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Asymmetric synthesis of (+)-indatraline using rhodium-catalyzed C–H activation

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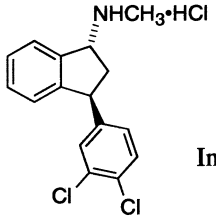
Abstract—The potent monoamine reuptake inhibitor (+)-indatraline, **1**, was prepared in greater than 98% ee employing a highly enantioselective carbenoid C–H insertion reaction into 1,4-cyclohexadiene catalyzed by the chiral rhodium complex, Rh_2(*S*-DOSP)$_4$.

Indatraline (Lu 19-005, **1**) is a potent psychoactive compound with high binding and inhibitory affinity for neuronal monoamine reuptake sites including the dopamine (DA) transporter and the serotonin (5HT) transporter.[1,2] In vivo dialysis and behavioral studies have indicated a potent dopaminergic mechanism of action for the effects of **1**[3] and that these effects have a long duration of action.[4] Studies in monkeys indicated that **1** reduced cocaine self administration[5] and that potency was more than 20 times higher in the (+)-(1*R*,3*S*) enantiomer than in the (–)-(1*S*,3*R*) enantiomer.[6]



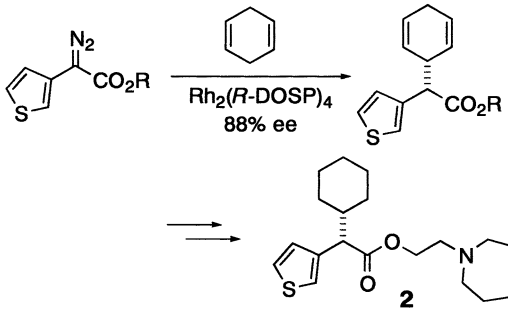
1

Indatraline

The 1-aminoindan scaffold of **1** has attracted interest in studies aimed at finding long-acting reuptake inhibitors that could prove useful in treating abuse of cocaine, methamphetamine and other dopaminergically operant substances.[7–9] Several reports have appeared recently describing the preparation of compounds related to **1** and their affinities for various monoamine transporters.[10,11]

Previous reports of the synthesis of **1** have outlined preparation of the compound in racemic form, and have relied on classical resolution or chiral HPLC techniques to obtain enantiomerically pure material.[1,10] While these approaches served, at the time, to ascertain the biologically active enantiomer, we are interested in preparing a large number of derivatives thus greatly expanding the SAR of the (1*R*,3*S*)-indatraline scaffold for binding at the DA and 5HT transporters. We have therefore undertaken a synthesis of (+)-**1** that could provide enantiomerically pure derivatives prior to the last step.

The first step in the synthesis employs a novel C–H activation process that we have developed for the rapid enantioselective assembly of complex structures.[12] This process has the potential to provide products equivalent to asymmetric Claisen,[13] aldol,[14] Michael[15] and Mannich reactions.[16] The enantioselective C–H insertion of methyl aryldiazoacetates into 1,4-cyclohexadiene gives access to chiral 2,2-diaryl acetates in high yield and with enantioselectivities of up to 95% ee in either enantiomeric series.[17] We have recently expanded the scope of this reaction to include the use of heteroaryldiazoacetates resulting in the efficient enantioselective synthesis of the antiepileptic compound (+)-cetiedil, **2**, illustrated in Eq (1).[18]



2 (1)

Keywords: indatraline; dopamine transporter; C–H activation; rhodium carbene; C–H insertion.

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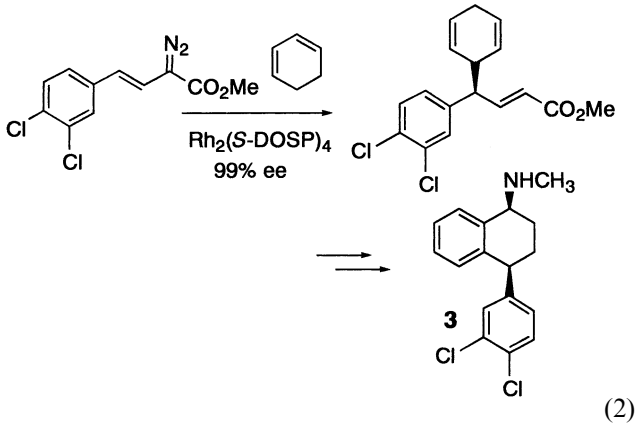
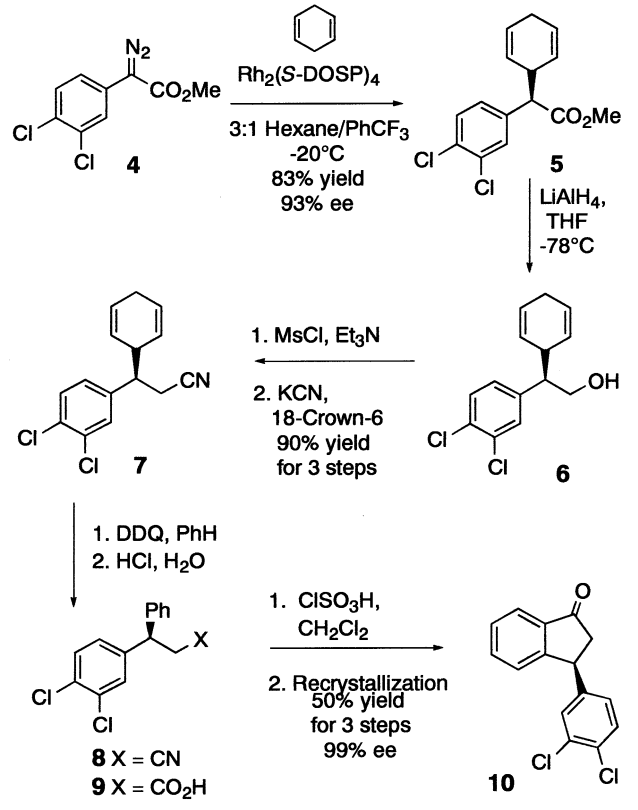
Furthermore, the closely related reaction of phenyldiazobutenoates with 1,3-cyclohexadiene provides 4,4-diarylbutanoates in high enantiomeric excess, and has been used in a formal total synthesis of (+)-sertraline, **3**, as illustrated in Eq (2).[17]

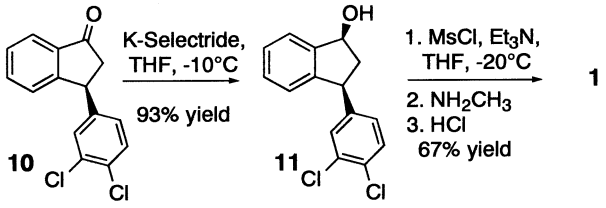


(2)

Our synthesis of (+)-**1** is depicted in Scheme 1. Reaction of (3,4-dichlorophenyl)diazoacetate, **4**, with 1,4-cyclohexadiene catalyzed by dirhodium tetrakis-((*S*)-*N*-dodecylbenzenesulfonyl)prolinate[19] (Rh_2(*S*-DOSP)$_4$) gave C–H insertion product **5** in 83% yield and 93% ee.[20] The cyclohexadienyl moiety in **5** was carried through the subsequent homologation steps in order to lessen the likelihood of epimerization at the already doubly activated chiral center. Reduction of **5** with $LiAlH_4$ (1.3 equiv.) at −78°C gave alcohol **6**. Homologation of the primary alcohol by formation of the mesylate, then treatment with KCN and 18-crown-6 (2 and 1 equiv., respectively) in refluxing acetonitrile gave nitrile **7** in 90% yield over the three steps. Aromatization of **7** with DDQ (2 equiv.) gave 3,3-diarylpropionitrile, **8**, and nitrile hydrolysis with aqueous HCl/AcOH gave carboxylic acid **9**. Cyclization using chlorosulfonic acid gave ketone **10** in 92% ee. This compound was recrystallized from hot heptane providing **10** in 50% yield for the three steps and in greater than 99% ee.



Scheme 1.



Scheme 2.

Reduction of **10** with K-Selectride® (Scheme 2) gave *cis* alcohol **11** in 93% yield. (1*R*,3*S*)-**1** was prepared by adapting the procedure of Froimowitz.[10] Thus, treatment of **11** and triethylamine in CH_2Cl_2 with mesyl chloride at −20°C followed by addition of condensed methylamine (20 equiv.) and slow warming of the reaction mixture to rt gave the free amine as a pale yellow oil. Treatment of this with HCl in ether gave the salt as a pale yellow solid, and recrystallization from ethyl acetate/ethanol (20:1) gave **1** in 67% yield for the three steps. To confirm the (1*R*,3*S*) absolute stereochemistry of **1**, the free amine was treated with 0.5 equiv. L-(+)-tartaric acid in MeOH to give a white solid which was recrystallized from ethyl acetate/MeOH to give the tartrate salt. Mp: 157–161°C; $[\alpha]_D^{25}=+31.7°$ (*c* 2.25, MeOH), (lit.[1] mp: 159–162°C; $[\alpha]_D^{25}=+33.5°$ (*c* 3, MeOH)).

In conclusion, intermolecular asymmetric C–H activation catalyzed by a chiral dirhodium species gives convenient entry into 3,3-diarylpropionates and provides the key step in the synthesis of the potent dopamine reuptake inhibitor, (+)-indatraline. The synthesis is well suited to preparation of a variety of related 3-aryl-1-aminoindan derivatives, the preparation and biological activity of which will be reported in the near future.

Acknowledgements

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20. A solution of 4.9 g (61 mmol) of 1,4-cyclohexadiene and 230 mg (0.120 mmol) of $Rh_2(S\text{-DOSP})_4$ in degassed hexane (150 ml) was cooled to −20°C. To this was added a degassed solution of 5.1 g (21 mmol) of **4** in 3:1 hexane/α,α,α-trifluorotoluene (200 ml) dropwise over 3 h. The reaction warmed to rt and stirred for 15 h. Evaporation of volatiles at reduced pressure and chromatography with 2–10% ethyl ether/pet. ether gave 5.1 g (17 mmol, 83%) of **5** as a colorless oil: R_f 0.43 (10% ethyl acetate/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, $J=2.1$ Hz, 1H), 7.31 (d, $J=8.2$, 1H), 7.11 (dd, $J=8.1$, 2.1 Hz, 1H), 5.70–5.78 (m, 1H), 5.60–67 (m, 1H), 5.55–5.59 (m, 1H), 5.19–5.24 (m, 1H), 3.69 (s, 3H), 3.30–3.39 (m, 2H), 2.45–2.58 (m, 2H); ^{13}C NMR δ 26.2 (CH_2), 38.5 (CH), 52.1 (CH_3), 57.1 (CH), 124.9 (CH), 125.9 (CH), 126.7 (CH), 126.7 (CH), 128.1 (CH), 130.2 (CH), 130.6 (CH), 131.5 (C), 132.4 (C), 136.8 (C), 172.5 (C); $[\alpha]_D^{25}=127°$ (*c* 0.97, $CHCl_3$); IR cm^{-1} 3029, 2951, 1736, 1471, 1160, 1031, 704. Anal. calcd for $C_{15}H_{14}Cl_2O_2$: C, 60.62; H, 4.75. Found: C, 60.61; H, 4.79%; HPLC, 25×4.6 mm i.d. Chiralcel OD-H column, 0.5% isopropanol 99.5% hexane, 0.9 ml/min, t_R(minor) 6.3 min; t_R(major) 10.9 min.