CENTENARY LECTURE*

Systematic Development of Strategy in the Synthesis of Polycyclic Polysubstituted Natural Products: The Aconite Alkaloids

By Karel Wiesner
NATURAL PRODUCTS RESEARCH CENTER, THE UNIVERSITY OF NEW BRUNSWICK, P.O. BOX 4400, FREDERICTON, NEW BRUNSWICK, E3B 5A3, CANADA

1 Introduction

During approximately the last 12 years my students and I at the University of New Brunswick have been involved in systematic studies which have had as the final goal the development of relatively simple and highly efficient methods for the synthesis of delphinine-type alkaloids.

We wished to develop a synthetic strategy in which all the many functional groups of the delphinine (1) system would materialize in the correct positions and configurations simultaneously with the construction of the hexacyclic polybridged skeleton.

It was my belief that this exercise, *i.e.* a systematic search for the simplest possible method to construct a complicated compound, would significantly contribute to the art of synthesis and advance the day when compounds of the complexity of delphinine (if sufficiently important and expensive) might be produced on the industrial scale.

A development of this type was seen after the second world war in the total synthesis of the far simpler steroids. This development motivated by the medicinal importance of steroid hormones and initiated by the classical syntheses of Robinson and Woodward finally lead to the design of the extremely simple and highly practical synthetic strategies of Torgov and Johnson.[1]

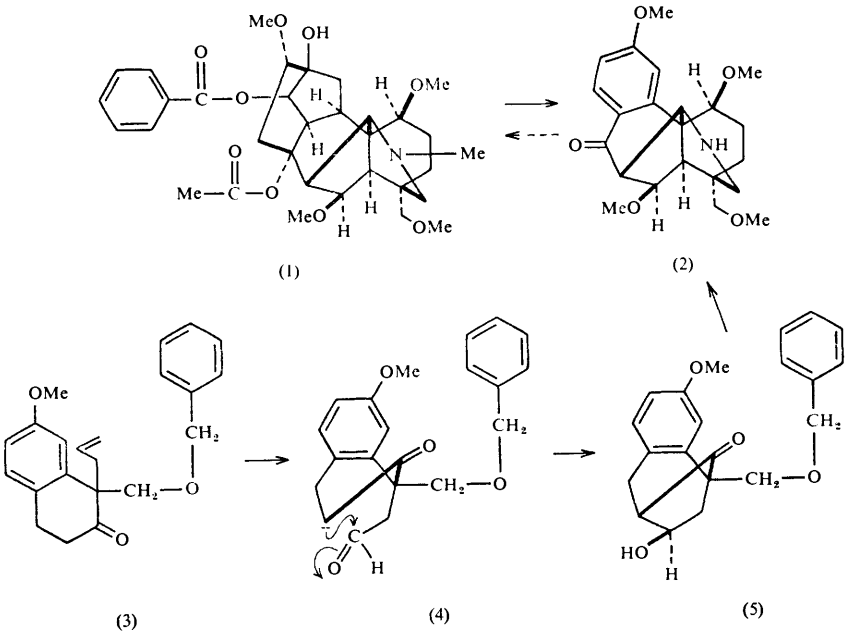
While many laboratories participated in the progressive simplification of steroid synthesis over many years, we came to regard this process as the very objective of our work, similar to a chess problem in which the task is to defeat the opponent in the smallest number of moves.

* Based on the Centenary Lecture of the Chemical Society given in Lancaster in March 1977.

[1] For comprehensive discussions of steroid total synthesis see: (*a*) A. A. Akhrem and Yu. A. Titov, 'Total Steroid Synthesis', Plenum Press, New York, 1970; (*b*) R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf, 'Total Synthesis of Steroids', Academic Press, New York, 1974; (*c*) R. Pappo in 'The Chemistry and Biochemistry of Steroids', ed. N. Kharasch, IntraScience Research Foundation, Santa Monica, Calif., 1969, vol. 3, No. 1, pp. 123—140; (*d*) G. Saucy and N. Cohen, *MTP Internat. Rev. Sci., Ser. One*, 1973, **8**, 1—26.

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 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, the third generation synthesis is now finished and the fourth and final generation is under way. It will be seen that this technique attains to a high degree the objectives and standards that we have initially set for ourselves.

The choice of the aconite alkaloids as our target naturally gave us a considerable advantage. Our degradation studies which resulted in the first correct structure proposals for this class of natural products[2] gave us a good understanding of the chemical properties of these systems. However, the advantage was hardly unfair. A similar understanding may also be clearly gained by a thorough study of the literature and thus our choice was motivated mainly by the pleasure a chemist can derive from the synthesis of 'his own' compounds which had seemed so formidable when their structures were first clarified.[3]



Scheme 1

[2] *cf.* for example K. Wiesner, *Pure and Applied Chemistry*, 1975, **41**, 93.
[3] R. B. Woodward, 'XIVth International Congress of Pure and Applied Chemistry', Main Congress Lectures, Birkhäuser Basel and Stuttgart, 1955.

2 The Aromatization Product of Delphinine

Our first approach to the delphinine system is illustrated in Scheme 1. It was still lengthy, classical, and was undertaken before I had clearly formulated my present ideas.

The aromatization product (2) obtainable in high yield by degradation of delphinine (1) was intended to serve as a relay compound.[4]

The starting material was the substituted tetralone (3) which was oxidized to the aldehyde (4). Base catalysed aldolization of this last product gave the synthon (5) in a high yield. The disposition of functional groups in (5) is very convenient and it permitted a relatively easy elaboration of this intermediate to the desired compound (2). Finally, a differential reaction of the racemate (2) with 1-camphorsulphonyl chloride resulted in a very efficient resolution and completed the total synthesis of the optically active relay (2).[5]

The routes from (2) to (1) which we studied on model compounds,[6] while entirely feasible, were unattractive, pedestrian, and if undertaken, would have absorbed the major part of our energy. Thus, this approach was abandoned in favour of more sophisticated methods to be described later.

3 The Synthesis of Talatisamine

Many years ago Professor Cookson and ourselves proposed independently that delphinine-type alkaloids might originate from the atisine system by a loss of a carbon atom, followed by bridging and then a rearrangement.[7] The order of these steps in the biosynthesis was, of course, unknown and the rearrangement could occur before or after the bridging of ring B.

The first laboratory implementation of the postulated rearrangement was accomplished by Overton[8] who reported the formation of the rearranged ketone (7) on high temperature pyrolysis of the atisine derivative (6). However, no way was found to introduce the ring B bridge (*i.e.* a bond between the asterisked carbons) in compound (7).

We studied the rearrangement of the readily obtainable model compound (8) and found that this material gives a high yield of the products (9) and (10) in equal amounts[9] when heated to 180 °C in dimethylsulphoxide with tetramethyl guanidine.

Since in degradation products of delphinine-type alkaloids which are analogous to compound (9) the ring B bridge can be easily closed,[10] we decided to base our second generation synthesis on this model.

[4] K. Wiesner, M. Götz, D. L. Simmons, and L. R. Fowler, *Coll. Czech. Chem. Comm.*, 1963, **28**, 2462.

[5] K. Wiesner, E. W. K. Jay, T. Y. R. Tsai, C. Demerson, Lizzie Jay, T. Kanno, J. Křepinský, A. Vilím, and C. S. Wu, *Canad. J. Chem.*, 1972, **50**, 1925.

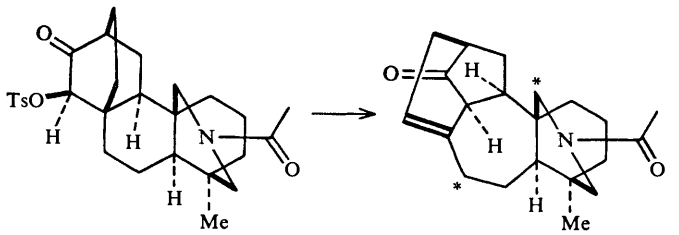
[6] K. Huber and J. Poslusny, unpublished data.

[7] *cf.* K. Wiesner and Z. Valenta in 'Progress in the Chemistry of Organic Natural Products', ed. L. Zechmeister, Springer, Vienna, 1958, vol. XVI, p. 26.

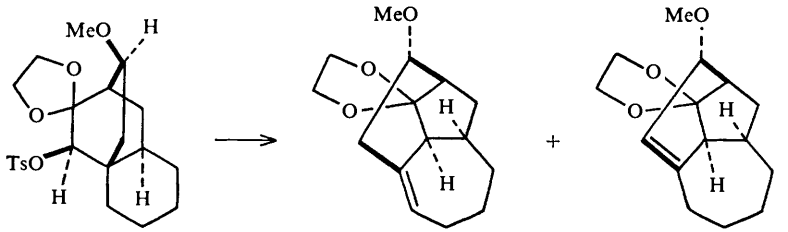
[8] J. P. Johnston and K. H. Overton, *J.C.S. Perkin I*, 1972, 1490.

[9] H. J. Wu, Ph.D. Thesis, University of New Brunswick, 1977.

[10] K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown, and G. Büchi, *Tetrahedron Letters*, 1959, 15; O. E. Edwards, L. Fonses, and Leo Marion, *Canad. J. Chem.*, 1966, **44**, 583; O. E. Edwards, *Chem. Comm.*, 1965, 318.



(6) (7)

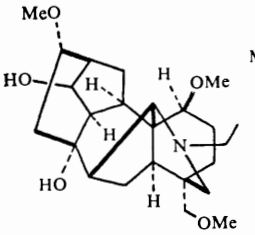


(8) (9) (10)

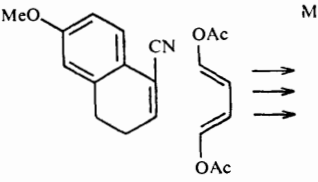
As the target we chose talatisamine[11] (11), a somewhat simplified version of delphinine with two substituents missing.

The tetracyclic 'aromatic intermediate' (13) was elaborated starting with the addition of the dienophile (12) and *trans,trans*-1,4-diacetoxy-1,3-butadiene. The conversion of (13) to the tetrasubstituted 'noratisine' intermediate (18) was performed along the lines of the synthesis of atisine which we published some time ago.[12] Photoaddition of allene to compound (14) [obtained by Birch-reduction, reacetylation, and acid treatment of (13)] gave stereospecifically the adduct (15) predictable by our addition rule.[13] Compound (15) was transformed to the acetal (16) and this material gave the product (17) by ozonolysis and borohydride reduction of the ozonide. Finally, treatment of (17) with aqueous acid resulted in the unmasking of the keto group, retroaldol reaction and an immediate stereospecific aldol condensation to (18). This last compound was now elaborated by standard methods to the highly crystalline key intermediate (19) (Scheme 2) the structure of which was corroborated by an *X*-ray crystallographic determination. The rearrangement of (19) proceeded as in our model study and gave a 45% yield of the intermediate (21) besides an equal amount of the useless by-product (20).

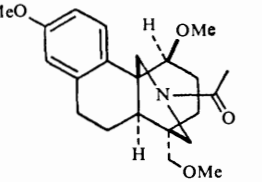
[11] M. A. Khaimova, M. D. Palamareva, N. M. Mollov, and V. P. Krestev, *Tetrahedron*, 1971 **27**, 819.
[12] R. W. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Letters*, 1966, 4645.
[13] K. Wiesner, *Tetrahedron*, 1975, **31**, 1655.



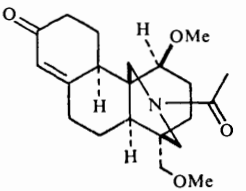
(11)



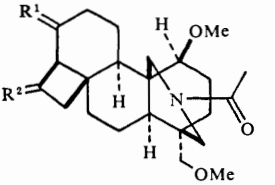
(12)



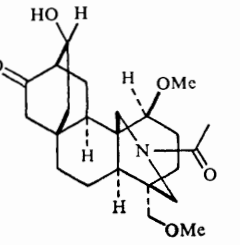
(13)



(14)



(15) $R^1 = O$; $R^2 = =CH_2$
(16) $R^1 = OCH_2CH_2O$; $R^2 = =CH_2$
(17) $R^1 = OCH_2CH_2O$; $R^2 = H$ and OH



(18)

Deacetalization of compound (21) followed by lithium aluminium hydride reduction and mercuric acetate oxidation of the product yielded finally compound (22) which cyclized spontaneously to talatisamine (11).[2,14]

4 The Synthesis of Chasmanine and Napelline

Although talatisamine was the first delphinine-type alkaloid to be synthesized, it was quite clear that its construction did not meet our requirements of simplicity and high efficiency.

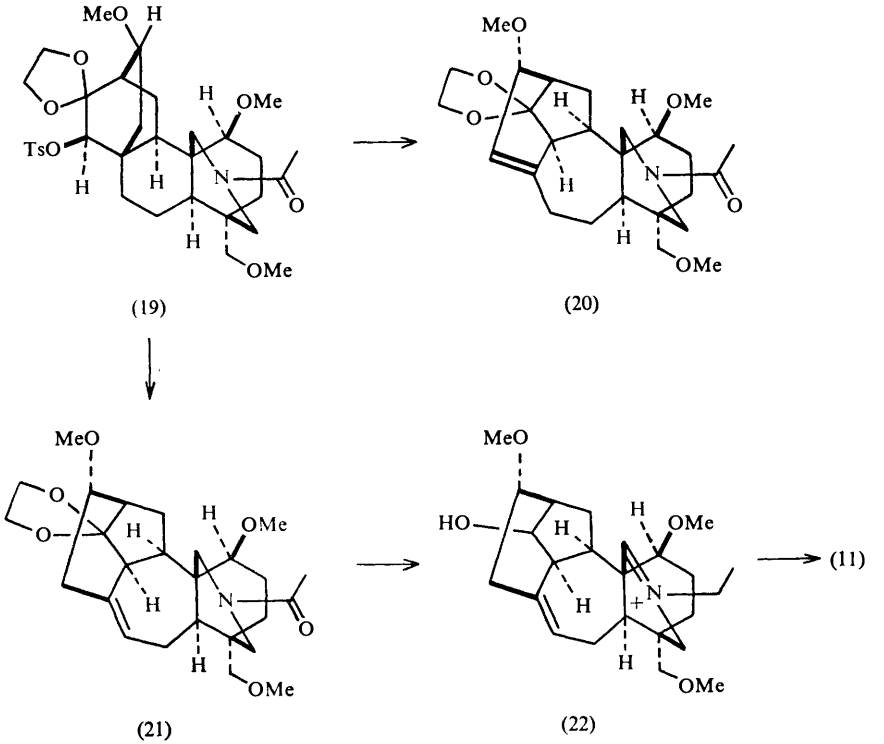
The main shortcomings of the synthesis were as follows:

(i) The formation of the useless by-product (20) in equal amounts together with the synthetic intermediate (21) on rearrangement of the 'noratisine' derivative (19).

(ii) The low yield (40%) of the mercuric acetate introduction of the ring B bridge, this low yield is clearly due to the non-regiospecificity of the oxidation.

(iii) The rather lengthy process which we had to use to introduce the β-tosyloxy group in compound (19).

[14] K. Wiesner, T. Y. R. Tsai, K. Huber, S. E. Bolton, and R. Vlahov, *J. Amer. Chem. Soc.*, 1974, **96**, 4990.



Scheme 2

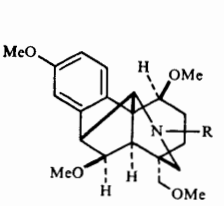
(iv) The typical ring B substituent of delphinine-type alkaloids is missing in talatisamine; this fact facilitated considerably the planning of the synthesis.

All these serious flaws might be removed (and, in fact, were removed) by introducing the ring B bridge at the beginning rather than at the end of the synthesis. Thus, we decided to carry out the total synthesis of chasmanine[15] (28), an alkaloid in which only one of the seven delphinine substituents is missing, *via* the main stages (23), (25), and (27). Later on as a result of model work and practical synthetic experience we modified the plan to the sequence (24), (26), (27), and (28).

The first problem to be solved was the synthesis of the ring B bridged 'aromatic intermediate' (24) with all its substituents appearing readily in the correct positions.

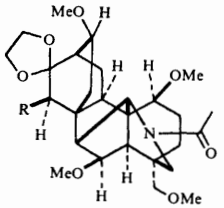
In order to explain how we arrived at a synthetic strategy, which satisfied *almost* all of our original principles, it is necessary to digress and to mention

[15] S. W. Pelletier, Z. Djarmati, and S. Lajšić, *J. Amer. Chem. Soc.*, 1974, **96**, 7817.

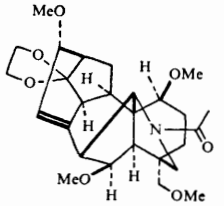


(23) R = COMe

(24) R = C(=O)H

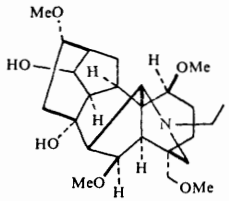


(25) R = OTs
(26) R = Br

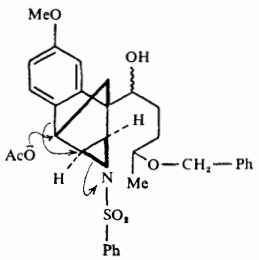


(27)

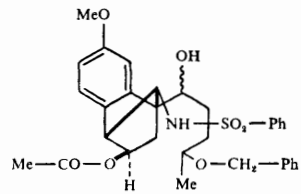
briefly our synthesis of napelline (32).[16] The key intermediate in the construction of (32) was the aromatic compound (31) obtained by elaboration of the tricyclic sulphonamide (30). This last product was prepared by a stereo- and regio-specific acetolysis of the aziridine (29). The mechanism of this process is portrayed by the arrows in formula (29). The regiospecificity of the rearrangement (29) → (30) is caused by the aromatic methoxy group which enhances the migratory aptitude of the substituent in the *para* position to such an extent that the alternative rearrangement initiated by the opening of the other aziridine C—N bond cannot successfully compete.



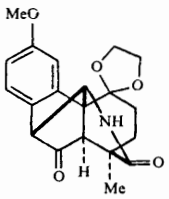
(28)



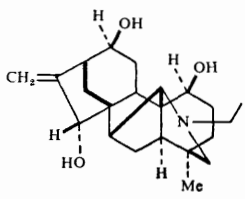
(29)



(30)



(31)



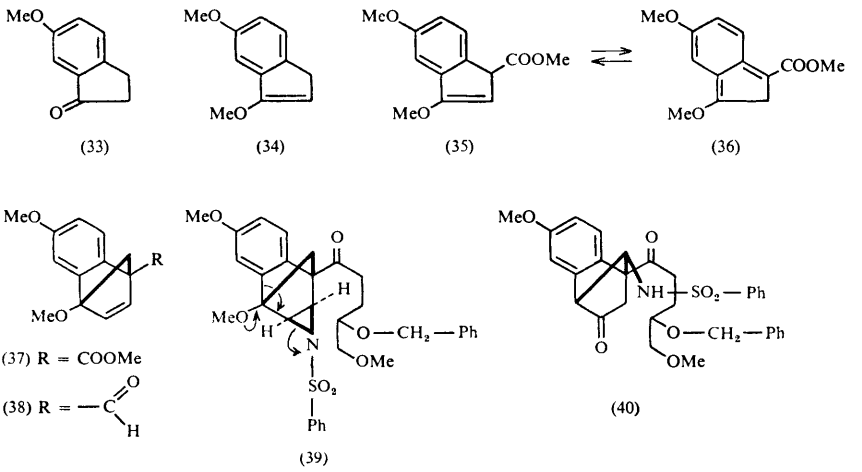
(32)

[16] K. Wiesner and A. Philipp, *Tetrahedron Letters*, 1966, 1467; K. Wiesner, P. T. Ho, R. C, Jain, S. F. Lee, S. Oida, and A. Philipp, *Canad. J. Chem.*, 1973, **51**, 1448; K. Wiesner. P. T. Ho, D. Chang, Y. K. Lam, C. S. J. Tsai, and W. Y. Ren, *Canad. J. Chem.*, 1973, **51**, 3978; K. Wiesner, P. T. Ho, C. S. J. Tsai, *Canad. J. Chem.*, 1974, **52**, 2353; K. Wiesner, P. T. Ho, C. S. J. Tsai, and Y. K. Lam, *Canad. J. Chem.*, 1974, **52**, 2355.

If we compare the structures of the chasmanine intermediate (24) and the napelline intermediate (31), we see at once that the technique used in the construction of (31) is capable of providing the entire array of aliphatic substituents in (24), since the primary methoxy group of (24) can be introduced into the starting material. Thus, the only difficulty to be overcome was the location of the aromatic methoxy group in (24) and its anticipated unfavourable influence on the aziridine rearrangement in the step corresponding to (29) → (30).

Although it includes novel features I shall not describe the conversion of (31) into napelline (32), as it is not relevant to the theme which I wish to develop in the present article and is also somewhat lengthy. I shall mention a far better synthesis of the same alkaloid now in progress in a brief discussion of the fourth generation approaches.

The starting material for the aromatic intermediate (24)[17] was the methoxyindanone (33). The enol ether (34) prepared from it may be readily carboxylated in the presence of n-butyl-lithium and thus the dimethoxyindene ester (35) was obtained. Compound (35) is in a thermal equilibrium with the quinonoid tautomer (36) and as a consequence yields practically quantitatively a maleic anhydride adduct. The adduct was decarboxylated by the method of Trost[18] and the tricyclic intermediate (37) was obtained in a yield of over 80%. The ester (37) was then modified to the corresponding aldehyde (38) and the stage was set for the introduction of the nitrogen and the annelation of ring A. The following three steps converted the aldehyde (38) into the unstable aziridine (39) which rearranged immediately to the diketone (40). (i) Treatment with the Grignard reagent prepared from 1-bromo-3-benzyloxy-4-methoxy butane, (ii) oxidation



[17] S. F. Lee, G. M. Sathe, W. W. Sy, P. T. Ho, and K. Wiesner, *Canad. J. Chem.*, 1976, **54**, 1039.

[18] B. M. Trost and F. Chen, *Tetrahedron Letters*, 1971, 2603.

with chromic acid, and (iii) treatment with a large excess of benzenesulphonyl-azide in acetic acid.

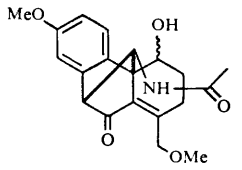
The function of the methoxy group attached to one bridgehead of the system is to accelerate the desired rearrangement [as shown by the arrows in formula (39)] while the keto group at the other bridgehead slows down the competing reaction. This competing rearrangement, initiated by the opening of the other aziridine carbon nitrogen bond, requires the development of a partial positive charge on the carbon directly bonded to the keto group and consequently the energy of its transition state is increased. The combined action of the two bridgehead groups succeeded to overcome the unfavourable accelerating influence of the aromatic methoxy group and to steer the rearrangement with moderate regioselectivity (60:40) in favour of the diketone (40). The absence of regiospecificity in this step is the only serious flaw of the synthesis and it can be corrected by a temporary replacement of the aromatic methoxy group by the electron withdrawing mesyloxy group (*cf.* ref. 16). The several steps required for this operation however make it profitless from the point of view of yield. The final generation synthesis does not suffer from this defect since it requires a substitution of the aromatic ring favourable to the desired rearrangement (*vide infra*).

The diketone (40) was now modified in a few simple steps to the $\alpha\beta$-unsaturated ketone (41). Photochemical addition of vinylacetate to this compound yielded, with complete regio- and stereo-specificity, the adduct (42), the stereochemistry of which was again predictable by our addition rule.[13] Saponification of the acetoxy group in (42) resulted in a retroaldol reaction and gave the homoaldehyde (43) which was degraded in very high yield to the ester (45) *via* the enolether (44). All these derivatives including the ester (45) turned out to prefer the A/B *cis* configuration in which the ester group is incapable of forming a lactame. However, reflux with absolute methanolic alkali caused, predictably, a gradual epimerization of the ring junction with the simultaneous formation of the lactame and loss of both acetyl groups in a high yield. Finally, chromic acid oxidation of the product completed the synthesis of the diketolactame (46).

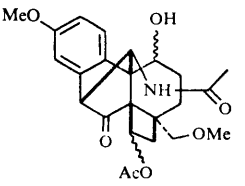
Compound (46) was now stereospecifically reduced with tri-butoxyaluminium hydride and the resulting diol (47) was methylated to the dimethoxy-*N*-methyl lactame (48). Reduction of (48) with lithium aluminium hydride and oxidation of the product (49) under carefully controlled conditions with permanganate gave a high yield of the aromatic intermediate (24).

Before proceeding with the conversion of the 'aromatic intermediate' (24) into chasmanine (28) we performed several studies,[19] which involved the synthesis of the tetracyclic compound (51) from the model starting material (50). I shall not discuss these studies in the present article, but I wish to emphasize the important role which they played in our ultimate success. While not every method worked out on the model system can be applied without modification in the synthesis proper, it is clear that the second part of the chasmanine synthesis would have

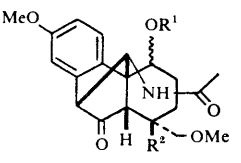
[19] K. Wiesner, P. T. Ho, W. C. Liu, and M. N. Shanbhag, *Canad. J. Chem.*, 1975, **53**, 2140; K. Wiesner, I. H. Sanchez, K. S. Atwal, and S. F. Lee, *Canad. J. Chem.*, 1977, **55**, 1091.



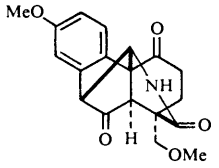
(41)



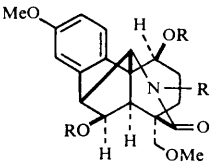
(42)



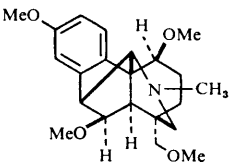
(43) $R^1 = H$; $R^2 = CH_2—\overset{O}{\overset{\|}{C}}—H$
(44) $R^1 = Ac$; $R^2 = CH{=}CHOMe$
(45) $R^1 = Ac$; $R^2 = CO_2Me$



(46)



(47) R = H
(48) R = Me



(49)

been almost impossible to accomplish without the preliminary experience on models. An additional advantage, which we derived from our preliminary studies, was the n.m.r. spectra of our model intermediates. These served us as a reliable and precise simulation of the corresponding n.m.r. patterns in the synthesis proper and helped us to recognize the various synthetic intermediates without a shadow of doubt.

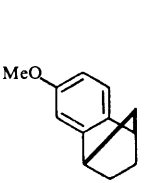
The conversion of the 'aromatic intermediate' to chasmanine was accomplished as follows. Reduction of compound (24) with lithium in liquid ammonia followed by acetylation and acid treatment gave the $\alpha\beta$-unsaturated ketone (52). In this product the new chiral centre was created as expected[19] by exoprotonation with respect to the bicycloheptane system and is consequently epimeric to the corresponding chiral centre in chasmanine. Compound (52) is somewhat more stable than the desired epimer and equilibration requires very drastic conditions which cause extensive destruction of the material. Consequently, the third variant[19] of our model synthesis (50) → (51) was successfully utilized.

Photochemical addition of allene to (52) gave a high yield of the single product (53), the configuration of which was predictable by our addition rule[13] and in agreement with the corresponding model compound whose structure had been corroborated by *X*-ray crystallographic studies.[19] The ethylene glycol acetal (54) prepared from the photo adduct was now converted into the acetoxy ketone (55) in an overall yield of 72% by the following three steps.

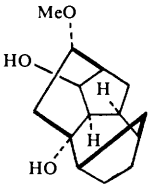
(i) Ozonolysis followed by borohydride reduction of the ozonide.

(ii) Acetylation.

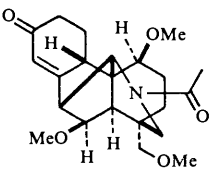
(iii) Removal of the acetal group by mild acid treatment.



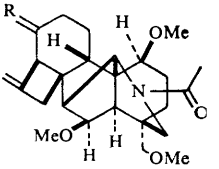
(50)



(51)



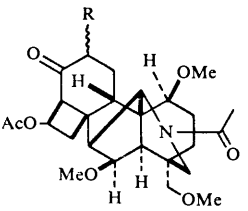
(52)



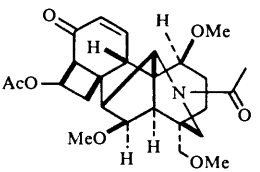
(53) R = =O

(54) R =

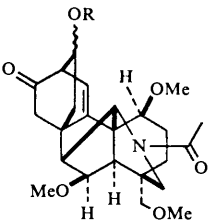
Bromination of (55) gave the monobromide (56) and dehydrobromination of this compound yielded 87% of the unsaturated ketone (57). The way was now prepared for the skeletal transposition to the nordenudatine system with the simultaneous disappearance of the 'offending' enantiomeric chiral centre. Treatment of compound (57) with mild alkali caused saponification of the acetoxy group followed by immediate reverse aldol reaction and conjugate aldol condensation and gave a 90% yield of the epimeric aldols (58). Acetylation yielded the acetates (59) and this material was transformed to the single crystalline keto-acetal (60) in high yield by a stereospecific α-hydrogenation with rhodium on alumina followed by a simple modification of the functional group system. Compound (60) was now simply and stereospecifically converted into our long



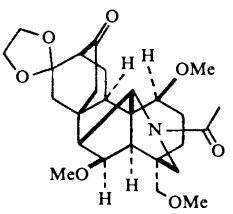
(55) R = H
(56) R = Br



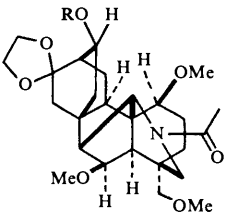
(57)



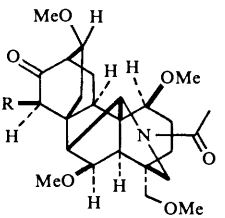
(58) R = H
(59) R = Ac



(60)



(61) R = H
(62) R = Me



(63) R = H
(64) R = Br

envisaged intermediate (26). Reduction with borohydride yielded the alcohol (61) which was methylated to (62). Deacetalization of this material gave the ketone (63) and this compound was brominated to the monobromide (64).

Finally, the bromoketone (64) was converted into the intermediate (26) using the acetalization method of Professor Barton[20] with diethylene orthocarbonate. I might mention that no other acetalization method seemed to work in this case and if Barton's paper had not appeared in time, the synthesis might well be still unfinished. As mentioned above, we were quite certain about the structures of all these intermediates since the corresponding model derivatives obtained in the same way gave n.m.r. spectra which were qualitatively and quantitatively identical in the relevant parts. As in the model series, however, the configuration of the bromine in (64) followed from the success of the subsequent rearrangement which requires antiplanarity rather than from an interpretation of the n.m.r. spectra.

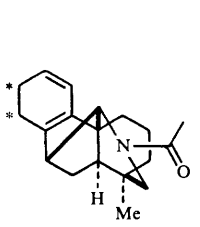
The rearrangement of the bromoacetal (26) to the oxopyrochasmanine derivative (27) was performed in the presence of a strong base in a mixture of xylene and DMSO. It proceeded, as expected, very cleanly in a yield of 85% and the racemate (27) was identical in its spectral and chromatographic properties with the corresponding optically active compound prepared from chasmanine. The synthesis of racemic chasmanine was completed with the synthetic racemate (27) without the use of a relay, but each remaining intermediate was again compared and found identical with the corresponding naturally derived chasmanine derivative. The remaining steps were simple: oxymercuration of the double bond, deacetalization, and a stereospecific reduction of the liberated keto group by lithium aluminium hydride, completed a stereospecific total synthesis of chasmanine (28).[21]

5 The Fourth Generation: Synthesis of the Denudatine System by Diene Addition

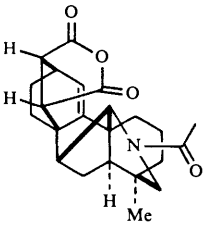
The synthesis of chasmanine has clearly demonstrated the superiority of the nordenudatine route (26) → (27) → (28) over the noratisine route, which we used three years ago for the synthesis of talatisamine. While very little can be improved in this sequence, fundamentally better methods could be developed for the synthesis of the nordenudatine intermediate (26). I started thinking about such possibilities several years ago in connection with the synthesis of the relatively simple alkaloid denudatine (67), the structure of which we had clarified at the Ayerst Laboratories.[22] A simple and obvious way to construct the system of (67) [or (26)] would be an addition between a diene of the type (65) and a suitable dienophile. However, one would first have to know whether such an addition would be stereospecific and if so, whether the dienophile would add to the β- or α-face of the diene (65). The well-known preferential exoreactivity of the bicyclo[2,2,1]heptene system in ionic reactions makes one favour the first

[20] D. H. R. Barton, C. C. Dawes, and P. D. Magnus, *J.C.S. Chem. Comm.*, 1975, 432.
[21] 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*), submitted for publication.
[22] M. Götz and K. Wiesner, *Tetrahedron Letters*, 1969, 4369.

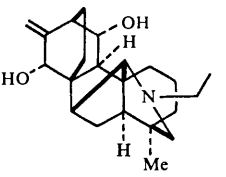
possibility, but it is necessary to find out with certainty before starting a full scale total synthesis. Thus, we first synthesized compound (65) using our aziridine rearrangement method and then studied its addition reaction with maleic anhydride.[23] The result was the stereospecific formation of the β-adduct (66) in high yield.



(65)



(66)



(67)

This type of adduct can clearly never serve as an intermediate in the construction of (67) since it lacks substitution in the α-branch of the bicyclo[2,2,2]-octane system and there is no way in which substituents can be introduced into the required positions. Consequently, in order to obtain adducts capable of further development, it is necessary to introduce substituents into the six-membered ring of (65) which contains the diene system.

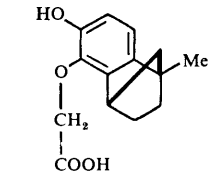
The compound which immediately comes to mind and which fills all the requirements is an *o*-quinone with the two carbonyl groups located at the asterisked carbons of (65).

Because of the notoriously unpleasant properties of *o*-quinones, I decided to try a masked *o*-quinone system which would be more stable and at the same time allow a regiospecific addition of unsymmetrical dienophiles. As the masking functionality I selected the spirolactone group which was previously used successfully by Deslongchamps[24] in his approach to ryanodine.

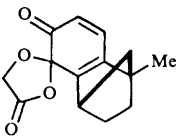
Before proceeding with actual total syntheses and investing much labour, time, and money, we decided to do one more preliminary study and to synthesize rapidly and efficiently compound (74), the C, D ring system model for denudatine (67). The starting material (68)[25] was oxidized with *N*-bromosuccinimide and the resulting spirolactone (69) was immediately allowed to react with ethylvinyl sulphide. The two epimeric adducts (70) were obtained in a yield of 85% based on compound (68). Mild hydrolysis of (70) with methanolic potassium carbonate gave the single highly crystalline diketone (71) in a 92% yield.

Compound (71) reacts selectively with Grignard reagents, thus, treatment of this material with a large excess of trimethylsilylmethyl magnesium chloride gave exclusively the product (72) in high yield. Desulphurization of (72) with

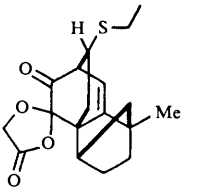
[23] K. Wiesner, P. T. Ho, and S. Oida, *Canad. J. Chem.*, 1974, **52**, 1042.
[24] D. Berney and P. Deslongchamps, *Canad. J. Chem.*, 1969, **47**, 515.
[25] K. P. Nambiar, Ph.D. Thesis, University of New Brunswick, 1977.



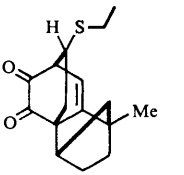
(68)



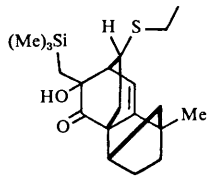
(69)



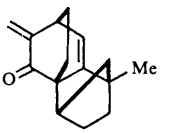
(70)



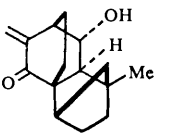
(71)



(72)



(73)



(74)

Raney nickel followed by an acid catalysed elimination of the trimethylsilyl group yielded 90% of the dienone (73).

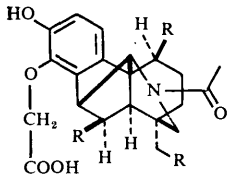
Finally, protection of the $\alpha\beta$-unsaturated ketone system, a stereospecific hydroboration, and deprotection gave hydroxyketone (74), the structure of which was corroborated by *X*-ray crystallographic studies of the *p*-bromobenzoyl derivative.[26]

If we now apply the above sequence to the aromatic intermediate (75), there is every reason to believe that a simple synthesis of denudatine (67) will result. Because of our limited resources, this problem is temporarily at a standstill.

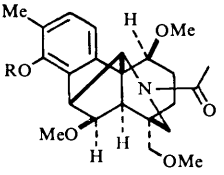
I shall now turn to the description of the work already accomplished in the direction of a new, more efficient, shorter, and completely regio- and stereospecific synthesis of chasmanine. In view of what I said in the introduction about the main purpose of our work, this is closer to my heart than denudatine and for this reason denudatine has to wait. The aromatic intermediate (76) was oxidized to a spirolactone as in the model system (68) → (69) and addition of benzylvinyl ether gave the adduct (83) in high yield. The analogy of compound (83) and of the 'old' chasmanine intermediate (59) is striking, as is the difference in the number of steps which the two similar products required to be synthesized. I shall first comment briefly on the synthesis of (76) and then outline the further development of the adduct (83) to chasmanine.

The compound (76) which was transformed to the nordenudatine derivative (83) in virtually one step was obtained in high yield (80—85%) from the standard 'aromatic intermediate' (77) as follows. The aromatic methoxy group was

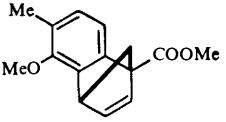
[26] K. Wiesner, T. Y. R. Tsai, G. I. Dmitrienko, and K. P. Nambiar, *Canad. J. Chem.*, 1976, **54**, 3307.



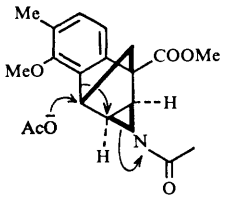
(75) R = H
(76) R = OMe



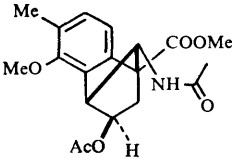
(77) R = Me
(78) R = H
(79) R = CH_2COOMe



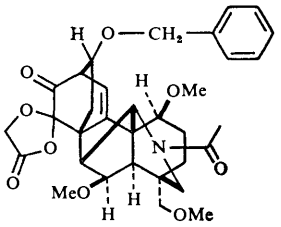
(80)



(81)



(82)



(83)

selectively cleaved by reflux with sodium thioethoxide in DMF to the phenol (78). Alkylation of (78) with methyl bromoacetate yielded (79). Under carefully controlled conditions the methyl group in (79) was oxidized with chromic acid to an aromatic aldehyde in a 90% yield. Finally, perbenzoic acid oxidation of the aromatic aldehyde followed by basic hydrolysis gave 85% of the phenolic acid (76).

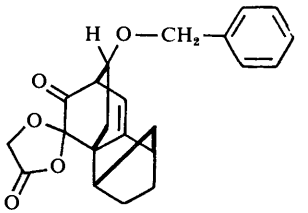
The preparation of compound (77)[27] is much more efficient than the synthesis of the 'old' chasmanine intermediate (24). The reason for this is the positions of the aromatic substituents which are favourable to a completely regiospecific aziridine rearrangement. Furthermore, several improvements in individual steps have contributed to a large increase in the overall yield and a significant decrease in the time and labour involved.

The most significant of the innovations[28] was the use of trimethylsilylazide[29] for the direct transformation of the tricyclic ester (80) to the acetyl aziridine (81). This product rearranged stereo- and regio-specifically on acetolysis to the synthon (82). The rearrangement portrayed by the arrows in formula (81) is accelerated by the methoxy group situated *ortho* to the migrating benzene bond, while the potentially competing rearrangement is slowed down by the ester carbonyl. Thus, complete regiospecificity results. Compound (82) was converted

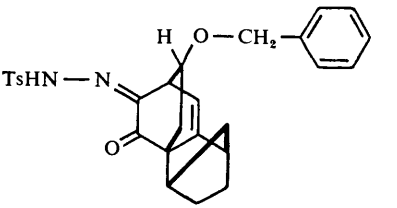
[27] Unpublished work by T. Y. R. Tsai, A. Feicht, R. Marini-Bettolo, and D. Krikoryan.
[28] Unpublished work by T. Y. R. Tsai.
[29] L. Birkofer, A. Ritter, and P. Richter, *Chem Ber.*, 1963, **96**, 2750.

into the 'aromatic intermediate' (77) by our standard methods.

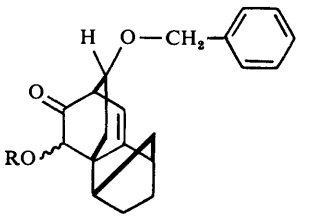
The development of the 'nordenudatine intermediate' (83) to chasmanine is foreshadowed only by model work.[30] The model-analogue of (83), compound (84), was converted into the tosylhydrazone (85). Borohydride reduction of (85) followed by acidic hydrolysis yielded the epimeric ketols (86) which were converted into the corresponding mesylates (87). Reduction of (87) with calcium in ammonia followed by acetylation yielded the intermediate (88) which is the same as in the photochemical approach. It was transformed to the bromoketal (89) and hence to the chasmanine model (51) as in the photochemical synthesis of chasmanine.



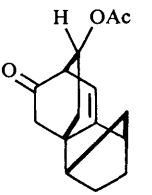
(84)



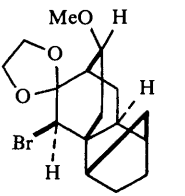
(85)



(86) R = H
(87) R = Ms



(88)



(89)

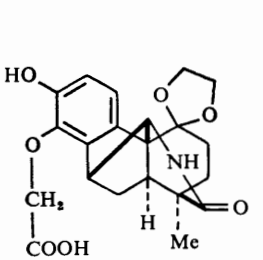
The flaw that a substituent present in (84) has been removed and subsequently reintroduced was made necessary by our inability to control stereospecifically the configuration of the ketol (86). Moreover, in the nordenudatine system bromine is required as a leaving group and we were unable to introduce the β-bromo-substituent by displacement. However, the flaw is only aesthetic, the yields of all steps were almost quantitative and introduction of the bromine by displacement would decrease the number of operations by only one.

Besides the increased efficiency in the synthesis of the aromatic intermediate (77) the construction of the C,D ring system in the potential fourth generation chasmanine synthesis has been shortened by seven steps and I believe that the entire process is now close to our initial objective.

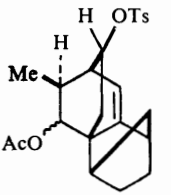
[30] Unpublished work by K. S. Atwal and I. Sanchez.

There is another advantage inherent in our fourth generation methods as compared with the already completed photochemical synthesis of chasmanine. It seems that it would be possible to place a substituent on the aromatic ring of the 'aromatic intermediate' which would end up on the bridgehead of the C,D ring system and be ultimately converted to a hydroxy group. Thus, delphinine (1) itself might be reached with about the same effort as chasmanine.

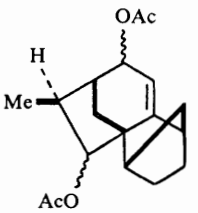
To illustrate the versatility of our fourth generation methods I wish to mention in conclusion a second very efficient synthesis of napelline (32) which is now in progress and is presently at the stage of compound (90).[31] The construction of the C,D ring system as foreshadowed by a model study[32] proceeded as follows: the spirolactone (84) was converted by unexceptional methods to the derivative (91) with a tosyloxy group suitably disposed for rearrangement, acetolysis of (91) gave a mixture of the epimeric acetates (92) which by saponification and oxidation yielded the diketone (93), which was identical to the corresponding intermediate in our 'old' napelline model work[33] and is an analogue of the intermediate (94) which we converted some time ago into napelline.[16]



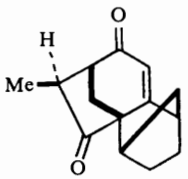
(90)



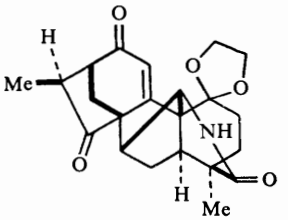
(91)



(92)



(93)



(94)

In conclusion, I wish to thank my younger colleagues who struggled with devotion, courage, and ingenuity to make this synthetic development possible. Their names are recorded in the references and it is perhaps interesting to point

[31] Unpublished work by W. W. Sy and C S. J. Tsai.
[32] Unpublished work by R. Marini-Bettolo.
[33] Unpublished work by C. S. J. Tsai.

out how few there were and how individual names are repeated in several of the references quoted. This testifies to the hard work these young men and women were doing, but perhaps also to the efficiency of our methods. I also wish to thank my secretary, Miss Judy Briggs, for the typing of the manuscripts and general help in my English composition not only in this article but in all the references quoted. Finally, it is a pleasure to thank the National Research Council, Ottawa, and the Hoffman–La Roche Company, Nutley, and Vaudreuil for supporting our studies in synthetic strategy over many years, and the Merck, Sharp and Dohme Company, Montreal, for a grant in the current year.