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A Highly Diastereoselective Chiral Pool Based Synthesis of *cis*- and *trans*- Indan-1,2-diols

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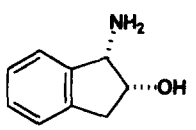
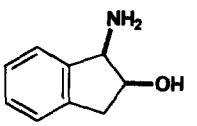
Abstract: Starting from the α-hydroxy acid chiral-pool, the 1*R*,2*S*- and 1*S*,2*S*-indan-1,2-diols have been prepared in a few steps with excellent diastereoselectivity.

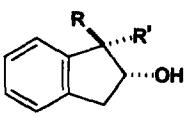
Homochiral *cis*-1-amino-2-indanols (**1** & **ent-1**) and the derived oxazolidinones and *bis*-oxazolines have recently emerged as versatile chiral auxiliaries for a wide variety of asymmetric reactions (aldol, Diels-Alder, cyclopropanation reactions, conjugate additions of anions and radicals, ketone and imine reductions, etc.).[1] Moreover, the amino indanol **1** constitutes a key structural element that is present in the anti-AIDS drug indinavir.[2] In view of these applications, much effort has been directed in recent years towards asymmetric



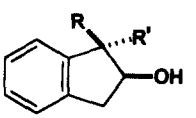
1



ent-1



2a: R=H, R'=OH
2b: R=OH, R'=H



ent-2a: R=OH, R'=H
ent-2b: R=H, R'=OH

synthesis of **1** and **ent-1**.[1,3] In 1995, the Merck-group reported a most practical synthesis of (±)-**1** via a highly diastereoselective Ritter reaction of acetonitrile on *cis*- or *trans*-indan-1,2-diols.[4] They also showed that by starting with optically active indane diols (**2a,b** & **ent-2a,b**), the respective homochiral amino indanols **1** & **ent-1** are produced with complete retention of the starting schalemicity. However, due to the limited access to optically pure indan-1,2-diols,[5] for which hydrolysis of homochiral indene oxide (prepared *via* Jacobsen asymmetric epoxidation)[6] remains the only reliable synthetic method, this, otherwise elegant, Merck-protocol has failed to attract broader ramifications. With a view to expanding this small repertoire for the homochiral synthesis of indan-1,2-diols which, we believe, would greatly enhance the overall appeal of the Merck-synthesis of **1** and **ent-1**, we now present a new and highly diastereoselective synthetic route to *cis*- and *trans*-indan-1,2-diols starting from the α-hydroxy acid chiral pool.[7]

Our synthesis started with the readily available (*S*)-2-hydroxy-3-phenylpropionic acid **3**[7] which via *O*-acetylation, acid chloride formation and an intramolecular Friedel-Crafts cyclization produced the crystalline (*S*)-2-acetoxy indanone **4** in 85% overall yield (**Scheme 1**). The latter was then reduced with $LiAlH(OBu\text{-}t)_3$ (THF, 0°) to produce the *cis*-diol monoacetate **5** (75%) with high diastereoselectivity (95:5).[8] $NaBH_4$ reduction of **4** was poorly stereoselective leading to only a 50/50 mixture of the *cis*/*trans*-isomers. Since **5** was found to be a regioisomeric mixture of the 1- and 2-acetates, it was better characterized through formation of the diacetate **6** (98%) which showed a large coupling constant between its H-1 and H-2 protons ($J_{1,2}$ = 6 Hz) thereby confirming the *cis*-stereochemistry. Subsequent hydrolysis of **5** (or **6**) with methanolic KOH then produced the 1*R*,2*S*-indan-1,2-diol (**ent-2a**) in 85% yield {$[\alpha]_D$ +45.7 (c 1.15, $CHCl_3$), lit[5c] $[\alpha]_D$ +41($CHCl_3$)}.

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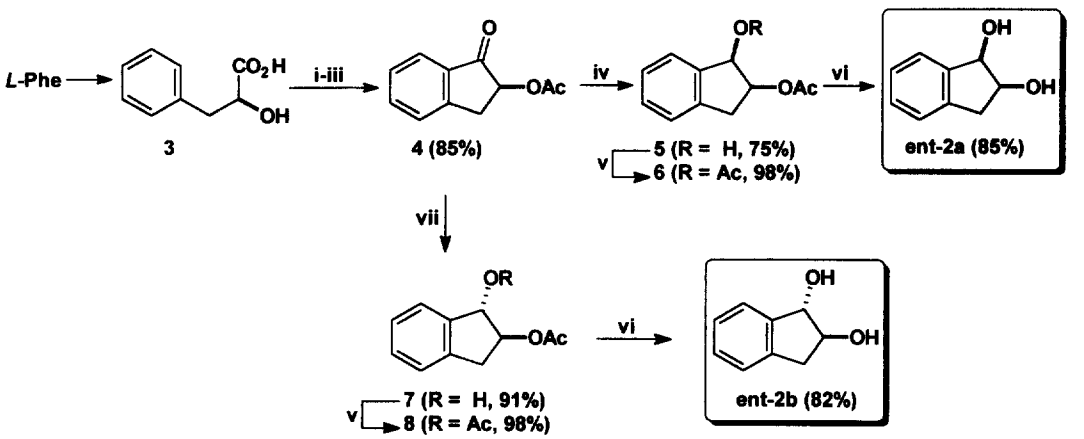

Scheme 1. **i)** AcCl, 40°; **ii)** $SOCl_2$, Bz, 80°; **iii)** $AlCl_3$, CH_2Cl_2, RT; **iv)** $LiAlH(OBu\text{-}t)_3$, THF, 0°; **v)** Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, RT; **vi)** KOH, MeOH, H_2O, reflux; **vii)** $PhMe_2SiH$, TFA, 0°.

To obtain the *trans*-diol (**ent-2b**), the acetoxy indanone **4** was reduced under Hiyama's chelation controlled conditions ($PhMe_2SiH$, TFA, 0°)[9] which led to the formation of the *trans*-diol monoacetate **7** (91%) as a single diastereomer (**Scheme 1**). The corresponding diacetate (**8**, 98%) was again prepared which confirmed the *trans*-diol stereochemistry ($J_{1,2}$ = 3.5 Hz). Hydrolysis of **7** (or **8**), as before, then gave 1*S*,2*S*-indan-1,2-diol (**ent-2b**) in 82% yield {$[\alpha]_D$ +30.5 (c 0.675, EtOH), lit[5c] $[\alpha]_D$ +30 (EtOH)}.

In summary, we have described a facile new synthetic route to homochiral indan-1,2-diols, specifically the 1*R*,2*S*- and the 1*S*,2*S*-isomers (**ent-2a,b**). A homochiral synthesis of **2a,b** should also be possible via the above methodology, simply by switching the chiral pool i.e. by starting with (*R*)-**3** (readily available from D-Phe). Synthetic use of these diols, not only in the preparation of amino indanols, but also as a new class of chiral auxiliaries, is currently under investigation.

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