TOTAL SYNTHESIS OF DELPHININE-TYPE ALKALOIDS BY SIMPLE, FOURTH GENERATION METHODS

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Abstract - A direct fully stereo- and regiospecific synthesis of crystalline racemic 13-desoxydelphonine from o-cresol is described.

INTRODUCTION

Some fourteen years ago my students and I have set ourselves the objective to develop relatively simple, fully regio- and stereospecific methods for the synthesis of the aconite alkaloids. We wished to achieve the highest degree of simplicity and efficiency by developing a synthetic strategy in which all the many functional groups of the aconite system would materialize in the correct positions and configurations simultaneously with the construction of the skeleton.

This objective has now been reached and I wish to report in this Lecture on the final form of our synthetic method.

However, more important than the conquest of the aconite alkaloids is the process by which an efficient synthesis of these polycyclic polybridged and polysubstituted natural products was systematically developed. This process may in principle be applied to any complex natural product and I would like to believe that our approach might constitute the first small step in the development of a new area of chemical engineering--synthetic engineering.

It is clear that just like the structure determination of natural products is no longer very interesting for academic organic chemists--the crystal-lographers do this now equally well and much faster--academic chemists will soon also cease to be interested in total synthesis. But the craft must not be lost! On the contrary, it must develop in the direction of practical usefulness, i.e., simplicity and efficiency, so that any complex organic compound if sufficiently important and inaccessible from natural sources could be produced in industry by total synthesis. In other words, the art of synthesis must develop into synthetic engineering. The technique which we used in the search for simplicity and efficiency is a common one in engineering. The key reactions of a first generation synthetic design were tested and modified on model compounds and then the synthesis proper was carried out. On the basis of the experience gained and the accidental discoveries made in the first generation synthesis, a second generation synthetic design was worked out, tested on models and carried out and the process then repeated. Thus, we have reached now the fourth and final generation which, as can be judged from the sequel, attains to a high degree the objectives and standards that we have initially set for ourselves (1).

An additional advantage that we have derived from our preliminary studies were the proton magnetic resonance (p.m.r.) spectra of the various model intermediates. These served us as a reliable and precise simulation of the corresponding p.m.r. patterns in the synthesis proper and helped us to recognize the various synthetic intermediates without a shadow of doubt.

THE SYNTHESIS OF THE POLYSUBSTITUTED DELPHININE SYSTEM

The final form of the synthetic strategy (2) which we have gradually evolved
by the technique described in the Introduction is portrayed in Scheme 1. It
starts with the stereo- and regiospecific synthesis of the "aromatic inter-
mediate" (1) by our aziridine rearrangement method--a common feature of most
of our synthetic work in this area (cf. 1). Conversion of compound (1) into
the masked o-quinone (2) followed by a stereospecific addition of benzyl-
vinyl ether yields the substituted nordenudatine intermediate (3) (see
Note a).

The functional group system of the adduct (3) is first simply and stereo-
specifically adjusted and the intermediate (4) is subjected to a Wagner
rearrangement which yields the "pyro-oxo" derivative (5). A further simple
adjustment of functionality finally gives the aconite alkaloid (6). It
should be noted that the Wagner rearrangement which is required to change
the nordenudatine skeleton of (4) to the delphinine system of the final
product (6) brings about automatically the desired redistribution of the
substitution pattern. The approach is in fact a variant of our first
chasmanine synthesis (3) which we completed a year ago. It achieves,

SCHEME 1

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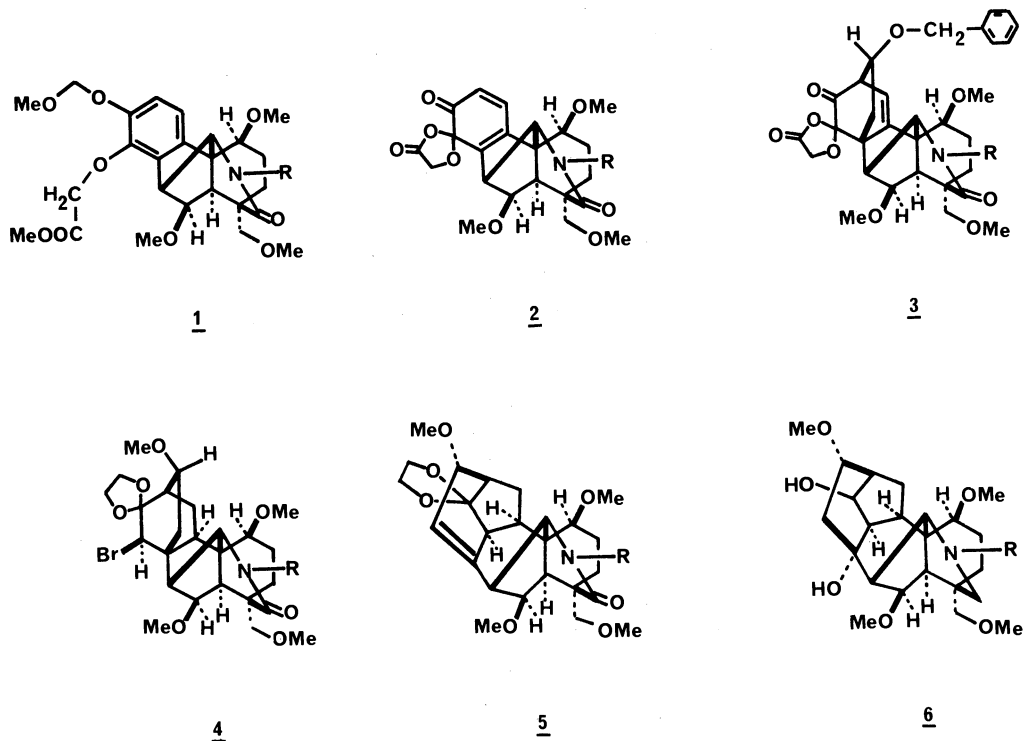
Note a. The exo-stereospecificity of the Diels-Alder addition to the
system (2) has been known to us for some time since we tested it on several
models (cf. 1). It is probably explainable by the operation of the same
factors which determine the preferential exo-reactivity of the benzo-
bicycloheptene system in ionic reactions whatever these factors may be.

however, much more closely our initial objective, being more than ten steps
shorter and an order of magnitude more efficient.

CONSTRUCTION OF THE AROMATIC INTERMEDIATE

As starting material for the preferred route to the aromatic intermediate
(1) we have chosen o-cresol (4). The methyl group of this compound may be
converted in high yield to a phenol at a point in the synthesis when the
electron releasing properties of the phenolic group can no longer affect
adversely the course of the crucial aziridine rearrangement. This we found
is simpler and more efficient than the other two alternatives, i.e., the
introduction of the second phenolic group at the end of the synthesis or its
presence in the starting material. This second possibility requires
mesylation of the phenol prior to the aziridine rearrangement and a dif-
ferent protection during some of the other steps.

The cresol (7) was simply converted to the indanone (9) via the β-chloro-
propionyl ester (8) by the procedure of S. Wagatsuma (5). Methylation of
(9) with dimethyl sulfate and potassium carbonate in acetone yielded the
methoxy derivative (10), which was transformed into the enol ether (11).
This last operation was carried out in two steps. The indanone (10) was
first converted into the corresponding dimethylacetal in methanol and
trimethyl orthoformate in the presence of the acidic ion exchanger Rexyn 101.
Pyrolytic elimination of methanol from the dimethylacetal in refluxing
o-xylene completed the preparation of the enol ether (11).

SCHEME 2
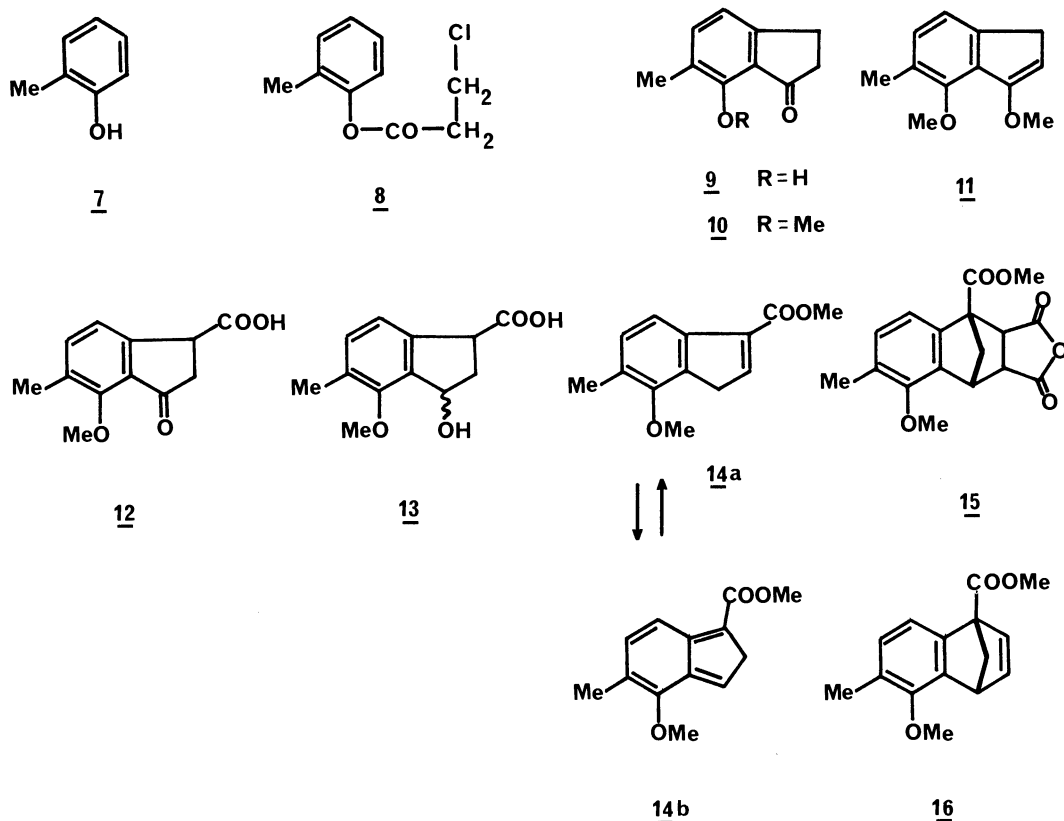
Compound (11) was now carboxylated in tetrahydrofuran at -70°C with n-butyl
lithium and carbon dioxide gas; hydrolysis of the enol ether group on work
up gave the crystalline keto acid (12). The keto group of (12) was reduced
with sodium borohydride and the product (13) was heated under reflux with
phosphoric acid in dioxane. The elimination of the hydroxyl was followed
by a shift of the double bond and the resulting indene acid was esterified
with methanolic hydrogen chloride to the ester (14a).

Compound (14a) is in a thermal equilibrium with the o-quinonoid tautomer
(14b) and as a consequence it adds maleic anhydride quantitatively and
yields the adduct (15). Finally, decarboxylation of this last product by
the method of Trost (6) gave the tricyclic olefin (16) in a yield of 85%.

I have reviewed the transformation of the indanone (10) to the tricyclic
compound (16) only briefly since the process is quite similar to our
previous work in the total synthesis of napelline (7) and chasmanine (8).

The tricyclic compound (16) was next converted to the acetylaziridine (17)
by treatment with trimethyl silyl azide followed by acetic acid and acetic
anhydride. The aziridine was not isolated, but it was rearranged in situ
by several days heating under nitrogen to 85°C. The product of the stereo-
and regiospecific aziridine rearrangement (18) was purified by crystalliza-
tion and it was obtained in a yield of 70%. The mechanism of the rearrange-
ment is portrayed by the arrows in formula (17). Its complete regio-
specificity is due to the aromatic methoxyl, which increases the migratory
aptitude of the bond in the ortho position and to the ester carbonyl,
which makes the competing rearrangement more difficult. This last process
is initiated by the opening of the other aziridine carbon-nitrogen bond
and it requires the transient development of a positive charge on the carbon
α to the carbonyl group--a situation well known to be energetically
unfavourable.

In all of our previous work (1) we have been using benzenesulfonyl
aziridines rather than acetylaziridines at a similar stage of the synthesis.
This led to some complications and additional steps, but we were unable to
prepare efficiently the required acetylaziridines prior to the development
of the trimethyl silyl azide method (9).

The rearrangement product (18) was oxidized in aqueous acetic acid with
ceric ammonium nitrate at room temperature and the aldehyde (19) was
obtained in a yield of 75% after crystallization. Methanolysis of (19) in
the presence of potassium carbonate yielded the alcohol (20) which was
benzylated in dichloromethane with benzyl chloride and potassium carbonate
to the benzyl ether (21).

Finally, the aldehyde group in (21) was degraded with m-chloroperbenzoic
acid in dichloromethane and the resulting unstable formate ester (22) was
immediately methanolyzed in the presence of potassium carbonate to the
crystalline phenol (23). The overall yield of the two steps was 96%.

The high yield of these operations shows clearly that in suitable situations
an aromatic methyl group may be used with advantage as a "stand-in" for a
phenol. In our case the substitution of an aromatic hydrogen for a phenolic
group at the end of the synthesis and the presence of a suitably blocked
phenol in the starting material were both tried and found inferior to the·
method just described. The second possibility suffers from the disadvantage
that different blocking groups are required at various stages of the
synthesis (cf. 4).

The phenolic group of compound (23) was finally blocked by alkylation
with chloromethyl-methyl ether and the product (24) was obtained in a yield
of 93%. It still required the transformation of the carbomethoxyl to an
aldehyde group, which was accomplished by reduction with lithium borohydride,
followed by reoxidation of the resulting primary alcohol with dimethyl
sulfoxide and dicyclohexylcarbodiimide. The overall yield of these trans-
formations was 86% and the synthon (25) was ready for the annelation of the
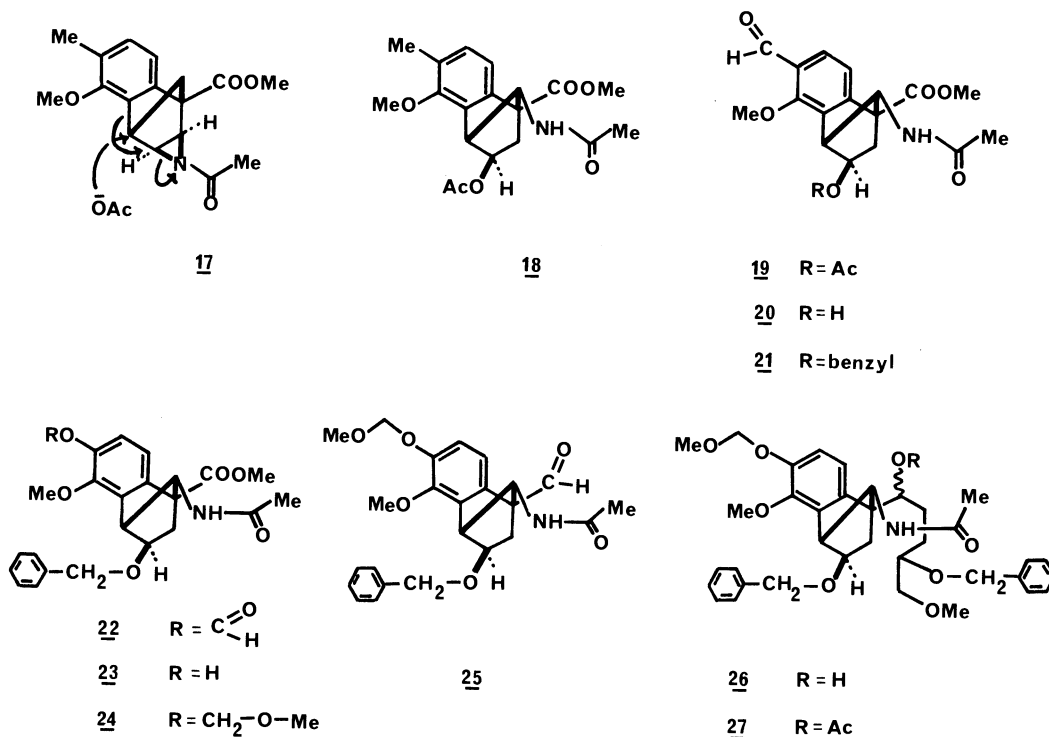substituted ring A.

The aldehyde (25) was treated with an excess of 3-benzyloxy-4-methoxy-n-butyl magnesium bromide (8) and the mixture of the epimeric alcohols (26) was obtained in a yield of 87%. For purposes of characterization and analysis, these and the subsequent epimeric mixtures were resolved by preparative thin layer chromatography. In the main preparative run, however, the epimers were not separated since they finally yielded one single inter- mediate, the keto lactam (36).

The alcohols (26) were now quantitatively acetylated to the acetates (27) and this material was hydrogenolysed over palladium on charcoal to the diols (28). Oxidation of the two secondary alcoholic groups in this last product with the dipyridine-chromium trioxide complex in dichloromethane yielded 85% of the epimeric diketones (29). The stage was now set for the closure of ring A. This was accomplished by boiling the diketone (29) under nitrogen with a saturated solution of potassium carbonate in absolute methanol and the α,β-unsaturated ketone (30) was isolated in a yield of 90%.
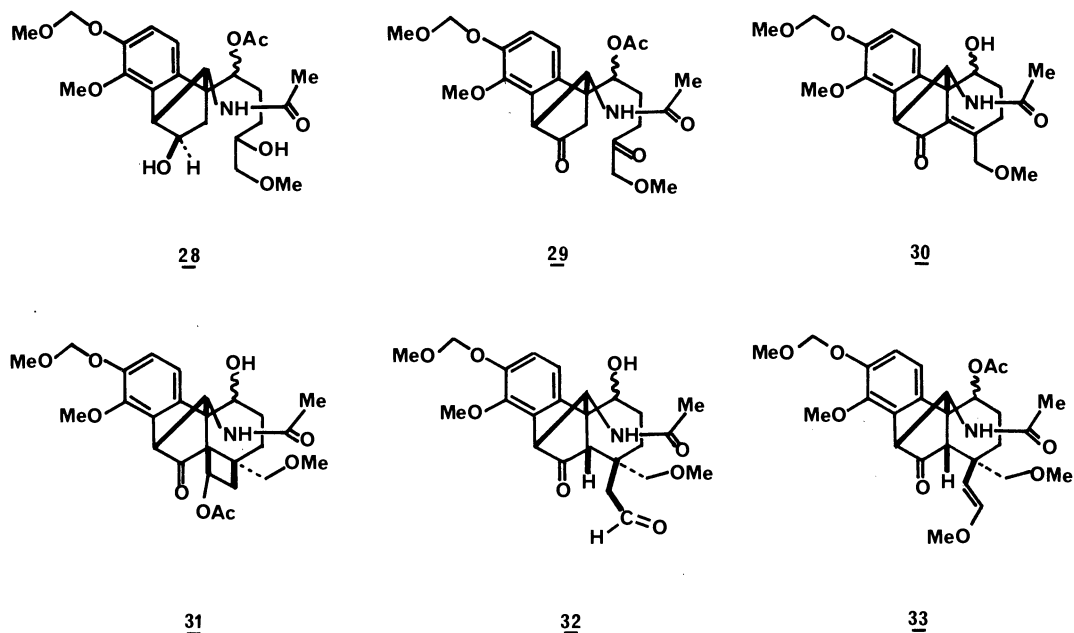
Photoaddition of vinyl acetate to the conjugated system of compound (30) under our standard conditions is a stereospecific process and the epimers (31) were obtained in a yield of 95%. While the regiospecificity of the photoaddition in unusual, the stereospecificity is predictable by our addition rule (10) and similar to the observed behaviour of related systems.

Saponification of the acetoxy group by mild treatment with base was accompanied by a retro aldol cleavage and the homo-aldehyde (32) was obtained in a yield of 97%. The configuration of the two newly created chiral centers in compound (32) was deduced (as in similar cases--cf. 1) from the proton magnetic resonance spectrum of this material. The singlet of the primary methoxyl in the p.m.r. spectrum of compound (32) was shifted

SCHEME 3

17

18

19   R = Ac

20   R = H

21   R = benzyl

22   R = C⟨O, H⟩

23   R = H

24   R = CH₂—O—Me

25

26   R = H

27   R = Ac

SCHEME   4

28   29   30

31   32   33

upfield to τ = 7.27 as a result of the shielding by the aromatic ring. The
only configuration in which the primary methoxyl can find itself in the
shielding zone of the aromatic ring is the one portrayed in the formula.
It is thus clear that the configuration of the quaternary carbon has been
set up correctly, but the configuration of the A/B ring junction was
dictated by the greater stability of the cisoid system.

It was now necessary to remove the extra carbon of the homo-aldehyde prior
to the closure of the nitrogen ring. Compound (32) was converted into the
dimethylacetal, acetylated and heated under reflux with dry pyridine.
Elimination of methanol from the acetal group yielded 92% of the acetylated
enol ether (33). Oxidation of compound (33) with permanganate-periodate
followed by esterification with diazomethane gave finally the ester (34)
in a yield of 81%. The p.m.r. spectrum of compound (34) (primary methoxyl
singlet τ = 7.44) showed clearly that no change has occurred in the A/B
cis stereochemistry during the various operations to which the material
was subjected. The system (34) is clearly unable to close a lactam ring
since the carbomethoxy group can sterically not reach the nitrogen.

However, reflux of compound (34) with dilute methanolic sodium methoxide
led, as expected, to the formation of the secondary lactam (35) with a
simultaneous epimerization of the ring junction in a yield of 85%. The
p.m.r. spectrum of compound (35) showed the singlet of the primary methoxyl
at lower field (τ = 6.63) in agreement with the inverted configuration of
the A/B ring junction. Finally, oxidation of the epimeric hydroxylactams
(35) with the chromium trioxide-pyridine complex in dichloromethane
completed the stereospecific synthesis of the beautifully crystalline
diketolactam (36) (m.p. 178-9°C) in a yield of 90%.

The transformation of the α,β-unsaturated ketone (30) to the keto lactam (35) was carried out in an overall yield of 60%. Nevertheless, we have been attempting for a long time without success to discover a shorter alternative route. Thus, for example, the photoaddition of an acetylenic derivative to compound (30) followed by a direct oxidative cleavage of the resulting cyclobutene was tried in many variations.

Another possibility is the construction of the nitrogen ring by attachment of a suitable side-chain to the nitrogen followed by base-catalysed cyclization. The schemes which we developed in this direction offered little advantage over our present process as regards to the number of steps needed and none of them could match our present yields. Nevertheless, I believe that the conversion of the α,β-unsaturated ketone (30) to the keto lactam (35) must be capable of some simplification and of a consequent small improvement in the overall yield.

The diketolactam (36) was next reduced with tri-t-butoxy aluminum hydride and the diol (37) was obtained stereospecifically in a yield of 86% after crystallization. Methylation of this material in dry dioxane with sodium hydride and methyl iodide at reflux temperature gave finally the poly-methoxylated N-methyl lactam (38).

The final modification of the "aromatic intermediate" (38) which was required before we could start with the construction of the C/D ring system was a selective cleavage of the aromatic methoxyl. This was accomplished in a yield of 95% by heating compound (38) with sodium thioethoxide in dimethylformamide at 120°C.

SCHEME   5

34

35

36

37

38

39
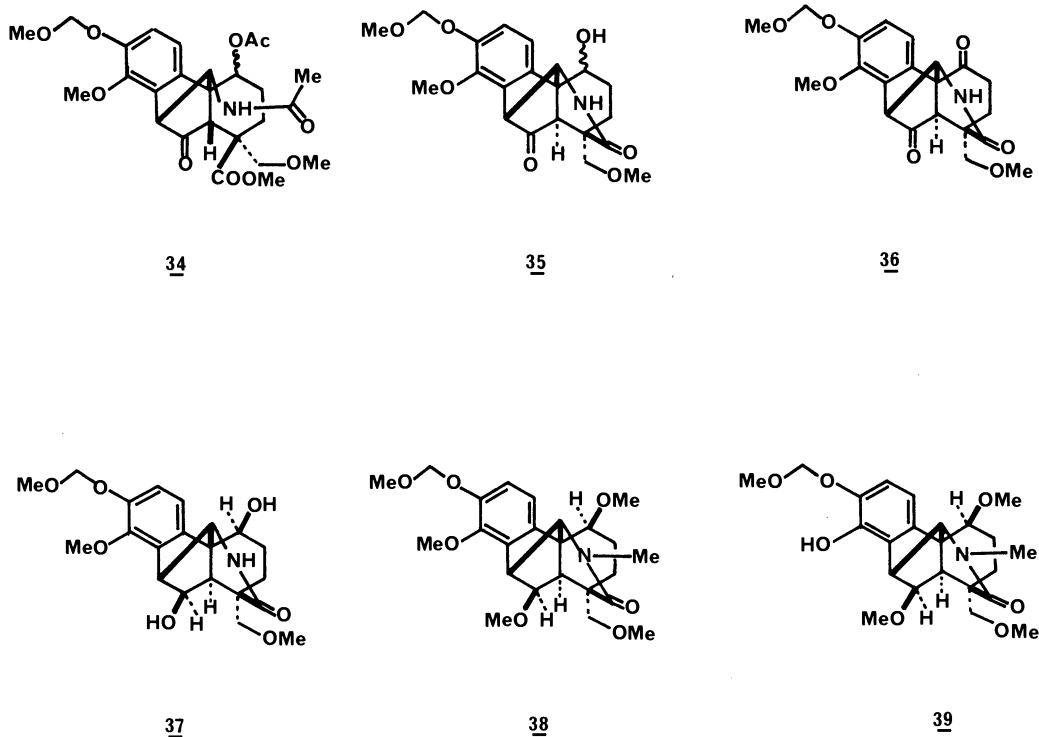
I should point out that the success of this transformation was crucial to
the entire synthesis. To say the least, if we had been compelled to use two
different labile blocking groups for the two phenols throughout the entire
synthesis, our path would have been much more complicated.

THE CONSTRUCTION AND REARRANGEMENT OF THE SUBSTITUTED DENUDATINE SYSTEM

We intended now to convert the phenol (39) in three simple steps to the
masked orthoquinone (42) using the oxidation procedure worked out by
Deslongchamps in his approach to ryanodine (11). This intention was well
supported by preliminary studies which as usual were conducted on a model
benzobicyclopentene system (12). The phenol (39) was alkylated with methyl
bromoacetate in dry acetone in the presence of potassium carbonate and
18-crown-6 ether. The product (40) was obtained in a yield of 90% and it
was quantitatively hydrolyzed with hydrochloric acid in tetrahydrofuran
to the phenolic acid (41). Oxidation of this material with N-bromo-
succinimide (11, 12) in methylene chloride and aqueous sodium acetate in a
two-phase system yielded a crude spirolactone, presumably (42) but actually
a mixture of (42) and (43), which was isolated and immediately allowed to
react with an excess of benzyl vinyl ether at room temperature for 24 hours.

While the yield of the oxidation and subsequent Diels-Alder addition was
satisfactory (compounds (44) and (45) were isolated in an overall yield of
70% from the ester (40)) the product was more heterogeneous than we expected
on the basis of our model work. Besides the crystalline epimeric mixture
(44), we have isolated also a pair of oily bromine-containing epimers
(45). The location of the bromine atom in (45) was easy to deduce. The
vinylic hydrogen appeared in the p.m.r. spectrum of the epimers (44)
as a doublet at $\tau = 4.35$. The spectrum of the bromine-containing epimers
(45) showed the same vinylic hydrogen as a singlet at $\tau = 4.21$. It is
clear that in the full pentacyclic system bromination of the phenol (41)
competed successfully with the oxidation of this material. The ratio of
(44) and (45) was approximately 2:1 and we were unable to suppress the
formation of the bromine-containing product (45). It was in fact possible
to raise the yield of the products (44) and (45) to 85% from the ester
(40) by increasing the amount of bromosuccinimide to compensate for the
oxidizing agent used up in the bromination.

It was clear that the increased strain imposed on the substituted benzene
ring of compound (41) by the two rings which were absent in our model
system has changed its reactivity in favour of an easier electrophilic
aromatic substitution. Thus, we had to learn how to handle a mixture of
four products or accept defeat in the form of an unsatisfactory non-
selective step. The inhomogeneity of the products (44) and (45), res-
pectively, was of course due to the chirality of the spirolactone carbon
and would disappear with the removal of this function, but the problem of
handling the bridgehead bromine was serious. After a considerable amount
of experimentation, we have found that both the products (44) and (45),
separately or in mixture, gave the single ketone (46) in a yield of 85% by
being heated under reflux with zinc and 18-crown-6 ether in glacial acetic
acid.

I might mention that this step shortened our planned and model-tested
synthesis by five operations and at the same time it was the only step
which was not worked out on the model system prior to the synthesis proper.
Thus, even in our approach to synthesis, there is room for opportunism and
luck!

The benzyl protecting group in compound (46) was removed by hydrogenation
in absolute ethanol over palladium on charcoal. The mixture of the epimeric
alcohols (47) was obtained in a yield of 96% and was immediately acetylated
with acetic anhydride in pyridine to the acetates (48). The partial
epimerization of the hydroxyl in compound (47) was clearly due to a reverse
aldol-aldol condensation reaction during hydrogenolysis or work up.

Compound (48) is analogous in structure to the corresponding intermediate
of our photochemical synthesis (3, 1), which was reached only after many

SCHEME   6

40

41

42   R = H

43   R = Br

44   R = H

45   R = Br

46

47   R = H

48   R = Ac
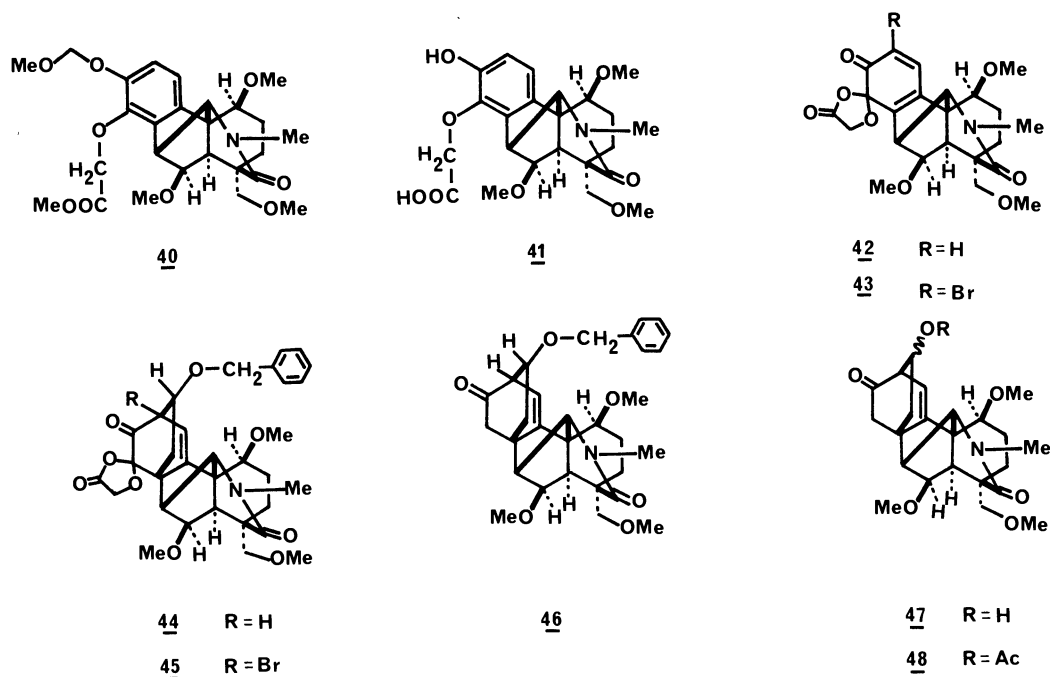
more synthetic operations. The only difference in the two series from this
point on is that the photochemical intermediates were N-acetyl tertiary
amides. The keto acetate (48) was converted to the saturated compound (49)
by hydrogenation with 5% rhodium on alumina in methanol at 85 psi for 18
hours, followed by oxidation with chromium trioxide-pyridine.

The saturated keto acetate (49) was obtained stereospecifically in a yield
of 88% and in spite of being a mixture of epimers it crystallized
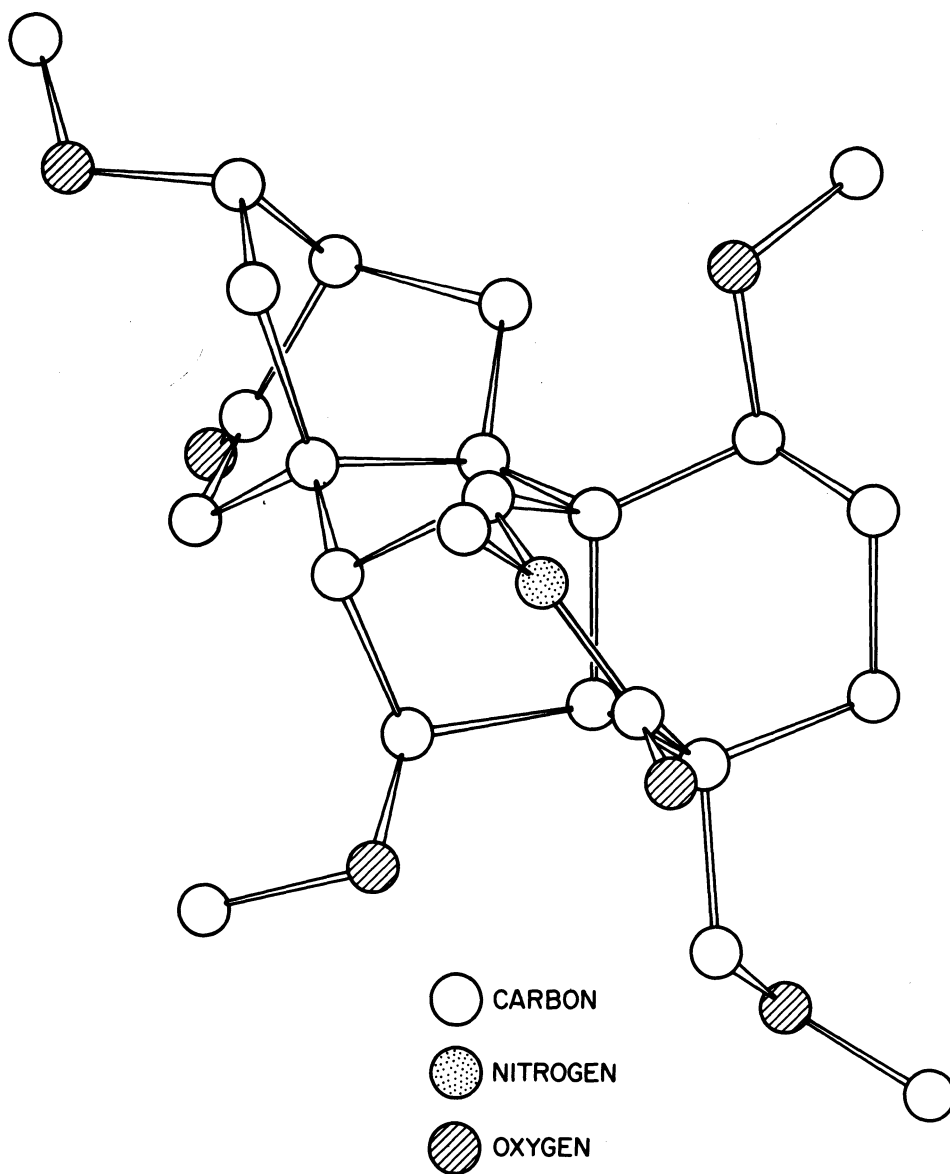beautifully.

Compound (49) was now transformed to the homogeneous keto acetal (50) by
the following three operations: 1) Reflux with p-toluenesulfonic acid and
ethylene glycol in benzene; 2) Hydrolysis with methanolic sodium hydroxide;
3) Oxidation with chromium trioxide-pyridine.

Compound (50) was obtained in an overall yield of 88% from (49) and was a
beautifully crystalline solid which melted at 206-7°C. Reduction of the
keto acetal (50) with sodium borohydride yielded quantitatively the alcohol
(51) and this material was methylated with sodium hydride and methyl iodide
in dioxane to the methoxy derivative (52) in a yield of 97%.

The acetal (52) was finally heated in 80% acetic acid and the ketone (53)
was obtained in a yield of 94%.

We have so far constructed with full regio- and stereospecificity the com-
plete polysubstituted nordenudatine system. Consequently not so much to
reassure ourselves that all our conclusions were correct, but more for the
sake of characterization and an "outside check" on our work we have sub-
mitted the beautifully crystalline ketone (53) to Dr. Maria Przybylska
(National Research Council, Ottawa) for an X-ray crystallographic study.

Scheme 8 shows the drawing which we received a few weeks later as a result of the structure determination performed on this material by M. Przybylska and F. R. Ahmed.

Bromination of the ketone (53) with bromine in a mixture of ether and dioxane yielded 90% of a sharply melting bromo ketone, to which we assigned the configuration shown in formula (54). This assignment was based mainly on the success of the subsequent transformations, i.e., the rearrangement to the pyro-derivative (56). Such a rearrangement presumably requires an antiperiplanar disposition of the leaving group and the migrating bond. The stereospecific bromination of the ketone (53) to the compound (54) is clearly due to the difficult approach of the bromine molecule to the enolized ketone (53) from the inside of the cavity of the bicycloheptane system.

It was now necessary to reconvert the bromo ketone (54) to an acetal, since the ejection of the bromine anion from the position α to the keto group in the subsequent rearrangement turned out to be, as expected, impossible (see Note b).

SCHEME 7

49

50

51   R = H

52   R = Me

53   R = H

54   R = Br

55

56

Note b. It is interesting that this reaction, i.e., the rearrangement of the unprotected α-bromo ketone was successful on the tricyclic model system (cf. 12).
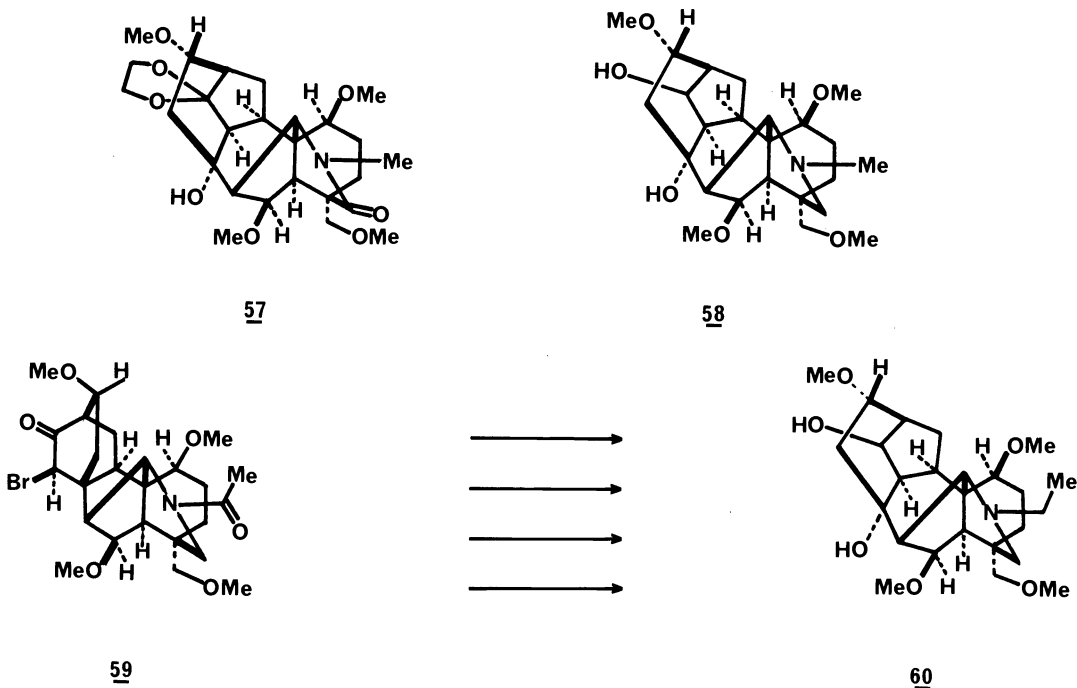
SCHEME 8

CARBON

NITROGEN

OXYGEN

The bromo derivative (54) was heated under reflux with an excess of
ethylene glycol and an equimolar amount of p-toluenesulfonic acid in
benzene. The formation of the acetal was slow and difficult but neverthe-
less the beautifully crystalline compound (55) was obtained in a yield of
80%.

The bromo acetal (55) was now heated to 180°C with an excess of DBN in a
mixture (1:1) of DMSO and o-xylene. The oily rearranged "pyro-derivative"
(56) was the only product formed and was isolated by preparative thin layer
chromatography in a yield of 89%. The p.m.r. spectrum of compound (56)
showed a vinylic hydrogen doublet (J = 6 Hz) at τ = 4.43. This is a well
known feature of the pyro derivatives of delphinine-type alkaloids in spite
of the fact that the structure of the prototype, pyrodelphinine itself, was
deduced by us almost exactly 20 years ago before p.m.r. spectrometry came
into general use, or at any rate, before we acquired a p.m.r. spectrometer
at the University of New Brunswick (13).

The remainder of the synthesis was uneventful. Oxymercuration of compound
(56) in acetone followed by borohydride reduction yielded 65% (the lowest
yield of the entire synthesis which could most certainly be improved) of
the acetal (57). Deacetalization of this compound in 80% acetic acid
followed by lithium aluminum hydride reduction of the resulting keto lactam
finally gave stereospecifically racemic totally synthetic 13-desoxy-
delphonine (58). It was recrystallized to a constant m.p. of 124-125.5°C
and was indistinguishable by spectral and chromatographic methods from the
optically active material of the same structure (m.p. 92°C) described some
time ago by Dr. L. Marion (14). Thus, we have finished (2) with complete
regio- and stereospecific control and without the use of a relay compound
the total synthesis of a fully substituted delphinine-type alkaloid
containing 13 chiral centers.

SCHEME   9

57

58

59   60

SCHEME 10

52   61   62   R = H

                                                              59   R = Br

37   63   64
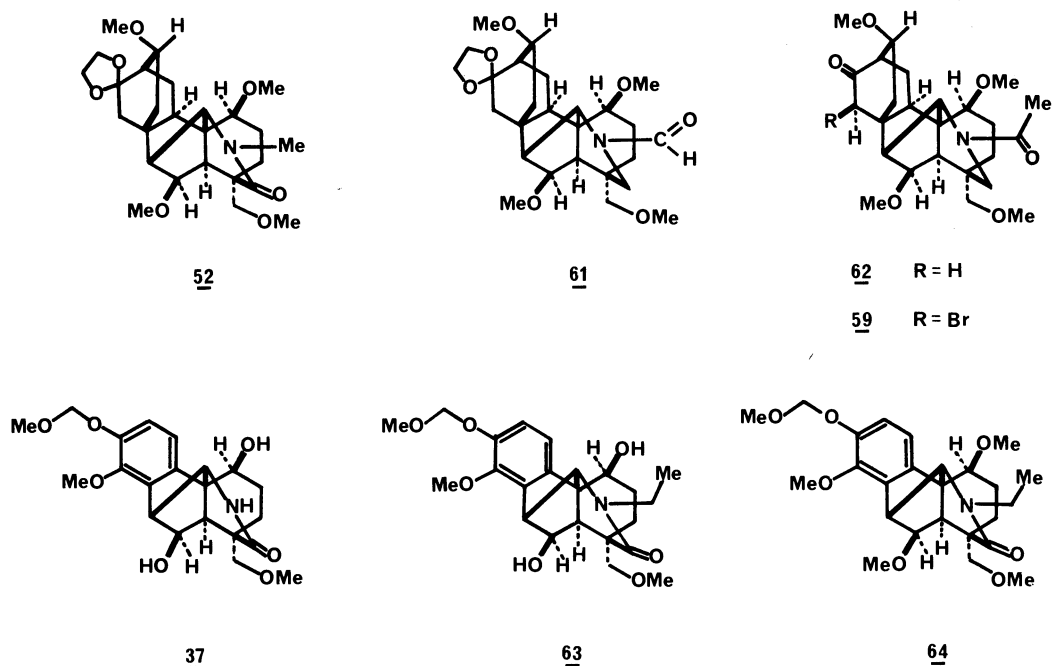
THE FORMAL SYNTHESIS OF CHASMANINE

About a year ago we have completed (3) a total synthesis of the alkaloid
chasmanine (60) via the bromo ketone (59) which was transformed to (60) by
a procedure precisely analogous to the just described preparation of 13-
desoxydelphonine (58) from the bromo ketone (54). The intermediate (59) was
synthesized by a fully stereospecific, but much more lengthy and laborious
photochemical method (3).

We have now first of all wished to formally connect both syntheses. This
was accomplished as follows: The intermediate (52) of our present series
was reduced with lithium aluminum hydride to the corresponding tertiary
amine and this compound was oxidized with potassium permanganate in acetone
in the presence of acetic acid at room temperature. The crude N-formyl
derivative (61) which was thus obtained was hydrolysed with hydrochloric
acid and the product was acetylated to the acetoxy ketone (62).

Finally, bromination of (62) yielded our old photochemical intermediate
(59) identified by melting point, mixture melting point, and spectral and
chromatographic behaviour.

While we were gratified to have successfully double checked all our work by
correlation--I am a firm believer in this since my stay in Professor L.
Ružička's Institute in Zurich 30 years ago--it is clear that this correlation
does not constitute a practical way to synthesize chasmanine. A better
method would be to transform 13-desoxydelphonine to chasmanine by oxidative
demethylation followed by ethylation. This was accomplished with the
optically active material in reasonably good yield, but we did not have
enough of the totally synthetic product (58) to carry it out with the
racemate.

However, there is a potentially efficient way which might be used if one
would wish to perform a direct synthesis of chasmanine by our new method.
In the alkylation of the intermediate (37) the lactam NH reacts much faster
than the two hydroxyls. Thus, the dimethoxy N-ethyl derivative (64) may be
prepared via the N-ethyl diol (63). A direct synthesis of chasmanine from
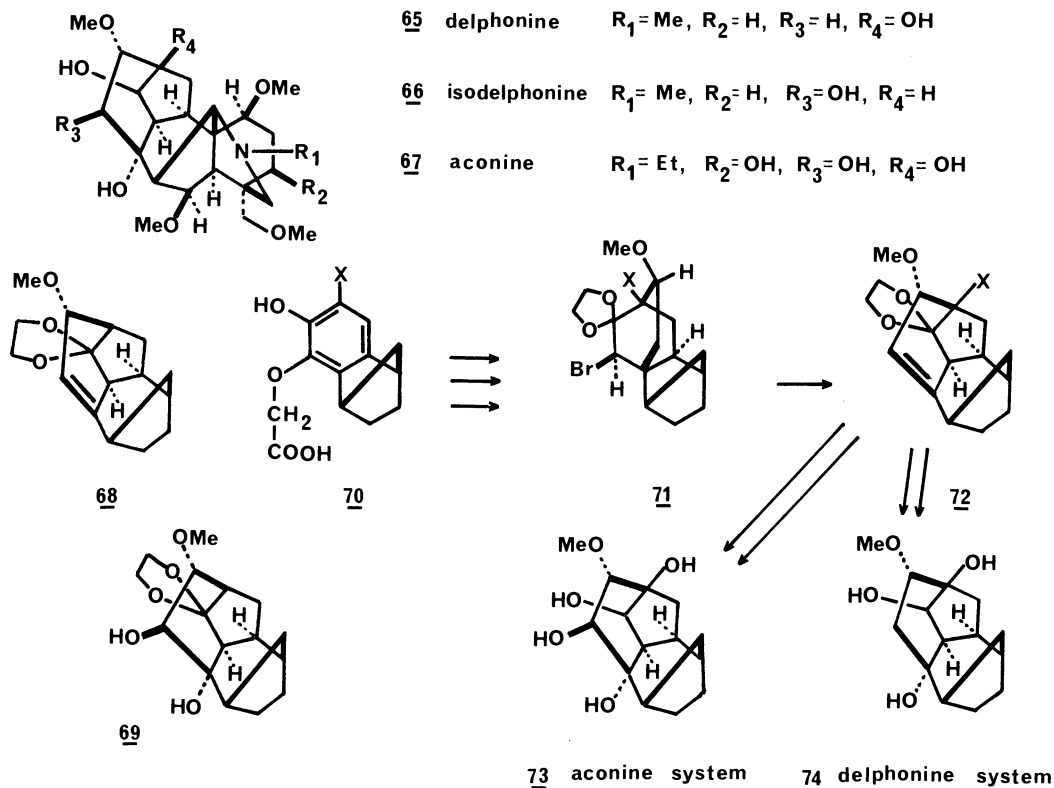(64) would almost certainly succeed. We have decided not to carry it out
since it would hardly bring anything new.

        OUTLOOK

Even more heavily substituted delphinine-type alkaloids occur in Nature.
They are mostly ester alkaloids and some of the corresponding alcohols are
shown in Scheme 11.

They differ from 13-desoxydelphonine and chasmanine by the additional
hydroxyl functions R_2, R_3 and R_4. The substituent R_2 occurs only in aconine
and its introduction into the "aromatic intermediate" in a suitably pro-
tected form should not be too difficult. The substituents R_3 and R_4 are
both present in aconine and only one of them in delphonine and isodelphonine,
respectively.

We have done some preliminary work which shows that our final generation
methods should allow a comparatively easy provision for one or both of the
substituents R_3 and R_4.

SCHEME 11

65 delphonine R_1=Me, R_2=H, R_3=H, R_4=OH

66 isodelphonine R_1=Me, R_2=H, R_3=OH, R_4=H

67 aconine R_1=Et, R_2=OH, R_3=OH, R_4=OH

68   70   71   72   69

73 aconine system   74 delphonine system

The model rearrangement product (68) was subjected to a hydroxylation with silver benzoate and iodine and a good yield of compound (69) was obtained. Thus, the synthesis of isodelphonine should present no problems.

The bridgehead hydroxyl which occurs in delphonine and aconine may be introduced as shown in the structures (70) → (73) → (74). A group X may be introduced into the aromatic intermediate (70) and converted to the bridgehead hydroxyl at the end of the synthesis. The simplest possibility a suitably blocked phenolic group has predictably not worked. However, a carbomethoxy gave promising results and this method should allow the synthesis of the aconine and delphonine models (73) and (74) in the near future. Whether we shall ever synthesize aconitine and delphinine themselves depends on many non-chemical factors and the synthesis of compounds (73) and (74) should not be regarded as a promise, but rather as an illustration of the versatility of our methods.

REFERENCES

1. For the systematic development of strategy and the first three generations of the synthetic methods see K. Wiesner, Centenary Lecture of the Chemical Society, Chem. Soc. Rev. 6, 413 (1977).
2. K. Wiesner, T. Y. R. Tsai, and K. P. Nambiar, Can. J. Chem. 56, 1451 (1978).
3. T. Y. R. Tsai, C. S. J. Tsai, W. W. Sy, M. N. Shanbhag, W. C. Liu, S. F. Lee, and K. Wiesner, Heterocycles (Woodward Issue) 7, 217 (1977).
4. Unpublished work by T. Y. R. Tsai, K. P. Nambiar, D. Krikorian, R. Marini-Bettòlo, and M. Botta. For an alternative route from vanillin, see K. P. Nambiar, Ph.D. Thesis, University of New Brunswick (1977).
5. S. Wagatsuma et al. Organic Preparations and Procedures 5 (2), 65-70 (1973).
6. B. M. Trost and F. Chen, Tetrahedron Lett. 2603 (1971).
7. K. Wiesner, P. T. Ho, D. Chang, Y. K. Lam, C. S. J. Tsai, and W. Y. Ren, Can. J. Chem. 51, 3978 (1973).
8. S. F. Lee, G. M. Sathe, W. W. Sy, P. T. Ho, and K. Wiesner, Can. J. Chem. 54, 1039 (1976).
9. T. Y. R. Tsai, unpublished experiments.
10. K. Wiesner, Tetrahedron 31, 1655 (1975).
11. D. Berney and P. Deslongchamps, Can. J. Chem. 47, 515 (1969).
12. K. S. Atwal, R. Marini-Bettòlo, I. H. Sanchez, T. Y. R. Tsai, and K. Wiesner, Can. J. Chem. 56, 1102 (1978).
13. For a summarizing reference, see K. Wiesner, F. Bickelhaupt, D. R. Babin, and M. Götz, Tetrahedron 9, 254 (1960).
14. O. Achmatowicz, Jr., Y. Tsuda, and L. Marion, Can. J. Chem. 43, 2336 (1965).