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(54) Title: ZINC HALIDE MEDIATED CYCLIZATION PROCESS LEADING TO TRICYCLIC INDOLES

(57) Abstract: The present invention relates to a method for the production of tricyclic indole compounds comprising a cyclization step wherein this step is improved over known methods.



CYCLIZATION

Technical Field of the Invention

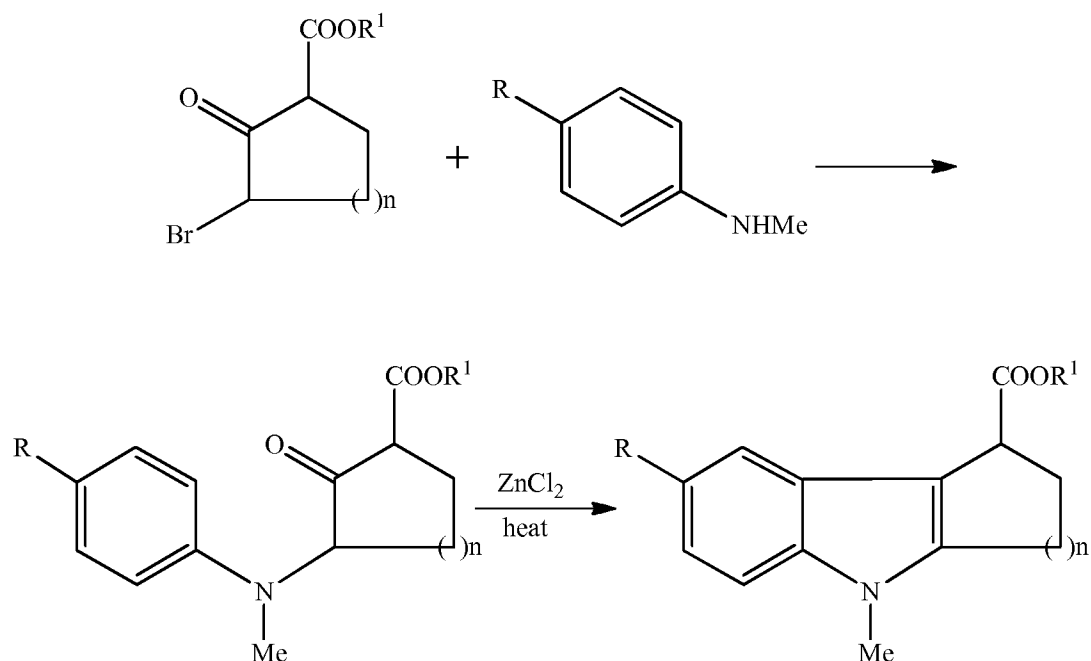
The present invention relates to a chemical method and in particular to a chemical method to obtain a tricyclic indole compound. The method of the invention can be
5 applied in the synthesis of tricyclic indole compounds that find use as pharmaceuticals and as radiopharmaceuticals.

Description of Related Art

Tricyclic indole compounds are known in the art and have been reported to have activity as melatonin antagonists (Davies 1998 J Med Chem; 41: 451-467), secretory
10 phospholipase A₂ inhibitors (Anderson *et al* EP 0952149 A1), treatment for Alzheimer's disease (Wantanabe WO 99/25340), treatment of inflammatory diseases such as septic shock (Kinnick *et al* WO 03/014082 and WO 03/016277) and high binding affinity to translocator protein (TSPO, formerly known as peripheral benzodiazepine receptor; Wadsworth *et al* (WO 2010/109007).

15 One reported method for the synthesis of these tricyclic indole compounds broadly comprises a condensation reaction between an aniline and a bromo oxocycloalkanecarboxylate, followed by cyclization in the presence of zinc chloride.

Davies *et al* (J Med Chem 1998; 41: 451-467) describe melatonin agonists and antagonists derived from tetrahydrocyclopent[*b*]indoles, tetrahydrocarbazoles and
20 hexahydrocyclohept[*b*]indoles. The general mechanism presented in this paper for the synthesis of these compounds comprises treating the appropriate *N*-methylaniline with the appropriate 3-bromo-2-oxocycloalkanecarboxylate as shown below followed by reaction with zinc chloride and heating for 16 hours:

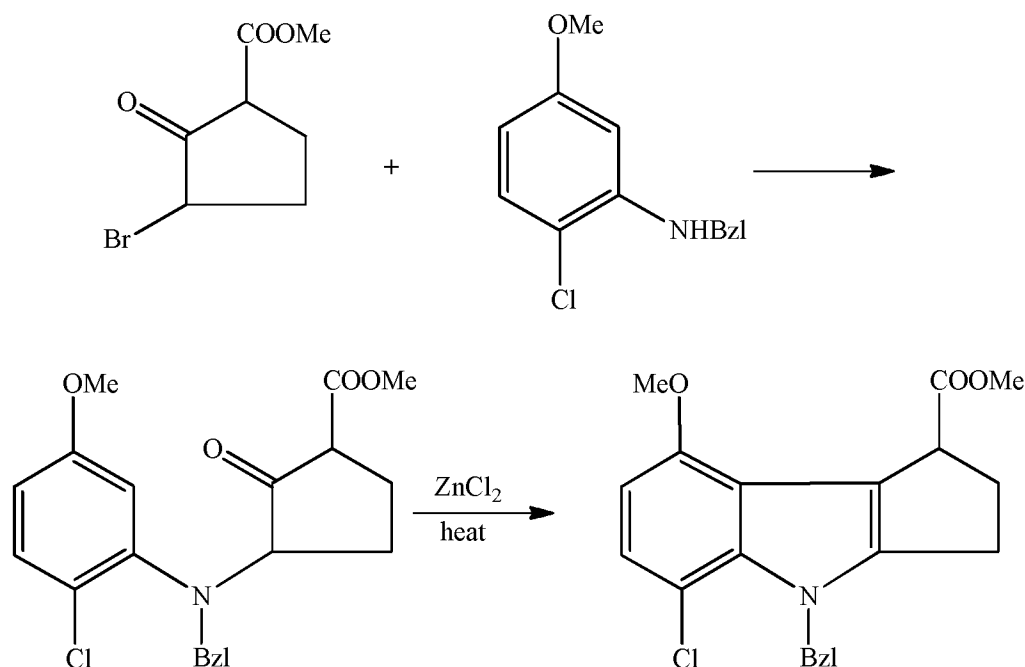


In the above scheme, Me is methyl and the variables R, R¹ and n are as defined by Davies *et al*, *supra*. Following the cyclization reaction, the product was extracted three times with a mixture of hydrochloric acid and ethyl acetate, washed with water and

5 Na₂CO₃, dried with MgSO₄ followed by evaporation of the solvent to obtain the ester in sufficient purity to be used in subsequent reactions.

Kinnick *et al* (WO 2003/014082) describe tricyclic indole compounds and a synthesis method for their preparation comprising condensation of 2-carbomethoxy-5-bromocyclopentanone and N-benzyl-2-chloro-5-methoxyaniline, followed by heating

10 with zinc chloride at reflux temperature over a period of 10-60 hours:



In the above scheme Me is methyl and Bzl is benzyl. Following the cyclization the reaction mixture was cooled, concentrated *in vacuo* and purified by chromatography. This reaction was adapted by the same group to obtain the heptane derivative,

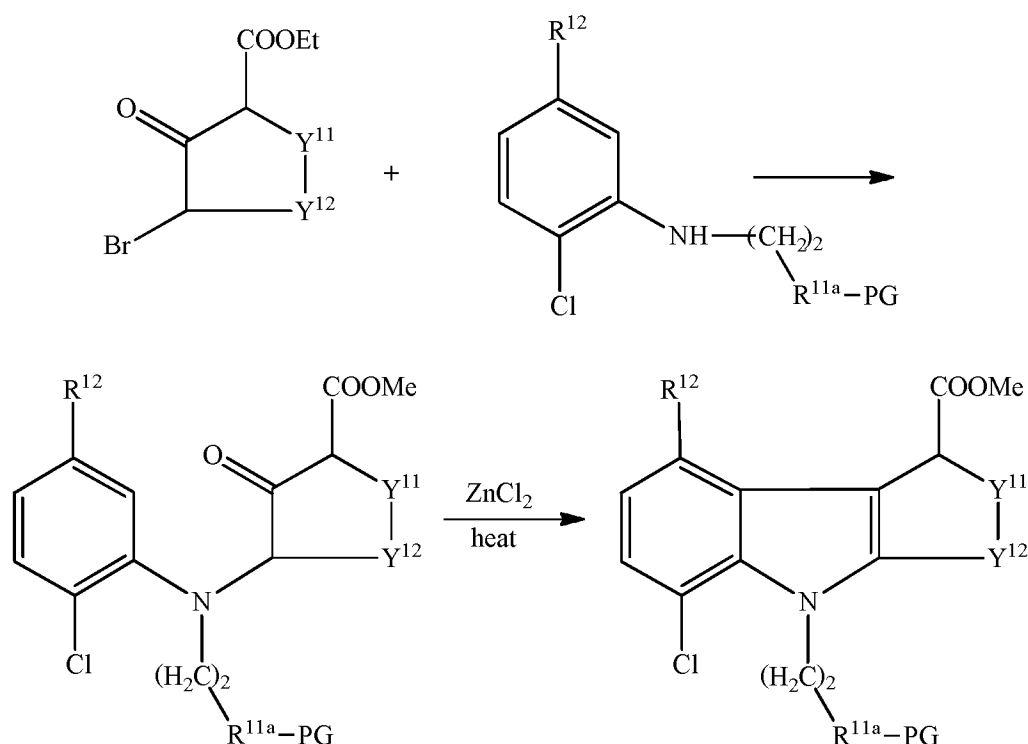
5 substituting the 2-carbomethoxy-5-bromocyclopentanone of the scheme above with 2-carbomethoxy-5-bromocycloheptanone (Kinnick *et al* WO 2003/016277), followed by cooling, filtration, washing, drying and concentration *in vacuo*. More specifically for this heptane derivative, Kinnick *et al* made 2 separate additions of ZnCl_2 : 1M ZnCl_2 in diethyl ether added to the intermediate dissolved in toluene, and then another 1M ZnCl_2

10 in diethyl ether added after 1 hour along with further toluene.

Anderson *et al* (EP0952149 B1) describe substituted carbazoles wherein the preparation of certain of these compounds comprises condensation of 2-carbomethoxy-6-bromocyclohexanone with an aniline followed by addition of zinc chloride and refluxing in benzene. Following the cyclization step, the residue worked up before being taken to

15 the subsequent step, e.g. in one example the residue was taken up in ethyl acetate, washed with hydrochloric acid, washed with water, dried over sodium sulfate, evaporated *in vacuo* and then purified by silica gel chromatography.

Wadsworth *et al* (WO 2010/109007) describe the synthesis of ^{18}F -labelled tricyclic compounds using similar methods according to the following scheme:



In the above Et is ethyl and PG is a protecting group and the variables Y¹¹, Y¹², R^{11a} and R¹² are defined therein. In the experimental examples, following the cyclization step, the reaction was dissolved in ethyl acetate, washed with hydrochloric acid and potassium carbonate (and in some cases also water), dried over magnesium sulphate, concentrated
 5 *in vacuo* and in some cases also purified by silica gel chromatography.

The present inventors have found that the above-described methods present difficulties during the cyclization reaction and/or require re-work of the cyclized product before any subsequent reactions to be carried out, which can be time-consuming and labour-
 10 intensive. There is therefore a need for improved methods for carrying out this cyclization reaction.

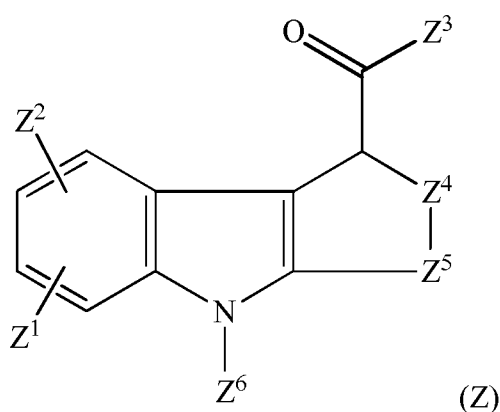
Summary of the Invention

The present invention relates to a method for the production of tricyclic indole compounds comprising a cyclization step wherein this step is improved over known
 15 methods. The present inventors have observed that the zinc halide reagent used for the cyclization appears to deactivate itself over time. The inventive method proposes to add the zinc halide using multiple additions at defined timepoints. With the method of the

invention it is not required to separate the two phases formed during the cyclization reaction and carry out a re-work of one of the phases in order to result in an acceptable yield. The lot-wise addition of zinc halide during cyclization has been observed to facilitate better conversion, thereby improving yield and avoiding significant rework of the cyclized product.

Detailed Description of the Preferred Embodiments

In one aspect the present invention provides a method for the production of a compound of Formula Z:



wherein:

Z^1 is an R^1 group selected from halo or C_{1-3} alkyl;

Z^2 is an R^2 group selected from hydrogen, hydroxyl, halo, cyano, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl, or C_{1-3} fluoroalkoxy;

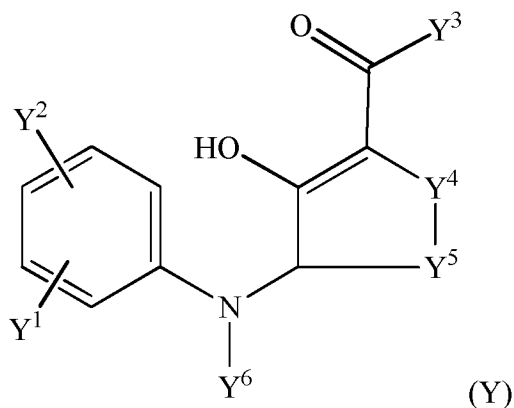
Z^3 is an R^3 group selected from C_{1-6} alkyl or $-O-R^7$ wherein R^7 is C_{1-6} alkyl;

Z^4 is an R^4 group selected from O, S, SO_2 or CH_2 ;

Z^5 is an R^5 group selected from CH_2 , CH_2-CH_2 , $CH(CH_3)-CH_2$ or $CH_2-CH_2-CH_2$;

Z^6 is an R^6 group selected from C_{1-10} alkyl or an amine protecting group, or R^6 is the group $-O-R^8$ wherein R^8 is C_{1-10} alkyl, C_{3-12} aryl, C_{7-14} arylalkyl or a hydroxyl protecting group;

wherein said method comprises cyclizing of a compound of Formula Y:



wherein each of Y^{1-6} are the same as each of Z^{1-6} ;

wherein said cyclizing is carried out by introduction of a zinc halide in a suitable solvent
 5 to a solution of said compound of Formula Y wherein said introduction comprises a first addition and a second addition carried out at least 6 hours after said first addition.

The term “halo” or “halogen” is taken to mean any one of chloro, fluoro, bromo or iodo.

The term “alkyl” used either alone or as part of another group is defined as any straight $-C_nH_{2n+1}$ group, branched $-C_nH_{2n+1}$ group wherein n is >3, or cyclic $-C_nH_{2n-1}$ group
 10 where n is >2. Non-limiting examples of alkyl groups include methyl, ethyl, propyl, isobutyl, cyclopropyl and cyclobutyl.

The term “hydroxyl” refers to the group $-OH$.

The term “cyano” refers to the group $-CN$.

The term “alkoxy” refers to an alkyl group as defined above comprising an ether linkage,
 15 and the term “ether linkage” refers to the group $-C-O-C-$. Non-limiting examples of alkoxy groups include, methoxy, ethoxy, and propoxy.

The terms “fluoroalkyl” and “fluoroalkoxy” refer respectively to an alkyl group and an alkoxy group as defined above wherein a hydrogen is replaced with a fluoro.

The term “aryl” refers to any molecular fragment or group which is derived from a

monocyclic or polycyclic aromatic hydrocarbon, or a monocyclic or polycyclic heteroaromatic hydrocarbon.

The term “arylalkyl” refers to an aryl-substituted alkylene group wherein aryl and alkylene are as defined above.

- 5 The term “protecting group” is meant a group which inhibits or suppresses undesirable chemical reactions, but which is designed to be sufficiently reactive that it may be cleaved from the functional group in question to obtain the desired product under mild enough conditions that do not modify the rest of the molecule. Protecting groups are well-known in the art and are discussed in detail in ‘Protective Groups in Organic
10 Synthesis’, by Greene and Wuts (Fourth Edition, John Wiley & Sons, 2007).

Non-limiting examples of suitable protecting groups for hydroxyl include methyl, ethyl, isopropyl, allyl, t-butanyl, benzyl ($-\text{CH}_2\text{C}_6\text{H}_5$), benzoyl ($-\text{COC}_6\text{H}_5$), and for ester groups include t-butyl, ester benzyl ester, isopropyl, and methyl and ethyl esters.

- The term “cyclizing” refers to the formation of a cyclic compound from an open-chain
15 compound.

A “zinc halide” is suitably selected from zinc chloride and zinc bromide and is preferably zinc chloride.

- The “suitable solvent” for said zinc halide is selected from diethyl ether, propan-2-ol, toluene, tetrahydrofuran (THF), 2-methyl-THF (MTHF) and cyclopentylmethylether
20 (CPME).

Said R^1 group is preferably at the bottom position (i.e. the 8 position of either Formula Y or Z) of the aryl ring to which it is attached.

Said R^2 group is preferably at the top position (i.e. the 5 position of either Formula Y or Z) of the aryl ring to which it is attached.

- 25 Said R^1 group is preferably halo and is most preferably chloro.

Said R^2 group is preferably C_{1-3} alkoxy, C_{1-3} or C_{1-3} fluoroalkoxy, most preferably C_{1-3}

alkoxy and most especially preferably methoxy.

Said R^3 group is preferably $-O-R^7$ wherein R^7 is C_{1-6} alkyl, preferably wherein R^7 is C_{1-3} alkyl and most preferably wherein R^7 is ethyl.

Said R^4 group is preferably S, SO, SO_2 or CH_2 and is most preferably CH_2 .

- 5 Said R^5 group is preferably CH_2 , CH_2-CH_2 , or $CH_2-CH_2-CH_2$ and is most preferably CH_2-CH_2 .

- Said R^6 group is preferably C_{1-10} alkyl or an amine protecting group. Alternatively preferably said R^6 group is the group $-O-R^8$ wherein R^8 is C_{1-10} alkyl, C_{3-12} aryl, C_{7-14} arylalkyl or a hydroxyl protecting group. In this alternative preferred embodiment R^8 is
10 preferably a hydroxyl protecting group and most preferably is benzyl.

For a preferred compound of either Formula Y or Formula Z:

Said R^1 group is halo;

Said R^2 group is C_{1-3} alkoxy, C_{1-3} or C_{1-3} fluoroalkoxy;

Said R^3 group is $-O-R^7$ wherein R^7 is C_{1-6} alkyl;

- 15 Said R^4 group is S, SO, SO_2 or CH_2 ;

Said R^5 group is CH_2 , CH_2-CH_2 , or $CH_2-CH_2-CH_2$; and,

Said R^6 group is C_{1-10} alkyl or an amine protecting group.

For an alternative preferred compound of either Formula Y or Formula Z:

Said R^1 group is halo;

- 20 Said R^2 group is C_{1-3} alkoxy, C_{1-3} or C_{1-3} fluoroalkoxy;

Said R^3 group is $-O-R^7$ wherein R^7 is C_{1-6} alkyl;

Said R^4 group is S, SO, SO_2 or CH_2 ;

Said R⁵ group is CH₂, CH₂-CH₂, or CH₂-CH₂-CH₂; and,

Said R⁶ group is the group -O-R⁸ wherein R⁸ is C₁₋₁₀ alkyl, C₃₋₁₂ aryl, C₇₋₁₄ arylalkyl or a hydroxyl protecting group.

For a most preferred compound of either Formula Y or Formula Z:

- 5 Said R¹ group is at the bottom position of the aryl ring to which it is attached and is halo;

Said R² group is at the top position of the aryl ring to which it is attached and is C₁₋₃ alkoxy, C₁₋₃ or C₁₋₃ fluoroalkoxy;

Said R³ group is -O-R⁷ wherein R⁷ is C₁₋₃ alkyl;

Said R⁴ group is CH₂;

- 10 Said R⁵ group is CH₂-CH₂; and,

Said R⁶ group is the group -O-R⁸ wherein R⁸ is a hydroxyl protecting group.

For an especially preferred compound of either Formula Y or Formula Z:

Said R¹ group is at the bottom position of the aryl ring to which it is attached and is chloro;

Said R² group is at the top position of the aryl ring to which it is attached and is C₁₋₃ alkoxy;

- 15 Said R³ group is -O-R⁷ wherein R⁷ is ethyl;

Said R⁴ group is CH₂;

Said R⁵ group is CH₂-CH₂; and,

Said R⁶ group is the group -O-R⁸ wherein R⁸ is benzyl.

For a most especially preferred compound of either Formula Y or Formula Z:

- 20 Said R¹ group is at the bottom position of the aryl ring to which it is attached and is chloro;

Said R² group is at the top position of the aryl ring to which it is attached and is methoxy;

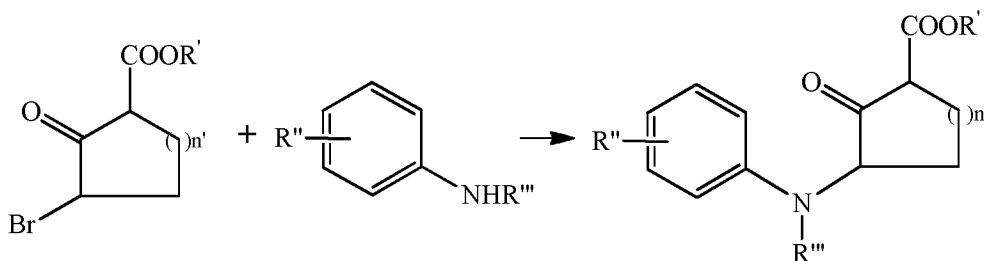
Said R³ group is -O-R⁷ wherein R⁷ is ethyl;

Said R⁴ group is CH₂;

Said R⁵ group is CH₂-CH₂; and,

Said R⁶ group is the group -O-R⁸ wherein R⁸ is benzyl.

- 5 It is an essential feature of the present invention that the zinc halide is introduced using more than one addition. The present inventors have found in addition that second and subsequent additions of zinc halide are suitably carried out at least 6 hours after the previous addition. If subsequent additions of zinc halide are made too early, the present inventors have faced significant problems stirring the reaction, which is assumed to be
- 10 due to precipitation of zinc halide. Addition of zinc halide can in another embodiment further comprise a third addition wherein said third addition is carried out at least 6 hours after said second addition. Preferably, the time between each addition is from 6-36 hours, most preferably from 12-24 hours. The quantity of zinc halide added at each addition is also important. Preferably, a significant surplus is used in the first addition
- 15 with half the amount of the first addition for each subsequent addition, e.g. around a gram of zinc halide *per* gram of uncyclized intermediate (i.e. compound of Formula Y) for the first addition and around half a gram *per* gram of uncyclized intermediate for each subsequent addition. In one embodiment, >3 molar equivalents can be used with the first addition.
- 20 Compounds of Formula Y can be obtained from commercial starting materials using or adapting methods described in the prior art. Reference is made in this regard to the teachings of Julia & Lenzi (Bulletin de la Societ  de France 1962: 2262-2263), Davies *et al* (J Med Chem 1998; 41: 451-467), Kinnick *et al* (WO 2003/014082 and WO 2003/016277), Anderson *et al* (EP0952149 B1) and Wadsworth *et al* (WO
- 25 2010/109007). In each of these publications compounds of Formula Y are obtained by condensation reaction between an aniline and a bromo oxocycloalkanecarboxylate as illustrated in Scheme 1 below:

**Scheme 1**

In the above scheme R' is an R⁷ group as defined herein, R'' is an R¹ and/or an R² group as defined herein, R''' is an R⁶ group as defined herein and n' is an integer of 1-3.

The compounds of Formula Z obtained by the above-described method of the invention
 5 may be further converted by means well-known to those of skill in the art to obtain additional compounds. Therefore, in another embodiment, the method of the present invention further comprises conversion of the group $-C(=O)-Z^3$ of Formula Z to the group $-C(=O)-Z^{13}$ wherein Z¹³ is hydroxyl or NR⁹R¹⁰ wherein R⁹ and R¹⁰ are independently C₁₋₃ alkyl, C₇₋₁₀ arylalkyl, or R⁹ and R¹⁰, together with the nitrogen to
 10 which they are attached, form a nitrogen-containing C₄₋₆ aliphatic ring optionally comprising 1 further heteroatom selected from nitrogen, oxygen and sulphur.

A “nitrogen-containing C₄₋₆ aliphatic ring” is a saturated C₄₋₆ alkyl ring comprising a nitrogen heteroatom. Examples include pyrrolidinyl, piperidinyl and morpholinyl rings.

This further step can be easily achieved using well-known synthetic chemistry
 15 techniques. For example, where Z³ in the group $-C(=O)-Z^3$ is $-O-R^7$ it can be converted to $-C(=O)-Z^{13}$ wherein Z¹³ is hydroxyl by straightforward removal of the R⁷ group by hydrolysis using an acid or a base, preferably by using a base such as NaOH.

In another embodiment, the method of the present invention further comprises conversion of the group $-N-Z^6$ to the group $-N-Z^{16}$ wherein Z¹⁶ is hydrogen, C₁₋₁₀
 20 alkylene-OH or C₁₋₁₀ alkylene-LG wherein LG is a leaving group.

The term “alkylene” refers to a divalent linear -C_nH_{2n}- group.

The term “leaving group” refers to a molecular fragment that departs with a pair of

electrons in heterolytic bond cleavage. Non-limiting examples of suitable leaving groups include halo groups selected from chloro, iodo, or bromo, aryl or alkyl sulfonates such as tosylate, triflate, nosylate or mesylate.

Z^{16} is preferably C_{1-10} alkylene-LG and most preferably C_{1-6} alkylene-LG.

- 5 LG is preferably halo, or an aryl or alkyl sulfonate, and is most preferably an aryl or alkyl sulfonate. Preferred aryl or alkyl sulfonates are selected from tosylate, triflate, nosylate and mesylate.

- Conversion of the group $-N-Z^6$ to the group $-N-Z^{16}$ can be carried out in a straightforward manner, e.g. by simply removing a protecting group in order to obtain –
- 10 NH_2 or $-N$ -alkylene-OH, and by further reacting with a suitable source of a leaving group to obtain $-N$ -alkylene-LG. Suitable sources of leaving groups are commercially available and well-known to those skilled in the art, e.g. sulfonyl chloride reagents such as p-toluenesulfonyl chloride (TsCl) and methanesulfonyl chloride (MsCl).

- In a yet further embodiment, the method of the invention further comprises conversion of
- 15 the group $-N-Z^{16}$ to the group $-N-Z^{26}$ wherein Z^{26} is C_{1-10} alkylene- ^{18}F .

- Labelling with ^{18}F can be achieved by nucleophilic displacement of LG in one step by reaction with a suitable source of $[^{18}F]$ -fluoride ion ($^{18}F^-$), which is normally obtained as an aqueous solution from the nuclear reaction $^{18}O(p,n)^{18}F$ and is made reactive by the addition of a cationic counterion and the subsequent removal of water. ^{18}F can also be
- 20 introduced by O-alkylation of hydroxyl groups with $^{18}F(CH_2)_3$ -LG wherein LG is as defined above.

- $[^{18}F]$ -radiotracers are now often conveniently prepared on an automated radiosynthesis apparatus. There are several commercially-available examples of such apparatus, including TracerlabTM and FastlabTM (GE Healthcare Ltd). Such apparatus commonly
- 25 comprises a “cassette”, often disposable, in which the radiochemistry is performed, which is fitted to the apparatus in order to perform a radiosynthesis. The cassette normally includes fluid pathways, a reaction vessel, and ports for receiving reagent vials as well as any solid-phase extraction cartridges used in post-radiosynthetic clean up

steps. In a preferred embodiment therefore the further step of conversion of the group –N-Z¹⁶ to the group –N-Z²⁶ wherein Z²⁶ is C₁₋₁₀ alkylene-¹⁸F is automated.

The following non-limiting examples serve to illustrate the invention in more detail.

Brief Description of the Examples

- 5 Example 1 describes how the method of the present invention can be carried out to obtain a compound of Formula Z by cyclizing a compound of Formula Y.

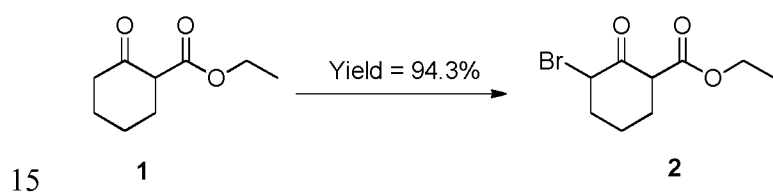
List of Abbreviations used in the Examples

- EtOAc: ethyl acetate
- HPLC: high performance liquid chromatography
- 10 TLC: thin-layer chromatography

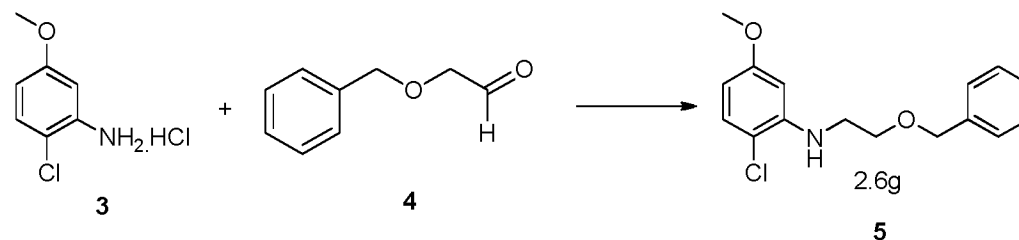
Examples

Example 1: Synthesis of ethyl 9-(2-(benzyloxy)ethyl)-8-chloro-5-methoxy-2,3,4,9-tetrahydro-1H-carbazole-4-carboxylate

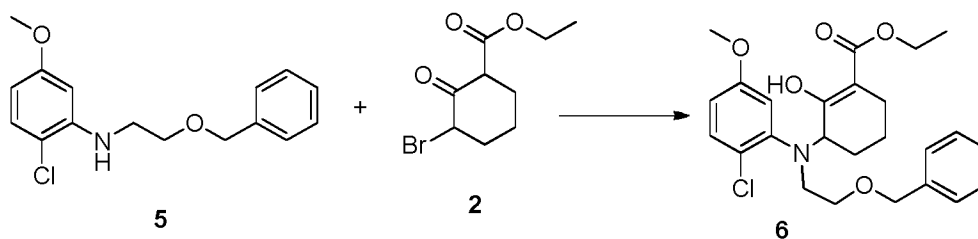
Step 1: Synthesis of ethyl 3-bromo-2-oxocyclohexanecarboxylate



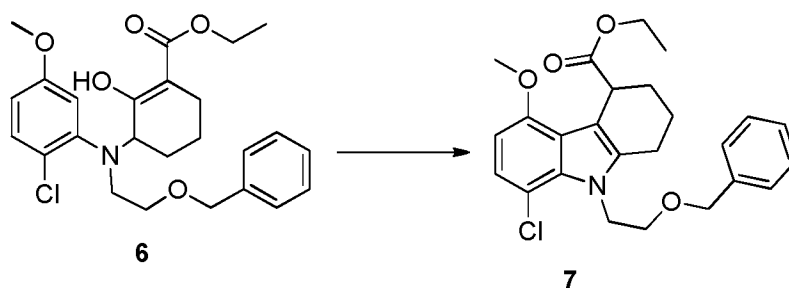
Step 2: Synthesis of N-(2-(benzyloxy)ethyl)-2-chloro-5-methoxyaniline



Step 3: Synthesis of ethyl 3-((2-(benzyloxy)ethyl)(2-chloro-5-methoxyphenyl)amino)-2-hydroxycyclohex-1-enecarboxylate



Step 4: Synthesis of ethyl 9-(2-(benzyloxy)ethyl)-8-chloro-5-methoxy-2,3,4,9-tetrahydro-1H-carbazole-4-carboxylate



Each of steps 1-3 was carried out as described by Wadsworth *et al* (WO 2010/109007 Example 1).

For step 4 the general procedure used was firstly to charge compound **6** (x g, 1 mole equivalent) and diethyl ether (20 ml/g compound **6**) under a nitrogen atmosphere. Zinc chloride was then added at ~1g *per* gram of compound **6** and the reaction mixture heated to a good reflux and maintained at reflux for ~1 day. Then additional zinc chloride was added at ~0.5g *per* gram of compound **6** and refluxed for a further ~1 day. A third addition of zinc chloride at 0.4-0.6g *per* gram of compound **6** was carried out with reflux maintained with monitoring of the reaction with TLC (eluent 25% EtOAc in heptane, UV 254nm), with the normal reaction time being approximately 5 days. Work up comprised evaporation of the reaction mixture (25-40°C) under vacuum to obtain an oily mass. The crude was weighed and then dissolved in ethyl acetate (1-10 ml/g crude) and washed with HCl (1 part concentrated HCl and 5 parts water (approximately 2M), 2 x 1-10ml/g crude). The ethyl acetate phase was then concentrated under vacuum at 25-50°C and a sample withdrawn for TLC (eluent 25% EtOAc in heptane, UV 254 nm).

Storage at room temperature or below.

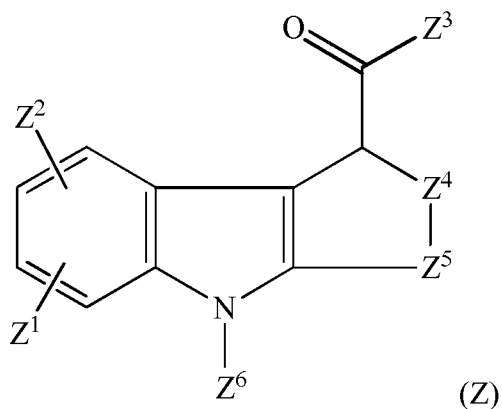
Table 1: shows the results of carrying out the cyclization step according to an embodiment of the present invention comprising multiple additions of zinc chloride wherein ~19-25 hours elapsed between each addition.

Intermediate 6 (g)	ZnCl₂ (g)	Reaction time	HPLC purity	Isolated cyclized product (g)
8.53	7.2 + 2.73	5 days	87.20%	7.79
3	3+1.5+1.5	5 days	91%	3.17
122	122+ 60+60	6 days	89.90%	117

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Claims

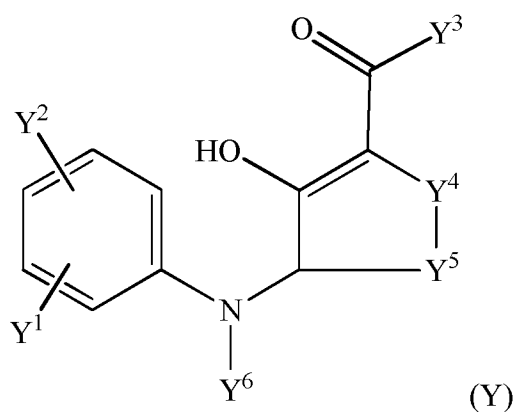
- (1) A method for the production of a compound of Formula Z:



wherein:

- 5 Z^1 is an R^1 group selected from halo or C_{1-3} alkyl;
- Z^2 is an R^2 group selected from hydrogen, hydroxyl, halo, cyano, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} fluoroalkyl, or C_{1-3} fluoroalkoxy;
- Z^3 is an R^3 group selected from C_{1-6} alkyl or $-O-R^7$ wherein R^7 is C_{1-6} alkyl;
- Z^4 is an R^4 group selected from O, S, SO, SO_2 or CH_2 ;
- 10 Z^5 is an R^5 group selected from CH_2 , CH_2-CH_2 , $CH(CH_3)-CH_2$ or $CH_2-CH_2-CH_2$;
- Z^6 is an R^6 group selected from C_{1-10} alkyl or an amine protecting group, or R^6 is the group $-O-R^8$ wherein R^8 is C_{1-10} alkyl, C_{3-12} aryl, C_{7-14} arylalkyl or a hydroxyl protecting group;

wherein said method comprises cyclizing of a compound of Formula Y:



wherein each of Y^{1-6} are the same as each of Z^{1-6} ;

wherein said cyclizing is carried out by introduction of a zinc halide in a suitable solvent to a solution of said compound of Formula Y wherein said introduction comprises a first addition and a second addition carried out at least 6 hours after said first addition.

- (2) The method as defined in Claim 1 wherein said R^1 group is at the bottom position of the aryl ring to which it is attached.
- (3) The method as defined in either Claim 1 or Claim 2 wherein said R^2 group is at the top position of the aryl ring to which it is attached.
- (4) The method as defined in any one of Claims 1-3 wherein said R^1 group is halo.
- (5) The method as defined in Claim 4 wherein said R^1 is group chloro.
- (6) The method as defined in any one of Claims 1-5 wherein said R^2 group is C_{1-3} alkoxy, C_{1-3} or C_{1-3} fluoroalkoxy.
- (7) The method as defined in Claim 6 wherein said R^2 group is C_{1-3} alkoxy.
- (8) The method as defined in Claim 7 wherein said R^2 group is methoxy.
- (9) The method as defined in any one of Claims 1-8 wherein said R^3 group is $-O-R^7$ wherein R^7 is C_{1-6} alkyl.
- (10) The method as defined in Claim 9 wherein R^7 is C_{1-3} alkyl.

- (11) The method as defined in Claim 10 wherein R^7 is ethyl.
- (12) The method as defined in any one of Claims 1-11 wherein said R^4 group is S, SO, SO_2 or CH_2 .
- (13) The method as defined in Claim 13 wherein said R^4 group is CH_2 .
- 5 (14) The method as defined in any one of Claims 1-13 wherein said R^5 group is CH_2 , CH_2-CH_2 , or $CH_2-CH_2-CH_2$.
- (15) The method as defined in Claim 14 wherein said R^5 group is CH_2-CH_2 .
- (16) The method as defined in any one of Claims 1-15 wherein said R^6 group is selected from C_{1-10} alkyl or an amine protecting group.
- 10 (17) The method as defined in any one of Claims 1-15 wherein said R^6 group is the group $-O-R^8$ wherein R^8 is C_{1-10} alkyl, C_{3-12} aryl, C_{7-14} arylalkyl or a hydroxyl protecting group.
- (18) The method as defined in Claim 17 wherein R^8 is a hydroxyl protecting group.
- (19) The method as defined in Claim 18 wherein R^8 is benzyl.
- 15 (20) The method as defined in any one of Claims 1-19 wherein said zinc halide is zinc chloride.
- (21) The method as defined in any one of Claims 1-20 which further comprises conversion of the group $-C(=O)-Z^3$ of Formula Z to the group $-C(=O)-Z^{13}$ wherein Z^{13} is hydroxyl or NR^9R^{10} wherein R^9 and R^{10} are independently C_{1-3} alkyl, C_{7-10} arylalkyl, or R^9 and R^{10} , together with the nitrogen to which they are attached, form a nitrogen-containing C_{4-6} aliphatic ring optionally comprising 1 further heteroatom selected from nitrogen, oxygen and sulphur.
- 20 (22) The method as defined in any one of Claims 1-21 which further comprises conversion of the group $-N-Z^6$ to the group $-N-Z^{16}$ wherein Z^{16} is hydrogen, C_{1-10} alkylene-OH or C_{1-10} alkylene-LG wherein LG is a leaving group.
- 25

- (23) The method as defined in Claim 22 wherein Z^{16} is C_{1-10} alkylene-LG.
- (24) The method as defined in Claim 23 wherein Z^{16} is C_{1-6} alkylene-LG.
- (25) The method as defined in either Claim 23 or Claim 24 wherein LG is halo, or an aryl or alkyl sulfonate.
- 5 (26) The method as defined in Claim 25 wherein LG is an aryl or alkyl sulfonate.
- (27) The method as defined in Claim 26 wherein said aryl or alkyl sulfonate is selected from tosylate, triflate, nosylate and mesylate.
- (28) The method as defined in Claim 23 which further comprises conversion of the group $-N-Z^{16}$ to the group $-N-Z^{26}$ wherein Z^{26} is C_{1-10} alkylene- ^{18}F .

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/075107

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/88
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	EP 0 950 657 A2 (LILLY CO ELI [US]) 20 October 1999 (1999-10-20) paragraph [0116] - paragraph [0116]; example F	1-28
A	----- WO 2010/109007 A2 (GE HEALTHCARE LTD [GB]; WADSWORTH HARRY JOHN [GB]; O'SHEA DENNIS [GB];) 30 September 2010 (2010-09-30) cited in the application the whole document	1-28
A	----- DAVIES: J MED CHEM, vol. 41, 1998, pages 451-467, XP002719424, cited in the application compounds 5a-5l	1-28



Further documents are listed in the continuation of Box C.



See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

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