The efficient and regioselective synthesis of the naphthoquinone core of streptovaricin U

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The efficient and regioselective synthesis of the naphthoquinone core of streptovaricin U 1 *via* the Diels–Alder reaction of 1-methoxy-2-methyl-3-trimethylsilyloxybuta-1,3-diene 5 with the 2,6-dibromo-3-methyl-1,4-benzoquinone 6 is described.

The streptovaricin family are representative ansamycin antibiotics as well as rifamycins and have been used clinically as an important class of antibiotics.¹ So far more than fifteen congeners have been isolated from *Streptomyces spectabilis* and all consist of a unique naphthoquinone core and a polypropionate ansa chain composed of nine contiguous chiral centres.¹ The unique structures and important biological activity of the streptovaricins have elicited considerable attention from synthetic chemists.²

Recently we reported the highly stereoselective synthesis of the ansa chain segment of streptovaricin U $\mathbf{1}$ and protostrepto-



varicins including nine contiguous chiral centres³ by the use of the stereospecific methylation of γ , δ -epoxy acrylates with trimethylaluminium.⁴ Streptovaricin U **1** is a unique open-chain ansamycin from the streptovaricin family and shows inhibitory activity against RAUSCHER leukemia virus RNA-dependent DNA polymerase.⁵ We now report the highly efficient synthesis of the naphthoquinone core of streptovaricin U **1** *via* the Diels– Alder reaction of the silyloxy diene **5** with the dibromoquinone **6**.

Although 1-methoxy-2-methyl-3-trimethylsilyloxybuta-1,3-diene **5** is a known compound and has often been used in Diels–Alder reactions,⁶ we prepared it by the modified procedure shown in Scheme 1 for improved yield and synthetic



Scheme 1 Reagents and conditions: i, NaH (1.5 equiv.), THF, 0 °C, 1 h; ii, $(MeO)_2SO_2$ (2 equiv.), DMF, 0 °C, 1 h, then 1 M aq. K₂CO₃, MeOH; iii, LDA, THF, -78 °C, then Me₃SiCl, -78 °C to room temp.

convenience. Thus butan-2-one **2** was treated with NaH and HCO_2Me in THF at 0 °C to give the sodium enolate **3**, which was treated, after the solvent was replaced from THF to DMF, with dimethyl sulfate to give *trans*-4-methoxy-3-methylbut-3-en-2-one **4**⁷ in 79% yield.[†] The butenone **4** was quantitatively transformed into the silyloxy diene **5** by treatment with LDA in THF followed by addition of Me₃SiCl. The crude diene **5** thus obtained was used directly for the Diels–Alder reaction. On the other hand, 2,6-dibromo-3-methyl-1,4-benzoquinone **6**, the dienophile for the Diels–Alder reaction, was synthesized according to the protocol of Trost and Pearson⁸ in two steps; (i) bromination of *m*-cresol with Br₂ in AcOH; (ii) oxidation of the resulting tribromide with chromium(III) oxide in AcOH (90% yield for the two steps).

The key Diels–Alder reaction was performed by heating a mixture of the diene **5** (4.1 mmol) and the dibromoquinone **6** (3.2 mmol) in benzene (20 ml) at 90 $^{\circ}$ C for 2 h in a sealed tube (Scheme 2). After cooling, the solvent was evaporated under



Scheme 2 Reagents and conditions: i, C_6H_6 , sealed tube, 90 °C, 2 h; ii, 2% HCl, DME, 12 h; iii, MeOCH₂Cl, Prⁱ₂NEt, CH₂Cl₂, 3.5 h; iv, NaN₃, PPh₃, DMSO, 3 h; v, aq. HCHO, THF, 2 d; vi, H₂, PtO₂, Boc₂O (5 equiv.), EtOH, 3 h, then O₂, 12 h; vii, H₂, PtO₂, EtOH, 1 h, then (MeO)₂SO₂ (10 equiv.), 1 M NaOH, 2 h; viii, Ph₂O, 185 °C, sealed tube, 12 h

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reduced pressure and the residue was treated with 2% HCl in DME, giving rise to the adduct 7. The crude product 7 was subsequently treated with ClCH2OMe and Pri2NEt in CH2Cl2 to afford the protected bromoquinone 8 as light yellow crystals (mp 169-172 °C) in 85% overall yield. Subsequent conversion of $\hat{\mathbf{8}}$ to the aminonaphthoquinone $\mathbf{10}$ was accomplished by the reaction of 8 with NaN₃ and PPh₃ in DMSO followed by treatment of the resulting iminophosphorane 9 with aqueous formaldehyde in THF. Thus the desired aminonaphthoquinone 10 was obtained as red crystals (mp 177–179 °C) in 68% yield. Although compound 10 is itself the naphthoquinone core of streptovaricin U 1, it is necessary to further transform it into the naphthalene derivative 13 for the coupling reaction with the ansa chain segment, since the amino group on a naphthoquinone ring such as 10 is not sufficiently basic for further transformation. The conversion of 10 into the target molecule 13 was, however, unexpectedly troublesome and required ingenuity. Eventually the desired transformation was overcome by the following reaction sequence. Hydrogenation of 10 over Adams' catalyst in EtOH in the presence of di-tert-butyl dicarbonate (Boc₂O) followed by treatment with oxygen gave rise to the N-Boc-aminonaphthoquinone 11 as light yellow crystals (mp 141-143 °C) in 85% yield. The product 11 was subsequently converted to the naphthalene dimethyl ether 12 (mp 104-106 °C) by hydrogenation over Adams' catalyst in EtOH followed by treatment of the resulting dihydroquinone with dimethyl sulfate and 1 M NaOH in 83% yield. The synthesis of the fully functionalized aromatic core 13 of streptovaricin U 1 was accomplished by removal of the Boc group in 12 by thermolysis in Ph₂O at 185 °C (sealed tube), resulting in formation of 13 in 87% yield.

Thus an efficient and regioselective synthesis of the naphthoquinone core of streptovaricin U 1 has been established. The overall yield of 13 from the dibromoquinone 6 was 35%. The manipulations employed in the conversion of 10 into 13 may be widely applicable to the synthesis of various aminonaphthoquinones. The coupling reaction of the aromatic core 13 with the ansa chain segment toward the total synthesis of 1 is now in progress. This work was also supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 08245101) and a Grant-in-Aid for Scientific Research (No. 09874149) from the Ministry of Education, Science, Sports, and Culture of Japan.

Footnotes and References

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