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SYNTHETIC STUDIES TOWARDS CYSTODYTIN A: THE PREPARATION OF NOVEL CYSTODYTIN CONGENERS

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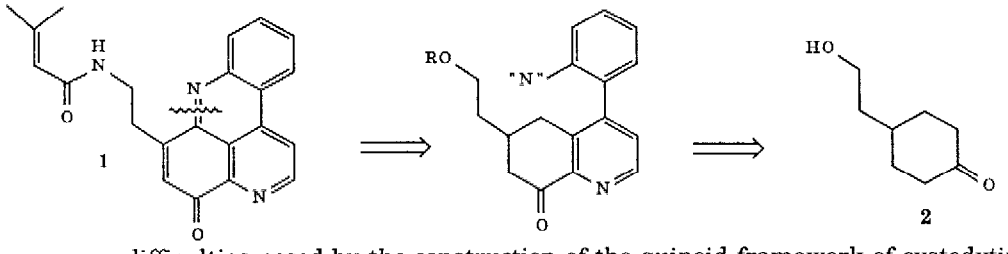
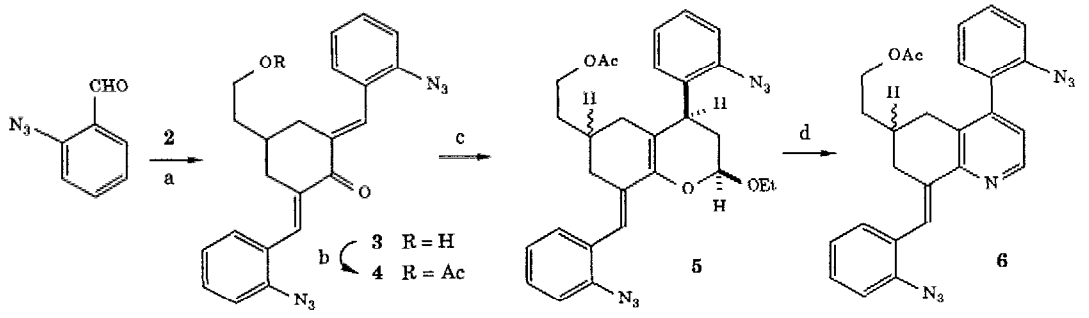
ABSTRACT: *A sequence involving a modified Knoevenagel-Stobbe pyridine synthesis, and an unusual intramolecular reaction between a quinone and an azide, permits expeditious assembly of the ring system of the cystodytin alkaloids.*

Cystodytin A, **1**, is a cytotoxic alkaloid isolated from the tunicate, *Cystodytes dellechiajei* (Della Valle).[2] Its novel ring system and its intriguing biological activity renders it particularly appealing both as a target for total synthesis, and as candidate for pharmacological evaluation. Cystodytins share architectural similarities with other recently discovered marine natural products incorporating highly condensed polycyclic heteroaromatic skeleta, some of which attain a considerable degree of complexity.[3] Interest in cystodytin A and in its relatives is reinforced, of course, by the recent discovery that many quinones, particularly heterocyclic ones, inhibit reverse transcriptase:[4] questions concerning possible antiretroviral activity of the new heterocycles therefore emerge. Significant quantities of these quinones are necessary for bioassay and for analogue work, but given the scarcity of the compounds in their natural sources, totally synthetic materials are clearly needed. Herein, we describe technology for the preparation of novel substances that incorporate the complete ring system of **1**. Our approach should be of considerable usefulness in the synthesis of complex polycyclic structures of the type found in the new natural products.



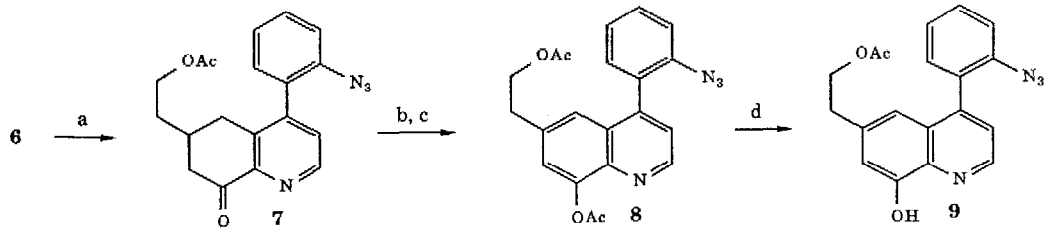
The numerous difficulties posed by the construction of the quinoid framework of cystodytins are alleviated to a considerable degree by the implementation of a strategy based on our recently described modification of the Knoevenagel-Stobbe pyridine synthesis.[5] Specifically, a process of symmetrization identified ketone **2** as the starting material.[6] Double aldol condensation with 2 - azidobenzaldehyde[7] in aqueous medium[8] provided **3**, m. p. 129-131 °C, which upon acetylation formed **4**, m. p. 98.5-100° C, in 88 % overall yield. Unlike an ordinary aliphatic enone,[9,5] 4

combined easily with ethyl vinyl ether, giving alkoxydihydropyrans **5**.[10a] The stereochemistry of the newly formed pyran ring was determined to be *cis* (NMR), suggesting that **5** had arisen from an *endo*-cyclocondensation.[10a] The cycloadducts are recognized as latent forms of 1,5-dicarbonyl compounds: such equivalence became manifest upon exposure of **5** to hydroxylamine hydrochloride in refluxing acetonitrile, whereupon clean conversion to pyridine **6**[10b] occurred (52 % overall yield). It is noteworthy that in this sequence a vinyl ether is utilized as the synthetic equivalent of the enolate of acetaldehyde. Clearly, any "classical" synthetic scheme involving such reactive intermediate in an expressed form would be fraught with severe difficulties.



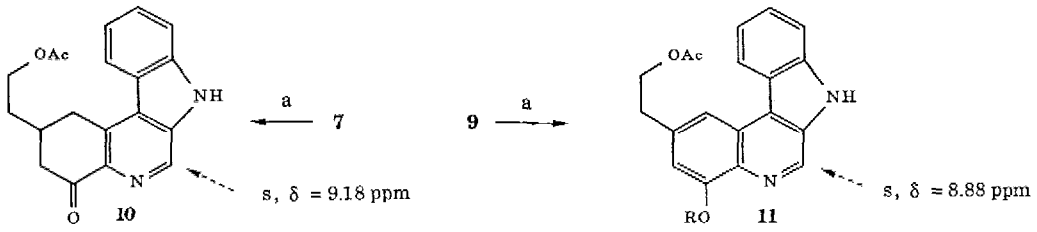
a. 10 % aq. NaOH, EtOH, 0 °C; b. Ac_2O, pyridine, 88 % overall a-b; c. CH_2=CH-OEt, $(CH_2Cl)_2$, Yb(fod)$_3$, reflux, 68 %; d. HO-NH_3^+ Cl^-, MeCN, reflux, 77 %.

Ozonolytic cleavage of the surviving benzylidene group afforded ketone **7**,[10b] obtained in 76 % yield after a rough chromatography (the first one in the entire scheme). Aromatization of **7** was smoothly achieved by a two-step sequence involving enol acetate formation and treatment with DDQ. Selective removal of the phenolic acetate from **8** yielded **9** in 56 % yield over three steps.



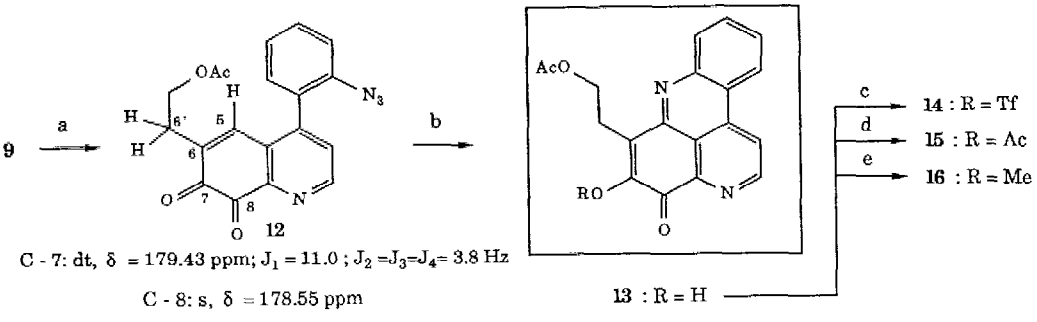
a. O_3, MeOH, -78 °C, then Me_2S, 76 %; b. isopropenyl acetate, cat. TfOH; c. 1 eq. DDQ, PhMe, reflux, 15 min; d. aq. $NaHCO_3$, MeOH, 25° C, 12 hr, 56 % overall b-d.

Compounds **7** and **9** were regarded as plausible candidates for cyclization to tetracyclic structures, *via* thermal activation of the azido functionality. Thermolysis occurred only upon heating above 180° C in *ortho*-dichlorobenzene, suggesting the intervention of (singlet) nitrenes during decomposition of the aryl azide.[11] A rapid, clean conversion into carbolines **10** and **11** occurred, but none of the desired cystodytin-like compound was apparently formed.



a. *ortho*-dichlorobenzene, T > 180° C.

While the new carbolines may be of interest as candidate antitumor agents and as DNA probes, a different approach to the desired ring system was necessary. Success was achieved as follows. Phenol **9** delivered only *o*-quinone **12** upon Fremy's salt oxidation.[12] The structure of **12** was unequivocally determined by its gated-decoupled ^{13}C NMR spectrum, which showed one of the two carbonyls as a sharp singlet, the other one as a doublet of triplets (J_1 = 11 Hz; $J_2 = J_3 = J_4$ = 3.8 Hz). The *ortho*, but not the *para* quinoid structure, is consistent with the observed spectrum.[13] Interestingly, Fremy's salt was the only oxidant tried that produced a clean product from **9**. Other reagents either gave complex mixtures (DDQ/aq. acetone; CAN/aq. MeCN) or did not oxidize **9** (O_2/salcomine/DMF). In sharp contrast to **7** - **9**, *quinone **12** thermolyzed at a considerably lower temperature (refluxing toluene), producing quinonimine **13** (orange crystals, dec. 210 °C) cleanly and directly*. The precise mechanism of quinonimine formation remains obscure. Whereas electron-transfer pathways that may lead to unusually facile nitrene formation from **12** may not be excluded at this time, it was found that compounds **7** - **9** are recovered unchanged and in quantitative yield after 24 hrs at reflux, in toluene. It is possible, therefore, that a 1,3-dipolar cycloaddition occurred as the initial chemical event.[11] Subsequent loss of N_2 and rearrangement would then lead to the product.[14] Unusual quinone-azide reactions of this type should be useful for the preparation of a variety of complex heterocycles.



C - 7: dt, δ = 179.43 ppm; J_1 = 11.0 ; $J_2 = J_3 = J_4$ = 3.8 Hz

C - 8: s, δ = 178.55 ppm

a. Fremy's salt, MeOH, phosphate buffer, 25° C, 65 %; b. toluene, reflux, 74 %; c. Tf_2O, Hünig base, CH_2Cl_2, 0° C, 70 %; d. Ac_2O, pyridine, 75 %; e. CH_2N_2, ether, CH_2Cl_2, 0° C, 70 %.

Quinonimine **13** possesses the complete ring system of the cystodytins, but relative to the

natural products it incorporates an extra OH group. This functionality was found to be amenable to derivatization to furnish compounds **14 - 16**, which are of potential interest in connection with SAR studies. The newly established availability of derivatives of cystodytins represents a significant advance, since the natural products do not lend themselves readily to chemical modification. The sequences outlined above demonstrate the usefulness of our methodology in connection with the synthesis of highly condensed heteroaromatic systems. Additional investigations in this area are underway and will be described in future disclosures.

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References and Footnotes

1. Recipient of the Robert A. Welch Predoctoral Fellowship
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3. See, e.g.: a. de Gutzman, F. S.; Schmitz, F. J. *Tetrahedron Lett.* **1989**, *30*, 1069; b. Rudi, A.; Benayahu, Y.; Goldberg, I.; Kashman, Y. *Tetrahedron Lett.* **1988**, *29*, 6655; c. Cooray, N. M.; Scheuer, P. J.; Parkanyi, L.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 4619; d. Cimino, G.; De Rosa, S.; De Stefano, S.; Sodano, G. *Pure Appl. Chem.* **1986**, *58*, 375; e. Schmitz, F. J.; Agarwal, S. K.; Gunasekera, S. P.; Schmidt, P. G.; Shoolery, J. N. *J. Am. Chem. Soc.* **1983**, *105*, 4835, and references cited therein.
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6. Prepared from 1,4-cyclohexanedione mono ethylene ketal: a. $(EtO)_2P(O)CH_2COOEt$, NaH, DME, 95%; b. H_2, Pd(C), EtOAc, 100%; c. LAH, Et_2O, 90 %; d. aq. HCl, MeOH, 96%.
7. Prepared from 2-aminobenzylalcohol (Aldrich): a. i. $NaNO_2$, aq. HCl, 0 °C, ii. aq. NaN_3, 0° C, 89 %; c. PCC, CH_2Cl_2, celite, $MgSO_4$, 25 °C, 80 %. We thank Professor Tohru Fukuyama of this Department for kindly sharing with us this procedure.
8. Cf.: Conard, C. R.; Dolliver, M. A. *Org. Synth., Coll Vol II*, 167.
9. Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721.
10. a. Mixture of stereoisomers. The pyran ring was apparently formed only as the cis isomer; b. 1:1 mixture of slowly interconverting (NMR) diastereomeric rotamers.
11. For a discussion see: Smith, P. A. S., in: "Azides and Nitrenes: Reactivity and Utility;" Scriven, E. F. V., Ed.; Academic Press: Orlando, FL., 1984, ch. 3, p. 95.
12. Cf. Deya, P. M.; Dopico, M.; Raso, A. G.; Morey, J.; Saa, J. M. *Tetrahedron* **1987**, *43*, 3523.
13. Oxidation to *p*-quinones appears to be disfavored on steric grounds when linearly fused, polycyclic phenols of the type **9** bear substituents *peri* to the site at which the new O atom should enter. For a discussion see: a. Zimmer, H.; Lankin, D. C. *Chem. Rev.* **1971**, *71*, 229; b. Naruta, Y.; Maruyama, K., in: "*The Chemistry of Quinonoid Compounds*;" Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, U. K., 1988, ch. 8. See also ref. 12.
14. For a similar reaction see: Bennett, III, R. B.; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580.

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