The Synthesis of Delphinine: A Stereoselective Total Synthesis of an Optically Active Advanced Relay Compound

K. WIESNER, E. W. K. JAY, T. Y. R. TSAI, C. DEMERSON, LIZZIE JAY, T. KANNO, J. KŘEPINSKÝ, A. VILÍM, AND C. S. WU

Natural Products Research Center, University of New Brunswick, Fredericton, N.B.

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A stereoselective total synthesis of the optically active delphinine degradation product 3*b* is described.

La synthèse totale et stéréosélective du produit 3*b* optiquement actif et issu de la dégradation de la delphinine, est décrite.

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Some time ago we deduced the structure **1***a* for the alkaloid delphinine (1). Among various degradative studies which led to this structure proposal a simple and comparatively high yield conversion of delphinine into the aromatization product **2** was discovered (2). It is clear that this aromatic degradation product or its derivatives constitute an extremely favorable advanced relay for the synthesis of delphinine. We wish to describe in the present paper in detail our total synthesis of this relay compound, the resolution of the synthetic racemate into optical antipodes, and the rigorous identification of one enantiomer with the naturally derived material of the same structure (3).

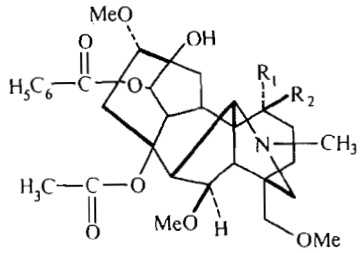
It will be seen in the sequel that the synthetic compounds which turned out to be identical with their "natural" counterparts had the configurations **2***b*, **3***b*, and **4***b* rather than **2***a*, **3***a*, and **4***a*. Thus, it is clear that the configuration of the ring A methoxyl in delphinine has to be reversed and this alkaloid has to be represented by the formula **1***b*.

The starting material for our synthesis was the methoxy tetralone **5** (4). This compound was converted by the Stork pyrrolidine–enamine procedure (5) to the allyl tetralone **6**[1] in a yield of 89%. A second alkylation with benzyl chloromethyl ether (6) and sodium hydride in benzene gave 70% of the geminally disubstituted tetralone **7** after purification by chromatography. Compound **7** was subjected to a catalytic osmylation with osmic acid – sodium chlorate in tetrahydrofuran (7). The two diastereoisomeric diols **8** (A, m.p. 108–109 °C; B, m.p. 125–130 °C) were obtained in equal amounts and practically quantitative yield. The absence of carbonyl absorption in the i.r. spectra of both products indicated that they existed as the hemiketal tautomers. The diastereoisomers **8** were treated with an excess of metaperiodate in aqueous tetrahydrofuran. The aldehyde **9** (i.r.: 1726, 1715 cm^{-1} (—CH=O, $\diagdown$C=O); n.m.r.: broad singlet (1H) τ 0.49 p.p.m. (—CH=O)) was obtained in both cases in a quantitative yield.

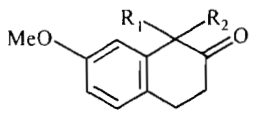
The next step which is actually the crucial operation of the synthesis involved a base-catalyzed aldol condensation portrayed by the arrows in formula **9***b*. The hydroxy ketone **10** obtained quantitatively in this manner was oily, but homogeneous in t.l.c. and sufficiently pure for further work. It showed a carbonyl maximum in the i.r. spectrum at 1755 cm^{-1} typical for the keto group in the apex of the benzobicyclooctane system. The cyclization **9** → **10** is thermodynamically controlled and thus the hydroxyl in compound **10** may be assigned the more stable *exo*-configuration. This is borne out by the n.m.r. spectrum of **10** which shows the hydrogen unshielded by the hydroxyl as a clean quadruplet centered at τ 5.7 p.p.m. The dihedral angle of this *endo*-hydrogen and the bridgehead hydrogen is 90° and consequently coupling occurs only with the methylenic protons on the other side of the hydroxyl.

We have now constructed three of the five rings of our target compound by an extremely simple reaction sequence. It should be pointed out that compound **10** was assembled in such a

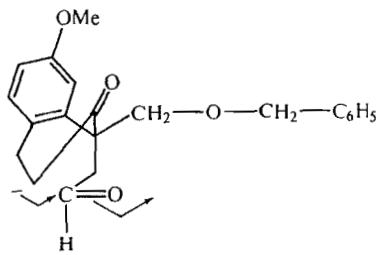
[1]All spectral data and properties of all compounds are recorded in the Experimental. They are mentioned in the Theoretical only in specially relevant cases.



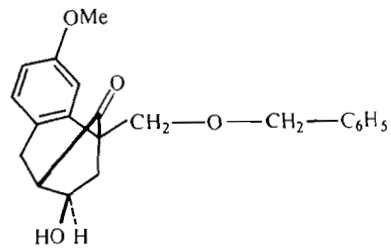
1*a* $R_1 = OMe; R_2 = H$
1*b* $R_1 = H; R_2 = OMe$



5 $R_1 = H; R_2 = H$
6 $R_1 = H; R_2 = -CH_2-CH=CH_2$
7 $R_1 = -CH_2-O-CH_2-C_6H_5;$ $R_2 = -CH_2-CH=CH_2$
8 $R_1 = -CH_2-O-CH_2-C_6H_5;$ $R_2 = -CH_2-CH(OH)-CH_2(OH)$
9 $R_1 = -CH_2-O-CH_2-C_6H_5;$ $R_2 = -CH_2-C(=O)H$



9*b*



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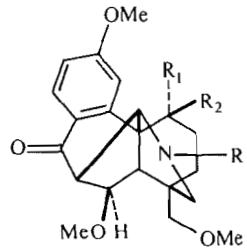
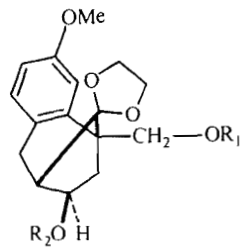


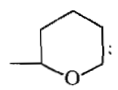
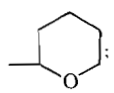
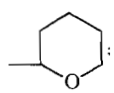
2*a* $R = -C(=O)H; R_1 = OMe; R_2 = H$

2*b* $R = -C(=O)H; R_1 = H; R_2 = OMe$

3*a* $R = H; R_1 = OMe; R_2 = H$
3*b* $R = H; R_1 = H; R_2 = OMe$
4*a* $R = -C(=O)-CH_3; R_1 = OMe; R_2 = H$

4*b* $R = -C(=O)-CH_3; R_1 = H; R_2 = OMe$



11 $R_1 = -CH_2-C_6H_5; R_2 = H$
12 $R_1 = -CH_2-C_6H_5; R_2 = -C(=O)-CH_3$
13 $R_1 = H; R_2 = -C(=O)-CH_3$
14 $R_1 =$  $; R_2 = -C(=O)-CH_3$
15 $R_1 =$  $; R_2 = H$
16 $R_1 =$  $; R_2 = -CH_2-C_6H_5$
17 $R_1 = H; R_2 = -CH_2-C_6H_5$

SCHEME 1

manner that the functional groups which are needed either for the continuation of the synthesis or as part of the functionality of the final product **2** automatically materialized in the correct positions. The hydroxy ketone **10** was converted to the ketal **11** (m.p. 95–97 °C) by treatment with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene. The yield of the recrystallized compound **11** was 88%.

The next operation which had to be executed was the transfer of the benzyl blocking group from the primary to the secondary alcoholic function, *i.e.* compound **11** had to be converted to its isomer **17**. While this process required a number of steps, it has to be emphasized that these were simple and nearly quantitative and thus *the overall yield was finally raised to 65%*.[2]

Acetylation of **11** with acetic anhydride and pyridine gave the acetoxy derivative **12** (m.p. 81–82 °C). Compound **12** was subjected to hydrogenolysis in ethanol with 10% palladium–charcoal. The oily product **13** was homogeneous in t.l.c. and immediately used for further work. The alcoholic function in **13** was now blocked by tetrahydropyranylation with dihydropyran in dry chloroform and a drop of hydrochloric acid. The product **14** was purified by chromatography and was homogeneous in t.l.c. The acetoxy group of **14** was cleaved by reduction with lithium aluminum hydride and the oily alcohol **15** was purified by chromatography on silica gel. The secondary alcoholic group in **15** was now benzylated in dry dioxane with sodium hydride and benzyl chloride at reflux temperature. Chromatography on silica gel yielded the pure oily compound **16**. The tetrahydropyranyl group was selectively removed by treating **16** with a large volume of methanol containing 1% concentrated hydrochloric acid at room temperature. The product **17** was purified by chromatography on silica gel and it was an oil homogeneous in t.l.c. The n.m.r. and i.r. spectra of **11** and **17** clearly showed the presence of an identical functional group system.

[2]Since the overall yield **11** → **17** was good, it did not seem worth while to start from the beginning with a modified starting material which would allow a much more direct conversion of **11** to **17**. One such modification which comes to mind would be the use of the acid sensitive *p*-methoxybenzyl group as R_1 in compound **11**. It would have been necessary to go back to step **6** → **7** to implement this modification.

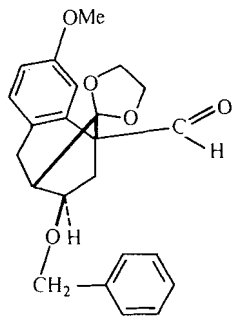
The primary alcohol **17** was oxidized by chromium trioxide in pyridine and the aldehyde **18** was obtained after chromatography on silica gel as an oil homogeneous in t.l.c. in a yield of 85% (i.r.: 2700, 1725 cm^{-1}; n.m.r.: singlet (1H) τ 0.17 p.p.m. (—CH=O)).

At this point the stage was set to attach the substituted butane derivative destined to form ring A. The synthesis of this element was carried out as follows.

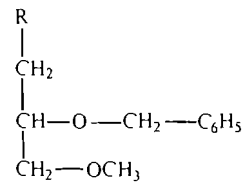
1-Methoxy-3-cyano-2-propene (**8**) (mixture of *cis*- and *trans*-isomers) was added to a solution of sodium in benzyl alcohol and the mixture was stirred for a week at room temperature. The crude product **19** was purified by distillation and the pure material was obtained in a yield of 32%. Compound **19** was heated at reflux for 50 h with 10% sulfuric acid in methanol. The methyl ester **20** was obtained in a yield of 72%. Reduction of the ester **20** with lithium aluminum hydride in ether gave the alcohol **21** in a yield of 68%. Finally, tosylation of **21** with tosyl chloride and pyridine followed by exchange of the tosyl group with lithium bromide in acetone gave the bromo derivative **22** in a 75% yield.

Both moieties of the convergent synthesis (**18** and **22**) were now ready and it was possible to couple them and proceed with the construction of ring A with its substituents.

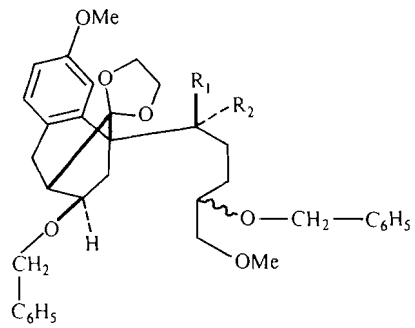
One mole of the aldehyde **18** in THF was added to 5 mol of the Grignard reagent prepared from the bromide **22** in the same solvent. Work-up and chromatography on silica gel gave the alcohol **23** in a yield of 91%. While compound **23** had an uncontrolled asymmetric center (benzyloxy group in the side chain), it was homogeneous in t.l.c., and all subsequent transformations (especially after the conversion of the side chain benzyloxy group into a ketone) proved that it was sterically homogeneous with respect to the R_1R_2 asymmetric center. It was thus clear that the Grignard reaction was stereospecific and produced only one of the two epimeric alcohols at the position of the future delphinine ring A methoxyl. At this point there was no completely reliable way to determine the configuration of this alcohol and to predict whether it corresponded (at the R_1R_2 asymmetric center) to the natural configuration of delphinine. It finally turned out that the configuration of **23** was in fact *epimeric* to the



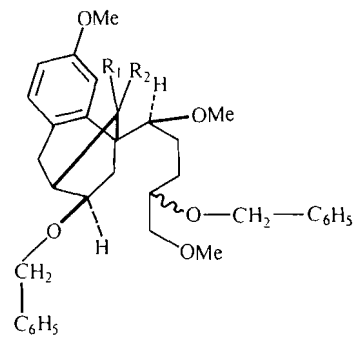
18



19 R = —C≡N
20 R = —$COOCH_3$
21 R = —CH_2—OH
22 R = —CH_2—Br



23 $R_1 = H; R_2 = OH$
24 $R_1R_2 = =O$
25 $R_1 = OH; R_2 = H$
26*a* $R_1 = H; R_2 = OMe$
26*b* $R_1 = OMe; R_2 = H$



27*b* $R_1R_2 = =O$
28*b* $R_1 = H; R_2 = NH_2$

SCHEME 2

natural configuration of delphinine and as given in the formula.

With this knowledge we may now interpret the stereospecificity of the Grignard reaction by the assumption that the aldehyde group is fixed in a single conformation by a magnesium complex involving the carbonyl oxygen and one or both of the dioxolane oxygens. In this complex the carbonyl group is attacked by the Grignard carbanion from the less hindered side. With the large benzyloxy group providing effective steric hindrance the less hindered approach is clearly from the side of the flat anisole ring.

The epimer of the Grignard alcohol **23**, *i.e.* compound **25**, was prepared as follows. The alcohol **23** was oxidized to the ketone **24** by the Jones' reagent in a yield of 94%. The product was homogeneous in t.l.c. without purification. Reduction of compound **24** with lithium aluminum hydride in dioxane at 90 °C (the stereochemical outcome is temperature dependent) gave a mixture (yield 97%) of the alcohols **25** and **23** in a ratio 7:3. The products were acetylated for 8 h with acetic anhydride and pyridine at room temperature. Only the epimer **25** acetylated under these conditions. The acetate was separated by chromatography on silica gel and the pure epimer **25** was obtained by saponification with methanolic potassium hydroxide. The recovered epimer **23** was added to the next oxidation run and thus the entire material was ultimately converted to **25**.

Both alcohols **23** and **25** were methylated in refluxing dioxane with sodium hydride and an excess of methyl iodide. The corresponding methyl ethers **26***a* and *b* were obtained in almost quantitative yield. The n.m.r. peaks of the three methoxy groups in compounds **26***a* and *b* (τ 6.29, 6.47, 6.67 and 6.27, 6.59, 6.62 p.p.m. respectively) were all narrow singlets and sufficiently

different to insure that the materials were completely homogeneous with respect to the R_1R_2 asymmetric center. Moreover, both compounds differ very strongly in t.l.c. and are easily separable by chromatography.

Since, as we already stated, there was no way to ascertain at this point which of the two compounds **26***a* and *b* corresponded to the natural configuration of the delphinine ring A methoxyl, we have decided to carry out the synthesis first with **26***a*.[3]

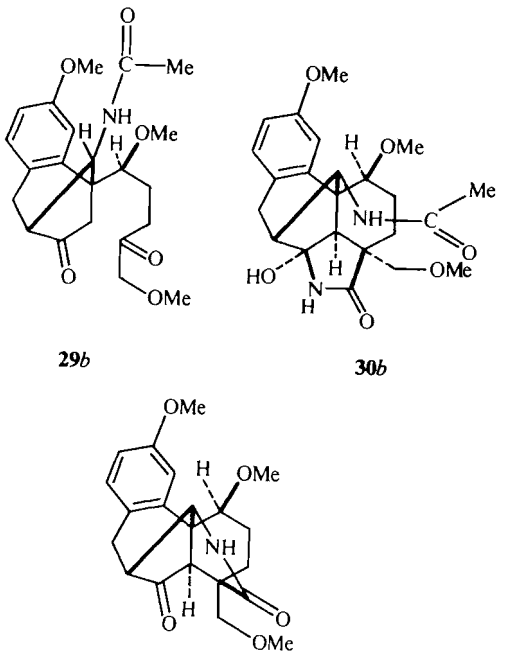
Proceeding via steps which will be outlined in the sequel we have synthesized the beautifully crystalline derivative **4***a* (m.p. 177 °C) and fully characterized it by high resolution mass spectrum and elemental analysis. While this synthetic racemate was very similar to the corresponding optically active delphinine derivative there were clear differences in t.l.c., i.r., and n.m.r. which made it certain that the two materials were not identical. On the other hand the synthetic and "natural" compound gave *identical* mass spectra and thus we concluded that the only difference between them was the configuration of the ring A methoxyl.

It was evident that, true to the proverb, the bread fell again on the buttered side, and it was necessary to repeat the synthesis starting with the epimer **26***b*. This time as expected the synthesis resulted in end-products which were identical with the naturally derived materials in every detail.

Since the individual steps in both series were performed in exactly the same manner, we shall describe only the sequence starting with **26***b*.[4] The conversion of compound **26***b* into the final products was executed as follows. The ketal was hydrolyzed under reflux with aqueous acetic acid and the product **27***b* was obtained in quantitative yield. It showed an i.r. maximum at 1755 cm^{-1}, typical for the keto group in the apex of the bicyclic system.

[3]It must be remembered that the configurations of the ring A methoxyl given in the formulae became known only after the completion of the synthesis.

[4]The description of both series may be found in the Experimental. For the sake of simplicity of the formula schemes we do not reproduce the structures of the intermediates belonging to the **26***a* series. In the Experimental these compounds are referred to by numbers with the subscript "a". Their structural formulae may be derived by inverting the configuration of the "ring A methoxyl" in the formula with the same number and the subscript "b".



29*b* **30***b*

31*b*

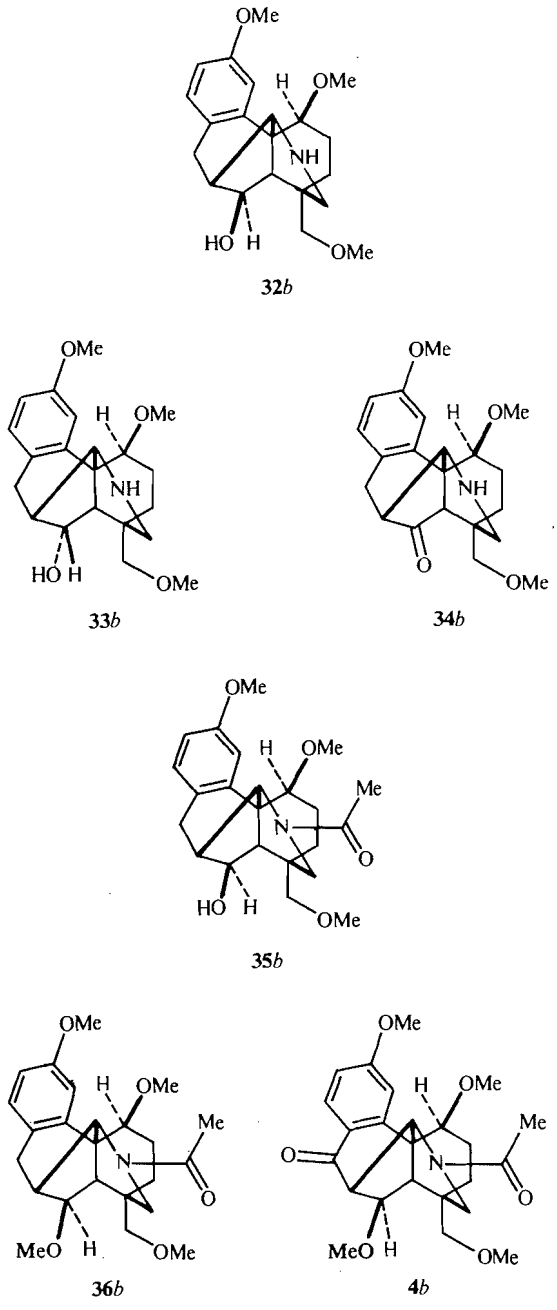
SCHEME 3

Compound **27***b* was now subjected to amination with Raney nickel in methanolic ammonia exactly as worked out in our model experiments (3, 9). However, in the present case the desired *anti*-isomer **28***b* was obtained stereoselectively (ratio *anti*:*syn* 10:1, overall yield 97%). The crude amine **28***b* was acetylated with acetic anhydride–pyridine, the benzyl groups removed by hydrogenolysis, and the two liberated alcoholic functions oxidized by chromium trioxide in pyridine.

The diketone **29***b* (m.p. 100–102 °C) was separated by chromatography on silica gel from the small amount of the undesired *syn*-epimer and purified by crystallization; (i.r.: 1745, 1720 cm^{-1} (ketones), 1660 cm^{-1} (amide); n.m.r.: singlets (3H each) τ 6.23, 6.52, 6.57 (3 OCH_3), singlet (2H) 5.93 p.p.m. (—CO—CH_2—O—)). The overall yield of pure **29***b* from the crude amine **28***b* was 50%.

The diketone **29***b* was now heated for 6 h with 5 mol of potassium cyanide in aqueous ethanol. The lactamol **30***b* (m.p. 238 °C) resulted stereospecifically in a yield of 91%.

While this reaction may seem remarkable it was fully anticipated from our extensive model



SCHEME 4

studies (9, 3). It is actually a sequence of simple steps all of which were part of our original plan. Thus, the only noteworthy feature of the transformation was the fact that conditions were found where all these steps occurred in high yield stereospecifically and in one reaction solution.

The mechanism of the conversion **29***b* → **30***b* may be visualized as follows. Base-catalyzed aldol condensation of **29***b* yielded first an $\alpha\beta$-unsaturated ketone. This intermediate, which we have not isolated, then added cyanide axially, in a thermodynamically controlled reaction. The nitrile group was subsequently hydrolyzed to a primary amide, which tautomerized to the lactamol **30***b*.

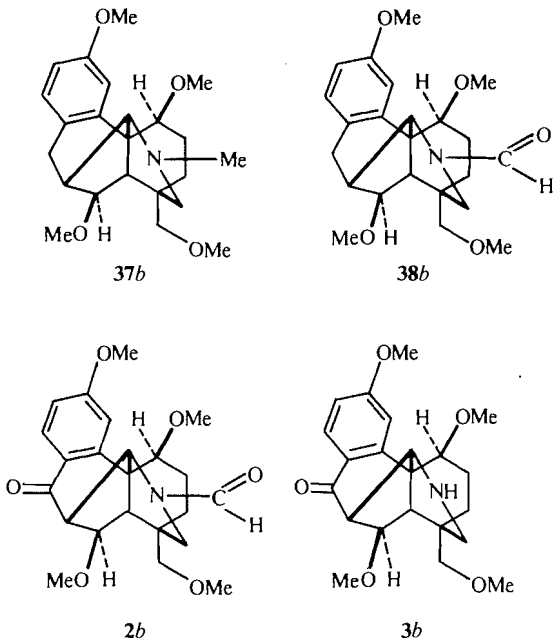
The conversion of the lactamol to the ketolactam **31***b* (m.p. 268 °C) was accomplished by heating in a mixture of methanol and concentrated hydrochloric acid in a yield of 64%; (i.r.: 1740 cm^{-1} (ketone), 1670 cm^{-1} (lactam); n.m.r.: singlets (3H each) τ 6.20, 6.57, 6.63 p.p.m. (3 OCH_3)).

With the synthesis of the ketolactam **31***b* accomplished, it remained only to modify the functional group system. This task was easy, since it required merely the reduction of the lactam group, the conversion of the ring B ketone into an *exo*-methoxy group, and the introduction of a keto group into the benzylic position. All these operations have been worked out previously in our model studies (3). The keto lactam **31***b* was reduced with lithium aluminum hydride in refluxing dioxane. The mixture of the two products **32***b* and **33***b* was separated by chromatography on alumina. The ratio of the two compounds was 1:1 and the yield was 76%.

The *exo*-alcohol **32***b* was crystalline (m.p. 228 °C); the *endo*-epimer **33***b* remained oily and it was converted to the ketone **34***b* by Jones oxidation. This last compound was subjected without purification to a reduction with sodium in refluxing absolute ethanol. The alcohols **32***b* and **33***b* were again obtained (yield 74%), but in this thermodynamically controlled reduction the desired *exo*-alcohol **32***b* predominated (ratio 7:3).

The *exo*-alcohol **32***b* was now acetylated with acetic anhydride in pyridine and the product hydrolyzed by heating with dilute methanolic potassium hydroxide. The crystalline alcohol **35***b* (m.p. 183 °C) was obtained in a yield of 95%.

Compound **35***b* was methylated in refluxing dioxane with sodium hydride and methyl iodide. The crystalline methoxy derivative **36***b* (m.p. 157 °C) was obtained in a yield of 87%. The n.m.r. spectrum of this material showed a singlet (11H) at τ 6.70 p.p.m. which includes



SCHEME 5

the three aliphatic methoxyls and the two hydrogens unshielded by the primary methoxyl. We have pointed out previously (3) that the ring B *endo*-methoxyl is located in the shielding region of the benzene ring and is consequently shifted upfield to τ 6.93 p.p.m. Thus, the n.m.r. spectrum of **36***b* is in agreement with the configuration portrayed in the formula. Compound **36***b* was converted into the final product **4***b* by Jones' oxidation in a yield of 89%. The racemate **4***b* was a crystalline sharply melting material (m.p. 188–190°C) and it was characterized by a high resolution mass spectrum and elemental analysis.

The i.r., n.m.r., u.v., and mass spectra of the synthetic racemate and the naturally derived compound of the same structure were superimposable. The two materials were also indistinguishable in several t.l.c. systems.

Since we wished to synthesize also the formyl derivative **2***b* and the secondary base **3***b* and since it turned out that the *N*-acetyl group of **4***b* is exceedingly difficult to hydrolyze, we have worked out a second variant of the final stages of the synthesis.

The *exo*-alcohol **32***b* was methylated in refluxing dioxane with sodium hydride and methyl iodide. The oily tetramethoxy *N*-methyl derivative **37***b* was obtained in a yield of 96%.

The conversion of **37***b* to the *N*-formyl derivative **38***b* was accomplished in a yield of 95% by oxidation with potassium permanganate in acetone at room temperature. Compound **38***b* was a highly crystalline, sharply melting solid (m.p. 158–160°C) and it was transformed into the final "delphinine aromatization product" **2***b* by Jones oxidation in a yield of 67%. A direct conversion of **37***b* to **2***b* was also accomplished by a prolonged oxidation with an excess of potassium permanganate in acetone acetic acid (yield 82%). The synthetic racemate **2***b* remained oily, but it was homogeneous in several t.l.c. systems and indistinguishable from the "natural" delphinine derivative. Both materials also gave identical i.r., n.m.r., and mass spectra.

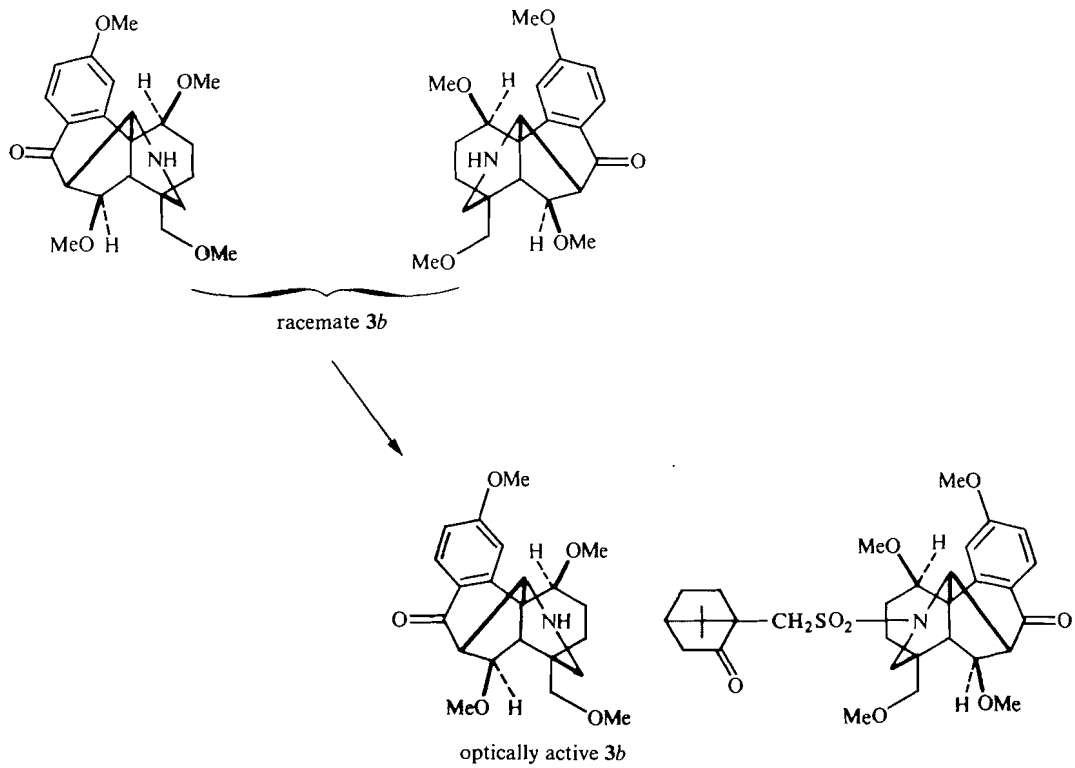
The formyl derivative **2***b* was finally smoothly hydrolyzed to the secondary base **3***b* (m.p. 176°C, yield 94%) by refluxing with dilute hydrochloric acid. The synthetic racemate **3***b* was characterized by elemental analysis and high resolution mass spectrometry and it was found to be indistinguishable from the optically active "natural" derivative of the same structure by t.l.c., i.r., n.m.r., and mass spectrometry.

Thus, the stereoselective total synthesis of the racemic relay compound **3***b* was complete. In spite of the stereoselectivity of the entire process (including the setting up of the configuration of the ring A methoxyl) the synthesis did not provide any reliable information about the configuration of the ring A methoxy group.

The only point rigorously established about this asymmetric center was that its configuration in the synthetic products was the same as in the natural alkaloid and its derivatives.

The configuration **1***a* (Scheme 1) of the ring A methoxyl in delphinine was assigned (1*c*) on the basis of a direct correlation (10) of delphinine with aconitine, in the course of which this asymmetric center remained undisturbed. The corresponding ring A methoxyl of aconitine in turn was tentatively assigned the configuration *trans* to the nitrogen bridge on the basis of a conformational argument (11). A similar conformational argument seemed also to hold when this substituent was studied directly in delphinine (1*c*). It was quite clear to us that these assignments were not completely secure, since there was some uncertainty about the conformation of ring A in alkaloids of the delphinine type.

While our synthetic objective was reached, we



SCHEME 6

felt that we wished to know the configuration of the ring A methoxyl in the synthetic compounds directly and not merely by correlation with a natural derivative. Consequently we have prepared the beautifully crystalline acid oxalate of the *racemate*[5] **3***b* [m.p. 189–192 °C] and submitted it for X-ray crystallography to Dr. Maria Przybylska at the National Research Council of Canada Laboratories, Ottawa, Canada. The structure determination performed by Dr. Karin Bjåmer Birnbaum (12) corroborated all the features of the molecule and revealed the configuration of the ring A methoxyl to be as portrayed in formula **3***b*.

Since we wished to use **3***b* as a relay compound and draw our supplies of this material for the continuation of the synthesis from natural sources it was imperative to resolve the racemate into optical antipodes.

After numerous unsuccessful attempts at resolution by conventional methods, we have noticed that if the racemate was allowed to react with D-camphor–sulfonyl chloride in pyridine, the reaction stopped when approximately 50% of the secondary amine was consumed. Isolation of the unreacted free base yielded material which was optically active and showed an optical rotatory dispersion (o.r.d.) curve antipodal to the o.r.d. recorded for the natural degradation product.

Consequently, we have achieved the preparation of the totally synthetic optically active antipode **3***b* with the natural absolute configuration in the following manner. The racemate **3***b* was dissolved in dry pyridine and treated with 1 mol of L-camphor–sulfonyl chloride at 0 °C. The temperature was allowed to rise to 20 °C and the mixture was kept overnight. The unreacted free base was converted to the acid

[5]The X-ray structure determination of the synthetic *racemate* is also important as an independent verification of the synthesis. Since long laborious total syntheses unlike other work may never be repeated in independent laboratories and since X-ray methods are increasingly fast and effective it seems to the authors that an X-ray of the synthetic *racemate* in a synthesis like the present one should be almost a requirement.

oxalate, which was recrystallized to a constant melting point of 195–196 °C. This melting point was identical with the melting point of the "natural" degradation base oxalate and the two products did not show melting point depression. Both materials gave also superimposable i.r. and n.m.r. spectra and o.r.d. curves. The totally synthetic optically active oxalate was decomposed and the synthetic optically active base **3***b* was recrystallized to a melting point of 144.5 °C. This melting point was undepressed by admixture of the "natural" base which had the same melting point. Both materials showed superimposable i.r., n.m.r., and mass spectra and t.l.c. behavior.

Thus, our objective has been fully achieved and a stepping stone created for the synthesis of alkaloids of the delphinine type. It should be pointed out that while compound **3***b* is structurally complex, it is operationally very simple. After suitable blockade of the nitrogen the entire system is solid saturated and unreactive, all except the *p*-methoxy acetophenone group which must be used for building up the CD ring system. Thus, the obstacles in the remaining part of the synthesis are more financial than chemical in nature.

Experimental

Allyl Tetralone **6**

Distilled pyrrolidine (135 ml, 1.65 mol) was added to a stirred solution of 7-methoxy-2-tetralone (164 g, 0.93 mol) in benzene (1500 ml). The solution was refluxed under nitrogen until all the water produced by the reaction had been removed by a Dean Stark trap (3 h). The reaction mixture was then cooled to room temperature and allyl bromide (195 ml, 2.28 mol) was added dropwise. The mixture was refluxed for 17 h, at the end of which, water (2000 ml) was added and the reflux continued for another period of 3 h.

The organic phase was separated, washed with water (3 × 500 ml), dried over anhydrous magnesium sulfate, and taken to dryness *in vacuo*. The crude product (193 g) was distilled *in vacuo* and gave 178 g of the pure allyl tetralone **6** (b.p. 118–120 °C, 0.05 mm Hg); yield 89%.

I.r. (CCl_4): 1715 (C=O); 915 cm^{-1} (C=CH_2).

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.80–3.50 (aromatic protons of the anisole ring); multiplet (3H) 4.20–5.20 (vinylic protons); singlet (3H) 6.28 p.p.m. (methoxyl protons).

Mass spectrum Calcd. for $C_{14}H_{16}O_2$: *m/e*, 216. Found: 216.

Disubstituted Tetralone **7**

The allyl tetralone **6** (66 g, 0.30 mol) was dissolved in dry benzene (500 ml). Sodium hydride (12.6 g, 0.31 mol; 60% suspension in mineral oil) was added and the resulting mixture was stirred under nitrogen at room temperature for 15 h then at 60° for 6 h. The mixture was cooled in an ice-water bath, and benzyloxymethyl chloride (59.4 g, 0.36 mol) in dry benzene (250 ml) was added dropwise. The mixture was then allowed to warm up to room temperature and stirring was continued for 18 h.

After addition of water (250 ml), the organic phase was separated and the aqueous phase was extracted with benzene (3 × 75 ml). The benzene extracts were combined, washed with water (3 × 150 ml), and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* gave the crude disubstituted tetralone **7** (112 g). Chromatography on silica gel (3 Kg) in benzene gave the pure compound **7** (67.5 g); yield 68%.

I.r. (CCl_4): 1715 (C=O); 915 cm^{-1} (C=CH_2).

N.m.r. ($CDCl_3$): multiplet (8H) τ 2.81–3.14 (aromatic protons of the anisole ring and the benzyl group); multiplet (3H) 4.50–5.50 (vinylic protons); singlet (2H) 5.70 (benzylic methylene protons); singlet (5H) 6.26 p.p.m. (aromatic methoxyl and the methylene protons deshielded by the benzyloxyl group).

Mass spectrum Calcd. for $C_{22}H_{24}O_3$: *m/e*, 336.1726. Found: 336.1719.

Diols **8**

A solution of compound **7** (51.9 g, 0.17 mol) in tetrahydrofuran (250 ml) was combined with osmic acid (0.25 g, 0.001 mol) in tetrahydrofuran (25 ml) and stirred at room temperature for 10 min. A solution of sodium chlorate (26.6 g, 0.25 mol) in water (250 ml) was added in several portions, and the stirring was continued for 16 h at 60°.

After distilling off most of the tetrahydrofuran under reduced pressure, water (200 ml) was added and the solution was extracted with ether (3 × 150 ml). The combined ether extracts were washed with water (3 × 150 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo* to give the crude diols. The dark viscous product was chromatographed on silica gel (2 Kg). Elution with a 2:8 ether–benzene mixture gave two epimeric diols (A, 22.4 g, m.p. 108–109 °C; B, 23.0 g, m.p. 125–130 °C). Both compounds were recrystallized from benzene; yield 79%.

I.r. of A and B (KBr pellet): 3200–3500 cm^{-1} (hydroxyl); no carbonyl absorption.

N.m.r. ($CDCl_3$): A and B multiplet (8H) τ 2.80–3.50 (aromatic protons); singlet (2H) A, 5.55, B, 5.58 (benzylic methylene protons); singlet (5H) A, 6.26, B, 6.34 p.p.m. (protons deshielded by the benzyloxyl and the aromatic methoxyl protons).

Mass spectrum Calcd. for $C_{22}H_{26}O_5$: *m/e*, 370. Found: 352 ($M^+ - H_2O$).

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found for Diol A: C, 71.37; H, 7.00. Found for Diol B: C, 71.13; H, 6.86.

Keto Aldehyde **9**

The epimeric diols **8** (46.4 g, 0.14 mol) were dissolved in a 1:1 THF–water mixture (660 ml). Sodium metaperiodate (232 g, 1.08 mol) was added over a period of 15 min and the mixture was stirred at room temperature under nitrogen for 8 h. The resulting white precipitates were filtered off and washed well with ether. Water (300 ml) was added and the filtrate was extracted with ether (5 × 200 ml). The combined ethereal extracts were washed with water (2 × 200 ml) and dried over anhydrous magnesium sulfate. The crude keto-aldehyde **9** (41 g) was obtained after evaporation of the

solvent *in vacuo*, and was used for the next step without further purification.

I.r. (CCl_4): 2720 (C—H, aldehyde); 1726 (C=O, aldehyde); 1715 cm^{-1} (C=O, ketone).

N.m.r. ($CDCl_3$): singlet (1H) τ 0.49 (aldehydic proton); multiplet (8H) 2.60–3.28 (aromatic protons of the anisole ring and the benzyl group); singlet (2H) 5.62 (benzylic methylene protons); singlet (5H) 6.21 p.p.m. (aromatic methoxyl and methylene protons deshielded by the benzyloxy group).

Hydroxy Ketone ***10***

A solution of the keto-aldehyde **9** (41 g, 0.12 mol) in methanol (3500 ml) was added to sodium hydroxide (5.32 g, 0.13 mol) in water (138 ml). The resulting brown solution was stirred at 55 °C under nitrogen for 30 h. Water (2000 ml) was added and the solution was neutralized with 20% hydrochloric acid. The methanol was partially evaporated *in vacuo* until the mixture just became cloudy. The mixture was extracted with ether (5 × 800 ml) and the combined ethereal extracts were washed with water (2 × 1000 ml), dried over anhydrous magnesium sulfate and evaporated to dryness *in vacuo* to give the crude hydroxy-ketone **10** (34.8 g). This material was purified by chromatography on silica gel (1 kg). Elution with benzene–ether gave the pure hydroxy ketone **10** (28.2 g).

I.r. (CCl_4): 3600, 3475 (O—H); 1755 cm^{-1} (five membered ketone).

N.m.r. ($CDCl_3$): singlet (5H) τ 2.78 (aromatic protons of the benzyl group); multiplet (3H) 3.25–3.50 (aromatic protons of anisole ring); singlet (2H) 5.42 (benzylic methylene protons); quadruplet (1H) centered at 5.70 (proton deshielded by the hydroxyl); singlet (2H) 6.08 (methylene protons deshielded by the benzyloxy group); singlet (3H) 6.31 p.p.m. (aromatic methoxyl protons).

Mass spectrum Calcd. for $C_{21}H_{22}O_4$: *m/e*, 338. Found: 338.

Both compounds **9** and **10** were rather unstable and had to be characterized by a derivative. The crystalline ketal **11** was used for this purpose.

Hydroxy Ketal ***11***

A mixture of the hydroxy ketone **10** (54.1 g, 0.16 mol), ethylene glycol (17.1 g, 0.27 mol), and *p*-toluenesulfonic acid (4.57 g, 0.034 mol) in benzene (1000 ml) was heated under reflux for 2 h using a Dean Stark water separator to remove the water produced by the reaction. The reaction mixture was cooled, washed with water (2 × 200 ml), then with 5% aqueous sodium bicarbonate (3 × 200 ml) and with water (2 × 200 ml). The organic phase was dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The pure ketal **11** was obtained by crystallization from ether (53.2 g, m.p. 97–99 °C), yield: 88%.

I.r. (KBr pellet): 3600–3200 cm^{-1} (hydroxyl); no carbonyl absorption.

N.m.r. ($CDCl_3$): singlet (5H) τ 2.74 (aromatic protons of the benzyl group); multiplet (3H) 3.25–3.30 (aromatic protons of the anisole ring); singlet (2H) 5.48 (benzylic methylene protons); broad singlet (6H) 6.18 (ketal methylenes and methylene protons deshielded by the benzyloxy group); singlet (3H) 6.43 p.p.m. (aromatic methoxyl).

Mass spectrum Calcd. for $C_{23}H_{26}O_5$: *m/e*, 382. Found: 382.

Anal. Calcd. for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.25; H, 6.83.

Acetoxy Ketal ***12***

The hydroxy-ketal **11** (50 g, 0.13 mol) dissolved in pyridine (100 ml) and acetic anhydride (100 ml) was allowed to stand at room temperature overnight. The solvent was evaporated *in vacuo*, and ether (1000 ml) was added. The ether solution was washed with 10% aqueous sodium bicarbonate (3 × 500 ml), then with water (2 × 300 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo*. The crude product was crystallized from ether to give a quantitative yield of the pure acetoxy-ketal **12** (56 g, m.p. 81–82 °C).

I.r. (KBr pellet): 1725 cm^{-1} (acetoxyl carbonyl).

N.m.r. ($CDCl_3$): singlet (5H) τ 2.68 (aromatic protons of the benzyl group); multiplet (3H) 2.70–3.40 (aromatic protons of the anisole ring); multiplet (1H) centered at 5.15 (proton deshielded by the acetoxyl); broad singlet (6H) 6.07 (ketal methylenes and protons deshielded by the benzyloxyl); singlet (3H) 6.30 (aromatic methoxyl); singlet (3H) 7.95 p.p.m. (acetoxyl methyl protons).

Mass spectrum Calcd. for $C_{25}H_{28}O_6$: *m/e*, 424. Found: 424.

Anal. Calcd. for $C_{25}H_{28}O_6$: C, 70.81; H, 6.66. Found: C, 71.16; H, 6.78.

Acetoxy Alcohol ***13***

The acetoxy-ketal **12** (54.5 g, 0.13 mol) was dissolved in ethanol (2000 ml), 10% palladium-on-charcoal (20 g) was added, and the reaction mixture was hydrogenated (room temperature, 1 atm) for 5 h. The catalyst was filtered off and the solvent evaporated *in vacuo* to yield the acetoxy-alcohol **13** (41.3 g, 96%) which was homogeneous on t.l.c.

I.r. ($CHCl_3$): 3550 (hydroxyl); 1726 cm^{-1} (acetoxyl carbonyl).

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.90–3.45 (aromatic protons of the anisole ring); quadruplet (1H) centered at 5.17 (proton deshielded by the acetoxyl); multiplet (4H) centered at 5.95 (ketal methylenes); singlet (5H) 6.27 (aromatic methoxyl and methylene protons deshielded by the primary hydroxyl); singlet (3H) 7.95 p.p.m. (acetoxy methyl protons).

Mass spectrum Calcd. for $C_{18}H_{22}O_6$: *m/e*, 334.1430. Found: 334.1426.

Tetrahydropyranyl Acetate ***14***

The acetoxy alcohol **13** (40 g, 0.12 mol) was dissolved in dry chloroform (2000 ml). Dihydropyran (25.5 g, 0.3 mol) and one drop of concentrated hydrochloric acid were added. The solution was stirred at room temperature for 18 h. The mixture was then washed with 10% aqueous sodium bicarbonate (2 × 500 ml), and with water (3 × 500 ml), dried over anhydrous magnesium sulfate, and finally, evaporated to dryness *in vacuo*. The crude product (60 g) was chromatographed on silica gel (1200 g). Elution with 4% ether in benzene gave the pure tetrahydropyranyl acetate **14** (43.3 g, 86%).

I.r. ($CHCl_3$): no hydroxyl absorption; 1725 cm^{-1} (acetoxyl carbonyl).

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.80–3.45 (aromatic protons of the anisole ring); multiplet (4H) centered at 6.05 (ketal methylenes); singlet (5H) 6.24 (aromatic methoxyl and methylene protons deshielded by the primary oxygen),

singlet (3H) 7.92 (acetoxy methyl protons), broad singlet (6H) 8.33 p.p.m. (methylene protons of the tetrahydropyran ring).

Mass spectrum Calcd. for $C_{23}H_{30}O_7$: *m/e*, 418. Found: 418.

Tetrahydropyranyl Alcohol **15**

The tetrahydropyranyl acetate **14** (42.2 g, 0.10 mol) was dissolved in dry ether (2000 ml). Lithium aluminum hydride (3.95 g, 0.10 mol) was added and the resulting suspension was stirred at room temperature for 1 h. The reaction mixture was poured into wet ether (2000 ml) and a few drops of water were added. The solid material was filtered off and the filtrate was dried over anhydrous magnesium sulfate and evaporated to dryness. The crude product was chromatographed on silica gel (1.5 kg). The pure tetrahydropyranyl alcohol **15** (38.3 g, 98%) was eluted with 10% ether in benzene.

I.r. ($CHCl_3$): 3500 cm^{-1} (hydroxyl); no carbonyl absorption.

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.80–3.50 (aromatic protons of the anisole ring); broad singlet (1H) 5.30 (proton deshielded by the hydroxyl); multiplet (4H) centered at 6.00 (ketal methylenes); singlet (3H) 6.24 (aromatic methoxyl); broad singlet (6H) 8.33 p.p.m. (methylene protons of the tetrahydropyran ring).

Mass spectrum Calcd. for $C_{21}H_{28}O_6$: *m/e*, 376.1885. Found: 376.1882.

Tetrahydropyranyl Benzyl Ketal **16**

The tetrahydropyranyl alcohol **15** (37.6 g, 0.10 mol) was dissolved in absolute dioxane (1000 ml); sodium hydride (6.5 g, 0.15 mol, 56% suspension in mineral oil) and benzyl chloride (25.6 g, 0.15 mol) were added and the mixture was heated at reflux for 18 h. The suspension was then cooled to room temperature and filtered through Celite. The filtrate was partially evaporated (about 100 ml remained), water (200 ml) was added, and the solution was extracted with chloroform (4 × 300 ml). The chloroform extracts were washed with water (3 × 200 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The crude product was chromatographed on silica gel (1.5 kg). Elution with 2% ether in benzene gave the pure benzyl derivative **16** (37.5 g, 81%).

I.r. ($CHCl_3$): no hydroxyl absorption.

N.m.r. ($CDCl_3$): singlet (5H) τ 2.64 (aromatic protons of the benzyl group); multiplet (3H) 2.70–3.50 (aromatic protons of the anisole ring); multiplet (4H) centered at 6.00 (ketal methylenes); singlet (3H) 6.22 (aromatic methoxyl); broad singlet (6H) 8.32 p.p.m. (methylene protons of the tetrahydropyran ring).

Mass spectrum Calcd. for $C_{28}H_{34}O_6$: *m/e*, 466. Found: 466.

Hydroxy Ketal **17**

The benzyloxy compound **16** (46.6 g, 0.1 mol) was dissolved in a mixture of concentrated hydrochloric acid and methanol (1:99, 500 ml) and stirred at room temperature for 1 h. After neutralization with 5% aqueous sodium bicarbonate, the methanol was partially evaporated *in vacuo*, water (500 ml) was added, and the solution was extracted with chloroform (3 × 500 ml). The organic phase was washed with water (2 × 300 ml), dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. The crude alcohol was purified by chromatography on silica gel (1.5 kg). Elution with 15% ether in benzene gave the pure hydroxy ketal **17** (34.4 g, 90%).

I.r. (CCl_4): 3550 cm^{-1} (hydroxyl).

N.m.r. ($CDCl_3$): singlet (5H) τ 2.64 (aromatic protons of the benzyl group); multiplet (3H) 2.90–3.40 (aromatic protons of the anisole ring); singlet (2H) 5.50 (benzylic methylene protons); multiplet (4H) centered at 5.90 (ketal methylene protons); singlet (3H) 6.21 p.p.m. (aromatic methoxyl).

Mass spectrum Calcd. for $C_{23}H_{26}O_5$: *m/e*, 382.1780. Found: 382.1772.

Aldehyde **18**

A solution of the primary alcohol **17** (12 g, 0.03 mol) in dry dichloromethane (100 ml) was added in 1 min to a solution of chromium trioxide–pyridine complex (50.4 g) in dichloromethane (1000 ml). The resulting mixture was stirred at room temperature for 10 min. Ether (2000 ml) was added, the solid material was filtered off, and the filtrate was evaporated *in vacuo*. The crude product was chromatographed on silica gel (800 g). Elution with 5% ether in benzene gave the pure aldehyde **18** (12.7 g, 85%).

I.r. (CCl_4): 2720 and 1725 cm^{-1} (aldehyde), no hydroxyl absorption.

N.m.r. ($CDCl_3$): singlet (1H) τ 0.17 (aldehydic proton); doublet (5H) centered at 2.67 (aromatic protons of the benzyl group); multiplet (3H) 2.70–3.80 (aromatic protons of the anisole ring); singlet (2H) 5.50 (benzylic methylene protons); multiplet (4H) centered at 6.00 (ketal methylene protons), singlet (3H) 6.30 p.p.m. (aromatic methoxyl).

Mass spectrum Calcd. for $C_{23}H_{24}O_5$: *m/e*, 380.1619. Found: 380.1623.

1-Methoxy-2-benzyloxy-3-cyano Propane **19**

Benzyl alcohol (300 g, 2.78 mol) and sodium (3.5 g, 0.155 mol) were stirred at room temperature until all the sodium was dissolved and then 1-methoxy-3-cyano-2-propene (8) (150 g, 1.55 mol) was added dropwise. The solution was stirred for a week at room temperature. After neutralization with acetic acid, ether (100 ml) and water (100 ml) were added and the mixture was extracted into ether (3 × 200 ml). The organic layer was washed with water (3 × 200 ml), dried over anhydrous magnesium sulfate, and finally the ether was evaporated *in vacuo*. The crude compound was distilled to give pure 1-methoxy-2-benzyloxy-3-cyano propane (102 g, b.p. 115–120 °C/0.3 mm Hg); yield: 32%.

I.r. (CCl_4) 2240 cm^{-1} (nitrile).

N.m.r. ($CDCl_3$): singlet (5H) τ 2.90 (aromatic protons of the benzyl group); singlet (2H) 5.39 (benzylic methylene protons); multiplet (1H) centered at 6.05 (proton deshielded by the benzyloxyl); doublet (2H) centered at 6.56 (protons deshielded by the methoxyl); singlet (3H) 6.65 (—OCH_3); doublet (2H) centered at 7.44 p.p.m. (C_3 methylene protons).

Mass spectrum Calcd. for $C_{12}H_{15}O_2N$: *m/e*, 205.1103. Found: 205.1102.

1-Methoxy-2-benzyloxy-3-carbomethoxy Propane **20**

A solution of 1-methoxy-2-benzyloxy-3-cyano propane (36 g, 0.175 mol) in methanol (1000 ml) and sulfuric acid (100 ml) was heated under reflux for 50 h. The excess of methanol was then evaporated *in vacuo*. The reaction mixture was poured into water (500 ml) and the product was extracted into ether (3 × 500 ml). The ethereal layer was

washed with 5% sodium carbonate in water (3 × 200 ml), then with water (3 × 500 ml), and dried over anhydrous magnesium sulfate. After evaporation of the ether *in vacuo*, the crude ester was purified by distillation (29.5 g, 71.5%, b.p. 115–125 °C/0.01 mm Hg).

I.r. ($CHCl_3$): 1735 cm^{-1} (ester carbonyl).

N.m.r. ($CDCl_3$): doublet (5H) centered at τ 2.80 (aromatic protons of the benzyl group); singlet (2H) 5.40 (benzylic methylene protons); multiplet (1H) centered at 6.00 (proton deshielded by the benzyloxyl); singlet (3H) 6.37 (carbomethoxy methyl protons); doublet (2H) centered at 6.57 (protons deshielded by the methoxyl); singlet (3H) 6.70 (—OCH_3); doublet (2H) centered at 7.65 p.p.m. (C_3 protons).

Mass spectrum Calcd. for $C_{13}H_{18}O_4$: *m/e*, 238. Found: 238.

1-Methoxy-2-benzyloxy-4-hydroxybutane ***21***

A suspension of lithium aluminum hydride (953 mg, 0.025 mol) in dry ether (200 ml) was stirred in an ice-water bath for 10 min. A solution of the ester **20** (5.0 g, 0.021 mol) in dry ether (80 ml) was added slowly and the reaction was stirred for 1.5 h at room temperature. The reaction mixture was then poured into wet ether (500 ml), the solid material was filtered off, the filtrate was dried over anhydrous magnesium sulfate, and finally, the solvent was evaporated *in vacuo*. The crude alcohol (5.0 g) was purified by chromatography on silica gel (200 g). Elution with 10–20% ether in benzene gave pure 1-methoxy-2-benzyloxy-4-hydroxybutane (2.0 g); yield 68%.

For large scale preparations, distillation was used as a purification method. The alcohol distilled at 120–125 °C/1 mm Hg.

I.r. ($CHCl_3$): 3600 cm^{-1} (OH); no carbonyl absorption.

N.m.r. ($CDCl_3$): singlet (5H) τ 2.65 (aromatic protons of the benzyl group); doublet (2H) centered at 5.37 (benzylic methylene protons); triplet (2H) centered at 6.28 (protons deshielded by the hydroxyl); doublet (2H) centered at 6.59 (protons deshielded by the methoxyl); singlet (3H) 6.70 (—OCH_3); broad singlet (1H) 7.24 (OH); quadruplet (2H) centered about 8.22 p.p.m. (C_3 methylene protons).

Mass spectrum Calcd. for $C_{12}H_{18}O_3$: *m/e*, 210.2156. Found: 210.2157.

1-Methoxy-2-benzyloxy-4-bromobutane ***22***

The alcohol **21** (30.0 g, 0.143 mol) was dissolved in dry pyridine (30 ml) and the solution was stirred in an ice-water bath for 30 min, after which *p*-toluenesulfonyl chloride (32.8 g, 0.172 mol) was added and stirring was continued with cooling for 3 h. The reaction mixture was then poured into ice water (150 ml) and the product was extracted into ether (3 × 200 ml). The combined ethereal layers were washed with water (5 × 200 ml), dried over anhydrous magnesium sulfate, and finally the ether was evaporated *in vacuo* giving 1-methoxy-2-benzyloxy-4-tosyloxybutane (45.2 g) which was homogeneous on t.l.c.; yield: 87%.

I.r. ($CHCl_3$): 1364, 1179 cm^{-1}, no hydroxyl absorption.

N.m.r. ($CDCl_3$): two doublets (2H each) centered at τ, 2.23 and 2.76 (aromatic protons of the tosyl group; singlet (5H) 2.74 (aromatic protons of the benzyl group); doublet (2H) centered at 5.55 (benzylic methylene protons); triplet (2H) centered at 5.89 (protons deshielded by the tosyloxyl); multiplet (1H) centered at 6.42 (proton deshielded by the benzyloxyl); doublet (2H) centered at 6.65 (protons deshielded by the methoxyl); singlet (3H) 6.71 (—OCH_3); singlet (3H) 7.62 (tosyl methyl protons); quadruplet (2H) centered about 8.12 p.p.m. (C_3 methylene protons).

The tosylate (43.2 g, 0.124 mol) was dissolved in acetone (750 ml, distilled over potassium permanganate) and lithium bromide (43.0 g, 0.476 mol) was added. The resulting solution was heated under reflux for 3 h. The reaction mixture was cooled, excess acetone was evaporated, and water (1500 ml) was added. After extraction into ether (3 × 500 ml) the combined ethereal layers were washed with water (3 × 500 ml), and dried over anhydrous magnesium sulfate. Evaporation of the ether *in vacuo* gave the crude bromide (34 g) which was purified by chromatography on silica gel (1200 g). Elution with benzene gave 1-methoxy-2-benzyloxy-4-bromobutane **22** (33 g, 83.5%).

N.m.r. ($CDCl_3$): singlet (5H) τ 2.67 (aromatic protons of the benzyl group); doublet (2H) centered at 5.38 (benzylic methylene protons); multiplet (1H) 6.21 (proton deshielded by the benzyloxyl); doublet (2H) centered at 6.53 (protons deshielded by bromine); doublet (2H) centered at 6.58 (protons deshielded by the methoxyl); singlet (3H) 6.65 (—OCH_3); quadruplet (2H) centered at 7.95 p.p.m. (C_3 methylene protons).

Mass spectrum Calcd. for $C_{12}H_{17}O_2Br$: *m/e*, 272, 274. Found: 272, 274.

High resolution mass spectrum Calcd. for $C_{12}H_{17}O_2Br$ (lower isotope): *m/e*, 272.0412. Found: 272.0411.

Grignard Alcohol ***23***

To a mixture of fine magnesium turnings (8.55 g, 0.35 mol) and a small grain of iodine in absolute tetrahydrofuran (700 ml), one third of a solution of 1-methoxy-2-benzyloxy-4-bromobutane **22** (95.5 g, 0.35 mol) in absolute tetrahydrofuran (700 ml) was introduced and the mixture was refluxed at 70° (bath temperature) under nitrogen. As soon as the color of the iodine had disappeared the remaining solution was added dropwise. The reaction mixture was then heated to 70 °C for 4 h, at the end of which most of the magnesium was dissolved and the mixture was cooled to room temperature. The benzyloxy-aldehyde **18** (22.8 g, 0.06 mol) in absolute tetrahydrofuran (180 ml) was added dropwise and the solution was stirred overnight.

The reaction mixture was poured into a saturated ammonium chloride solution (1000 ml) and extracted with chloroform (5 × 500 ml). The chloroform extract was washed with water (3 × 500 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the crude product was chromatographed on silica gel (1.2 kg). Elution with a 2:8 ether–benzene mixture gave the pure Grignard alcohol **23** (31.3 g, 91%).

I.r. (CCl_4): 3510 cm^{-1} (hydroxyl); no carbonyl absorption.

N.m.r. ($CDCl_3$): singlet (10H) τ 2.68 (aromatic protons on two benzyl groups); two singlets (2H each) 5.38 and 5.52 (methylene protons of two benzyl groups); multiplet (4H) centered at 6.00 (ketal methylene protons), and two singlets (3H each) 6.31 and 6.66 p.p.m. (two methoxyls).

Mass spectrum Calcd. for $C_{35}H_{42}O_7$: *m/e*, 574.2933. Found: 574.2944.

Methylation ***23*** → ***26a***

Sodium hydride (13 g, 50% oil suspension (0.26 mol)) was added to the alcohol **23** (27.2 g, 0.047 mol) in absolute dioxane (1500 ml) and the solution was refluxed for 3 h. After cooling to room temperature, excess methyl iodide

(100 ml) was added and the solution was stirred at room temperature for 1 h and then refluxed for 5 h. The solution was filtered, the filtrate was washed with water (3 × 600 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The crude product (28.9 g) was chromatographed on silica gel. Elution with 15% ether in benzene gave the pure methylation product **26***a* (25.4 g, 92%).

I.r. (CCl_4): no hydroxyl absorption.

N.m.r. ($CDCl_3$): singlet (10H) τ 2.68 (aromatic protons of the two benzyl groups); multiplet (3H) 3.0–3.50 (aromatic protons of the anisole ring); two singlets (2H each) 5.37 and 5.50 (protons of two benzylic methylene groups); multiplet (4H) centered at 6.00 (ketal methylene protons); three singlets (3H each) 6.27, 6.59, and 6.62 (three methoxyls); singlet (2H) 6.50 p.p.m. (methylene protons deshielded by the primary side chain methoxyl).

Mass spectrum Calcd. for $C_{36}H_{44}O_7$: *m/e*, 588.3075. Found: 588.3087.

Ketone **27***a*

Compound **26***a* (25.4 g, 0.043 mol) was dissolved in 75% aqueous acetic acid (850 ml) and heated under reflux for 18 h. The acetic acid was evaporated *in vacuo* and chloroform (500 ml) was added. The solution was washed with 10% sodium bicarbonate (3 × 300 ml) and with water (2 × 300 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The ketone **27***a* (23 g) which was homogeneous on t.l.c. was obtained in quantitative yield.

I.r. (CCl_4): 1755 cm^{-1} (five-membered ketone).

N.m.r. ($CDCl_3$): two singlets (5H each) τ 2.68 and 2.70 (aromatic protons of the two benzyl groups); two singlets (2H each) 5.40 and 5.52 (benzylic methylene protons); three singlets (3H each) 6.27, 6.49, 6.67 p.p.m. (three methoxyls).

Mass spectrum Calcd. for $C_{34}H_{40}O_6$: *m/e*, 544.2824. Found: 544.2818.

Conversion of **27***a to the Diketone* **29***a*

The ketone **27***a* (23 g, 0.042 mol) was dissolved in methanol (90 ml) and cooled in a methanol – Dry Ice bath. Raney nickel (9.5 g) and liquid ammonia (125 ml) were added. The mixture was hydrogenated (165 °C, 4000 p.s.i. H_2) for 10 h. The catalyst was removed by filtration through Celite and washed thoroughly with methanol. The filtrate was evaporated to dryness and yielded the amine **28***a* (20.5 g, 90%) which was used without purification for the subsequent step.

I.r. (CCl_4): 3400 cm^{-1} (N—H), no carbonyl band.

N.m.r. ($CDCl_3$): two singlets (5H each) τ 2.70 and 2.77 (aromatic protons of the two benzyl groups); multiplet (3H) 3.0–3.40 (aromatic protons of the anisole ring); doublet (2H) centered at 5.42 (benzylic methylene protons); singlet (2H) 5.60 (benzylic methylene protons); three singlets (3H each) 6.30, 6.51, and 6.67 p.p.m. (three methoxyl).

Mass spectrum Calcd. for $C_{34}H_{43}O_5N$: *m/e*, 545.3141. Found: 545.3128.

The amine **28***a* (20 g, 0.036 mol) was dissolved in pyridine (60 ml) and acetic anhydride (60 ml). The mixture was allowed to remain at room temperature for 10 h. The pyridine and acetic anhydride were evaporated in high vacuum, chloroform (200 ml) was added, and the solution was washed with 5% aqueous sodium bicarbonate (3 × 150 ml), water (2 × 150 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The product (20 g, 95%) was homogeneous on t.l.c. and was used without further purification.

I.r. (CCl_4): 3395 (N—H); 1670 cm^{-1} (acetyl amino carbonyl).

N.m.r. ($CDCl_3$): multiplet (13H) τ 2.70–3.42 (aromatic protons of the two benzyl groups and the anisole ring); doublet centered at 5.74 (apex proton of *anti*-epimer); multiplet centered at 5.24 (apex proton of *syn*-epimer); singlet 8.05 (N—CO—CH_3, *anti*), singlet 8.24 p.p.m. (N—CO—CH_3, *syn*).

The above material (20 g, 0.034 mol) was dissolved in ethanol (1000 ml) and 10% palladium-on-charcoal (10 g) was added. The mixture was hydrogenated (1 atm H_2; room temperature) for 16 h. The catalyst was removed by filtration through Celite and washed thoroughly with ethanol. The ethanol was evaporated *in vacuo* and the crude diol (14 g), was purified by chromatography on silica gel (800 g). Elution with 2% methanol in chloroform yielded the pure material (12.5 g, 90%).

I.r. (CCl_4): 3645, 3435, and 3390 (O—H, N—H); 1660 cm^{-1} (acetylamino carbonyl).

Mass spectrum Calcd. for $C_{22}H_{33}O_6N$: *m/e*, 407.2308. Found: 407.2304.

The above material (12.25 g, 0.03 mol) in dry dichloromethane (100 ml) was added over 1 min to a stirred solution of the chromium trioxide – pyridine complex (100.8 g) in dry dichloromethane (2000 ml). The resulting mixture was stirred at room temperature for 20 min. It was then poured into ether (2000 ml) and the precipitate was removed by filtration. The filtrate was evaporated to dryness in high vacuum and the crude product was purified by chromatography on silica gel (1 kg). Elution with 2% methanol in chloroform gave the pure diketone **29***a*. After crystallization from ether the compound melted at 154–156 °C (7.85 g, 65%).

I.r. (KBr pellet): 3390 (N—H); 1740 (five-membered ketone); 1721 (ketone); 1666 cm^{-1} (*N*-acetyl).

N.m.r. ($CDCl_3$): multiplet (3H) τ, 2.9–3.36 (aromatic protons of the anisole ring); doublet (1H) 5.70 (apex proton); singlet (2H) 5.99 (—CO—CH_2—OCH_3); three singlets (3H each) 6.15 (aromatic methoxyl), 6.42 (side chain methoxyl at C_1), 6.57 (primary methoxyl); singlet (3H) 8.03 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{22}H_{29}O_6N$: *m/e*, 403.1995. Found: 403.1995.

Anal. Calcd. for $C_{22}H_{29}O_6N$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.46; H, 6.82; N, 3.37.

Lactamol **30***a*

The diketone **29***a* (4.44 g, 0.011 mol) was dissolved in ethanol (520 ml). Potassium cyanide (3.7 g, 0.056 mol) in water (120 ml) was added and the mixture was heated under reflux for 6 h. Most of the ethanol was then evaporated *in vacuo* and water (100 ml) was added. The mixture was extracted with chloroform (5 × 100 ml), and the combined chloroform extracts were washed with water (2 × 100 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness. The crude product (4.6 g) was crystallized from methanol and gave the pure lactamol **30***a* (4.04 g, 85.5%), m.p. 246.5 °C.

I.r. (KBr pellet): 3450 (hydroxyl), 3345 (acetylamino N—H), 3280 (lactamol N—H), 1700 (five-membered lactam), 1675 cm^{-1} (N—CO—CH_3).

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.87–3.40 (aromatic protons of the anisole ring); singlet (3H) 6.22 (aromatic

methoxyl); singlet (8H) 6.7 (two methoxyls and the protons deshielded by the primary methoxyl); singlet (3H) 8.03 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{23}H_{30}O_6N_2$: *m/e*, 430.2104. Found: 430.2104.

Anal. Calcd. for $C_{23}H_{30}O_6N_2$: C, 64.15; H, 7.02; N, 6.50. Found: C, 64.08; H, 6.82; N, 6.82.

Ketolactam 31a

The crystalline lactamol **30***a* (3.5 g, 0.008 mol) was dissolved in a 1:1 concentrated hydrochloric acid–methanol mixture (200 ml) and the solution was heated under reflux for 24 h. After cooling to room temperature, water (100 ml) was added and the methanol was evaporated *in vacuo*. The aqueous solution was extracted with chloroform (5 × 50 ml), and the chloroform extract was washed with 10% aqueous hydrochloric acid (2 × 50 ml) and with water (2 × 100 ml). The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. The crude product **31***a* crystallized from a chloroform–ether mixture was recrystallized from methanol to a constant melting point of 244–248 °C (463 mg). The mother liquor and the aqueous phase were evaporated to dryness and dissolved in methanol–HCl for further reaction under exactly the same conditions. The yield was 846 mg of **31***a* in the first re-run and 470 mg in the second. The overall conversion into the ketolactam in three successive runs was 1.78 g (60%).

I.r. (KBr pellet): 3190, 3084 (lactam N—H), 1745 (five-membered ketone), 1665 cm^{-1} (six-membered lactam).

N.m.r. ($CDCl_3$): three singlets (3H each) τ 6.24 (aromatic methoxyl), 6.70 (ring A methoxyl), 6.80 (primary methoxyl), singlet (2H) 6.67 p.p.m. (methylenic protons deshielded by primary methoxyl).

Mass spectrum Calcd. for $C_{21}H_{25}O_5N$: *m/e*, 371.1733. Found: 371.1732.

Anal. Calcd. for $C_{21}H_{25}O_5N$: C, 67.92; H, 6.78; N, 3.71. Found: C, 67.72; H, 6.67; N, 3.89.

Hydroxy Amines 32a and 33a

Lithium aluminum hydride (380 mg, 10 mmol) was added to the keto lactam **31***a* (371 mg, 1 mmol) dissolved in dry dioxane (50 ml). After stirring at room temperature for 15 min, the solution was heated under reflux for 3 h. The reaction mixture was cooled, poured into wet ether (300 ml), and a few drops of water were added. The precipitate was removed by filtration and the filtrate was evaporated to dryness. The product was a mixture of the α-hydroxy amine **33***a* and the β-hydroxy amine **32***a*. The two compounds were separated and purified by preparative t.l.c. on neutral alumina, with 10% methanol in chloroform as solvent. The pure α-hydroxy amine **33***a* (157 mg, crystallized from ether–chloroform, m.p. 155–156 °C) and the β-hydroxy amine **32***a* (145 mg, crystallized from methanol, m.p. 196–198 °C) were obtained in an 84% yield.

I.r. (KBr pellet) α-hydroxy amine **33***a*: 3580, 3375, 3160 (N—H, O—H), 1575 cm^{-1} (N—H bending); β-hydroxy amine **32***a*: 3600, 3390, and 3140 (N—H, O—H), 1565 cm^{-1} (N—H bending).

N.m.r. ($CDCl_3$) α-hydroxy amine **33***a*: singlet (3H) τ 6.20 (aromatic methoxyl), singlet (3H) 6.67 (ring A methoxyl at C_1), singlet (2H) 6.84 (protons deshielded by the primary methoxyl), singlet (3H) 6.93 p.p.m. (primary methoxyl); β-hydroxy amine **32***a*: singlet (3H) τ 6.22 (aromatic methoxyl), singlet (5H) 6.68 (ring A methoxyl at C_1 and the protons deshielded by the primary methoxyl), singlet (3H) 6.90 p.p.m. (primary methoxyl).

Mass spectrum Calcd. for $C_{21}H_{29}O_4N$: *m/e*, 359.2097. Found for **32***a*: 359.2090.

Anal. Calcd. for $C_{21}H_{29}O_4N$: C, 70.18; H, 8.13; N, 3.90. Found for **33***a*: C, 70.11; H, 8.08; N, 3.86. Found for **32***a*: C, 70.15; H, 8.08; N, 3.91.

The N-Acetyl Alcohol 35a

The β-hydroxy amine **32***a* (143.6 mg, 0.4 mmol) was dissolved in pyridine (1 ml) and acetic anhydride (1 ml) and the resulting mixture was allowed to stand at room temperature for 24 h. The pyridine and acetic anhydride were evaporated in high vacuum and the residue was dried at 60 °C in high vacuum for 5 h. The *N,O*-diacetyl derivative was obtained in a quantitative yield (175 mg) and it was homogeneous on t.l.c.

I.r. (CCl_4): 1745 (ester), 1645 cm^{-1} (amide).

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.20–3.34 (aromatic protons of the anisole ring), singlet (3H) 6.20 (aromatic methoxyl), doublet (6H) 6.67, 6.70 (ring A methoxyl and the primary methoxyl), singlet (2H) 6.78 (protons deshielded by the primary methoxyl), singlet (3H) 7.84 (N—CO—CH_3), singlet (3H) 7.92 p.p.m. (O—CO—CH_3).

The *N,O*-diacetate (145 mg, 0.35 mmol) was dissolved in 5 ml of methanol and 5 ml of 0.2 *N* aqueous potassium hydroxide were added. The reaction mixture was heated to 50 °C for 2 h. The mixture was then cooled, extracted with chloroform (4 × 10 ml), the chloroform extracts were washed with water (2 × 10 ml), dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo*. Compound **35***a* (130.5 mg, 93%) was recrystallized from ether–chloroform to a m.p. 229–231 °C.

I.r. (CCl_4): 3615, 3400 (O—H), 1640 cm^{-1} (amide).

N.m.r. ($CDCl_3$): singlet (3H) τ 6.20 (aromatic methoxyl); singlet (6H) 6.67 (ring A methoxyl and the primary methoxyl); singlet (2H) 6.78 (protons deshielded by the primary methoxyl); singlet (3H) 7.87 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{23}H_{31}O_5N$: *m/e*, 401.2202. Found: 401.2196.

Compound 36a

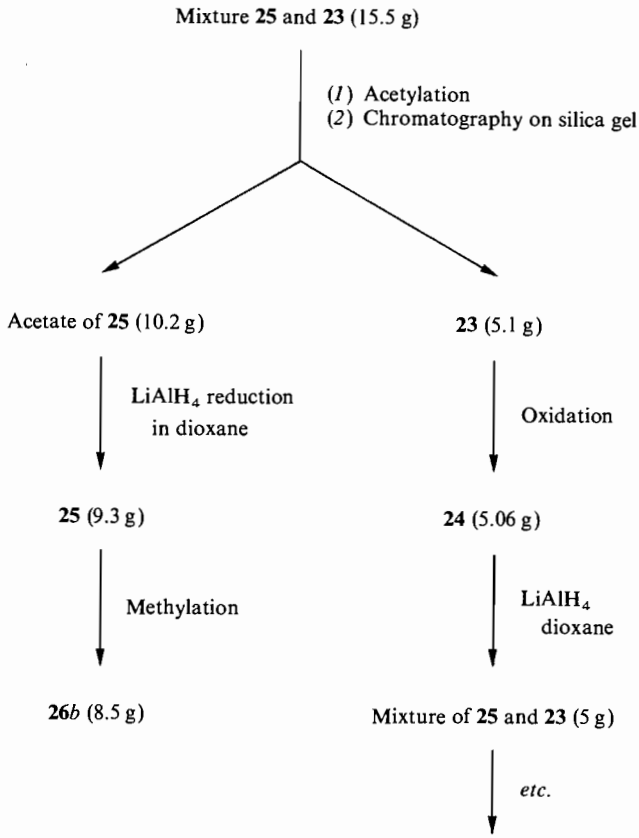
A solution of compound **35***a* (125 mg, 0.31 mmol) and sodium hydride (89.68 mg, 1.86 mmol, 50% mineral oil suspension) in absolute dioxane was heated under reflux for 1 h. The reaction mixture was cooled, methyl iodide (1.5 ml) was added and the mixture was refluxed for another 3 h. The solution was cooled again, the precipitate was removed by filtration through Celite and the filtrate was evaporated to dryness. The crude product was purified by preparative t.l.c. on silica gel (5% methanol in chloroform). The pure compound **36***a* (110 mg, 85%) was crystallized from ether, m.p. 137–139 °C.

I.r. (CCl_4): 1650 cm^{-1} (amide), no hydroxyl absorption.

N.m.r. ($CDCl_3$): singlet (3H) τ 6.21 (aromatic methoxyl), doublet (9H) 6.68, 6.73 (ring A methoxyl, primary methoxyl and ring B methoxyl), singlet (2H) 6.76 (protons deshielded by the primary methoxyl), singlet (3H) 7.86 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{24}H_{33}O_5N$: *m/e*, 415.2359. Found: 415.2351.

Anal. Calcd. for $C_{24}H_{33}O_5N$: C, 69.37; H, 8.01; N, 3.37. Found: C, 69.09; H, 7.83; N, 3.20.



SCHEME 7

Compound 4a

Compound **36***a* (100 mg, 0.24 mmol) was dissolved in acetone (30 ml, distilled over $KMnO_4$) and Jones' reagent was added dropwise to the solution over a period of 6 h. Methanol (1.6 ml) was then added, the mixture was neutralized with 10% aqueous sodium bicarbonate and filtered. The filtrate was partially evaporated, saturated aqueous sodium chloride (15 ml) was added, and the aqueous solution was extracted with chloroform (4 × 15 ml). The chloroform extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by preparative t.l.c. on silica gel (5% methanol in chloroform). The pure *N*-acetyl ketone **4***a* (86.5 mg, 84%) was crystallized from ether to a m.p. 174–177 °C.

I.r. (CCl_4): 1690 (conjugated ketone), 1655 cm^{-1} (amide).

N.m.r. ($CDCl_3$): doublet (1H) τ 2.05 (aromatic proton deshielded by the benzylic ketone), multiplet (2H) 2.66–3.06 (aromatic protons), singlet (3H) 6.13 (aromatic methoxyl), doublet (11H) 6.68, 6.73 (three methoxyls and methylene protons deshielded by the primary methoxyl), singlet (3H) 7.90 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{24}H_{31}O_6N$: *m/e*, 429.2151. Found: 429.2141.

Anal. Calcd. for $C_{24}H_{31}O_6N$: C, 67.11; H, 7.28; N, 3.26. Found: C, 66.97; H, 7.23; N, 3.68.

Ketone 24

The Grignard alcohol **23** (30 g, 0.052 mol) dissolved in acetone (1.5 l, distilled over potassium permanganate) was cooled in an ice bath. Jones' reagent (18 ml) was added dropwise over a period of 15 min. After 10 min stirring, methanol (10 ml) was added to destroy the excess of Jones' reagent. The inorganic precipitate was removed by filtration and the filtrate was neutralized with 10% aqueous sodium bicarbonate. Most of the acetone was evaporated under reduced pressure, water (500 ml) was added, and the solution was extracted with chloroform (4 × 400 ml). The chloroform extracts were washed with water (2 × 400 ml), dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. The ketone **24** (28 g, 94%) was homogeneous on t.l.c.

I.r. ($CHCl_3$): 1700 cm^{-1} (C=O), no hydroxyl absorption.

N.m.r. ($CDCl_3$): singlet (10H) τ 2.70 (aromatic protons of two benzyl groups); two singlets (2H each) 5.40, 5.53 (protons of two benzylic methylene groups); broad singlet (4H) 6.03 (ketal methylene protons), two singlets (3H each) 6.33 (aromatic methoxyl); 6.66 p.p.m. (primary methoxyl).

Mass spectrum Calcd. for $C_{35}H_{40}O_7$: *m/e*, 572.2774. Found: 572.2766.

Reduction of the Ketone 24

The ketone **24** (28 g, 0.049 mol) in absolute dioxane

(200 ml) was added dropwise to a suspension of lithium aluminum hydride (11 g, 0.24 mol) in absolute dioxane (2000 ml) which had been preheated to 90 °C. The reaction mixture was stirred at 90 °C for 1 h, cooled, and poured into wet ether (2000 ml, saturated with water). The inorganic precipitate was removed by filtration and the filtrate was evaporated under reduced pressure to dryness. The mixture (27.2 g, 97%) of alcohols **25** and **23** was homogeneous on t.l.c. and it was shown in the next methylation step to be in a ratio of 7:3.

I.r. (CCl_4): 3550 cm^{-1} (hydroxyl).

N.m.r. (CCl_4): singlet (10H) τ 2.70 (aromatic protons of the two benzyl groups); multiplet (3H) 2.80–3.40 (aromatic protons of the anisole ring); two singlets (2H each) 5.38, 5.52 (four benzylic methylene protons); multiplet (4H) centered at 6.07 (ketal methylene protons); two singlets (3H each) 6.32 (aromatic methoxyl), 6.67 p.p.m. (primary methoxyl).

Methylation of Alcohols ***25*** *and* ***23***

The mixture of the alcohols **25** and **23** (25.8 g, 0.045 mol) was methylated under the same conditions used in the preparation of compound **26***a*. Work-up and chromatography on silica gel (1.5 kg, elution with 10–15% ether in benzene) gave compound **26***b* (17.5 g) (larger R_f) and compound **26***a* (7.7 g) (smaller R_f) in an overall yield of 95%.

I.r. (CCl_4): no hydroxyl absorption.

N.m.r. ($CDCl_3$): (for compound **26***b*) singlet (10H) τ 2.69 (aromatic protons of the two benzyl groups); multiplet (3H) 2.50–3.50 (aromatic protons of the anisole ring); doublet (2H) 5.39 (benzylic methylene protons); singlet (2H) 5.51 (benzylic methylene protons); multiplet (4H) centered at 6.10 (ketal methylene protons); three singlets (3H each) 6.29 (aromatic methoxyl), 6.47 (side chain methoxyl at C_1), 6.67 (primary methoxyl); singlet (2H) 6.55 p.p.m. (methylenic protons deshielded by the primary methoxyl).

Mass spectrum (**26***b*) Calcd. for $C_{36}H_{44}O_7$: *m/e*, 588.3075. Found: 588.3086.

Compound **26***b* was also obtained by the method shown in Scheme 7. While this process increased the stereoselectivity of the preparation of **26***b*, we have used the simpler less stereoselective method described in detail to supply large amounts of material with less effort.

Ketone ***27b***

Compound **26***b* (17.5 g, 0.03 mol) was deketalized under the same conditions used in the preparation of compound **27***a*. Work-up gave the ketone **27***b* (16.2 g) in a quantitative yield.

I.r. (CCl_4): 1755 cm^{-1} (ketone).

N.m.r. ($CDCl_3$): two singlets (5H each) τ 2.68, 2.70 (aromatic protons of the two benzyl groups); two singlets (2H each) 5.40 and 5.52 (benzylic methylene protons); three singlets (3H each) 6.27 (aromatic methoxyl); 6.48 (side chain methoxyl at C_1); 6.64 p.p.m. (primary methoxyl).

Mass spectrum Calcd. for $C_{34}H_{40}O_6$: *m/e*, 544. Found: 544.

Diketone ***29b***

The ketone **27***b* (16.2 g, 0.03 mol) was dissolved in 70 ml of methanol and subjected to reductive amination under the same conditions which were used in the preparation of compound **29***a*. Work-up gave the crude amine **28***b* (16 g, 97%) which was used without purification for the subsequent step.

I.r. (CCl_4): 3400 cm^{-1} (N—H); no carbonyl absorption.

N.m.r. ($CDCl_3$): two singlets (5H each) τ 2.63 and 2.66 (aromatic protons of the two benzyl groups); multiplet (3H) 2.40–3.50 (aromatic protons of the anisole ring); doublet (2H) centered at 5.41 (benzylic methylene protons); singlet (2H) 5.52 (benzylic methylene protons); three singlets (3H each) 6.28, 6.47, and 6.66 p.p.m. (three methoxyls).

The crude amine **28***b* (16 g, 0.029 mol) was acetylated under the same conditions used in the preparation of compound **29***a*. Work-up gave the *N*-acetyl derivative (16.4 g, 96%) which was homogeneous on t.l.c. and was used without further purification for the subsequent step.

I.r. (CCl_4): 3400 (N—H), 1675 cm^{-1} (N—CO—CH_3).

N.m.r. ($CDCl_3$): multiplet (13H) τ 2.40–2.70 (aromatic protons of the two benzyl groups and the anisole ring); doublet (1H) centered at 3.64 (—HN—CO—); doublet (2H) centered at 5.40 (benzylic methylene protons); singlet (2H) 5.50 (benzylic methylene protons); three singlets (3H each) 6.30, 6.47, and 6.64 (three methoxyls); singlet 8.05 (N—CO—CH_3 of the *anti*-epimer); singlet at 8.19 p.p.m. (N—CO—CH_3 of the *syn*-epimer).

The above material (16 g, 0.027 mol) was subjected to hydrogenolysis under the same conditions used in the "a" series. Work-up and chromatography on silica gel (600 g, 2% methanol in chloroform) gave the corresponding diol (10.1 g, 92%).

I.r. (CCl_4): 3400 (O—H, N—H), 1655 cm^{-1} (N—CO—CH_3).

N.m.r. ($CDCl_3$): multiplet (3H) τ 3.00–3.50 (aromatic protons of the anisole ring); two singlets (3H each) 6.26 and 6.48 (two methoxyls); singlet (5H) 6.63 (methoxyl and the protons deshielded by the primary methoxyl); singlet 7.95 (N—CO—CH_3 of the *anti*-epimer); singlet 8.15 p.p.m. (N—CO—CH_3 of the *syn*-epimer).

Mass spectrum Calcd. for $C_{22}H_{33}O_6N$: *m/e*, 407.2308. Found: 407.2313.

The above diol (9.8 g, 0.024 mol) was oxidized with the chromium trioxide – pyridine complex under the same conditions used in the preparation of the diketone **29***a*. Work-up gave the crude product which was purified by chromatography on silica gel (1 kg). Elution with 2% methanol in chloroform gave the pure diketone **29***b* which was crystallized from benzene–ether to a constant m.p. of 100–102 °C (6.5 g, 58%).

I.r. (KBr pellet): 3600–3300 (N—H), 1745 (five-membered ketone), 1720 (side chain ketone), 1660 cm^{-1} (N—CO—CH_3).

N.m.r. ($CDCl_3$): doublet (1H) centered at τ 2.47 (—NH—CO—); multiplet (3H) 2.90–3.30 (aromatic protons of the anisole ring); singlet (2H) 5.93 (—CO—CH_2—OCH_3); three singlets (3H each) 6.23, 6.51, and 6.56 (3—OCH_3); singlet (3H) 7.92 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{22}H_{29}O_6N$: *m/e*, 403.1995. Found: 403.1990.

Anal. Calcd. for $C_{22}H_{29}O_6N$: C, 65.49; H, 7.24; N, 3.47. Found: C, 65.03; H, 7.08; N, 3.34.

Lactamol ***30b***

The diketone **29***b* (4.068 g, 0.010 mol) was converted to the lactamol **30***b* under the same conditions used in the preparation of the lactamol **30***a*. Work-up of the reaction mixture gave 4.2 g of crude product which was crystallized from chloroform–ether to a constant m.p. of 235–238 °C (3.85 g, 90%).

I.r. (KBr pellet): 3550–3200 (O—H, N—H), 1720 (five-membered lactam), 1665 cm^{-1} (N—CO—CH_3).

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.80–3.40 (aromatic protons); three singlets (3H each) 6.18, 6.60, and 6.67 (3 —OCH_3); singlet (3H) 8.07 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{23}H_{30}O_6N_2$: *m/e*, 430.2104. Found: 430.2100.

Anal. Calcd. for $C_{23}H_{30}O_6N_2$: C, 64.15; H, 7.02; N, 6.50. Found: C, 64.08; H, 6.94; N, 6.82.

Keto Lactam 31b

The pure lactamol **30***b* (3.44 g, 0.008 mol) was subjected to an acid-catalyzed cyclization under the same conditions used in the preparation of the ketolactam **31***a*. Work-up and crystallization in the same manner gave the pure ketolactam **31***b*, m.p. 266–268 °C (3.32 g) in a yield of 64%.

I.r. (KBr pellet): 3455 and 3335 (N—H), 1738 (ketone), 1670 cm^{-1} (lactam).

N.m.r. ($CDCl_3$): multiplet (3H) τ 3.00–3.50 (aromatic protons); three singlets (3H each) 6.20, 6.57, and 6.63 p.p.m. (3 —OCH_3).

Mass spectrum Calcd. for $C_{21}H_{25}O_5N$: *m/e*, 371.1733. Found: 371.1736.

Anal. Calcd. for $C_{21}H_{25}O_5N$: C, 67.92; H, 6.78; N, 3.71. Found: C, 67.62; H, 6.67; N, 3.89.

The Hydroxy Amines 32b and 33b

The pure ketolactam **31***b* (1.484 g, 0.004 mol) was converted to the hydroxy amines **32***b* and **33***b* by exactly the same procedure used in the "a" series. Crystallization of the crude products from methanol gave the pure crystalline β-hydroxy amine **32***b* (442 mg). The mother liquor was purified by chromatography on neutral alumina (120 g). Elution with chloroform gave the oily α-hydroxy amine **33***b* (610 mg) and more of the β-hydroxy amine (150 mg), which was recrystallized from methanol to a constant melting point of 226–228 °C. The overall yield of recrystallized β-hydroxy amine was 625 mg.

I.r. ($CHCl_3$) α-hydroxy amine **33***b*: 3600–3400 cm^{-1} (N—H, O—H); β-hydroxy amine **32***b*: 3500–3320 cm^{-1} (N—H, O—H).

N.m.r. ($CDCl_3$) α-hydroxy amine **33***b*: singlet (3H) τ 6.22 (aromatic methoxyl); doublet (6H) 6.66, 6.70 (ring A methoxyl and primary methoxyl); singlet (2H) 6.87 p.p.m. (protons deshielded by the primary methoxyl); β-hydroxy amine **32***b*: singlet (3H) τ 6.28 (aromatic methoxyl); singlet (8H) 6.70 p.p.m. (two methoxyls and protons deshielded by the primary methoxyl).

Mass spectrum Calcd. for $C_{21}H_{29}O_4N$: *m/e*, 359. Found for α-hydroxy amine **33***b*: 359. Found for β-hydroxy amine **32***b*: 359.

Anal. Calcd. for $C_{21}H_{29}O_4N$ **32***b*: C, 70.18; H, 8.13; N, 3.90. Found: C, 70.29; H, 8.23; N, 3.90.

The N-Acetyl-β-alcohol 35b

Compound **32***b* (359 mg, 1 mmol) was acetylated with acetic anhydride (2.5 ml) and pyridine (2.5 ml) as in the "a" series. The *N*-acetyl-β-acetate was obtained in a quantitative yield (441 mg).

I.r. (CCl_4): 1745 (—O—CO—CH_3), 1645 cm^{-1} (N—CO—CH_3).

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.80–3.40 (aromatic protons); singlet (3H) 6.20 (aromatic methoxyl); singlet (8H) 6.72 (two methoxyls and the protons deshielded by the primary methoxyl); singlet (3H) 7.87 (N—CO—CH_3); singlet (3H) 7.95 p.p.m. (O—CO—CH_3).

The above material (400 mg, 0.9 mmol) was saponified exactly as in the "a" series. The *N*-acetyl-β-alcohol **35***b* (350 mg, 95%) was crystallized from ether to a m.p. of 182–183 °C.

I.r. (CCl_4): 3600–3200 (O—H), 1620 and 1645 cm^{-1} (N—CO—CH_3).

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.87–3.30 p.p.m. (aromatic protons); singlet (3H) 6.20 (aromatic methoxyl); doublet (8H) 6.67, 6.72 (two methoxyls and the protons deshielded by the primary methoxyl); singlet (3H) 7.85 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{23}H_{31}O_5N$: *m/e*, 401.2202. Found: 401.2298.

Anal. Calcd. for $C_{23}H_{31}O_5N$: C, 68.82; H, 7.78; N, 3.47. Found: C, 69.02; H, 7.84; N, 3.75.

Compound 36b

The alcohol **35***b* (200 mg, 0.5 mmol) was methylated exactly as in the "a" series. Crystallization from hexane–ether gave compound **36***b* which melted at 155–157 °C in a yield of 87%.

I.r. (CCl_4): no hydroxyl absorption; 1640 cm^{-1} (N—CO—CH_3).

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.89–3.33 (aromatic protons); singlet (3H) 6.20 (aromatic methoxyl); singlet (11H) 6.70 (three methoxyls and protons deshielded by the primary methoxyl); singlet (3H) 7.87 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{24}H_{33}O_5N$: *m/e*, 415.2359. Found: 415.2358.

Anal. Calcd. for $C_{24}H_{33}O_5N$: C, 69.37; H, 8.01; N, 3.37. Found: C, 69.39; H, 8.00; N, 3.39.

Compound 4b

The above material (120 mg, 0.29 mmol) was oxidized exactly as in the "a" series. Crystallization from *n*-hexane–ether gave compound **4***b* which melted at 188–190 °C in a yield of 89%.

I.r. (CCl_4): 1685 (ketone); 1650 cm^{-1} (N—CO—CH_3).

N.m.r. ($CDCl_3$): doublet (1H) τ 2.00 (aromatic proton deshielded by the benzylic ketone); multiplet (2H) 2.90–3.20 (aromatic protons); singlet (3H) 6.11 (aromatic methoxyl); doublet (11H) 6.70–6.72 (three methoxyls and protons deshielded by the primary methoxyl); singlet (3H) 7.90 p.p.m. (N—CO—CH_3).

Mass spectrum Calcd. for $C_{24}H_{31}O_6N$: *m/e*, 429.2151. Found: 429.2151.

Anal. Calcd. for $C_{24}H_{31}O_6N$: C, 67.11; H, 7.28; N, 3.26. Found: C, 67.17; H, 7.37; N, 3.66.

The Amino Ketone 34b

Concentrated hydrochloric acid (five drops) was added to the α-hydroxy amine **33***b* (30 mg, 0.084 mol) in 5 ml of methanol and the solution was evaporated to dryness *in vacuo*. The residue was redissolved in acetone (25 ml, distilled over potassium permanganate) and cooled in an ice-water bath for 10 min. A slight excess of Jones' reagent was added and the solution was stirred for 10 min. Saturated aqueous sodium chloride (20 ml) was added, the solution was basified with bicarbonate and extracted with chloroform (3 × 10 ml). The chloroform extracts were washed with water (1 × 10 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The amino ketone **34***b* (29 mg) which

was homogeneous in t.l.c. was obtained in a quantitative yield.

I.r. (CCl_4): 1740 cm^{-1} (ketone).

N.m.r. (CCl_4): multiplet (3H) τ 3.00–3.50 (aromatic protons); two singlets (3H each) 6.27 and 6.61 (2 —OCH_3), singlet (5H) 6.74 p.p.m. (OCH_3 and protons deshielded by the primary methoxyl).

Mass spectrum Calcd. for $C_{21}H_{27}O_4N$: *m/e*, 357. Found: 357.

Hydroxy Amines 32b and 33b from the Amino Ketone 34b

Sodium (about 20 mg) was added in 0.5 h intervals to the amino ketone **34***b* (29 mg, 0.084 mmol) in refluxing absolute ethanol (2 ml). After 4 h under reflux, methanol (1 ml) was added followed by water (8 ml). The solution was extracted with chloroform (4 × 10 ml), and the combined chloroform extracts were washed with water (2 × 10 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The crude hydroxy amines were separated by preparative t.l.c. on silica gel (12% methanol in chloroform) to yield pure **33***b* (6.5 mg) and **32***b* (15.3 mg) in a ratio of 3:7.

Both materials were identical (m.p., i.r., and mass spectra) with the samples described above.

The Tertiary Amine 37b

Sodium hydride (202 mg, 4.2 mmol) was added to the solution of compound **32***b* (250 mg, 0.7 mmol) in absolute dioxane (50 ml) and the mixture was heated under reflux for 1 h. Methyl iodide (1 ml) was added and reflux was continued for another 3 h. The reaction mixture was cooled and filtered through Celite. The filtrate was evaporated to dryness, chloroform (50 ml) was added, and the solution was washed with water (3 × 20 ml). The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness to yield the crude methylated compound **37***b*. The crude product was purified by chromatography on silica gel (2% methanol in chloroform) and the pure tertiary amine **37***b* (260.5 mg) was obtained in a yield of 96%.

I.r. (CCl_4): no N—H and O—H absorption.

N.m.r. ($CDCl_3$): multiplet (3H) τ 2.90–3.40 (aromatic protons); four singlets (3H each) 6.23, 6.68, 6.73, and 6.77 (4 —OCH_3); singlet (3H) (7.73 p.p.m. (—N—CH_3).

Mass spectrum Calcd. for $C_{23}H_{33}O_4N$: *m/e*, 387.2410. Found: 387.2405.

The N-Formyl Compound 38b

A solution of the tertiary amine **37***b* (200 mg, 0.52 mmol) and potassium permanganate (200 mg) in acetone (40 ml, distilled over permanganate) and acetic acid (2 ml) was stirred at room temperature for 24 h. The precipitate was removed by filtration and washed thoroughly with chloroform. The filtrate was evaporated to dryness *in vacuo*, chloroform (50 ml) was added, and washed with water (2 × 30 ml), dried over anhydrous sodium sulfate, and evaporated to dryness. The crude product was purified by preparative t.l.c. on silica gel (5% methanol in chloroform) to give the pure *N*-formyl compound **38***b* (198 mg) which was crystallized from ether (m.p. 158–160 °C).

I.r. (CCl_4): 1662 cm^{-1} (—N—CH=O).

N.m.r. ($CDCl_3$): broad singlet (1H) τ 2.17 (—N—CH=O); multiplet (3H) 3.00–3.50 (aromatic protons); singlet (3H) 6.26 (aromatic —OCH_3); broad singlet (11H) 6.77 p.p.m. (3 —OCH_3 and protons deshielded by the primary —O—CH_3).

Mass spectrum Calcd. for $C_{23}H_{31}O_5N$: *m/e*, 401.2202. Found: 401.2200.

Anal. Calcd. for $C_{23}H_{31}O_5N$: C, 68.81; H, 7.78; N, 3.49. Found: C, 68.72; H, 7.69; N, 3.40.

The N-Formyl Ketone 2b

Compound **38***b* (180 mg, 0.45 mmol) was dissolved in acetone (50 ml, distilled over potassium permanganate). Jones' reagent was added dropwise over a period of 6 h. The reaction mixture was stirred at room temperature and a slight excess of the Jones' reagent was maintained during the entire period. A few drops of methanol were added and the precipitate was removed by filtration. Saturated aqueous sodium chloride (50 ml) was added to the filtrate and the solution was extracted with chloroform (3 × 40 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by t.l.c. on silica gel (5% methanol in chloroform) to yield the pure *N*-formyl ketone **2***b* (120 mg, 67%) which was identical with the corresponding derivative obtained from delphinine by i.r., n.m.r., and mass spectra. Identity was also established by t.l.c. in several systems.

I.r. (CCl_4): 1690 (—N—CH=O); 1655 cm^{-1} (ketone).

N.m.r. ($CDCl_3$): singlet (1H) τ 1.93 (N—CH=O); doublet (1H) centered at 1.96 (aromatic proton deshielded by the benzylic ketone); multiplet (2H) 3.00–3.50 (aromatic protons); four singlets (3H each) 6.12, 6.72, 6.74, and 6.77 p.p.m. (4 OCH_3).

Mass spectrum Calcd. for $C_{23}H_{29}O_6N$: *m/e*, 415.1995. Found: 415.1995.

Direct Conversion of Compound 37b to the N-Formyl Ketone 2b

A mixture of compound **37***b* (25 mg, 0.064 mmol) and potassium permanganate (250 mg) in acetone (15 ml, distilled over potassium permanganate) and acetic acid (0.75 ml) was stirred at room temperature for 5 days. Acetone (10 ml) was added and the precipitate was removed by filtration. The filtrate was evaporated to dryness *in vacuo*, the residue dissolved in chloroform (30 ml) and washed with water (2 × 10 ml). The chloroform was dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was purified by preparative t.l.c. on silica gel (5% methanol in chloroform) to yield the *N*-formyl ketone **2***b* (21 mg, 82%) which was identical by its i.r., n.m.r., and mass spectra with the material obtained via the compound **38***b*.

The Amino Ketone 3b

The *N*-formyl ketone **2***b* (100 mg, 0.24 mmol) dissolved in a 1:9 concentrated hydrochloric acid methanol solution (30 ml) was heated under reflux for 24 h. The solution was evaporated to dryness, taken up in 5% sodium bicarbonate (20 ml), and extracted with chloroform (4 × 20 ml). The chloroform extracts were dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The crude product (98 mg) was crystallized from ether to yield 72 mg of the pure amino ketone **3***b* (m.p. 176 °C). The mother liquor was purified by preparative t.l.c. on silica gel (5% methanol in chloroform) and gave another 19 mg of the amino ketone. This material was identical with the delphinine degradation product of the same structure by i.r., n.m.r., and mass spectroscopy and t.l.c. in several systems.

I.r. (CCl_4): 3400–3200 (N—H); 1683 cm^{-1} (ketone).

N.m.r. ($CDCl_3$): doublet (1H) centered at τ 2.04 (aro-

matic proton deshielded by the conjugated ketone); multiplet (2H) 2.80–3.30 (aromatic protons); four singlets (3H each) at 6.11, 6.68, 6.70, and 6.73 (4 —OCH_3).

Mass spectrum Calcd. for $C_{22}H_{29}O_5N$: *m/e*, 387.2046. Found: 387.2040.

Anal. Calcd. for $C_{22}H_{29}O_5N$: C, 68.19; H, 7.54; N, 3.62. Found: C, 68.22; H, 7.37; N, 3.68.

Resolution of 3b

The synthetic racemic ketone **3b** (125 mg, 0.32 mmol) was dissolved in absolute pyridine and the solution was cooled in an ice-water bath. L-camphor–sulfonyl chloride (69.7 mg, 0.32 mmol) was added and the solution was allowed to stand overnight. Water (0.5 ml) was added and the mixture was stirred for 0.5 h. The mixture was then evaporated to dryness and the products were separated and purified by preparative t.l.c. on silica gel (5% methanol in chloroform) to give 78 mg of sulfonamide and 56 mg of the unreacted amino ketone. This last material (56 mg) was dissolved in ether, a large excess of oxalic acid in ether was added, and the oxalate precipitated. The mixture was kept in the refrigerator overnight, and the ethereal solution was decanted. The oxalate was recrystallized from methanol ether five times until a constant m.p. of 195–196 °C was reached (34 mg). The resolved synthetic oxalate and the corresponding oxalate derived from the degradation of delphinine were compared as follows: (*1*) melting ranges (°C) 195–196 synthetic, 194–196 "natural", 194–196 mixture; (*2*) identical i.r. spectra in KBr and in $CHCl_3$; (*3*) identical optical rotatory dispersion curves, $[\alpha]^{26}_{295} = +1 \times 10^5$, $[\alpha]^{26}_{250} = -7 \times 10^4$.

Anal. Calcd. for $C_{24}H_{31}O_9N$: C, 60.36; H, 6.54; N, 2.93. Found: C, 60.38; H, 6.57; N, 2.82.

Synthetic Optically Active 3b Free Base

The optically active oxalate (28 mg) was dissolved in chloroform (2 ml) and passed through a short column of basic alumina (1 g). The free amine was obtained by eluting the column with 5% methanol in chloroform (50 ml). After evaporation *in vacuo* to dryness, absolute ether (1.5 ml) was added, and the mixture was kept in the refrigerator for 4 days. The mother liquor was removed by a pipette and the crystals were washed with ether and dried in high vacuum. The crystalline free base **3b** was recrystallized to a constant m.p. of 144.5 °C from ether.

Identity with compound **3b** prepared from delphinine was established as follows: (*1*) m.p. (°C) 144.5 synthetic, 143 "natural", 144 mixture; (*2*) identical i.r. (KBr and $CHCl_3$) spectra; (*3*) identical mass spectra; (*4*) identical n.m.r. spectra; (*5*) identical R_f in several t.l.c. systems.

Mass spectrum Calcd. for $C_{22}H_{29}O_5N$: *m/e*, 387.2040. Found: 387.2046.

Racemic Oxalate of 3b for X-Ray Analysis

The synthetic racemic compound **3b** (58 mg) was converted to the racemic oxalate by treating with a large excess of oxalic acid under the same conditions which were employed for the preparation of the optically active oxalate **3b**.

The salt was recrystallized from ether–methanol until a constant melting point (189–193 °C) was reached (32 mg).

Anal. Calcd. for $C_{24}H_{31}O_9N$: C, 60.36; H, 6.54; N, 2.93. Found: C, 60.52; H, 6.45; N, 2.90.

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