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Preparation of a chiral azadiene for the synthesis of 5-aza analogues of angucyclinones

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ABSTRACT

We have developed an efficient synthesis of both enantiomers of a key azadiene for the preparation of 5-aza analogues of angucyclinones through a hetero Diels–Alder reaction. These dienes were efficiently prepared via a 4-step procedure from known and readily available chiral diketoesters.

The angucyclines and angucyclinones are natural products having an angularly condensed benz[*a*]anthraquinone skeleton which is biosynthetically derived from a dekaketide chain. These compounds, which are secreted by *Actinomycetes*, often exhibit an array of biological activities including antitumor, antiviral, antifungal and enzyme inhibitory effects. Among the subclass of angucyclinones, some members display a ring B fully aromatised and a stereogenic centre at C3 in ring A. A representative example is provided by (+)-ochromycinone **1** (Scheme 1). Some years ago, we reported the synthesis of a series of angucyclinone 5-aza-analogues **4** with the aim of creating novel chemical structures with enhanced biological activities.[1] These compounds, which exhibited encouraging cytotoxicity against MCF-7 (breast) and KB (nasopharynx) cancer cell lines were efficiently prepared following a strategy based on a regioselective hetero Diels–Alder reaction featuring push-pull dienes **3a** or **3b** and a substituted 2-bromo-[1,4]naphthoquinone **2** (Scheme 1).

In order to prepare chiral variously substituted 5-aza analogues of angucyclinones **4** (R = Me) and also to best delineate the importance of the configuration of the methyl group at C3 on the cytotoxic properties of these compounds, we became interested in the preparation of diene **3b** in each of its chiral non-racemic form. Preparation of diene (*S*)-**3b** was considered first and we thought that diene **5** could serve as a useful equivalent since, after accomplishment of the [4+2]cycloaddition-aromatisation sequence (**5** + **9**, Scheme 3), the ester moiety (located β to the carbonyl at C1) was expected to be easily removed. Our strategy to reach diene **5** is pictured in retrosynthetic Scheme 2. Thus, diene **5** would be prepared by amidination of enaminoketone **6**, itself derived from diketone **7** whose preparation had already been reported by Myers et al. in the course of their synthesis of (+)-dynemicin A.[2]

In the synthetic direction (Scheme 3), condensation of (−)-menthylacetoacetate with *trans*-ethyl crotonate (*tert*-BuOK, *tert*-BuOH, reflux) afforded an approximately 1:1 mixture of *trans* diastereomers **7** and **8**, from which **7** could be isolated by selective crystallisation from toluene.[3] Exposure of diketone **7** to a slight excess of ammonium acetate in toluene at reflux was remarkably regioselective, affording a single enaminone. A 2D HMBC experiment, and an infra-red spectroscopic study revealing the absence of an intramolecular hydrogen bond, both suggested that this enaminone was best represented by formula **6** and this was later fully ascertained by a single-crystal X-ray analysis (Fig. 1).[4,5]

Treatment of **6** with *N,N*-dimethylformamide dimethyl acetal afforded diene **5** (75% yield) which was next condensed to 2-bromo-quinone to afford the tetracyclic adduct **10** in 67% yield. At this stage, attempts at saponification or hydrolysis of the (−)-menthylester moiety in **10** followed by decarboxylation of the resulting β-ketoacid to give the 5-aza-angucyclinone derivative **11** appeared unexpectedly difficult. Indeed, we were not able to form **11** under

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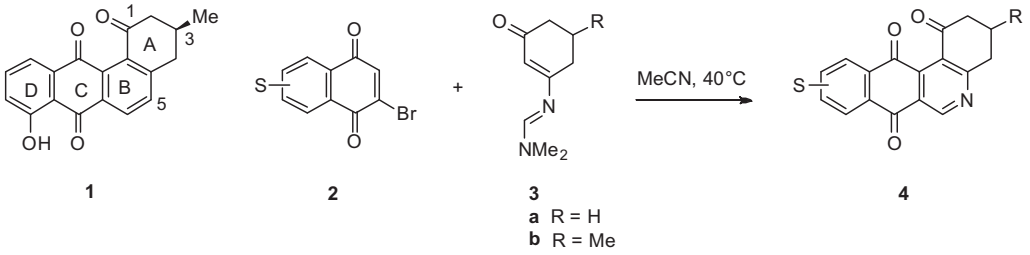
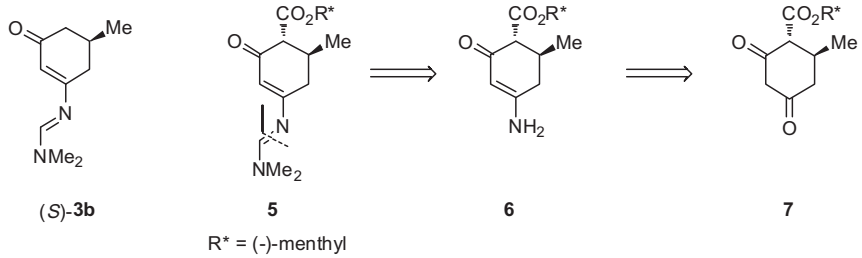
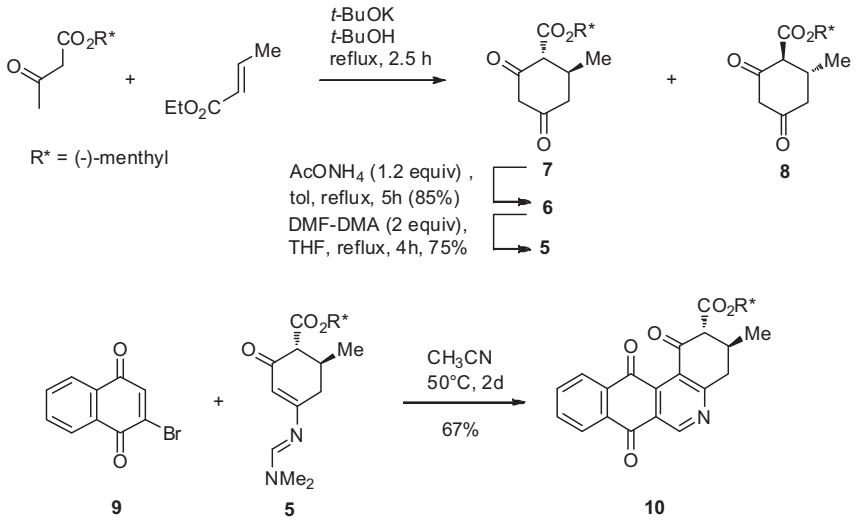


Scheme 1.



Scheme 2.



Scheme 3.

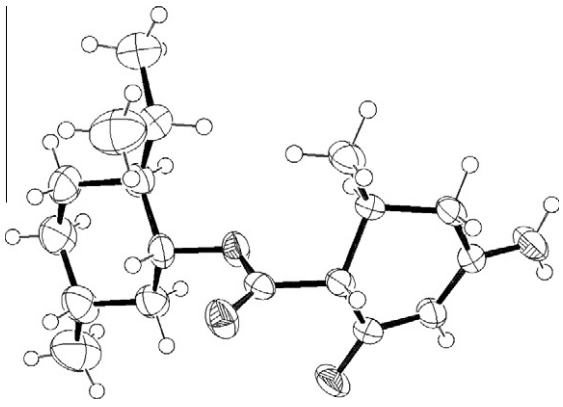
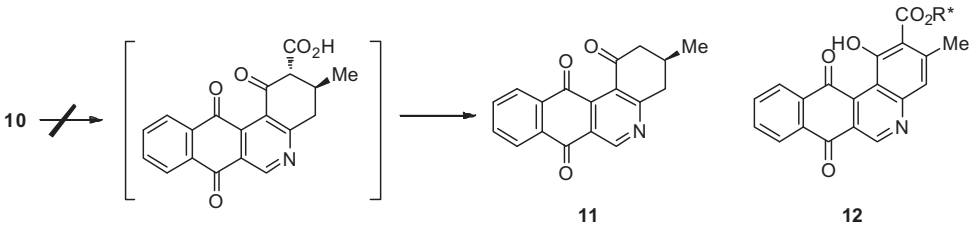


Figure 1.

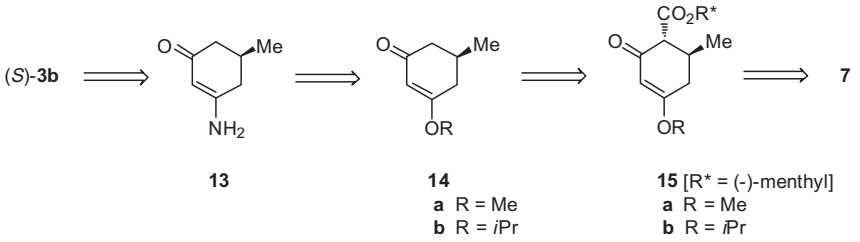
several different acidic and basic conditions, all attempts invariably leading to the formation of the fully aromatised compound **12** (Scheme 4).

The adverse behaviour exhibited by compound **10** led us to devise a new synthetic scheme for the formation of compound 4 featuring the direct use of diene (*S*)-**3b**, the synthesis of which was envisaged as depicted in Scheme 5.

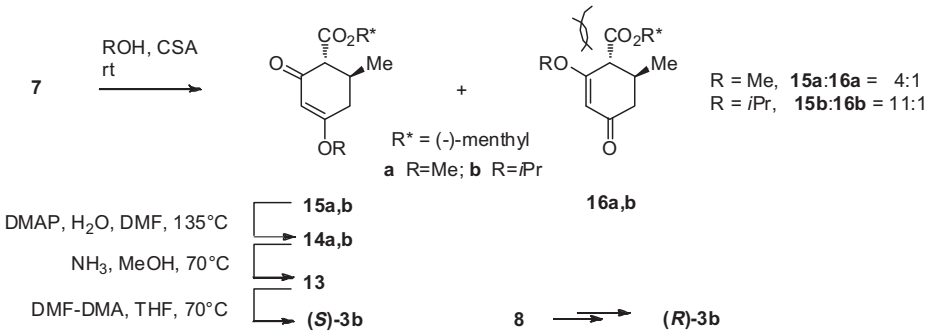
Accordingly (Scheme 6), exposure of diketone ester **7** to methanol in the presence of a catalytic amount of camphorsulphonic acid (CSA) led to the formation of a chromatographically separable 4:1 mixture of enol ethers **15a** and **16a** as already described.[2] Since compound **16a** was reported to return an apparently thermodynamic 4:1 mixture of **15a** and **16a** when resubjected to an acidic methanolic solution, we anticipated that the use of isopropanol instead of methanol would lead to enol ether products with an improved selectivity due to increased OR/CO_2R^* interactions in **16b** versus **16a**. Indeed, exposure of diketone **7** to an acidic isopropanol



Scheme 4.



Scheme 5.



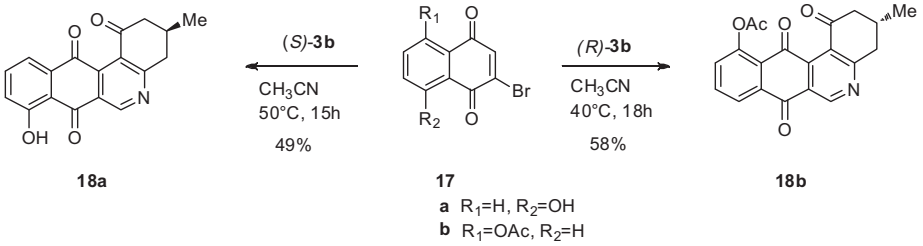
Scheme 6.

solution afforded a 11:1 mixture of enol ethers **15b** and **16b**, which furthermore were more easily separated by column chromatography than the diastereomeric pair **15a**:**16a**.

With **15a** and **15b** now in hand, we were in a position to effect the key (−)-menthylester excision. As for β-ketoester **10** this transformation proved difficult but we finally discovered that it could be satisfactorily accomplished by heating **15a (15b)** in DMF at 135 °C for 80 h in the presence of DMAP (1 equiv) and H_2O (12 equiv).[6] Under these conditions, enol ethers **14a (14b)** were isolated in 60% yield.[7] The remaining steps towards **3b** were completed as follows. Exposure of **14a** to ammonia, (ca. 2 N solution in methanol) in a sealed tube maintained at 70 °C for 2 days afforded enaminone **13** in almost quantitative yield.[8,9] The same conditions, when applied to **14b**, led to an incomplete transformation and enaminone **13** was isolated in 65–78% yield. Finally, diene (*S*)-**3b** was reached after the treatment of **13** with DMF-DMA in THF at 70 °C for 4 h (89%).[10] In a parallel manner, enantiomeric diene *(R)*-**3b** was prepared from diketone ester **8** by an identical sequence of reactions.

According to the general Scheme 1, dienes (*S*)- and (*R*)-**3b** were condensed with 2-bromonaphthoquinones **17a** and **17b** in acetonitrile under moderate thermal activation to provide adducts **18a** [(*S*)-5-aza-ochromycinone] and **18b**, respectively (Scheme 7).[11]

In conclusion, we have reported a 5-step preparation of the chiral azadienes (*S*)- and (*R*)-**3b** for the synthesis of chiral 5-aza analogues of angucyclinones displaying an aromatised B-ring.



Scheme 7.

Acknowledgements

The authors would like to thank Dr J. Graton for IR studies and A. Planchat for the X-ray structure of enaminone **6**.

References and notes

1. (a) Collet, S.; Rémi, J.-F.; Cariou, C.; Laïb, S.; Guingant, A.; Vu, N. Q.; Dujardin, G. *Tetrahedron Lett.* **2004**, *45*, 4911–4915; (b) Vu, N. Q.; Dujardin, G.; Collet, S.; Raiber, E.-A.; Guingant, A.; Evain, M. *Tetrahedron Lett.* **2005**, *46*, 7669–7673.
2. Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072–6094.
3. After two crystallisations from toluene the purity of **7** was better than 99% as judged by HPLC analysis; $[\alpha]_D^{20}$ +67.9 (*c* 0.77 MeOH) (lit.[2] +66.9). Mp 186 °C (lit.[2] 180–181 °C). The diastereomeric diketone **8** was isolated as described in Ref.2 along with 6% of **7** (measured by HPLC analysis). $[\alpha]_D^{20}$ −51.4 (*c* 0.77 MeOH). Mp 143 °C (lit.[2] 140–141 °C).
4. A similar regioselectivity has already been observed for enamination of β-diketones structurally closed to **7**. Foster, J. E.; Nicholson, J. M.; Butcher, R.; Stables, J. P.; Edafiogho, I. O.; Goodwin, A. M.; Henson, M. C.; Smith, C. A.; Scott, K. R. *Bioorg. Med. Chem.* **1999**, *7*, 2415–2425.
5. *Crystal data for enaminone* **6**: $C_{18}H_{29}NO_3$, M_r = 307.43, monoclinic, $P2_1$, a = 8.8546(5), b = 14.1110(14), c = 7.2647(6) Å, β = 98.944(6), V = 896.66(11) Å^3, Z = 2, ρ_{calcd} = 1.1383 g cm^{-3}, μ = 0.076 mm^{-1}, $F(0\,0\,0)$ = 336, colourless block, 0.13 × 0.10 × 0.08 mm^3, $2\theta_{max}$ = 56°, T = 298 K, 18192 reflections, 2229 unique (99% completeness), R_{int} = 0.0584, 206 parameters, GOF = 1.45, wR_2 = 0.1317, R = 0.0584 for 3124 reflections with $I > 2\sigma(I)$. CCDC 799310 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
6. (a) Taber, D. F.; Amedio, J. C., Jr.; Gulino, F. J. *Org. Chem.* **1989**, *54*, 3474–3475; (b) Koyama, Y.; Yamaguchi, R.; Suzuki, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1084–1087.
7. *Compound* **14a**: Ee 98% (determined by chiral GC on a Lipodex E column). $[\alpha]_D^{20}$ +82.6 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.29 (s, 1H), 3.62 (s, 3H), 2.37–2.43 (m, 2H), 2.30–1.97 (m, 3H), 1.01 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.7, 178.1, 102.9, 55.7, 45.1, 36.9, 29.7, 20.9. IR (KBr) 1647, 1598, 1218 cm^{-1}. MS (CI): m/z = 141.0 [M+H]$^+$, 158.0 [M+NH$_4$]$^+$. HRMS (EI) calcd for $C_8H_{12}O_2$ [M$^+$] 140.0837, found 140.0839. **14b**: Mp 42 °C. Ee 98% (determined by chiral GC on a Lipodex E column). $[\alpha]_D^{20}$ + 91.7 (*c* 0.8, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.33 (s, 1H), 4.42 (sep, J = 5.8 Hz, 1H); 2.32–2.44 (m, 2H), 2.30–1.97 (m, 3H), 1.29 (t, J = 5.8 Hz, 6H), 1.06 (d, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.9, 176.3, 102.6, 70.9, 45.0, 37.7, 28.8, 21.5, 21.4, 20.9. IR (KBr) 1647, 1598, 1217 cm^{-1}. MS (EI): m/z (%) = 168 (5), 84 (100). HRMS (EI) calcd for $C_{10}H_{16}O_2$ [M$^+$] 168.1145, found 168.1143.
8. Pita, B.; Masaguer, C. F.; Raviña, E. *Tetrahedron Lett.* **2000**, *41*, 9829–9833.
9. Mp 128 °C. Ee 98% (determined by chiral GC on a Lipodex E column). $[\alpha]_D^{20}$ +82.3 (*c* 0.75, MeOH). ^{1}H NMR (300 MHz, MeOD): δ = 5.12 (s, 1H), 2.40–2.30 (m, 2H), 2.05–2.24 (m, 3H), 2.00–1.85 (m, 1H), 1.00 (d, J = 6 Hz, 3H). ^{13}C NMR (75 MHz, MeOD): δ = 199.7, 178.1, 102.9, 45.1, 35.9, 29.7, 20.9. IR (KBr): 3117, 1680, 1559, 1268 cm^{-1}. MS (EI): m/z (%) = 125 (24) [M$^+$], 83 (100). HRMS (EI) calcd for $C_7H_{11}NO$ [M$^+$] 125.0835, found 125.0835.
10. *Compound* (*S*)-**3b**: $[\alpha]_D^{20}$ +295.3 (*c* 0.76, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (s, 1H), 5.41 (s, 1H), 3.04 (s, 3H), 3.01 (s, 3H), 2.53–2.37 (m, 2H), 2.29–2.10 (m, 2H), 2.06–1.97 (m, 1H), 1.04 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 172.0, 152.1, 110.2, 45.0, 40.4, 38.9, 34.4, 29.4, 20.9. IR (neat): 1614–1620, 1555, 1108 cm^{-1}. MS: m/z (%) = 180 (79) [M$^+$], 123 (85), 109 (100). HRMS (EI) calcd for $C_{10}H_{16}N_2O$ [M$^+$] 180.1263, found 180.1261. *Compound* (*R*)-**3b**: $[\alpha]_D^{20}$ −270.7 (*c* 1.02, CH_2Cl_2). Contamination with (*S*)-enantiomer is due to the fact that the starting diketone ester 8 was difficult to be obtained in pure form and remained contaminated with some amount of 7 (cf. Ref.3).
11. *Characteristic data for (S)-5-aza-ochromycinone* **18a**. Yellow powder, mp 159–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.12 (s, 1H), 9.51 (s, 1H), 7.73–7.67 (m, 2H), 7.33 (dd, J = 4.2, 5.5 Hz, 1H), 3.34 and 2.91 (AB part of ABX system, J = 17,6, 10,4, 4,3 Hz, 2H), 3.02 and 2.64 (AB part of ABX system, J = 15,1, 11.2, 4.5 Hz, 2H), 2.58–2.45 (m, X part of ABX systems 1H), 1.25 (d, J = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 187.0, 182.1, 169.7, 162.1, 151.4, 141.0, 137.5, 134.5, 128.2, 126.4, 124.6, 120.0, 115.1, 47.4, 41.6, 29.5, 21.3. IR (KBr): 1771, 1700, 1685, 1633 cm^{-1}. MS (CI): m/z = 308 [M+H]$^+$. HRMS (ESI) calcd for $C_{18}H_{14}NO_4$ [M+H]$^+$ 308.0917, found 308.0910. $[\alpha]_D^{20}$ +5 (*c* 0.1, $CHCl_3$). *Characteristic data for (R)*-**18b**. Dark powder, mp 192 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.45 (s, 1H), 8.16 (dd, J = 7.8, 1.2 Hz, 1H), 7.80 (t, J = 7.8 Hz, 1H), 7.47 (dd, J = 7.8, 1.2 Hz, 1H), 3.33 and 2.91 (AB part of ABX system, J = 17.8, 9.8, 4.2 Hz, 2H), 2.97 and 2.59 (AB part of ABX system, J = 15.1, 11.2, 3.4 Hz, 2H), 2.55–2.41 (m, X part of ABX systems 1H), 2.44 (s, 3H), 1.23 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.5, 181.8, 181.1, 169.6, 168.4, 151.5, 149.3, 142.5, 134.7, 133.9, 130.3, 127.3, 125.9, 125.0, 47.2, 41.5, 29.3, 21.2, 20.9. IR (KBr): 1771, 1700, 1685, 1633 cm^{-1}. MS (CI): m/z = 350 [M+H]$^+$. HRMS (ESI) calcd for $C_{20}H_{16}NO_5$ [M+H]$^+$ 350.1028, found 350.1030. $[\alpha]_D^{20}$ −39 (*c* 0.1, $CHCl_3$) (ee 88% measured by HPLC analysis on a Chiralcel OJ-H column).