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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 1609–1612

Diastereoselective synthesis of polyfunctionalized piperidines as precursors of dopamine transporter imaging agents

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Received 16 November 2006; revised 19 December 2006; accepted 22 December 2006
Available online 23 January 2007

Abstract—The design and synthesis of a new kind of precursors of radiolabelled tracer agents for dopamine transporters imaging is described. The concept is based on the possibility of introducing the radioelement far from the sites of recognition and on the fact that only the labelled marker could cross the blood brain barrier to reach the dopamine transporters. For this purpose, a polyfunctionalized piperidine was synthesized bearing two aldehyde functions in the configuration allowing the formation of a tropane analog after the introduction of complexing moieties and complexation of a radioactive metal.

Normal brain functions are controlled by neurotransmitters among which dopamine takes an important part. The depletion of dopaminergic neurons is observed in neurodegenerative disorders, such as Parkinson and Alzheimer diseases, but the first symptoms appear when half of these neurons are affected. Hence, the measurement of their viability through radioactive labelling of the dopamine transporters (DAT) which are located presynaptically, would be a good way to diagnose the disorder very early and also to monitor the progression of these diseases after treatment.[1,2] The nuclear imaging techniques, PET (positron emission tomography) or SPECT (single photon emission computed tomography), allowing non-invasive functional explorations, require the development of radiolabelled tracer agents which present a high affinity for the target receptors.

A large number of DAT imaging agents based on cocaine or other tropane derivatives have been reported as useful PET[3,4] and SPECT[5–7] radiotracers. The PET tracers are labelled with ^{11}C, ^{18}F or ^{123}I but the practical usefulness of these radionuclides is limited due to their short lives (^{11}C, ^{18}F) or high cost (^{123}I). On the other hand, SPECT imaging with γ-emitters such as ^{99m}Tc is the most commonly used method for routine diagnostic nuclear medicine procedures. The PET and SPECT tracers which gave the best results are given in Figure 1.

None of these compounds showed a sufficiently interesting affinity towards DAT, perhaps because the modifications brought by the introduction of the radioelement were performed on the nitrogen atom, or on the C2/C3 positions, which are important sites of interactions of cocaine with the DAT.[8] The structure–activity relationship data suggest that good affinities for the DAT had been obtained with a methyl group on the nitrogen atom, a methyl ester on the C2β position and a tolyl group on the C3β position.[9]

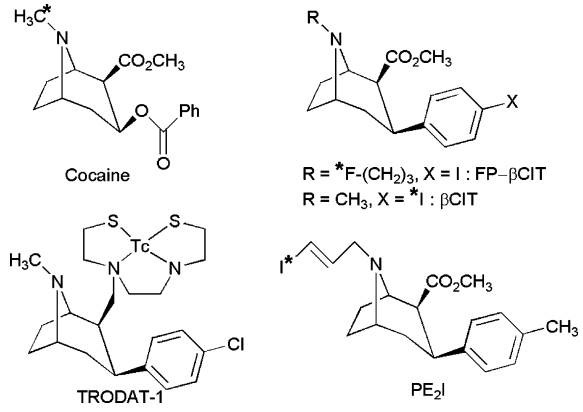

Figure 1. Labelled tropane derivatives synthesized for DAT imaging.

Keywords: Diastereoselectivity; Polyfunctionalization; Tropanes; Piperidines.
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doi:10.1016/j.tetlet.2006.12.141

In this context, we propose an original approach to the labelling of tropane analogues with ^{99m}Tc, by integrating the metal in the bicyclic structure. Indeed, these piperidines, after complexation of the metal, would become a tropane analog able to cross the blood brain barrier to reach dopamine transporters. This concept that we called the 'piperidine ⟺ tropane concept' is illustrated in Figure 2.

The two functions on the C2 and C6 positions of the piperidine could be two amino thiols[10] or two derivatives of *S*-methyl dithiocarbazate[11] allowing, respectively, TcO^{3+} or TcN^{2+} complexation in high yields to give lipophilic neutral complexes. Neutrality and lipophilicity are two conditions required for molecules to cross the blood brain barrier.

This Letter describes the synthesis of polyfunctionalized piperidines bearing the three substituents necessary to the recognition by DAT and two aldehyde functions on the C2 and C6 positions. These aldehyde functions will be the precursors of moieties allowing the introduction of the radioactive metal, so they have to be cis. The target molecules are given in Figure 3.

Although the two substituents on the C2 and C3 positions of natural cocaine are in β position, we thought that it would be interesting to obtain the other isomers besides the 3β4β piperidines: after the natural *R*-cocaine, the most active stereoisomer towards DAT is the *R*-allococaine with C2 substituent in β position and C3 substituent in α position.[12]

The access to the target molecules was guided by the worry of obtaining the proper relative configuration for the two stereogenic centres C2 and C6. We thought

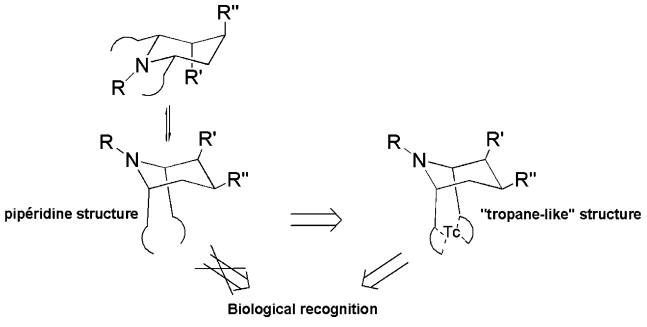


Figure 2. The piperidine/tropane concept.

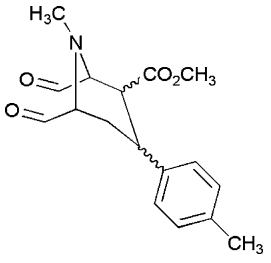
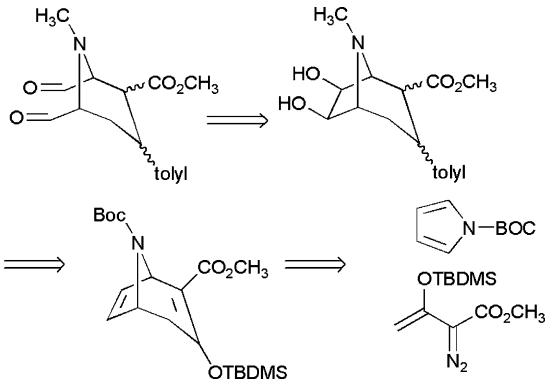


Figure 3. Target molecules **1**.

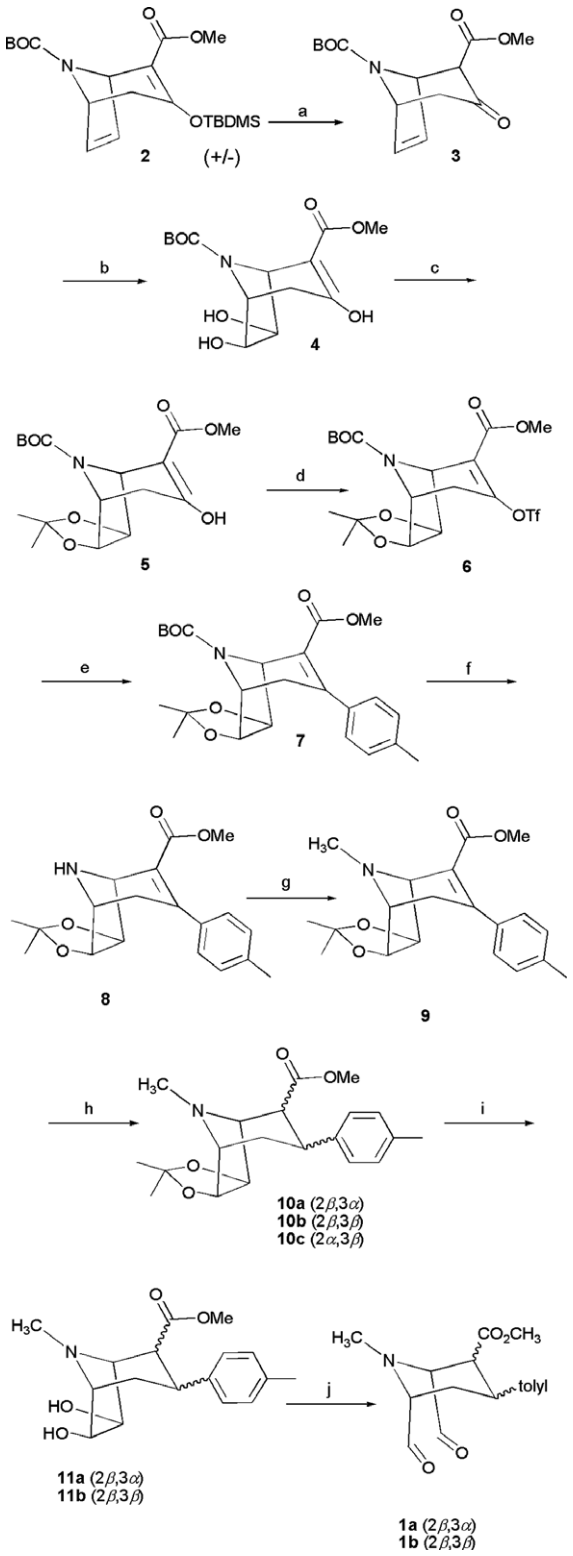


Scheme 1. Retrosynthetic analysis.

that the best way to obtain these configurations was to synthesize a tropane bicycle, functionalized on the C6–C7 bridge so as to allow an oxidative cleavage. This strategy required the total synthesis of the bicycle (Scheme 1).

The synthesis began with a reaction of cyclopropanation/azaCope rearrangement between *N*-Boc-pyrrole and 3-(*tert*-butyldimethylsilanyloxy)-2-diazobut-3-enoic acid methyl ester in the presence of Rhodium(II) octanoate which catalyses diazo group decomposition and stabilize the formed carbenoid. This reaction was first described by Davies on a chiral ester: 3-(*tert*-butyldimethylsilanyloxy)-2-diazobut-3-enoic acid (1*S*)-2-ethoxy-1-methyl-2-oxoethyl ester.[13] We followed the typical procedure and obtained **2** in a 77% yield. The synthesis we developed from the obtained bicycle **2** is outlined in Scheme 2.

The first step of the modification of tropene **2** substitutions consisted in the regeneration of the masked ketone function in the C_3 position by enolate scission using tetrabutylammonium fluoride in THF at 0 °C in a yield of 88%. The double bound was then dihydroxylated with catalytic osmium tetraoxide in the presence of an excess of morpholine-*N*-oxide in order to reoxide osmium. The reaction was highly stereoselective: only the *syn-exo* diol was obtained, in a 95% yield. Before performing the triflation step, it was necessary to protect diol **4** in the acetonide form **5** using 2,2-dimethoxypropane and *para*-toluenesulfonic acid in DMF (91% yield). For the triflation step leading to **6**, we tested the method described in the literature for this kind of molecule,[13] which used NaHMDS in THF as the base and $PhNTf_2$ as the triflating agent. Unfortunately, under these conditions, the maximal yield of **6** was 31%, starting from **5**. Also, we chose a more classical method, Tf_2O in pyridine at 0 °C and obtained **6** in an 81% yield. The following step was a classical Suzuki coupling leading to **7** in a 90% yield, following Zhao's procedure.[14] Before reducing the C2–C3 double bond, we preferred first to substitute the carbamate protective group on the nitrogen for a methyl group. This might have failed because the deprotection of *tert*-butyloxycarbamates and acetonides takes place under similar conditions, but it turned out that only the amino group was regenerated using *para*-toluenesulfonic acid in acetonitrile, giving **8** in a 91%



Scheme 2. Reagents and conditions: (a) TBAF, THF, 0 °C; (b) OsO_4, NMO, acetone/H_2O, rt; (c) $(CH_3)_2C(OCH_3)_2$, PTSA, DMF, rt; (d) Tf_2O, pyridine, 0 °C; (e) *p*-$CH_3C_6H_4B(OF)_2$, LiCl, Na_2CO_3/H_2O, Pd_2dba_3, DME, reflux; (f) PTSA, CH_3CN, 50 °C; (g) HCHO, $NaBH_3CN$, CH_3CN, reflux; (h) SmI_2, THF, −78 °C then MeOH, −78 °C to rt; (i) CF_3COOH, MeOH; (j) $NaIO_4$, Et_3BnNCl, DCE/H_2O, 0 °C to rt.

yield. Methylation of the amino group was performed under classical conditions: formaldehyde in acetonitrile in the presence of sodium borohydride. Compound **9** was obtained in a yield of 79%.

Reduction of the C2–C3 double bond in tropene derivatives is often carried out with samarium iodide in THF at −78 °C using methanol as the proton source, followed by quenching with acetic acid[14] or water.[15] This is the only method which leads mainly to the 2β3β and 2β3α isomers with generally a light preference for the first one by quenching with water and the second one by quenching with acetic acid . So we used the method of Meltzer using water and obtained 84% yield with markedly more 2β3β than 2β3α isomer. These proportions were determined by integration of the singlets attributed to the methyl group on the nitrogen in the four isomers. They are reported in Table 1 as well as the different chemical shifts.

The four isomers present very close chromatographic behaviours, so we only succeeded at this stage in separating two groups: **10a**(2β3β)/**10b**(2β3α) on one hand and **10c**(2α3β)/**10d**(2α3α) on the other hand.

The following step consisted in the regeneration of the diol function before oxidative cleavage. In an unexpected way, the deprotection using classical conditions (HCl in MeOH, CH_3COOH in H_2O, TFA in THF/H_2O) failed or gave many by-products. The only method which gave good results was CF_3COOH used as the solvent, with a few drops of MeOH, at 50 °C. Under these conditions, the reaction was slow but led to **11** in a good yield (86%). This deprotection was carried out on the **10a/10b** mixture and the two diols **11a** and **11b** were separated. The stereochemical assignments for the two isomers were determined by NMR coupling constants analysis. The 1,2-diols are easily cleaved by lead tetracetate or periodic acid depending on the solubility of the glycol in organics or water. The use of lead tetracetate (1.2 equiv) in CH_2Cl_2 in the presence of Na_2CO_3 (3 equiv) was satisfactory for **11a** but gave an undetermined product for **11b**. So we tried another method on both diols using $NaIO_4$ in water, 1,2-dichloroethane and benzyltriethylammonium chloride as the phase transfer agent.[16] Dialdehydes **1a** and **1b** were obtained in good yields (84% and 88%, respectively).

The synthesis of target molecules **1** has been achieved in 10 steps from the tropene derivative of Davies, in their racemic form. Each step was optimized. We obtained two dialdehydes, 3β4α and 3β4β sufficiently stable to be characterized. Thus, we showed the validity of our approach. Starting from these aldehydes, a variety of complexes could be prepared by reaction with primary amine functions of various aminothiols or *S*-methyl dithiocarbazate, then complexation of the metal. A

Table 1. Reduction of compound **9** into compounds **10** by SmI_2

	2β3α	2β3β	2α3β	2α3α
Compounds **10**	**10a**	**10b**	**10c**	**10d**
^{1}H NMR: δCH_3–N	2.85 ppm	2.77 ppm	2.59 ppm	2.72 ppm
Relative %	30%	57%	Traces	13%

preliminary assay of reaction between the two aldehyde functions of **1a** and *S*-methyl dithiocarbazate was positive according to ^{1}H and ^{13}C NMR spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.141.

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