Synthesis of *N*-Benzyl*homo*-(–)-anisomycin

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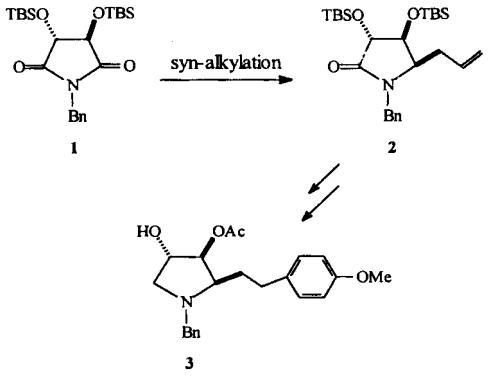
Anisomycin, a fermentation product of various species of *Streptomyces*,[1] is an antibiotic that possesses marked activities against pathogenic protozoa and fungi, and has been used successfully clinically in the treatment of amebic dysentery and trichomonas vaginitis.[2] Considerable synthetic efforts, derivative syntheses as well as total syntheses, have been reported until recently.[3] Especially, the synthesis of its analogues has revealed the structure-activity relationships of synthetic antibiotics.[4] However, few result of the chain extention effect of the *p*-methoxybenzyl group has been reported.

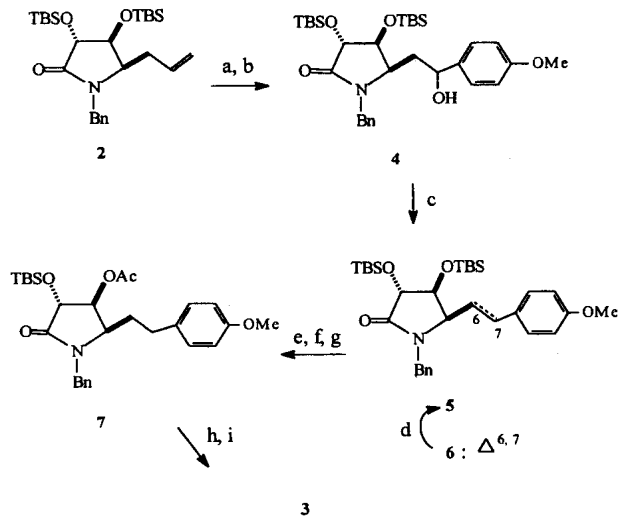
In this respect, this report concerns a new synthetic approach to a *homo*anisomycin analogue **3**. And we considered that intermediate **2** would be suitable for furnishing the desired stereochemistry and the extended side chain of the molecule. The compound **2** can be readily obtained via cis-amidoalkylation of tartrimide.[5]

First, in order to set the side group, the allylic amide **2** prepared as described[5] was subjected to ozonolysis and the dimethyl sulfide reductive work-up. Without purifcation, the corresponding aldehyde was treated with (*p*-methoxyphenyl) magnesium bromide in THF to yield an epimeric mixture of benzylic alcohols in 59% overall yield. The mixture was then reduced by triethylsilane under trifluoroacetic acid treatment in THF. The reducing step under the acidic conditions afforded β-elimination product **6** in less than 10% as well as the desired compound **5** in 70% yield. Compound **6** was readily converted to **5** via catalytic hydrogenation.

The desired acetate funtionality at the 3 position could be installed via three step sequence. Firstly, the TBS protection groups were removed to provide a diol by tetrabutylammonium fluoride (TBAF), and the sterically less hindered 4-α-hydroxyl group of the diol was selectively protected with 1.2 equiv. of *tert*-butyldimethylsilyl chloride in DMF at room temperature. Only single isomer was detected. Thirdly, acetylation of the 3-hydroxyl group with acetic anhydride in pyridine provided the acetate **7** in overall yield of 52%. The final steps to the compound **3**[7] from **7** involved removal of the protecting silyl group with TBAF followed by reduction of the amide group with borane-methyl sulfide complex, affording 3 in 34% overall yield.

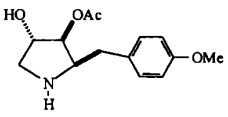


Scheme 1.



Scheme 2. Reagents and conditions: (a) i. O_3, CH_2Cl_2-MeOH ii. Methyl sulfide (b) (*p*-Methoxyphenyl) magnesium bromide, THF (c) Et_3SiH, CH_2Cl_2, TFA (d) Pd/5%, H_2 (e) TBAF, THF (f) TBSCl, imidazole, DMF (g) Ac_2O, pyridine (h) TBAF, THF (i) BH_3-DMS, THF, rt.

In summary, we described a concise synthetic pathway to *N*-benzyl*homo*-(–)-anisomycin, the first synthetic derivative of homoanisomycins, from the precursor **2**. Further synthetic study of the related analogues is under progress and will be reported in due course.



(–)-Anisomycin

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7. **3**: $[\alpha]_D^{23}$ – 45.4° (c=0.35, $CHCl_3$), ^1H NMR (300 MHz $CDCl_3$) δ 7.4-7.2 (m, 5H) 7.1 (d, *J*=9 Hz, 2H), 6.8 (d, *J*=9 Hz, 2H), 4.8 (dd, *J*=2.4, 2.4 Hz, 1H), 4.1 (td, *J*=6.3, 2.4 Hz, 1H), 4.0 (d, *J*=13 Hz, 1H), 3.8 (s, 3H), 3.3 (d, *J*=13 Hz, 1H), 3.2 (dd, *J*=8, 6.6 Hz, 1H) 2.9 (br. s, 1H), 2.7 (m, 1H), 2.4-2.7 (m, 2H), 2.2 (s, 3H), 2.1 (m, 1H), 1.9-2.1 (m, 2H), IR ($CHCl_3$) 3430, 3054, 2987, 2361, 1699, 1540, 1421, 1265, 896, 738 cm^{-1}, MS (FAB, glycerol) 370 (M^+)