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MODEL STUDIES AIMED AT *ARISTOTELIA* ALKALOIDS: INTRAMOLECULAR CYCLOADDITION OF N-*t*-BOC-6-AMINO-1,7,9-DECATRIEN-3-ONE

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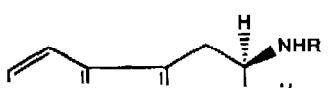
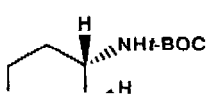
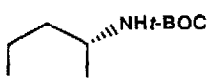
Abstract: An asymmetric approach for the synthesis of some *Aristotelia* alkaloids utilizing an intramolecular cycloaddition of a decatrienone derived from L-glutamic acid is reported.

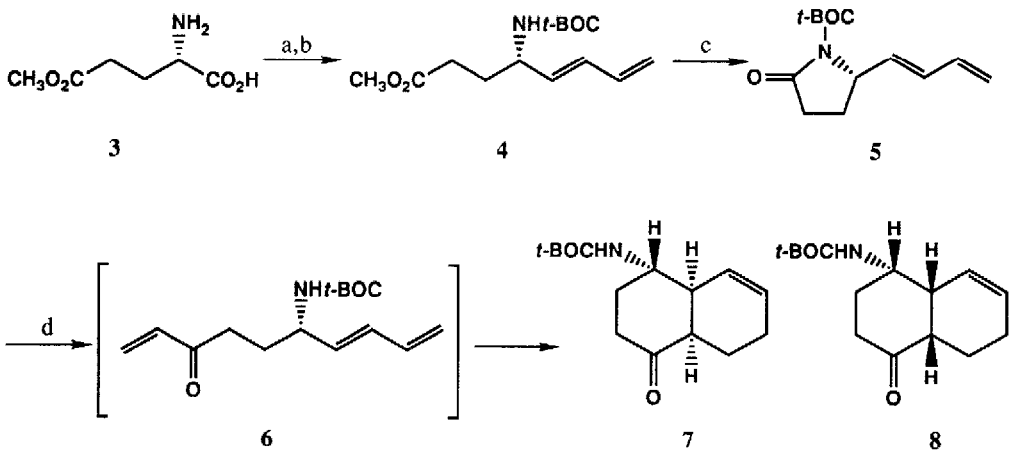
The *Aristotelia* alkaloids are a group of indole alkaloids derived from tryptamine and a terpenoid fragment. However, the terpene portion has not undergone prior rearrangement to an iridoid before being embodied into the final alkaloid. Due to their limited occurrence in nature, not much is known concerning the biological activity of these alkaloids. However, some *Aristotelia* species have been utilized as folk medicines for burns, sores, eye problems, and rheumatism.[1] Two members of the *Aristotelia* alkaloids, Aristomakinine **1**[2] and Aristomakine **2**[3], are depicted below.[4] Based on the analysis outlined below, these appeared to be well suited to construction via an intramolecular cycloaddition of an appropriately substituted decatrienone. The approach would also provide a testing ground for an examination of the effect of a nitrogen which is allylic to the diene, but not part of the tether, on the stereochemical outcome of the intramolecular cyclization. Kozikowski, *et. al.* have reported the results of an intermolecular Diels-Alder of a diene which possessed an allylic nitrogen in the course of the total syntheses of actinobolin and *epi*-actinobolin.[5] The following account reports the results of the intramolecular cycloaddition with a diene bearing an allylic nitrogen.







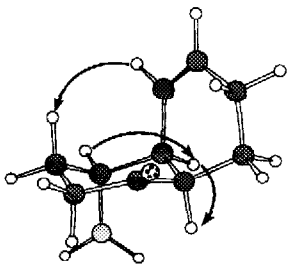
The desired substrate for study was prepared in a short sequence of reactions beginning with L-glutamic acid-5-methyl ester (**3**). The choice of an L-glutamic acid derivative, which would ultimately produce an antipodal derivative, was made on the basis of economics.[6] The amine was first protected as its *t*-BOC derivative.[7] The carboxylic acid functionality was manipulated into the requisite *E*-diene **4** ($[\alpha]_D$ = -4.82 (c 1.39, $CHCl_3$)) by first converting it to the aldehyde utilizing the Fukuyama procedure[8] and then reacting the aldehyde with allyl diphenyl allylidene phosphorane.[9] The diene was >20:1, *E*:*Z* as judged by ^1H NMR.[10] Reaction of **4** with Me_3Al afforded lactam **5** ($[\alpha]_D$ = -14.61 (c 1.02, $CHCl_3$)). When lactam **5** was treated with vinyl magnesium bromide,[11] none of the trienone was observed. This compound underwent spontaneous cycloaddition to produce a 2:1 mixture of *cis*-fused cycloadducts **7** ($[\alpha]_D$ = 4.95 (c 1.01, $CHCl_3$)) and **8** ($[\alpha]_D$ = -34.91 (c 0.55, $CHCl_3$)), respectively.[10] Careful examination of the Grignard reaction showed that the cycloaddition occurred after the workup of the Grignard reaction and not during. These two compounds turned out to be separable by selective crystallization. In the beginning, a problem with racemization of the intermediate aldehyde produced in the conversion of **3** to **4** was encountered. This racemization problem has since been suppressed.[12] However, the NMR studies and X-ray structure (*vide infra*) were performed on the racemic cycloadducts.



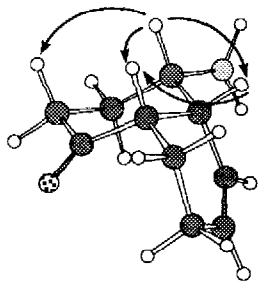
(a) i. $(t\text{-BuOCO})_2O$, Et_3N, THF/H_2O, 99%; ii. EtSH, DCC, DMAP, CH_2Cl_2, 86%; (b) i. Et_3SiH, Pd/C, acetone; ii. $Ph_2P^+(CH_2CH{=}CH_2)_2Br^-$, *n*-BuLi, THF, -78 °C, 66% overall; (c) 2.0 Me_3Al, $PhCH_3$, 87%; (d) $CH_2{=}CHMgBr$, THF, 76%.

The simple analysis of the coupling constants in an effort to elucidate the stereochemistry of the two products proved fruitless as most of the peaks of interest were ill-defined. The stereochemistry of the cycloadducts was therefore ascertained by means of a combination of NMR studies including: COSY, HETCOR, and most importantly, difference NOE. The results of the NOE studies are summarized in the diagrams below. It was the NOE between the methine next to the nitrogen and the two ring juncture protons which allowed for the assignment of structure **8** to the minor isomer. The major isomer had an NOE between the two ring juncture protons indicative of their *cis*-relationship but lacked the NOE between

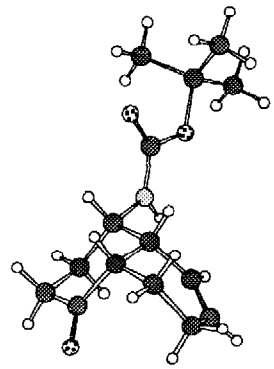
the methine next to nitrogen and the ring juncture proton α to the carbonyl. The *t*-BOC groups have been removed from the NOE diagrams for clarity. Subsequent to the NOE studies, an X-ray crystal structure of the minor isomer **8** corroborated the original structural assignment.[14]



NOE-Major Isomer

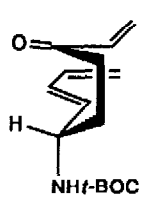


NOE-Minor Isomer

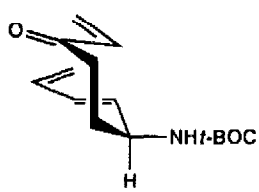


Chem3D model based on X-ray coordinates

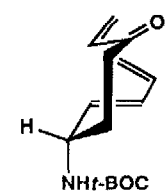
The two cycloadducts could arise from the transition states depicted below. Roush has recently shown that decatrienones tend to cyclize via boat transition states.[15] If this is the case, the major isomer is the result of cyclization through the endo-boat transition state with the nitrogen perpendicular to the diene. The minor isomer results from the endo-boat arrangement with the nitrogen parallel to the diene. In these two transition states the eclipsing interaction[16] between the allylic nitrogen and the olefinic proton outweighs the preference for a parallel arrangement of the nitrogen which would minimize the electron withdrawal on the diene by the carbon-nitrogen σ* orbital.[5] The alternative chair transition states, however, can not be completely disregarded. The major difference in these two possibilities would be the stereoelectronic preference for the parallel arrangement of the allylic nitrogen, as the steric interactions would be similar.



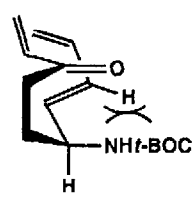
endo-boat with the nitrogen perpendicular to the diene



endo-chair with the nitrogen parallel to the diene



endo-chair with the nitrogen perpendicular to the diene



endo-boat with the nitrogen parallel to the diene

Work is now underway in an effort to sort out the steric vs. stereoelectronic arguments as well as the preparation of the methyl substituted dienophile to examine what effect this will have on the outcome of the intramolecular cycloaddition and to extend this approach to the preparation of **1** and **2**. The results of these studies will be reported in forthcoming communications.

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10. Spectral data: **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41(s, 9H), 1.83(m, 2H), 2.35(t, 2H, *J* = 7.6 Hz), 3.64(s, 3H), 4.12(m, 1H), 4.51(m, 1H), 5.05(dd, 1H, *J* = 9.9, 1.7 Hz), 5.17(dd, 1H, *J* = 16.4, 1.7 Hz), 5.54(dd, 1H, 15.1, 6.5 Hz), 6.13(ddd, 1H, *J* = 15.1, 10.4, 1.4 Hz), 6.26(ddd, 1H, *J* = 16.4, 10.4, 9.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 30.2, 30.6, 51.7, 79.5, 117.6, 131.3, 133.6, 136.1, 155.2, 173.7.

    7: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44(s, 9H), 1.48(m, 1H), 1.80(m, 1H), 1.90-2.25(m, 4H), 2.35(m, 2H), 2.50-2.70(m, 2H), 3.80(br m, 1H), 4.82(br m, 1H), 5.52(m, 1H), 5.74(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 23.0, 28.3, 28.8, 36.7, 41.9, 45.4, 50.5, 79.7, 129.4, 131.6, 155.5, 211.4.

    8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44(s, 9H), 1.45(m, 1H), 1.64(m, 1H), 1.83-1.98(m, 2H), 2.10-2.28(m, 2H), 2.34(m, 1H), 2.57(m, 1H), 3.08(br m, 1H), 4.08(br m, 1H), 4.68(br m, 1H), 5.53(m, 1H), 5.82(m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.0, 22.1, 27.7, 28.4, 39.8, 40.0, 45.5, 50.8, 79.7, 123.3, 131.7, 155.1, 209.6.

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12. Diene **4** can be obtained in ≥90% ee by using the crude aldehyde immediately in the Wittig reaction. This was verified by removing the *t*-BOC (CF_3COOH/CH_2Cl_2) and derivatizing the amine as the (+)- and (-)-Mosher amides.[13]

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14. A colorless plate (~0.3 x 0.3 x 0.1 mm) of **8**, $C_{15}H_{23}NO_3$ (265.3), was grown from hexane/EtOAc. Crystal data for **8** at 293 °K with Mo K_α radiation (λ = 0.71073 Å): *a* = 12.829(3) Å, *b* = 11.838(2) Å, *c* = 10.278(2) Å, β = 109.67(3)°, Z = 4, ρ_{calcd} = 1.199 gcm^{-3}, V = 1469.8(5) Å^3, monoclinic, space group $P2_1/c$. Intensity data were collected from 3° ≤ 2θ ≤ 45°. Refinement to convergence on the 1432 (74.1%) unique reflections, $|F_o| \geq 4.0\sigma|F_o|$, resulted in final agreement factors R(F) = 6.6% and R_w(F) = 7.7%. All calculations were performed with the use of SHELXTL program (Siemens Corp., Madison, WI).

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