New synthesis of pyridoacridines based on an intramolecular aza-Diels–Alder reaction followed by an unprecedented rearrangement†

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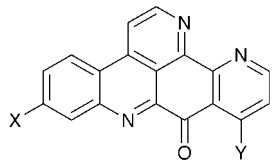
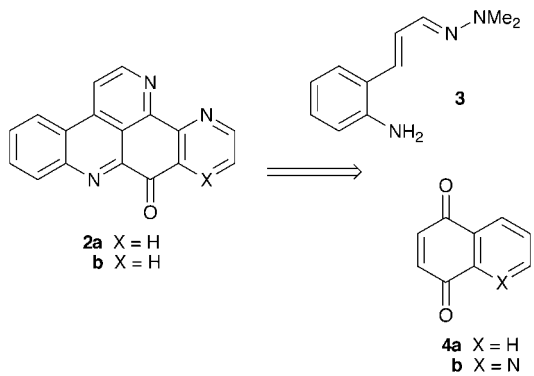
The synthesis of pyridoacridines related to the ascididemins can be performed by an intramolecular aza-Diels–Alder cycloaddition of an α,β-unsaturated hydrazone to a quinone followed by an unprecedented rearrangement to yield benzo- or pyrido-[*b*]acridine-6,11-diones.

Pyridoacridine alkaloids of marine origin, such as amphimedine and the ascididemins (**1a**–**c**),[1] have attracted much attention due to their structural novelty and cytotoxic properties.[2,3] Strategies based on Diels–Alder azacycloadditions are amongst the most conceptually simple and potentially general approaches for the synthesis of these heterocycles.[2,4] However, the practical realisation of these schemes has been hampered by the lack of suitable reactivity of 4-substituted 1-azadienes towards 1,4-quinones.[4–6]



1a X = Y = H
b X = Br, Y = H
c X = H, Y = OH

Herein we report a new approach for the synthesis of heterocycles **2a**–**b**[7,8] related to the ascididemins (**1a**–**c**) based on an intramolecular aza-Diels–Alder reaction of 1-dimethylamino-1-azadienes[9] followed by an unprecedented rearrangement which occurs under oxidative conditions. The bond connectivity achieved between azadiene **3**[4] and 1,4-naphthoquinones **4a**,**b** in the cycloaddition–rearrangement is shown in Scheme 1. This scheme is formally equivalent to an intermolecular cycloaddition of diene **3** with the corresponding 1,2-naphthoquinones.



2a X = H
b X = H

3

4a X = H
b X = N

Scheme 1

† Dedicated to Professor José Elguero on the occasion of his 65th birthday.

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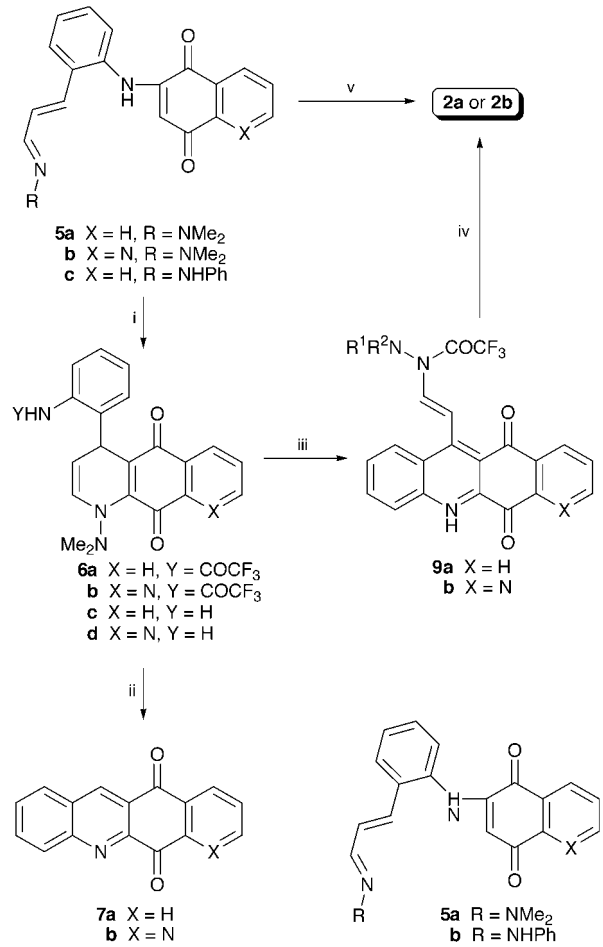
The intramolecular cycloaddition of **5a**–**c** was examined as part of a projected synthesis of the alkaloid meridine[1c,10] and related compounds (Scheme 2). These aminoquinones were readily available by the addition of the aniline **3**[3] to **4a** or **4b** in MeOH at 23 °C the presence of $CeCl_3 \cdot 7H_2O$ (0.1 equiv) (70% for **4a**, 48% for **4b**).[11] On the other hand, a hydroxy group in the position 4 of quinolinequinone directs the nucleophilic attack of aniline derivatives allowing the synthesis of adducts **5d**–**e** with the opposite regioselectivity.[12]

After much experimentation, the desired cycloadditions were realised by trifluoroacetylation of the amines of **5a**,**b** (NaH, TFAA, 3 equiv. each, THF, 23 °C) followed by replacement of THF by CH_2Cl_2 and addition of excess TFA (23 °C, 1 h) to furnish quinones **6a** (45%) and **6b** (47%),[13] respectively. Under these conditions, the intermediate cycloadducts, which could not be isolated, suffer elimination of the trifluoroacetamides to form the quinone chromophores.



5a X = H, R = NMe_2
b X = N, R = NMe_2
c X = H, R = NHPh

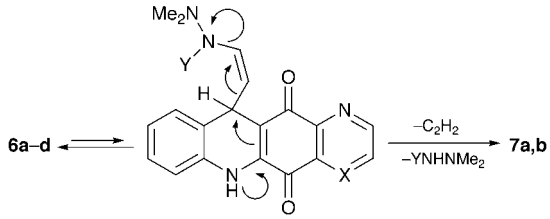
6a X = H, Y = $COCF_3$
b X = N, Y = $COCF_3$
c X = H, Y = H
d X = N, Y = H

9a X = H
b X = N

7a X = H
b X = N

5a R = NMe_2
b R = NHPh

Scheme 2



Scheme 3

Much to our surprise, **6a** was cleanly transformed into tetracycle **7a**[14] by heating with acid (1:1 10% aq HCl–1,4-dioxane, reflux; 94%). Quinone **7a** could also be obtained directly from **5a** by thermolysis (xylene, reflux; 55%) or by treatment with TFA (23 °C; 68%).[15] Under these latter conditions, heterocyclic quinone **7b** was similarly obtained from **5b** (66%).[13] Scheme 3 suggests a possible mechanism for these remarkable transformations in which the dimethylhydrazine and two carbons are lost under relatively mild conditions. Accordingly, a 6-*endo-trig* cyclization of the trifluoroacetamide (from **6a**,**b**) or the amine (*via* **6c**,**d** formed *in situ* from **5a**,**b**) onto the quinone double bond with concomitant (or subsequent) transacylation would lead to intermediates **8**, which may undergo aromatization to form a pyridine ring by a Grob-type fragmentation to give acetylene and the hydrazine derivative. The first step of this process, nucleophilic addition–elimination on a quinone, is somewhat reminiscent of the so-called mitomycin rearrangement.[16]

According to the hypothetical equilibrium of Scheme 3, oxidation of intermediate **8** could yield a precursor of tetracycles related to the ascididemins (**1**). In the event, treatment of **6a**,**b** with excess MnO_2 in CH_2Cl_2 at 23 °C smoothly led to tetracycles **9a**,**b** in quantitative yield as single isomers. The rearrangement also takes place in the presence of DDQ or CAN as the oxidants. A *trans* configuration was assigned for the alkenyl portion of these derivatives on the basis of a vicinal coupling constant of 15.5 Hz. However, the configuration around the enamine nitrogen was not rigorously assigned. Reaction of **9a**,**b** with NH_4Cl and NaOAc in EtOH under refluxing conditions gave pentacyclic **2a**[4] (93%) and **2b** (84%).[13] After examining several hydrazone and oxime derivatives,[17] we found that thermolysis of phenylhydrazone **5c** directly furnished **2a** (refluxing xylene, 40%), probably through intermediate **10a**. In fact, related tetracyclic derivative **10b** could be isolated in 54% yield by thermolysis of **5b** in xylene.

In summary, a highly concise synthesis of heterocycles **2a**,**b** has been developed based on an intramolecular aza-Diels–Alder cycloaddition followed by a novel rearrangement in which the aminoaryl formally undergoes a 1,2-shift.

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Notes and references

1 Isolation: (*a*) Ascididemin: J. Kobayashi, J. Cheng, H. Nakamura, Y. Ohizumi, Y. Hirata, T. Sasaki, T. Ohta and S. Nozoe, *Tetrahedron Lett.*, 1988, **29**, 1177; (*b*) 2-bromoascididemin (2-bromoleptoclidinininone): J. J. Bloor and F. J. Schmitz, *J. Am. Chem. Soc.* 1987, **109**, 6134; 11-Hidroxyascididemin (*c*): F. Schmitz, F. S. DeGuzman, M. B. Hossain and D. van der Helm, *J. Org. Chem.*, 1991, **56**, 804.

2 Reviews: T. F. Molinski, *Chem. Rev.*, 1993, **93**, 1825; B. S. Davidson, *Chem. Rev.* 1993, **93**, 1771; A. M. Echavarren, in *Advances in Nitrogen Heterocycles*, ed. C. J. Moody, JAI Press, Greenwich, 1996, vol. 2. ch. 5.

3 Indeed, we have found that analogue **2b** is highly cytotoxic *in vitro* to mouse lymphoma (P-388), human lung carcinoma (A-549), human colon carcinoma (HT-29), and human melanoma (MEL-28) (IC_{50} values of 0.01, 0.0012, 0.005 and 0.0025 μg ml^{-1}, respectively).

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6 The first step of a synthesis of the alkaloid meridine is a Diels–Alder cycloaddition of the nitro analogue of **3** which proceeds in low yield (6%): Y. Kitahara, F. Tamura and A. Kubo, *Chem. Pharm. Bull.* 1994, **42**, 1363; S. Nakahara, Y. Tanaka and A. Kubo, *Heterocycles*, 1996, **43**, 2113; a similar reaction was used for the synthesis of cistodamine: Y. Kitahara, F. Tamura and A. Kubo, *Tetrahedron Lett.* 1997, **38**, 4441. Alternative synthesis of aromatized adducts: P. Molina, A. Pastor and M. Villaplana, *Tetrahedron* 1995, **51**, 1265.

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8 Synthesis of another regioisomer of **1a** and **2b**: E. Gómez-Bengoa and A. M. Echavarren, *J. Org. Chem.*, 1991, **56**, 3497.

9 Intramolecular cycloaddition of 1-dimethylamino-1-azadienes: N. Bushby, C. J. Moody, D. A. Riddick and I. R. Waldron, *Chem. Commun.*, 1999, 793; R. E. Dolle, W. P. Armstrong, A. N. Shaw and R. Novelli, *Tetrahedron Lett.*, 1988, **29**, 6349.

10 P. J. McCarthy, T. P. Pitts, G. P. Gunawardana, M. Kelly-Borges and S. A. Pomponi, *J. Nat. Prod.*, 1992, **55**, 1664.

11 Hydrazones **5c**–**e** were obtained in three steps by: (i) reaction of the quinolinequinone with *o*-aminocinnamol ($CeCl_3 \cdot 7H_2O$, MeOH, 23 °C); (ii) oxidation of the allyl alcohol to the aldehyde with PCC or MnO_2; (iii) condensation of the aldehyde with the hydrazine.

12 By using the reaction pathway outlined in Scheme 2, adducts **5d**–**e** could be converted into 11-hydroxyascididemin (**1c**).

13 Yield based on unrecovered starting material.

14 A. Ettienne and A. Staehelin, *Bull. Soc. Chim. Fr.*, 1954, 748; V. Zanker and F. Mader, *Chem. Ber.*, 1960, **93**, 850. 2-Chloro derivative: M. Prato, G. Scorrano, M. Stivanello, P. Tecilla and V. Lucchini, *Gazz. Chim. Ital.*, 1987, **117**, 325.

15 Quinone **5a** was quantitatively converted into **7a** and *N*,*N*-dimethylhydrazine at 50–55 °C (3:1 benzene-d_6–TFA-*d* solution, sealed NMR tube). In addition, a small signal at 1.8 ppm attributable to dissolved acetylene was also observed.

16 M. Kono, Y. Saitoh, K. Shirahata, Y. Arai and S. Ishii, *J. Am. Chem. Soc.*, 1987, **109**, 7224; T. Fukuyama and L. Yang, *J. Am. Chem. Soc.*, 1987, **109**, 7881; T. Fukuyama and L. Yang, *J. Am. Chem. Soc.*, 1989, **111**, 8303.

17 The methoxime and diphenylhydrazone analogues of **5a** afforded **7a** after being treated with TFA.

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