine the primary goal of this project was achieved. There remained, however, the question of the C-20 stereochemistry of methyl adirubine and its precursor, diester **35-IV**. At the outset of our work we

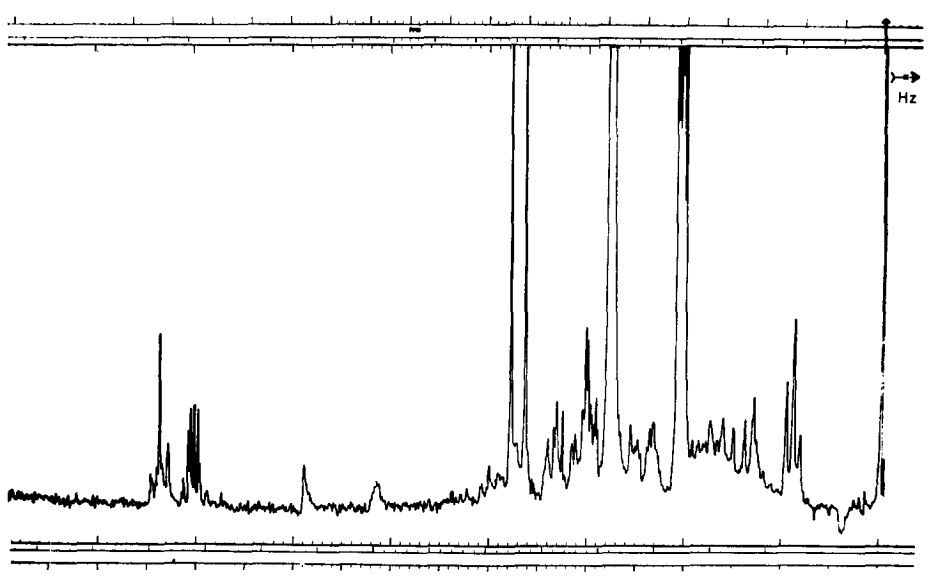
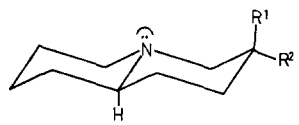


FIG. 2. Nmr spectrum (100 MHz) of methyl adirubine (synthetic).

hoped to apply the nmr criteria established by Trager, Lee, and Beckett for corynantheidine (**36b**) type alkaloids (*33*), where the *cis* and *trans* relationship of the C-15 and C-20 side chains is correlated to the "degree of resolution" (or "degree of perturbation") of the C-18 methyl signal, i.e., by observing the extent to which the C-18 signal resembles a first-order triplet. A chemical shift difference of 0.26 ppm had been observed for the methyl signals of the two possible 3-methylquinolizidines (**41a** and **41b**) (*35*). Thus if the C-19 methylene protons in 15,20 *cis* compounds are shifted downfield relative to the methylene protons in the corresponding *trans* examples, one would expect the condition for first order spin–spin splitting ($\Delta\nu > 6J$) (*36*) to be more closely approximated by the 15,20 *cis* series. It was demonstrated experimentally that discernible differences in the shape of the C-18 "triplet" do exist for the *cis* and *trans* series of corynantheidine type alkaloids. In the *cis* series the middle peak of the "triplet"



41 a) $R^1 = CH_3$ (1.08), $R^2 = H$
b) $R^1 = H$, $R^2 = CH_3$ (0.82)

is of higher amplitude than the outer peaks, while in the *trans* series the downfield peak is the strongest (at 100 MHz). At 60 MHz the entire methyl signal of a 15,20 *trans* alkaloid approximates a right triangle, rising sharply from the baseline on the downfield side and sloping more gradually down on the upfield side. Reproductions of the 18-methyl signals (at 60 MHz) for corynantheidine (**36b**) and dihydrocorynantheine (**36a**) are shown in Fig. 3.

Before this nmr correlation could be applied in the current work it was necessary to verify its applicability in molecules with a C-15 side chain other than the β-methoxyacrylate of corynantheidine type structures. Unfortunately, the C-18 signal of the dihydrositsirikine diastereomer **40** (15,20 *trans*) is as "well resolved" as any corresponding methyl signal in the 15,20 *cis* corynantheidine type series. Apparently the change of geometry in the C-15 side chain from the essentially linear β-methoxyacrylate

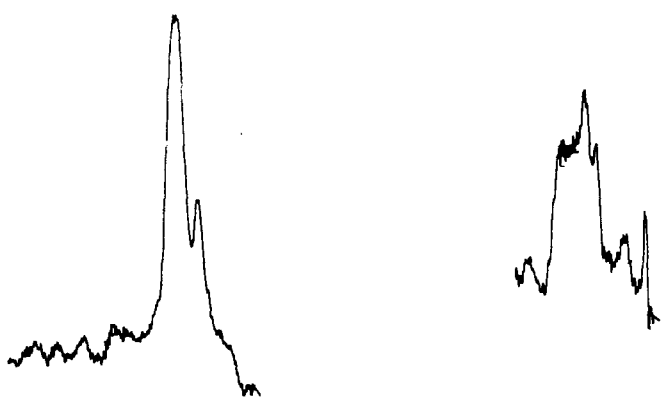
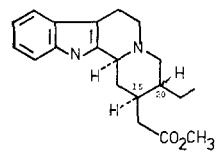


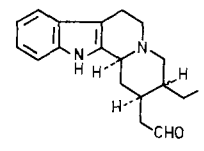
FIG. 3. C-18 nmr signals (60 MHz, 250 Hz s.w.) for dihydrocorynantheine (**36a**) (left) and corynantheidine (**36b**) (right).

to the "bent" β-hydroxypropionate is sufficient to permit one of the oxygens of the side chain to exert a deshielding effect on the methylene protons in **40** roughly equivalent to that produced by the nitrogen lone pair in corynantheidine (**36b**). Therefore, one can draw no conclusion whatsoever regarding the 15,20 stereochemistry of a *Corynanthé* skeleton with a β-hydroxypropionate group at C-15.

Since the criteria of Lee *et al.* could not be applied to methyl adirubine itself, we sought to determine their applicability to compounds like diesters **35** having an acetic ester side chain at C-15. The nmr spectra of *trans* and *cis* esters **38a** and **38b** were in fact



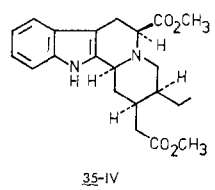
38 a) H-20 β
b) H-20 α



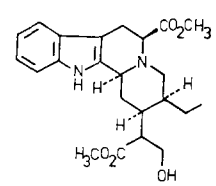
37 a) H-20 β
b) H-20 α

found to display characteristic "*trans*" and "*cis*" signals, respectively, for the C-18 methyl. *Trans* and *cis* aldehydes **37a** and **37b**, on the other hand, both display "*trans*" type C-18 signals, indicating that an acetaldehyde side chain lacks sufficient bulk to effectively stabilize the conformation of ring D at room temperature.

Since the Lee criteria are realized in structures of type **38**, their application to diesters of structural type **35**, particularly to diester **35-IV**, would seem to be also appropriate. As previously illustrated, given the known partial stereochemistry of diester **35-IV**, the 5-carbomethoxy group will be equatorial and will be directed well away from the 20-ethyl group. Moreover, the 5-carbomethoxy group, an equatorial side chain of considerable bulk, should contribute to the overall conformational rigidity of the molecule. Therefore upon observing a rather well-defined triplet for the C-18 methyl in the 100 MHz nmr spectrum of diester **35-IV** (Fig. 1) we may be reasonably confident that this compound possesses a *cis* relationship to the C-15 and C-20 side chains and is therefore a member of the *allo* series of *Corynanthé* structures, as represented in **35-IV**. Accordingly, the stereostructure of methyl adirubine may be expanded to **11b**.

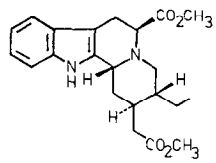


35-IV

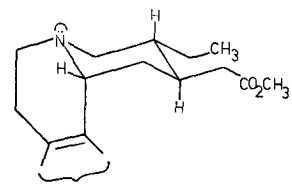


11b

Of the remaining diesters only diester **35-II** was fully characterized. The nmr spectrum of diester **35-II** displays a "*trans*" pattern for the C-18 methyl and signals at δ 3.87 and δ 4.3 attributable to hydrogens *cis* to a nitrogen lone pair. The circular dichroism spectrum (negative C. E. in the 250–300 nm region) establishes the configuration of H-3 as β, and the ir spectrum lacks "Bohlmann bands." These data are best accommo-



35-II



dated by assigning diester **35-II** to the *pseudo* series, assuming such a *pseudo* diester would have the equilibrium conformation suggested by Trager *et al.* (*33a*) for a corynantheidine type structure in the *pseudo* series. There were not sufficient data for diesters **35-I**, **35-III**, and **35-V** to permit reasonable speculation concerning their stereochemistry.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage apparatus and are uncorrected.

Microanalyses were carried out at the Stanford University Microanalytical Laboratory by Messrs. E. Meier and J. Consul.

Infrared (ir) spectra were recorded on a Perkin–Elmer Model 421 grating spectrometer (bands reported in centimeters^{-1}) or a Perkin–Elmer Model 137 spectrometer (bands reported in micrometers). Nuclear magnetic resonance (nmr) spectra were recorded with Varian A-60, T-60, and XL-100 instruments, the latter used in both continuous wave and pulsed Fourier transform modes. Tetramethylsilane was the internal standard. Circular dichroism (cd) spectra were recorded by Ms. Ruth Records at Stanford. Mass spectra (low resolution) were recorded by Dr. James Trudell of the Department of Anaesthesiology, Stanford University Medical School, and by Ms. Anne-Marie Wegman (high resolution), Department of Chemistry, Stanford.

Column chromatographies were run using E. Merck silica gel 60 (70–230 mesh). Preparative layer chromatography (plc) plates were made from E. Merck silica gel GF and silica gel PF. Analytical thin layer chromatography plates were purchased from Analtech Inc. Petroleum ether for chromatography was distilled over 60–68°C prior to use.

1-Benzyloxy-2-(Δ^3-Cyclopentenyl)-butane (**26**)

Approximately 4.8 g (114 mmoles) of 57% sodium hydride suspension was placed in a 500 ml round bottom flask and was rinsed free of most of the oil by swirling with dry tetrahydrofuran (THF), decanting excess solvent, and repeating the operation with two fresh portions of solvent. A reflux condenser was attached, the apparatus purged with nitrogen, and 250 ml of dry THF was added to the clean hydride. A THF solution of 7.3 g (52 mmoles) of 2-(Δ^3-cyclopentenyl)-1-butanol (*21*, *23*) was added dropwise with stirring. The mixture was refluxed for 1 hr, after which 6.5 ml (9.37 g, 55 mmoles) of benzyl bromide was added. The reaction was completed by refluxing the mixture for 4 hr. After cooling, excess sodium hydride was destroyed by careful addition of wet THF. The reaction mixture was then transferred to a separatory funnel, 200 ml

of water added, and the mixture extracted with three portions of ether. The combined ether extracts were shaken with saturated sodium chloride, dried over anhydrous sodium sulfate, and evaporated. The 14.5 g of crude product thus obtained was chromatographed on a column of 290 g of slightly deactivated silica gel eluted with 2% ethyl acetate in petroleum ether. Following the course of the chromatography by tlc, the major product eluted comprised 10 g (43.7 mmoles, 83.5% yield) of benzyl ether **26**, characterized by comparison of its spectra with spectra obtained by earlier workers.

bp (approx. 0.1 mm) 105–115°C.

ir (neat): 3.26, 3.43, 6.19 (wk), 9.13, 13.60, 14.36 μm.

nmr ($CDCl_3$): δ 0.90, ("t", 3, $-CH_2CH_3$); 3.43, (d, 2, $-CH_2O$); 4.48, (s, 2, $-OCH_2$-Ar); 5.68, (s, 2, vinyl H); 7.3 (s, 5, Ar*H*).

1-Benzyloxy-2-(3,4-Dihydroxycyclopentyl)-butane (**27**)

After the method of Wiberg (*29*), 13.4 g (58 mmoles) of olefin/benzyl ether **26** was dissolved in a mixture of 500 ml of *t*-butyl alcohol and 112 ml of water; 14 ml of ethylene glycol was added to the solution, and the flask was stirred in an ice bath until the first sign of freezing. At that time a chilled solution of 9.5 g of potassium permanganate (60 mmoles) and 2.51 g of sodium hydroxide (63 mmoles) in 390 ml of water was added all at once. The reaction mixture immediately turned brown, and manganese dioxide precipitated. Stirring in the ice bath was continued for 5 min after addition of the permanganate, after which portions of solid sodium metabisulfite were added until the brown color of manganese dioxide had been discharged. A white precipitate appeared at this point. The bulk of the *t*-butanol was removed on the rotary evaporator, and the aqueous residue was extracted with several portions of ether. The ether extracts, after drying, yielded 9.6 g (36.4 mmoles, 62.7%) of diol **27**, whose ir and nmr spectra corresponded to those obtained by prior workers (*21c*, *24a*). (Wiberg reported a 55% yield for the oxidation of cyclopentene (*29*). Yields of up to 83% of this oxidation have been claimed (*24a*).)

ir (neat): 2.95 (broad), 3.45, 9.25 (v. broad), 13.62, 14.37 μm.

nmr ($CDCl_3$): δ 0.87, (t, 3, $-CH_2CH_3$); 3.375, (d, 2, $-CHCH_2O$); 3.81, (s, 2, (2)–O*H*); 4.03, (t, 2, $(CH_2CH(O)-)_2$); 4.46 (s, 2, $-OCH_2Ar$); 7.32 (s, 5, Ar*H*).

Acetone Ketal of 1-Benzyloxy-2-(3,4-Dihydroxycyclopentyl)-butane (**28**)

A solution of 1 g (3.8 mmoles) of diol **27**, 2.4 g (23 mmoles) of 2,2-dimethoxypropane, and 100 mg of *p*-toluenesulfonic acid in 50 ml of acetone was refluxed for 2.5 hr. The cooled reaction mixture was neutralized with saturated aqueous sodium bicarbonate, and the organic solvents were removed on the rotary evaporator. Water (approx. 50 ml) was added to the residue, and the resulting mixture was extracted three times with ether. The combined ether extracts were rinsed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and evaporated yielding 1.13 g (3.72 mmoles, 98%) of the acetone ketal **28**.

ir (neat): 3.41, 7.30, 13.6, 14.37 μm.

nmr ($CDCl_3$): δ 0.88, (t, 3, $-CH_2CH_3$); 1.28 and 1.44, (2s over methylene envelope, $(CH_3)_2C(O)_2$); 3.41, (d, 2, $-CHCH_2O$); 4.48, (s, 2, $-OCH_2Ar$); 4.59, (m, 2, $(CH_2-CH(O)-)_2$); 7.33 (s, 5, Ar*H*).

A sample was double distilled in a kugelrohr apparatus (bp 140°C at approx 0.5 mm) for analysis. $C_{19}H_{28}O_3$ requires: C, 74.9%; H, 9.27%. Found: C, 74.58%; H, 9.29%.

Acetone Ketal (Glycol) of 2-(3,4-Dihydroxycyclopentyl)-1-butanol (**29**)

Three hundred milligrams of 10% palladium on carbon catalyst was suspended in 40 ml of dry methanol in a 125 ml hydrogenation flask and was equilibrated with hydrogen on the atmospheric pressure hydrogenation unit. Benzyl ether/diol **28**, 1.13 g (3.72 mmoles), was introduced into the flask and hydrogen uptake commenced. Uptake leveled off after 1 hr, after which the catalyst was filtered off and the solvent removed on the rotary evaporator giving 800 mg (3.74 mmoles, trace moisture?, quant. yield) of alcohol **29**.

ir (neat): 2.9, 3.4, 7.3 μm.

nmr ($CDCl_3$): δ 0.916, (t, 3, $-CH_2CH_3$); 1.28 and 1.43, (2s, $(CH_3)_2C(O)_2$); 3.60, (d, 2, $-CHCH_2O$); 4.61, ("d", 2, $(CH_2CH(OH)-)_2$).

An analytical sample was double distilled in a kugelrohr apparatus (bp ~130°C at approx 0.5 mm). $C_{12}H_{22}O_3$ requires: C, 67.26%; H, 10.35%. Found: C, 66.89%; H, 10.38%.

Acetone Ketal of 2-(3,4-Dihydroxycyclopentyl)-butanal (**16**)

Twenty-one grams (81 mmoles) of chromium trioxide–pyridine complex (*37*) was added to 250 ml of freshly distilled dichloromethane in a round bottom flask purged with nitrogen. A solution of 2.85 g (13.3 mmoles) of alcohol **27** in a small amount of dichloromethane was added quickly with vigorous stirring. Stirring was continued for 15 min, during which time a copious tarry residue formed. The supernatant liquid was slowly filtered through a 100 ml volume of 60–100 mesh Florisil in a fritted glass funnel, followed by rinses with generous amounts of dichloromethane. The dichloromethane was dried over anhydrous sodium sulfate, evaporated on the rotary evaporator, and the residual oil placed on the vacuum pump to remove traces of pyridine. The yield of aldehyde (which was too unstable to distill for analysis and had to be utilized in the subsequent reductive alkylation as quickly as possible) was 2.4 g (11.32 mmoles, 85% yield).

ir (neat): 3.4, 5.83, 7.32 μm.

nmr ($CDCl_3$): δ 0.91, (t, 3, $-CH_2CH_3$); 1.29 and 1.45, (2s, $(CH_3)_2C(O)_2$); 4.65, (m, 2, $(CH_2CH(O)-)_2$); 9.38 and 9.45, (2"s", $-CHO$ diastereomers).

Reductive Alkylation of Methyl-L-Tryptophanate (**2c**) *with Aldehyde* **16**

Aldehyde **16** (632 mg, 2.98 mmoles) and methyl-L-tryptophanate (*39*) (800 mg, 3.67 mmoles) were dissolved in 40 ml of acetonitrile. Three hundred milligrams (4.76 mmoles) of sodium cyanoborohydride (Ventron) was added to the solution, followed by 380 μl (6.64 mmoles) of glacial acetic acid, whereupon a slight ebullation indicated commencement of the reaction. The flask was stoppered with a serum cap pierced with a 20 gauge needle and the mixture was stirred overnight at room temperature (for convenience only, the reaction is complete in 3 hr). When the reaction was complete, the acetonitrile solution was poured into ether and extracted three times with 1 *N*

sodium hydroxide. The base washings were extracted again with ether, and the ether solutions were rinsed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and evaporated on the rotary evaporator. The residue was taken up in ethyl acetate and applied to four 20 × 20 cm × 2 mm silica gel PF plates, which were developed once with ethyl acetate. Examination of the plates under uv light showed a band containing methyl tryptophanate near the origin and a somewhat diffuse band of high R_f containing the diastereomeric alkylation products. Elution of the latter band gave 676 mg (1.63 mmoles, 54.8%) of diastereomeric **17**, not further purified.

ir ($CHCl_3$): 2.84, 3.40, 5.80, 6.90, 7.31, 9.59, 11.22 μm.

nmr ($CDCl_3$): δ 0.767, (distorted t, 3, $-CH_2CH_3$); 1.25 and 1.41, (2s, 3, $(CH_3)_2C(O)_2$); approx 3.7, (several s, 3, $-CO_2CH_3$ diastereomers); 4.52, ("d", 2, $(CH_2CH(O))_2$); approx 7.3, (m, 5, indole C*H*); 8.39, (broad s, 1, indole N*H*).

(It was not possible to remove water, solvents, etc. from this diastereomeric mixture, which was obtained as a glassy solid. Accordingly, a satisfactory elemental analysis could not be obtained.)

Diol **33**

Tryptophan/acetonide **17**, 773 mg (1.87 mmoles), was dissolved in 100 ml of methanol and 67 ml of water was added. The pH of the solution was adjusted to approximately 1.5 (paper) by addition of 2 *N* hydrochloric acid. After swirling to assure proper mixing the flask was stoppered and put aside to rest, without stirring, for 5½ days At that time the mixture was neutralized with saturated aqueous sodium bicarbonate, and the bulk of the alcohol was removed on the rotary evaporator, causing most of the products to separate out on the sides of the flask. The aqueous phase was extracted with ethyl acetate and combined with an ethyl acetate solution of the residue from the reaction flask. The ethyl acetate solution was shaken with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and evaporated, yielding 710 mg of crude material. The crude products were applied to two 20 × 20 cm × 2 mm silica gel PF plates and developed once with ethyl acetate. Diol **33**, 360 mg (0.964 mmoles, 51.5%), was eluted from a band near the origin and 166 mg (0.401 mmoles, 21.5%) of acetonide **17** was recovered from a high R_f band for an overall yield of 73% with 71% conversion. The diastereomeric diols were utilized without further purification.

ir ($CHCl_3$): 2.85 (broad), 3.40, 5.80, 6.91, 7.50, 8.55, 9.20 μm.

nmr ($CDCl_3$): δ 0.742 (distorted t, 3, $-CH_2CH_3$); 3.62 and 3.63, (2 overlapping s, 3, $-CO_2CH_3$); 3.98, (broad, $(CH_2CH(O))_2$); approx 7.3 (m, 5, indole C*H*); 8.67, (broad s, 1, indole N*H*). (For the same reasons cited above for alkylation product **17**, a satisfactory analysis could not be obtained.)

Cleavage/Cyclization of Diol **33**

Diol **33** (230 mg, 0.615 mmole) was dissolved in the minimal quantity of THF and 60 ml of a buffer solution 0.025 *M* in both acetic acid and sodium acetate was added with stirring. The flask was purged with nitrogen, after which 130 mg of periodic acid dissolved in 57 ml of the same buffer was added. The flask was wrapped in foil to exclude light and the mixture was stirred in the dark for 24 hr. During this time the

reaction mixture became cloudy and a green film of the product appeared on the sides of the flask. At the end of the reaction time the mixture was neutralized with sodium bicarbonate and extracted several times with chloroform. The residue in the reaction flask was taken up in chloroform, combined with extracts, shaken with saturated aqueous sodium chloride, and dried over anhydrous potassium carbonate. Removal of the solvent on the rotary evaporator gave 200 mg of crude aldehyde **18** (mixture of diastereomers) which was immediately oxidized according to the following procedure.

Amino Acid **34**

The procedure follows that of K. Yamada *et al.* (*26b*). Crude aldehyde **18** (200 mg) from the previous reaction was dissolved in 14 ml of 95% ethanol and a solution of silver nitrate (260 mg, 1.44 mmoles) in 0.8 ml of distilled water was added. Four milliliters of 1.05 *N* potassium hydroxide was added dropwise to the solution with vigorous stirring over a period of 5 min generating a brown precipitate of silver oxide. The suspension was stirred in the dark at room temperature for 1 hr after which the mixture was filtered through Celite. The filter cake was rinsed thoroughly with 95% ethanol to which a small amount of additional water had been added. The pH of the brown filtrate was adjusted to approx 4 (paper), and the solution was taken to dryness on the rotary evaporator. Benzene and absolute ethanol were used to remove the last traces of water azeotropically. No characterization was attempted on the residual brown powder, which was immediately esterified by the following procedure.

Diester **35**

The crude products from the previous reaction were dissolved in 125 ml of dry methanol, 10 ml of 2,2-dimethoxypropane was added (to consume water), and concentrated hydrochloric acid was added dropwise until the pH of the mixture was approximately 1.5 (paper). The mixture was then refluxed overnight under nitrogen. After the reaction had been completed the reaction mixture was neutralized with saturated aqueous sodium bicarbonate, taken to near dryness on the rotary evaporator, and the residue partitioned between water and ethyl acetate. The ethyl acetate extracts were rinsed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and evaporated, yielding 179 mg of crude products. The crude material was applied to a 20 × 20 cm × 2 mm silica gel PF plate and developed once with ethyl acetate. Elution of the high R_f band ($R_f = 0.577$–0.852) gave 94.3 mg (0.246 mmole, 39.8% from **33**) of diastereomeric diesters **35** separated and characterized as described below.

Separation and Characterization of the Diastereomers of **35**

The procedure described below represents one attempt to carry out the separation of the diastereomers of **35**. In no one attempt was the goal of maximum quantities of fully purified diastereomers with minimum manipulation achieved; however, the general methodology required to bring about the separation will be presented.

A 94.3 mg sample of mixed diesters was applied to a 20 × 20 cm × 2 mm silica gel PF plate, which was developed twice with 40% ethyl acetate in petroleum ether. Five uv

absorbing bands were eluted and were designated bands 1 through 5 in order of decreasing R_f. Bands 1 and 2 (10.6 mg total) were not of interest. Band 3 (42 mg) was found by analytical tlc to consist of diesters **35-I**, **35-II**, and **35-III**. Band 4 (12 mg) was chiefly diester **35-IV**, with a small amount of **35-III**. Band 5 (10.7 mg) comprised diester **35-V** chiefly, with some **35-IV** present.

Bands 3 and 5 were rechromatographed as follows: Band 3 was applied to two 10 × 20 cm × 0.5 mm silica gel GF plates, which were developed repeatedly with 20% ethyl acetate in petroleum ether until separation of three bands was complete. The top band comprised 6.3 mg of **35-I**, with a trace of **35-II**; the second band comprised 25.8 mg of pure **35-II**; and the third band comprised 1.2 mg of pure **35-III**. Band 5 was chromatographed on a 10 × 20 cm × 0.5 mm silica gel plate, which was developed twice with 30% ethyl acetate in petroleum ether. Two principal bands were eluted, the top band comprising 1.2 mg of **35-II** with a trace of **35-I**, and the bottom band comprising 5 mg of still unresolved **35-IV** and **35-V**. **35-V** could be obtained pure by additional chromatography.

The mostly crystalline material from band 4 was triturated with ethyl acetate leaving behind a residue (7.5 mg) consisting mostly of **35-IV**. Analytical tlc of the band 4 residue shows an additional spot at an R_f intermediate between **35-IV** and **35-V**. This material was never isolated pure, however. Owing to the limited solubility of **35-IV** in most solvents, attempts to separate this additional compound ("**35-IVb**") failed due to the streaking of **35-IV** into the "**35-IVb**" band on the chromatography plates. The best way to obtain pure **35-IV** was to repeatedly triturate the band 4 crystals until no trace of **35-IVb** remained upon dissolving and analyzing the residue. The washings of the various triturations were combined and rechromatographed, giving more pure **35-IV** and a **35-IV** and **35-IVb** mixture.

Characterization data for the isolated diastereomers are summarized below. In general these compounds were too unstable and/or precious to permit elemental analysis; however, a satisfactory high resolution mass spectrum was obtained on diester **35-IV**, the precursor to methyl adirubine. R_f values are reported for the following analytical conditions: silica gel plates (Analtech), 0.25 mm thickness, developed three times with 25% ethyl acetate in petroleum ether.

35-I: Glassy solid, $R_f = 0.626$.
ir ($CHCl_3$): 3485, 2970, 1725, 1450 cm^{-1}.
nmr ($CDCl_3$): δ 0.89, (t "cisoid", $-CH_2CH_3$); 3.58 and 3.71, (2s, $-CO_2CH_3$); 4.04, (m); 4.27, (m); approx 7.2 (m, indole C*H*); 7.28, (s, indole N*H*).

35-II: Glassy solid, $R_f = 0.601$.
ir ($CHCl_3$): 3490, 2960, 1728, 1450 cm^{-1}.
nmr ($CDCl_3$): δ 0.92, ("t", transoid, $-CH_2CH_3$); 3.59 and 3.71, (2s, $-CO_2CH_3$); 3.86, (m); 4.29, (m); approx 7.2, (m, indole C*H*); 8.1, (s, indole N*H*).
cd (dioxane): Negative Cotton effect in the 250–300 nm region.

35-III: Glassy solid, $R_f = 0.519$.
nmr ($CDCl_3$): δ 0.92, ("t", $-CH_2CH_3$); 3.60, 3.72, and 3.82 (weak, contaminant?), (3s, $-CO_2CH_3$); 4.32, (m); 4.56, (m); approx 7.2, (m, indole C*H*); 7.79, (s, indole N*H*).

35-IV: Crystalline solid, mp 253.5–255°C, $R_f = 0.461$.

ir ($CDCl_3$): 3485, 2960, 2890, 2870, 2810, 2775 (last four are "Bohlmann bands"), 1730, 1450 cm^{-1}.

nmr ($CDCl_3$): See Fig. 1. δ 0.91 (t, "cisoid", $-CH_2CH_3$); 3.74 and 3.85, (2s, $-CO_2CH_3$); approx 7.2, (m, indole C*H*); 7.82, (s, indole N*H*).

cd (dioxane): Positive Cotton effect over the 250–300 nm region.

ms (high resolution): M+ at *m/e* 384.20531, tolerance of 0.408 mmμ for $C_{22}H_{28}N_2O_4$; base peak at *m/e* 325.19226.

35-V: Glassy solid, $R_f = 0.292$.

ir ($CHCl_3$): 3485, 2860, 1730, 1450 cm^{-1}.

nmr ($CDCl_3$): δ 0.87, (t, $-CH_2CH_3$); 3.65, 3.73, and 3.84 (weak, contaminant?), (3s, $-CO_2CH_3$); approx 7.2, (m, indole C*H*); 7.86, (s, indole N*H*).

"Trans Ester" (**38a**) *and "Cis Ester"* (**38b**)

Dihydrocorynantheal was oxidized with silver oxide using the same procedure described for the oxidation of aldehyde **18** to amino acid **34**: dissolving the aldehyde in 10 ml of ethanol, adding 185 mg of silver nitrate in 0.57 ml of water, and dropwise addition of 3.0 ml of 1 *N* potassium hydroxide. After work-up the crude amino acid was dissolved in 125 ml of dry methanol, 5 ml of 2,2-dimethoxypropane was added, and the pH of the mixture was adjusted to approx 1.5 (paper) with concentrated hydrochloric acid. The mixture was refluxed overnight and was worked up in the same manner as diester **35** giving 147 mg of crude ester **38a**, which was quite sensitive to aerial oxidation. The crude ester was applied to a 20 × 20 cm × 1 mm silica gel PF plate and developed four times with 25% ethyl acetate in petroleum ether. Elution of the main band gave 49.6 mg (0.152 mmole, 33.3% from **36a**) of *trans* ester **38a** as a glassy solid.

ir ($CHCl_3$): 2.85, 3.41, 3.55 and 3.62 ("Bohlmann bands"), 5.82, approx 6.95 (several), 7.32, 7.42, 7.62, 7.77, 8.69 μm.

nmr ($CDCl_3$): δ 0.97, ("t," "transoid," 3, $-CH_2CH_3$); 3.67, (s, 3, $-CO_2CH_3$); approx 7.2, (m, 4, indole C*H*); 7.87, (s, 1, indole N*H*).

Corynantheidal (158 mg) was oxidized in the same manner as above using 206 mg of silver nitrate and 3.3 ml of 1 *N* potassium hydroxide. The resulting amino acid was esterified using the same quantity of reagents and procedures as above, yielding 115 mg of crude ester. The crude product was chromatographed on one 20 × 20 cm × 1 mm silica gel PF plate developed twice with 25% ethyl acetate in petroleum ether. After chromatography 41.7 mg (0.128 mmole, 24% from **36b**) of *cis* ester **38b** was recovered.

ir ($CHCl_3$): 2.86, 3.40, 3.57 and 3.62 ("Bohlmann bands"), 5.82, 6.95 (broad), 7.31, 7.50, 7.65, 8.59, 8.71 μm.

nmr ($CDCl_3$): δ 0.93, ("t," "cisoid," 3, $-CH_2CH_3$); 3.67, (s, 3, $-CO_2CH_3$); approx 7.2, (m, 4, indole C*H*); 7.77, (s, 1, indole N*H*).

Desmethyldihydrocorynantheine (**39**)

Following the procedure of K. Yamada *et al.* (*26*), 1.75 ml of freshly distilled TFH and 245 μl (1.75 mmole) of diisopropylamine were placed in a small round bottom flask, purged with nitrogen and equipped with a magnetic stirring bar and a serum

stopper. Stirring was started, the flask was chilled to −30°C in an acetone/Dry Ice bath, and 655 μl of 2.4 *M* *n*-butyl lithium (1.57 mmoles) was injected dropwise. After stirring 10 min the Gilman test was still positive, and two additional small portions of diisopropylamine added at 5 min intervals were required to bring about a negative test. When formation of lithium diisopropylamide was complete a solution of 54.6 mg (0.168 mmole) of *trans* ester **38a** in 1.73 ml of dry THF was added dropwise to the solution of the base, after which the mixture was stirred at −30°C for 15 min. Methyl formate (520 μl, 8.42 mmoles) (stored over anhydrous potassium carbonate and distilled from phosphorus pentoxide just prior to use) was then added dropwise to the mixture. The bath was allowed to warm to −20°C and the reaction was held at −20 to −15°C for 1 hr. At the end of that time the reaction mixture was chilled to −50°C and 200 μl of glacial acetic acid (3.5 mmoles) was injected to quench the reaction. The flask was removed from the cooling bath and allowed to come slowly to room temperature. When warm, the mixture was diluted with ether and repeatedly extracted with water and dilute acetic acid. The aqueous extracts were made basic with concentrated ammonia water and were extracted several times with chloroform. The chloroform extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated leaving 53.2 mg of crude products. The crude material was applied to a 20 × 20 cm × 1 mm silica gel PF plate and developed twice with 1:1 ethyl acetate/petroleum ether. Two bands appeared; the principal band, at the lower R_f value, was eluted yielding 29 mg (0.082 mmole, 49%) of desmethyldihydrocorynantheine (**39**).

ir ($CHCl_3$): 2.84, 3.37, 3.54 and 3.62 ("Bohlmann bands"), 5.81 (weak), 6.04 (strong), 6.97 μm.

nmr ($CDCl_3$): Presence of diisopropyl amine contaminant was noted by the appearance of two doublets at δ 1.19 and 1.23 and a multiplet at δ 4.09, otherwise the spectrum is superimposable on a spectrum of a sample of **39** prepared according to the method of Kutney (*27*) by mild acid hydrolysis of dihydrocorynantheine. Major features of the spectrum are: δ 0.90, (broad, $-CH_2CH_3$); 3.55 and 3.72, (s, $-CO_2CH_3$); approx 7.2, (m, indole C*H*); 8.05, (s, indole N*H*).

Formylation/Reduction of **38a**

Dicyclohexylamine (100 μl, 0.511 mmole) was added to 0.5 ml of THF in a small nitrogen purged flask. The solution was chilled to 0°C, and 135 μl of approx 3 *M* *n*-butyl lithium (0.405 mmole) was added dropwise with stirring. The solution was allowed to gradually warm to room temperature, and stirring was continued for 1 hr, after which a negative Gilman test indicated that no excess *n*-butyl lithium was present. The mixture was chilled to 0°C again, and 20 mg (0.0613 mmole) of ester **38a** dissolved in 0.5 ml of dry THF was added dropwise. After stirring 15 min 150 μl (2.43 mmoles) of freshly distilled methyl formate was added. Stirring was continued for 5 hr, the reaction mixture being allowed to warm gradually to room temperature. At the end of that time the reaction was quenched by the injection of 75 μl (1.37 mmoles) of glacial acetic acid. The reaction mixture was diluted with water, made basic with ammonia, and extracted with chloroform. The chloroform extracts were dried over anhydrous potassium carbonate and the solvent was removed on the rotary evaporator. The residue was taken up in methanol and an excess of sodium borohydride was added. After 1 hr of stirring at room temperature the solvent was removed on the rotary

evaporator, the residue was diluted with water, and the mixture was extracted with chloroform. The chloroform extracts were dried, evaporated on the rotary evaporator, and the residue was placed on the high vacuum pump to remove the dicyclohexylamine. The solid residue was applied to a 10 × 20 cm × 0.5 mm silica gel GF plate. After multiple elutions with 1:1 ethyl acetate/petroleum ether, three bands were visible. The high R_f band, well separated from the others, yielded 3.7 mg of starting material (**38a**). The other two bands yielded 4.2 mg (19.2%) and 2.4 mg (11%) of substances characterized by nmr as the C-16 diastereomers of dihydrositsirikine (**40**).

nmr (4.2 mg sample, $CDCl_3$): δ 0.93 (t, 3, $-CH_2CH_3$); 3.66 (s, 3, $-CO_2CH_3$); 3.90, (m, 2, $-CHCH_2OH$); approx 7.2 (m, 4, indole C*H*); 8.0, (s, 1, indole N*H*). lit. (*27*): δ 0.93, 3.58, 3.90, 7.20.

Formylation/Reduction of Diester **35-II**

Following the method described below for the formylation/reduction of diester **35-IV**, 29 mg (0.0755 mmole) of diester **35-II** was formylated/reduced using 147 μl (0.75 mmole) of dicyclohexylamine, 252 μl (0.6 mmole) of 2.38 *M* *n*-butyl lithium, 225 μl (3.65 mmole) of methyl formate and 105 μl (1.84 mmole) of acetic acid. The resulting products were chromatographed on a 10 × 20 cm × 0.5 mm silica gel GF plate developed twice with 1:1 ethyl acetate/petroleum ether. Six bands were eluted from the plate: Band 1 (4.9 mg, $R_f = 0.75$) had the same R_f as **35-II**. Band 2 (0.5 mg, $R_f = 0.685$) and band 3 (0.8 mg, $R_f = 0.62$) were not characterized. Bands 4 (2.6 mg, 8.3%, $R_f = 0.374$), 5 (1.6 mg, 5.1%, $R_f = 0.206$), and 6 (2.0 mg, 6.4%, $R_f = 0.174$) were submitted for nmr spectra. Bands 5 and 6 were also submitted for mass spectra. Based on the data, the material of bands 4–6 consists of diastereomers of methyl adirubine,

nmr ($CDCl_3$): Band 4: δ 0.945, (broad t, $-CH_2CH_3$); 3.59, 3.68, 3.83, (3s, $-CO_2CH_3$) (the δ 3.59 signal is roughly twice the magnitude of the other two); approx 4.1, (m, $-CH_2OH$ *inter alia*); approx 7.2, (m, indole C*H*); 7.79 and 7.85, (2 overlapping s, indole N*H*). From these data it was concluded that band 4 comprised a roughly 1:1 mixture of two methyl adirubine diastereomers.

Band 5: δ 0.94, (t, $-CH_2CH_3$); 3.59, 3.69, 3.85 (weak), (3s, $-CO_2CH_3$); approx 4.1, (m, $-CH_2OH$, *inter alia*); approx 7.2 (m, indole C*H*); 7.78, (s, indole N*H*).

Band 6: δ 0.97, (t, $-CH_2CH_3$); 3.59, 3.70 (weak), 3.84, (3s, $-CO_2CH_3$); approx 4.1, (m, $-CH_2OH$, *inter alia*); approx 7.2, (m, indole C*H*); 7.77, (s, indole (N*H*)).

Bands 5 and 6 appear to be substantially pure single diastereomers of methyl adirubine. Some cross contamination is indicated by the presence of the small third *O*-methyl singlet in the spectra.

ms: M+ at *m/e* 414 for both band 5 and band 6 samples. The spectra are otherwise virtually identical.

Methyl Adirubine (**11b**)

A 1 dram vial was equipped with a small magnetic stirring bar, was purged with nitrogen, and was stoppered with a serum stopper. A nitrogen inlet was connected to a 20 gauge needle, which was inserted through the stopper. Dicyclohexylamine (20 μl, 0.102 mmole) was injected into the vial, followed by 250 μl of freshly distilled THF.

Stirring was initiated and 42 μl of nominally 2.38 *M* *n*-butyl lithium (0.099 mmole) was injected dropwise. After stirring for 10 min at room temperature the Gilman test was ambivalent. With the addition of an additional 10 μl of the *n*-butyl lithium solution a positive test was obtained, indicating that the desired quantity of lithium dicyclohexylamide had been formed. Excess *n*-butyl lithium was consumed by addition of 10 μl of dicyclohexylamine and stirring at room temperature for 15 min, after which the expected negative Gilman test was obtained. The solution of lithium dicyclohexylamide was chilled to −30°C in an acetone/dry ice bath, and a solution of 4.1 mg (0.0107 mmole) of diester **35-IV** in 175 μl of THF and 75 μl of HMPTA was added dropwise. The resulting dark brown solution was stirred at −30°C for 15 min. At that time 33 μl (0.535 mmole) of freshly distilled methyl formate was added dropwise. The reaction mixture was stirred at −20 to −15°C for 1 hr. Near the end of the reaction time a few microliters of additional methyl formate were added. At the end of the hour the reaction mixture was chilled to −50°C and the reaction was quenched by addition of 20 μl (0.349 mmole) of glacial acetic acid. The mixture was allowed to warm to room temperature, and volatile material was removed by blowing a stream of nitrogen over the liquid. The residue was diluted with water, made basic with ammonia, and extracted five times with chloroform. The extraction was performed by adding 1 ml portions of chloroform to the aqueous phase in the same vial in which the reaction was carried out and stirring rapidly with the magnetic stirrer to ensure thorough mixing of the two phases. After stirring for 30 sec to 1 min, stirring was stopped and, following separation of the phases, the chloroform layer was removed with a syringe. The chloroform extracts were dried over anhydrous potassium carbonate and evaporated under a stream of nitrogen. The residue was dissolved in dry methanol, treated with excess sodium borohydride, and stirred overnight. When the reduction was complete the methanol was evaporated under a stream of nitrogen and the residue was diluted with water and made basic with ammonia. The aqueous phase was extracted with chloroform in the same manner as above, and the chloroform extracts were dried over anhydrous potassium carbonate. The chloroform was removed on the rotary evaporator, and low volatility material (dicyclohexylamine and HMPTA) was removed on the high vacuum pump. The solid residue (6.2 mg) was combined with the crude products (1.7 mg) of the formylation/reduction of 1 mg of **35-IV** and was applied to one 5 × 18 cm × 0.25 mm silica gel GF plate (Analtech). The plate was developed twice with 30% ethyl acetate in petroleum ether and three times with 1:1 ethyl acetate/petroleum ether. Five bands were visible on the plate: Band 1, near the top of the plate (1.52 mg) was recovered starting material and some miscellaneous material not characterized. Band 2 (0.69 mg), immediately below, was trailings from band 1. Band 5 (0.76 mg) was very polar material near the origin, not characterized. Bands 3 and 4, roughly one-third of the way up the plate, were narrowly but distinctly separated from one another and were well separated from the other bands. Band 3 (compound A, 0.50 mg, 0.00121 mmole, 9.1%) and band 4 (compound B, 0.21 mg, 0.000507 mmole, 3.8%) were assumed to be methyl adirubine and its C-16 epimer. Compound A, compound B, authentic methyl adirubine, and a mixture of the authentic alkaloid and compound A were spotted on a 5 × 18 cm × 0.25 mm silica gel GF plate which was developed three times with 1:1 ethyl acetate/petroleum ether. Compound A, authentic methyl adirubine, and the mixture of the two all showed a single sharp spot at $R_f = 0.3685$ after develop-

ment, while compound B shows a sharp spot at $R_f = 0.2948$ plus a faint spot at $R_f = 0.3685$. Compound A was accordingly judged to be methyl adirubine on the basis of the foregoing and the following data:

mp: Both authentic and synthetic methyl adirubine, even when recrystallized (aqueous acetone) display erratic melting point behavior, and reproducible melting points are difficult to obtain. When heated, the crystals undergo a physical change at approx 210–220°C, with fracturing of the crystals and occasional appearance of a liquid. An occasional crystal will actually liquify and resolidify prior to melting again. Considerable sublimation also occurs prior to final melting. Melting points of 243–247 and 243–245°C were obtained for authentic methyl adirubine, 240–245 and 239–242°C for synthetic, and 240–245°C for the mixture.

ir ($CHCl_3$): 3500, 2960, 2950, 2895, 2860, 1730 cm^{-1}.

nmr (acetone-d_6): See Fig. 2, δ 0.91, (t, $-CH_2CH_3$); 2.07, (acetone); 2.76, (water); 3.64 and 3.79, (2s, $-CO_2CH_3$); 3.9, (m, $-CH_2OH$); approx 7.2 (m, indole C*H*).

ms: M+ at *m/e* 414, base peak at *m/e* 355, major peaks at *m/e* 337, 311, 309, 251, 169, 168 (both samples). Probe temperature 20°C, ionizing potential 20 eV.

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