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Synthesis of Octahydro 1H-Pyrrolo[1,2-a]indol-3-ones Via Intramolecular Diels-Alder Reaction of 5-Substituted N-Dienyl Lactams[1]

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Abstract: N-dienyl-5-alkenyl-lactams can be prepared from succinimide. Heating leads to an intramolecular Diels-Alder cyclization that produces tricyclic products useful for the preparation of related alkaloids.

Many tricyclic alkaloids have important biological activities, and they are continual targets for total syntheses. The hydropyrrolo[1,2-a]quinoline, gephyrotoxin, isolated from skin extracts of the Colombian poison dart frog *Dendrobates histrionicus* is one example.[2] At 5μM it diminishes acetylcholine elicited smooth muscle contractures,[3]

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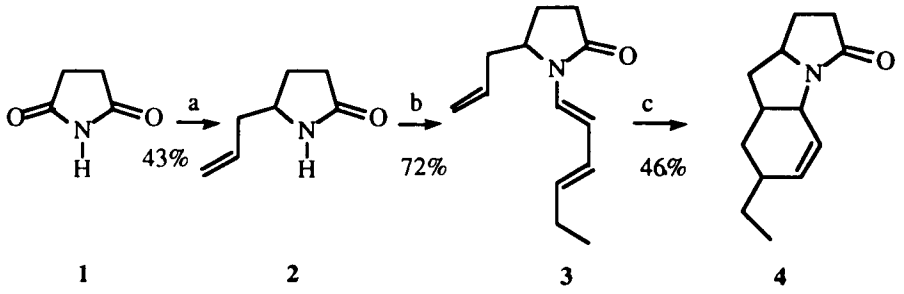
and it has been synthesized.[4] The perhydro 1H-pyrrolo[1,2-a]indole called mitomycin C is a known anti cancer compound[5] that has been the target of synthesis.[6]

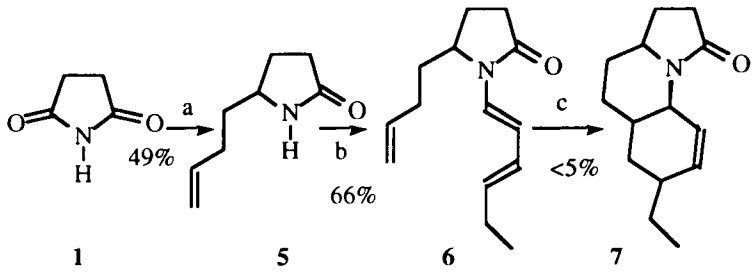


(a) 1. 3.2 eq. CH_2=$CHCH_2MgCl$, ether, 0°C, 2h cannulation, sonication; 2. H_2O, RT overnight 3. $NaBH_3CN$, 4M HCl , RT methyl orange indicator, 1.5h
(b) 2-hexenal, *p-TsOH* , PhMe , reflux
(c) 1,2-dichlorobenzene, reflux , 20 h

In recent years we have attempted to use pyroglutamate in synthesis, and this included its use in the Diels-Alder reaction.[7] Our synthetic route converted pyroglutamate to a triene derivative and an internal Diels-Alder cyclization would produce a tricyclic alkaloid skeleton. Initial work with S-ethyl pyroglutamate was aimed at an asymmetric synthesis of gephyrotoxin, but we were unable to convert the ester moiety to an allylic or butenyl unit. We therefore turned our attention to a chiral, racemic triene precursor that was available from succinimide that would allow us to probe the feasibility of the intramolecular Diels-Alder route. We can now report that the triene intermediate can be prepared and that it cyclizes to the desired tricyclic compound upon heating.

Speckamp[8] reported that succinimide (**1**) reacts with Grignard reagents to give 5-substituted 2-pyrrolidinone derivatives such as **2** or **5**, after reduction of an intermediate iminium derivative. Polniaszek reported the preparation of **2** by a different

route.[9] Compounds such as **5** have also been prepared by reaction of the enolate of 2-pyrrolidinone and alkenyl iodides.[10] For our purposes, we reacted succinimide with allylmagnesium bromide and butenylmagnesium bromide, but found that the yield of 5-allyl or 5-butenyl-2-pyrrolidinone was very poor and there was extensive decomposition. When 3.2 equivalents of allylmagnesium chloride was added slowly to an ether solution of succinimide with the reaction flask immersed in an ultrasonic bath, however, we obtained a 43% yield of 5-allyl-2-pyrrolidinone, **3**. The reaction of succinimide and buten-3-ylmagnesium bromide under identical conditions gave a 49% yield of 5-(3-butenyl)-2-pyrrolidinone, **5**.



(a) 1. 3.2 eq. CH_2=$CHCH_2CH_2MgCl$, ether, 0°C, 2h cannulation, sonication; 2. H_2O, RT overnight 3. $NaBH_3CN$, 4M HCl , RT methyl orange indicator, 1.5h
(b) 2-hexenal, *p*-TsOH, PhMe , reflux
(c) 1,2-dichlorobenzene, reflux , 24 h

In previous work, we showed that lactams react with conjugated aldehydes to give N-dienyl lactams.[7] Reaction of crotonaldehyde and **1** in refluxing toluene (Dean-Stark trap) and a catalytic amount of tosic acid, for example, gave the corresponding N-dienyl derivative in 61% yield. Similar reaction with 2-hexenal gave a 72% yield of **3**. Although the reaction of **5** and crotonaldehyde gave a poor yield of triene, the reaction of 2-hexenal with **5** gave a 66% yield of **6**.

Our first attempts to cyclize **3** by passage through a hot tube (550°C), using a Kügelrohr to volatilize the triene, gave poor yields of the Diels-Alder adduct and extensive decomposition of the starting material. When **3** was refluxed in 1,2-dichlorobenzene, we isolated octahydropyrrolo[1,2-a]indol-3-one **4** in 46% yield. Unexpectedly, cyclization of **6** gave less than 5% of the 8-ethyl derivative (**7**), with extensive decomposition of starting material.

With Diels-Alder adduct **4** in hand, we turned our attention to the stereochemistry of the Diels-Alder adducts. Modeling suggested that a *trans*-ring juncture would be preferred, but proton NMR of the products did not allow us to confirm this. Both **3** and **5** were a mixture of E,E and E,Z dienes, and the resulting cycloadducts (**4** and **7**) were a complex mixture of stereoisomers. The ring-juncture protons appeared in a region of the proton NMR that was too complex for resolution by our instrumentation. We mixed **4** with 10 mol% of $Eu(fod)_3$ and obtained the proton NMR and via COSY determined that the C=C-H proton closest to the lactam nitrogen in **4** appeared at 5.86 ppm in the Eu-shifted spectrum and the other alkenyl proton appeared at 5.93 ppm. The coupling constant between these two protons was determined to be 9.3 Hz, but the ring juncture proton closest to nitrogen appeared at 4.49 ppm as a broadened singlet. The mixture of diastereomeric products prevented us from determining the stereochemistry of the ring juncture in **4**.

Although the stereochemical questions remain unresolved, the initial goal of preparing triene-lactams such as **4** and demonstrating it undergoes Diels-Alder cyclization to the desired tricyclic system was realized. This information leads us to believe that a modified approach for refunctionalizing the ester group of pyroglutamate will allow us to produce chiral, non-racemic derivatives.

Experimental Conditions

(racemic)-5-(2'-propenyl)-2-pyrrolidinone, 2. A solution of 78.8 mmol of allylmagnesium bromide in 35.0 mL (2.25M in diethyl ether) was slowed added (via

cannula) to a solution of 2.00 g (20.2 mmol) of succinimide in 40 mL of freshly distilled THF at 0°C, under a positive pressure of N_2. The milky solution was stirred at 0°C for 2 h, treated with 15 mL of distilled water, and stirred for three hours at room temperature. In order, 1.27 g (20.2 mmol) of $NaBH_3CN$, approximately 100 mg of methyl orange, and 4M HCl were added until the reaction mixture remained pink. After stirring for two hours at room temperature, 6M NaOH was added. Extraction with dichloromethane, washing with brine and drying ($MgSO_4$) was followed by chromatographic separation (silica gel, EtOAc/Hexane-1:1) to give 1.06 g (8.47 mmol, 42%) of **2** as a light yellow oil: ^1H NMR ($CDCl_3$):[9] δ 1.78 (m, 2H), 2.29 (bd m, 4H), 3.74 (p, 1H), 5.77 (q, 2H), 5.65 (m, 1H),and 6.42 (bd s, 1 NH) ppm; ^{13}C NMR ($CDCl_3$): δ 25.0, 28.6, 39.2, 52.2, 116.8, 131.9, and 176.6 ppm; IR ($CHCl_3$): 3202, 3069, 2969, 1670, 1421, 783 cm^{-1}; Anal. Calcd for $C_7H_{11}NO$ 125.0841; Found 125.0838 (± 0.6 mmu).

(racemic)-5-(2'-butenyl)-2-pyrrolidinone, 5. A solution of 62.6 mmol of 1-butenyl-4-magnesium bromide in 35.0 mL (1.80 M in diethyl ether) was slowed added (via cannula) to a solution of 2.00 g (20.2 mmol) of succinimide in 40 mL of freshly distilled THF at 0°C, under a positive pressure of N_2. The milky solution was stirred at 0°C for 2 h with sonication, treated with 15 mL of distilled water, and stirred for three hours at room temperature. In order, 1.27 g (20.2 mmol) of $NaBH_3CN$, approximately 100 mg of methyl orange, and 4M HCl were added until the reaction mixture remained pink. After stirring for two hours at room temperature, 6M NaOH was added. Extraction with dichloromethane, washing with brine and drying ($MgSO_4$) was followed by chromatographic separation (silica gel, EtOAc/Hexane-1:1) to give 1.36 g (9.78 mmol, 49%) of **5** as a light yellow oil: ^1H NMR ($CDCl_3$):[9] δ 1.6 (m, 2H), 1.7 (m, 2H), 2.1 (m, 2H), 2.2 (m, 2H), 3.6 (m, 1H), 4.9 (q, 2H), 5.7 (m, 1H), and 6.8 (bd s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 27, 30, 31, 36, 54, 116, 137, and 179 ppm; IR ($CHCl_3$): 3213, 2925, 1692, 1421, 1271, and 911 cm^{-1}; Mass spectrum,

m/z (Rel. intensity): 140 (0.3), 139 (0.3), 110 (5), 97 (16), 84 (100), 67 (4), and 56 (10); Anal. Calcd for $C_8H_{13}NO$ 139.0997; Found 139.1001 (± 0.7 mmu).

(racemic)-5-(2′-propenyl)-N-(1,3-hexadienyl)-2-pyrrolidinone, 3. A mixture of 1.06g of **2** (8.48 mmol), 1.24 g of 2-hexenal (12.7 mmol) and 50 mg of *p*-toluenesulfonic acid was refluxed in 100 mL of toluene for six h (fitted with a Dean-Stark trap). The solution was cooled, washed with saturated $NaHCO_3$ and then brine. The organic phase was dried ($MgSO_4$), the solvent evaporated and chromatographic separation (silica gel, EtOAc/Hexane-1:1) gave 1.25 g (6.09 mol, 72%) of **3** as a dark viscous oil. ^1H NMR ($CDCl_3$):[8,10] δ 1.01 (t, 3H), 1.71-2.80 (m, 8H), 4.12 (m, 1H), 5.17 (q, 2H), 5.74 (m, 2H), 6.01 (m, 2H), and 6.90 (d, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 13.7, 22.7, 25.8, 30.0, 35.7, 56.0, 113.4, 118.9, 123.2, 127.1, 132.8, 134.2 and 174.0 ppm; IR (neat): 2954, 1699, 1399, 1284, 973, 915, and 731 cm^{-1}; Anal. Calcd for $C_{13}H_{19}NO$ 205.1467; Found 205.1459 (± 1.0 mmu).

(racemic)-5-(3′-butenyl)-N-(1,3-hexadienyl)-2-pyrrolidinone, 6. A mixture of 1.36 g of **5** (9.78 mmol), 1.44 g of 2-hexenal (14.7 mmol) and 50 mg of *p*-toluenesulfonic acid was refluxed in 100 mL of toluene for four h (fitted with a Dean-Stark trap). The solution was cooled, washed with saturated $NaHCO_3$ and then brine. The organic phase was dried ($MgSO_4$), the solvent evaporated and chromatographic separation (silica gel, EtOAc/Hexane--1:1) gave 1.41 g (6.43 mol, 66%) of **6** as a dark viscous oil. ^1H NMR ($CDCl_3$): δ 1.1 (t, 3H), 1.6 (m, 2H), 1.9 (q, 2H), 2.1 (m, 2H), 2.4 (m, 2H), 2.6 (m, 2H), 3.6 (m, 1H), 5.1 (q, 2H), 5.8 (bd m, 4H), and 6.9 (d, 1H) ppm; IR (neat): 2925, 1699, 1399, 1284, 973, 925, and 751 cm^{-1}; Mass spectrum, m/z (Rel. intensity): 219 (40), 190 (8), 164 (44), 150 (26), 137 (100), 108 (14), 81 (44), 67 (27), and 55 (40); Anal. Calcd for $C_{14}H_{21}NO$ 219.1623; Found 219.1623 (± 1.0 mmu).

(racemic)-6-Ethyl-1,2,3b,6,7,7a,8,8a-octahydro-3a-azacyclopenta[a]-inden-3-one, 4. Refluxing 0.717 g (3.50 mmol) of **3** in 35 mL of *o*-dichloro-

benzene for 24 hours was followed by chromatographic purification (SiO_2; EtOAc-hexane) to give 0.335 g (1.63 mmol, 47%) of **4** as a brown oil: ^1H NMR ($CDCl_3$): δ 1.0 (t, 3H), 1.4 (m, 2H), 1.4 (m, 2H), 1.6 (m, 1H), 1.8 (m, 2H), 2.3 (m, 3H), 2.6 (m, 3H), 4.1 (m, 1H), 5.8 (q, 1H), and 5.9 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ 11.1, 27.3, 28, 28.5, 29.6, 32.5, 35.9, 51.8, 59.3, 125.2, 134.8, and 175.2 ppm; Mass spectrum, m/z (Rel. Int.): 205 (62), 176 (42), 150 (15), 149 (100), 121 (16), 98 (8), 94 (22), 91 (24), 84 (19), 77 (24), and 55 (20); Anal. Calcd for $C_{13}H_{19}NO$ 205.1462; Found 205.1467 (± 1.0 mmu).

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1 Presented, in part, at the 209th meeting of the American Chemical Society, Anaheim, CA., **ORGN 179**, 4/4/95.

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