

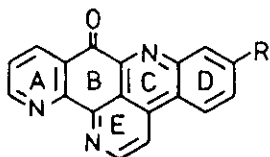
TOTAL SYNTHESIS OF THE PENTACYCLIC ALKALOID ASCIDIDEMIN¹

Franz Bracher

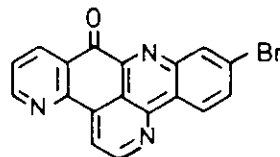
Institut für Pharmazeutische Chemie der Philipps-Universität
 Marbacher Weg 6, D-3550 Marburg (Fed. Rep. of Germany)

Abstract - The antileukemic alkaloid ascididemin (1) was prepared from quinoline-5,8-quinone (4) by oxidative amination with o-aminoacetophenone (5), followed by acid catalysed cyclisation and subsequent one pot annelation of ring E.

Ascididemin (1), a pentacyclic alkaloid with antileukemic activity, was isolated by Kobayashi and co-workers² from the Okinawan tunicate *Didemnum sp.* in low yield (0.006%). The structure was elucidated on the basis of spectroscopic data. Recently de Guzman and Schmitz³ found out that reductive debromination ($H_2/Pd/EtOH$) of bromoleptoclinidinone gave a compound identical with ascididemin (1). On the basis of these results the structure of bromoleptoclinidinone had to be revised from 3 to 2.



1 R = H
 2 R = Br

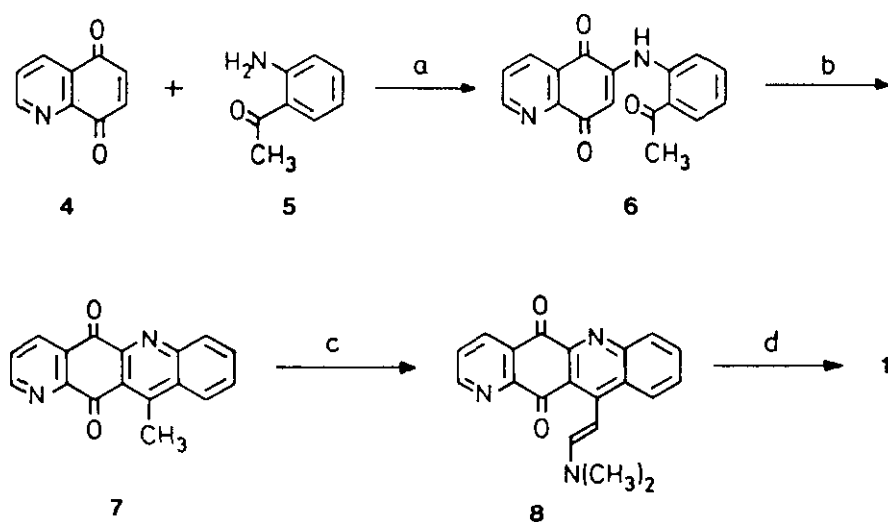


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In this paper we report the first total synthesis of ascididemin (1).

Quinoline-5,8-quinone (4), prepared by dichromate oxidation of 5-amino-8-hydroxyquinoline,⁴ was converted to the diaryl amine 6⁵ by oxidative amination with o-aminoacetophenone (5) in the presence of $CeCl_3$ and air.⁶ The regioselectivity of the amination is most certainly due to the complexation of the quinolinequinone with the cerium ions.^{6,7}

Cyclisation of 6 to the tetracyclic quinone 7⁸ proceeded smoothly on heating with conc. H₂SO₄ in glacial acetic acid.⁹ The formation of ring E was accomplished by means of a one pot annelation method recently developed in this laboratory in the course of the synthesis of the alkaloids sampangine^{10a} and eupolauridine.^{10b} Thus, the reaction of 7 with dimethylformamide diethyl acetal gave enamine 8. Treatment of the crude 8 with NH₄Cl in refluxing acetic acid gave ascididemin (1). The spectroscopic data obtained for 1 was in accordance with the values published for ascididemin (1) by Kobayashi² and Schmitz.³



Conditions: a) CeCl₃ · 7 H₂O, C₂H₅OH, air, 20°C, 16 h (78%);
 b) conc.-H₂SO₄-AcOH(1:10), reflux, 10 min (94%);
 c) HC(OC₂H₅)₂N(CH₃)₂, DMF, 120°C, 1 h;
 d) NH₄Cl, AcOH, reflux, 1h (59%).

Work is in progress as to the synthesis of the related alkaloid bromoleptoclidinone (2) following the same strategy.

ACKNOWLEDGEMENT

This work has been supported by the Deutsche Forschungsgemeinschaft, Bonn.

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5. mp 224-228°C (decomp); ¹H-nmr (400 MHz, CDCl₃) δ 2.73 (s, 3H), 6.95 (s, 1H), 7.22 (br td, J= 1.5 and 7.5 Hz, 1H), 7.62 (br td, J= 1.5 and 7.5 Hz, 1H), 7.67 (m, 2H), 8.00 (dd, J=1.5 and 8 Hz, 1H), 8.51 (dd, J= 1.8 and 8 Hz, 1H), 9.07 (dd, J= 1.8 and 4.7 Hz, 1H), 11.37 (br s, NH); ms (m/z, %) 292 (M⁺, 100), 274 (41), 263 (26), 250 (48), 249 (39), 235 (17), 221 (13), 186 (45); hrms 292.0891 (C₁₇H₁₂N₂O₃ requires 292.0848).
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Received, 18th Augsut, 1989