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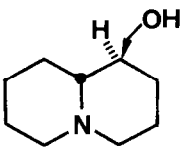
A STEREOSELECTIVE TOTAL SYNTHESIS OF EPI-LUPININE

Martin L. Bremmer and Steven M. Weinreb*

Department of Chemistry
The Pennsylvania State University
University Park, PA 16802

Summary: An intramolecular imino Diels-Alder reaction has been used both to construct the quinolizidine ring system and to set the proper relative stereochemistry of the alkaloid epi-lupinine (1).

We have recently demonstrated the effectiveness of intramolecular imino Diels-Alder cycloadditions in synthesis of a variety of indolizidine alkaloids including δ-coniceine[1], tylophorine[1], elaeokanine A and B[1], and slaframine[2]. This paper describes the first total synthesis of a quinolizidine alkaloid using this methodology. We have developed a stereoselective approach to synthesis of epi-lupinine (1)[3] which uses the intramolecular imino



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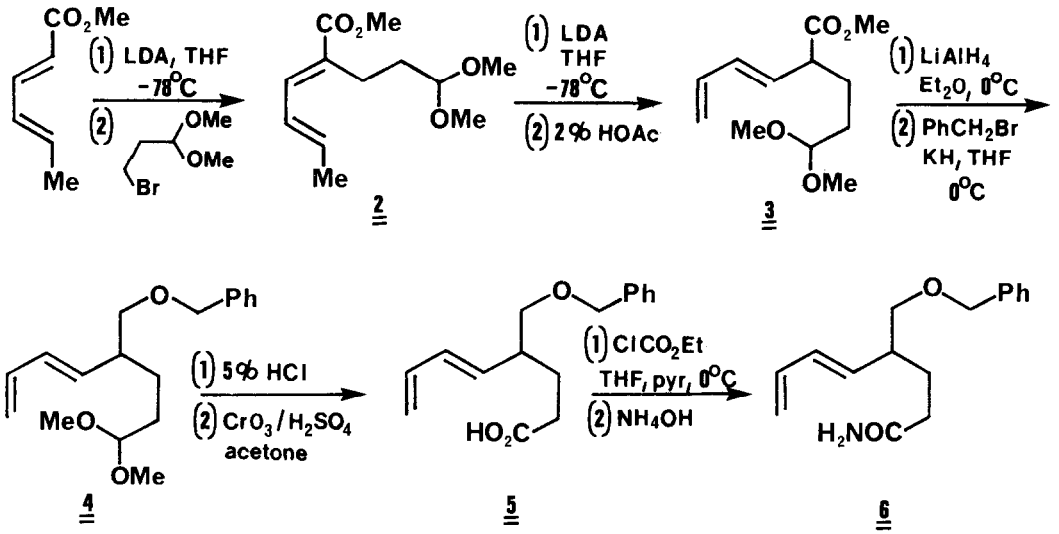
Diels-Alder reaction to efficiently construct the necessary bicyclic ring system and to establish the proper relative stereochemistry.

Alkylation of the known[4] anion derived from methyl sorbate with β-bromopropionaldehyde dimethyl acetal afforded a 44% yield of diene 2 (Scheme I). To our knowledge, this carbanion has not previously been alkylated. Only the fully conjugated isomer shown could be isolated.[5] This diene ester could, however, be readily deconjugated by the method of Stevens, et al.[4] to afford compound 3 (92%) having the diene moiety necessary for the Diels-Alder step.[5] The disubstituted double bond of diene 3 was assigned the trans geometry based upon the presence of an infrared band at 955 cm^{-1} and the absence of any peaks near 700 cm^{-1}. The ester group of 3 was reduced with lithium aluminum hydride to the corresponding alcohol (68%) which was protected as its benzyl ether 4 (86%). Hydrolysis of the dimethyl acetal functionality of 4

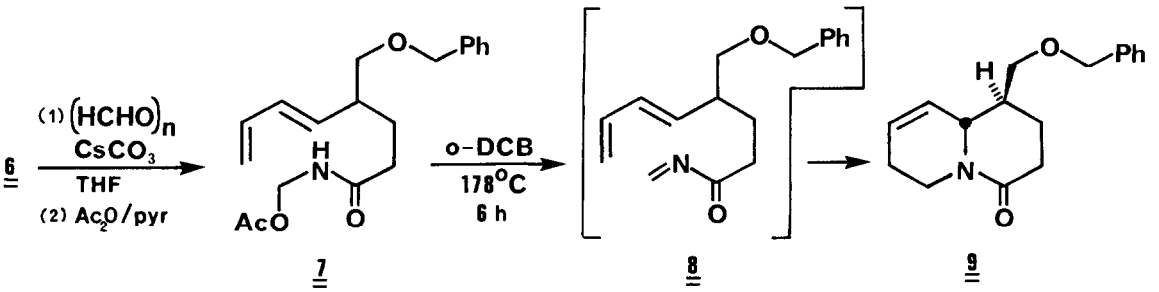
and Jones oxidation of the resulting aldehyde afforded carboxylic acid 5 (85%). Standard methodology was then used to convert 5 to primary amide 6 (97%).



Scheme I

Amide 6 was transformed to "methylol acetate" 7 (66%)[5] using the modified procedure which we recently described.[1] Upon heating in refluxing o-dichlorobenzene, acetate 7 cleanly cyclized to afford a single bicyclic lactam (93%) to which we have assigned structure 9 based upon its eventual conversion to epi-lupinine (vide infra).[5]

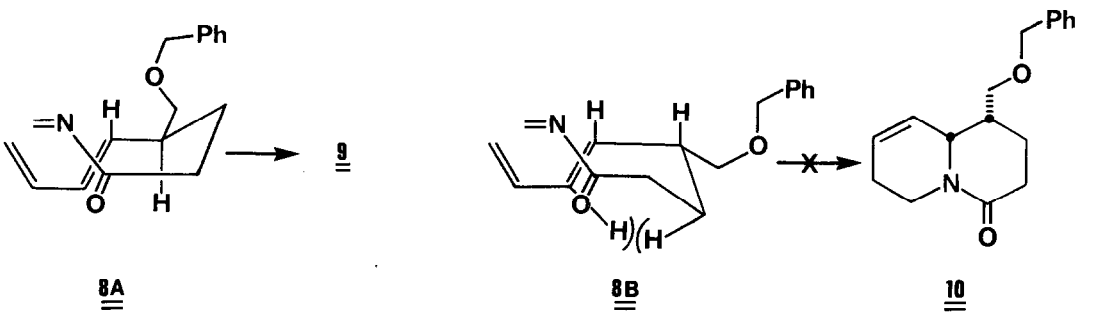
We believe that this cycloaddition proceeds via N-acylimine 8 which, as in our previous



Scheme II

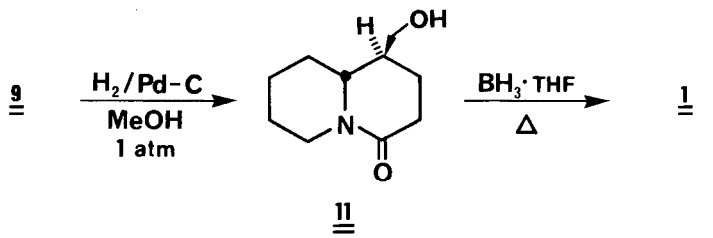
imino Diels-Alder work,[1,2] was not directly observed.[6] It seemed reasonable to us that imine 8 should cyclize via transition states 8A and/or 8B. In both, the acyl imine carbonyl group is

endo to the diene[7] and the bulky benzyloxymethyl chain assumes a quasi equatorial position in the six-membered lactam ring which is forming. In transition state 8A the connecting chain is a quasi boat, and this transition state would lead to the stereochemistry observed in cycloadduct 9. On the other hand, in transition state 8B the lactam ring is a quasi chair, and would produce the lupinine stereochemistry 10, which was not detected in our experiments. Inspection of molecular models indicates that, in fact, the chair-like transition state 8B has an unfavor-



able non-bonded interaction between a vinyl hydrogen of the diene and a quasi axial hydrogen of the connecting chain. In the boat-like transition state 8A this unfavorable steric interaction is removed. Taber has recently used an identical argument to rationalize the stereochemical outcome of a similar "all carbon" intramolecular Diels-Alder reaction.[8] Our imino Diels-Alder reaction, however, inexplicably shows a higher degree of stereoselectivity than does the analogous carbon system.

To complete the alkaloid synthesis, adduct 9 was hydrogenated to both saturate the double bond and to remove the benzyl ether protecting group, affording hydroxylactam 11 (94%).



Reduction of the carbonyl group of 11 with diborane afforded racemic epi-lupinine (1) (57%) which had spectra identical to that of authentic material.[9]

Acknowledgment. We are grateful to the National Institutes of Health for support of this research on grant CA-25145.

References

(1) Khatri, N.A.; Schmitthenner, H.F.; Shringarpure, J.; Weinreb, S.M. J. Am. Chem. Soc. 1981, 103, 6387.

(2) Gobao, R.A.; Bremmer, M.L.; Weinreb, S.M. J. Am. Chem. Soc. 1982, 104, 0000.

(3) For recent syntheses of lupinine and epi-lupinine see: Tufariello, J.J.; Tegeler, J.J. Tetrahedron Lett. 1976, 4037, and references cited.

(4) Stevens, R.V.; Cherpeck, R.E.; Harrison, B.L., Lai, J.; Lapalme, R. J. Am. Chem. Soc. 1976, 98, 6317.

(5) Spectral data for selected compounds: 2: IR (film) 3040, 2950, 2840, 1710, 1640, 1610, 1440, 1380, 1300, 1240, 1220, 1195, 1170, 1130, 1070, 975, 920, 880, 840, 800, 765 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.15 (d, 1H), 6.4 (m, 1H), 6.1 (m, 1H), 4.33 (t, 1H), 3.73 (s, 3H), 3.30 (s, 6H), 2.43 (t, 2H), 1.85 (m, 3H), 1.72 (m, 2H); mass spectrum (chemical ionization) 229 ($m + H^+$). 3: IR (film) 3100, 2960, 2840, 1740, 1650, 1605, 1440, 1260, 1200, 1165, 1135, 1070, 1005, 975, 955, 910 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.32 (m, 1H), 6.14 (m, 1H), 5.66 (m, 1H), 5.10 (m, 2H), 4.35 (t, 1H), 3.75 (s, 3H), 3.67 (s, 6H), 3.05 (t, 1H), 1.90 - 1.60 (4H); mass spectrum m/e (relative intensity) 228 [M^+] (7.5), 197 (14.9), 165(22.1), 137(16.8), 105(20.5), 75(100). 7: IR (film) 3700-3200, 3050, 2950, 2860, 1740, 1680, 1605, 1535, 1455, 1370, 1230, 1100, 1020, 960, 910, 740, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.33 (s, 5H), 6.62 (broad, 1H), 6.40 - 6.02 (m, 2H), 5.56 - 5.44 (m, 1H), 5.20 (m, 2H), 5.18 - 5.00 (m, 2H), 4.50 (s, 2H), 3.40 (m, 2H), 2.47 - 1.52 (5H), 2.061 (m, 3H); mass spectrum m/e (relative intensity) 331 [$M^+ - C_2H_3O_2$] (0.5), 180(24.2), 150(10.3), 91(100); high resolution mass spectrum: Calcd for $C_{17}H_{22}NO_2$ [$M^+ - C_2H_3O_2$]: 272.1650 Found: 272.1634. 9: IR ($CHCl_3$) 3005, 2940, 2880, 1955, 1880, 1820, 1630, 1470, 1420, 1370, 1280, 1240 - 1200, 1120, 1100, 700 - 660 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38 - 7.29 (5H), 5.85 (m, 1H), 5.75 (m, 1H), 4.80 (m, 1H), 4.53 (s, 1H), 4.52 (s, 1H), 3.93 (m, 1H), 3.56 (t, 2H), 2.64 - 1.65 (8H); mass spectrum m/e (relative intensity) 271 [M^+] (14.3), 180(100), 150(14.6), 108(0.1), 91(85.9), 82(37.8).

(6) For recent isolation and spectral characterization of an acylimine of this type see: Lasne, M.C.; Ripoll, J.L.; Thuiller, A. J. Chem. Res. (S) 1982, 214.

(7) Nader, B.; Bailey, T.R.; Franck, R.W.; Weinreb, S.M. J. Am. Chem. Soc. 1981, 103, 7573. There appears to be a strong driving force for an N-acyl group to be endo in such intramolecular imino Diels-Alder cycloadditions.

(8) Taber, D.F.; Gunn, B.P. J. Am. Chem. Soc. 1979, 101, 3992.

(9) We thank Professor J.J. Tufariello for providing IR and ^1H NMR spectra of lupinine and epi-lupinine.

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