Short and efficient enantioselective total synthesis of angucyclinone type antibiotics (+)-rubiginone B_2 and (+)-ochromycinone

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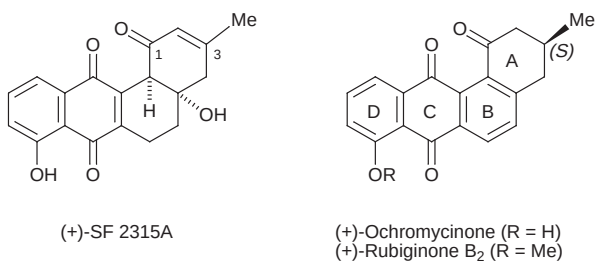
Received (in Liverpool, UK) 26th February 1999, Accepted 15th March 1999

The enantioselective total synthesis of antibiotics rubiginone B_2 and ochromycinone is achieved from enantiopure (*S*)-5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone and a racemic vinylcyclohexene through a short sequence involving a tandem Diels–Alder reaction–sulfoxide elimination process with simultaneous kinetic resolution of the racemic diene, followed by controlled aromatization and functional group deprotection.

Ochromycinone and rubiginone B_2, first isolated respectively by Bowie[1] and Oka,[2] are components of the anguciclinone family, a growing class of natural products with remarkable antibiotic activity and cytotoxicity.[3] The major components of this family show a benz[*a*]anthracene framework of decaketide origin[4] bearing a methyl group at C-3 and an oxygen function at C-1. The 3*S* absolute configuration is also a common characteristic of C-3 non-oxygenated angucyclinones. The main structural differences are found in the aromatic or hydroaromatic nature of the A and/or B rings. The regioselective construction of the angularly fused tetracyclic skeleton has been achieved applying several methods which are summarized in a recent review article.[5] The most general strategy employed is based on the Diels–Alder reaction between a substituted naphthoquinone and a vinylcyclohexene. While several efficient total syntheses have focused on the racemic forms, access to the isolated optically active species remains a problem. The asymmetric syntheses of antibiotics (+)-SF 2315A and urdamycinone B were reported by Sulikowski[6] who used an asymmetric Diels–Alder reaction with an appropriately functionalized chiral diene obtained from (−)-quinic acid as the key step. A second Diels–Alder approach was described by Larsen[7] who achieved the total syntheses of antibiotics (+)-emycin A and (+)-ochromycinone by using a chiral catalyst in the cycloaddition step which allowed the kinetic resolution of the diene partner in a single operation. Finally, chromatographic separation of the diastereoisomeric mixture resulting in the cycloaddition between a *C*-glycosyl juglone and a racemic vinylcyclohexene has also allowed the asymmetric synthesis of urdamycinone B.[8,9] In spite of the structural similarities between (+)-ochromycinone and (+)-rubiginone B_2 (ochromycinone methyl ether), to the best of our knowledge, the latter has never been synthesized in an optically active form.

Our previous work devoted to the use of enantiopure (*S*)-2-(*p*-tolylsulfinyl)-1,4-quinones as dienophiles[10] had shown a high ability of the sulfoxide to control the regiochemistry, *endo*-selectivity and π-facial diastereoselectivity of their Diels–Alder cycloadditions with a wide range of cyclic and acyclic dienes. We established the tandem Diels–Alder reaction–pyrolytic sulfoxide elimination as a general one-pot strategy to enantiomerically pure polycyclic dihydroquinones. More recently,[11,12] we envisaged the ability of the sulfinyl group to promote a double induction in the cycloaddition process leading to the efficient kinetic resolution of differently substituted chiral racemic vinylcyclohexenes.[11] The high facial selectivity achieved was explained by invoking the favored transition state indicated in Scheme 1. This strategy provided a diastereoselective entry into the tetracyclic framework of angucyclinones.[12] To account for this, we reasoned that cycloaddition of a methoxy substituted sulfinylnaphthoquinone such as **1** would provide a short and convergent asymmetric entry into the angucyclinone family. Here we report the application of this novel methodology for the total synthesis of natural antibiotics (+)-rubiginone B_2 and (+)-ochromycinone.

Our approach to an immediate tetracyclic precursor to both natural products is outlined in Scheme 1. We selected the TBDMS protected derivative of *trans*-3-hydroxy-5-methyl-1-vinylcyclohexene **2** as starting material since our previous studies had shown that free OH was less efficient in the *anti/syn* discrimination of the cycloaddition transition states.[11,12] Diene **2** was synthesized from *cis*-3-hydroxy-5-methyl-1-vinylcyclohexene through a Mitsunobu inversion of C-3 followed by protection of the OH group.[11] Thus, cycloaddition of enantiopure (*S*)-5-methoxy-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone (+)-**1**[13] with two equivalents of chiral racemic *trans*-3-[(*tert*-butyldimethylsilyl)oxy]-5-methyl-1-vinylcyclohexene **2** af-



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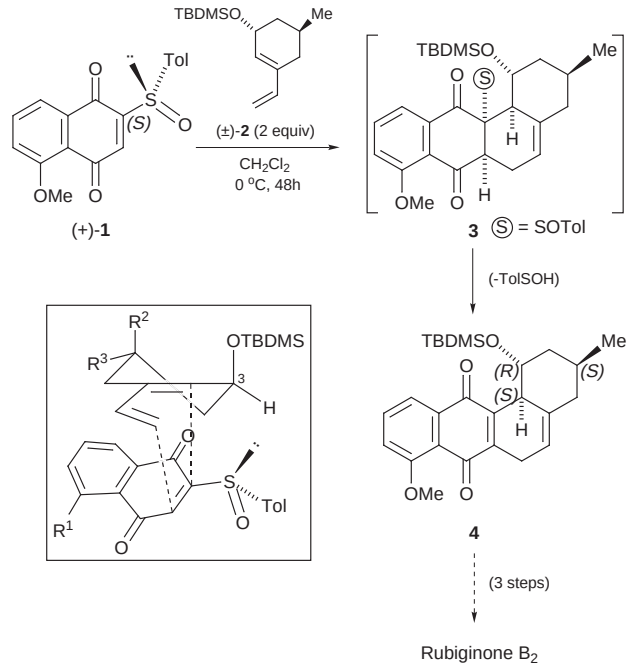
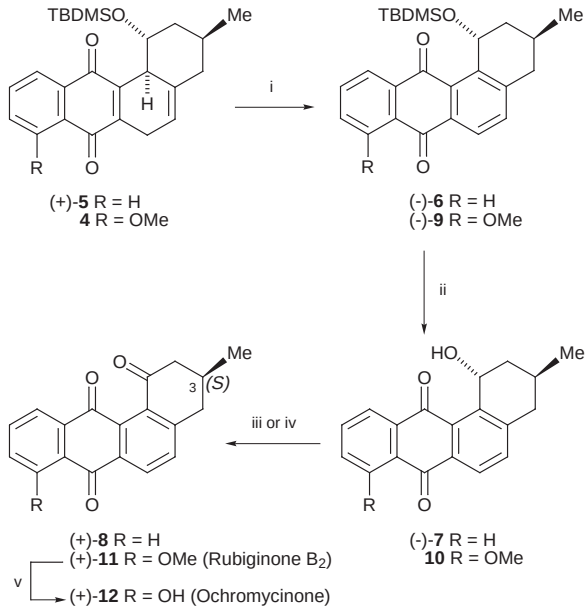


Scheme 1



Scheme 2 *Reagents and conditions*: i, DBU, CH_2Cl_2, 0 °C, 2 h, 81% from **5**, 58% from **1** for two steps; ii, 40% aq. HF, CH_3CN, rt, 1 h, 52% from **6**; iii, air, *hv*, CH_2Cl_2, rt, 2 h, 70% from **7**, 48% from **9** for two steps; iv, PCC, CH_2Cl_2, rt, 8 h, 74% from **7**; v, $AlCl_3$, CH_2Cl_2, rt, 20 h, 86%.

forded the 1,4-dihydroquinone derivative **4**, after pyrolytic elimination of the sulfoxide in the initially formed adduct **3** which occurred spontaneously even at 0 °C. The formation of **4** as a single regioisomer and *anti* diastereoisomer revealed a high efficiency of the sulfinylquinone **1** in controlling both the regioselectivity and diastereoselectivity of the cycloaddition step. Transformation of **4** into rubiginone B_2 only required three steps: aromatization of the B ring, deprotection of the OTBDMS group and further oxidation of the benzylic alcohol function. Unfortunately, compound **4** was not stable enough to be isolated pure due to its easy decomposition. We thus turned our attention to the more stable demethoxy analogue (+)-**5** (Scheme 2), which had been obtained in the reaction between (*S*)-2-(*p*-tolylsulfinyl)-1,4-naphthoquinone and diene (±)-**2**.[11]

Upon treatment with DBU,[14] partial aromatization of compound **5** proceeded rapidly to give the benz[*a*]anthraquinone (−)-**6** in 81% yield (Scheme 2). The OTBDMS protecting group of **6** was removed by treatment with 40% aqueous HF in CH_3CN[15] to provide alcohol (−)-**7** in 52% yield. The oxidation of **7** into the 8-deoxyangucyclinone (+)-**8** was carried out in 70% yield following a photooxygenation process,[16] in which a CH_2Cl_2 solution of **7** was exposed to daylight. This transformation could also be achieved by using a PCC oxidation (74% yield). The optical rotation of **8** was $[\alpha]_D^{20}$ +97 (*c* 0.5, $CHCl_3$), in accordance with those of natural angucyclinones rubiginone B_2[2] and ochromycinone,[1] suggesting the correct *S* absolute configuration at C-3, the only stereocenter present in the molecule. From a ^{1}H-NMR study an 80% ee was determined for (+)-**8** using $Pr(hfc)_3$ as chiral lanthanide shift reagent,‡ showing that no racemization had occurred during the reaction sequence outlined in Scheme 2, which started from derivative (+)-**5** (ee = 80%).

The natural products **11** and **12** were then synthesized following a similar reaction sequence (Scheme 2). Thus, after cycloaddition between (+)-**1** and (±)-**2** (Scheme 1), the crude reaction mixture containing compound **4** was aromatized into benz[*a*]anthraquinone (−)-**9** by treatment with DBU at 0 °C. Derivative **9** could thus be obtained in 58% yield for the one-pot three steps cycloaddition–sulfoxide elimination–aromatization process from (+)-**1**. Further deprotective treatment of OTBDMS derivative **9** with 40% aqueous HF in CH_3CN gave rise to the very unstable alcohol **10** which, without isolation, was oxidized in the presence of air and daylight to the corresponding ketone **11** in 48% yield from **9** for the one-pot two step desilylation–oxydation sequence. Synthetic **11** {$[\alpha]_D^{20}$ +62 (*c* 0.5, $CHCl_3$), 80% ee} was shown to be identical in all physical and spectroscopic properties to the natural (+)-rubiginone B_2 {$[\alpha]_D^{20}$ +78 (*c* 0.5, $CHCl_3$)}.[2] Finally, demethylation of rubiginone B_2 (+)-**11** was achieved in 86% yield by using $AlCl_3$ in CH_2Cl_2 at room temperature, to afford the hydroxy derivative **12** {$[\alpha]_D^{20}$ +163 (*c* 0.05, CH_2Cl_2), 80% ee} which was identical in all physical and spectroscopic data[14] to the natural (+)-ochromycinone {$[\alpha]_D^{20}$ +204.5 (*c* 0.05, CH_2Cl_2)}.[1] The analoguous rotary power of synthetic and natural products confirmed the (3*S*) configuration of the former as well as the (1*R*,3*S*,12b*S*) configuration for intermediate **5** which resulted in the cycloaddition process shown in Scheme 1. On this basis, a transition state similar to that indicated in Scheme 1 explains the major formation of the observed diastereoisomer.

In summary, we have reported a short enantioselective synthesis of the angucyclinone antibiotics rubiginone B_2 and ochromycinone, based on the asymmetric Diels–Alder reaction between the enantiopure methoxy substituted 2-(*p*-tolylsulfinyl)-1,4-naphthoquinone (+)-**1** and the racemic chiral vinylcyclohexene (±)-**2**, through the efficient kinetic resolution of the diene partner and the spontaneous sulfoxide elimination which recovers the quinone skeleton in a single step. The total synthesis of natural derivative (+)-**11** was thus achieved in a two-pot four step procedure starting from (+)-**1** with 80% ee and 28% overall yield. Ochromycinone (+)-**12** was obtained from (+)-**11** after an additional demethylation step with the same optical purity and 25% overall yield.

We thank DGICYT (PB95-0174) for financial support and FAPESP for a post-doctoral fellowship to C. D. V.

Notes and references

‡ The racemic derivative **8** necessary for such evaluation was prepared from racemic sulfinylnaphthoquinone **1**.

1 J. H. Bowie and A. W. Johnson, *Tetrahedron Lett.*, 1967, 1449.
2 M. Oka, H. Kamei, Y. Hamagishi, K. Tomita, T. Miyaki, M. Konishi and T. Oki, *J. Antibiot.*, 1990, **43**, 967.
3 R. H. Thomson, in *Naturally Occurring Quinones IV*, 4th edn., Blackie Academic & Professional, London, 1996; J. Rohr and R. Thiericke, *Nat. Prod. Rep.*, 1992, **9**, 103; M. Ogasawara, M. Hasegawa, Y. Hamagishi, H. Kamei and T. Oki, *J. Antibiot.*, 1992, **45**, 129.
4 S. J. Gould, X. C. Cheng and C. Melville, *J. Am. Chem. Soc.*, 1994, **116**, 1800 and refs. cited therein.
5 K. Krohn and J. Rohr, *Top. Curr. Chem.*, 1997, **188**, 128. For other recent references, see: D. S. Larsen and M. D. O'Shea, *J. Org. Chem.*, 1996, **61**, 5681; K. Krohn, N. Böker, U. Flörke and C. Freund, *J. Org. Chem.*, 1997, **62**, 2350.
6 K. Kim and G. Sulikowski, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2396; V. A. Boyd and G. Sulikowski, *J. Am. Chem. Soc.*, 1995, **117**, 8472.
7 D. S. Larsen, M. D. O'Shea and S. Brooker, *Chem. Commun.*, 1996, 203.
8 G. Matsuo, Y. Miki, M. Nakata, S. Matsumura and K. Toshima, *Chem. Commun.*, 1996, 225.
9 Based on a polyketide condensation, (−)-urdamycinone B had been synthesized in the first example of the asymmetric synthesis of an angucyclinone: M. Yamaguchi, T. Okuma, A. Horiguchi, C. Ikeura and T. Minami, *J. Org. Chem.*, 1992, **57**, 1647.
10 For an overview of our work, see: M. C. Carreño, *Chem. Rev.*, 1995, **95**, 1717. For more recent references, see: M. C. Carreño, J. L. García Ruano, M. A. Toledo, A. Urbano, V. Stefani, C. Z. Remor and J. Fischer, *J. Org. Chem.*, 1996, **61**, 503; M. C. Carreño, R. Hernández-Sánchez, J. Mahugo and A. Urbano, *J. Org. Chem.*, 1999, **64**, 1387.
11 M. C. Carreño, A. Urbano and C. Di Vitta, *J. Org. Chem.*, 1998, **63**, 8320.
12 M. C. Carreño, A. Urbano and J. Fischer, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1621.
13 M. C. Carreño, J. L. García Ruano and A. Urbano, *Synthesis*, 1992, 651.
14 D. S. Larsen and M. D. O'Shea, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1019.
15 B. H. Lipshutz and D. F. Harvey, *Synth. Commun.*, 1982, **12**, 267.
16 K. Krohn, F. Ballwanz and W. Baltus, *Liebigs Ann. Chem.*, 1993, 911; K. Krohn, K. Khanbabaee, U. Flörke, P. G. Jones and A. Chrapkowski, *Liebigs Ann. Chem.*, 1994, 471.

Communication 9/01642B