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Synthesis of (-)-δ-*N*-Normethylskytanthine

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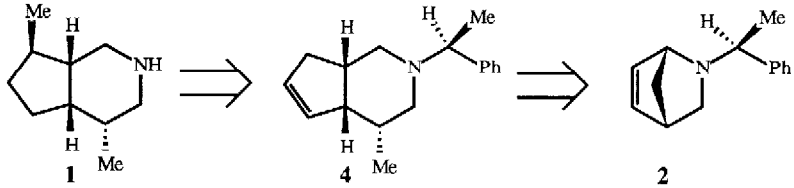
Key words: terpene alkaloids, 3-azabicyclo[4.3.0]nonane, ketene amino-Claisen rearrangement.

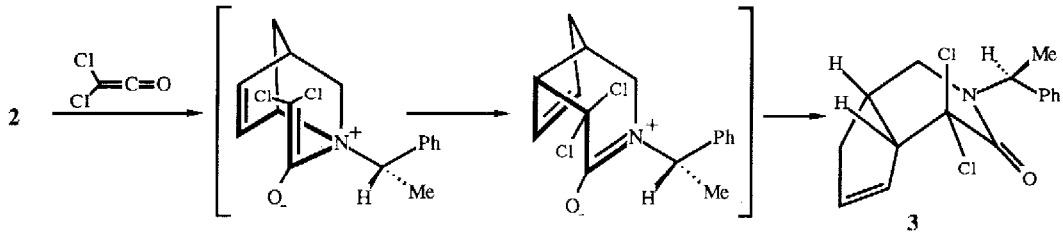
Abstract: *(-)-δ-N-normethylskytanthine (**1**) has been synthesised from (1R,4R,1'S)-2-(phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene (**2**) which undergoes a ketene-amino-Claisen rearrangement by reaction with dichloroketene to generate (1S,6R,1'S)-3-(phenylethyl)-5,5-dichloro-4-keto-3-azabicyclo[4.3.0]non-7-ene (**3**), which could be converted to **1** in eleven steps.*

Recently, several syntheses of alkaloids with the 3-azabicyclo[4.3.0]nonane skeleton,[1] as well as reports of isolation of new members of this family possessing varied biological activities[2] have appeared in the literature. In 1988 (-)-δ-*N*-normethylskytanthine (**1**) was reported to be the main alkaloid from *Tecoma arequipensis* by F. R. Stermitz and coworkers. Its structure was established by X-ray diffraction from a crystalline N-4-bromophenyl thiourea derivative.[3]



1 **4** **2**

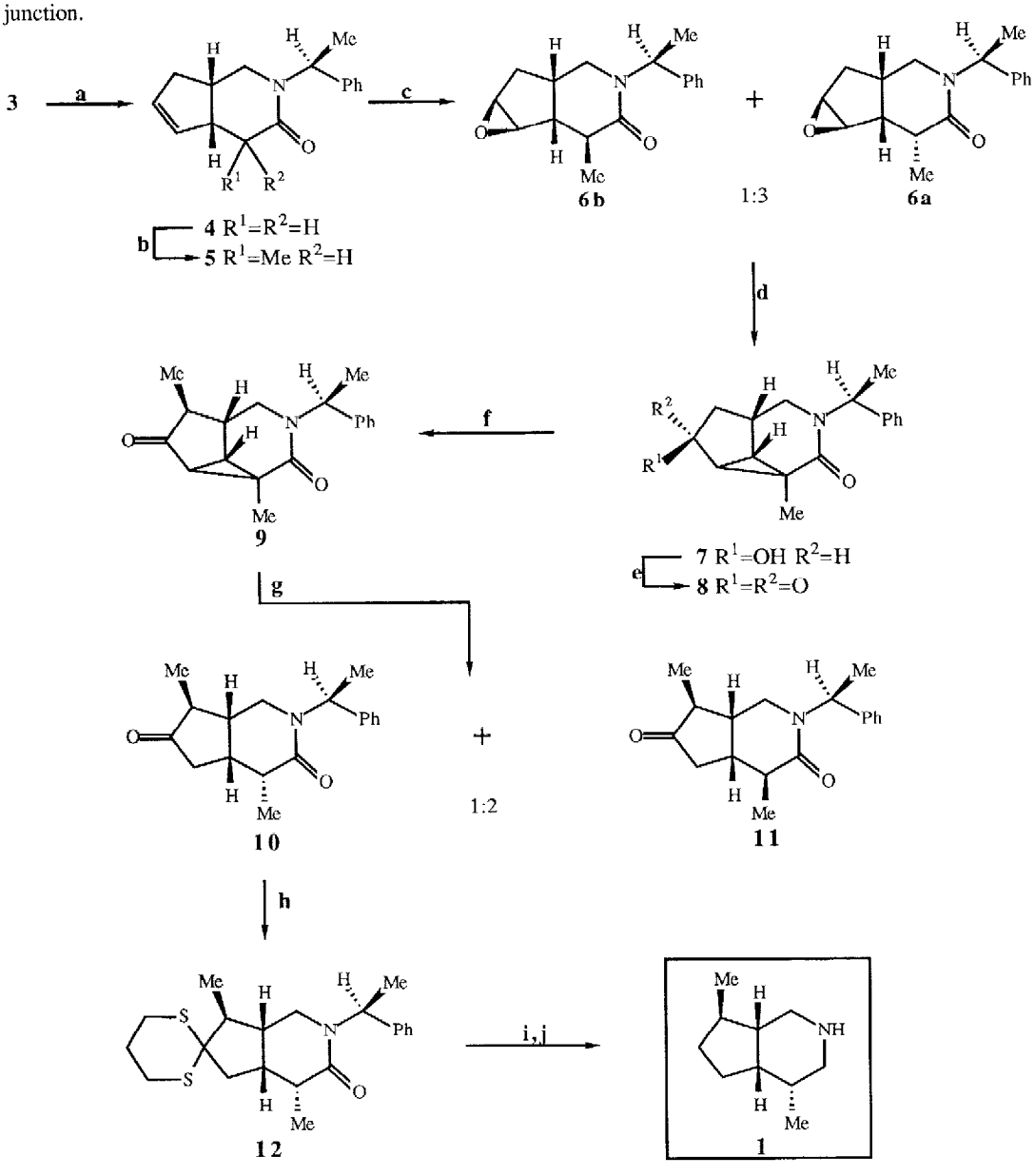
S. Roberts *et.al.*[4] recently reported the ketene amino-Claisen rearrangement of racemic 2-azabicyclo[2.2.1]heptanes, which provides a rapid entry to the azabicylo[4.3.0]nonane skeleton, with appropriate functionality for further elaboration. This rearrangement is analogous to the ketene Claisen rearrangement published by Malherbe and Bellus in 1978.[5] We have now used this rearrangement in the enantioselective synthesis of **1**,[6] according to the retrosynthetic analysis shown above. Starting from (*S*)-phenylethylamine, optically pure (1*R*,4*R*,1'*S*)-2-(phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene (**2**) ($[\alpha]_D^{20}$=+17 (c=0.83, CH_2Cl_2)) was obtained in 50% yield from the hetero-Diels Alder reaction described by Grieco and Larsen,[7] after chromatographic separation of the diastereoisomeric adducts.



3

Reaction of **2** with dichloroketene in CH_2Cl_2, generated *in situ* from dichloroacetyl chloride with Hünig's base, at 2°C, gave lactam[8] **3** (mp 48-50 °C, $[\alpha]_D^{20}$=-67.8 (c=0.9, CH_2Cl_2)) in 61% after 16h. Higher temperatures decreased the yield of rearranged product, and increased the quantity of tarry side products. The

gross structure of **3** was deduced from its ^{1}HNMR spectrum. The coupling constant between the ring junction protons H-1 and H-6 was 10 Hz, too large to be considered unambiguous evidence of the expected cis ring junction.



Reagents: a) Zn/NH_4Cl/MeOH, 81%; b) LDA/MeI/THF/82%; c) MCPBA/CH_2Cl_2, 81%; d) $LiNEt_2$/ethyl ether, 80%; e) DMSO/$(COCl)_2$/Et_3N, 95%; f) LDA/MeI/HMPA/THF, 80%; g) Zn/AcOH, 70%; h) propan-1,3-dithiol/$BF_3.Et_2O$/$CHCl_3$, 81%; i) $LiAlH_4$/THF, 90%; j) Raney Ni; H_2/Pd/C, 59%.

Reductive dehalogenation of lactam **3** with excess Zn in MeOH and NH_4Cl, followed by monomethylation[9] in position 5, led to a mixture of epimers **5**. This mixture was treated with *m*-chloroperbenzoic acid in the presence of $NaHCO_3$, to give epoxides **6a** ($[\alpha]_D^{20}$=-70.9 (c=1.05, CH_2Cl_2) and **6b** ($[\alpha]_D^{20}$=-128.0 (c=1.0, CH_2Cl_2) in a 3:1 ratio, respectively, which were separated by chromatography. The relative configuration and conformation of epoxides **6a** and **6b** was then studied with NMR spectroscopy.[10] In both epoxides, the 6-membered ring adopts the boat conformation in which the methyl at position 5 is pseudo-equatorial; therefore the fused 5-membered ring is thus forced to occupy an endo position in **6b** or an exo position in **6a**. Evidence for the cis ring junction in both **6a** and **6b** was provided by ^{1}HNMR coupling constants and a COSY/NOESY experiment, in **6a** $J_{5,6}$=8.8, $J_{6,1}$=8.8, H-7 has NOE with H-6 and Me-C-5 and H-5 with H-2ax, in **6b** $J_{5,6}$=10.0 and $J_{1,6}$=10.0, H-7 has NOE with H-6, Me-C-5 and H-5, H-5 with H-2ax.

Treatment of either **6a** or **6b** with lithium diethylamide resulted, as expected, in the same tricyclic alcohol **7** (mp 141-143°C, $[\alpha]_D^{20}$=-132.0 (c=0.5, CH_2Cl_2), 43% overall yield from **3**) by intramolecular opening of the epoxide. Swern oxidation of the alcohol **7** gave the ketone **8** (mp 109-111°C, $[\alpha]_D^{20}$=-55.8 (c=0.55, CH_2Cl_2)) which was then cleanly monomethylated using a procedure analogous to that described by P. Callant et al.[11] to afford the tricyclic cyclopropane-γ-dicarbonyl **9** (mp 113°C, $[\alpha]_D^{20}$=-35.4 (c=0.55, CH_2Cl_2)). Reductive opening of **9** with Zn in acetic acid[12] gave a 1:2 mixture of the two diastereoisomers **10** (mp 87°C, $[\alpha]_D^{20}$=-207 (c=0.3, CH_2Cl_2)) and **11** ($[\alpha]_D^{20}$=-86.4(c=1.43, CH_2Cl_2)) which were separated by preparative tlc (EtOAc:hexane 2:3, Rf=0.6 and 0.4 respectively). Cleavage of the cyclopropane ring could also be achieved with lithium in ammonia with a similar ratio of diastereomers, albeit with concomitant debenzylation of the amide. For reasons of ease of handling of the compounds, however, it was considered desirable to leave the phenylethyl group on the nitrogen until the last step. Compound **10** was treated with propane-1,3-dithiol in the presence of $BF_3.Et_2O$ in dichloromethane to generate the dithiane **12** ($[\alpha]_D^{20}$=-32.3 (c=0.6, CH_2Cl_2)) in 81% yield. The dithiane **12** was then converted to the natural product **1** in 51% yield by reduction of the amide group with $LiAlH_4$/THF, and hydrogenolysis with Raney nickel in EtOH followed by Pd in acetic acid (15% Pd/C, 70 Psi H_2, 45°C, 18 h).

The structure of **1** ($[\alpha]_D^{20}$= -22.7 (c= 0.3, $CHCl_3$); Lit[3]:$[\alpha]_D^{20}$=-21.5 (c=7.7, $CHCl_3$)) was assigned from spectroscopic data, and confirmed by comparison with a sample of the natural product, kindly provided by Prof. Stermitz.[13]

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8. ^{1}HNMR (360 MHz ,$CDCl_3$): 1.50 (d, J=6.0, 3H, H-2'); 2.15 (m, 1H, H-9 or H-1); 2.55 (m, 2H, H-9 or/and H-1); 3.15 (dd, J=13.0 and 6.0, 1H, H-2); 3.25 (dd, J=13.0 and 6.0, 1H, H-2); 3.88 (dm, J= 10 Hz, 1H, H-6); 5.80 (m, 1H, H-7 or H-8); 5.91 (m, 2H, H-7 or H-8 and H-1'); 7.29-7.40 (m, 5H, ArH).
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10. ^{1}HNMR (500 MHz, $CDCl_3$) **6a**: 1.38 (d, J= 7.9, 3H, Me-(C-5)); 1.45 (d, J=8.0, 3H, H-2'); 1.59 (ddd, J=1.9, 6.0, 14.0, 1H, H-9ax); 2.11 (dd, J=8.0 and 14.0, 1H, H-9eq); 2.27 (m, 1H, H-1); 2.50 (quin., J=8.8, 1H, H-5); 2.69 (t, J=8.8, 1H, H-6); 2.78 (dd, J=2.0 and 12.4, 1H, H-2ax.); 2.87 (dd, J=2.3 and 12.4, 1H, H-2eq); 3.39 (br s, 1H, H-7); 3.43 (br s, 1H, H-8); 5.71 (c, J=8.0, 1H, H-1'); 7.15-7.25 (m, 5H, ArH). **6b**: 1.28 (d, J=6.5, 3H, Me-(C-5)); 1.36 (d, J=7.0, 1H, H-2'); 1.46 (m, 1H, H-9); 1.79 (m, 2H, H-1 and H-9); 1.97 (t, J=10.0, 1H, H-6), 2.61 (m, 1H, H-5); 2.72 (dd, J=5.3 and 12.0, 1H, H-2eq); 2.90 (t, J=12.0, 1H, H-2ax); 3.47 (s, 1H, H-8); 3.50 (s, 1H, H-7); 5.89 (c, J=7.0, 1H, H-1'); 7.25 (m, 5H, ArH).
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13. All compounds reported presented satisfactory analytical data, and their structures were unambiguously confirmed by MS, NMR, IR and, where appropiate, CD spectroscopy.

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