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A hetero Diels–Alder approach to the synthesis of the first angucyclinone and angucycline 5-aza-analogues

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Abstract—The synthesis of two new heterodienes and their regioselective [4+2]cycloaddition reactions with several bromo-naphthoquinones allowed us to prepare the first angucyclinone and angucycline 5-aza-analogues.

Angucyclines are secondary metabolites of microorganisms, which belong to the group of Actinomycetes spore-forming bacteria. These natural products are structurally characterised by an angular tetracyclic benz[*a*]anthracene framework originating from a decaketide chain precursor and by the unusual presence of a C-glycosidic moiety. Among the angucycline group some members exhibit biological activities (e.g., antitumoural, antiviral, inhibition of enzymes, etc.) although, until to now, none of them has been recognised as a clinically useful drug.[1] Creating chemical diversity from structures already validated by Nature is an important task in the ongoing search for new drug candidates[2] and this problem has been recently addressed in the field of polyketides by recourse to combinatorial biosynthesis techniques.[3] A chemical approach to the problem would be to synthesise angucycline or angucyclinone analogues bearing structural modifications on the aglycone moiety and (or) on the associated sugar unit, if present. Towards this end we have explored the abilities of two new dienes, namely (*EE*)-**1a** and (*EE*)-**1b**, to react with several naphthoquinone-type dienophiles. In the present communication we wish to present the results of this preliminary study, which establish that the strategy outlined in Scheme 1 is effective for the preparation of 5-aza-analogues of angucyclines (angucyclinones) with the B-ring aromatised (e.g., **2**). It is worth mentioning that the nitrogen element has not been found in the angucycline class in contrast to the related class of tetracycline antibiotics. Nitrogen can be found, however, in the structurally related angucyclins phenanthroviridine **3** and the more complex jadomycins.[4]

The push–pull dienes (*EE*)-**1a** and (*EE*)-**1b**, required for our study, were not known in the literature. Diene (*EE*)-**1a** was prepared in three simple steps from the commercially available cyclohexane-1,3-dione **4** as depicted in Scheme 2.

The 1,3-dione was first transformed (80% yield) to the enaminone **5** following a reported procedure.[5] Treatment of the latter compound with a slight excess of *N*-(dimethoxymethyl)-*N*,*N*-dimethylamine afforded diene **1a** as a 3/1 mixture of *E*,*E*:*Z*,*E*-isomers. Heating a toluene solution of this mixture at reflux finally delivered the desired and most stable *EE*-isomer **1a**[6] in 92% yield from **5**. Diene (*EE*)-**1b** was prepared from 5-methylcyclohexane-1,3-dione **6**[7] in a manner identical to that described for diene (*EE*)-**1a** and in an overall yield of 52%.

Keywords: Angucycline; Angucyclinone; Angucyclin(one) 5-aza-analogues; Azadiene; Bromo-naphthoquinone; Hetero Diels–Alder reaction; C-Glycoside.
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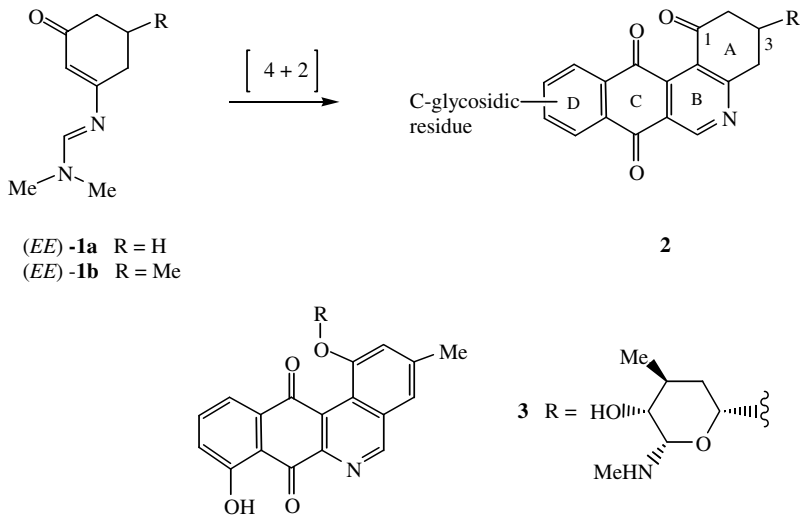
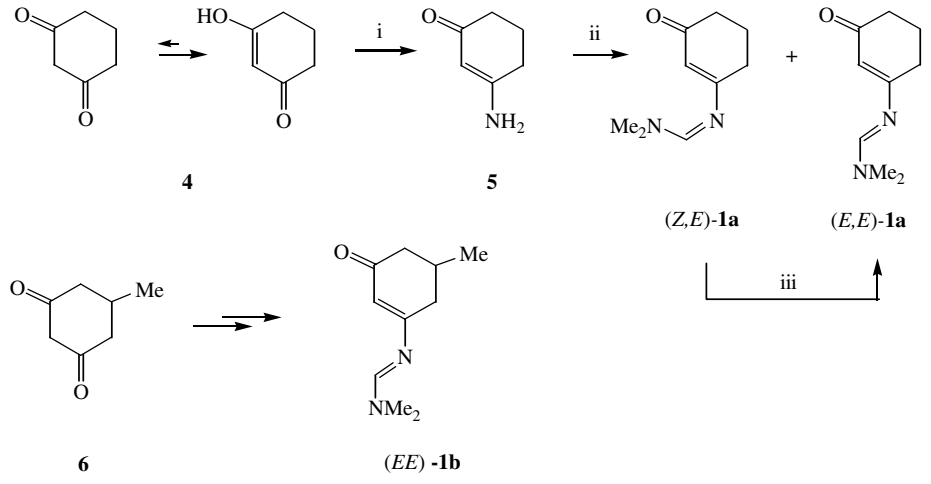


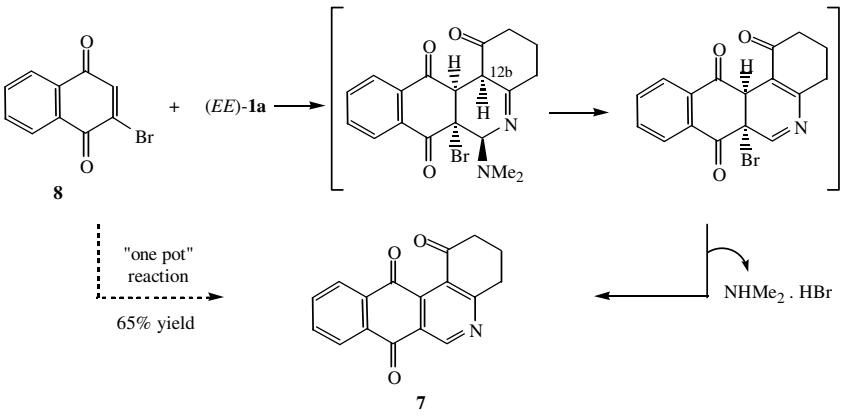
Scheme 1.



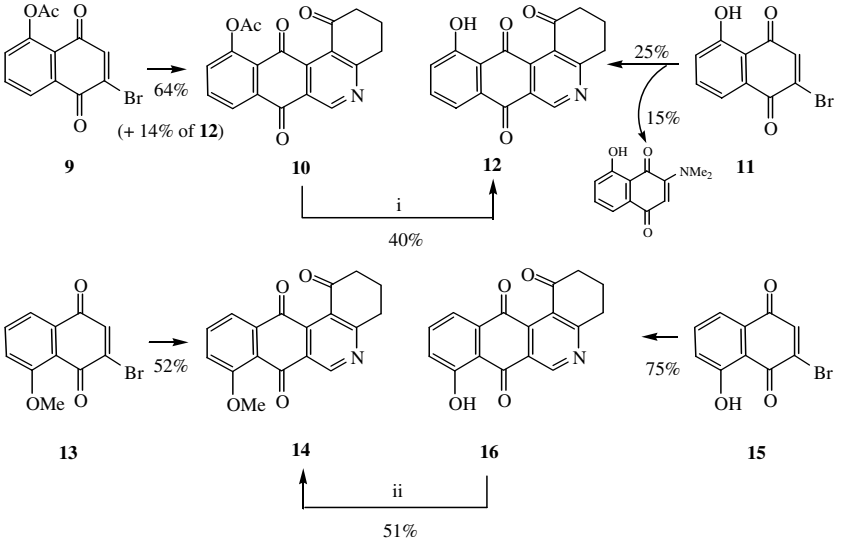
Scheme 2. Synthesis of dienes (*EE*)-**1a** and (*EE*)-**1b**. Reagents and conditions: (i) NH_4OAc, reflux in toluene (Dean–Stark apparatus) for 5 h; (ii) NMe_2–$CH(OMe)_2$, reflux in anhydrous THF for 2 h 30 min; (iii) reflux in dry toluene for 1 h.

The cycloaddition reaction of diene (*EE*)-**1a** towards a set of diversely substituted naphthoquinone-type dienophiles was next considered. The first such dienophile investigated was naphthoquinone itself. Heating both partners in a toluene solution at reflux for days gave only faint indication of success, the reaction leading to the expected angucyclinone 5-aza-analogue **7** in less than 10% isolated yield. Similar results were obtained with juglone as the dienophile and no improvement of the yield could be achieved in the presence of a Lewis acid. We then reasoned that the presence of an electron-withdrawing substituent on the naphthoquinone double bond should enhance [4+2]cycloaddition based on FMO considerations. In full agreement with this expectation, we were pleased to observe that the readily prepared 2-bromo-[1,4]naphthoquinone **8**[8] reacted with diene (*EE*)-**1a** (heating in acetonitrile at 40 °C for 4 h then at 60 °C overnight) to give **7** as the sole isolated compound in 65% yield. The formation of **7** can be accounted for by assuming that, due to the acidity of the hydrogen at C-12b (angucycline numbering), the initial Diels–Alder adduct, supposed to arise from an *endo* event, is subject to an aromatisation process resulting of the facile elimination of dimethylamine and HBr (Scheme 3). This cascade sequence thus represents an efficient one-pot approach towards the 5-aza-angucyclinone skeleton in which the ABCD framework is assembled in a single operation and in an acceptable overall yield.

In an effort to investigate the scope of the preceding [4+2]cycloaddition–aromatisation cascade we next explored the reactivity of diene (*EE*)-**1a** with several 2-bromo-[1,4]naphthoquinones substituted at carbons C-5 or C-8. The results of these experiments are depicted in Scheme 4. The 5-acetoxy-2-bromo-[1,4]naphthoquinone **9**,[9] 5-hydroxy-2-bromo-[1,4]naphthoquinone **11**,[9b] 8-methoxy-2-bromo-[1,4]naphthoquinone **13**[10] and 8-hydroxy-2-bromo-[1,4]naphthoquinone **15**[11] were all prepared following the reported procedures. Their cycloaddition with diene (*EE*)-**1a**[12] closely paralleled the cycloaddition of **8** with the same diene and gave the angucyclinone 5-aza analogues **10**, **12**, **14** and **16**,



Scheme 3. Proposed reaction mechanism for the formation of the angucyclinone 5-aza-analogue **7**.



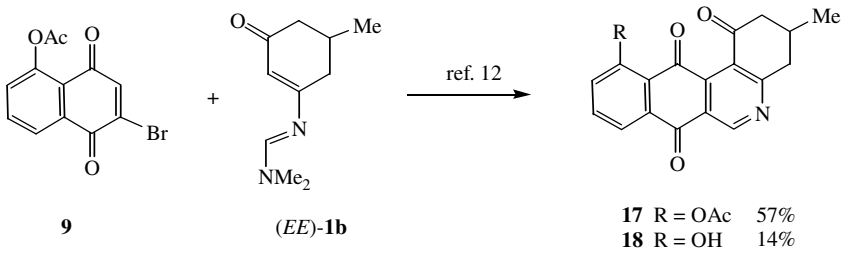
Scheme 4. Synthesis of angucyclinone 5-aza-analogues **10**, **12**, **14**, **16**.[12] Reagents and conditions: (i) 6 N H_2SO_4/EtOH (1/3), reflux 1 h 30 min; (ii) 1.1 equiv Ag_2O, 20 equiv MeI, 40 °C, 16 h.

respectively, each of them featuring, like **7**, a 3,4-dihydro-2*H*-benzo[*j*]phenanthridin-1,7,12-trione framework. These compounds were obtained in moderate to good yields except for the 5-aza analogue **12**, which was isolated in significantly reduced yields. In that case, non-negligible amounts (15%) of the dimethylamine addition product to **11** were also isolated. The chemical structures of the four angucyclinone 5-aza-analogues were determined by ^{1}H NMR[13] and subsequently confirmed by establishing structural correlations between **10** and **12** as well as between **16** and **14**, as indicated in Scheme 4.

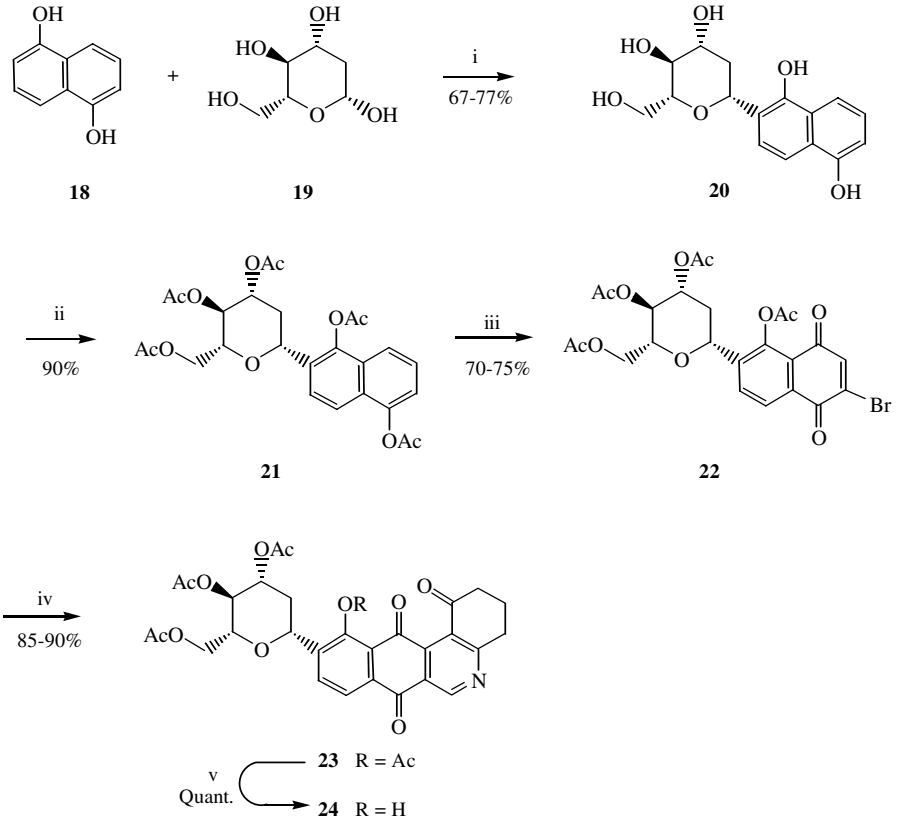
Another significant aspect of these cascade reactions worth noting is the complete regioselectivity of the initial [4+2]cycloaddition, which is mainly governed by the bromine atom.

Additionally, we also effected the synthesis of adduct **17** by reacting diene (*EE*)-**1b** with the 5-acetoxy-2-bromo-[1,4]naphthoquinone **9** in a manner similar to the preparation of **10**.[12] Compound **17** was isolated in 57% yield along with small amounts (14%) of its deacetylated product **18** (Scheme 5).

Having establish the suitability of the sequential [4+2]cycloaddition–aromatisation protocol to generate angucyclinone 5-aza-analogues, we turned our attention to the application of the same protocol to the synthesis of angucycline 5-aza-analogues. Towards this end, the 2-bromo-[1,4]naphthoquinone **22**, bearing a C-glycoside residue at carbon C-6 was selected as the test dienophile. As illustrated in Scheme 6, its synthesis could be efficiently accomplished in three steps. In the first operation, and following the procedure reported by Toshima et al.[14] for aryl C-glycosidation of unprotected sugars, the commercially available 1,5-naphthalene diol **18** and D-deoxyglucose **19** were reacted in the presence of trimethylsilyltriflate to give **20**, which was next subjected to peracetylation conditions to give the pentaacetate **21**. Exposure of **21** to an excess of NBS in aqueous acetic acid proceeded without events as expected from literature precedents,[9a,15] and provided the targeted



Scheme 5. Synthesis of angucyclinone 5-aza-analogue **17**.



Scheme 6. Synthesis of angucycline 5-aza-analogue **24**. Reagents and conditions: (i) **18** (2 equiv), TMSOTf (0.33 equiv), dry CH_3CN, rt for 15 h, then Et_3N; (ii) pyridine/Ac_2O (3/1), 80 °C for 15 h; (iii) NBS (6 equiv), AcOH/H_2O (1/2), 65–70 °C for 3 h; (iv) **1a**, CH_3CN, 40 °C for 3 days; (v) NH_4OAc (8 equiv) in MeOH/H_2O (4:1), rt for 7 h.

dienophile **22** in good yield. Admixture of **22** with diene (*EE*)-**1a** followed by a prolonged heating in acetonitrile afforded the angucycline 5-aza-analogue **23** along with its monodeacetylated product **24**. Treatment of the mixture with an excess of ammonium acetate[16] effected the total and chemoselective conversion of **23** into the angucycline 5-aza-analogue **24**, which was isolated in 85–90% yield for the two steps.

In summary, the simple and efficient synthesis of two new 'push–pull' heterodienes, namely (*EE*)-**1a** and (*EE*)-**1b**, were described. Starting from these dienes we established a domino [4+2]cycloaddition–aromatisation protocol as a simple and efficient method for the one-pot synthesis of angucyclinone and angucycline 5-aza-analogues having an aromatised B-ring and bearing various substituents at carbons C-8, C-10 or C-11 in ring D. The extension of this protocol to the synthesis of further analogues of angucyclinones and angucyclines as well as the utilisation of diene **1a** in the synthesis of natural products of biological significance are currently underway.

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12. A representative experimental procedure is as follows (preparation of the 8-hydroxy-3,4-dihydro-2*H*-benzo[*j*]phenanthridine-1,7,12-trione **16**). To a solution of diene **1a** (1 mmol) in dry CH_3CN (5 mL), 2-bromo-8-hydroxy-[1,4]naphthoquinone **15** (1 mmol) was added at room temperature with stirring. After 4 h at this temperature and 18 h at 40 °C, the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (Toluene/AcOEt = 4:1) to give the trione **16** (75% yield): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.30 (m, 2H), 2.94 (t, $J = 7.1$ Hz, 2H), 3.23 (t, $J = 6.3$ Hz, 2H), 7.27–7.35 (m, 1H), 7.65–7.73 (m, 2H), 9.48 (s, 1H), 12.11 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5, 33.4, 39.1, 115.2, 120.1, 124.7, 126.7, 128.8, 134.6, 137.6, 141.1, 151.2, 162.2, 169.6, 182.1, 187.1, 197.5. FT-IR (KBr, cm^{-1}): 3500, 1700, 1680, 1634. MS (EI, 70 eV): $m/z = 293$ ($M^{+\cdot}$, 56), 265 (100), 237 (15), 209 (12), 181 (3), 180 (4), 153 (8), 126 (9). Anal. Calcd $C_{17}H_{11}NO_4$: C, 69.62; H, 3.78; N, 4.78. Found C, 69.39; H, 3.84; N, 4.71.
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