Alkaloid Total Synthesis by Intramolecular Imino Diels–Alder Cycloadditions

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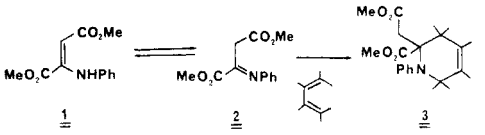
In a 1943 review article on the diene synthesis, Alder briefly described the first example of a [4 + 2] cycloaddition using an imine as a dienophile.[1] Reaction of enamine **1** with "aliphatic dienes" did not afford the carbocyclic systems as expected but gave instead tetrahydropyridine **3** (in unspecified yields) through the intervention of imine tautomer **2** as the reactive species.



This observation did not stimulate a significant volume of research in the next few decades despite the fact that reduced pyridines abound in natural products of interest to synthetic chemists. In fact, a review on the subject of imino Diels–Alder chemistry published in 1967 contained only about 20 references.[2,3] This is not to say that the early period lacked important contributions. In particular, the work of Kresze and Albrecht[4] on *N*-acylimines and iminium salts and of Merten and Muller[5] on *N*-sulfonylimines demonstrated the generality of the Diels–Alder reaction with electron-deficient imino species. During the 1970s, considerably more examples of imino dienophile cycloadditions were published,[3] with a focus still on charged and neutral *N*-sulfonyl- and *N*-acylimines. At this time it would be fair to say that there has been little systematic study of the reaction, not to mention a severely limited amount of mechanistic work.[6]

The long-standing lack of interest by the synthetic community may rest with the reactive nature of this type of dienophile. Electron-deficient imines and iminium salts are usually unstable and thus often need be produced in situ. They are prone to undergo a variety of other reactions with alkenes. For example, *N*-acylimines are good electrophiles[7] and can also act as *dienes*[8] in Diels–Alder cycloadditions. *N*-Sulfonylimines are excellent enophiles.[9] Both types of imine are rapidly hydrolyzed in the presence of traces of water.

It seemed to us that many of these undesired side reactions might be avoided if one could generate the requisite imino dienophile in close proximity to a 1,3-diene, thereby increasing the relative rate of [4 + 2] cycloaddition. Thus, an intramolecular Diels–Alder strategy appeared ideally suited to imino dienophiles.

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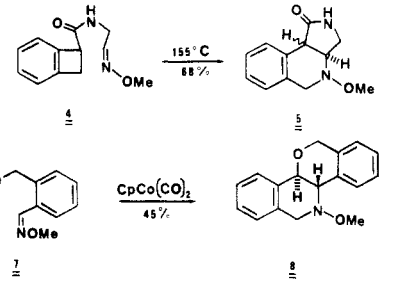
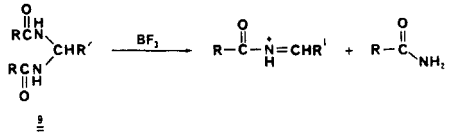
At the outset of our work, only one example of an intramolecular imino Diels–Alder reaction had appeared. Oppolzer reported in 1971 that, upon heating benzocyclobutene **4**, a mixture of epimeric tricyclic lactams **5** is produced in good yield.[10] This cycloaddition proceeds via a highly reactive *o*-quinonedimethide diene which adds to an oxime methyl ether, a group that is unreactive in intermolecular cycloadditions. In a variation of this reaction Funk and



Vollhardt elegantly applied a cobalt-catalyzed cooligomerization of bis(trimethylsilyl)acetylene (**6**) with diyne **7** to yield one diastereomeric tetracycle **8**, again via an *o*-quinonedimethide.[11]

For our proposed imino Diels–Alder route to alkaloid total syntheses, *N*-acylimino compounds were the most attractive type of dienophile since they had been substantially studied in intermolecular processes. Acyliminium dienophiles are most commonly generated from bisamides and biscarbamates, such as **9**, under Lewis acid catalysis.[2,3] This method was not appealing



for the intramolecular cycloaddition because half of the diene component (R) would be unavoidably wasted.

(1) Alder, K. "Neuer Methoden der Praperative Organischen Chemie"; Verlag Chemie: Weinheim/Bergstr., 1943.
(2) Lora-Tomayo, M. In "1,4-Cycloaddition Reactions"; Hamer, J., Ed.; Academic Press: New York, 1967; pp 127–142.
(3) For more recent reviews of imino dienophiles, see: (a) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. (b) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.
(4) Albrecht, R.; Kresze, G. *Chem. Ber.* **1964**, *97*, 490.
(5) Merten, R.; Muller, G. *Angew. Chem.* **1962**, *74*, 866; *Chem. Ber.* **1964**, *97*, 682.
(6) For a study of reaction stereochemistry, see: Krow, G.; Rodebaugh, R.; Carmosin, R.; Figures, W. Pannella, H.; DeVicaris, G.; Grippi, M. *J. Am. Chem. Soc.* **1973**, *95*, 5273.
(7) (a) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062. (b) Zaugg, H. E. *Synthesis* **1984**, *85* and references cited in these pages.
(8) Schmidt, R. R. *Synthesis* **1972**, 333.
(9) Achmatowicz, O.; Pietraszkiewicz, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2680. Tschaen, D. M.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *23*, 3015.
(10) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1971**, *11*, 1031.
(11) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1980**, *102*, 5245.

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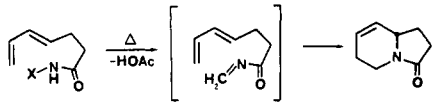
Furthermore, we were concerned (with some justification, it later turned out) about diene instability in the presence of Lewis acids. We therefore preferred using neutral *N*-acylimines which might be generated from an unsymmetrical precursor under mild thermal conditions. Although less reactive than charged species, the *N*-acylimines would be more than satisfactory for the intended intramolecular reactions. We first set out to evaluate the strategy on a simple system containing an aliphatic 1,3-diene.

Indolizidine Alkaloids

The abundance of alkaloids possessing a saturated indolizidine skeleton strongly influenced our choice of a test case and of subsequent applications of the methodology. δ-Coniceine (**10**), the simplest indol-

10

izidine alkaloid, was selected as an initial target.[12] Amide diene **11**, readily available in two steps from divinylcarbinol, was converted to methylol **12** with aqueous formaldehyde and sodium hydroxide in glyme.[7b] The crude product was acetylated with acetic anhydride/pyridine to afford methylol acetate **13** in good yield. This type of *N*-acylimine precursor has proven to be the most generally useful one in our intramolecular cycloadditions (vide infra). Pyrolysis of this acetate through a hot tube of glass helices yielded lactam **15** (73%) via the unstable *N*-acylimine intermediate **14** formed by elimination of acetic acid from **13**. Not surprisingly, **14** was never detected, but more recent work by Lasne et al.[13] has clearly demonstrated that this acylimine is, in fact, involved in the cycloaddition. Catalytic hydrogenation of the double bond of **15**, followed by lactam carbonyl reduction with diborane, afforded δ-coniceine.

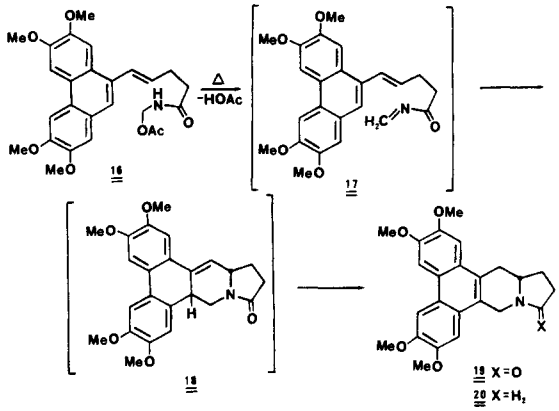


11 X=H
12 X=CH_2OH
13 X=CH_2OAc

14 **15**

Having proven the viability of the method, we began to investigate increasingly more complicated applications in the area of indolizidine alkaloids. Tylophorine (**20**), a member of the phenanthroindolizidine alkaloid group, was chosen as the next target in order to establish whether an intramolecular imino Diels–Alder cycloaddition could be effected with a diene incorporated into an aromatic system. Methylol acetate **16**, prepared by straightforward chemistry[12] similar to that used to synthesize **13**, was heated as a dilute solution in bromobenzene at 220 °C in a sealed tube to afford a 50% yield of the desired pentacyclic lactam **19** (Scheme I). This transformation undoubtedly involves the *N*-acylimine **17** which undergoes [4 + 2] cycloaddition to **18** followed by a 1,3-hydrogen shift to give the observed product. It might be noted here that the best experi-

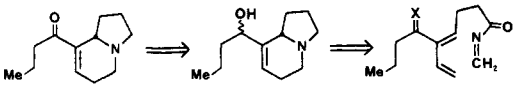
Scheme I



16 **17** **18** **19** X=O **20** X=H_2

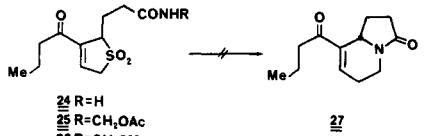
mental conditions for *N*-acylimine formation from a methylol acetate and subsequent cyclization (i.e., whether hot tube or heating in a solvent) need be arrived at by trial and error. In general, the hot-tube procedure seems to work best for lower molecular weight systems. Reduction of lactam **19** with lithium aluminum hydride gave racemic tylophorine (**20**).

Moving to a more complex structural array, we looked at the possibility of employing this strategy in total synthesis of the *Elaeocarpus* alkaloids elaeokanine A (**21**) and B (**22**, indeterminate stereochemistry).[14,15] This indolizidine alkaloid type particularly appealed to us since the double bond produced in the Diels–Alder reaction (and removed in the δ-coniceine synthesis) could potentially be directly incorporated into the final products. Retrosynthetic analysis of the problem pointed to a diene acylimine such as **23** as a requisite precursor to the indolizidine skeleton of the elaeokanines. This was prepared in masked form via amide dihydrothiophene dioxide **24**.[12b,16]



21 **22** **23**

Treatment of **24** with formalin and various bases gave only what appeared to be C-alkylated products. Alternatively, **24** could be transformed with chloromethyl methyl sulfide in TFA[17] to thiomethyl derivative **26**, further reaction of which with mercuric acetate in glacial acetic acid yielded the desired methylol acetate **25**. Unfortunately, all attempts to cyclize either **25** or **26** to bicyclic lactam **27** failed. Surmising that the major



24 R=H
25 R=CH_2OAc
26 R=CH_2SMe

27

(12) (a) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073. (b) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *Ibid.* **1981**, *103*, 6387.

(13) Lasne, M. C.; Ripoll, J. L.; Thuiller, A. *J. Chem. Res. Synop.* **1982**, 214.

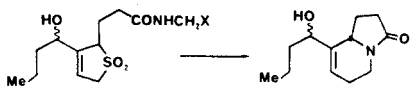
(14) Schmitthenner, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372.

(15) For other recent syntheses of eleaokanine A and/or B, see: Tufariello, J. J.; Ali, Sk. A. *Tetrahedron Lett.* **1979**, *20*, 4445. Howard, A. S.; Gerrans, G. C.; Meerholz, C. A. *Ibid.* **1980**, *21*, 1373. Watanabe, T.; Nakashita, Y.; Katayama, S.; Yamauchi, M. *Heterocycles* **1980**, *14*, 1433. Wijinberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 5079. Otomatsu, H.; Takatsu, N.; Honda, T.; Kametani, T. *Tetrahedron* **1982**, *38*, 2627. Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300.

(16) McIntosh, J. M.; Sieler, R. A. *J. Org. Chem.* **1978**, *43*, 4431 and references cited therein.

(17) Bernardi, L.; DeCostiglione, R.; Scarponi, U. *J. Chem. Soc., Chem. Commun.* **1975**, 320.

problem with this transformation might be the instability of a 2-acyl diene, we decided to reduce the ketone carbonyl group. The Luche procedure[18] applied to **26** afforded an epimeric mixture of allylic alcohols **28**, which was transformed to methylol acetates **29**. In order to fully optimize the yield in the Diels–Alder step, it was necessary to O-silylate the alcohol mixture with trimethylsilyl chloride. The crude product in toluene was passed through a tube of glass helices at about 370 °C, giving, after acidic workup, a 5:4 mixture of epimeric lactam alcohols **30** (68% yield) presumably via *N*-acylimine diene **23** (X = H, O~$SiMe_3$). Reduction of

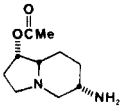


28 X=SMe
29 X=OAc

30

the mixture with diisobutylaluminum hydride afforded a difficulty separable mixture of amino alcohols corresponding to elaeokanine B (**22**). Since the stereochemistry (as well as the stereochemical purity) of this alkaloid is unknown,[19] and since an authentic sample of natural material was not available, a comparison could not be made. In any event, synthetic **22** was oxidized by the Swern method to give elaeokanine A (**21**), which had spectra identical with those of natural material.[20]

As a final test of the synthetic strategy in the indolizidine alkaloid field, we turned to the fungal neurotoxin slaframine (**31**).[21] The primary challenge in

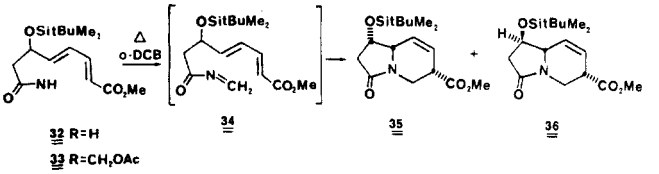


31

constructing this molecule is establishing the proper relative configuration of the three chiral centers. Our projected imino Diels–Alder approach looked perfect for setting the cis stereochemistry in the six-membered ring of **31** by using an *E,E*-diene, but it was not clear what control, if any, would be possible at the remaining center.[22]

Diene amide **32** was prepared in a few steps from readily available precursors.[21] Conversion of amide **32** to methylol acetate **33** under the "usual" conditions described above for **13** and **16** proved difficult to achieve cleanly in this case. Fortunately, Dr. H. Zaugg (Abbott Laboratories) suggested an alternative method to us which utilizes paraformaldehyde in anhydrous THF catalyzed by cesium carbonate for initial methylol formation. By this procedure, acetate **33** could be synthesized reproducibly in good overall yield.

When methylol acetate **33** was heated in refluxing *o*-dichlorobenzene, a separable 1:1.8 mixture of epimeric Diels–Alder adducts **35** and **36** (82%) was obtained via the *N*-acylimine **34**. It was not possible to assign stereochemistry to the individual adducts here, but this was done by the eventual conversion of **35** to slaframine.

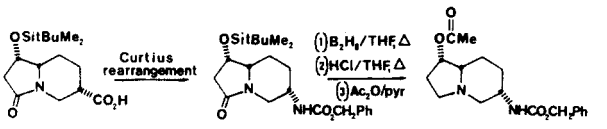


32 R=H
33 R=CH_2OAc

34 **35** **36**

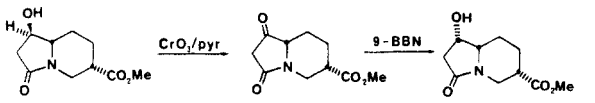
We had hoped that there might be good stereocontrol with respect to the chiral center in the bridging chain due to unfavorable nonbonded interactions in one of the Diels–Alder transition states.[23] Unfortunately, this was not the case. However, it did prove possible to easily adjust the stereochemistry of the undesired C-1 epimer **36** as outlined below.

Catalytic hydrogenation of adduct **35**, followed by basic ester hydrolysis produced acid lactam **37**. Curtius rearrangement of this compound led to carbamate lactam **38**, which was readily converted to known carbamate ester **39**[22a] in good overall yield. Subsequent hydrogenolysis of **39** afforded racemic slaframine (**31**).



37 **38** **39**

The unnatural epimer **36** was hydrogenated and deprotected to give β-hydroxy lactam **40**, which was oxidized to the unstable β-keto lactam **41**. After some explortion with various reagents, it was discovered that **41** could be reduced with total stereoselectivity with use of 9-BBN to give hydroxy lactam **42** having the slafr-amine configuration at C-1.



40 **41** **42**

Quinolizidine Alkaloids

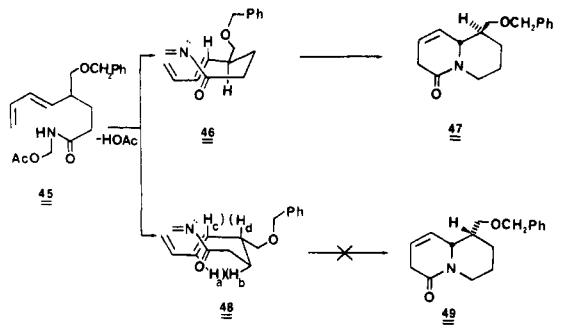
Application of intramolecular imino Diels–Alder methodology to some quinolizidine alkaloids was undertaken with the intent of determining whether bridging chain stereochemistry might be controlled in cycloadditions producing 6/6 fused ring systems,[24] as was not possible in the synthesis of slaframine. We believed that this facet could be probed via synthesis of lupinine (**43**) and/or *epi*-lupinine (**44**).

43 **44**

The requisite methylol acetate precursor **45** for the Diels–Alder reaction was easily prepared from methyl sorbate.[25] Upon heating of **45** in refluxing *o*-dichlorobenzene, a *single* bicyclic lactam **47** was formed in 93% yield (Scheme II). None of the epimeric compound **49** could be detected. The structure and stereochemistry

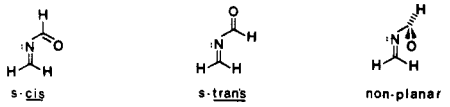
(18) Luche, J. L. *J. Am.* Chem. *Soc.* **1978**, *100*, 2226.
(19) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *J. Chem. Soc. D* **1971**, 360. *Aust. J. Chem.* **1972**, *25*, 817.
(20) Spectra were kindly provided by Dr. J. A. Lamberton.
(21) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065.
(22) For previous syntheses, see: (a) Cartwright, D.; Gardiner, R. A.; Rinehart, K. L. *J. Am. Chem. Soc.* **1970**, *92*, 7615. (b) Gensler, W. J.; Hu, M. W. *J. Org. Chem.* **1973**, 3848.
(23) Cf. Nicolaou, K. C.; Magolda, R. L. *J. Org. Chem.* **1981**, *46*, 1508. Roush, W. R.; Meyers, A. B. *Ibid.* **1981**, *46*, 1509.
(24) (a) Bremmer, M. L.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 261. (b) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661.
(25) Houk, K. N.; Paddon-Row, M. N., unpublished results.

Scheme II



of **47** were established via its conversion into racemic *epi*-lupinine (**44**) by catalytic hydrogenation followed by borane reduction.

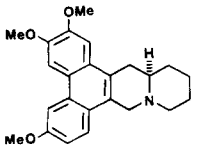
Several points have to be considered in rationalizing the stereoselective formation of adduct **47**. The first is the *N*-acylimine structure. Definitive experimental information regarding this subject is not available due to the general instability of such functionality. However, Houk and Paddon-Row[25,26] have calculated that the most stable *N*-acylimine conformer is the s-cis form, which is about 3 kcal/mol better than the s-trans conformer and 4 kcal/mol lower in energy than the orthogonal nonplanar form. In addition, calculations



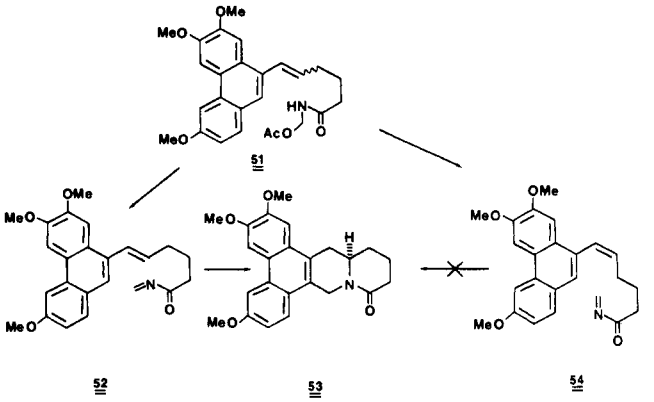
show that the nonplanar conformation should be considerably less reactive as a dienophile. A second assumption we have made is that there is a strong preference for the *N*-carbonyl group of an acylimine to be endo in the Diels–Alder transition state. This hypothesis is based upon empirical observations by Krow et al.[6,27] in intermolecular imino cycloadditions and by our own results in some intramolecular cases (vide infra). If one also assumes that the (benzyloxy)methyl group takes a quasi-equatorial position in the bridging chain, two reasonable conformational possibilities **46** and **48** emerge for the intermediate acylimine in the above cycloaddition. Conformation **46**, leads to the observed *epi*-lupinine stereochemistry **47**, and **48** gives the unobserved lupinine stereochemistry **49**.

In a closely related "all carbon" intramolecular Diels–Alder reaction, Taber and Gunn found a high preference (~9:1) for the product derived from a reacting conformation like **46**.[28] This selectivity was rationalized by an unfavorable 1,4-nonbonded interaction (cf. Ha/Hb) in a transition-state structure such as **48** but absent in **46**. Molecular mechanics calculations[29] indicate that, in fact, in the Taber/Gunn system and in our imino case an eclipsing interaction between Hc/Hd in **48** is primarily responsible for the difference in energy of the two transition states.

The phenanthroquinolizidine alkaloid cryptopleurine (**50**) was also approached with the hope of discovering more about stereochemical features of the intramolecular cycloaddition.[24b] This compound, which is a homologue of tylophorine (**20**), was synthesized via methylol acetate **51**, prepared as an inseparable 3:1 mixture of *E*:*Z* isomers. Heating this mixture at 210 °C in *o*-dichlorobenzene gave a 66% yield of lactam **53** and 30% of the uncyclized primary amide derived from the *Z* isomer of **51**. Reduction of **53** with $LiAlH_4$ yielded racemic cryptopleurine (**50**).



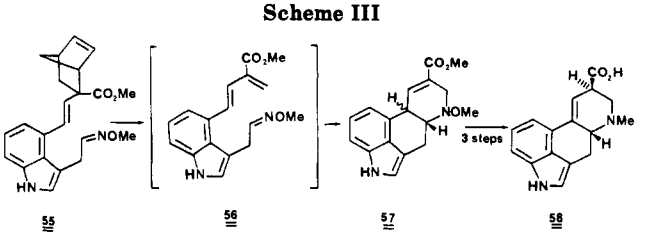
When the recovered amide was reconverted to *Z*-methylol acetate **51** and heated, none of lactam **53** was produced. One can see from inspection of molecular models that the acylimine **52** in the *E* series can nicely assume a Diels–Alder transition state having a planar s-cis dienophile conformation. The acylimine **54** in the *Z* series can only cyclize via an unfavorable nonplanar dienophile conformation due to bridging chain restraints and thus produces just decomposition products. Clearly, these results are fully in line with the stereochemical postulates discussed in relation to the *epi*-lupinine work.



Ergot Alkaloids

The Oppolzer group recently described a notable total synthesis of lysergic acid (**58**) which utilized a key intramolecular imino Diels–Alder cycloaddition (Scheme III).[30] A dilute solution of **55** was heated at 200 °C in 1,2,4-trichlorobenzene to afford a 67% yield of adduct **57** as a 3:2 mixture of epimers. This cycloaddition proceeds through undetected diene oxime ether **56** produced by retro-Diels–Alder loss of cyclopentadiene. It is not clear whether the mixture of stereoisomers isolated from the cycloaddition results from epimerization of the α,β-unsaturated ester under the reaction conditions or from a lack of stereoselectivity in the

Scheme III

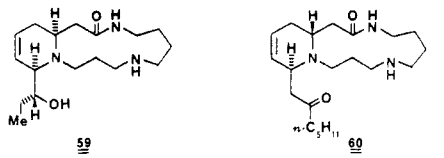


(26) See also: Wurthwein, E. U.; Kupfer, R.; Kaliba, C. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 252. Ben-Ishai, D.; Hirsch, S. *Tetrahedron Lett.* **1983**, *24*, 955.
(27) Krow, G. R.; Johnson, C.; Boyle, M. *Tetrahedron Lett.* **1978**, 1971.
(28) Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992.
(29) We thank Professor P. Jurs and T. Stouch for these calculations.
(30) Oppolzer, W.; Francotte, E.; Battig, K. *Helv. Chim. Acta* **1981**, *64*, 478.

Diels–Alder reaction. Synthetically, this mixture was converted to racemic lysergic acid (**58**).

Spermidine Alkaloids

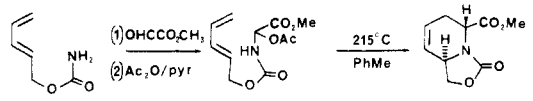
One of our major objectives in the field of intramolecular imino Diels–Alder chemistry has been application of the methodology to macrocyclic spermidine-derived alkaloids such as palustrine (**59**)[31] and anhydrocannabisativene (**60**).[32] We hoped that cyclization



59 **60**

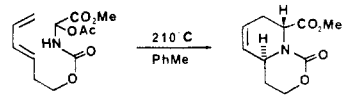
of an appropriately substituted imino dienophile might lead to the tetrahydropyridine nucleus of these alkaloids and might simultaneously be used to establish the stereochemistry at the centers α to nitrogen. Interestingly, palustrine (**59**) has a cis relationship of hydrogens at these carbons whereas anhydrocannabisativene (**60**) has a trans relationship. At the outset of this project, we had little idea of what to expect stereochemically in the proposed cycloaddition and thus decided to conduct some preliminary experiments aimed at exploring this point.[33] Since palustrine and anhydrocannabisativene also possess different oxygenation patterns in their alkyl side chains, it was decided to investigate systems potentially leading to either alkaloid.

Diene carbamate **61** was converted to methylol acetate **62** with use of methyl glyoxylate followed by the usual acetylation of the intermediate methylol. Heating of **62** produced a single Diels–Alder adduct **63**, whose structure was proven by X-ray crystallography of a derivative.[33] Although **63** has the palustrine ring system and oxygenation pattern, it possesses the incorrect relative stereochemistry at the two chiral centers.



61 **62** **63**

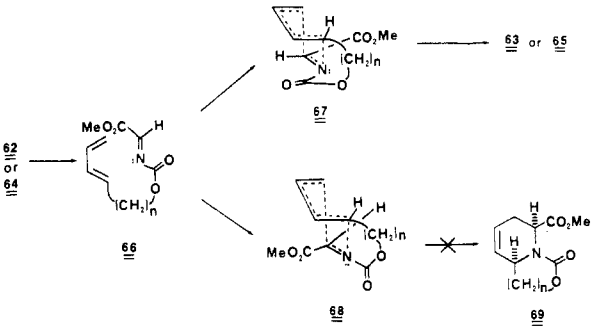
Methylol acetate **64** was also synthesized by using similar methodology. Heating of this compound produced only one adduct, which was shown to have structure **65** by X-ray crystallography on the corresponding carboxylic acid. Clearly, this product has both the anhydrocannibisativene oxygenation pattern and trans stereochemistry.



64 **65**

To rationalize the stereochemical outcome of these cycloadditions we assumed the involvement of an *E*-acylimine like **66** (Scheme IV). The corresponding *Z*-acylimine has been discounted primarily because it would require a Diels–Alder transition state having both dienophile carbonyl groups exo to produce the observed trans products. Acylimine **66** can cyclize through transition states like **67** or **68**. Transition-state **67**, which has the nitrogen carbonyl endo and the carbomethoxyl group exo, leads to the observed trans products **63** and **65**. On the other hand, transition-state **68**, having the *N*-acyl group exo and the carbomethoxyl group endo, would have produced cis stereoisomer **69**, which was not found. From inspection of molecular models there seems to be little to choose between **67** and **68** assuming reacting acylimine conformations as suggested above in the quinolizidine alkaloid section.

Scheme IV



62 or **64** **66** **67** **63** or **65** **68** **69**

A priori, one might have expected either mode of cyclization of **66**. Krow has shown that in intermolecular imino Diels–Alder reactions the nitrogen carbonyl group prefers an endo orientation,[6,27] thus supporting formation of trans adducts **63** and **65** in our intramolecular cases. Alternatively, in some intramolecular "all carbon" Diels–Alder reactions of fumarates it is the *terminal* carbonyl group which prefers to take an endo position,[34] which in the imino system would correspond to transition-state **68**. At present we have no good theoretical rationale for the apparently strong endo preference for an *N*-acyl group in both inter- and intramolecular imino dienophile reactions, although secondary orbital effects may well be operating here.

Since it was now obvious that anhydrocannabisativene (**60**) should be accessible via this sort of cycloaddition, we prepared the required Diels–Alder precursor **70** by a short straightforward sequence starting from 1,4-pentadiene.[35] Pyrolysis of **70** at 215 °C in toluene afforded in 83% yield a single bicyclic adduct **72** whose structure was confirmed by X-ray crystallography on acid **73**. As before, this cyclization occurs through an *E*-acylimine having the *N*-acyl group endo in the transition state. Furthermore, a conformation such as **71**, like conformer **46** in the *epi*-lupinine system would predominate. Thus, conversion of **70** to stereoisomer **72** was expected on the basis of the stereochemical principles previously delineated.

In order to complete the synthesis of anhydrocannabisativene, acid **73** was first homologated by an Arndt–Eistert sequence to **74**, which was subsequently converted to amino ester **75**. For steric reasons, **75** was difficult to alkylate on nitrogen, but triflate **76** gave a good yield of **77**. This compound was transformed in

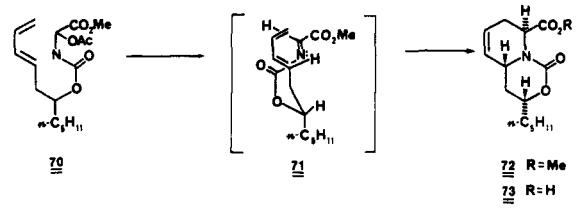
(31) Walchli-Schaer, W.; Eugster, C. H. *Helv. Chim. Acta* **1978**, *61*, 928 and references cited therein. See also: Wasserman, H. H. Leadbetter, M. R.; Kopka, I. E. *Tetrahedron Lett.* **1984**, *25*, 2391.

(32) Elsohly, M. A.; Turner, C. E.; Phoebe, C. H.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. J. *J. Pharm. Sci.* **1978**, *67*, 124.

(33) Nader, B.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1153. Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. *Ibid.* **1981**, *103*, 7573.

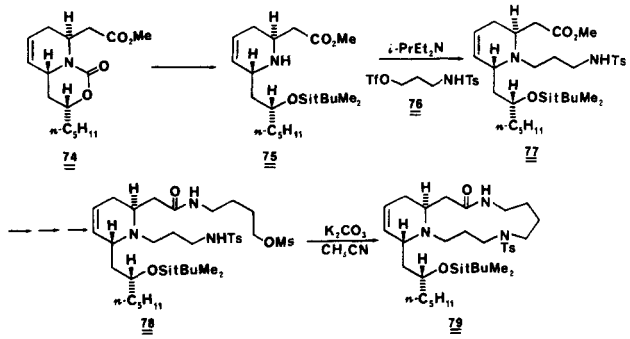
(34) Cf. Gschwend, H. W. *Helv. Chim. Acta* **1973**, *56*, 1763. Cox, M. T. *J. Chem. Soc., Chem. Commun.* **1975**, *903*.

(35) Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.



70 71 72 R=Me 73 R=H

three steps to mesylate **78**, which upon treatment with potassium carbonate under high dilution yielded the 13-membered lactam **79** (58%). Removal of the *N*-



74 75 76 77 78 79

tosyl protecting group of **79** was effected with sodium in ammonia, after which the *O*-silyl group was cleaved and the resulting alcohol oxidized with *Jones* reagent to afford racemic anhydrocannabisativene (**60**). Thus, a stereoselective synthesis of this alkaloid has been achieved in approximately 18 steps from commercially available starting materials.

Conclusion

The research surveyed here has demonstrated that intramolecular [4 + 2] cycloadditions of imino dienophiles can be used to synthesize a structurally diverse group of alkaloids. The methodology is basically simple to employ and yields are good. Importantly, the methodology shows good stereocontrol the direction of which is usually predictable. As mentioned at the beginning of this Account, there is still a need for serious theoretical and mechanistic studies not only of the imino Diels–Alder reaction but also of cycloadditions with hetero dienes and dienophiles in general.

I am extremely grateful for the enthusiasm and hard work of several postdocs and graduate students whose names are mentioned in the references. This research program was supported by the National Science Foundation and the National Institutes of Health.