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Expeditious synthesis of tri-substituted cyclopentane derivatives

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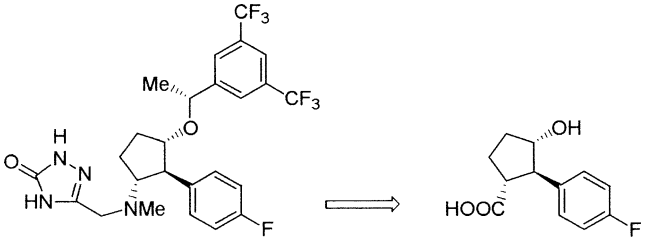
Abstract—An efficient preparation of the cyclopentane scaffold **2**, a key precursor to the potent human NK1 antagonist **1** having three contiguous chiral centers is described. © 2002 Published by Elsevier Science Ltd.

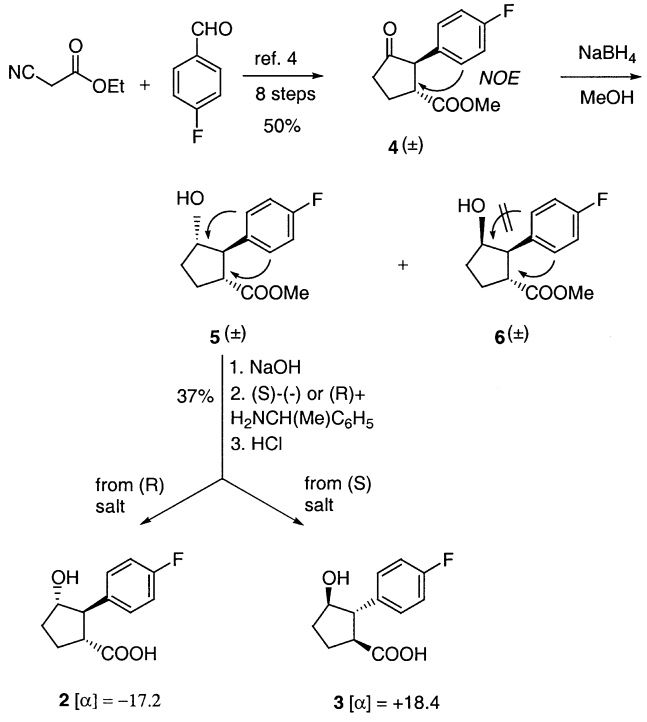
Human neurokinin-1 (hNK1) is a member of the G-protein coupled family of receptors. The endogenous ligand for this receptor is the tachykinin peptide Substance P (SP), which has been implicated in the pathophysiology of a diverse range of conditions, including asthma, inflammatory bowel disease, pain, migraine, emesis, anxiety/depression, and schizophrenia.[1] This profile has stimulated an intense search for potent, non-peptide antagonists of hNK1.[2] Recently, we have reported a series of potent, orally active antagonists of hNK1 having a cyclopentane core structure as illustrated in structure **1**.[3] Compound **1** was derived from the cyclopentane **2** which has three contiguous chiral centers in an all *trans* relationship.



1 hNK1 IC_{50} = 0.18 nM **2**

Our initial approach for the synthesis of compound **2** is shown in Scheme 1. The key intermediate (±)-*trans*-3-oxo-2-(4-fluorophenyl)cyclopentane carboxylic acid methyl ester **4** was synthesized based on the literature procedure of Baker and Leeds.[4] Reduction of ketone **4** with L-Selectride produced only the 1,2-*cis* diastereomer **6**, while use of $NaBH_4$ resulted in a separable 4:1 mixture in which the *trans* isomer **5** now predominated. The assignments for isomers **5** and **6** were confirmed by NOE experiments on the corresponding acid derivatives. Hydrolysis of **5** followed by the resolution of the acid using (*S*) or (*R*)-α-methylbenzylamine furnished chiral acids **2** and **3**.

The absolute stereochemistry of the *trans* derivative **3** was unequivocally established using the X-ray crystallography. While this approach met our initial objective of synthesizing intermediate **2**, it became apparent that for a larger scale (>50 g) preparation required for the SAR development of this class, there was a need for an alternative process. This was due to the length of the



Scheme 1.

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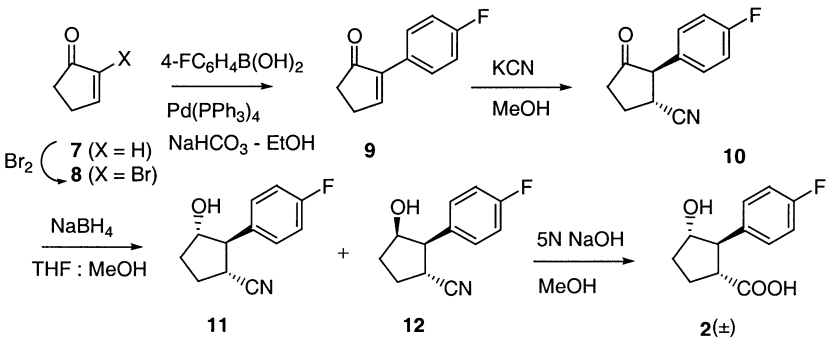

Scheme 2.

synthesis (10 steps to **2**) and the need to handle a large amount of concentrated hydrochloric acid in the preparation of the starting keto derivative **4**. Herein, we describe an efficient synthesis of the cyclopentane scaffold **2** (Scheme 2).

The starting 2-bromo-2-cyclopenten-1-one **8** was conveniently prepared from cyclopenten-1-one **7** as described by Smith et al.[5] The Suzuki coupling of **8** and 4-fluorophenylboronic acid was achieved using $Pd(PPh_3)_4$ as the catalyst to furnish compound **9** in 67% yield.[6] The stage was now set for the introduction of the desired carboxylic acid functionality at C-3. Towards this end, the conjugate addition of cyanide to **9** was carried out with aqueous KCN in methanol at 0°C to provide **10** in 71% yield after chromatography. Subjecting compound **10** to sodium borohydride reduction at −78°C gave a mixture of **11** and **12**. Separation of this mixture by silica gel chromatography furnished the desired intermediate **11** in 72% yield.

Hydrolysis of nitrile group of **11** with 5N aqueous sodium hydroxide in methanol afforded the racemic cyclopentane carboxylic acid **2** as a white solid in 91% yield.[7] This material was found identical to the all *trans* derivative obtained via Scheme 1. Subsequent resolution as described before provided chiral **2**.

In conclusion, we have developed a shorter and more efficient five step synthesis of the key racemic cyclopentane intermediate **2** having three contiguous chiral centers. This process employs a Suzuki coupling as the key step to install the substituted phenyl functionality onto a cyclopentene ring with a subsequent conjugate addition of the nitrile. The wide availability of substituted phenylboronic acids makes this approach highly attractive for the synthesis of a variety of interesting targets. We have also successfully extended this method to the synthesis of the cyclohexane derivatives which will be the subject of a future publication.

Acknowledgements

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7. Selected ^{1}H NMR data. Ester **4** ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.08 (2H, m), 6.98 (2H, m), 3.66 (1H, d, $J=11.4$), 3.65 (3H, s), 3.17 (1H, dt, $J=6.5$, 11.4), 2.59 (1H, dd, $J=8.5$, 18.7), 2.41 (1H, m), 2.34 (1H, m), 2.05 (1H, m). Carboxylic acid of **5** ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.18 (2H, m), 6.98 (2H, m), 4.15 (1H, q, $J=7.0$), 3.18 (1H, dd, $J=7.7$, 9.6), 2.90 (1H, m), 2.12 (3H, m), 1.79 (1H, m). Carboxylic acid of **6** ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.19 (2H, m), 6.97 (2H, m), 4.20 (1H, t, $J=4.3$), 3.27 (1H, dd, $J=4.3$, 11.5), 3.24 (1H, dd, $J=8.6$, 11.4), 2.28 (1H, m), 2.06 (1H, m), 1.91 (1H, m), 1.80 (1H, m).