SYNTHESIS OF 2,4-DIMETHYLTHIOBENZO[*c*][2,7]NAPHTHYRIDIN-5(6H)-ONE: A POTENTIALLY USEFUL INTERMEDIATE FOR THE SYNTHESIS OF PYRIDOACRIDINE ALKALOIDS

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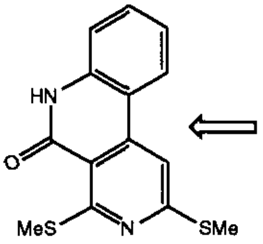
Abstract - Synthesis of the titled benzo[*c*][2,7]naphthyridinone (1) is described using intramolecular inverse electron demand Diels-Alder chemistry of 1,2,4-triazines (**10**) and (**11**).

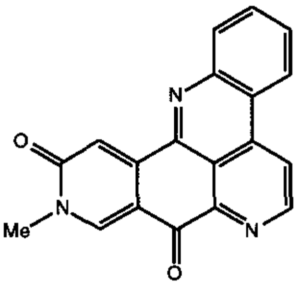
Over the past decade a family of over forty alkaloids have been isolated from marine organisms which have in common the benzo[*c*][2,7]naphthyridine ring system. Most of these tetra- and pentaheterocyclic natural products exhibit significant cytotoxicity. [1] Some have also shown antiviral [2] and calcium releasing [3] properties. Consequently, these marine alkaloids have generated much interest among synthetic chemists and several synthetic approaches to these compounds have been reported. [4] We have recently become interested in developing a simple, versatile and unified synthetic strategy to these biologically interesting natural products and their derivatives.

The synthesis of the benzo[*c*][2,7]naphthyridine system has been the topic of several recent articles. The following four distinct synthetic strategies to this heterocycle have emerged: (i) The use of Pd(0) - catalyzed cross coupling of protected 2-aminophenylboronic acids with 4-halo-3-carbonylpyridine derivatives [5] or a cross coupling reaction between a 4-pyridylborane derivative and 2-iodoanilines. [5c] Similarly, a Stille cross coupling approach between 4-trimethylstannyl-3-pyridine carbonyl derivatives and 2-bromoacetanilides [6] has also been described. (ii) An intramolecular Diels-Alder reaction of a 4,5-disubstituted oxazole with a suitably tethered alkene (the Kondrat'eva pyridine synthesis). [7] (iii) An azido-ring expansion of a fluorenol derivative. [8] (iv) An intramolecular pyridyne cyclization approach from 5-bromo-3-anilinomethylpyridine derivatives. [9]

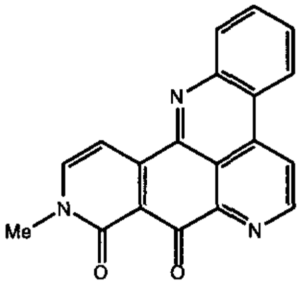
We envisioned that the titled benzo[*c*][2,7]naphthyridinone (1) could be a versatile intermediate for the synthesis of several pyridoacridine alkaloids (such as amphimedine (2), neoamphimedine (3) and ascididemine (4)). Furthermore, nucleophilic substitution of the 2-methylthio group from 1 could allow for the synthesis of a number of analogs. Here we report our synthetic approach to 1 using inverse electron demand Diels-Alder chemistry of 1,2,4-triazines as the key step.



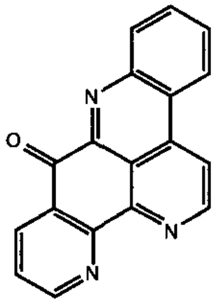
1



Amphimedine (2)



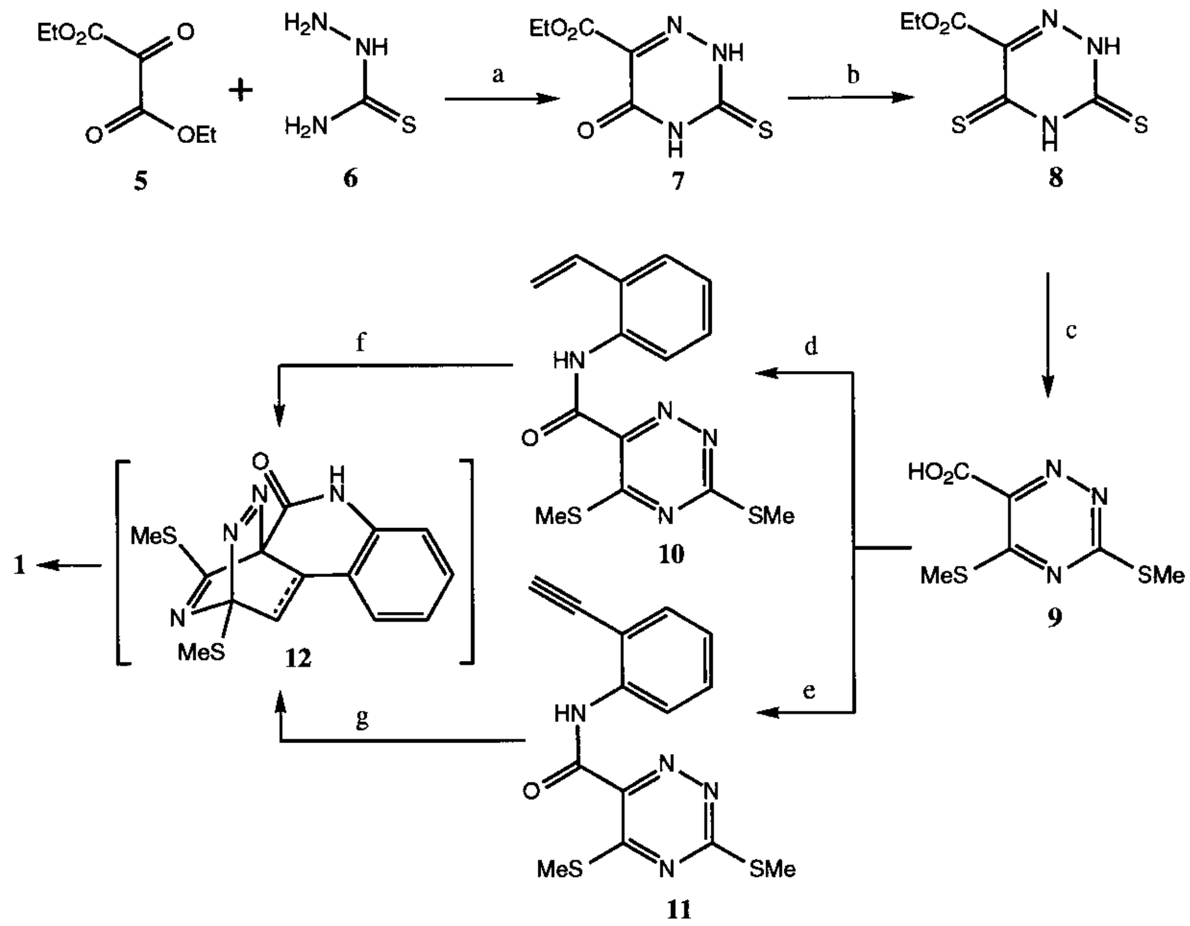
Neoamphimedine (3)



Ascididemine (4)

The use of 1,2,4-triazines as dienes in inverse electron demand Diels-Alder reactions is well known and many examples of the intramolecular version of this reaction have been documented.[10] Surprisingly, there are only a few reports of such reactions where the dienophile is tethered to the 6-position of the 1,2,4-triazine.[11] There are, however, no reports for the synthesis of the benzo[*c*][2,7]naphthyridine system using 1,2,4-triazine chemistry.

Our synthesis of 1 began with the reaction of diethyl ketomalonate with thiosemicarbazide which provided the triazine derivative (7) in 90% yield (Scheme).[12] Treatment of 7 with P_4S_{10} in refluxing dioxane gave the dithione (8) in 72% yield, after purification by chromatography on silica gel. Reaction of 8 with three equivalents of aqueous sodium hydroxide at room temperature for 10 h followed by treatment with two equivalents of methyl iodide and acidification of the reaction mixture gave a 64% yield of the triazinecarboxylic acid (9). This was converted to the corresponding carboxylic acid chloride by treatment with excess thionyl chloride at reflux. The intermediate acid chloride was further treated, without purification, with 2-aminostyrene[7] in methylene chloride in the presence of triethylamine to give an 82% yield of the amide (10),[13] after chromatography on silica gel. Heating the triazine (10) in 1,2-dichlorobenzene resulted in the formation of the desired benzo[*c*][2,7]naphthyridinone 1[14] in 60% yield. The product precipitated from the reaction mixture and was simply filtered. We have also prepared the triazine (11)[15] from reaction of the acid chloride derived from 9 with 2-ethynylaniline.[16] Interestingly, this failed to react in refluxing 1,2-dichlorobenzene. When the solvent was changed to the higher boiling 1,2,4-trichlorobenzene, however, the triazine (11) underwent smooth intramolecular Diels-Alder reaction to provide the desired benzonaphthyridinone (1) in 65% yield. With this pivotal intermediate at hand, we are exploring synthetic routes to convert **1** to some of the pyridoacridine natural products and their derivatives.



Reagents and yields: (a) H_2O, 100 ° C, 5 h (90%); (b) P_4S_{10}, dioxane, 80 ° C, 6 h (72%); (c) 1. NaOH (3eq.), rt, 10 h; 2. MeI (2 eq.), rt, 0.5 h; 3. H_3O^+, (64%); (d) 1. $SOCl_2$, 79 ° C, 2 h; 2. 2-aminostyrene, CH_2Cl_2, Et_3N, 0 ° C to rt, 8 h (82%); (e) 1. $SOCl_2$, 79 ° C, 2 h; 2. 2-aminoethynylbenzene, CH_2Cl_2, Et_3N, 0 ° C to rt, 8 h (85%); (f) 1,2-dichlorobenzene, 180 ° C, 10 h (60%); (g) 1,2,4-trichlorobenzene, 214 ° C, 10 h (65%).

Scheme

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13. ^{1}H Nmr spectrum of **10**: (300 MHz; $CDCl_3$) δ 2.54 (s, 3H), 2.71 (s, 3H), 5.73 (dd, 1H, J = 1.12, 11.07 Hz), 5.73 (dd, 1H, J = 1.16, 17.35 Hz), 6.91 (dd, 1H, J = 10.95, 17.34 Hz), 7.17 (dd, 1H, J = 1.22, 7.49 Hz), 7.32 (dd, 1H, J = 1.53, 7.36 Hz), 7.46 (dd, 1H, J = 1.28, 7.64 Hz), 8.16 (d, 1H, J = 8.14 Hz), 9.28 (br s, 1H).
14. ^{1}H Nmr spectrum of 1: (300 MHz; DMSO-d_6) δ 2.47 (s, 3H), 2.69 (s, 3H), 7.30 (m, 2H), 7.57 (m, 1H), 7.95 (s, 1H), 8.41 (d, 1H, J = 7.6 Hz), 11.65 (br s, 1H).
15. ^{1}H Nmr spectrum of 11: (300 MHz; $CDCl_3$) δ 2.54 (s, 3H), 2.70 (s, 3H), 3.62 (s, 1H), 7.12 (dd, 1H, J = 1.12, 7.58 Hz), 7.40-7.52 (m, 2H), 8.57 (d, 1H, J = 7.43 Hz), 10.6 (br s, 1H).
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