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

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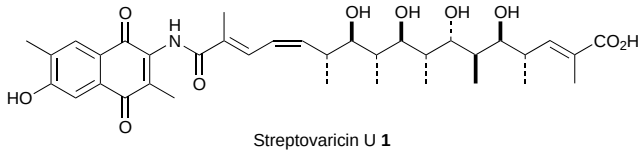
The efficient and regioselective synthesis of the naphthoquinone core of streptovaricin U 1 *via* the Diels–Alder reaction of 1-methoxy-2-methyl-3-trimethylsilyloxybuta-1,3-diene 5 with the 2,6-dibromo-3-methyl-1,4-benzoquinone 6 is described.

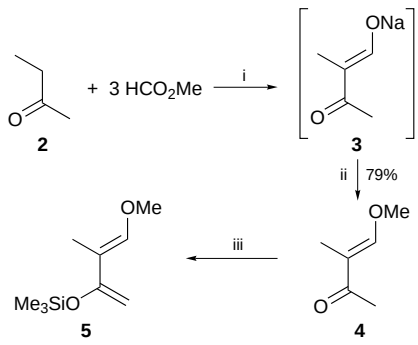
The streptovaricin family are representative ansamycin antibiotics as well as rifamycins and have been used clinically as an important class of antibiotics.[1] So far more than fifteen congeners have been isolated from *Streptomyces spectabilis* and all consist of a unique naphthoquinone core and a polypropionate 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 **1** and protostreptovaricins including nine contiguous chiral centres[3] 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**.



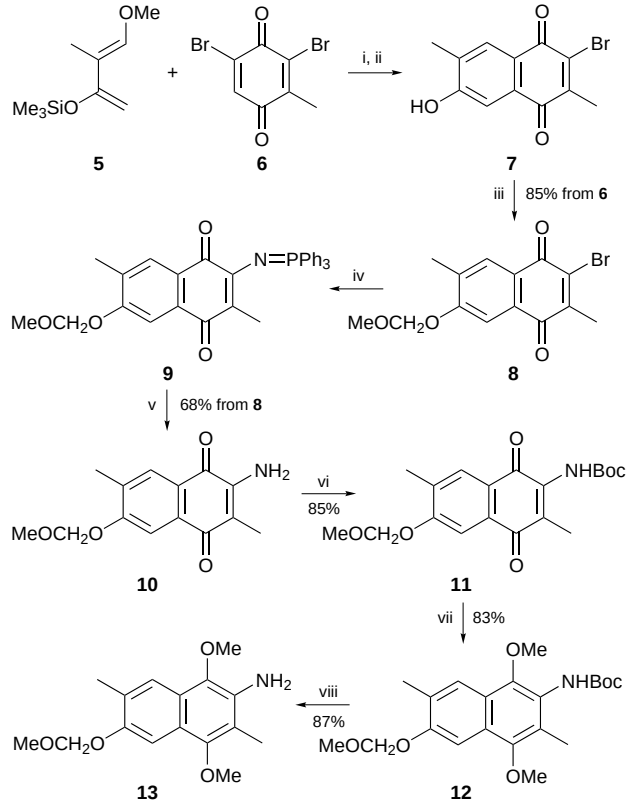
Streptovaricin U **1**

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 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 Me_3SiCl. 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 Pearson[8] in two steps; (i) bromination of *m*-cresol with Br_2 in AcOH; (ii) oxidation of the resulting tribromide with chromium(III) oxide in AcOH (90% yield for the two steps).



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. K_2CO_3, MeOH; iii, LDA, THF, −78 °C, then Me_3SiCl, −78 °C to room temp.

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 °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, $MeOCH_2Cl$, Pr^i_2NEt, CH_2Cl_2, 3.5 h; iv, NaN_3, PPh_3, DMSO, 3 h; v, aq. HCHO, THF, 2 d; vi, H_2, PtO_2, Boc_2O (5 equiv.), EtOH, 3 h, then O_2, 12 h; vii, H_2, PtO_2, EtOH, 1 h, then $(MeO)_2SO_2$ (10 equiv.), 1 M NaOH, 2 h; viii, Ph_2O, 185 °C, sealed tube, 12 h

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 $ClCH_2OMe$ and Pr^i_2NEt in CH_2Cl_2 to afford the protected bromoquinone **8** as light yellow crystals (mp 169–172 °C) in 85% overall yield. Subsequent conversion of **8** to the aminonaphthoquinone **10** was accomplished by the reaction of **8** with NaN_3 and PPh_3 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 (Boc_2O) 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 Ph_2O 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.

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Footnotes and References

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† All new compounds exhibited satisfactory spectra (^1H and ^{13}C NMR, IR) and elemental analyses.

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