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Short Research Article

C-14, C-13, H-2 labeling of NVP-ACQ090 – a potent and selective somastatin sst_3-receptor antagonist†

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Introduction

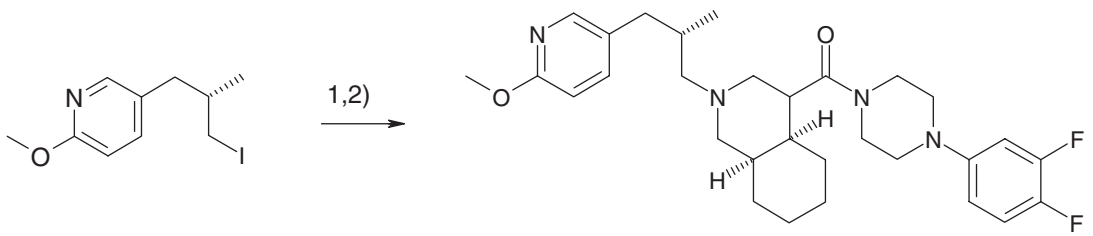
Somastatin is a widely distributed peptide hormone originally isolated from the hypothalamus as an inhibitor of growth hormone release.[1] To date, five somastatin receptor subtypes (sst_1 to sst_5) have been characterized.[2a,2b] Data show that NVP-ACQ090 **2** is a highly potent and selective somastatin sst_3-receptor antagonist.

Due to structural simplicity the chiral intermediate **1** was identified as a suitable structural component for labeling in a metabolically stable position (Scheme 1).

Different approaches for the synthesis of the key intermediate 1

The research approach (Scheme 2) was not applicable, since the labeled analogues of the pyridine derivative **3** and the chiral propionate **4** were not easily accessible. Due to elevated reaction conditions (80 bar, 60°C) labeling by chiral hydrogenation was not feasible either (Scheme 3).

Therefore, a diastereoselective approach appeared to be most promising. The (–)-bornane-10,2-sultam moiety is known to be an excellent auxiliary for



1 2

Scheme 1 Synthesis of ACQ090. *Reaction conditions:* (1) amine derivative, K_2CO_3, DMF, 25°C, 24 h, 95%; (2) fumaric acid, 2-propanol/diethyl ether.

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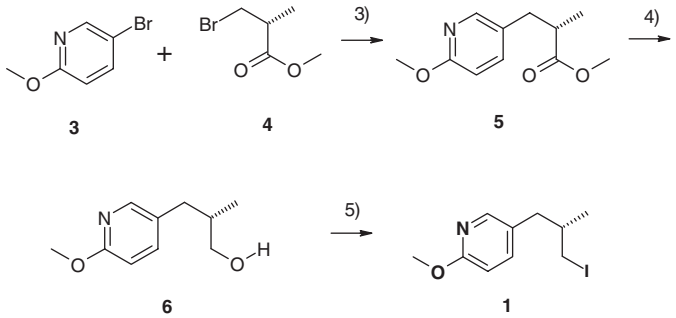
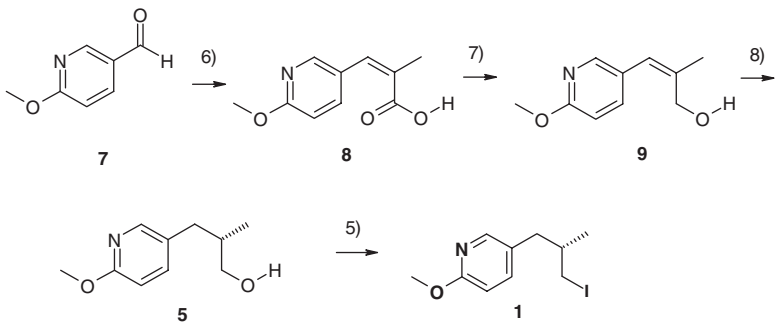
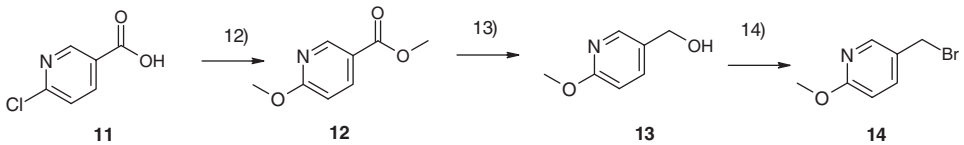


Scheme 2 Research synthesis. *Reaction conditions*: (3) methyl-3-bromo-2(*S*)-2-methyl propionate **4**, $ZnEt_2$, $MnBr_2$, CuCl, DMPU/THF, Pd(dppf)Cl_2, CH_2Cl_2, 43%; (4) $LiAlH_4$, THF, 82%; (5) MeP(I)$(OPh)_3$, DMF, 89%.



Scheme 3 Chemical development synthesis.[3] *Reaction conditions*: (6) $(EtO)_2HPO$/NaH, $HOOCCHBrCH_3$, 79%; (7) $LiAlH_4$, THF, 89%; (8) H_2/[Rh(nbd)Cl_2], (*R*)-*p*-DMA-MeObiphep, $p(H_2) = 80$ bar, 60°C, 19 h, 92% ee, 97%.



Scheme 4 Synthesis of the intermediate **14**. *Reaction conditions*: (12) MeOH, H_2SO_4, 65°C, 12 h, 58%; (13) $LiAlH_4$, diethyl ether, 30°C, 1 h, 68%; (14) PBr_3, CH_2Cl_2, 61% (unstable).

this particular approach.[4] The diastereoselective synthesis makes use of an α-alkylation of the propionyl derivative **10** with the corresponding nucleophile **14**.

Results

Labeling of NVP-ACQ090 2 (overview)

Since it readily polymerized the picolyl bromide **14** was immediately used (Schemes 4 and 5).[5]

Conclusion

The *N*-[^{14}C]propionyl bornane-10,2-sultam **10** provided an excellent auxiliary for the diastereoselective synthesis of labeled 5-((*S*)-3-iodo-2-methyl-propyl)-2-methoxy-pyridine **1** – a suitable key intermediate of labeled ACQ090 **2**.

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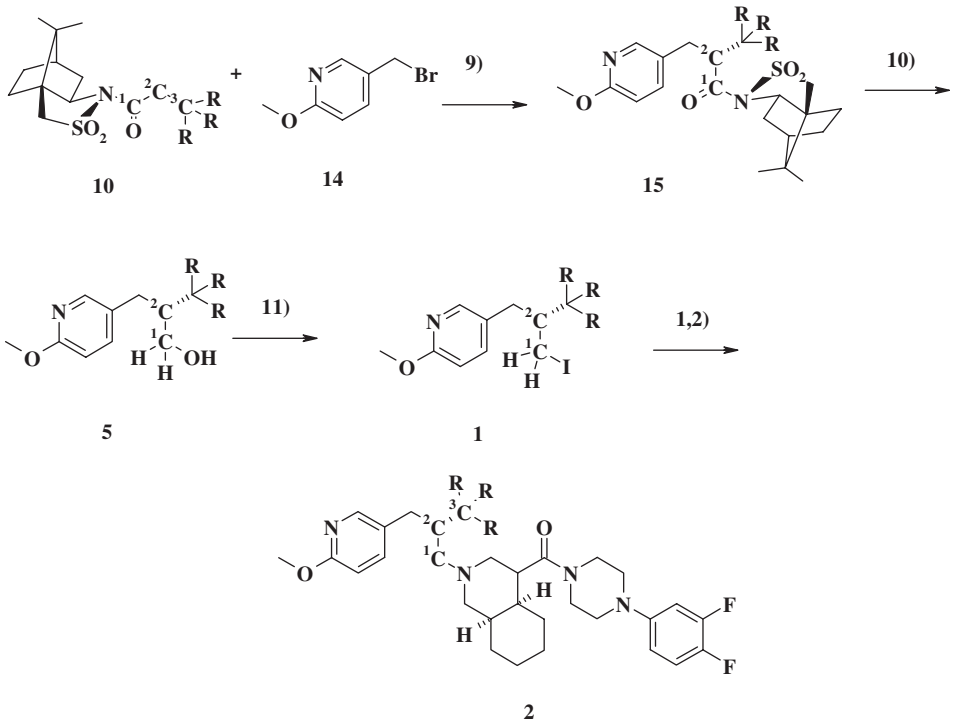

Name	^{1}C	^{2}C	^{3}C	R
A	^{14}C	^{12}C	^{12}C	^{1}H
B	^{13}C	^{13}C	^{13}C	^{2}H

Scheme 5 Synthesis of NVP-ACQ090 **2**. *Reaction conditions*: (9) THF, −78°C, 1 M NaHMDS, HMPT, **14**, N(*n*-Bu)$_4$ I, −78°C, 5 min, 62%; (10) THF, Et_2O, 1 M $LiAlH_4$ in Et_2O, 0°C, 3 h, 64%; (11) DMF, methyltriphenoxyphosphonium iodide, 0°C, 1 h, 30%; (1) K_2CO_3, DMF, 25°C, 24 h, 56%; (2) fumaric acid, 2-propanol/diethylether. *Analytical characterization of* 2A/B: (R)TLC, HPLC >98% (RS), >98%ee, MS 2.2 GBq/mmol, NMR.

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