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Enantiospecific Synthesis of *C*-Methyl Azidoinositols and Aminocyclitols from Toluene

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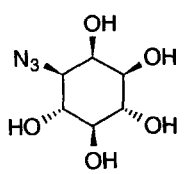
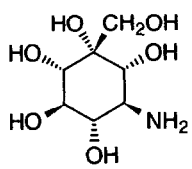
Abstract: The total synthesis of the homochiral *C*-methyl azidoinositols (**9**), (**17**) and (**20**), and the aminocyclitols (**10**), (**18**) and (**21**) from toluene has been achieved, *via* the key steps of microbial oxidation of toluene and photo-oxidation of the resulting cyclohexadienediol (**4**).

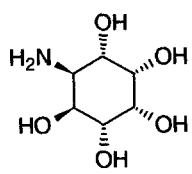
The importance of the aminoglycoside antibiotics[1] ensures that there is continuing interest in the synthesis of aminocyclitols, both as naturally-occurring isomers[2,3] and as synthetic analogues.[3,4] The ability of various aminocyclitols to act as powerful glycosidase enzyme inhibitors[5] adds further relevance to this area. In addition, Kozikowski and co-workers have found that azidoinositols such as the *myo* isomer (**1**) can have an inhibitory effect on the growth of tumour cells.[6] Recently published routes to chiral aminocyclitols have used a variety of approaches: the *myo*-configuration aminocyclitol (**2**) has been synthesised from D-glucose utilising Ferrier cyclisation,[7] whereas the azidoinositol (**1**)[6] was prepared from the cyclitol L-quebrachitol, which occurs in rubber latex. Examples of enantiospecific syntheses from symmetrical intermediates are fewer:[3] the *allo*-aminocyclitol (**3**) has been prepared *via* a chiral Diels-Alder cycloaddition of a nitrosodienophile to *cis*-cyclohexa-3,5-diene-1,2-diol diacetate.[8] We now describe enantiospecific total syntheses of three *C*-methyl azidoinositols [(**9**), (**17**), (**20**)], and the corresponding aminocyclitols (**10**), (**18**) and (**21**), starting from toluene and using microbial oxidation as the source of homochiral intermediates.



(1)

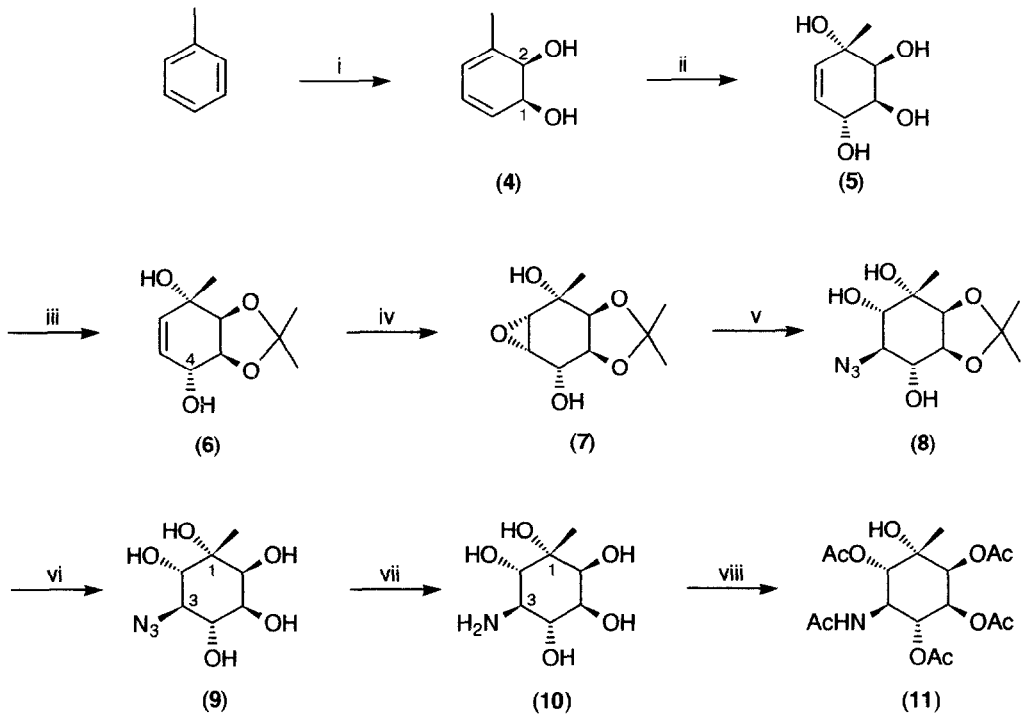


(2)



(3)

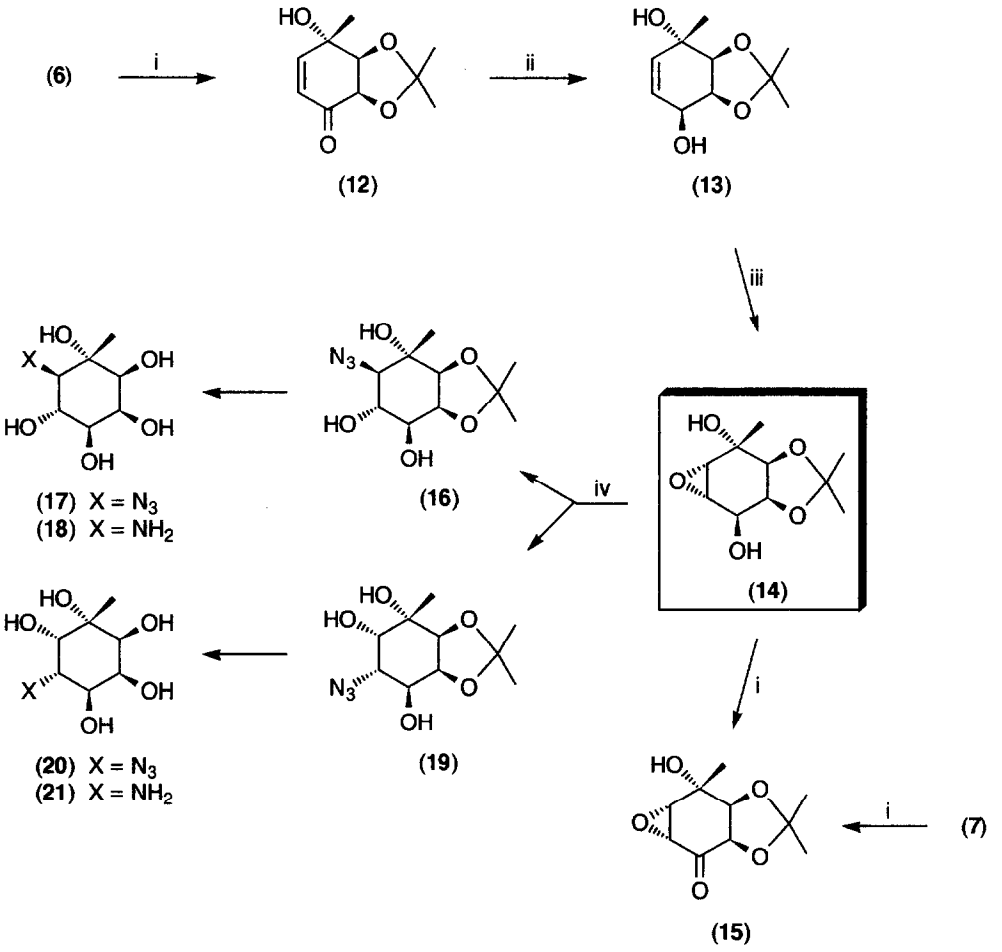
Microbial oxidation of toluene by *Pseudomonas putida* mutants gave the chiral cyclohexadienediol (**4**) (>98% *ee*) having (1*S*,2*R*) stereochemistry.[9] Dye-sensitised photo-oxidation of (**4**), followed by thiourea reduction, gave the tetrol (**5**) as major product,[10] as a result of attack by $^1O_2$ *anti* to the hydroxyl groups of the cyclohexadiene system. Isopropylidenation of (**5**) and epoxidation of the bis-allylic alcohol (**6**) gave a single stereoisomer of epoxide (**7**). Ring opening of the epoxide (**7**) by azide ion proceeded regioselectively, to afford in 71% yield the protected azidoinositol (**8**) having the *chiro*-configuration. Acid-catalysed hydrolysis gave 1L-1-*C*-methyl-3-azido-3-deoxy-*chiro*-inositol (**9**). Hydrogenation using platinum yielded the corresponding *chiro*-aminocyclitol (**10**), additionally purified as its penta-acetate (**11**).



Scheme 1: **i**, *Pseudomonas putida*; **ii**, O_2, CH_2Cl_2, methylene blue, hν; then thiourea, MeOH, 18 h (53%); **iii**, Me_2CO, $(MeO)_2CMe_2$, TsOH (92%); **iv**, *m*-CPBA, CH_2Cl_2, 2 days (61%); **v**, DMF, H_2O (20:1), NaN_3, reflux, 20 h (71%); **vi**, HOAc, H_2O (1:9), 80°C, 1 h (96%); **vii**, Pt, H_2, 50 psi, EtOH, 4 h (92%); **viii**, Ac_2O, pyridine (83%).

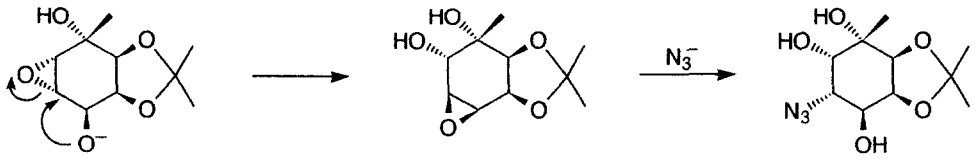
To gain access to the *myo*-inosamine stereochemistry, it was necessary to change the configuration at C-4 in the protected tetrol (**6**). This was achieved by tetrapropylammonium perruthenate (TPAP) oxidation (73%),[11] followed by Luche reduction[12] of the enone (**12**) (57%). Epoxidation of the bis-allylic alcohol (**13**) gave a single stereoisomer of epoxide (**14**), whose configuration was confirmed from the fact that both it and epoxyalcohol (**7**) were oxidised in good yield by TPAP to the same αβ-epoxyketone (**15**).

The key intermediate (**14**) underwent ring opening by heating with sodium azide in DMF/water, to give a mixture of azidoalcohols in which the two main components were (**16**) and (**19**), separated in 30% and 25% yields, respectively (Scheme 2). The *myo* configuration of (**16**) was clearly shown from ^{1}H nmr coupling constants, and it was converted to 1D-4-*C*-methyl-5-azido-5-deoxy-*myo*-inositol (**17**) and the corresponding *myo*-inos-5-amine (**18**) by similar reactions to those shown in Scheme 1.



Scheme 2: **i**, TPAP, *N*-methylmorpholine-*N*-oxide, CH_2Cl_2, 4 Å molecular sieves (73-79%); **ii**, $CeCl_3.7H_2O$, $NaBH_4$, MeOH (57%); **iii**, *m*-CPBA, CH_2Cl_2, 4 days (70%); **iv**, DMF, H_2O (20:1), NaN_3, reflux, 14 h.

Compound (**19**) proved to have the *neo*-inositol configuration and was converted to 1L-1-*C*-methyl-3-azido-3-deoxy-*neo*-inositol (**20**) and then to the corresponding *neo*-inos-3-amine (**21**). The *neo*-inositol stereochemistry is seen as arising from Payne rearrangement[13] of the epoxyalcohol (**14**) to give epoxide (**22**), and subsequent azide ring opening to give (**19**), as shown in Scheme 3.



(22) (19)

Scheme 3

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