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ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-NEGAMYCIN

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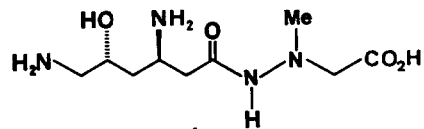
Summary. An efficient enantioselective total synthesis of the antibiotic (+)-negamycin is described, the absolute stereochemistry deriving from (R)-(+)-malic acid and subsequent use of the Sharpless asymmetric epoxidation reaction.

Negamycin (2-[(3R,5R)-3,6-diamino-5-hydroxyhexanoyl]-1-methylhydrazinoacetic acid) 1 is an unusual hydrazide antibiotic, isolated[1a] from Streptomyces purpeofuscus, which displays strong inhibitory activity against Gram-negative bacteria. Following the structural determination[1b] a good deal of synthetic work has been devoted to this interesting target molecule, and several syntheses of the antibiotic in both racemic[2a-c] and optically active[3a-c] form have been reported as well as a route to the 3-aza-analogue[4]. The present paper describes an efficient, highly stereocontrolled and relatively brief enantioselective total synthesis of the title antibiotic (see Scheme 1).



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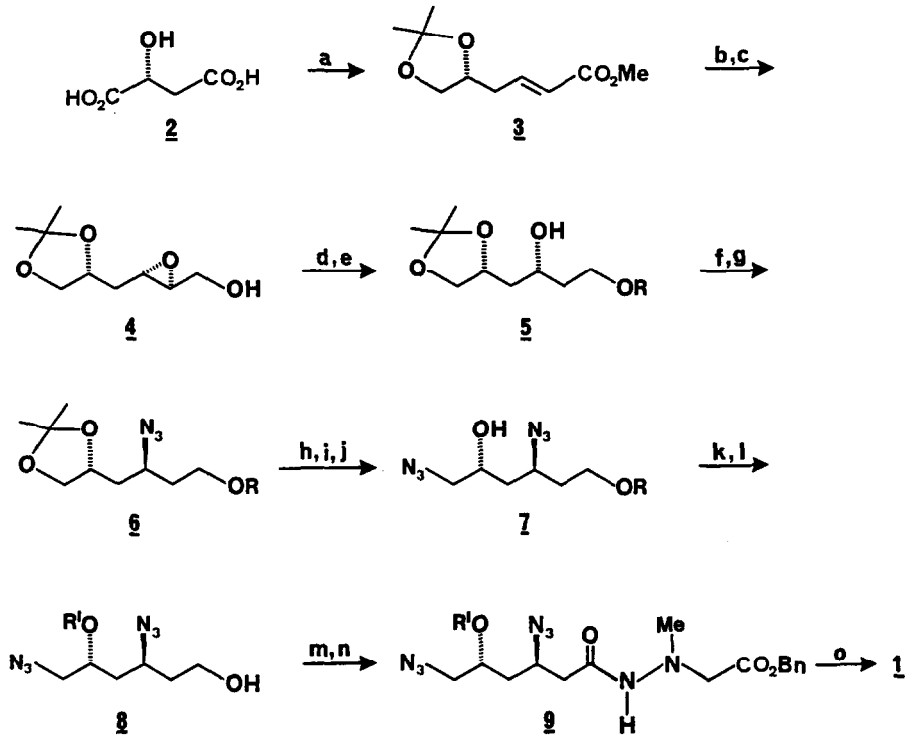
Standard chemistry[5,6,7] was used to convert commercially available (R)-(+)-malic acid (2, Aldrich) to the trans-α,β-unsaturated ester 3 ($[\alpha]_D$ +11.63°, c = 1.07,CH_2Cl_2). After DIBAL reduction the resultant allylic alcohol was subjected to the catalytic version[8] of the Sharpless asymmetric epoxidation reaction to yield 4 ($[\alpha]_D$ -34.0°, c = 1.00,CH_2Cl_2) as a single diastereomer within the limits of high-field NMR-spectroscopic detection. Regioselective (C-2) ring-opening of this epoxy alcohol by means of Red-Al in THF[9] led to the relevant 1,3-diol, the primary hydroxyl of which was protected selectively[10] as the ^{t}butyldiphenylsilyl ether (5, $[\alpha]_D$ -3.00°, c = 2.80,CH_2Cl_2). The free secondary hydroxyl was then mesylated and the leaving group displaced smoothly in S_N2 fashion by sodium azide, furnishing 6 ($[\alpha]_D$ +12.6°, c = 1.00,CH_2Cl_2). The acetonide moiety of 6 was



R = Si^tBuPh_2, R^1 = CH_2OCH_2Ph

SCHEME 1. (a) See refs. 5,6,7. (b) DIBAL,CH_2Cl_2,-78°C, 96% yield. (c) (+)-DET,Ti(O^iPr_4),TBHP,CH_2Cl_2,-20°C, 92%. (d) Red-Al,THF,-40°C to RT, 98%. (e) $^tBuPh_2SiCl$,DMAP,NEt_3,CH_2Cl_2,RT, 89%. (f) MsCl,THF,0°C, 100%. (g) NaN_3,15-crown-5 (cat.),DMF,50°C, 99%. (h) $CuCl_2.2H_2O$,EtOH,RT, 87%. (i) pTsCl,pyridine,-20°C, 92%. (j) as for (g), 91%. (k) BOMCl,$^iPr_2NEt$, CH_2Cl_2,RT, 93%. (l) $^nBu_4NF$,THF, 94%. (m) $RuCl_3$ (cat.),$NaIO_4$,$CH_3CN/CCl_4/H_2O$, RT, 67%. (n) $ClCO_2Et$,NEt_3,toluene,-5°C,then benzyl(1-methylhydrazino)-acetate, 63%. (o) H_2,Pd-C,MeOH/AcOH.aq, 89%.

dismantled *via* the mild and efficacious method of Iwata and Ohrui[11] and after selective tosylation of the resultant 1,2-diol at the primary site use of sodium azide in DMF yielded the bis-azide 7 (IR: 2150 cm^{-1} (vs), $[\alpha]_D$ +8.83°, c = 0.60, CH_2Cl_2). The remaining secondary alcohol function was then protected as the benzyloxymethyl (BOM) ether and the silyl ether cleaved by fluoride anion in THF[12]. Primary alcohol 8 ($[\alpha]_D$ +27.5°, c = 2.85 CH_2Cl_2) was then oxidised[13] carefully (with some not unexpected interference from the BOM protecting group) to the corresponding acid (structure not shown, IR: 1715 cm^{-1} (s), $[\alpha]_D$ +30.1°, c = 0.45, CH_2Cl_2) which was coupled using the mixed anhydride method[14] with the known[4] benzyl(1-methylhydrazinoacetate to yield hydrazide 9. This material displayed a temperature-dependent ^1H NMR spectrum (270 MHz, $C_2Cl_4D_2$ solution, +30° to +120°C, all spectral changes being reversible) consistent with the presence of amide-type rotamers. The key coupling reaction proceeded smoothly in 63% isolated yield and compound 9 could subsequently be transformed in a one-pot hydrogenolysis reaction (entailing removal of both the protecting groups and reduction of both the azide moieties) to the desired (+)-negamycin in 89% isolated yield after purification[2b]. The spectral and physical data of our synthetic material were in excellent accord with the literature values[15], the 270 MHz ^1H NMR spectrum being identical to that kindly provided by Professor Chihiro Kibayashi. The antibiotic was thus synthesised in its natural form in 14 steps and 18% overall yield from the readily available 3, and we have used the present methodology to prepare a 2.5-gram quantity of the key (bis-azido)alcohol 8[16].

In conclusion, we would like to point out that the present route is potentially very flexible in that by suitable combinations of a given enantiomer of the malic acid starting material with the appropriate enantiomer of the tartrate auxiliary used in the asymmetric epoxidation step, both enantiomers of negamycin should be equally easily available as well as the epinegamycins[2c,3c].

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REFERENCES and NOTES

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