THE TOTAL SYNTHESIS OF RACEMIC TALATISAMINE

KAREL WIESNER

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

ABSTRACT

The first synthesis of a hexacyclic polysubstituted aconite alkaloid with a rearranged skeleton is described. The crucial step of the synthesis is a rearrangement of an atisine-type intermediate. This rearrangement step is related to the assumed biogenesis of delphinine-type alkaloids.

It is many years since we started to study the chemistry of diterpene alkaloids in my New Brunswick Laboratory. We have proposed the structures of the first two relatively simple ones, veatchine and atisine **3**, in 1953[1], and finally deduced the constitutions of the two most complex ones, delphinine **2** and aconitine†, in 1959[2]. Immediately after the conclusion of the structural exploration, which with no nuclear magnetic resonance and mass spectroscopy available to us yet was still quite a challenge, we started considering the synthetic problem.

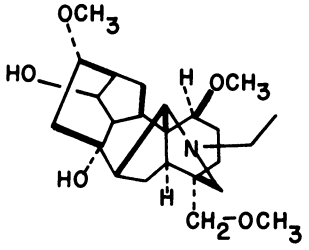
From all the compounds which presented themselves as possible targets for synthesis, we were from the beginning attracted most to delphinine **2**. However, it was clear that with its bridged hexacyclic skeleton and seven substituents the delphinine fortress could not be taken by direct assault of inexperienced troops.

Thus, we have decided to sharpen our skill and develop the necessary methods by travelling patiently the same road as in the structure elucidation, proceeding from the simpler to the more complex. We have gradually synthesized the garrya alkaloids[3], atisine[4], the 'delphinine aromatization product'[5] in which the C/D ring system of delphinine is replaced by an anisole ring and, finally, recently the first naturally occurring hexacyclic alkaloid, napelline[6].

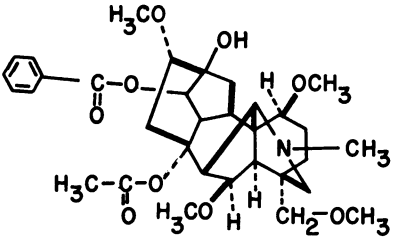
In the present lecture I wish to discuss the nearest approach to the delphinine system to date: the total synthesis of the alkaloid talatisamine **1**[7]. In this compound Nature has conveniently presented us with a slightly simplified version of delphinine with two substituents missing, and we have decided to test on talatisamine one of the main approaches under consideration for a delphinine synthesis.

---

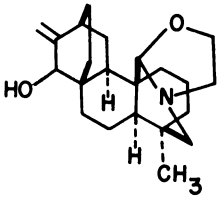
†The structure of aconitine was derived in collaboration with Professor G. Büchi.



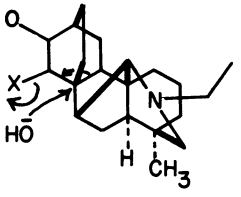
1



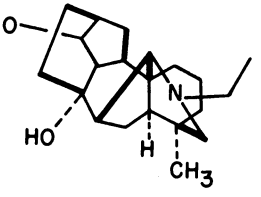
2



3

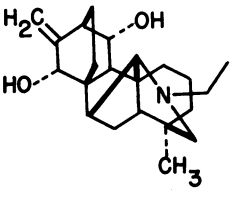


4

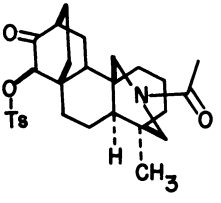


5

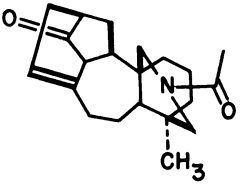
Scheme 1



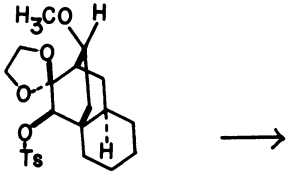
6



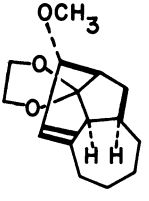
7



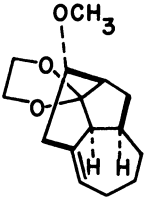
8



9



10



11

Scheme 2

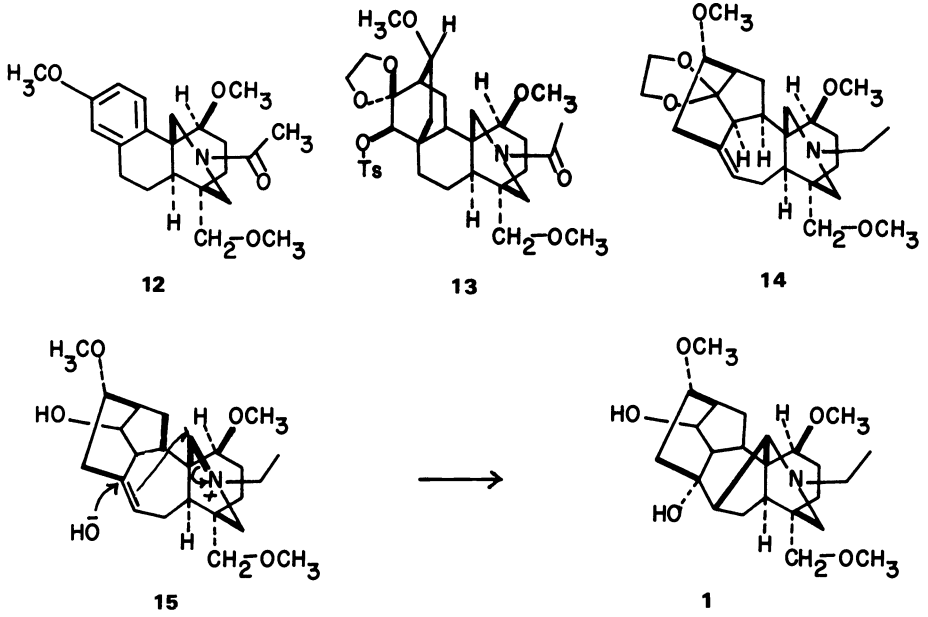
The method chosen is of some interest, since in its last phase it imitates the possible biosynthesis of delphinine-type alkaloids. It was proposed a long time ago independently by Professor Cookson and by us[8] that the delphinine system **5** might originate from the atisine system **3** by a loss of a carbon atom bridging and the rearrangement shown in formula **4**. The order of these steps during the biosynthesis is of course unknown, and the rearrangement might occur either before or after the bridging of ring B. It is perhaps significant that many years later the alkaloid denudatine **6** has been found[9] to possess a ring B bridged atisine skeleton.

The postulated biogenetic rearrangement of the atisine skeleton was accomplished for the first time in the laboratory when Johnston and Overton[10] subjected the atisine derivative **7** to pyrolysis and obtained a high yield of compound **8**.

We have been studying in my laboratory the rearrangement of the easily available compound **9** in order to ascertain whether such a process could be used as a step in a talatisamine synthesis. It turned out that a solvolysis of **9** in dimethyl sulphoxide and tetramethyl guanidine at 180°C gave a one-to-one mixture of the double bond isomers **10** and **11** in a yield of 85 per cent.

It will be clear from the sequel that in the actual talatisamine synthesis the product analogous to **11** can be converted to the natural alkaloid in three simple steps. This has not been possible with the double bond isomer analogous to **10** or **8**.

Since Overton's and our own studies gave us confidence in the feasibility of the crucial rearrangement step, we have planned the main stages of the synthesis as shown in the formula Scheme 3.



Scheme 3

The aromatic intermediate **12** may be converted to the polysubstituted atisine system **13** by the application of our photochemical atisine synthesis[4]. The rearrangement and reduction of **13** should yield compound **14**, which by a modification of the ketal group into a secondary alcohol of the correct configuration and by mercuric acetate oxidation could be converted to **15**.

It was established some time ago, first by Büchi[2b] and later by Edwards[11, 12], that compounds of this type cyclize (as shown by arrows in formula **15**) spontaneously, and thus **15** should yield talatisamine **1**.

The method which we have actually used was the one worked out by Dr Edwards, and I wish to thank him for giving me the precise experimental conditions of this process.

The starting material for the synthesis was *trans, trans*-1,4-diacetoxy-1,3-butadiene **16**[13] and 1-cyano-6-methoxy-3,4-dihydronaphthalene **17**[14]. Heating these two compounds together neat at 150°C for 3 days gave a high yield of the two Diels–Alder adducts **18** and **19** in equal amounts. This was a seemingly disappointing result in the first step of the synthesis, but not an unexpected one. Both the cyano group and the anisole ring in the dienophil **17** try to obey the endo rule, and neither of the two substituents succeeds in overcoming the influence of the other one.

Hydrogenation of the two adducts **18** and **19** with palladium on charcoal gave the two dihydro derivatives **20** and **21** in quantitative yield. Inspection of the nuclear magnetic resonance (n.m.r.) spectra revealed immediately the configurations of the two products. While the chemical shift of both acetate methyls in compound **20** was normal (τ = 7.9 p.p.m.), in compound **21** one acetate methyl appeared at high field at τ = 8.4 p.p.m. and the other one at the normal value τ = 7.9 p.p.m. As can be seen on models, in compound **21** one acetoxy group is located in the shielding region of the anisole ring and its n.m.r. peak is thus shifted to high field.

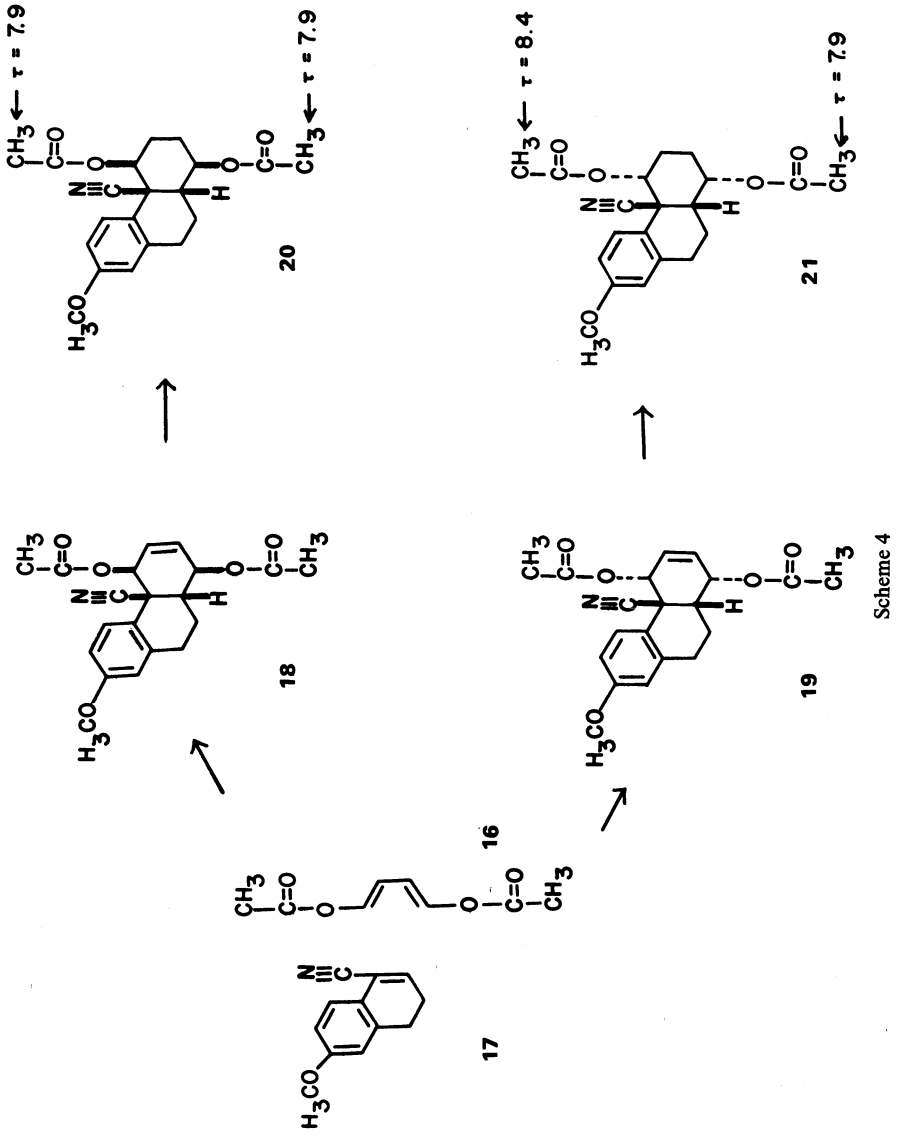
Selective hydrolysis of compounds **20** and **21** under controlled conditions gave a 97 per cent yield of the two products **22** and **23**. The structure of compound **23** was clear, since its formation involved the loss of the 'high field' acetoxyl from compound **21**.

The structure of compound **22** could of course not be directly deduced from its n.m.r. spectrum, but it followed from the subsequent conversion of **23** and **22** into the *identical methoxy ketone* **27**.

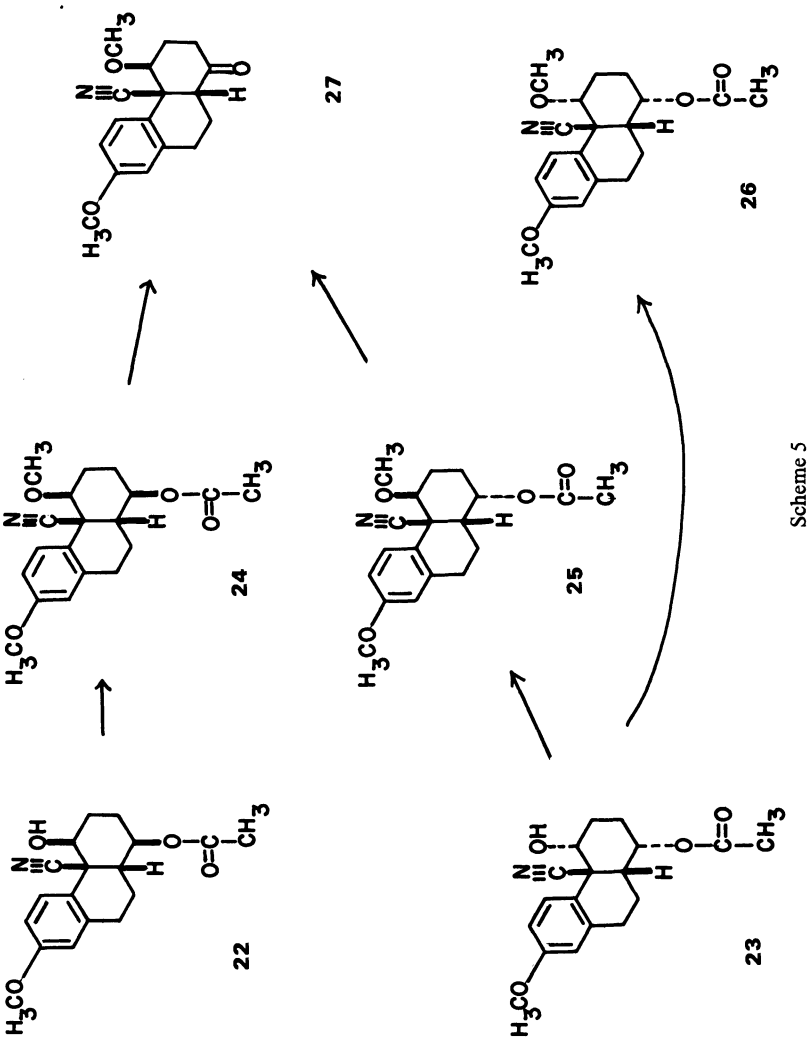
Rapid methylation of the acetoxy alcohol **23** in concentrated dioxane solution with methyl iodide and sodium hydride gave a high yield of the normal expected methylation product **26**. If, on the other hand, the alkoxide ion formed from **23** by the action of sodium hydride was allowed to equilibrate before the addition of methyl iodide, the epimeric product **25** resulted in a yield of 96 per cent. Saponification of the acetoxy group followed by oxidation with chromium trioxide in pyridine gave the methoxy ketone **27**.

It would clearly not be possible to assign configuration to compound **27** with certainty on the basis of this mode of formation. However, the same methoxy ketone was obtained in a much simpler manner from our second acetoxy alcohol **22**.

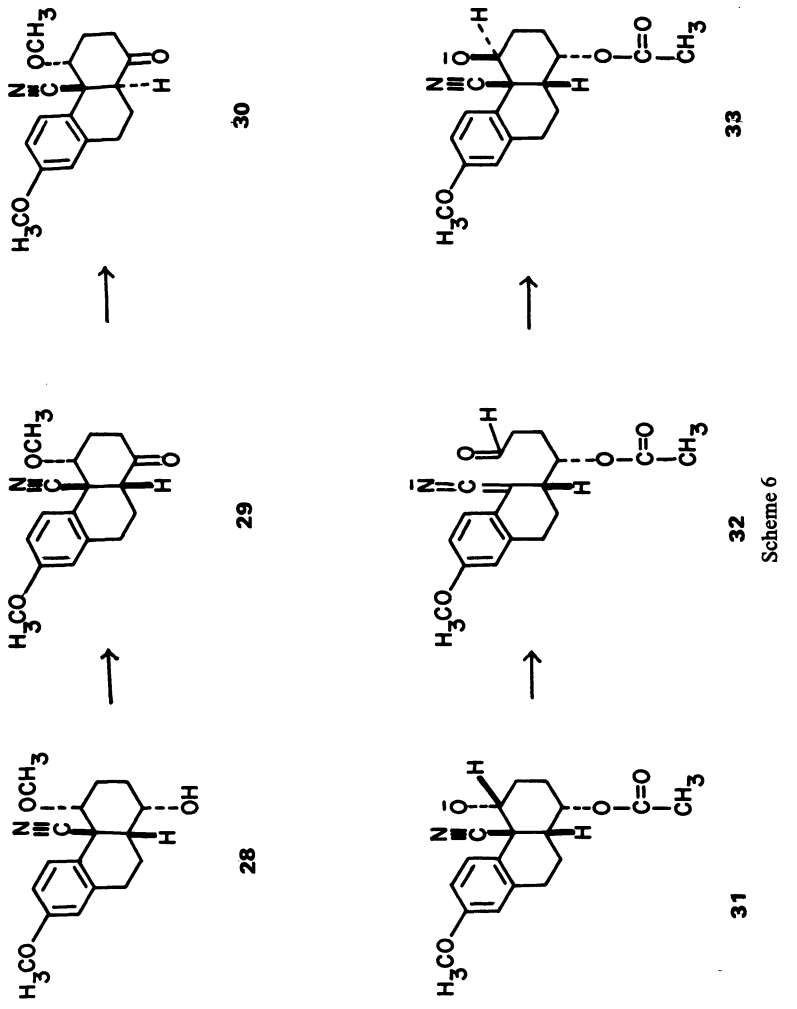
Methylation of compound **22** with or without prior equilibration of the alkoxide ion gave the same normal methylation product **24**, which by saponification of the acetoxyl and oxidation of the liberated hydroxy group



Scheme 4



Scheme 5



Scheme 6

yielded the methoxy ketone **27**. This mode of formation of **27** proved its configuration, since **27** was obtained from **22** under conditions in which no configurational change of any asymmetric centre has occurred.

The ketone **27** turned out to be stable under reflux with alkali, and thus we had to assume that the A/B *cis*configuration was the energetically favoured one in this case. This must be due to the strong non-bonded interaction of the β-methoxyl and the aromatic ring in the A/B *trans*system. It was possible to prove this last assumption as follows.

Compound **26** was saponified to the alcohol **28**, and this product was oxidized to the methoxy ketone **29**. Compound **29** is the methoxy epimer of the ketone **27** and it readily epimerized at the A/B ring junction to yield the transoid ketone **30** on heating with alkali.

The methylation of the alcohol **23** to the methoxy derivative **25** must proceed by a retroaldol cleavage aldol condensation mechanism portrayed by the structures **31** → **32** → **33**.

Such a mechanism could clearly epimerize not only the methoxyl but also the ring junction. That this in fact does not take place must be due to the preferential stability of the system **33**.

The large-scale stereospecific production of the methoxy ketone **27** turned out to be remarkably simple.

It was possible to subject the mixture of the two diastereoisomeric Diels–Alder adducts **18** and **19** to five high-yield steps without separation and to end up with the single homogeneous product **27**, which was readily purified by crystallization.

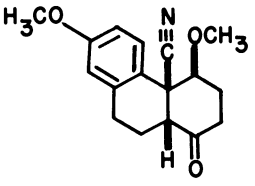
This may be a good lesson to remember. I have seriously considered abandoning the Diels–Alder addition as a source of our starting material, when it turned out to be non-stereospecific.

Treatment of the methoxy ketone **27** with n-butyl lithium and 1,3-dithiane in tetrahydrofurane[15] gave the two epimeric alcohols **34** in a yield of 96 per cent. While the two crystalline epimers were separated for characterization purposes, the next step was performed on the unresolved mixture. Elimination of the tertiary alcoholic group from **34** with thionyl chloride in pyridine yielded 75 per cent of the exocyclic compound **35** and a varying amount of the endocyclic product **38**. The two materials were converted by separate routes into the same cisoid aldehyde **37**. Compound **35** was reduced at room temperature in methylene chloride and trifluoroacetic acid with triethylsilane[16] to the crystalline saturated thioacetal **36** in a yield of 95 per cent.

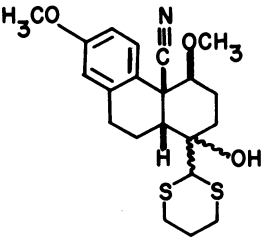
The thioacetal group was cleaved with mercuric chloride and cadmium carbonate in aqueous acetonitrile to yield 93 per cent of the oily epimeric cisoid aldehydes **37**.

The endocyclic derivative **38** obtained in the dehydration of compound **34** was cleaved by the same method and the resulting α,β-unsaturated aldehyde **39** was hydrogenated with palladium on charcoal to the cisoid aldehydes **37**.

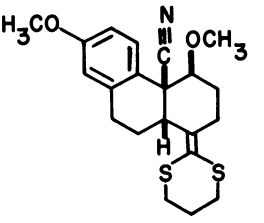
It was now necessary to invert the ring junction of compound **37**. Bromination of **37** in acetic acid yielded a single crystalline monobromoderivative **40** which was dehydrobrominated with lithium bromide and lithium carbonate in dimethylformamide to the crystalline unsaturated aldehyde **41** in a yield of 97 per cent.



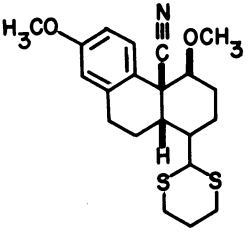
27



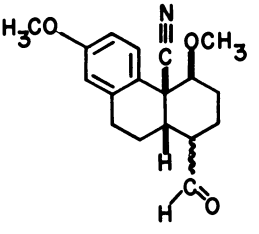
34



35

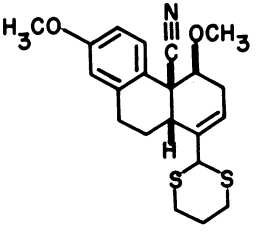


36

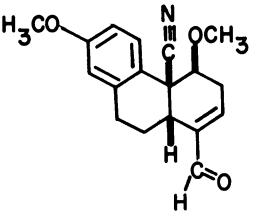


37

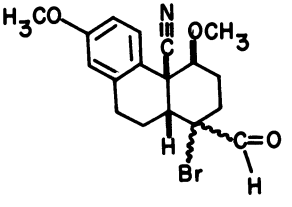
Scheme 7



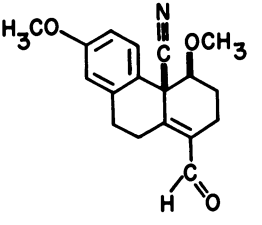
38



39

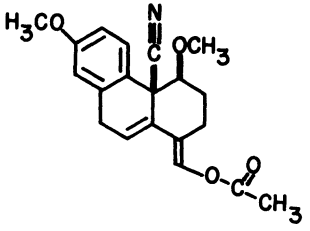


40

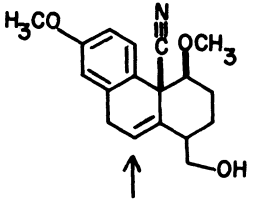


41

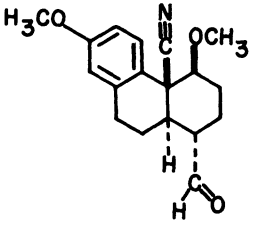
Scheme 8



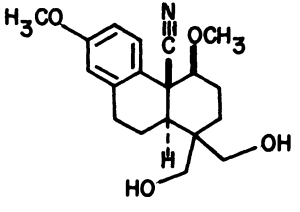
42



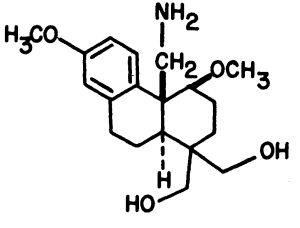
43



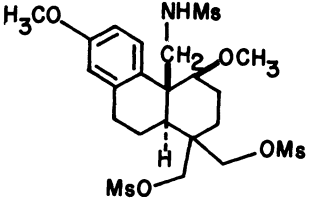
44



45



46



47

Scheme 9

Enolacetylation of **41** gave compound **42**, which was reduced with sodium borohydride in aqueous tetrahydrofurane to the crystalline unsaturated alcohol **43**. The over-all yield of these two steps was 95 per cent.

At this point we were tempted to switch our sights to delphinine. Since we had to expend several (almost quantitative) steps to adjust the stereochemistry of the A/B ring junction, we could introduce, if we so desired, an oxygen function at the point indicated by the arrow in formula **43** with no extra effort. However, the bridgehead substituent in the C/D ring system of delphinine presented a complication which we decided not to face as yet. The best target at our present stage of synthetic development would be an alkaloid with a complete delphinine system in which only the C/D bridgehead substituent would be missing. This compound, regrettably, nature has failed to provide*.

Hydrogenation of compound **43** with palladium on barium carbonate followed by oxidation with chromium trioxide in pyridine yielded the crystalline *trans* aldehyde **44**, which was readily separated by chromatography from some regenerated *cis* aldehyde mixture **37**. This last material was added to the next bromination batch, and thus ultimately the entire amount of our substance was converted to **44**.

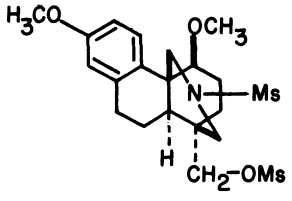
The remaining steps to the aromatic intermediate **48** followed closely the process worked out by Nagata *et al.*[17].

The *trans* aldehyde **44** gave with formaldehyde 90 per cent of the crystalline diol **45**. Reduction of **45** with lithium aluminium hydride under Nagata's conditions caused demethylation of the ring A methoxyl. No modification of the method which would avoid this difficulty was found if the same reducing agent was used. However, sodium dihydro-bis(2-methoxyethoxy) aluminate in benzene at room temperature gave quantitatively the desired crude amine **46**, which was immediately used in the next step. Mesylation of this material to the crude trimesylate **47** and the cyclization (with sodium hydride in tetrahydrofurane) of **47** to the beautifully crystalline compound **48** was again performed under Nagata's conditions. The over-all yield from the diol **45** to the bridged compound **48** was 70 per cent.

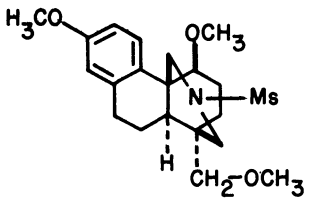
Finally, reductive cleavage of the mesyloxy group—with dihydro-bis(2-methoxyethoxy) aluminate—to the corresponding primary alcohol, and the methylation of this material with sodium hydride and methyl iodide in dioxane, concluded the first stage of the synthesis and yielded the tetracyclic trimethoxy derivative **49**. It was a beautifully crystalline compound melting at 190–191°C and it showed in its n.m.r. spectrum peaks corresponding to its entire functionality—singlet (6H) $\tau = 6.65$ p.p.m. (ring A and primary $-OCH_3$); singlets (3H each) $\tau = 6.20$, 7.24 p.p.m. (aromatic $-OCH_3$, $>N-SO_2-CH_3$). To construct the C/D ring system we used the photochemical method we developed some time ago for the synthesis of atisine[4].

Compound **49** was subjected to Birch reduction and the dihydroderivative **50**, which has also lost the *N*-mesyl group, was converted to the α,β-unsaturated ketone **51** by acetylation and treatment with aqueous methanolic hydrochloric acid.

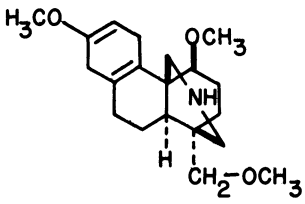
* Added to proof. This supposedly missing compound is in fact chasmanine the structure of which has been revised recently.



48

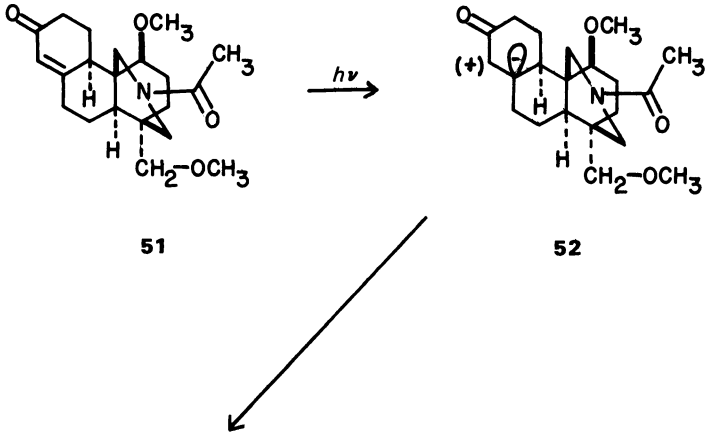


49

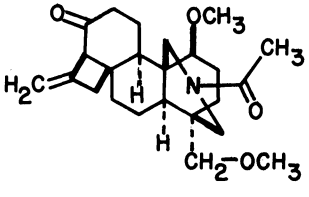


50

Scheme 10



51 52



53

Scheme 11

Photoaddition of allene to compound **51** in tetrahydrofurane at −80°C gave stereospecifically 99 per cent of the adduct **53**.

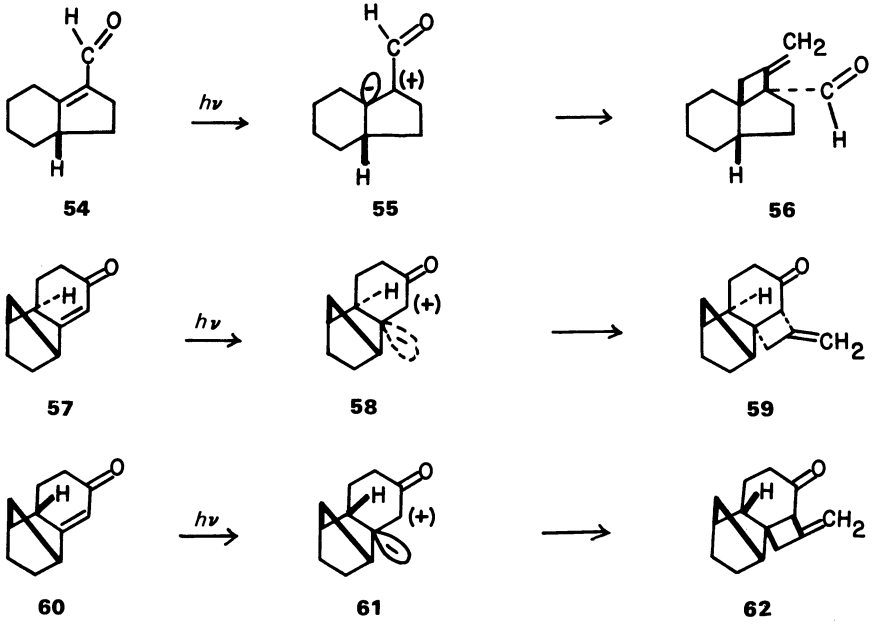
We have studied in our laboratory several cases of addition of olefins to α,β-unsaturated ketones in connection with our synthetic work on diterpene and lycopodium alkaloids. In all these cases the unsaturated ketone was part of a polycyclic system and the addition was completely stereospecific. It turned out that the stereochemistry of the adduct *always* obeyed the following simple rule, the theoretical implications of which still have to be evaluated.

If we assume[18] that the excited state of, for example, compound **51** is polarized as indicated in formula **52**, then the position α to the carbonyl is trigonal and the β position is tetragonal with an orbital containing an electron pair. This orbital may swing through the plane of the three substituents, and the asymmetric centre is free to assume the most stable configuration.

This in the case of **52** corresponds to the *trans*–anti-*trans* configuration of the hydrophenanthrene system, and consequently the stereochemistry of the adduct is as shown in **53**.

The trouble with the rule until recently was that, while the half-dozen examples that we had encountered worked perfectly, they were all to a certain extent similar. A quite different case was reported last year by Ziegler and Kloek[19].

The excited state of the indene aldehyde **54** must clearly prefer the cisoid configuration **55**, and thus the adduct **56** is formed on irradiation with allene.



Scheme 12

We have encountered at about the same time in connection with some model studies for diterpene alkaloid synthesis the following two examples. The two epimeric compounds **57** and **60** prefer the excited states **58** and **61**, respectively, with the cyclohexane ring annelated to the bicycloheptene system either exo–exo (**58**) or endo–endo (**61**). Allene addition was in both cases completely stereospecific, and the two adducts are portrayed by the stereostructures **59** and **62**. The structure of both products followed from x-ray analysis performed on suitable derivatives of **59** and **62** by Dr M. Przybylska and Dr F. R. Ahmed at the National Research Council Laboratories, Ottawa.

Returning now to the talatisamine synthesis, the photoadduct **53** was ketalized with ethylene glycol under standard conditions to yield quantitatively the ketal **63**. Oxidation of **63** with osmic acid–metaperiodate in aqueous dioxane gave a crystalline cyclobutanone, and this product yielded by reduction with sodium borohydride the alcohol **64**. Treatment of this last compound with hydrochloric acid in aqueous tetrahydrofurane caused the unmasking of the keto group, opening of the cyclobutanole by a reverse aldol reaction and an immediate aldol condensation of the aldehyde group on the other side of the ketone.

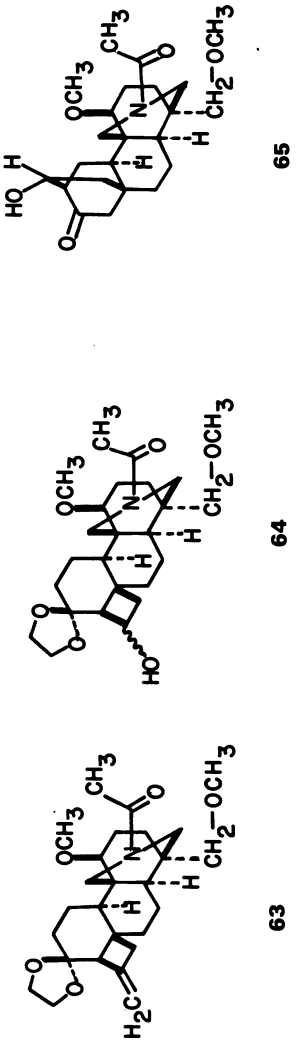
The ketoalcohol **65** was produced in this sequence of reactions stereospecifically in a yield of 90 per cent. The stereospecific formation of this system was already known to us from previous model experiments, and the configuration of the alcohol **65** was corroborated by an x-ray structure analysis of the final poly-substituted atisine derivative **13**.

The alcoholic group of compound **65** was finally methylated with sodium hydride and methyl iodide in dioxane to yield the crystalline trimethoxy derivative **66**. Thus, the stereospecific synthesis of a tetra-substituted atisine derivative was completed and it merely remained to introduce one more substituent in the only activated position of the molecule adjacent to the ketone.

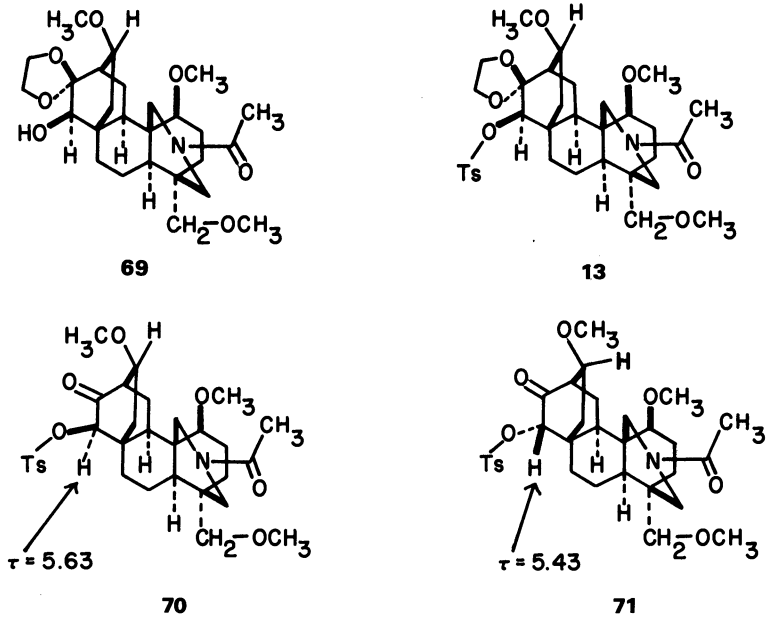
Treatment of compound **66** with sodium hydride in refluxing dioxane, followed by cooling and addition of dibenzoyl peroxide[20] yielded 65 per cent of the oily α-benzoate **67**. Ketalization of this product with ethylene glycol, trimethyl orthoformate and sulphuric acid, alkaline hydrolysis of the benzoyl group and oxidation with the chromic acid–pyridine complex in methylene chloride gave in an over-all yield of 85 per cent the ketal ketone **68**.

Compound **68** showed in the infra-red spectrum the ketonic carbonyl adjacent to the ketal group at 1735 cm^{-1}. Borohydride reduction of this ketone proceeded stereospecifically from the α side to yield quantitatively the alcohol **69**. Finally, tosylation of **69** with *p*-toluenesulphonyl chloride and pyridine gave the beautifully crystalline β-tosylate **13** (m.pt, 236–237°C). Thus, all substituents were in place and the stage was set for the rearrangement of the skeleton.

In order to establish the configuration of the tosyl group, we have also prepared the two epimeric tosyloxy ketones **70** and **71**. The first one was obtained simply by a mild acid catalysed deketalization of compound **13**. Its epimer **71** was prepared by an alkaline hydrolysis of the original α-benzoate **67** followed by tosylation.



Scheme 13



Scheme 14

It is interesting that these α-substituted carbonyl derivatives showed very little tendency to epimerize on mild treatment with acid or base. This is in agreement with the vigorous conditions which were necessary to bring about the enolization of the ketone **66**.

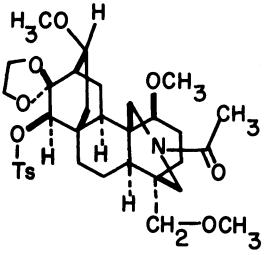
The n.m.r. spectra of the epimeric tosyloxy ketones **70** and **71** showed the hydrogen unshielded by the tosyloxy group as a singlet. This signal was shifted in the α-tosyloxy derivative **71** (τ = 5.43 p.p.m.) downfield with respect to the same signal in the β-tosyloxy compound **70** (τ = 5.63 p.p.m.). The shift is clearly due to the deshielding influence of the methoxyl in compound **71**, and this effect thus confirms the configurations, which we have originally assigned on the basis of steric hindrance to the approach of reagents.

The best chemical proof for the configuration of the tosyloxy group in compound **13** is of course the success of the subsequent rearrangement step, which does not work with the epimeric derivative.

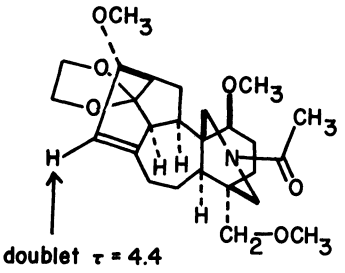
The final rigorous corroboration of the entire structure and stereochemistry of compound **13** was achieved by Dr F. R. Ahmed (National Research Council of Canada, Ottawa), who kindly performed an x-ray analysis on it[21].

The stage was set at this point to try the crucial rearrangement, on the outcome of which the entire venture depended.

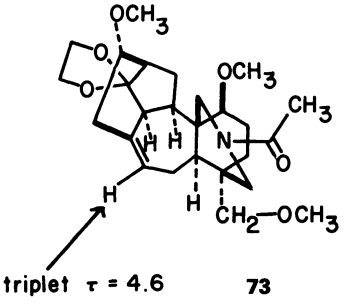
As I have mentioned before, we were well prepared by the study of models, and consequently the optimum conditions for the solvolysis were already known to us. Nevertheless, it was with a feeling of anticipation that we applied these conditions to our intermediate **13**.



13

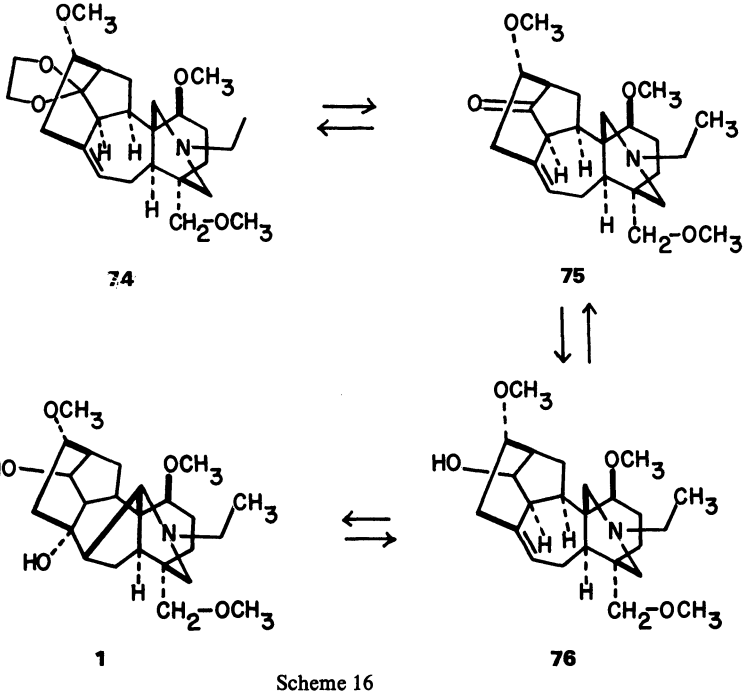


72



73

Scheme 15



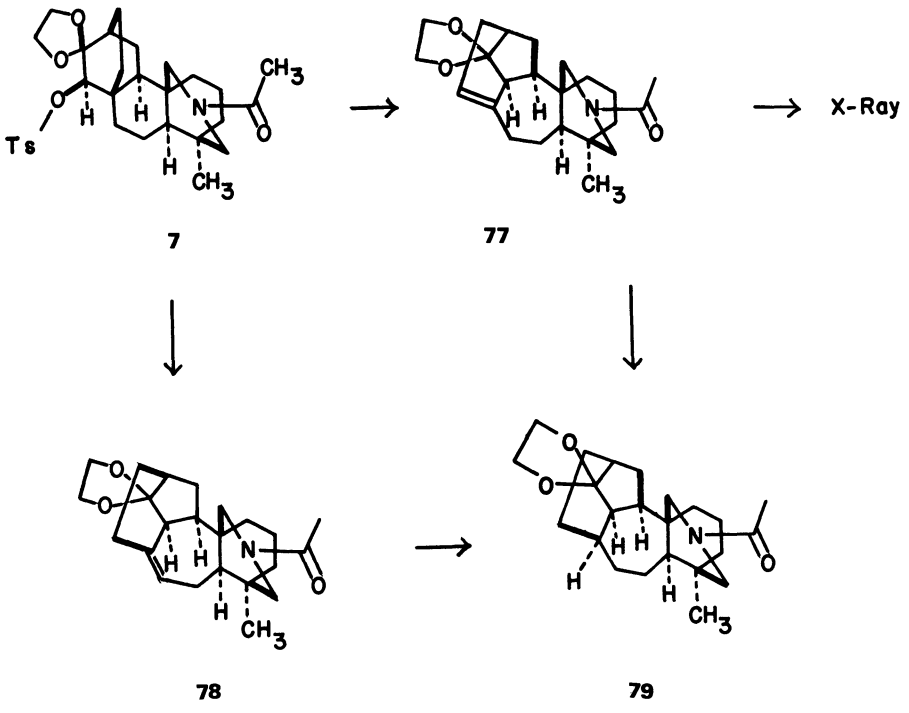
74 75 1 76

Scheme 16

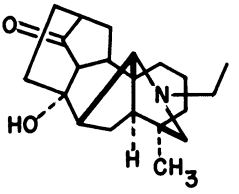
The racemate **13** was heated in a 1:1 mixture of dimethylsulphoxide and tetramethylguanidine to 180°C for 24 h. Two products were obtained, each in a yield of 40 per cent. Both compounds contained a double bond which showed in the n.m.r. spectrum the presence of one vinylic hydrogen. The splitting of this proton, which appeared as a doublet (τ = 4.4 p.p.m.) in compound **72** and triplet (τ = 4.6 p.p.m.) in compound **73** enabled us to decide which formula represented which material, even before a connection with talatisamine was established.

Compound **73** was reduced with lithium aluminium hydride to the racemic amine **74**. The optically active form of this substance is very easily obtainable from talatisamine, and we were delighted to find that both materials were indistinguishable in thin layer chromatography and in infra-red, n.m.r. and mass spectroscopy. The last three simple steps of the synthesis were carried out with the naturally derived optically active compound **74**.

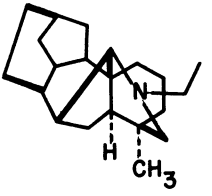
This substance was first deketalized in aqueous methanolic hydrochloric acid to the ketone **75**, which showed in the infra-red spectrum a carbonyl maximum at 1760 cm^{-1}, typical of the apex keto group in the C/D ring system of delphinine-type alkaloids. Sodium borohydride reduction of the keto group in compound **75** was stereospecific, probably as a result of the steric hindrance to the approach of the hydride ion from the side shielded



Scheme 17



80



81

Scheme 18

by the methoxyl. The product of this reduction **76** was now oxidized by mercuric acetate, utilizing the conditions worked out by Edwards[12], and, as expected, crystalline talatisamine **1** was obtained in a yield of 40 per cent.

The reverse process from talatisamine to the relay compound **74** proceeded as follows. Talatisamine was converted to the diacetate and this material gave by the reductive pyrolysis in the presence of lithium aluminium hydride, also discovered by Edwards[12], the alcohol **76**. Oxidation to the ketone **75** and ketalization of this last product to compound **74** completed the preparation of the optically active relay.

Before concluding, I should like to mention the conversion of an atisine derivative to a compound with a full delphinine skeleton, which was recently completed in my laboratory.

The ketal tosylate **7** prepared from atisine was solvolysed in dimethylsulphoxide and tetramethylguanidine, exactly as in the talatisamine synthesis, and the two products **77** and **78** were obtained. Compound **77** was known, since it had been already described by Overton[10], and its structure was secured by x-ray crystallography. The new product **78** must be a double bond isomer of **77**, since both materials yielded the same dihydro derivative **79**. Taking into consideration the mechanism of rearrangement of the tosylate **7**, the n.m.r. spectrum of **78**, which shows one vinylic hydrogen as a triplet at $\tau = 4.66$ p.p.m., and the correlation of **77** and **78** mentioned above, the structure of the new rearrangement product **78** is rigorously proved. Lithium aluminium hydride reduction, deketalization and mercuric acetate oxidation of **78** yielded the beautifully crystalline hydroxy ketone **80**, which melted

at 159°C. Finally, the substituents were removed from this last compound, and the parent skeleton of the rearranged C_{19} aconite alkaloids **81** was obtained.

This work was accomplished by the hard work, persistence and ingenuity of a small band of young chemists in a relatively short time. It was an exceptional pleasure to work with all four of them, and I wish to thank them again for their effort and enthusiasm. They were Dr T. Y. R. Tsai, Mr (now Dr) Kurt Huber and Mr Stephen E. Bolton in my laboratory, and Dr Radoslav Vlahov at the Institute of Organic Chemistry, Bulgarian Academy of Sciences.

The financial support of the National Research Council of Canada, Ottawa, is gratefully acknowledged.

Finally, I wish to express special gratitude to the Hoffmann-La Roche Company, Nutley, New Jersey, and Vaudreuil, Quebec, for continuous financial assistance, without which, among other things, I would be unable to pay the summer salaries of some of my best students.

REFERENCES

[1] K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chem. & Ind.* 132 (1954).
[2] (a) K. Wiesner, F. Bickelhaupt, D. R. Babin and M. Götz, *Tetrahedron Letters,* No. 3, 11 (1959).
(b) K. Wiesner, M. Götz, D. L. Simmons, L. R. Fowler, F. W. Bachelor, R. F. C. Brown and G. Büchi, *Tetrahedron Letters,* No. 2, 15 (1959).
[3] Z. Valenta, K. Wiesner and C. M. Wong, *Tetrahedron Letters,* No. 36, 2437 (1964);
K. Wiesner, S. Uyeo, A. Philipp and Z. Valenta, *Tetrahedron Letters,* No. 60, 6279 (1968);
K. Wiesner, Z. I. Komlossy, A. Philipp and Z. Valenta, *Experientia,* **26**, 471 (1970).
[4] R. W. Guthrie, Z. Valenta and K. Wiesner, *Tetrahedron Letters,* No. 38, 4645 (1966).
[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.* **50**, 1925 (1972).
[6] K. Wiesner, P. T. Ho, D. Chang, Y. K. Lam, C. S. J. Pan and W. Y. Ren, *Canad. J. Chem.* **51**, 3978 (1973);
K. Wiesner, P. T. Ho and C. S. J. (Pan) Tsai, *Canad. J. Chem.* (in press);
K. Wiesner, P. T. Ho, C. S. J. (Pan) Tsai and Y. K. Lam, *Canad. J. Chem.* (in press).
[7] M. A. Khaimova, M. D. Palamareva, N. M. Mollov and V. P. Krestev, *Tetrahedron,* **27**, 819 (1971).
[8] cf. K. Wiesner and Z. Valenta in L. Zechmeister, *Progress in the Chemistry of Organic Natural Products,* Vol. XVI, p 26. Springer: Vienna (1958).
[9] M. Götz and K. Wiesner, *Tetrahedron Letters,* No. 50, 4369 (1969).
[10] J. P. Johnston and K. H. Overton, *J. Chem. Soc.* 1490 (1972).
[11] O. E. Edwards, L. Fonzes and Leo Marion, *Canad. J. Chem.* **44**, 583 (1966).
[12] O. E. Edwards, *Chem. Commun.* 318 (1965).
[13] R. K. Hill and R. M. Carlson, *J. Org. Chem.* **30**, 2414 (1965).
[14] W. Nagata and M. Joshioka, *Tetrahedron Letters,* No. 18, 1913 (1966).
[15] D. Seeback, N. R. Jones and E. J. Corey, *J. Org. Chem.* **33**, 300 (1966).
[16] F. A. Carey and J. R. Neergaard, *J. Org. Chem.* **36**, 2731 (1971).
[17] W. Nagata, T. Wakabayashi, M. Narisada, Y. Hayase and S. Kamata, *J. Amer. Chem. Soc.* **93**, 5740 (1971).
[18] E. J. Corey, J. D. Bass, R. LeMahieu and R. B. Mitra, *J. Amer. Chem. Soc.* **86**, 5570 (1964).
[19] F. E. Ziegler and J. A. Kloek, *Tetrahedron Letters,* No. 4, 315 (1974).
[20] S. O. Lawesson, T. Busch and C. Berglund, *Chem. Scand.* **15**, 260 (1961).
[21] F. R. Ahmed, *Acta Cryst.* (in press).