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A convenient enantioselective synthesis of 3-asymmetrically substituted oxindoles as progesterone receptor antagonists

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ABSTRACT

A convenient enantioselective synthesis of 3-asymmetrically substituted oxindoles is reported. Compound (**2**) prepared by radical cyclisation of (**1**) was used for the synthesis of racemic and enantiomerically pure 3-asymmetrically substituted oxindoles. Desulfurisation of (**2**) using Raney Ni yielded the racemate (**5**). Addition of (*S*)-1-phenylethanol to compound (**2**) yielded the diastereoisomer (**21**) the structure of which was determined using X-ray crystallography. Using a sequence of steps (**21**) was converted to the enantiomer (**8**). The enantiomer (**9**) was similarly prepared from (**2**) using (*R*)-1-phenylethanol.

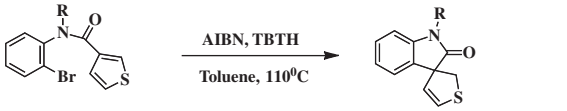
In a previous publication[1] from our laboratory we reported the conversion of compound (**1**–**2**) using tributyltin hydride, 2,2′-azobisisobutyronitrile (AIBN) in toluene solution at 110 °C (Scheme 1). We repeated the reaction with (**3**) and obtained (**4**). Compounds (**1**) and (**3**) were easily prepared by treating ortho bromoaniline with the acid chloride derived from thiophene-3-carboxylic acid in the presence of pyridine, followed by N-alkylation of the amides.

In this Letter we wish to report the conversion of (**2**–**5**) and (**4**–**6**) both of which are asymmetrically substituted oxindoles (Scheme 2), a feature present in several natural products and pharmaceutical molecules.[2,3] We have also successfully used (**2**) for the enantioselective synthesis of this class of compounds. Using our synthetic procedure described in this Letter we have synthesised[4] racemic (**7**) and enantiomerically pure (**8**) and (**9**) (Fig. 1). These compounds are novel and related to Wyeth 255348,[5a] which has been reported to be a potent progesterone receptor antagonist. Excepting racemic (**10**)[5b] all the compounds synthesized by Wyeth scientists were symmetrically substituted oxindoles. We wish to report the progesterone receptor antagonist activity of our compounds. Progesterone receptor antagonist, mifepristone[6a] has been in use in the clinic as an abortifacient. They are also potentially useful for the treatment of cancer and non-malignant chronic conditions such as uterine fibroids and endometriosis.[6b–f]

Thus the key intermediates (**2**) and (**4**) when treated with Raney Ni in the presence of isopropyl alcohol under refluxing conditions provided the desulfurised products (**5**) and (**6**), respectively. Bromination of (**5**) and (**6**) using Br_2/AcOH and NaOAc afforded the 5-bromooxindoles (**11**) and (**12**), respectively (Scheme 3). Palladium-catalyzed Suzuki coupling of (**11**) with phenylboronic acid (**13**) in dimethoxyethane and water (1:1) as solvent and in the presence of sodium bicarbonate afforded (**14**) as a racemate. The *N*-benzyl analog (**15**) was similarly synthesized from (**12**). Suzuki coupling of (**11**) with 4-fluorophenylboronic acid (**16**) and 2-thiopheneboronic acid (**17**) yielded (**7**) and (**18**), respectively.

The synthesis of N–H analog (**20**) is shown in Scheme 4. Compound (**6**) on treatment with *N*-bromosuccinimide and AIBN in ethyl acetate under refluxing conditions afforded (**19**) wherein the debenzylation and bromination occurred in one step.[7] The bromo intermediate (**19**) was further reacted with phenylboronic acid (**13**) under Suzuki coupling conditions to yield (**20**).

The racemic compounds (**14**), (**15**), (**7**), (**18**), and (**20**) were evaluated for progesterone receptor antagonist activity. In this assay compound (**7**) was most potent with an $IC_{50} = 50$ nM and (**15**) was inactive.



(1) R= -CH_3
(3) R= -CH_2-Ph

(2) R= -CH_3; Y: 52%
(4) R= -CH_2-Ph;Y: 51%

Scheme 1. Radical reaction.

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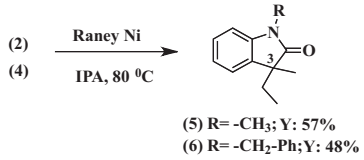


Scheme 2. 3-Unsymmetrically substituted oxindoles.

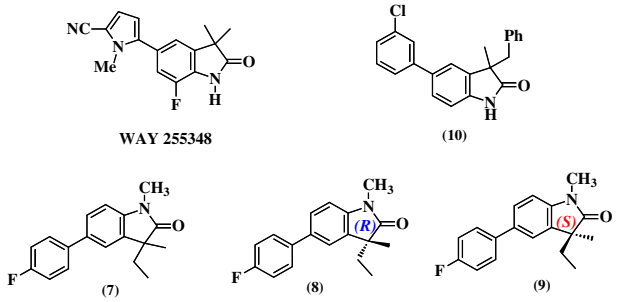
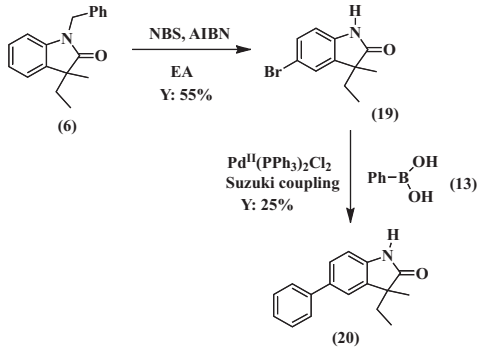


Figure 1. Spiro-oxindoles.



Scheme 4. Synthesis of (**20**).

Compound (**18**) showed IC_{50} = 295 nM. The N-unsubstituted compound (**20**) showed IC_{50} = 161 nM and the corresponding *N*-methyl compound (**14**) showed IC_{50} = 141 nM.

We decided to use the key intermediate (**2**) for the enantioselective synthesis of the enantiomers of (**7**) to determine their activities compared to the racemate. Thus treatment of spirooxindole (**2**) with (*S*)-1-phenylethanol in the presence of *p*-toluenesulfonic acid and toluene at room temperature afforded a mixture of diastereoisomers. Purification by chromatographic techniques yielded diasteroisomer (**21**)[8] (Scheme 5). The absolute stereochemistry of (**21**) was established as C3(*S*), C13(*R*), C17(*S*) using X-ray crystallographic analysis[9] (Fig. 2).

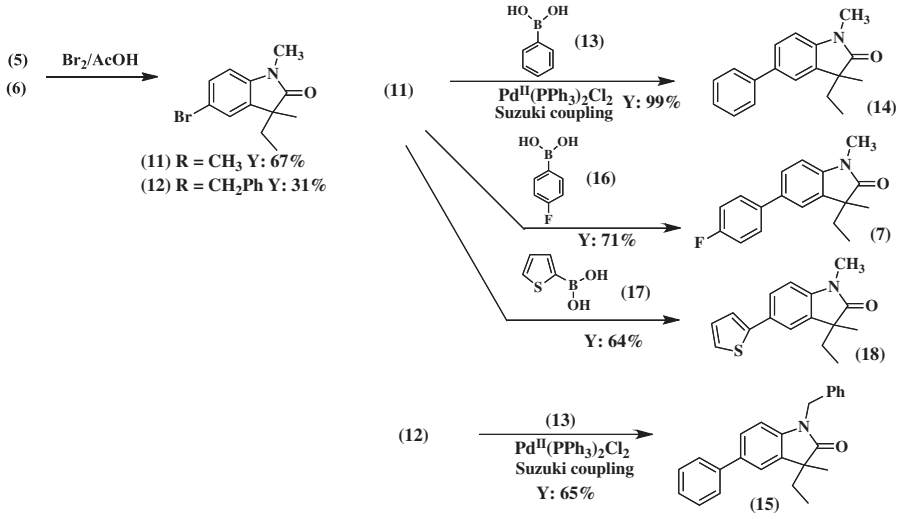
Treatment of compound (**21**) with Raney Ni in isopropyl alcohol under refluxing conditions gave the alcohol (**23**). The above step, however, yielded the alcohol in variable yields. Thus we investigated alternative methods for desulfurisation.

After several experiments desulfurisation of compound (**21**) was achieved reproducibly using nickel boride.[10] Compound (**21**) was thus converted to (**22**) using nickel boride (prepared in situ using nickel chloride/sodium borohydride in 3:1 mixture of methanol and THF). Hydrogenation of compound (**22**) in the presence of 10%Pd/C and catalytic amount of trifluoroacetic acid in methanol gave the alcohol (**23**). In the literature, compound (**24**) was reported as a key intermediate in the asymmetric synthesis of physostigmine and physovenine.[11] Our synthetic approach will thus provide an alternative way of making these alkaloids.

Bromination of (**23**) using NBS and AIBN in refluxing ethanol yielded (**25**) which underwent Suzuki coupling with 4-fluorophenylboronic acid (**16**) to give the alcohol (**26**).

Deoxygenation[12] of (**26**–**8**) was achieved using the following two steps. Compound (**26**) was treated with *p*-toluenesulfonyl chloride and pyridine in DCM to yield (**27**), which upon treatment with NaI, AIBN and TBTH using dimethoxyethane as solvent at 80 °C yielded the (*R*)-enantiomer (**8**).

Having established the synthetic procedures for the preparation of the (*R*)-enantiomer (**8**) we followed a similar concept for the preparation of the corresponding (*S*)-enantiomer (**9**). Thus spirooxindole (**2**) when treated with (*R*)-1-phenylethanol and *p*-toluenesulfonic acid in toluene gave the diastereoisomer (**28**) (Scheme 6). Compound (**28**) was determined to be the enantiomer of (**21**) the absolute stereochemistry of which was assigned based on the X-ray crystallographic analysis. Compounds (**21**) and (**28**) were identical in their spectroscopic properties including NMR spectroscopy however in CD studies they showed similar rotation values with opposite signs. Thus the absolute stereochemistry of compound (**28**) is assigned to be C3(*R*), C13(*S*), C17(*R*). Following the same sequence of steps as in Scheme 5, compound (**28**) afforded the desulfurised product (**29**), which upon hydrogenation yielded



Scheme 3. Bromination and Suzuki coupling.