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TOTAL STEREOSPECIFIC SYNTHESIS OF (+) AZIMIC AND (+) CARPAMIC ACIDS FROM D-GLUCOSE

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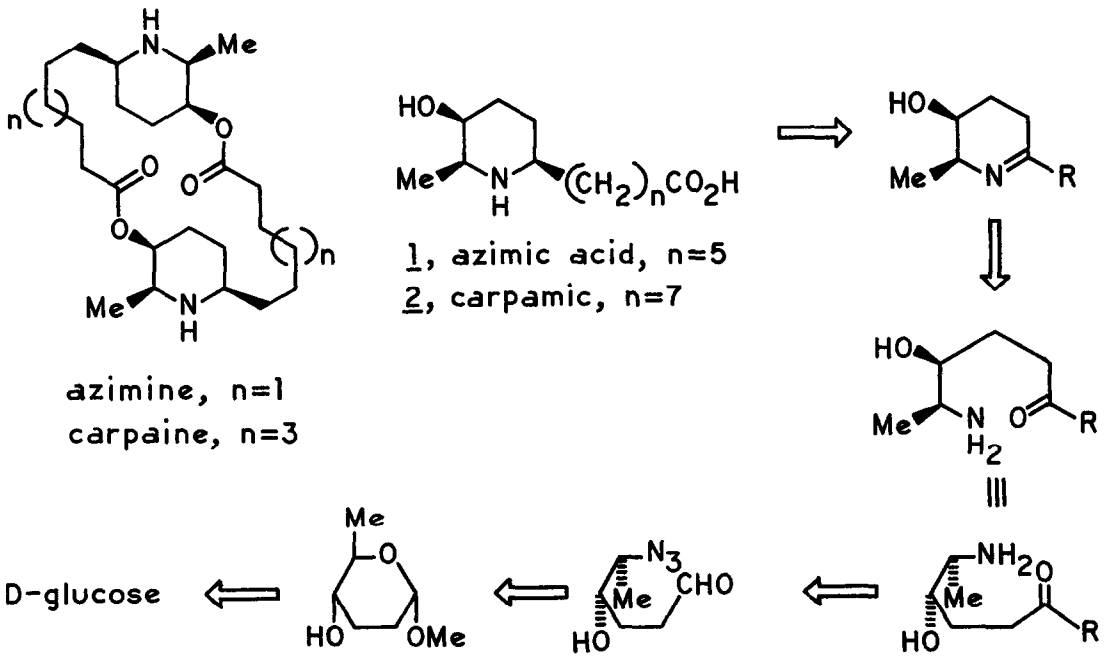
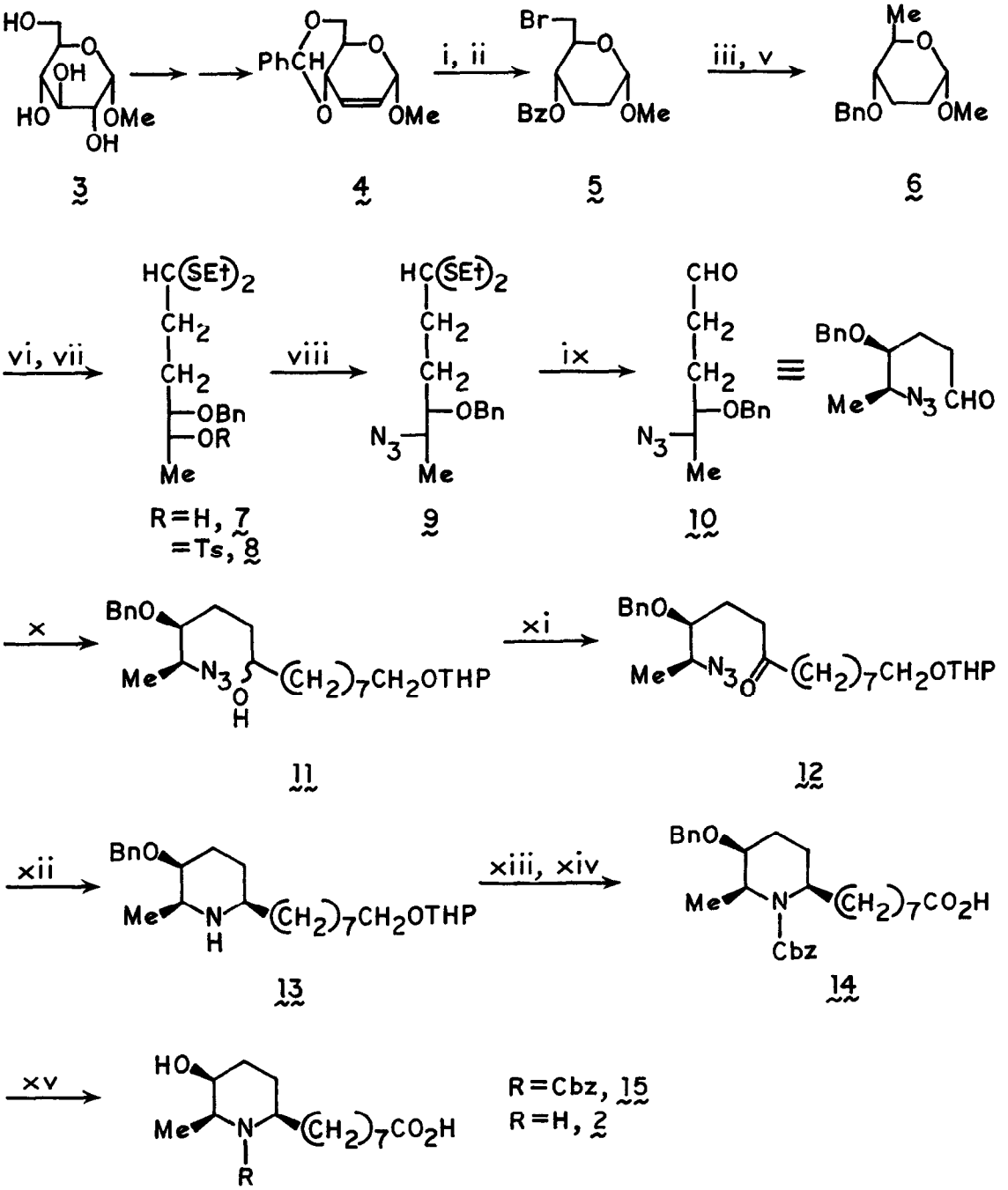
Summary: The total synthesis of (+)-azimic and (+)-carpamic acids are described, based on a biomimetic heterocyclization of optically active precursors derived from D-glucose.

The piperidine alkaloids constitute a large family of naturally occurring substances many of which possess important physiological and antibiotic properties[2]. The macrocyclic dilactones azimine[3] and carpaine[4] belong to a small subgroup containing a 2,3,6-trisubstituted piperidine skeleton whose constitutional structures and stereochemistry have been arrived at by spectroscopic and degradative studies. Azimic 1 and carpamic 2 acids, are stereochemically related and have been shown to be 2(*S*)-methyl-3(*S*)-hydroxy-6(*R*)-(carboxyalkyl)piperidines with an "all cis" configuration, a stereochemical feature found in other piperidinol-type alkaloids as well[5]. We describe herein a total and stereospecific synthesis of 1 and 2 from D-glucose, based on the concept of "chiral templates"[6], as illustrated in the retrosynthetic analysis shown below.



The synthesis of (+)-carpamic acid starts with methyl α-D-glucopyranoside 3 which can be transformed into the unsaturated derivative 4 in high overall yield by known procedures[7].

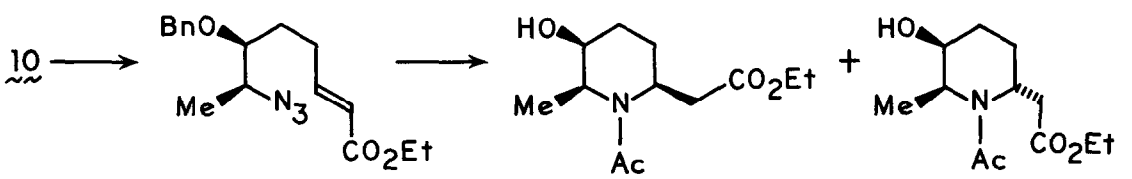


i. 5% Pd/C,H_2, MeOH (quant.); ii. NBS/CCl_4, reflux, 30 min. (95%); iii. NaOMe, MeOH; iv. LAH. THF, 25°; v. BnBr. NaH, DMF (86% overall); vi. EtSH, HCl (71%); vii. TsCl, pyr. (98%); viii. NaN_3, DMF, 80°, o.n (98%); ix. Br_2, ether, H_2O (63%); x. $BrMg(CH_2)_7CH_2OTHP$, THF, -50°, 30 min. (48-53%); 80% based on recovered 10); xi. pyridinium chlorochromate NaOAc, CH_2Cl_2, o.n. (83%); xii. Pd/C,H_2, EtOAc, 85%; xiii. CbzCl, aq. acetone (88%); xiv. CrO_3, aq. H_2SO_4, acetone, (57%), xv. 10% Pd/C, H_2, MeOH, 8h (83%).

Selective reduction of the double bond, followed by treatment with NBS gave 5 as a syrup[9], $[\alpha]_D$ + 130°. Sequential reduction, O-benzylation to 6, $[\alpha]_D$ + 141.2°, followed by ethanethiolysis gave 7 (syrup). The tosylate 8, $[\alpha]_D$ + 3.8°, prepared in the usual way, was then treated with excess sodium azide in hot DMF to give the desired azido derivative 9 as a syrup $[\alpha]_D$ + 9.1°. Among several procedures attempted to regenerate the aldehyde function from 7, none were as effective as that utilizing bromine in aqueous ether[10], which led to the syrupy aldehydo derivative 10, $[\alpha]_D$ - 9.45°. Completion of the synthesis resolved itself in the introduction of the acid side chain, and the reductive cyclization[11] of an aminoketone derivative generated from 12 as called for in our synthetic plan. A high degree of stereocontrol was expected in this step, since the intermediate Δ^1-piperideine derivative should be hydrogenated[12] from the α-face of the molecule. Treatment of the aldehyde 10 with the Grignard reagent[13] prepared from 8-bromo-1(tetrahydropyran-2-yloxy)octane led to the formation of 11, presumably as a mixture of epimers. Oxidation with pyridinium chlorochromate[14] produced the azidoketone derivative 12, $[\alpha]_D$ - 7.3°, which upon hydrogenation, gave 13. Conversion to the N-benzyloxycarbonyl derivative $[\alpha]_D$ - 18.7°, followed by oxidation of the terminally protected primary alcohol led directly to N-benzyloxycarbonyl-3-O-benzyl carpamic acid 14, $[\alpha]_D$ - 22.8°, m/e 338 ($M^+ - C_{13}H_{25}O_2$). Finally, reductive removal of the N,O-protecting groups gave crystalline carpamic acid 2 mp 225-227° (EtOH, acetone[15]); $[\alpha]_D$ + 5°; M^+ calcd. 257.2021; meas. 257.1990, lit.[16] mp 225-226°; $[\alpha]_D$ + 7°[17]. The transformation of carpamic acid into carpaine has been reported by Corey and coworkers[18]. Following the same sequence, but using the Grignard reagent[19] derived from 6-bromo-1-(tetrahydropyran-2-yloxy)hexane, it was possible to prepare crystalline azimic acid in the same relative yields as described for carpamic acid. Azimic acid showed mp 214-215° (EtOH)[15]; $[\alpha]_D$ + 8° (MeOH): M^+ calcd. 229.1677; meas. 229.1620, and was identical (t.l.c., mass spectrum) with a sample of (±)-azimic acid[20].

In addition to being stereospecific, the synthetic approach to piperidinol alkaloids shown in this paper, is also a biomimetic one[21] and of general applicability to other, more complex alkaloidal structures, as well as related heterocycles[22].

In an alternate approach, the aldehyde 10 was condensed with carboethoxymethylene triphenylphosphorane (CH_2Cl_2, 25°, 2h) to give the corresponding olefinic derivative as a syrup (57%). Treatment with Ra-Ni in ethanol, followed by N-acetylation led directly to the desired the N-acetylpiperidine derivative, (m/e 290, M^+ - Ac), presumably as a mixture of epimers at C-6, which could be debenzylated to the corresponding hydroxypiperidines (m/e 220, M^+ - Ac; m/e 156, N-acetyl 2-methyl-3-hydroxy-Δ^1-piperideinium ion).



The stereochemistry of the intramolecular addition and further chemical modifications in this series are presently under study. This approach constitutes another type of biomimetic heterocyclization[23], involving precursors derived from optically active, acyclic carbohydrates and provides an alternate strategy for the asymmetric synthesis of piperidine and pyrrolidine alkaloids.

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