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BIOMIMETIC SYNTHESES OF SYNCARPUREA

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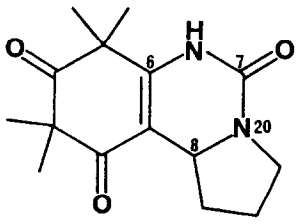
Summary: Simple syntheses of syncarpurea (1) from syncarpic acid and the amino acids ornithine or citrulline are presented.

Plants of the genus Uvaria have been a rich source of unusual natural products.[1] A recent report by Hufford et al.[2] described the isolation and structural characterization of syncarpurea (1), a minor metabolite of Uvaria afzelii. We were interested in the synthesis of syncarpurea (1) since crude extracts of this plant had interesting antibiotic and antitumor properties, but the limited amounts of syncarpurea had precluded adequate biological testing. Syncarpurea (1) is also interesting because of its novel skeleton and lack of optical activity. One possible explanation for its racemic nature involves a nonenzymatic synthesis from other Uvaria secondary metabolites. We now wish to report two syntheses based on this idea.



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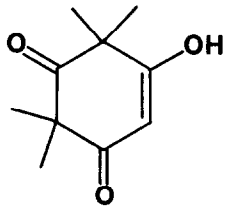

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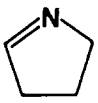

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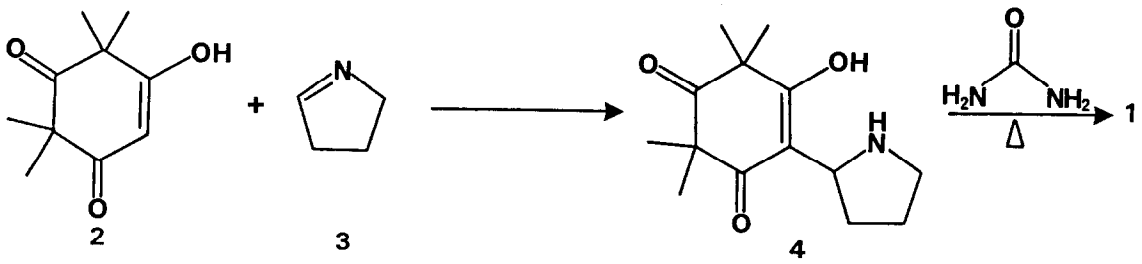
Syncarpurea (1) can be dissected retrosynthetically into syncarpic acid (2), Δ^1-pyrroline (3), and urea. Syncarpic acid (2) as well as several metabolites derived from syncarpic acid have been isolated from Uvaria afzelii.[1,2,3,4] Syncarpic acid is easily prepared from 2,4,6-trihydroxyacetophenone.[5] Δ^1-pyrroline has previously been shown to be a precursor for other natural products,[6,7] although not in the genus Uvaria.[1] The α-amino acid ornithine

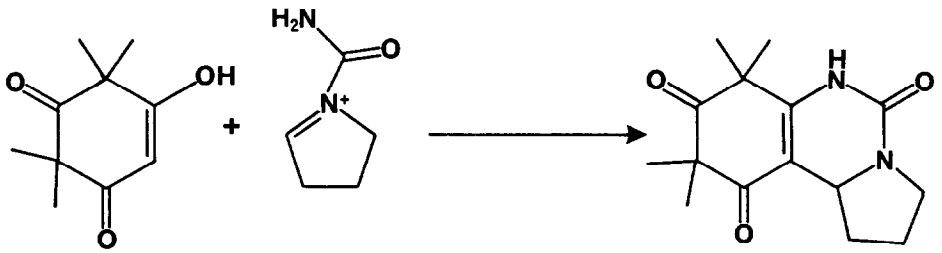
was a plausible Δ^1-pyrroline (3) precursor since it had been reported that Δ^1-pyrroline was generated enzymatically from ornithine.[8,9] An excellent laboratory equivalent of this enzymatic transformation was the treatment of ornithine with N-bromosuccinimide.[10]

Our first synthesis involved two steps (Scheme 1). Δ^1-pyrroline was generated from ornithine hydrochloride (335 mg, 1.99 mmole) and N-bromosuccinimide (354 mg, 1.99 mmole) in 10 mL of H_2O. The HBr generated was removed by vacuum aspiration and passed through a 40% KI solution. After one hour at room temperature, the reaction mixture was placed under a N_2 atmosphere and warmed gently on a steam bath for a few minutes until colorless. To this solution, 204 mg (1.12 mmole) of syncarpic acid in 40 mL of 1:1 MeOH:H_2O (pH 7, phosphate buffer) was added by syringe. The reaction was stirred for two days at room temperature.[11] Workup consisted of rotary evaporation to dryness, addition of CH_2Cl_2, drying over $MgSO_4$, filtration and column chromatography on silica gel with 1:1 EtOAc:hexane followed by EtOAc and finally MeOH. The desired compound 4 was in the MeOH fraction, and the isolated yield was 93%.[12] Compound 4 was then reacted with 7 equivalents of urea in H_2O in a sealed tube (110°, 16 hrs).[13] The reaction mixture was filtered, concentrated, extracted with CH_2Cl_2, and the organic layer dried with $MgSO_4$. Open column chromatography (39:1 CH_2Cl_2:MeOH) gave syncarpurea (1) in 20% yield. The synthetic material was identical to natural syncarpurea by IR, ^1H and ^{13}C NMR, EI and CI mass spectrometry, and TLC comparison with an authentic sample.[2]



SCHEME 1

While this procedure did give syncarpurea, the overall yield (19%) was somewhat disappointing. The problem was clearly in the second step. Since previous experience with syncarpic acid derivatives suggested that conjugate addition at C-6 was relatively facile, the low yield was attributed to the formation of the C-7 to N-20 bond. In order to test this we explored a similar route but used citrulline, rather than ornithine, as a precursor of the 1-carboxamido-Δ^1-pyrrolinium ion (5) (Scheme 2). Citrulline has been reported as a free amino acid in Uvaria.[1] A 25 mL aqueous solution of 575 mg (3.29 mmole) of citrulline and 585 mg (3.29 mmole) of N-bromosuccinimide was prepared, and the resulting HBr was evacuated through a KI solution. After 1.5 hours the solution was warmed on a steam bath for 5 minutes and cooled to room temperature under N_2. Then 15 mL of a 1:1 MeOH:0.005N HCl solution containing 60 mg (0.33 mmole) of syncarpic acid (1) was added by syringe. The reaction mixture was stirred at room temperature for 48 hours. The reaction was opened to the atmosphere and stirring halted. Syncarpurea (1) precipitated from the reaction mixture as a white powder and filtration yielded 37 mg of 1 (40% yield). The solution was treated as described above and after chromatography an additional 12 mg of syncarpurea was obtained. The combined isolated yield was 49 mg (53%).



SCHEME 2

Whether these laboratory syntheses are possible models for the biosynthesis of syncarpurea will have to be determined by biosynthetic studies. It should be noted that the lack of optical activity does not appear to be an artifact of the isolation procedure. We have not found conditions whereby the hydrogen at C-8 can be removed, and it is difficult to write a mechanism for the racemization of syncarpurea that does not involve breaking this bond.

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REFERENCES

1. Leboeuf, M; Cave, A; Bhaumik, P.K.; Mukherjee, B.; Mukherjee, R. Phytochemistry **1982**, 21, 2783-2813.

2. Hufford, C.D.; Oguntimein, B.; Martin, M.; Clardy, J. Tet. Lett. **1984**, 25, 371-374.

3. Hufford, C.D.; Oguntimein, B.O.; Van Engen, D.; Muthard, D.; Clardy, J. J. Am. Chem. Soc. **1980**, 102, 7365-7367.

4. Martin, M.; Clardy, J.; Tet. Lett. **1981**, 22, 3365-3366.

5. Jain, D.C.; Seshadri, T.R.; Proc. Indian Acad. Soc. Sect. A **1955**, 42, 279-284.

6. Bhakuni, D.S.; Mangla, V.K. Tetrahedron **1981**, 37, 401-407.

7. Leete, E. J. Am. Chem. Soc. **1967**, 89, 7081-7084.

8. Morris, D.R.; Pardee, A.B.; Biochem. Biophys. Res. Commun. **1965**, 20, 697-702.

9. Jakoby, W.B.; Frederich, J. J. Biol. Chem. **1959**, 234, 2145-2150.

10. This procedure is a slight modification of that described in reference 9.

11. This procedure is an adaptation of that described in reference 6.

12. Chemical and spectral data for **4**: m.p. 160-163° (dec.) (CH_2Cl_2); IR ($CDCl_3$) 2970, 1700, and 1505 cm^{-1}; EIMS m/z 252 (M^+, 28%), 251 (M^+-1, 17%), 223 (M^+-29, 11%), 183 (M^+-69, 17%), 70 (M^+-182, 100%); ^1H NMR ($CDCl_3$) δ 10.16 (OH, br s, ex D_2O), 8.79 (NH, br s, ex D_2O), 4.81 (H7, 1H, m), 3.41 (H10, 2H, m), 2.16 (H8, 2H, m), 2.1-1.8 (H9, 2H, m), 1.30 and 1.27 (CH_3, both singlets, 6H each); ^{13}C NMR ($CDCl_3$) δ 214.2 (C3, s), 192.9 (C1 and C3, s), 101.9 (C6, s), 58.2 (C7, d), 52.4 (C2 and C4, s), 44.8 (C10, q), 29.7 (C8, t), 24.6 (C9, t), 25.3 and 24.3 (C11 to C14, both q).

13. Lower temperatures gave no reaction and higher temperatures led to excessive decomposition of **4** with lower yields and recovery of syncarpic acid. The sealed tube prevented loss of urea or cyanic acid on heating.

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