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SYNTHESES OF CHIRAL OXAZOLO[2,3-a]TETRAHYDROISOQUINOLINE AND ITS ASYMMETRIC ALKYLATION. SYNTHESIS OF (S)-(-)- AND (R)-(+)-SALSOLIDINES

Masatoshi Yamato,* Kuniko Hashigaki, Shigetaka Ishikawa, and Nazmul Qais
Faculty of Pharmaceutical Sciences, University of Okayama
Tsushima-naka, Okayama 700, Japan

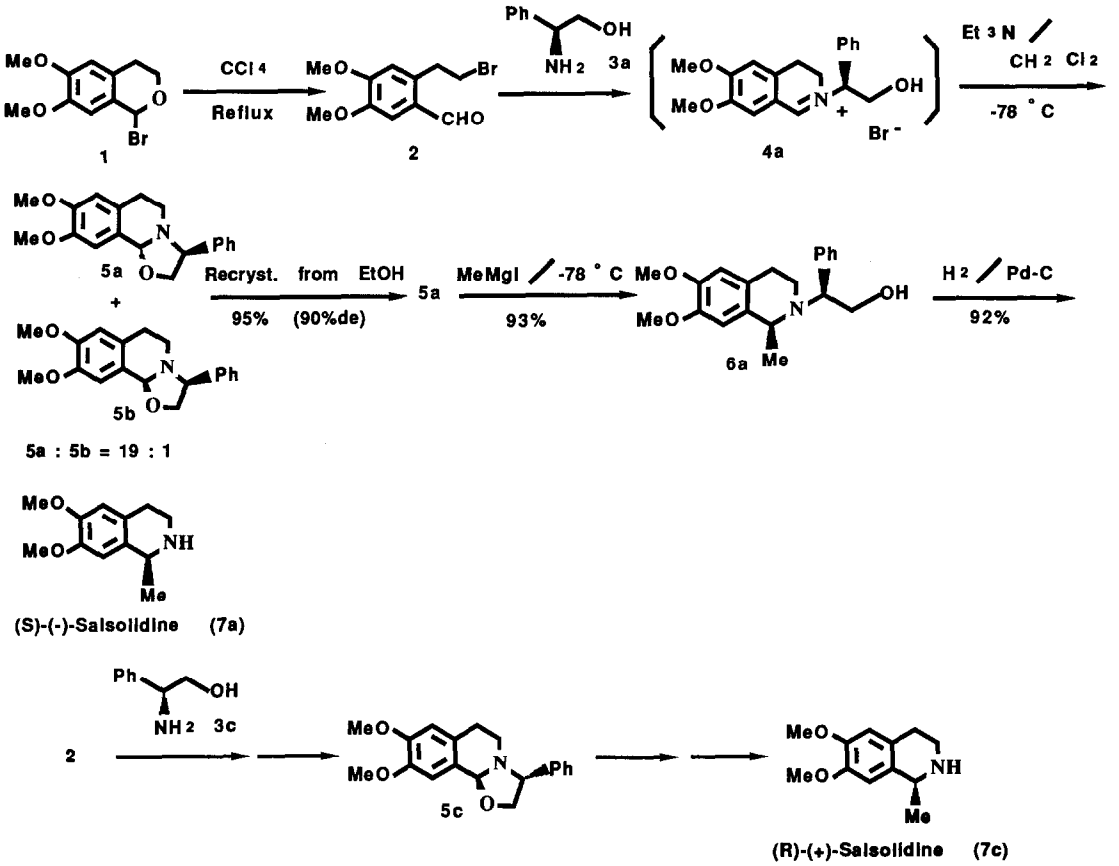
Abstract: The isoquinolinium bromide (4), on treatment with base, underwent cyclization to give the chiral oxazolotetrahydroisoquinoline (5) with a high diastereoselectivity, which was converted to optically pure salsolidine.

Chiral 1-alkyltetrahydroisoquinolines are useful as key intermediates for the synthesis of isoquinoline alkaloides. Several reports on the highly stereoselective synthesis of 1-alkyltetrahydroisoquinolines have recently been appeared.[1)]

We have previously found that 1-ethoxy-2-methyltetrahydroisoquinoline, derived from isochroman, undergoes a facile nucleophilic substitution by ketones to give 1-(2-oxoalkyl)tetrahydroisoquinolines.[2)] This finding drew our attention towards the synthesis of cyclic chiral 1-alkoxytetrahydroisoquinolines, namely oxazolo[2,3-a]tetrahydroisoquinolines (5a,c), as intermediates for the synthesis of chiral 1-alkyltetrahydroisoquinolines. This report describes highly stereoselective syntheses of 5a,c from 1-bromoisochroman (1) and their utility in the syntheses of optically pure (S)-(-)- and (R)-(+)- salsolidines (7a,c).

Compound 5a (3S,10bR) was prepared by a facile method (Scheme): 2-Formylphenethyl bromide[3)] (2; 2.2 mmol), prepared by heating of 1, was stirred with D-phenylglycinol (3a: 2.2 mmol) and acetic acid (2.2 mmol) in EtOH (11 h, r.t.). Concentration in vacuo afforded the crude isoquinolinium bromide (4a), which, on treatment with base, afforded the cyclized products containing 5a and a small amount of 5b (3S, 10bS). The most highly selective cyclization of 4a to 5a was achieved as follows: Triethylamine (4.4 mmol) was added at -78°C to crude 4a (2.2 mmol) in CH_2Cl_2 (50 ml). After stirring (1 h, -78°C), usual work-up afforded a 19:1 mixture of 5a and 5b, which was crystallized from EtOH to give optically pure 5a[4)] (95% yield, 90% de), mp 115-116°C, $[\alpha]_D^{22}$ -38°(c = 0.1, EtOH).

Asymmetric methylation of the chiral 5a was achieved by the reaction with MeMgI: Compound 5a (1.6 mmol) in THF (10 ml) was added to MeMgI (6 mmol) in Et_2O at -78°C. After stirring for 1 h (-78°C), usual work-up afforded 6a, which was hydrogenated on Pd-carbon in acidic EtOH to give optically pure (S)-(-)-salsolidine (7a; 92%), $[\alpha]_D^{24}$ -62.5°(c = 0.1, EtOH) {Lit. $[\alpha]_D$ -63° (EtOH)[5)]; $[\alpha]_D^{16}$ -59.7°(c = 20, EtOH)[6)]}.



The enantiomer of 5a, (3R,10bS)-oxazolotetrahydroisoquinoline (5c) {mp 114-115°C, $[\alpha]_D^{28}$ +34.2°(c = 0.1, EtOH)}, was also prepared from 2 by using L-glycinol (3c) in 94% yield (90% de), and converted to pure (R)-(+)- salsolidine (7c), $[\alpha]_D^{27}$ +63°[c = 0.1, EtOH] {Lit.[6] $[\alpha]_D^{16}$ +59.9°(c = 25, EtOH)}.

The data described here implies chiral 5a or 5c, easily derived from 1 with D- or L-glycinol, to be very useful as intermediate for asymmetric synthesis of 1-alkyltetrahydroisoquinolines.

References and Notes

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