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AN ENANTIOSELECTIVE SYNTHESIS OF THE CARZINOPHILIN DEGRADATION PRODUCT (2S,3S) 4-AMINO-2,3-DIHYDROXY-3-METHYLBUTYRIC ACID

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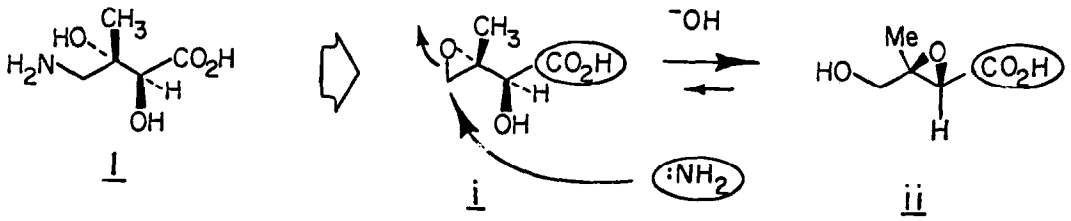
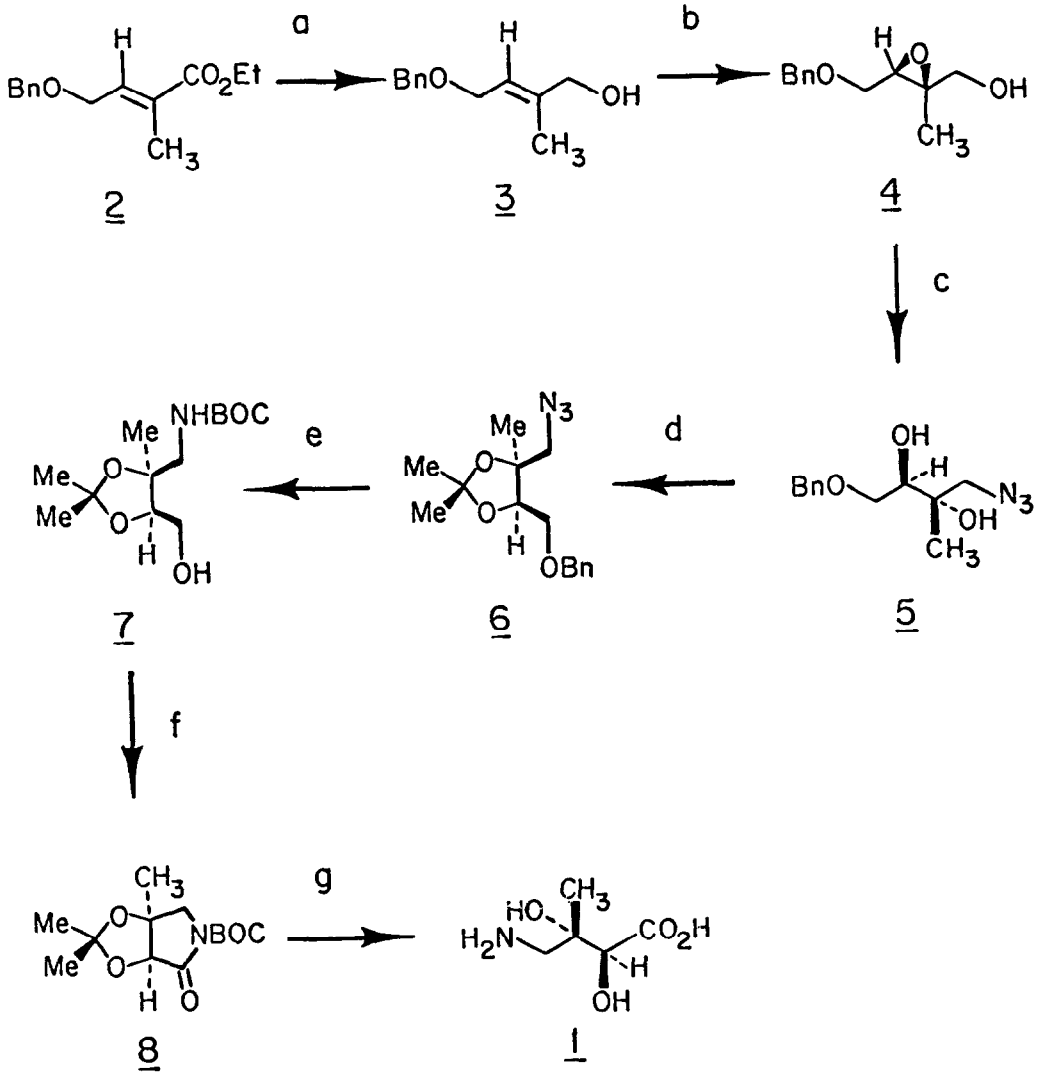
Abstract: An efficient, enantioselective synthesis of (2S,3S) 4-amino-2,3-dihydroxy-3-methylbutyric acid (1) is described. The sequence includes the direct use of azide to selectively open a secondary epoxy alcohol formed under Payne rearrangement conditions.

Carzinophilin is an antitumor antibiotic produced by **Streptomyces sahachiroi**. It selectively inhibits the synthesis of cellular DNA,[2] presumably via an intercalation/alkylation sequence that leads to covalently cross-linked DNA incapable of replication. Though it was first isolated and studied some 30 years ago, the gross structure of carzinophilin (based primarily on NMR evidence) has only recently been proposed.[2b] But some issues still remain, especially regarding stereochemistry. Early degradation work did however lead to the isolation of well defined products, one of which was identified as (2S,3S) 4-amino-2,3-dihydroxy-3-methylbutyric acid (1). Our interest in the carzinophilin problem and the synthesis of polyfunctional amino acids in general,[3] prompted us to pursue an efficient synthesis of the title compound 1, which we describe below. A related carzinophilin derived substance had been synthesized from D-glucose via a somewhat lengthier route.[2d]



Retrosynthetic analysis shows that the desired 2S,3S configuration would arise from nucleophilic opening of the terminal epoxide i as it is produced by a Payne rearrangement of epoxy alcohol ii. This strategy has been extensively investigated by Sharpless and Masamune over the last few years with numerous applications to the synthesis of sugars and related natural products.[4] However, the direct introduction of **nitrogen** at the primary site has to our knowledge been limited to the use of diethylamine and NaNHTs as nucleophiles. The preparation of primary azides under these equilibrating conditions has thus far been unsuccessful and a 4-step sequence is required to achieve such a transformation.[4b] We have found that a primary azide may be produced directly and selectively by simply including a phase-transfer catalyst in the reaction mixture. The ready preparation of optically active epoxy alcohols such as ii makes this approach all the more attractive.



(a) DIBAH, 0°C; (b) (-)-DIPT, $Ti(O^iPr)_4$, TBHP, -15°C; (c) 15 equiv. NaN_3, 5 equiv.(1:1) dioxane - 1N NaOH, 0.2 equiv. CTAB, 100°C; (d) DMP, cat. TsOH; (e) Na/NH_3 then $(BOC)_2O$, NaOH; (f) $NaIO_4$ + cat. $RuO_2.H_2O$, H_2O - acetone; (g) 1N HCl.

Thus, reaction of α-benzyloxyacetaldehyde[5] with $Ph_3PCH(Me)CO_2Et$ in CH_2Cl_2 at room temperature proceeded to give a 74% yield of substituted tiglates 2 (E:Z = 16:1 by ^1H NMR).[6] This mixture was reduced with DIBAH at 0°C to give pure allylic alcohol 3, isolated in 96% yield after chromatography. Enantioselective epoxidation according to Sharpless' procedure produced an optically active epoxy alcohol 4, $[\alpha]^{22}_D$+22° (c=0.87, $CHCl_3$), in 87% yield after chromatography. This material was shown to have an enantiomeric excess of 90% by a chiral LSR ^1H NMR experiment using 25 mol% $Eu(hfc)_3/CDCl_3$.[7] Heating a mixture of 4 and excess NaN_3 (15 equiv.) in (1:1) dioxane - 1N NaOH (5 equiv.) containing cetyltrimethylammonium bromide (CTAB - 0.2 equiv.) at 100°C led to the expected Payne rearrangement/epoxide opening and gave the desired azide-diol 5, $[\alpha]^{24}_D$+12.1° (c=2.19, $CHCl_3$), in 52% yield after chromatography.[8] **The use of a phase-transfer catalyst was found to be crucial for the success of this reaction.**[9] With compound 5 in hand the final series of reactions were quite straightforward. Thus temporary protection of the diol was achieved with DMP + cat. TsOH and produced the acetonide 6, $[\alpha]^{20}_D$-52.5° (c=1.86, $CHCl_3$), in 94% yield. Reduction with Na/NH_3 produced a γ-amino alcohol which was treated directly with $(BOC)_2O$ in aq. NaOH to give the N-protected alcohol 7, $[\alpha]^{22}_D$-30.7° (c=1.71, $CHCl_3$), in 60% yield. Oxidation with $NaIO_4$ + cat. RuO_4 resulted in the spontaneous formation of the crystalline bicyclic lactam derivative 8, mp 93°C, $[\alpha]^{26}_D$+43° (c=1.19, $CHCl_3$), in 71% yield. Finally, exhaustive hydrolysis of 8 with 1N HCl gave the desired γ-amino acid 1, mp 205-206°C, $[\alpha]^{26}_D$+18.2° (c=0.50, H_2O), in 74% yield after ion-exchange chromatography (H_2O then 1N HOAc/Bio-Rad AG 1-X, OH form). The physical and spectral properties (including a positive Cotton effect in the CD spectrum) of our synthetic material were consistent with those reported by Onda.[10]

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K. B. Sharpless, Aldrichimica Acta, 16, 67 (1983), and most recently (c) C. E. Adams, F. J. Walker, and K. B. Sharpless, J. Org. Chem., 50, 421 (1985).

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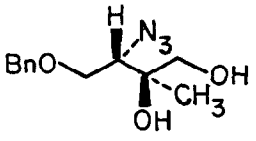
6. All compounds shown have been characterized by IR and 300 ^1H NMR spectroscopy.

7. $Eu(hfc)_3$: Tris[3-(heptaflouropropylhydroxymethylene)-d-camphorato], europium(III) derivative - Aldrich Chem. Co.

8. In addition to 5, two minor isomeric azide-diols 9, $[\alpha]^{23}_D$+57° (c=1.0, $CHCl_3$), and 10 (stereochemical assignment at C(2) is tentative) were isolated. That 9 was the product



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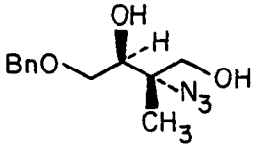

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of nucleophilic opening of epoxy alcohol 4 at C(3) was shown by preparing the corresponding diacetate (Ac_2O, C_5H_5N, cat. DMAP) and observing a downfield shift of ~1 ppm for the C(1) methylene protons only in the ^1H NMR spectrum.

9. HPLC analysis of the crude reaction mixture showed the clean formation of products 5, 9, and 10 in a ratio of 11.6:2.9:1.0. However, when this reaction was conducted without the CTAB catalyst, a new product ratio of 1.0:5.4:1.9 was observed with 5 now being the minor constituent! These results are consistent with the CTAB facilitating the Payne rearrangement (evident from TLC of the reaction mixture prior to heating) as well as forming the more nucleophilic, dioxane-soluble $CH_3(CH_2)_{15}(CH_3)_3N^+N_3^-$ species.

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300 ^1H NMR data for synthetic 1/D_2O relative to TSP-d_4 (0.00 ppm): δ1.27 (s, 3H), δ3.03 (d, J=13.2 Hz, 1H), δ3.25 (d, J=13.2 Hz, 1H), δ3.95 (s, 1H).

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