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THE CHEMISTRY OF VICINAL TRICARBONYLS. AN EFFICIENT SYNTHESIS OF (±)-VASICINE

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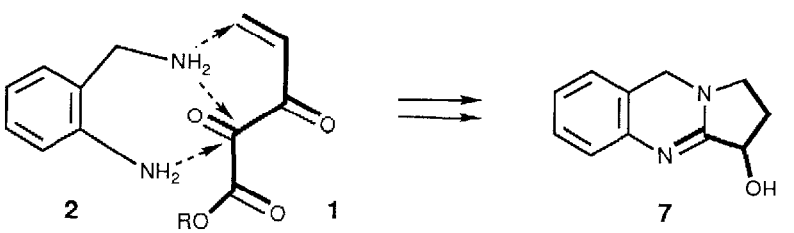
Summary: Addition of 2-aminobenzylamine to the vinyl vicinal tricarbonyl reagent leads to a short synthesis of (±)-vasicine. In this reaction, the VTC reagent acts as a trielectrophile.

Vasicine (peganine) **7**, the alkaloid of *Adhatoda vasica Nees*, is of special interest in connection with its marked hypotensive and respiratory stimulant activity.[1,2] Following the early syntheses of vasicine by Späth *et al.*[3], Southwick and Casanova[4] prepared this product in a low-yield, six-step sequence starting from 2-nitrobenzylamine. Somewhat later, the Schopf-Oechler biomimetic scheme for the formation of vasicine from 2-aminobenzaldehyde and γ-amino-α-hydroxybutyraldehyde was realized by the Leonard synthesis, generating **7** in 39% overall yield.[5] More recently, a synthesis based on a mercuric ion-promoted intramolecular dehydration-cyclization was reported by Möhrle and Gundlach.[6]

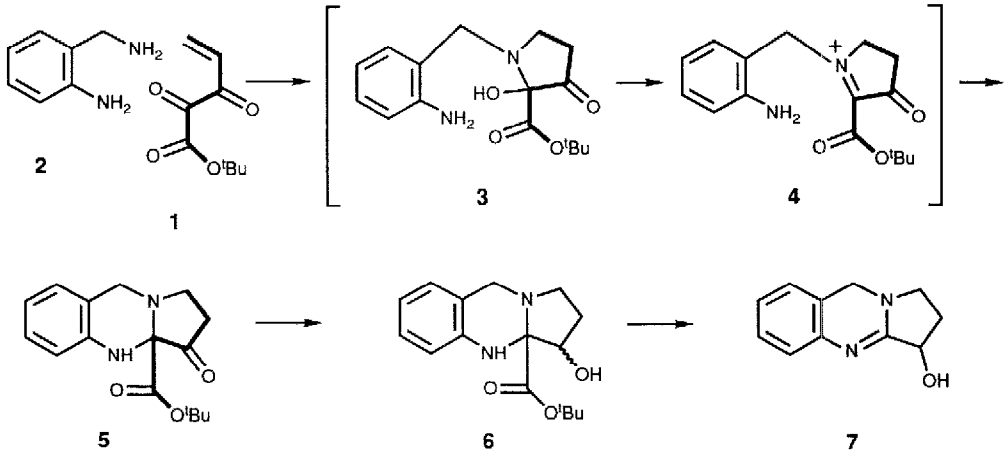


2 **1** **7**

In connection with our recent studies on the reactions of the vinyl vicinal tricarbonyl reagent **1** (VTC) as a trielectrophile,[7] we envisioned a reaction sequence whereby 2-aminobenzylamine **2** could act as a trinucleophile, forming the tricyclic carbon skeleton of vasicine in a threefold donor-acceptor process. The reaction sequence would involve initial conjugate addition of the primary amino group to the double bond along with addition to the central carbonyl group. The resulting carbinolamine could then give rise to the iminium ion which would then serve as an acceptor for the aromatic amine moiety, forming the central ring of the tricyclic system.

When we treated 2-aminobenzylamine with the vinyl vicinal tricarbonyl reagent **1** in chloroform at 20°C for 2 h, in the presence of silica gel, the tricyclic compound **5** was formed directly (68%). In the absence of silica gel, the carbinolamine intermediate **3** was isolated. Formation of **5** takes place most probably through the salt **4**, formed from **3** in mild acid.

Product **5** could be reduced with sodium borohydride in methanol to a diastereomeric mixture of alcohols **6** (3:1, 82%). In the final step of the synthesis, treatment of **6** with trifluoroacetic acid at 40°C for 2 h in the presence of air led directly to (±)-vasicine (45%).[8,9] Our synthetic product was identified (IR, ^{1}H NMR, ^{13}C NMR, mass spec.) by comparison with an authentic sample of (-)-vasicine kindly supplied by Dr. K.L. Dhar, Jammu Tawi, India. We are investigating the nature of the cleavage reaction represented by the conversion of **6** to **7**, particularly with respect to the possible role of air oxidation in the transformation. Alternatively, an elimination, decarbonylation process may be taking place through a mixed anhydride intermediate.



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References and Notes

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(8) All new compounds have been fully characterized by ^{1}H NMR, IR and high resolution mass spectroscopy.
(9) ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24-7.09 (m, 2H), 7.05-6.84 (m, 2H), 4.77 (dd, J=7.7, 6.1 Hz, 1H), 4.60 (s, 2H), 3.41 (m, 1H), 3.23 (m, 1H), 2.35 (m, 1H), 2.11 (m, 1H); MS, m/e 189 (8.3, M+1), 188 (70.5, M), 187 (100, M-1), 169 (5.4), 159 (21.0), 131 (29.0), 104 (7.1), 89 (1.5), 77 (3.1); Calc'd for $C_{11}H_{12}N_2O$: 188.0951. Found: 188.0958.

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