Pergamon

Tetrahedron Letters, Vol. 36, No. 27, pp. 4709-4712, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00848-9

Total Synthesis of Cystodytin J, Diplamine and Shermilamine B

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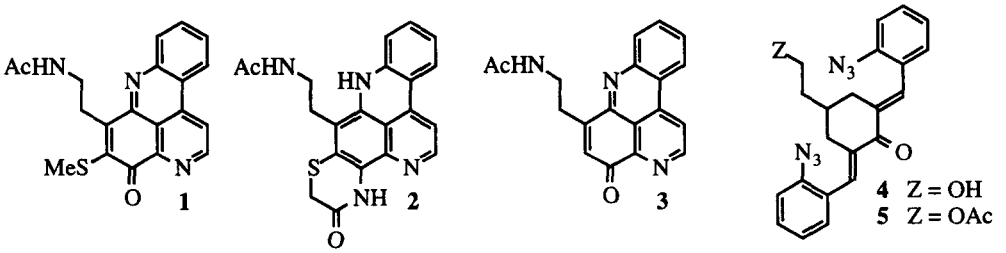
ABSTRACT: *Concise, efficient total syntheses of three cytotoxic marine alkaloids are described. Key phases of the synthesis are a useful pyridine-forming reaction and a triplet-sensitized thermophotolysis of an aryl azide that established a C-N bond to an unactivated benzylic site.*

Marine organisms have recently yielded a multitude of bioactive compounds, notable among which are the pyridoacridine alkaloids.[2] Many of these substances display desirable pharmacological properties, e.g., antitumor activity. To illustrate, diplamine, **1**,[3] a pigment produced by a tunicate of the *Diplosoma* species, is highly cytotoxic, with a reported potency against L1210 leukemia corresponding to an IC_{50} of 20 ng / mL (≈ 54 nM). By contrast, shermilamine B, **2**, and related compounds[4] obtained from a poorly characterized *Tridemnun* tunicate, are weakly bioactive (IC_{50} ≈ 5 μg / mL against KB cells).[5] Pyridoacridine alkaloids are excellent targets for synthetic work,[6] not only because their architecture offers much opportunity for the development of new reactions, but also because their scarcity severely hampers further pharmacological evaluation. In the latter respect, provocative results are beginning to accumulate,[7] and the family as a whole may soon become of interest as a source of new lead structures for the development of future generations of therapeutic agents.

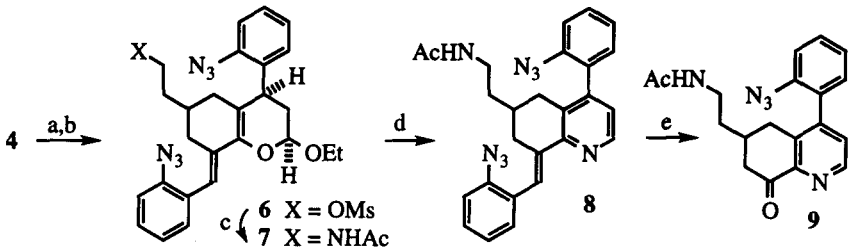


A very interesting total synthesis of diplamine has been described,[8] but, to our knowledge, the shermilamine problem has remained heretofore unresolved. **1** and **2** formally arise through oxidative condensation of a mercaptan with the quinoninimine[9] unit of a cystodytin-like intermediate, e.g. cystodytin J, **3**,[10] followed by further metabolism. We wish to describe the total synthesis of **1** and **2** by an application of this general principle.

The synthesis of **1** commenced with the known dienone **4**.[11] Mesylation and combination of the resulting sulfonate ester with ethyl vinyl ether under Yb(III) catalysis[12] provided pyran **6**, which emerged as a 1:1 mixture of diastereomeric rotamers. These inseparable products displayed substantially only the *cis* relative stereochemistry of the aryl– and ethoxy groups, suggestive of *endo*-like addition of the vinyl ether to the

dienone. Displacement of the mesylate occurred smoothly upon exposure to N-sodioacetamide in DMF, and the resulting **7** furnished **8**, m.p. 61-62° C ,under the conditions of our pyridine-forming reaction[6,12] (Scheme 1). It should be noted that compound **8**, and indeed all of the later azidophenyl intermediates, were obtained as a 1:1 mixture of inseparable diastereomeric rotamers.

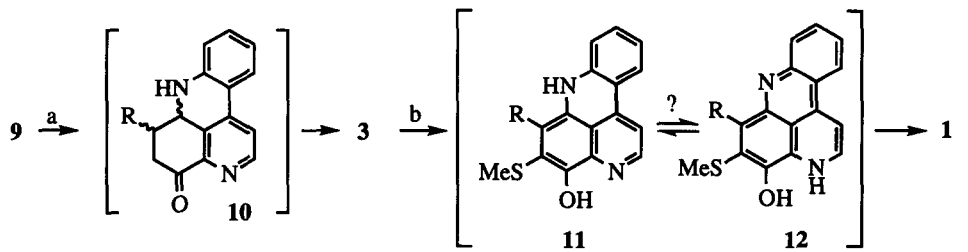
Scheme 1[a]



[a](*a*) MsCl, CH_2Cl_2, Et_3N, 0° C to RT, 99 %; (*b*) EtO-CH=CH_2, cat. Yb(fod)$_3$, DCE, reflux, 99 %; (*c*) $AcNH_2$, NaH, DMF, 0° C to RT, 97 %; (*d*) moist HO-NH_2·HCl, MeCN, reflux, 62 %; (*e*) O_3, 4:1 CH_2Cl_2/MeOH, –78° C, then Me_2S, –78° C to RT, 67 % chromatographed.

Ozonolysis of **8** smoothly yielded ketone **9**, m.p. 188-189° C. Thermophotolysis (chlorobenzene, 110° C, Sylvania sunlamp, pyrex, argon) of **9** *à la* Meth-Cohn,[13] but without an external triplet sensitizer,[14] delivered tetracyclic intermediate **10**. This sensitive compound, a deep purple substance, was oxidized *in situ* with DDQ to bright yellow cystodytin J, **3**, m.p. 196-197° C (dec.).[15] When MeSH was bubbled at room temperature into a 4:1 CH_2Cl_2/AcOH solution of this material, an immediate color change from bright yellow to deep purple occurred, signaling formation of adduct **11**. This substance was obtained as an intensely purple, air-sensitive solid, upon thorough removal of the volatiles. We attribute its color to equilibration with tautomer **12**.[6] Redissolution of **11/12** in CH_2Cl_2 and titration of the purple solution with a solution of DDQ in CH_2Cl_2 caused rapid color change to a dull orange, suggesting formation of the diplamine chromophore. The orange solution was directly applied to a column of silica gel, and fully synthetic **1**, m.p. 200-201° C (dec.) (lit. 202-204° C, dec.)[3] was eluted with 10 % MeOH in $CHCl_3$ (94 % yield, Scheme 2).

Scheme 2[a]

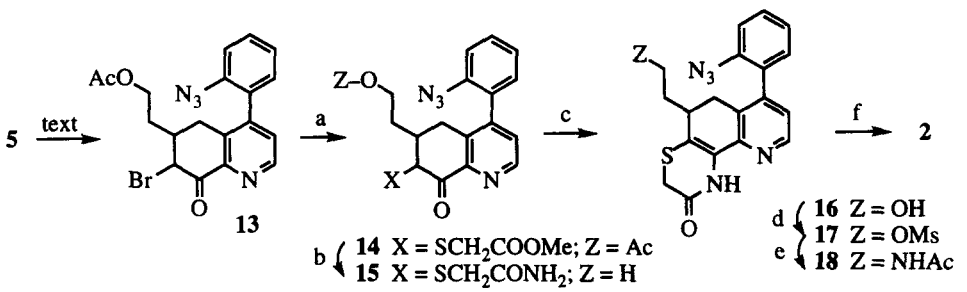


[a](*a*) hv, PhCl, 110° C, then cool to RT and titrate with DDQ, 30 % chromatographed; (*b*) MeSH, 4:1 CH_2Cl_2/AcOH, RT, then remove volatiles, take up in CH_2Cl_2 and titrate with DDQ, 94 %.

For reasons that remain unclear at this time, the reaction of **3** with 2-mercaptoacetate derivatives did not proceed in the same fashion as observed for MeSH. This forced us to resort to an alternative strategy in order to reach shermilamine B. Bromoketone **13**, readily available from **5**[11] (pyridinium tribromide),[16] reacted rapidly with methyl 2-mercaptoacetate in the presence of Hünig's base. Exposure of the resultant **14** to methanolic

ammonia in the presence of K_2CO_3 induced amide formation and loss of the side-chain acetate. The emerging compound **15** cyclized readily to **16**, yellow prisms, m.p. 101-103° C, upon brief reaction with BF_3·OEt_2. The correct side chain substitution was expeditiously installed through mesylation of **16** and mesylate displacement with N-sodioacetamide. This potentially troublesome sequence proved to be free from complications, and afforded **18** in 59 % yield.[17] Not unexpectedly,[16] thermophotolysis of **18** in a true Meth-Cohn fashion (triplet sensitizer: acetophenone) proceeded with *in situ* oxidation of a presumed dihydroaromatic intermediate, and yielded fully synthetic shermilamine B, dec. 252-254° C without melting (lit. dec. 254° C w/o melting), in 67 % chromatographed yield (Scheme 3).[18]

Scheme 3[a]



[a](*a*) $HSCH_2COOMe$, iPr_2NEt, EtOH, RT, 10 min, 66 % chromatographed from **5**; (*b*) NH_3, MeOH, RT, 12 hrs, then add K_2CO_3, 91 %; (*c*) BF_3·OEt_2, $CHCl_3$, RT, 90 %; (*d*) MsCl, CH_2Cl_2, Et_3N, 0° C to RT, 100 %; (*e*) $AcNH_2$, NaH, DMF, RT, 59 %; (*f*) hv, 10% PhCOMe in PhCl, 110° C, 67 % chromatographed.

The work described here and elsewhere[6] provides a coherent paradigm for the chemical synthesis of the major classes of bioactive pyridoacridine alkaloids, which are now readily available despite their natural paucity. Surely, the newly established supplies of these substances will contribute to their evolution from exciting structural curiosities to subjects of detailed pharmacological scrutiny.

Acknowledgement. We are deeply grateful to the National Institutes of Health (CA-55268), the National Science Foundation (CHE 91-16820), the Robert A. Welch Foundation (C-1007), and the Alfred P. Sloan Foundation for support of our research.

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17. Serious difficulties were experienced with α-bromination of the ketone in compound **9**, wherein the side chain acetamide is already in place. Attempts in that sense delivered an unstable product, probably the N-bromo acetamide, that was not readily amenable to further manipulations.
18. Physical data for our synthetic materials were in perfect agreement with those reported in the literature for the natural products, and relevant data are as follows. **3**: ^{1}H NMR ($CDCl_3$): 8.98 (d, 1H, J = 4.6 Hz); 8.46 (d, 1H, J = 8 Hz); 8.31 (d, 1H, J = 7.9 Hz); 8.23 (d, 1H, J = 4.9 Hz); 7.96 (app. dt, 1H, J_1 = 7.3 Hz, J_2 = 1.2 Hz); 7.85 (app. dt, 1H, J_1 = 7.3 Hz, J_2 = 0.9 Hz); 6.87 (s, 1H); 6.62 (br. s, 1H); 3.81 (q, 2H, J = 6.4 Hz); 3.27 (t, 2H, J = 6.4 Hz); 2.04 (s, 3H). ^{13}C NMR ($CDCl_3$): 183.4; 170.4; 152.2; 150.3, 149.8; 146.5; 145.3; 137.0; 132.8; 131.9; 129.9; 122.9; 121.8; 119.1; 117.9; 39.3; 31.7; 23.3. IR (film):3311; 3086; 2987; 2938; 1659; 1581; 1553; 1462; 1441; 1377; 1328; 1293; 1173; 1096; 1054; 758; 695. HRMS (EI, 70 eV): calc. for $C_{19}H_{15}N_3O_2$: 316.1164; obs. 316.1163. **1**: ^{1}H NMR ($CDCl_3$): 9.08 (d, 1H, J = 5.5 Hz); 8.49 (dd, 1H, J_1 = 7.9 Hz, J_2 = 1.2 Hz); 8.36 (d, 1H, J = 5.5 Hz); 8.29 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.9 Hz); 7.94 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 7.6 Hz; J_3 = 1.2 Hz); 7.83 (app. dt, 1H, J_1 = 7.6 Hz, J_2 = 7.6 Hz, J_3 = 1.5 Hz); 6.50 (br. s, 1H); 3.75 (br. s, 4H); 2.64 (s, 3H); 1.94 (s, 3H). ^{13}C NMR ($CDCl_3$): 176.6; 170.3; 151.6; 150.0; 149.8; 146.8; 145.6; 143.4; 137.0; 131.9; 131.8; 129.7; 122.9; 121.5; 119.2; 117.3; 39.9; 29.9; 23.3; 17.9. IR (film): 3332; 3079; 2924; 1659; 1609; 1539; 1476; 1441; 1377; 1286; 1194; 1152; 1089; 878; 773; 730. HRMS (EI, 70 eV): calc. for $C_{20}H_{17}N_3O_2S$: 363.1041; obs. 363.1040. **2**: ^{1}H NMR (DMSO-D6) 10.24 (br. s, 1H); 9.24 (br. s, 1H); 8.54 (br. t, 1H, J = 5.1 Hz); 8.49 (d, 1H, J = 4.9 Hz); 8.00 (d, 1H, J_1 = 7.9 Hz); 7.49 (d, 1H, J_1 = 5.1 Hz); 7.43-7.35 (c. m, 2H, overlapping resonances of an aromatic H and one of the NH's); 7.01 (br. dt, app. J_1 = 5.6 Hz; J_2 = 1.3 Hz); 3.32 (s, 2H); 3.12-3.07 (br. m, 2H); 2.95-2.92 (br. m, 2H); 1.93 (s, 3H). ^{13}C NMR (DMSO-D6): 171.5; 163.6; 150.8; 140.0; 139.5; 136.9; 132.0; 131.2; 124.0; 121.6; 121.5; 120.9; 116.6; 116.4; 115.4; 108.8; 107.2; 37.1; 29.3; 27.7; 22.4. IR (film): 3339; 3283; 3212; 3072; 2966; 2931; 2861; 1637; 1602; 1588; 1553; 1497; 1441; 1377; 1335; 1300; 1251; 1202; 1152; 1117; 1068; 1040; 998; 941; 913; 829; 794; 738. HRMS (EI, 70 eV): calc. for $C_{21}H_{18}N_4O_2S$: 390.1150; obs. 390.1151.

(*Received in USA* 10 *May* 1995; *accepted* 12 *May* 1995)