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AZINOTHRICIN SYNTHETIC STUDIES. 1. EFFICIENT ASYMMETRIC SYNTHESES OF *(3R)*- AND *(3S)*-PIPERAZIC ACIDS

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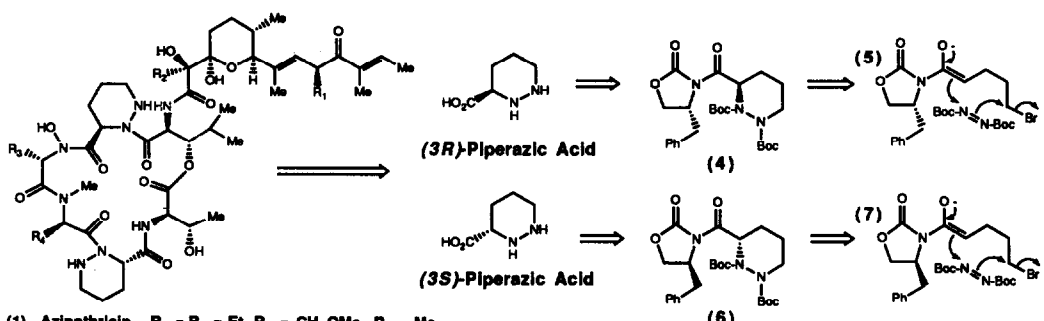
Summary: A convenient asymmetric synthesis of both *(3R)*- and *(3S)*-piperazic acids has been developed that is based on electrophilic hydrazination of a chiral bromovaleryl carboximide enolate with di-*tert*-butyl azodicarboxylate, followed by subsequent intramolecular S_N2 displacement of the bromide by the resulting substituted aza anion. The diastereoselectivity of the process is typically greater than 96%.

For our total synthesis programme on the Azinothricin family of antitumour antibiotics (**1-3**),[1,2] we recently required a convenient method for obtaining large quantities of *(3R)*- and *(3S)*-piperazic acids[3] in high optical purity. The technology currently available for preparing these enantiomers consists of a four-step cycloaddition sequence to *(3RS)*-N^1-benzyloxycarbonylpiperazic acid,[3] an optical resolution of the racemate with (+)- and (-)-ephedrines,[4] and a deprotection of the benzyloxyurethane group with hydrogen-bromide in acetic acid. Typically, this procedure delivers each enantiomer in approximately 1.5% overall yield and is very uneconomical to operate on large scale. In this letter, we wish to report an efficient four-step asymmetric synthesis of both *(3R)*- and *(3S)*-piperazic acids, that proceeds in 48% overall yield and which gives each antipode in ee's greater than 96%.

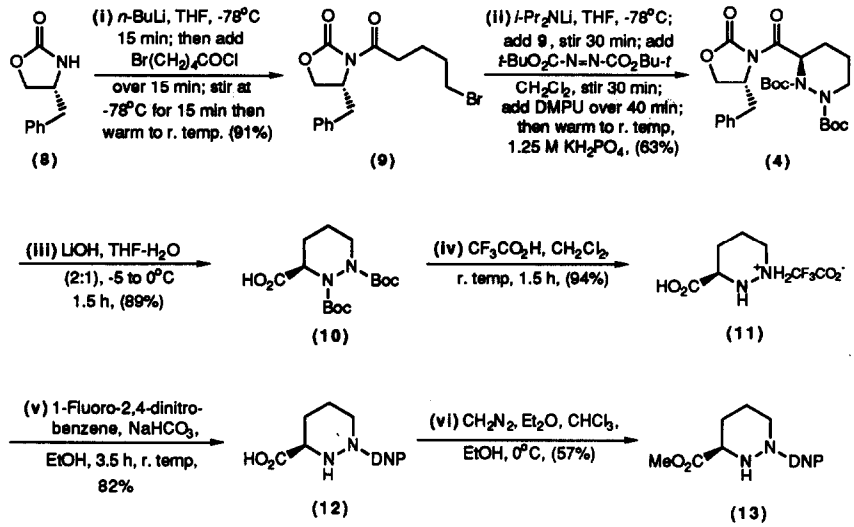


(1) Azinothricin, $R_1 = R_2 = Et$, $R_3 = CH_2OMe$, $R_4 = Me$.
(2) A83586C, $R_1 = R_3 = R_4 = Me$, $R_2 = Et$.
(3) Citropeptin, $R_1 = R_2 = Me$, $R_3 = CH_2OMe$, $R_4 = CH_2CH(Me)_2$.

Our retrosynthetic planning for *(3R)*- and *(3S)*-piperazic acids called for stereoselective Evans-Vederas[5,6] alkylation of chiral bromovaleryl carboximide enolates **5** and **7** with di-*tert*-butyl azodicarboxylate (DBAD). In both cases, this was expected to regiospecifically generate a stabilised N^1-aza anion that could participate in intramolecular nucleophilic displacement of the bromide to give **4** and **6** respectively. Subsequent hydrolysis of the chiral auxiliary and *N*-deprotection would then afford the target α-hydrazino acids.

In the case of *(3R)*-piperazic acid, the pivotal intermediate for testing this proposal was compound **9**. It was prepared in 91-96% yield by deprotonating *(4R)*-(phenylmethyl)-2-oxazolidinone (**8**) with *n*-butyllithium (1.0 equiv., 1.6 M in hexanes) at -78°C for 15 min,[5] and slowly adding neat 5-bromovaleryl chloride over 15 min (Scheme 1). After warming the reactants to room temperature, conventional extractive workup with sat. NH_4Cl and dichloromethane

Scheme 1



furnished a syrup that crystallised (m.p. 66-67°C) from ether-light petroleum on storage at 0°C. The structure of **9**[7] was apparent from inspection of its ^{13}C NMR spectrum; specifically, there were resonances at δ 172.5 and 153.3 ppm, which were highly characteristic of carbonyl groups in an *N*-acylated oxazolidinone.[5] In addition, the IR spectrum of **9** contained two intense carbonyl absorptions at 1786 and 1698 cm^{-1}, while the mass spectrum displayed a molecular ion peak at m/e 340. Microanalytical data further corroborated the identity of **9**, indicating an empirical formula of $C_{15}H_{18}NO_3Br$.

Enolisation of bromide **9** was accomplished using the Evans procedure,[5] wherein a precooled solution of **9** in THF (*ca.* 0.8 M) was added to lithium diisopropylamide (1.0 eq.) in THF (*ca.* 0.8 M) at -78°C. After stirring the reactants for 30 min, a precooled solution of di-*tert*-butylazodicarboxylate (1.2 eq.) in dichloromethane (*ca.* 0.66 M) was added to **5** in one portion, and the mixture maintained at -78°C for a further 30 min. Although electrophilic hydrazination proceeded at -78°C, cyclisation to **4** only occurred in good yield when 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (26 eq.) was introduced over a 30-40 min period, and the frozen reactants allowed to warm to room temperature for 15 min. After diluting with ether and excess 1.25 M KH_2PO_4 buffer, the products were rapidly extracted several more times into ether, and the organic layer washed with sat. $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated *in vacuo*.[8] This gave a crude syrup that was purified by flash chromatography to remove DBAD by-products; compound **4**[7] was isolated in 63% yield. The ^1H NMR spectrum of **4** at 23°C was difficult to analyse due to extensive broadening of the resonances, arising from restricted rotation of the Boc groups; however, its features were in complete accord with the proposed structure.

In order to assess the diastereoselectivity of the α-hydrazination/cyclisation process, compound **4** was converted to known **13** by the following sequence of reactions. The first step entailed removal of the oxazolidinone moiety by treatment of **4** in THF (*ca.* 0.25 M) with lithium hydroxide (2.31 eq.) in H_2O (*ca.* 1.14 M), at -5°C for 1.5 h; this

delivered acid **10**[7] as an amorphous solid (m.p. 115-118°C) in 89% yield. The urethane protecting groups were then detached in 94% yield by reacting **10** with anhydrous trifluoroacetic acid (20 ml per mmol of **10**) in dichloromethane (*ca.* 0.3 M). This provided *(3R)*-piperazic acid trifluoroacetate salt (**11**)[7,9] which was selectively converted to its N^1-2,4-dinitrophenyl derivative (**12**)[7] {m.p. 150.5-151.5°C, Lit.[4] m.p. 151.5-152°C, $[\alpha]_D$ +341° (*c*.1 MeOH), Lit.[4] $[\alpha]_D$ +324.6° (*c*.1 MeOH)} by treatment with excess 1-fluoro-2,4-dinitrobenzene (18.7 eq.) and sodium bicarbonate (11.1 eq.) in ethanol (*ca.* 0.1 M). The 400 MHz ^{1}H NMR spectrum of **12** was identical to that of a sample prepared from authentic *(3S)*-piperazic acid. Methylation of **12** with excess ethereal diazomethane gave **13**[7] as a yellow crystalline solid, whose enantiomeric purity was judged to be at least 96% by HPLC comparison with methyl *(3RS)*-N^1-(2,4-dinitrophenyl)piperazate on a CHIRALCEL™ high-performance analytical column. Compound **13** had a retention time of 27.6 min on this column using 75:25 Hexane/Isopropanol as eluant.

We have also synthesised methyl *(3S)*-N^1-(2,4-dinitrophenyl)piperazate[7] by the above route starting from *(4S)*-(phenylmethyl)-2-oxazolidinone, and determined its ee to be greater than 96% by chiral HPLC analysis. *(3S)*-N^1-(2,4-Dinitrophenyl)piperate had a retention time of 18.2 min on the above CHIRALCEL™ column when 75:25 Hexane/Isopropanol was employed as the eluant.

In conclusion, we have completed efficient, stereocontrolled, syntheses of *(3R)*- and *(3S)*-piperazic acids. Further progress towards the total synthesis of the Azinothricin family of antibiotics will be reported in due course.

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7. The structure assigned to this compound is accord with its MS, IR, 400 MHz ^1H, and 100 MHz ^{13}C NMR spectra. In addition, an analytical sample of this compound gave a satisfactory C, H, and N combustion microanalysis.
8. A small amount of hydrolysis (1-4%) of the chiral auxiliary occurs during the 1.25 M KH_2PO_4 quench; it is not reduced significantly by quenching with glacial acetic acid or with 10% aq. HCl. Acid **10** can be recovered in pure condition by acidification of the $NaHCO_3$ washings with 10% aq. HCl, and extraction with ethyl acetate.
9. We have prepared *(3RS)*-piperazic acid trifluoroacetate salt using the route of Dr. Durette *et al.* (ref. 2), and found it to be identical to **11** by 400 MHz ^1H NMR spectroscopy, and by subsequent chemical conversions.
10. **Selected** analytical data: **(9)** m.p. 66-67°C; $[\alpha]_D$ -83° (*c* 1, MeOH); 100 MHz ^{13}C NMR ($CDCl_3$): 172.5, 153.3, 135.1, 129.3,128.9, 127.3, 66.2, 55.0, 37.8, 34.5, 33.1, 31.9, 22.7; Anal. Calcd for $C_{15}H_{18}NO_3Br$: C, 52.95; H, 5.33; N, 4.12; Br, 23.49. Found: C, 52.79; H, 5.43; N, 4.02; Br, 23.39.
(4) $[\alpha]_D$ -34° (*c* 1, MeOH); 400 MHz ^1H NMR ($CDCl_3$): δ 7.34-7.15 (m, 5H), 6.01 (br s) and 5.74 (br d, 1H combined), 4.62 (br s, 1H), 4.19-3.86 (br m, 4H), 3.34 (br m, 1H), 3.1-2.54 (br m, 2H), 2.10-1.6 (br m, 3H), 1.45 (s) and 1.42 (s, 18H); EI mass spectrum M^+ 489; Anal. Calcd for $C_{25}H_{35}N_3O_7$: C, 61.33; H, 7.21; N, 8.58. Found: C, 61.17; H, 7.36; N, 8.31.
(10) m.p. 115-118°C; IR (KBr): 3209, 2986, 1738, 1705, 1667, 1456, 1431, 1394, 1371, 1163, 1136, 1090, 880, 753, 738 cm^{-1}.
(11) m.p. 147-149°C; 400 MHz ^1H NMR (D_2O): δ 3.87 (m, 1H), 3.30 (m, 1H), 3.19 (m, 1H), 2.17 (m, 1H), 1.90 (m, 3H); FAB Mass Spectrum : (M+1) 131; Anal. Calcd. for $C_7H_{11}N_2F_3O_4$: C, 34.43; H, 4.54; N, 11.48. Found: C, 34.64; H, 4.48; N, 11.38.
(12) m.p. 150.5-151.5°C, Lit.[4] m.p. 151.5-152°C; $[\alpha]_D$ +341° (*c* 1, MeOH), Lit.[4] $[\alpha]_D$ +324.6° (*c* 1, MeOH); 100 MHz ^{13}C NMR ($CDCl_3$): δ 175.7, 147.4, 138.4, 127.4, 122.3, 115.0, 57.3, 47.6, 27.6, 22.8; FAB Mass Spectrum: (M+1) 297; Anal. Calcd for $C_{11}H_{12}N_4O_6$: C, 44.6; H, 4.08; N, 18.91. Found:C, 44.48; H, 3.96; N, 18.76.
(13) m.p. 96-97.5°C, Lit.[3] m.p. 37-39°C; $[\alpha]_D$ +299° (*c* 1, $CHCl_3$), Lit.[3] $[\alpha]_D$ +250° (*c* 1, $CHCl_3$); 400 MHz ^1H NMR spectrum (C_6D_6): δ 8.12 (d, *J* = 2.7 Hz,1H), 7.68 (dd, *J* = 2.7, 9.3 Hz, 1H), 5.82 (d, *J* = 9.3 Hz, 1H), 3.40 (td, *J* = 3.4, 11.3 Hz, 1H), 3.18 (s, 3H), 3.12 (d, *J* =11.5 Hz, 1H), 2.61 (dt, *J* = 3.9, 12.6 Hz, 1H), 1.82 (m, 1H), 1.47 (m, 1H), 1.10-0.85 (complex m, 3H); FAB Mass Spectrum: (M+1) 311; Anal. Calcd. for $C_{12}H_{14}N_4O_6$: C, 46.45; H, 4.55; N, 18.06. Found: C, 46.40; H, 4.61; N, 17.86.

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