Carbohydrate-based Syntheses of the Goldinonolactone and the Tetrahydrofuran Fragments of Aurodox and Efrotomycin

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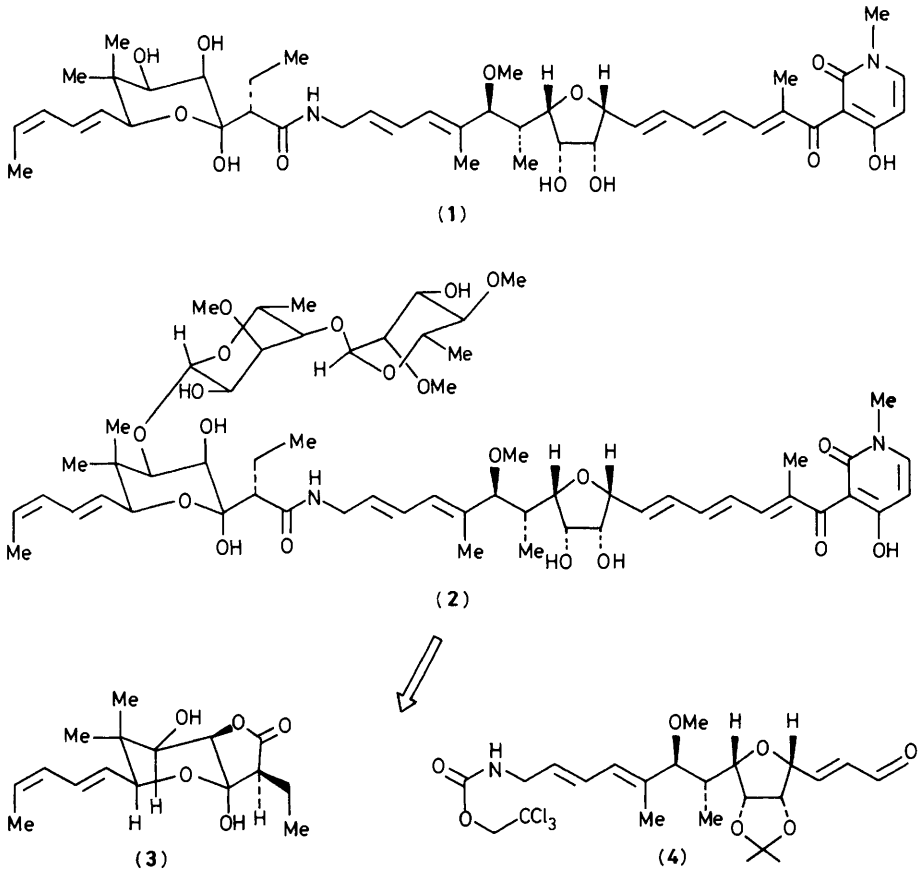
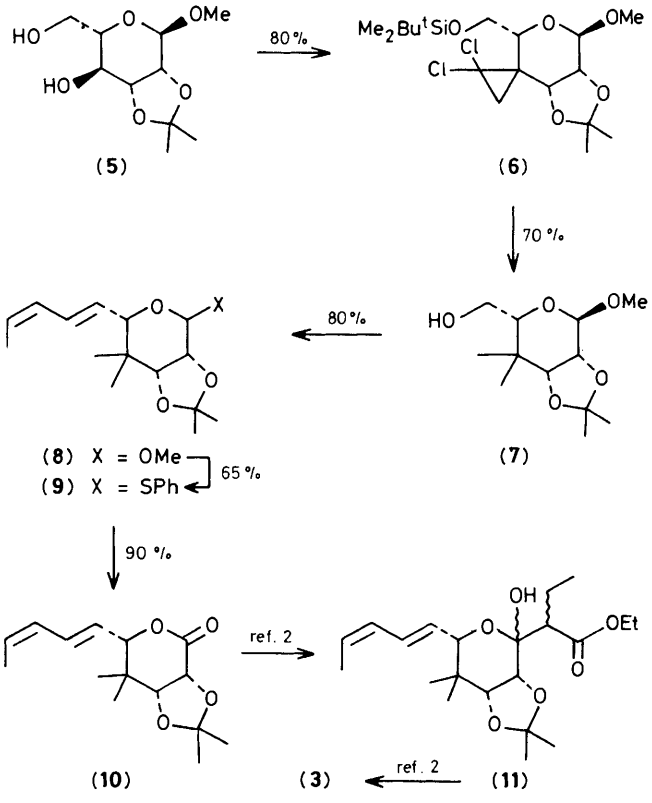
Carbohydrate-based syntheses of two key intermediates for the total synthesis of aurodox and efrotomycin are reported.

Aurodox (**1**) and efrotomycin (**2**) (Scheme 1) are two of the most important members of the elfamycin family of antibiotics.[1] We have recently reported the first total synthesis of these complex molecules in which fragments (**3**) (goldinonolactone) and (**4**) (Scheme 1) served as key intermediates.[2] Their construction was based on acyclic stereoselection techniques starting with prochiral compounds. In this communication, we describe alternative and efficient routes to these subtargets (**3**) and (**4**) based on a carbohydrate approach and chirally-rich starting materials. The readily available L-(−)-mannose derivative (**5**)[3] (Scheme 2), containing three of the five stereocentres of goldinonolactone (**3**), was recognized as a potential precursor of this intermediate. Thus, monosilylation† of (**5**) (1.1 equiv. Bu^tMe_2SiCl, 1.3 equiv.

† All new compounds exhibited satisfactory spectroscopic and analytical data.



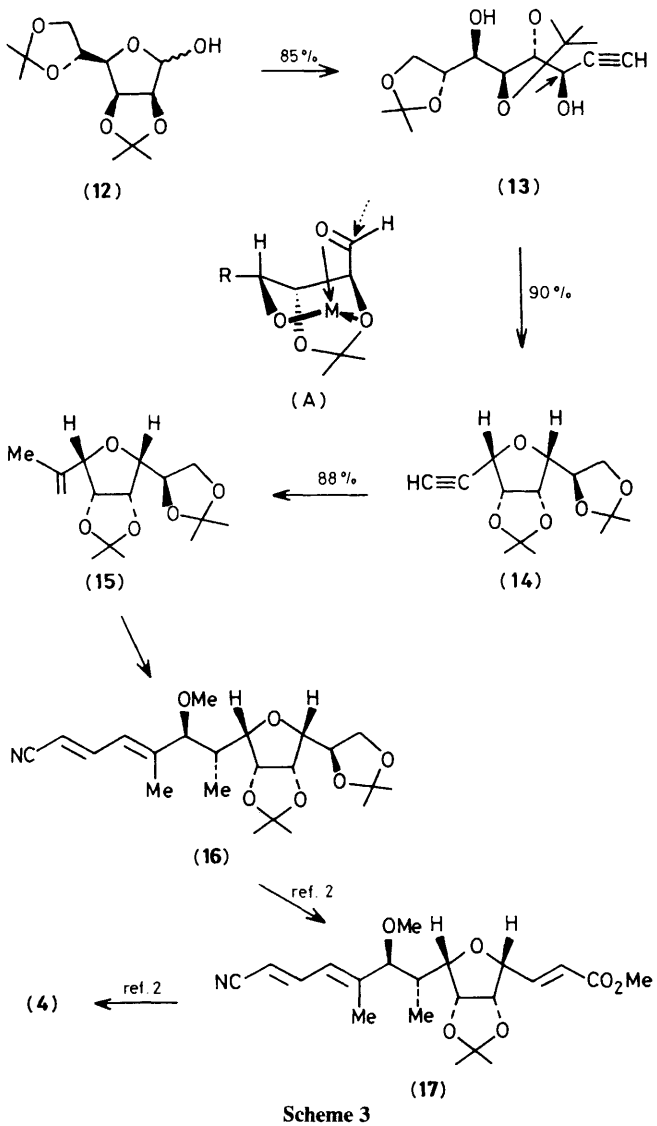
Scheme 1



Scheme 2

imidazole, dimethylformamide, 0 → 25 °C) followed by oxidation [1.2 equiv. $(CF_3CO)_2O$, 1.2 equiv. Me_2SO, 5.0 equiv. Et_3N, CH_2Cl_2, −78 → 25 °C] and then olefination (2.5 equiv. $Ph_3P{=}CH_2$, toluene, 0 → 45 °C) and dichlorocarbene addition[4] ($CHCl_3$, excess of powdered NaOH, cat. $C_{16}H_{33}NMe_3{}^+Br^-$, 25—60 °C) afforded the adduct (**6**), in 80% overall yield. Sequential reduction of (**6**) first with $LiAlH_4$ [1.0 equiv., tetrahydrofuran (THF), reflux], and then hydrogen (cat. Pt, AcOH, 400 psi, 30 °C) led to the *gem*-dimethyl compound (**7**) in 70% overall yield from (**6**). Oxidation of (**7**) to give the corresponding aldehyde (1.5 equiv. $CrO_3 \cdot HCl \cdot$ pyridine, 4 Å molecular sieve, CH_2Cl_2, 0 → 25 °C) and condensation with the anion of *cis*-crotyldiphenylphosphine oxide[5] (2.0 equiv. oxide, 2.0 equiv. Bu^nLi, THF, −110—25 °C) furnished stereoselectively diene (**8**) in 80% overall yield. Transformation of (**8**) to (**10**) required the intermediacy of phenylthioglycoside (**9**) formed by exchange of the 1-substituent with SPh (3.0 equiv. $PhSSiMe_3$, 3.0 equiv. ZnI_2, 2.0 equiv. $Bu^n{}_4NI$, $ClCH_2CH_2Cl$, 80 °C, 65% yield)[6] cleavage (1.2 equiv. *N*-bromosuccinimide, MeCN–H_2O, 0 °C)[7] and oxidation [1.5 equiv. $CrO_3 \cdot HCl \cdot$ pyridine, 4 Å molecular sieve, CH_2Cl_2, 0 → 25 °C, 90% yield from (**9**)]. Conversion of (**10**) into (**3**) *via* (**11**) has been described previously.[2]

D-Mannose diacetonide (**12**)[8] (Scheme 3) containing three of the stereocentres of the tetrahydrofuran fragment (**4**) and the necessary functionality for further elaboration served as an excellent precursor for this construction. Thus, compound (**12**) reacted according to Buchanan's procedure[9] with excess of HC≡CMgBr in THF (10 °C), presumably by a 'chelation controlled' mechanism [see transition model (A), Scheme 3], to afford diol (**13**) in *ca.* 15:1 stereoselectivity and in 85%



Scheme 3

yield. Following a chemoselective tosylation at the propynylic position (1.1 equiv. *p*-$MeC_6H_4SO_2Cl$, pyridine, 0—25 °C), an internal displacement by the remaining hydroxy group (25—60 °C) resulted in the formation of the tetrahydrofuran system (**14**) with the correct stereochemistry (90%, note inversion at the propynylic position).[9] Regioselective methylation of (**14**) [1.1 equiv. $AlMe_3$, 1.1 equiv. $Zr(\eta^5\text{-}C_5H_5)_2Cl_2$, PhMe, −78—25 °C][10] led to the terminal alkene (**15**) in 88% yield which was then converted into the advanced intermediate (**16**) by a sequence previously described for a related intermediate (involving asymmetric hydroboration, oxidation, organometallic addition, hydrolysis and two phosphonate condensations).[2] Selective monodeacetonization ($AcOH\text{–}H_2O$, 3 : 1, 60 °C) followed by cleavage of the resulting 1,2-diol (1.2 equiv. $NaIO_4$, $MeOH\text{–}H_2O$, 1 : 1, pH 12) led to the corresponding aldehyde which was sequentially converted into (**17**) and (**4**) as previously reported.[2]

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