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ASYMMETRIC SYNTHESIS OF *(R)*-RETICULINE - A NEW STRATEGY FOR THE ASYMMETRIC SYNTHESIS OF ISOQUINOLINES VIA ENANTIOSELECTIVE EPOXIDATION OR DIHYDROXYLATION

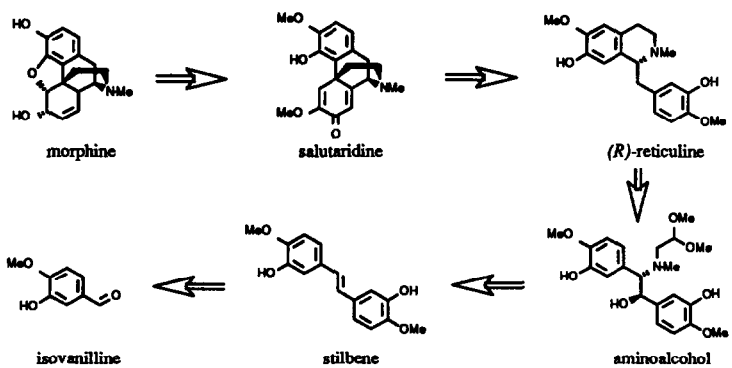
Rolf Hirsenkorn

Consortium für elektrochemische Industrie GmbH,
Zielstattstr. 20, D-8000 München 70, FRG,
eine Gesellschaft der Wacker-Chemie GmbH

Summary: A new strategy for the asymmetric synthesis of 1-benzyl-1,2,3,4-tetrahydroisoquinolines **7** - **9** has been developed. The route involves introduction of asymmetry via enantioselective epoxidation or dihydroxylation of corresponding stilbene precursors followed by aminolysis and Pomeranz-Fritsch cyclization. The strategy has been successfully applied to the asymmetric synthesis of *(R)*-reticuline (**9**), the key-intermediate in the synthesis of morphine alkaloids on the biomimetic route.

According to their pharmacological and economical importance, a variety of strategies have been developed for the total synthesis of morphine alkaloids,[1] including the biomimetic route.[1h-o] Considering stereochemical aspects this approach seems to be the most promissing one. Starting with just one stereocentre in the morphinane-precursor *(R)*-reticuline, the asymmetric information is doubled first by transformation into the morphinanedienone salutaridine, a pretentious reaction, which has been subject of a series of investigations.[2] Due to the rigidity of the morphine sceleton the other asymmetric centres, in morphine there are five in total, are gained almost automatically during a well established synthesis.[3] Thus the asymmetric synthesis of *(R)*-reticuline and its transformation into salutaridine are the key-technologies for the total synthesis of morphine alkaloids following the biomimetic route (scheme 1).

Scheme 1



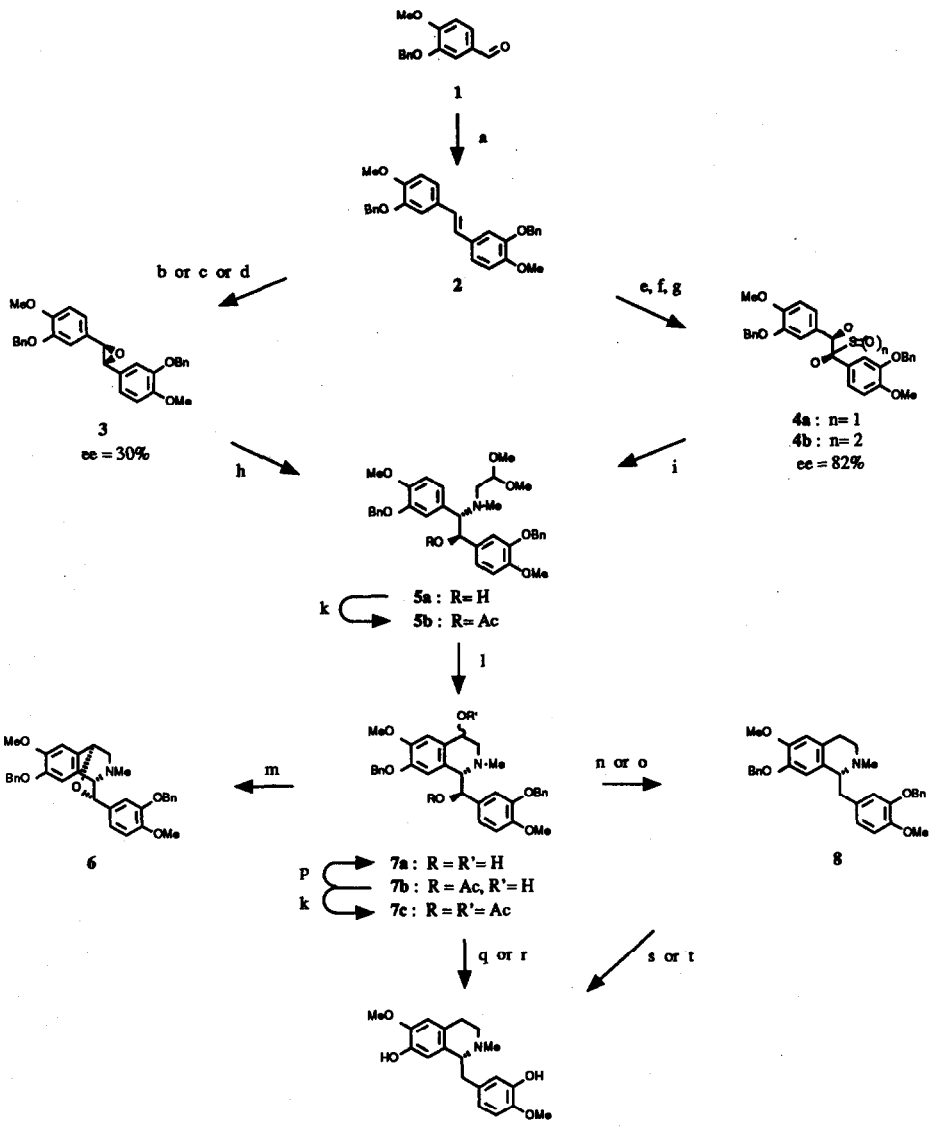
All previous syntheses of reticuline usually build up the two aromatic subunits separately, which are combined later in the key-step of the synthesis. Typically this is accomplished either by classical Bischler-Napieralski cyclization[4] or by modern enantioselective alkylation methodologies.[5] All these syntheses are tedious, none of them is feasible economically. In order to avoid this complicated proceeding we developed a completely new strategy, that was based on the symmetry of the target molecule. By abstracting reticuline to an appropriately substituted stilbene a useful synthon for the target was found. The overall synthetic approach is outlined in scheme 1.

Commercially available isovanillin derivative **1** was reductively coupled by McMurry reaction[6] to give the trans-stilbene **2** in high yield and high stereospecifity.[7a] **2** was readily oxidized by several methods[8] under non-acidic conditions (scheme 2) to give the trans-stilbene oxide **3**. As the absolute configuration of the epoxide **3** determines the absolute configuration of the final product (e.g. *(R)*-reticuline), it was necessary to use an enantioselective epoxidation technique at this point. Regard to economical aspects the catalytic enantioselective epoxidation employing chiral manganese-salene catalysts[8c] seemed most promissing. Unfortunately the enantiomeric excess (ee) achieved by this method did not exceed 30%. Alternatively, the synthesis of the epoxide analoga **4a** and **4b** was accomplished via catalytic enantioselective Sharpless dihydroxylation[7b] (ee= 79-93%), and subsequent transformation into the cyclic sulfite or sulfate intermediate.[9] Cleavage of the epoxide **3** by methylaminoacetaldehyde dimethylacetal (MADMA) proceeded smoothly to give the erythro-aminoalcohol **5a** in high yield and high stereospecifity.[7c] However aminolysis of the cyclic sulfite- (**4a**) or sulfate-analogon (**4b**) under the same conditions (MADMA, SiO_2, n-butanol) gave minor amounts (circa 10 - 20%) of the corresponding threo-isomer[7d] as by-product, which was a clear indicator for the mixed S_N1 / S_N2-character of the reaction. By omitting the SiO_2-catalyst and changing to more polar solvents - MADMA itself was the best - the formation of the undesired threo-isomer could almost be avoided completely.

After protection of the benzylic alcohol the isoquinoline precursor[7e] **5b** was ready for Pomeranz-Fritsch cyclization, which, when carried out under carefully controlled conditions (tlc), proceeded smoothly and yielded the 4-hydroxy-isoquinolines **7b** as a mixture of diastereoisomers.[7f] This is not a trivial result, normally the Pomeranz-Fritsch cyclization is not a feasible reaction for the synthesis of 1-benzyl-4-hydroxy-1,2,3,4-tetrahydroisoquinolines and usually yields pavine- and isopavine-type main-products.[10] In our case, however, the reaction clearly stopped at the 4-hydroxy-isoquinolines **7b** and no pavines or isopavines were detectable. Under non-controlled conditions the reaction proceeded to give the cyclic ether **6**. Finally, removal of the protecting groups and of the surplus benzylic alcohol functions was achieved either by hydride reduction of the corresponding benzylic chlorides or acetates with subsequent hydrolysis of the phenolic benzyl protecting groups, or straightforward by catalytic hydrogenation of the diacetate **7c**, respectively of the Pomeranz-Fritsch product **7b** in the presence of oxalic acid.

(R)-reticuline (**9**) was obtained in 82% ee, thus the enantiomeric excess, achieved in the dihydroxylation-step was successfully transferred into the target. By simply changing the chiral ligand in the dihydroxylation step from dihydroquinidine 4-chlorobenzoate to its pseudo-enantiomeric dihydroquinine congener, the corresponding R,R-diol was obtained with similar asymmetric induction (ee= 72%), thus allowing the asymmetric synthesis of *(S)*-reticuline as well.

The outlined new synthetic strategy should be applicable to the synthesis of a variety of isoquinolines. It allows the introduction of asymmetry at an early stage of the synthesis using established catalytic methods. By the appropriate choice of the catalyst's ligands both enantiomers of the desired final products are available. As demonstrated in the synthesis of reticuline, the shortest route is a 7-step sequence starting from technical isovanilline; this strategy allows extremely short and efficient asymmetric syntheses, especially for "symmetric 1-benzyl-1,2,3,4-tetrahydroisoquinolines". To our knowledge, this is not only the shortest racemic and asymmetric synthesis of reticuline, but it is also an economical route which is technically practicable, e.g. on a 10kg-scale. Having an efficient access to *(R)*-reticuline, we are currently focussing on the phenolic coupling to salutaridine.



Scheme 2

Reagents: (a) $TiCl_4$, py., Zn, THF, reflux, 2h, 93%; (b) m-CPBA, CH_2Cl_2/$NaHCO_3$(aq), r.t., 96%, m.p.= 102°C (ethanol); (c) 2mol% Ni-salene, 10mol% $BnBu_3Cl$, NaOCl, CH_2Cl_2/$NaHCO_3$(aq), r.t.; (d) 5mol% Mn-(*S,S*)-diphenylsalene, Me_3PhIO, CH_2Cl_2, 5°C (ee= 30%); (e) 2mol% $OsCl_3$, 10mol% dihydroquinidine 4-chlorobenzoate, N-methylmorpholine N-oxide, acetone/H_2O (9:1), r.t., 1d slow addition, 88%, α= 106° (c= 1, CH_2Cl_2, ee= 82%), m.p.= 41-43° (petroleum benzene/diethylether 95:5); (f) $SOCl_2$, NEt_3, diethylether, 0°C to r.t., 1h; (g) $RuCl_3$, NaOCl, CH_3CN; (h) 2 MADMA, 10weight% SiO_2, n-butanol, r.t. to 90°C, 2h, 79%; (i) MADMA (as solvent), r.t. to 130°C, 2h, 57% from 2; (k) Ac_2O, 5mol% NaOAc, xylene, reflux, 2h, 85%; (l) HCl (aq)/acetone (4:6), 0°C to r.t., tlc-control, 87%; (m) as described for (l), no tlc-control; (n) i: $SOCl_2$, py., CH_2Cl_2; ii: $LiAlH_4$, THF, 54% from 7a; (o) i: $NaBH_4$, TFA, THF, r.t.; ii: 25% NaOH, 72% from 7a; (p) NaOH, methanol/H_2O, 50°C, 1h, 88%; (q) 20weight% Pd(10%)/C, H_2(50atm), i-propanol/H_2O (3:2), 88%; (r) 20weight% Pd(10%)/C, 6eq. $(COOH)_2$, H_2(50atm), i-propanol, 69%; (s) cat. Pd/C, H_2(1atm), methanol, 93%; (t) HCl (aq)/methanol, reflux, 5h, 81%

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7. (a) No cis-stilbene detectable; (b) the ee's of the dihydroxylation step were in the range between 72% and 93%, depending on reaction conditions and were determined by ^{1}H NMR of the bis-mosher ester of the diol [integration of the glycolic signals of the diastereoisomeric Mosher esters at δ= 6.13ppm (R-R,R-isomer) and δ= 6.01ppm (R-S,S-isomer)]; the ee could easily be raised e.g. from 73% to 82% by a single recrystallization from ether/petroleum ether (40-60°C); (c) erythro-aminoalcohol: $J_{1,2}$= 4.5Hz, no threo-product detectable, $[\alpha]_D$= -86.4° (c= 1, CH_2Cl_2), resulting from diol having 72% ee; (d) threo-aminoalcohol: $J_{1,2}$= 10.0Hz, the threo-product also showed optical activity $[a]_D$= +41.8°(c= 1, CH_2Cl_2), resulting from diol having 72% ee; this unambiguously indicates its origin from an asymmetric diol and not from a meso-diol! (e) ee's have been controlled by ^{1}H NMR of the R-O-acetyl-mandelic acid (ROAMA) salt of 5b, a technique, developed by D.Parker, R.J.Taylor, Tetrahedron 43(22), 5451-6 (1987); the signals for the acetyl groups of the diastereomeric salts are clearly separated and can be integrated: δ= 1.67ppm for the 1R,2S-(5b)-ROAMA salt, δ= 1.82ppm for the 1S,2R-(5b)-ROAMA salt; (f) (7b, high-R_f-isomer) : (7b, low-R_f-isomer) = 1:3; the conformation of the diastereomeric 4-hydroxy-isoquinolines (7b) was determined by Swern oxidation and subsequent $NaBH_4$ reduction of the corresponding 4-keto-isoquinoline, which gave a mixture of (7b, high-R_f-isomer) : (7b, low-R_f-isomer) = 4:1; on mechanistic reasons the α-alcohol is assumed to be the main-product in the reduction step, thus, the β-product is the main product of the Pommeranz-Fritsch cyclization.[10]
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