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An Application of Quinic acid to the Synthesis of Linear Homochiral Molecules: A Synthesis of (+)-Negamycin.

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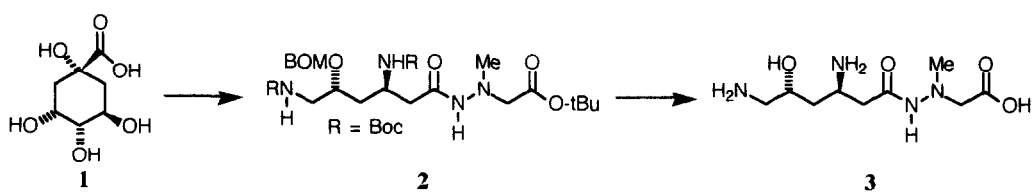
Abstract: The use of quinic acid for the synthesis of linear molecules is demonstrated by an efficient stereoselective synthesis of the antibiotic (+)-negamycin.



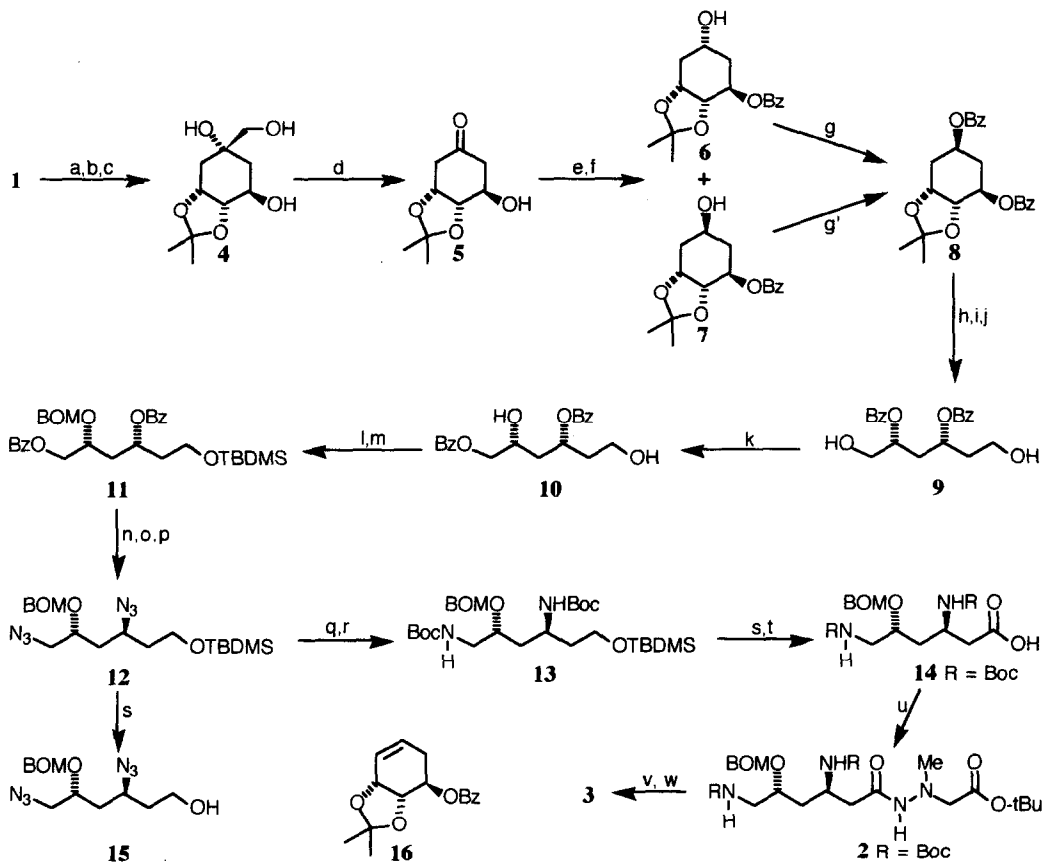
1 2 3

Scheme 1.

Quinic acid **1** has recently become of interest as a starting material for organic synthesis. Most of these applications have been to the synthesis of cyclohexane derivatives[1-10] and little attention has been paid to its potential for the synthesis of linear molecules[11]. We present here a synthesis of the antibiotic (+)-negamycin **3** which demonstrates the versatility of quinic acid as a starting material in the synthesis of linear homochiral natural products. (+)-Negamycin was first isolated from the culture filtrates of three species of *Streptomyces purpeofuscus*[12,13] and shows potent antibacterial activity against Gram-negative strains. Since its discovery

several syntheses have been reported for both racemic[14-16] and optically active[17-20] forms of the parent compound and also of some analogues[16,18,19].

Compound **4** was prepared in high yield from quinic acid **1** using improved literature[2] procedures and oxidised using sodium periodate[21], to the ketone **5** which was benzoylated using standard reagents but with careful temperature control, to produce the corresponding benzoate. The elimination of benzoic acid occurred to a considerable extent at temperatures higher than 5°C and other acyl groups increased this tendency to eliminate. The planarity of the isopropylidene protected diol system causes the cyclohexane ring to adopt a boat conformation which places the benzoylated hydroxyl group in an axial position[22] facilitating elimination.



Scheme 2. (a,b,c,) See reference 2. (d) $NaIO_4$, H_2O, 25°C, pH 5-6, 95%. (e) BzCl, Pyridine, DMAP, 0°C, 90%. (f) $NaBH_4$, EtOH, 25°C, 24% epimer **1S** e 74% epimer **1R**. (g) BzOH, DEAD, TPP, THF, 25°C, 50%. (g') BzCl, Pyridine, DMAP, 25°C, 90%. (h) 1,2-Ethanedithiol, $BF_3.OEt_2$, CH_2Cl_2, 25°C, 99%. (i) $Pb(OAc)_4$, CH_2Cl_2, 0°C, 98%. (j) $NaBH_4$, EtOH, 25°C, 97%. (k) $(i\text{-}Pr)_2NEt$, CH_2Cl_2, 25°C, 88%. (l) TBDMSCl, $(i\text{-}Pr)_2NEt$, DMAP, CH_2Cl_2. (m) BOMCl, $(i\text{-}Pr)_2NEt$, DMAP, CH_2Cl_2, 79% (steps l,m). (n) KOH, MeOH, 25°C, 92%. (o) MsCl, DMAP, Pyridine, 25°C, 98%. (p) NaN_3, DMF, 80°C, 88%. (q) H_2, Pd/C:5%, EtOH, 25°C. (r) Boc_2O, $(i\text{-}Pr)_2NEt$, $CHCl_3$, reflux., 84% (steps q,r). (s) Bu_4NF, THF, 25°C, 97%. (t) $NaIO_4$, $RuCl_3$ (cat.), CH_3CN, CCl_4, H_2O, 25°C, 82%. (u) $ClCO_2Et$, Et_3N, t-butyl N-methylhydrazinoacetate, CH_2Cl_2, -10 to -5°C, 98%. (v) 10% Pd/C-H_2. (w) CF_3COOH.

Reduction of the ketone **5** afforded a 3:1 mixture of the diastereoisomers **6** and **7** which were easily separated by chromatography. The isomer **7** $[\alpha]_D$= -97.8, (c=1.11, $CHCl_3$) has the desired configuration and was benzoylated using benzoyl chloride to give **8** $[\alpha]_D$= -24.3, (c=1.20, $CHCl_3$). This compound was also prepared from the alcohol **6** $[\alpha]_D$= -63.5, (c=1.53, $CHCl_3$) by using the Mitsunobu inversion procedure[23]. The moderate yield for the inversion process is due to the simultaneous and selective formation of the unsaturated compound **16** $[\alpha]_D$= -134.6, (c=1.74, $CHCl_3$), which is formed in a competing elimination reaction which is promoted by the conformation of the molecule[24]. Compound **16** is formed exclusively when no benzoic acid is included in the reaction mixture. Mitsunobu inversion of the epimeric alcohol **7** affords exclusively the expected benzoate and no elimination. Treatment of the dibenzoate **8** with 1,2-ethanedithiol and $BF_3.OEt_2$ afforded the corresponding diol which was cleaved using lead tetraacetate to yield the dialdehyde which was reduced immediately to the diol **9** $[\alpha]_D$= +16.5, (c=2.02, $CHCl_3$) using borohydride. No epimerisation at the benzoate groups was observed (nmr) during this process. At this stage we had in hand a compound with two primary hydroxyl groups which were difficult to differentiate by intermolecular reactions.Treatment of this diol **9** with diisopropylethylamine, however, resulted in the preferential 1,4-migration of the benzoyl group over the other possible 1,5-migrations. By controlling the reaction time it was possible to isolate the required compound **10** $[\alpha]_D$= -2.7, (c=1.43, $CHCl_3$) in 88% yield. Other bases were tested for this process; the migration in all other cases were either too slow or too rapid to be useful. The remaining primary hydroxyl group was selectively protected with the TBDMS group and the secondary hydroxyl with the benzyloxymethyl (BOM) group affording **11** $[\alpha]_D$= +4.0, (c=3.37, $CHCl_3$). Hydrolysis of the benzoate esters was affected using KOH in methanol and the resulting diol converted to the dimesylate. Displacement of the mesylates by the azido group was easy and compound **12** $[\alpha]_D$= -3.2, (c=0.23, $CHCl_3$) obtained in high yield. Its stereochemistry was confirmed by conversion to the known alcohol **15** and comparison of its physical properties[26] with those in the literature[20]. Compound **15** has previously been converted to (+)-negamycin and so ours, up to this stage, constitutes a formal synthesis. We continued, however, to study a variation on the published scheme and the use of other protecting groups. The diazide **12** was reduced to the diamine in the presence of the BOM group by using 5%Pd/C-H_2 without causing cleavage of the latter. The resulting amino groups were protected as their BOC derivatives, compound **13** $[\alpha]_D$= -25.8, (c=1.35, $CHCl_3$), the silyl group removed with fluoride[27] and the primary alcohol group oxidised to the corresponding carboxylic acid **14** $[\alpha]_D$= -8.3, (c=4.92, $CHCl_3$) using catalytic ruthenium oxidation ($NaIO_4$/$RuCl_3$)[28]. It has been reported[20] that the BOM group interferes during these oxidations. In our hands the process resulted in a high yield of the required product with very little, if any, interference from the BOM protecting group. The hydrazide **2** $[\alpha]_D$= -12.9, (c=5.18, $CHCl_3$) was prepared in high yield from **14** by formation of its mixed anhydride with ethyl chloroformate and subsequent reaction of the activated carbonyl with tert-butyl N-methylhydrazinoacetate. The use of the BOM group allows for selective liberation of the hydroxyl group by hydrogenolysis. Treatment of the product of this process with trifluoroacetic acid removed the BOC and t-butyl ester functions, affording the trifluoroacetate salt of (+)-negamycin[29]. A synthesis of the **3S** epimer is also possible by only slight modification of this scheme. It is also possible to invert the configuration of the other chiral centre at an early stage during this synthesis thus making all four stereoisomers of negamycin available.

Quinic acid is a very versatile starting material for homochiral synthesis. The benzoyl migration process can be very useful synthetic trick to overcome problems of selectivity at hydroxyl groups.

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24. Compound **6** adopts the boat form as was evident from the observed vicinal coupling constants for the ring protons.
25. The absence of diastereoisomers was indicated by nmr and chromatographic analysis.
26. $[\alpha]_D$ = + 29.5, c = 1.83, CH_2Cl_2, Lit.[20] $[\alpha]_D$ = + 27.5, c = 2.85 CH_2Cl_2.

    ^1H NMR (300 MHZ, $CDCl_3$) δ: 7.357 and 7.342 (5H, ss, Ar); 4.886 (1H, AB d, J = 6.5, one of $OC\underline{H_2}OBn$); 4.833 (1H, AB d, J = 6.5, one of $OC\underline{H_2}OBn$); 4.696 (1H, AB d, J = 11.5, one of $OCH_2OC\underline{H_2}Ph$); 4.656 (1H, AB d, J = 11.5, one of $OCH_2OC\underline{H_2}Ph$); 3.964 - 3.890 (1H, m, J = 10.0, 3.0, C-2 C<u>H</u>); 3.741 (3H, t, J = 6.0, C-6 $C\underline{H_2}$ and C-4 C<u>H</u>); 3.524 (1H, ABX dd, J = 13.0, 4.0, C-1 one of $C\underline{H_2}$); 3.299 (1H, ABX dd, J = 13.0, 4.0, one of $C\underline{H_2}$); 1.997 (1H, s, O<u>H</u>); 1.868 - 1.755 (3H, m, C-5 $C\underline{H_2}$ and C-3 one of $C\underline{H_2}$); 1.576 (1H, ABMX h, J = 13.5, 10.0, 3.0, C-3 one of $C\underline{H_2}$).
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29. The proton nmr of this compound was consistent with the structure proposed.

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