Synthesis of Optically Pure 1-Amino-3-aryl Indanes Exemplified by (+)-Indatraline

Niels Grøn Nørager,[a,b] Linda Luise Reeh Lorentz-Petersen,[a,c] Lars Ole Lyngsø,[d] Jan Kehler,[a] Karsten Juhl*[a]

[a] Discovery Chemistry and DMPK, H., Lundbeck A/S, Otilliavej 9, 2500 Valby, Denmark
Fax +45(364)38237; E-mail: kaju@lundbeck.com

[b] Department of Chemistry, Aarhus University, Langelandsgade 140, 8000 Aarhus C, Denmark

[c] Department of Chemistry, Technical University of Denmark, Bldg. 201, Kemitorvet, 2800 Kgs. Lyngby, Denmark

[d] Process Research, H. Lundbeck A/S, Ottiliavej 9, 2500 Valby, Denmark

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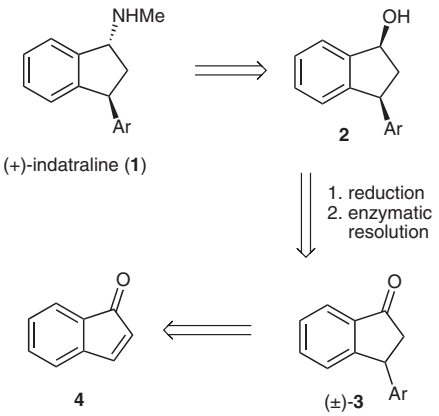
Abstract: A versatile procedure for the synthesis of optically pure 1-amino-3-aryl indanes is presented, exemplified by the synthesis of the triple uptake inhibitor (+)-indatraline (**1**).

Key words: indane, indatraline, enzymatic resolution, conjugate addition, rhodium

The 1-aryl indane motif is a common scaffold, which is found in several compounds of interest to medicinal chemists. The scaffold has been used in drug candidates aiming at modulating a diverse group of target structures, e.g. the dopamine,[1] serotonin[2] and neurokinin-2 receptors,[3] as well as the monoamine transporters.[4] Among these drug candidates are (+)-indatraline (Lu 19-005, **1**) a potent reuptake inhibitor of serotonin, noradrenalin and dopamine that has been investigated as a potential drug for the treatment of major depressive disorder and cocaine addiction.[4,5]

In this letter, we report a method for the synthesis of optically pure 1-amino-3-aryl indanes, illustrated by the synthesis of (+)-indatraline (**1**). Earlier syntheses of this scaffold have primarily been based on assembling of the indane motif by cyclization reactions, e.g. by intramolecular electrophilic aromatic substitution.[5,6] These cyclization reactions have required harsh, strongly acidic conditions resulting in limited scope tolerance, especially of substituents at the C4–C7 positions. Heck cross-coupling,[7] Claisen-type cyclization[8]and iodide(III)-mediated ring contraction[9] have also been applied in the syntheses of 1-amino-3-aryl indanes. To expand the scope of tolerated substrates we set out to develop a mild procedure that would also allow easy variation of the 3-aryl moiety. We envisaged that this could be achieved by starting from 1-indanone, where the bicyclic moiety is already formed, thus circumventing the scope limitations associated with the ring-closing reactions. Related approaches have previously been reported by Itoh et al.[8] and Cossy et al.[10]

Scheme 1 outlines our approach to the synthesis of (+)-indatraline (**1**). Functional group interconversion of the amine to the alcohol would result in a secondary alcohol, which we envisioned could act as a handle for an enzymatic resolution, thus introducing enantioselectivity to our synthesis. The *cis*-indanol **2** would be obtained by a diastereoselective ketone reduction of the racemic 3-aryl-1-indanone **3**. This intermediate would be synthesized by a rhodium-catalyzed conjugate addition of an arylboronic acid to 1-indenone (**4**), which could be obtained from the commercially available 1-indanone.



Scheme 1 Retrosynthetic analysis of (+)-indatraline (**1**)

The starting point of our synthesis was 3-bromo-1-indanone (**5**), which can be prepared from 1-indanone by a Wohl–Ziegler bromination.[11]The first steps were an elimination reaction followed by a conjugate addition. Addition of one equivalent of triethylamine in THF at room temperature led to complete elimination of hydrogen bromide within an hour. The elimination occurred so cleanly that the crude 1-indenone (**4**) could be used directly in the next step after filtration and evaporation of solvent. Avoidance of purification of the 1-indenone was desired, as 1-indenones are generally unstable, readily polymerizing.[12]

Inspired by the work of Miyaura and Hayashi,[13] we developed a method for transformation of the enone **4** into the 3-aryl-1-indanone **3** using a rhodium-catalyzed conjugate addition of 3,4-dichlorophenylboronic acid. Enone **4** was treated with a mixture of 3 mol% of bis(norbornadiene)rhodium(I) tetrafluoroborate and racemic BINAP, one equivalent of triethylamine and two equivalents of arylboronic acid in 1,4-dioxane–water (9:1). Heating at

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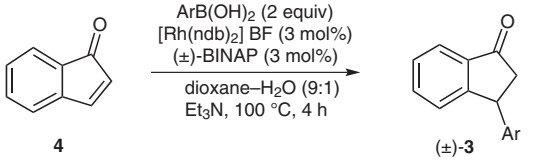
100 °C for four hours resulted in 74% of **3** over the two steps. An excess of boronic acid was required to counter decomposition of the aryl substrate via protonolysis of either the boron–phenyl or rhodium–phenyl bonds.[13a] To explore the scope of boronic acids tolerated by this procedure, a simple phenylboronic acid, as well as an electron-rich 4-methoxyphenylboronic acid, were screened. They were both tolerated, albeit in lower yields than the 3,4-dichlorophenylboronic acid (Table 1). In our initial synthetic strategy, we envisioned that this conjugate addition could be made enantioselective if catalyzed using an enantiopure chiral catalyst. A related conjugate addition of a boronic acid to an inden-1-one catalyzed by a chiral rhodium(I)-chiraphos complex has previously been reported to proceed in 27% yield with an enantiomeric excess of 8%.[8] Despite a substantial screening of chiral ligands only low enantioselectivity was obtained. The best selectivity was observed when (*R*)-BINAP was used, as shown in Table 1. Thus, we decided to introduce enantioselectivity later in the synthesis instead.

Table 1 Exploration of the Scope of Tolerated Boronic Acids

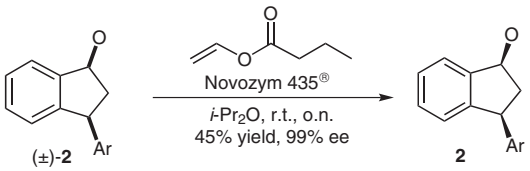


Indanone	Ar	Yield[a]	ee of (*R*)-BINAP[b]
3a	Ph	43%	34%
3b	3,4-$Cl_2C_6H_3$	74%	25%
3c	3-$OMeC_6H_4$	55%	22%

[a] Yield of isolated product with (±)-BINAP as ligand.
[b] Enantiomeric excess from separate experiment with (*R*)-BINAP as ligand. Enantiomeric excess was measured using chiral HPLC.

Indanone **3** was subsequently diastereoselectively reduced with two equivalents of sodium borohydride in THF–water (10:1) at –15 °C overnight. The *cis* isomer of the 3-aryl-1-indanol **2** was formed with a diastereomeric excess of 92%. The two diastereomers could be separated by flash chromatography resulting in pure *cis*-**2** in 91% yield. The *cis* configuration was verified using NOESY spectroscopy.

At this point enantioselectivity was introduced to the synthesis by enzymatic resolution of **2** (Scheme 2).[14] Novozym 435®, which is a lipase capable of enantioselective acylation of secondary alcohols, was used. The Kazlauskas' Model, which states that the lipase distinguishes between the pair of enantiomers on basis of the relative size of the aliphatic substituents, was used to predict the selectivity of the acylation.[15] Thus, in this case the *R*-enantiomer would be acylated. Vinyl butyrate was chosen as the acylation reagent, as the aliphatic chain would incorporate a significant structural difference between the original and the acylated enantiomer, thus facilitating the following chromatographic separation. Acylation in diisopropyl ether at room temperature overnight resulted in a 45% yield of the non-acylated *S*-enantiomer with an enantiomeric excess of more than 99%.

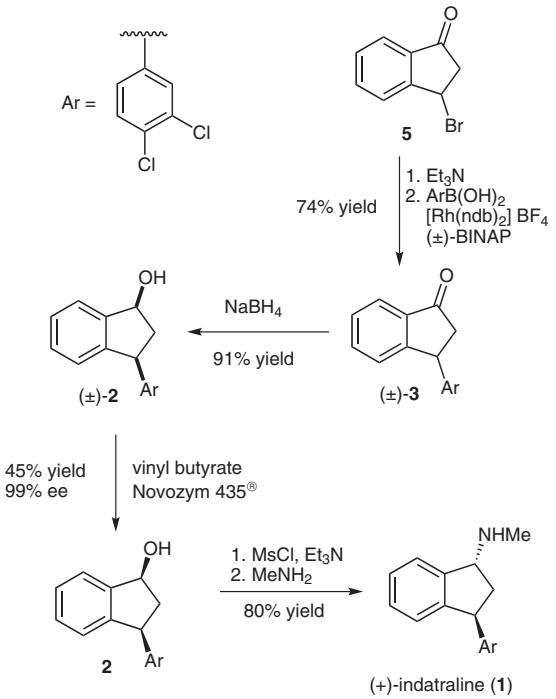


Scheme 2 Enzymatic resolution of (±)-**2**

The synthesis of (+)-indatraline (**1**), was concluded by a methylamine substitution of the hydroxyl group with stereoinversion of the benzylic C1-centre. To obtain complete stereoinversion an azide substitution–reductive alkylation procedure was tested. The hydroxyl group was activated as the corresponding phosphate moiety and substituted by an in situ generated azide nucleophile following a protocol reported by Thompson et al.[16] The azide was subsequently reductively alkylated in a one-pot reaction using dimethylboron bromide.[17] A NOESY experiment verified that the pure *trans* configuration had been formed. However, a moderate yield of 60% for the two steps was obtained.

Thus, a simple one-pot mesylation–nucleophilic substitution procedure developed by Froimowitz et al. was tested as well.[5,6c] The alcohol was mesylated with three equivalents of mesyl chloride and triethylamine in THF at –20 °C. After one hour the mesylated intermediate was treated with a large excess (20 equivalents) of methylamine at –20 °C. Reaction overnight led to a 97:3 (*trans*/*cis*) mixture of the 1-amino-3-aryl indane **1**. Subsequent separation of the diastereomers by crystallization in ethyl acetate–heptane resulted in an 80% yield of the pure *trans* (+)-indatraline (**1**). To verify the absolute configuration of the product it was recrystallized as the L-(+)-tartaric acid salt from diethyl ether–methanol; mp 159–162 °C (lit. mp 159–162 °C);[6a] specific rotation: $[\alpha]_D^{20}$ +29.5 (*c* = 1.0, MeOH) {lit. $[\alpha]_D^{20}$ +33.5 (*c* = 1.0, MeOH)}.[6a]

In conclusion we have synthesized enantiopure (+)-indatraline (**1**), in a yield of 24% over five steps starting from 3-bromo-1-indanone (Scheme 3). The two key steps of the synthesis were a rhodium-catalyzed conjugate addition of an arylboronic acid, and an enzymatic resolution introducing enantioselectivity. The main advantage compared to earlier reported syntheses is avoidance of the scope limitations associated with the ring-closing reactions. Mild conditions and reagents were used throughout the synthesis, ensuring a broad scope of tolerated substrates. Additionally, the developed conjugate addition was shown to tolerate simple phenyl groups as well as electron-poor and electron-rich aryl groups. The enzymatic resolution generates pure samples of both enantiomers, thus synthesis of both the (+)- and (–)-enantiomers is possible using this procedure.



Scheme 3 The complete synthetic pathway

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References

(1) Bøgesø, K. P.; Arnt, J.; Frederiksen, K.; Hansen, H. O.; Hyttel, J.; Pedersen, H. *J. Med. Chem.* **1995**, *38*, 4380.
(2) Bøgesø, K. P.; Arnt, J.; Hyttel, J.; Pedersen, H. *J. Med. Chem.* **1993**, *36*, 2761.
(3) Guillon, J.; Dallemagne, P.; Léger, J.-M.; Sopkova, J.; Bovy, P. R.; Jarry, C.; Rault, S. *Bioorg. Med. Chem.* **2002**, *10*, 1043.
(4) Hyttel, K.; Larsen, J.-J. *J. Neurochem.* **1985**, *44*, 1615.
(5) Froimowitz, M.; Wu, K.-M.; Moussa, A.; Haidar, R. M.; Jurayj, J.; George, C.; Gardner, E. L. *J. Med. Chem.* **2000**, *43*, 4981.
(6) See for example: (a) Bøgesø, K. P.; Christensen, A. V.; Hyttel, J.; Liljefors, T. *J. Med. Chem.* **1985**, *28*, 1817. (b) Bøgesø, K. P. *J. Med. Chem.* **1983**, *26*, 935. (c) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *42*, 4951.
(7) See for example: (a) Püschl, A.; Rudbeck, H. C.; Faldt, A.; Confante, A.; Kehler, J. *Synthesis* **2005**, 291. (b) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550.
(8) Itoh, T.; Mase, T.; Nishikata, T.; Iyama, T.; Tachikawa, H.; Kobayashi, Y.; Yamamotod, Y.; Miyaurad, N. *Tetrahedron* **2006**, *62*, 9610.
(9) Silva, L. F. Jr.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguetto, A. C. *Org. Lett.* **2007**, *9*, 1433.
(10) Cossy, J.; Belotti, D.; Maguer, A. *Synlett* **2003**, 1515.
(11) Podgorsek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Tetrahedron Lett.* **2006**, *47*, 1097.
(12) Marvel, C. S.; Hinman, C. W. *J. Am. Chem. Soc.* **1954**, *76*, 5435.
(13) See for example: (a) Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052. (c) Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem.* **2003**, *68*, 6000.
(14) Ghanem, A. *Tetrahedron* **2007**, *63*, 1721; and references therein.
(15) See for example: (a) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656. (b) Cygler, M.; Grochulski, P.; Kazlauskas, R. J.; Schrag, J. D.; Bouthillier, F.; Rubin, B.; Serreqi, A. N.; Gupta, A. K. *J. Am. Chem. Soc.* **1994**, *116*, 3180.
(16) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.
(17) Dorow, R. L.; Gingrich, D. E. *J. Org. Chem.* **1995**, *60*, 4986.