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Asymmetric Synthesis. XLI.[1] Totally Stereoselective Synthesis of 1,3-disubstituted tetrahydroisoquinolines via the CN(*R*,*S*) Method.

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Abstract : Optically active *cis*- or *trans*- 1,3-disubstituted tetrahydroisoquinolines can be prepared selectively from the same oxazolidine **4**. This latter is easily obtained from keto-acid **1** and (*R*)-(-)-phenylglycinol. Copyright © 1996 Elsevier Science Ltd

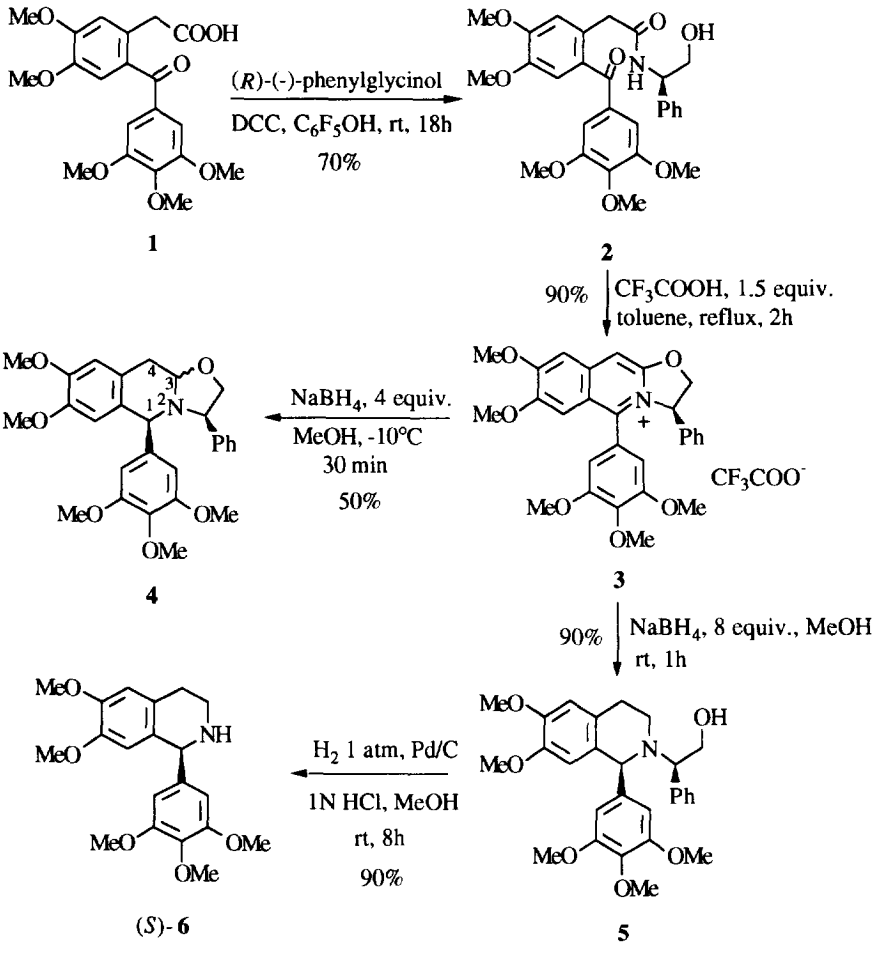
Although there are several methods for the asymmetric synthesis of 1-alkyl or 1-aryl tetrahydroisoquinolines,[2] the only example of asymmetric synthesis of all isomers of 1,3-disubstituted tetrahydroisoquinolines has been described by Bringmann *et al.*[3] However, while this method allows a variety of substituents at C-1, it is limited for the substitution at C-3, which requires the preparation of enantiomerically pure 1-alkyl-2-phenylethylamine. Indeed, 1,3-disubstituted tetrahydroisoquinoline is a structural feature found in a large variety of alkaloids[4] and we have initiated a project aimed at the synthesis of natural products in this series and analogues of biological interest.

In continuation of our work on the development of general synthetic methodologies for the construction of a wide diversity of structures, by means of equivalents of non-racemic synthons using phenylglycinol as source of chirality,[5] we present here an efficient approach to the title compounds in enantiomerically pure form.

The condensation of δ-ketoacids with optically active β-aminoalcohols is known to afford chiral bicyclic lactams.[2b] More interestingly, we have discovered that the stepwise condensation of **1**[6] with (*R*)-(-)-phenylglycinol (Scheme 1) led to amide[7] **2** (yield 70%) which was cyclized to the isoquinolinium salt **3** (90% yield) by treatment with trifluoroacetic acid. The sodium borohydride reduction of **3** under controlled conditions furnished oxazolidine **4** (50% yield) as a 60:40 mixture of stereomers at C-3. The absolute configuration at C-1 was unambiguously established as (*S*) from the synthesis of the known (-)-norcryptostyline III **6**[8] by sodium borohydride treatment of **4** followed by hydrogenolysis of the chiral appendage.

At this stage, it was possible to envisage the stereoselective creation of an ***R*** or ***S*** chiral centre at C-3 of oxazolidine **4** using the CN(***R***,***S***) strategy which has proved to be a powerful tool in this and other laboratories.[5a,d,9]

Scheme 1

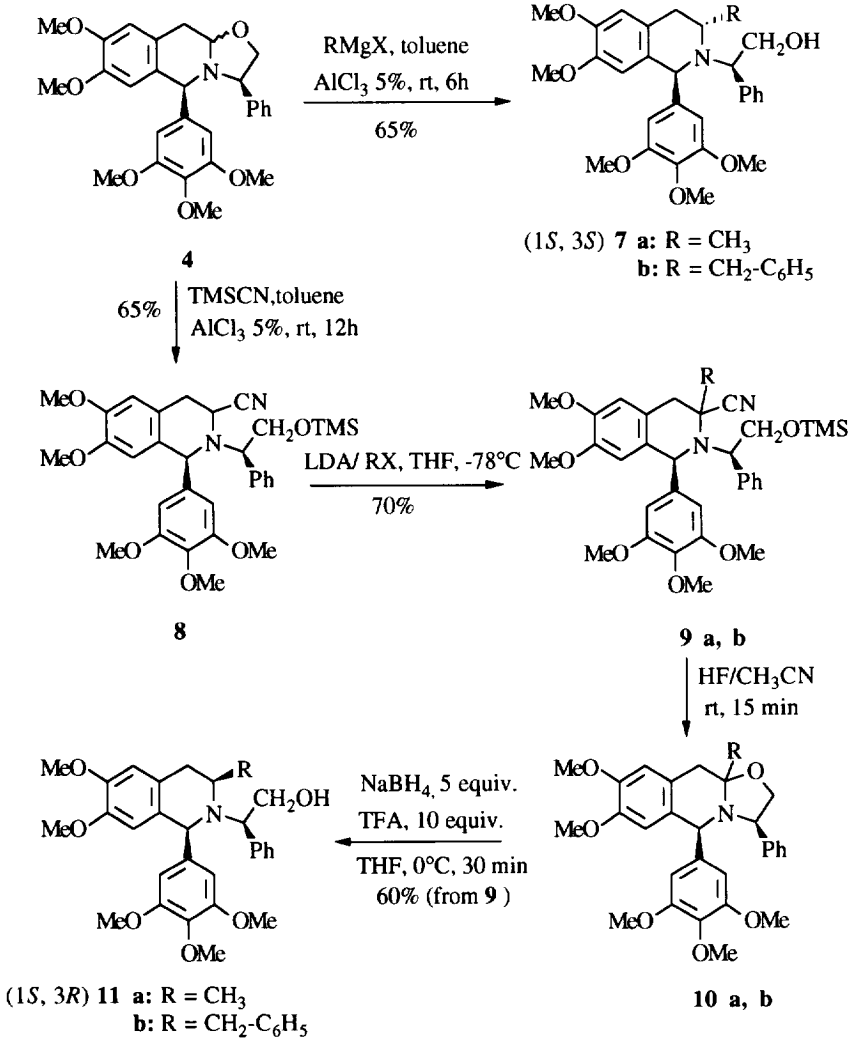


Thus, the single (1*S*, 3*S*) aminoalcohols **7**[10] (Scheme 2) were isolated on treatment of oxazolidine **4** with methyl magnesium bromide or benzyl magnesium chloride[11] in the presence of a catalytic amount of aluminium chloride (65% yield).

The access to the (1*S*, 3*R*) diastereomeric C-3 substituted derivative is a less obvious goal. On the basis of observations made during earlier work,[12] we reasoned that it was necessary to transform oxazolidine **4** into aminonitrile **8**. Reaction of **4** with trimethylsilyl cyanide in the presence of a catalytic amount of aluminium chloride gave **8** (65% yield). This latter was deprotonated (LDA, 4 equiv.) to give the corresponding anion which could be alkylated with methyl iodide or benzyl bromide to give **9**. As the crude product contained significant quantities of the recyclized compounds **10**, it was treated by a solution of 5% aqueous hydrofluoric acid in acetonitrile to effect complete cyclization of **9** to **10**. Reductive opening of the oxazolidine ring of **10** was performed in the presence of trifluoroacetic acid yielding aminoalcohols **11** (60% yield).[10]

The relative configuration of the newly-created asymmetric centre could be determined by comparison of the ^{13}C NMR data of **7** and **11**: a γ-gauche effect observed for C-3 of **7** is diagnostic of a *trans* relationship between the C-1 and C-3 substituents.[13]

Scheme 2



The remarkable stereocontrol in the reaction leading to diastereomeric compounds **7** and **11** was interpreted in terms of an elimination-addition mechanism wherein Grignard reagents or hydride ion approach the intermediate iminium ion under stereoelectronic control from the axial direction on the less hindered face.

As in the preparation of **6**, the chiral appendage of **7** and **11** could be easily removed by hydrogenolysis to give a secondary amine allowing further substitutions or cyclizations.

Using (*S*)-(+)-phenylglycinol, it should be possible to obtain the enantiomeric C-1 substituted compounds and hence the four isomers of 1,3-disubstituted tetrahydroisoquinolines in optically-pure form.

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6. Prepared in 70% yield by stirring methyl-3,4-dimethoxyphenylacetate and 3,4,5-trimethoxybenzoyl chloride in the presence of PCl_5 and $AlCl_3$ in CH_2Cl_2 for 2 days then saponification.
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10. Compound **7a**, oil: $[\alpha]_D^{20}$= + 21 (c 0.80, $CHCl_3$). ^1H NMR (300MHz, $CDCl_3$) δ 7.20 (m, 3H), 7.05 (m, 2H), 6.40 (s, 2H), 6.30 (s, 1H), 6.22 (s, 1H), 5.20 (s, 1H), 4.20 (m, 2H), 3.85 (s, 3H), 3.80 (m, 1H), 3.80 (s, 9H), 3.70 (s, 3H), 3.50 (m, 1H), 2.62 (dd, 1H,*J*= 17.0, 5.0 Hz), 2.45 (dd, 1H, *J*=17.0, 10.0 Hz), 1.3 (d, 3H, *J*= 6.7 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 152.8, 140.8, 130.3, 128.6, 128.1; 127.7, 127.4, 110.9, 106.5, 61.6, 60.8, 60.6, 60.4, 56.1, 55.9, 55.6, 46.9, 33.8, 19.3. **7b**, oil: $[\alpha]_D^{20}$= +5 (c 0.94, $CHCl_3$). ^1H NMR (300MHz, $CDCl_3$) δ 7.10 (m, 5H), 6.95 (m, 3H), 6.85 (m, 2H), 6.30 (s, 2H), 6.20 (s,1H), 6.15 (s, 1H), 5.20 (s, 1H), 4.05 (m, 2H), 3.80 (s, 3H), 3.65 (s, 12H), 3.6 (m, 2H), 3.00 (dd, 1H, *J*= 14.4, 8.0 Hz), 2.85 (dd, 1H, *J*= 14.4, 7.5 Hz), 2.40 (d, 2H, *J*=7.5 Hz); ^{13}C (75 MHz, $CDCl_3$) δ 152.7, 147.2, 146.9, 140.5, 139.1, 138.5, 128.8, 128.5, 128.2, 127.6, 126.2, 111.1, 110.8, 106.6, 61.7, 61.1, 60.8, 60.3, 55.9, 55.6, 51.9, 38.4, 31.4.
Compound **11a**, oil: $[\alpha]_D^{20}$= -31 (c 0.61, $CHCl_3$). ^1H NMR (300MHz, $CDCl_3$) δ 7.10 (s, 5H), 6.51 (s, 1H), 6.45 (s, 2H), 6.05 (s, 1H), 4.78 (s, 1H), 3.90 (m, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 3.71 (s, 6H), 3.61 (s, 3H), 3.15 (m, 1H), 2.50 (dd, 1H, *J*= 15.0, 11.0 Hz), 2.35 (dd, 1H, *J*=15.0, 4.5 Hz), 1.30 (d, 3H, *J*= 6.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 146.6, 141.6, 138.8, 130.4, 128.3, 128.1, 127.5, 110.5, 110.3, 104.0, 66.9, 62.4, 60.8, 60.4, 55.9, 55.8, 54.7, 35.9, 23.5. **11b**, oil: $[\alpha]_D^{20}$= -40 (c 1.04, $CHCl_3$). ^1H NMR (300MHz, $CDCl_3$) δ 7.21 (m, 8H), 7.10 (m, 2H), 6.60 (s, 2H), 6.50 (s, 1H), 6.10 (s, 1H), 4.90 (s, 1H), 4.10 (m, 2H), 4.00 (m, 1H), 3.88 (s, 3H), 3.80 (s, 9H), 3.7 (s, 3H), 3.50 (m, 1H), 3.10 (dd, 1H, *J*= 13.0, 4.0 Hz), 2.55 (m, 2H), 2.30 (dd, 1H, *J*=15.0, 9.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 147.5, 146.7, 140.8, 139.3, 139.1, 136.6, 130.6, 129.2, 128.4, 128.2, 127.9, 127.7, 126.2, 110.8, 104.7, 68.0, 62.3, 60.9, 60.7, 60.5, 56.0, 55.8, 44.5, 32.2.
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