Enantioselective Synthesis of Cyclic Amino Alcohols: *cis*-1-Amino-2-indanol

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(1*S*,2*R*)-*cis*-1-Amino-2-indanol has been synthesized. A unique feature of the synthesis involves securing the functionalities and the configurations of the two stereocenters on an acyclic precursor before cyclizing it into the final ring-skeleton. The strategy allows both the stereocenters to be controlled in an absolute manner.

Key Words : *cis*-1-Amino-2-indanol, Enantioselective synthesis, Absolute stereocontrol

Introduction

β-Amino alcohols play important roles in medicinal and organic chemistry.[1] The functional group is often found in many bioactive compounds. It is also a popular structural motif in many chiral auxiliaries and ligands. *cis*-1-Amino-2-indanol is exemplary. The (1*S*,2*R*)-enantiomer is a key component of the HIV-protease inhibitor Indinavir and other related compounds. Oxazolidinones, acetonides and sulfonamides derived from *cis*-1-amino-2-indanol have been used as chiral auxiliaries in several asymmetric reactions, while oxazolines and oxazaborolidines with *cis*-1-amino-2-indanol backbone have been used as chiral ligands in asymmetric reagents or catalysts. The chemistry of *cis*-1-amino-2-indanol has been documented in review articles,[2] and scores of efforts have so far resulted in various synthetic routes, including an *Organic Synthesis* procedure.[3]

cis-1-Amino-2-indanol is unique among β-amino alcohol synthetic targets in that its amino alcohol function is imbedded in a carbocycle. The various synthetic routes so far reported for this compound – and other cyclic amino alcohol targets as well – generally start with compounds possessing the carbocyclic skeleton already in place. Indene and indanone are examples of such carbocyclic starting materials in the cases of *cis*-1-amino-2-indanol syntheses. This imposes certain bearings on the subsequent functionalization and stereocontrol steps.

Focusing on the cases of *cis*-1-amino-2-indanol, the existing synthetic routes have adopted the strategies wherein the configurations of the two stereocenters are set in separate steps. Thus, one stereocenter is fixed in an *absolute* manner, which then induces the second in a *relative* mode. Even when the configurations of both stereocenters have initially been secured in a single step *and* in an absolute manner – *via* asymmetric epoxidation or dihydroxylation on indene, for example – the configuration of one center is subsequently sacrificed, then recreated by virtue of the second center. The Mn-salen catalyzed *enantioselective* epoxidation of indene (establishing *both* stereocenters in an absolute manner) followed by *diastereoselective* Ritter reaction (turning one of the stereocenters momentarily trigonal, therefore non-stereogenic, then reinstalling it *via* 1,2-asymmetric induction) is a typical example of this strategy.[3] The key Ritter conditions have been worked out to render the step highly diastereoselective and the whole process has been developed for a large-scale synthesis of *cis*-1-amino-2-indanol.

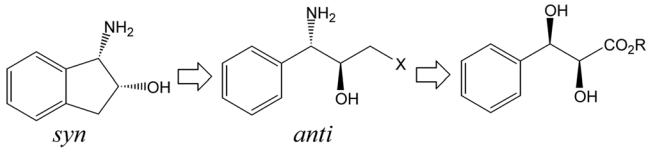
While this strategy works very effectively for the synthesis of *cis*-1-amino-2-indanol, its applicability to similarly related structures may not be guaranteed. A seemingly innocuous substitutent may alter the stereochemical outcome of the Ritter step, and it's been already noted that a larger ring system, such as tetralin or benzosuberane, requires new sets of reaction conditions and /or suffers from a low diastereoselectivity.[4] These are the features inherent to substrate-control reactions, of which the 1,2-asymmetrically inductive Ritter reaction is a typical example.

We aimed to develop an alternative synthetic strategy for *cis*-1-amino-2-indanol wherein the configurations of both the stereocenters would be controlled in an absolute (or stereospecific) manner.[5] Such a strategy would allow a care-free introduction of the stereocenters, and it could also be applicable to other similarly related cyclic amino alcohol structures.

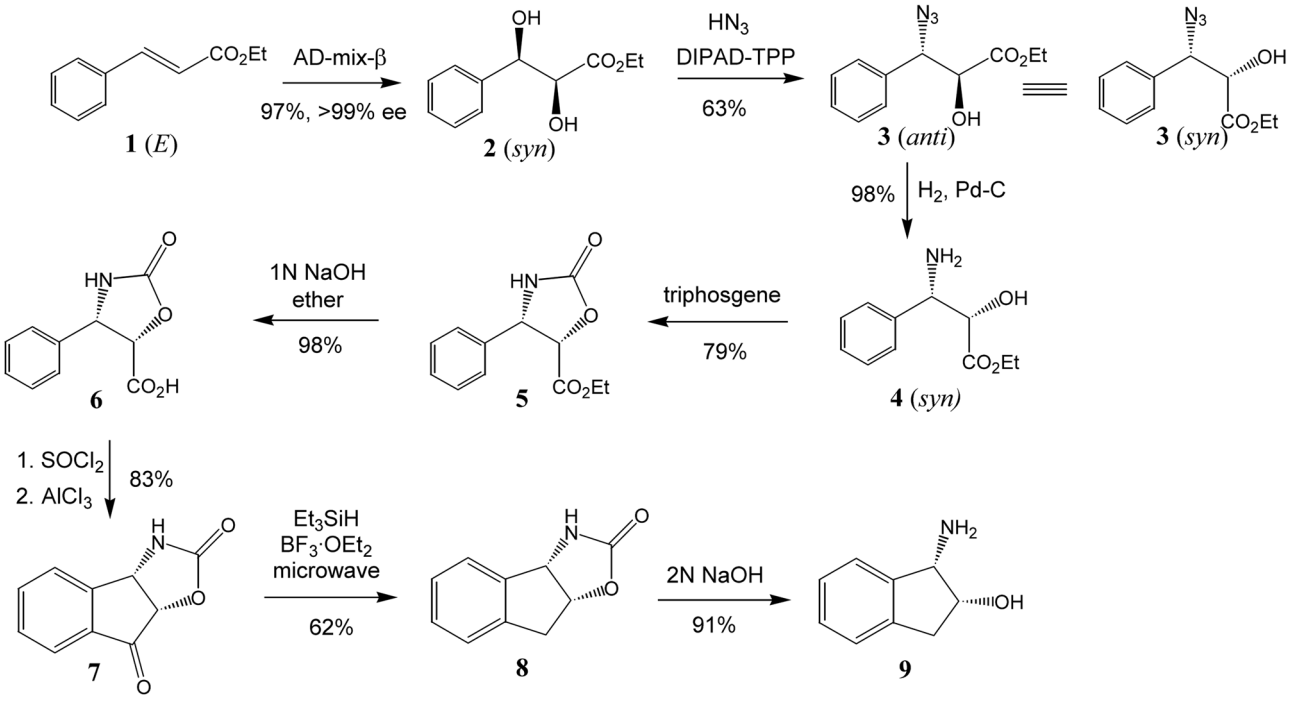
Results and Discussion

The key to our work was a realization that the *syn* relative stereochemistry of *cis*-1-amino-2-indanol on the cyclic backbone was a disguised *anti* form on an acyclic precursor (Scheme 1).[6] More general synthetic strategies for (acyclic) *anti*-β-amino alcohols could then be considered for a synthesis of this cyclic amino alcohol compound. Among the possible routes was a conversion of *syn*-diols to *anti*-amino alcohols.

Thus, (*E*)-cinnamate ester was subjected to the Sharpless asymmetric dihydroxylation protocol (AD-mix-β, 97%, >99% ee, Scheme 2).[7] The *syn*-diol **2** was then treated with HN_3 under the Mitsunobu conditions. As reported earlier, the Mitsunobu azidation was completely regioselective (for



Scheme 1



Scheme 2

the β-hydroxyl group) as well as stereospecific (inversion of configuration) to yield the *anti*-azido alcohol **3** (63%).[8] The correct configurations had thus been secured. The azido group was reduced and the resulting amino function was protected together with the hydroxyl group in the form of oxazolidinone to give **5**. The reason for choosing this particular protecting group was three-fold. First, the simultaneous protection of the two functional group (and deprotection at the end) made the operation simpler; second, as the two stereocenters became now a part of the oxazolidinone ring, any epimerization in the subsequent steps would be readily noticeable so that the monitoring of the stereochemical integrity might be easy (*vide infra*); third, and most importantly, locking the amino alcohol function in a ring system, particularly with its relative stereochemistry as it was, forced the aromatic ring and the carbonyl carbon in proximity, which would help the subsequent cyclization to proceed readily.[9]

The ester function in **5** was hydrolyzed (1 N *aq*. NaOH-Et_2O). The choice of the organic co-solvent was critical as use of more polar co-solvents (such as THF) led to partial epimerization, which was detectable on NMR. The carboxylic acid (**6**) was then converted to the acid chloride. An intramolecular Friedel-Crafts acylation resulted in the required cyclization to produce the indane ring-skeleton (**7**). The keto function was fully reduced with Et_3SiH-BF_3·OEt_2.[10] While initial attempts under thermal conditions (heating in an oil bath at 120 °C) resulted in low conversions, microwave irradiation (at 90 °C) produced the desired product in 62% within 10 min. Unmasking the amino alcohol function (2 N *aq*. NaOH) produced the desired (1*S*,2*R*)-*cis*-1-amino-2-indanol.

In conclusion, we have achieved an enantioselective synthesis of *cis*-1-amino-2-indanol. A unique feature of our synthesis is that the functionalities and the configurations of the two stereocenters have been secured on an acyclic precursor before cyclizing it into the final ring-skeleton. This strategy allowed both the stereocenters to be controlled in a stereospecific manner, and it could also be applicable to other similarly related cyclic amino alcohol structures.

Experimental Part

Asymmetric Dihydroxylation of Ethyl (*E*)-Cinnamate (1). AD-mix-β (50 g) was added to a *tert*-butanol-water mixture (1 : 1 v/v, 200 mL). Methansulfonamide (4.7 g, 50 mmol) was added and the mixture was cooled to 0 °C. Ethyl (*E*)-cinnamate (**1**, 7.5 mL, 45 mmol) was added. The mixture was warmed to rt, where it was stirred overnight. Saturated Na_2SO_3 solution (100 mL) was added and the mixture was stirred for 1 hr. It was extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by CC (silica-gel; hexane/AcOEt 1 : 1) to give ethyl (2*S*,3*R*)-3-phenyl-2-3-dihydroxypropanoate (**2**, 9.17 g, 99% ee) as a white solid. m.p. = 76-77 °C; [α] = –4.1 (*c* 1.45, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.41-7.26 (5H, m), 5.01 (1H, dd, *J* = 3.0 Hz, *J* = 5.0 Hz), 4.37 (1H, dd, *J* = 3.1 Hz, *J* = 6.0 Hz), 4.28 (2H, q, *J* = 7.1 Hz), 3.09 (1H, d, *J* = 5.8 Hz), 2.71 (1H, d, *J* = 7.2 Hz), 1.28 (3H, t, *J* = 7.1 Hz).

Mitsunobu Azidation of Ethyl (2*S*,3*R*)-3-Phenyl-2-3-dihydroxypropanoate (2). NaN_3 (40 g, 0.6 mol) was dissolved in warm water (40 mL). Benzene (240 mL) was added and the mixture was cooled to 0 °C. H_2SO_4 (17 mL)

was added dropwise over 1 hr. After stirring 1 hr, the mixture was dried over Na_2SO_4 and the liquid was decanted and stored over molecular sieves.

The *syn*-diol **2** (8.78 g, 41.8 mmol) was dissolved in THF (120 mL). PPh_3 (13.2 g, 50.2 mmol) was added followed by the HN_3 solution (200 mL) prepared above. The mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (9.7 mL, 50.2 mmol) was added dropwise as a solution in THF (30 mL). After 1 hr, the cooling bath was removed and the mixture was stirred at rt overnight. The mixture was washed with 10% $NaHCO_3$, then with brine. After drying (Na_2SO_4) and concentration, the crude product was purified by CC (silica-gel; hexane/AcOEt 8 : 1, 4 : 1, then 2 : 1) to give ethyl (2*S*,3*S*)-3-phenyl-3-azido-2-hydroxypropanoate (**3**, 6.17 g, 63%) as an oil. [α] = +79.1 (*c* 1.15, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.39-7.33 (5H, m), 4.89 (1H, d, *J* = 3.9 Hz), 4.53 (1H, dd, *J* = 3.9 Hz, *J* = 7.5 Hz), 4.17 (2H, q, *J* = 7.2 Hz), 2.98 (1H, d, *J* = 6.5 Hz), 1.20 (3H, t, *J* = 7.2 Hz).

Reduction of the Azido Alcohol 3. The azido alcohol **3** (6.1 g, 26.1 mmol) was dissolved in ethanol (200 mL). 10% Pd/C (3.1 g) was added and the mixture was stirred under hydrogen atmosphere for 6 hr. It was filtered through a pad of Celite, which was washed with additional ethanol. Evaporation of ethanol gave ethyl (2*S*,3*S*)-3-phenyl-3-amino-2-hydroxypropanoate (**4**, 5.44 g, 99%) as an oil. [α] = +13.1 (*c* 1.45, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.35-7.28 (5H, m), 4.48 (1H, d, *J* = 3.9 Hz), 4.35 (1H, d, *J* = 3.9 Hz), 4.10 (2H, q, *J* = 7.0 Hz), 2.05-1.75 (3H, br), 1.17 (3H, t, *J* = 7.2 Hz).

Protection of the Amino Alcohol 4. The amino alcohol **4** (60 mg, 0.29 mmol) was dissolved in dichloromethane (6 mL) and the solution was cooled to 0 °C. Triphosgene (42 mg, 0.14 mmol) was added followed by diisopropylethylamine (0.12 mL, 0.7 mmol). After 1 hr, the mixture was washed with water, dried (Na_2SO_4) and concentrated. The crude product was purified by CC (silica-gel; hexane/AcOEt 2 : 1, then 1 : 2) to give ethyl (4*S*,5*S*)-4-phenyloxazolidin-2-one-5-carboxylate (**5**, 54 mg, 79%) as a white solid. m.p. = 146-148 °C; [α] = +84.6 (*c* 1.30, EtOH); ^{1}H NMR ($CDCl_3$) δ 7.38-7.26 (5H, m), 5.35 (1H, br), 5.25 (2H, dd, *J* = 9.2 Hz, *J* = 17.3 Hz), 3.83-3.63 (2H, m), 0.85 (3H, t, *J* = 7.2 Hz).

Hydrolysis of the Ester Function in 5. The oxazolidinone **5** (2.0 g, 8.5 mmol) was dissolved in ether (100 mL) and the solution was cooled to 0 °C. 1 N NaOH (50 mL) was added and the mixture was stirred for 30 min. The mixture was acidified to pH 2-3 by adding 1.0 N HCl, and extracted with AcOEt. After drying (Na_2SO_4) and concentration, the crude product was purified by CC (silica-gel; hexane/AcOEt 1 : 9, then MeOH/AcOEt 1 : 2) to give (4*S*,5*S*)-4-phenyloxazolidin-2-one-5-carboxylic acid (**6**, 1.8 g, 98%) as a white solid. m.p. = 245-248 °C; [α] = +63.3 (*c* 1.20, DMF); ^{1}H NMR (DMSO) δ 7.79 (1H, s), 7.24 (5H, s), 4.86 (2H, s).

Friedel-Crafts Acylation of the Oxazolidinone 6. The compound **6** (1.54 g, 5.8 mmol) was dissolved in $SOCl_2$ (60 mL) and the mixture was heated to reflux for 6 hr. After removal of $SOCl_2$, the residue was dissolved in dichloromethane (60 mL) and $AlCl_3$ (3.9 g, 29 mmol) was added. The mixture was stirred at rt for 2 days. It was washed with water. The water layer was extracted with portions of chloroform. The combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was purified by CC (silica-gel; hexane/AcOEt 1 : 3, 1 : 5, then AcOEt) to give (3a*S*,8a*S*)-3a,8a-dihydro-3*H*-indeno[1.2-*d*]oxazole-2,8-dione (**7**, 0.91 g, 83%) as a white solid. m.p. = 250-254 °C; [α] = +33.6 (*c* 1.10, DMF); ^{1}H NMR (DMSO) δ 8.67 (1H, s), 7.89-7.78 (2H, m), 7.70-7.60 (2H, m), 5.29 (1H, d, *J* = 7.3 Hz), 5.14 (1H, d, *J* = 7.3 Hz).

Reduction of the Ketone 7. The Friedel-Crafts product **7** (44 mg, 0.23 mmol) was mixed with $BF_3{\cdot}OEt_2$ (0.4 mL, 3.45 mmol) and Et_3SiH (0.4 mL, 2.76 mmol). The mixture was subjected to microwave irradiation (100W, 90 °C) for 10 min. It was diluted with AcOEt and washed with 10% $NaHCO_3$ then with brine. After drying (Na_2SO_4) and concentration, the crude product was purified by CC (silica-gel; hexane/AcOEt 1 : 3) to give (3a*S*,8a*R*)-3,3a,8,8a-tetrahydro-indeno[1.2-*d*]oxazol-2-one (**8**, 24 mg, 62%) as a white solid. m.p. = 203-210 °C; [α] = −84.6 (*c* 0.70, $CHCl_3$). Lit.[11] $[\alpha]_D^{25}$ −79.4. (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.34-7.22 (4H, m), 6.67 (1H, br), 5.42 (1H, dt, *J* = 2.2 Hz, *J* = 7.3 Hz), 5.18 (1H, d, *J* = 7.3 Hz), 3.40-3.36 (2H, m).

Deprotection of the Oxazolidinone 8. The oxazolidinone **8** (88 mg, 0.5 mmol) was dissolved in ethanol (2.8 mL). 2 N *aq*. NaOH (2.8 mL, 5.6 mmol) was added and the mixture was heated to 80 °C for 6 hr. It was neutralized by adding 1.0 N HCl and extracted with portions of AcOEt. After drying (Na_2SO_4) and concentration, the crude product was purified by CC (silica-gel; MeOH/AcOEt 5 : 1) to give (1*S*,2*R*)-*cis*-1-amino-2-indanol (**9**, 68 mg, 91%) as a white solid. m.p. = 117-118 °C; [α] = −63.5 (*c* 0.87, $CHCl_3$), Lit.[12] $[\alpha]_D^{25}$ −64.7. (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31-7.23 (4H, m), 4.39 (1H, dt, *J* = 3.0 Hz, *J* = 5.4 Hz), 4.33 (1H, d, *J* = 5.4 Hz), 3.11 (1H, dd, *J* = 5.3 Hz, *J* = 16.5 Hz), 2.95 (1H, dd, *J* = 2.8 Hz, *J* = 16.5 Hz), 2.39 (3H, br).

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