TOTAL SYNTHESIS OF THE PENTACYCLIC ALKALOID ASCIDIDEMIN[1]

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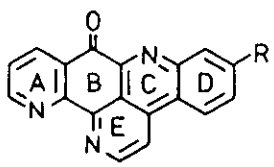
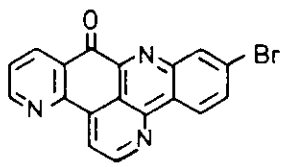
Abstract - The antileukemic alkaloid ascididemin (1) was prepared from quinoline-5,8-quinone (4) by oxidative amination with o-aminoacetophenone (5), followed by acid catalysed cyclisation and subsequent one pot annelation of ring E.

Ascididemin (1), a pentacyclic alkaloid with antileukemic activity, was isolated by Kobayashi and co-workers[2] 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 Schmitz[3] 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.



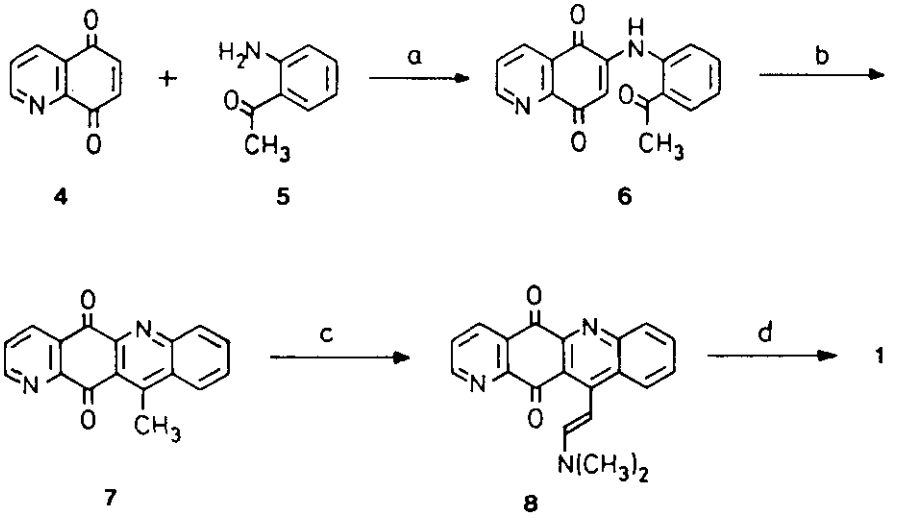
1 R = H
2 R = Br



3

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 6[5] 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 7[8] proceeded smoothly on heating with conc. H_2SO_4 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 NH_4Cl in refluxing acetic acid gave ascididemin (1). The spectroscopic data obtained for 1 was in accordance with the values published for ascididemin (1) by Kobayashi[2] and Schmitz.[3]



4 5 6 7 8

Conditions: a) $CeCl_3 \cdot 7\ H_2O$, C_2H_5OH, air, 20°C, 16 h (78%);
b) conc.-H_2SO_4-AcOH(1:10), reflux, 10 min (94%);
c) $HC(OC_2H_5)_2N(CH_3)_2$, DMF, 120°C, 1 h;
d) NH_4Cl, AcOH, reflux, 1h (59%).

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

ACKNOWLEDGEMENT

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

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3. F. S. de Guzman and F. J. Schmitz, Tetrahedron Lett., 1989, 30, 1969.

4. Y. T. Pratt and N. L. Drake, J. Am. Chem. Soc., 1960, 82, 1155.

5. mp 224-228°C (decomp); ^{1}H-nmr (400 MHz, $CDCl_3$) 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 ($C_{17}H_{12}N_2O_3$ requires 292.0848).

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7. Regioselective oxidative aminations of quinolinequinones were also conducted in the presence of $Ce(SO_4)_2$ or $NiCl_2$: E. A. Ibrahim, I. Chaaban, and S. M. El-Khawass, Pharmazie, 1976, 31, 405; K. Yoshida, M. Yamamoto, and M. Ishiguro, Chem. Lett., 1986, 1059.

8. mp 240-248°C (decomp); ^{1}H-nmr (400 MHz, $CDCl_3$) δ 3.34 (s, 3H), 7.77-7.83 (m, 2H), 7.95 (ddd, J= 1.4, 6.9 and 8,5 Hz, 1H), 8.40 (dd, J= 0.8 and 8.5 Hz, 1H), 8.46 (dd, J= 0.8 and 8.5 Hz, 1H), 8.74 (dd, J= 1.8 and 7.8 Hz, 1H), 9.17 (dd, J=1.8 and 4.6 Hz, 1H); ms (m/z, %) 274 (M^+, 100), 246 (27), 218 (8), 217 (10), 216 (7), 190 (6); hrms 274.0756 ($C_{17}H_{10}N_2O_2$ requires 274.0742).

9. For related intramolecular acylations of arylaminonaphthoquinones see:
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    b) F. Bracher, Arch. Pharm. (Weinheim), 1989, 322, 293.

Received, 18th Augsut, 1989