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(54) Titre : PROCEDE DE PREPARATION DE 10,11-DIHYDRO-5H-DIBENZO(A,D)CYCLOHEPT-5-ENES ET DE LEURS
DERIVES
(54) Title: PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-5H-DIBENZO[A,D]CYCLOHEPT-5-ENES AND
DERIVATIVES THEREOF

(57) **Abrégé/Abstract:**

A process for preparing 10,11-dihydro-5H-dibenzo[a,d]cyclohept-5-enes (e.g. loratadine) by reacting a dibenzozuberone with an aliphatic ketone in the presence of low valent titanium.





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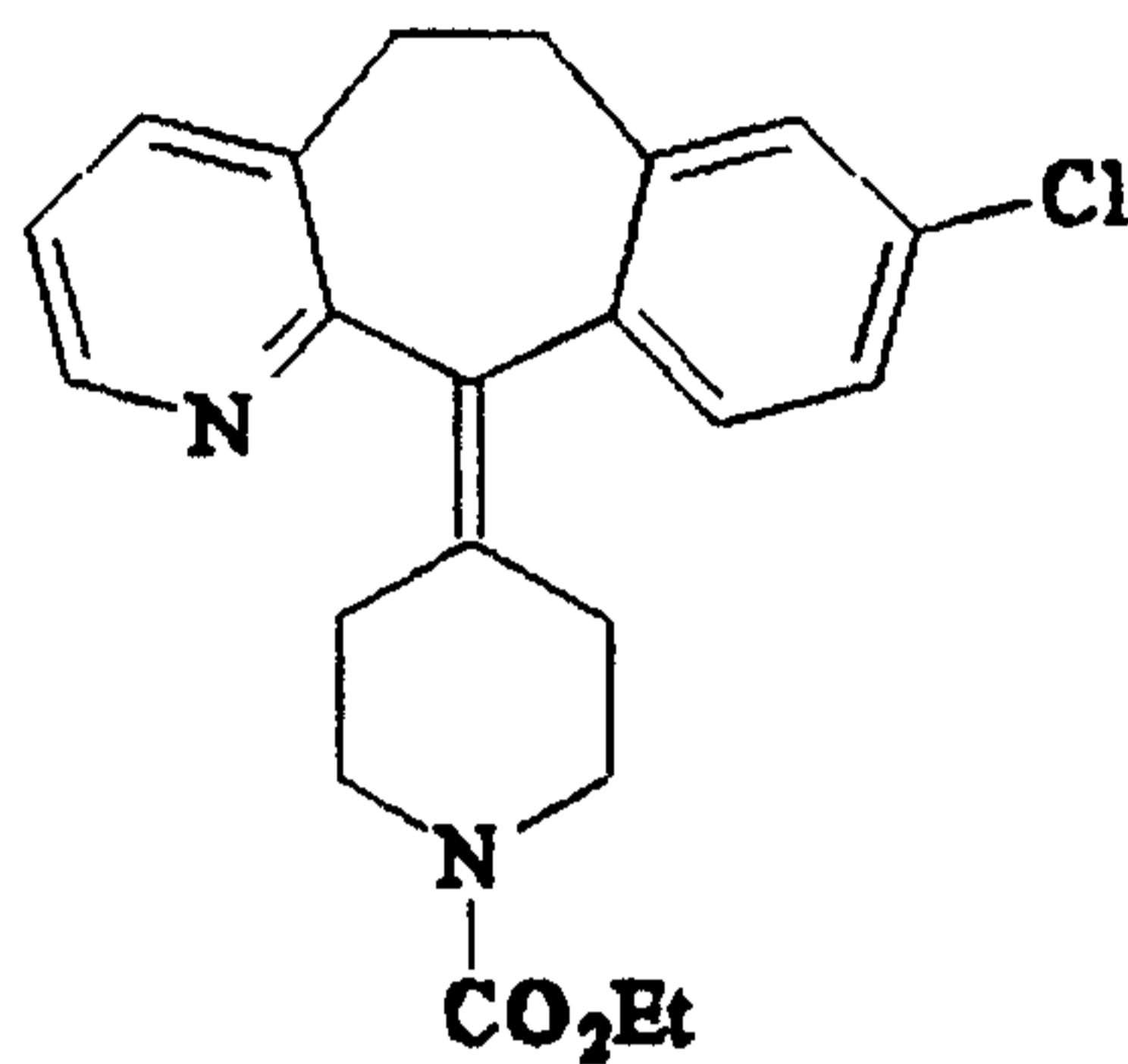
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<p>(21) International Application Number: PCT/GB98/00605</p> <p>(22) International Filing Date: 26 February 1998 (26.02.98)</p> <p>(30) Priority Data: 9703992.9 26 February 1997 (26.02.97) GB</p> <p>(71) Applicant (for all designated States except US): ROLABO S.L. [ES/ES]; Balmes, 85-3, E-08008 Barcelona (ES).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): JACKSON, William, Paul [GB/GB]; 245 Waldegrave Road, Twickenham, Middlesex TW1 4SY (GB).</p> <p>(74) Agents: COCKBAIN, Julian, R., M. et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-5H-DIBENZO[A,D]CYCLOHEPT-5-ENES AND DERIVATIVES THEREOF</p>		
<p>(57) Abstract</p> <p>A process for preparing 10,11-dihydro-5H-dibenzo[a,d]cyclohept-5-enes (e.g. loratadine) by reacting a dibenzozuberone with an aliphatic ketone in the presence of low valent titanium.</p>		

PROCESS FOR THE PREPARATION OF 10,11-DIHYDRO-5H-DIBENZO[A,D]CYCLOHEPT-5-ENES AND DERIVATIVES THEREOF

5 The present invention relates to a process for the preparation of 10,11-dihydro-5H-dibenzo[a,d]cyclohept-5-enes such as loratadine.

 The anti-histamine ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene) piperidine-1-carboxylate (loratadine) is a potent, long acting derivative of azatadine which shows negligible CNS side effects.

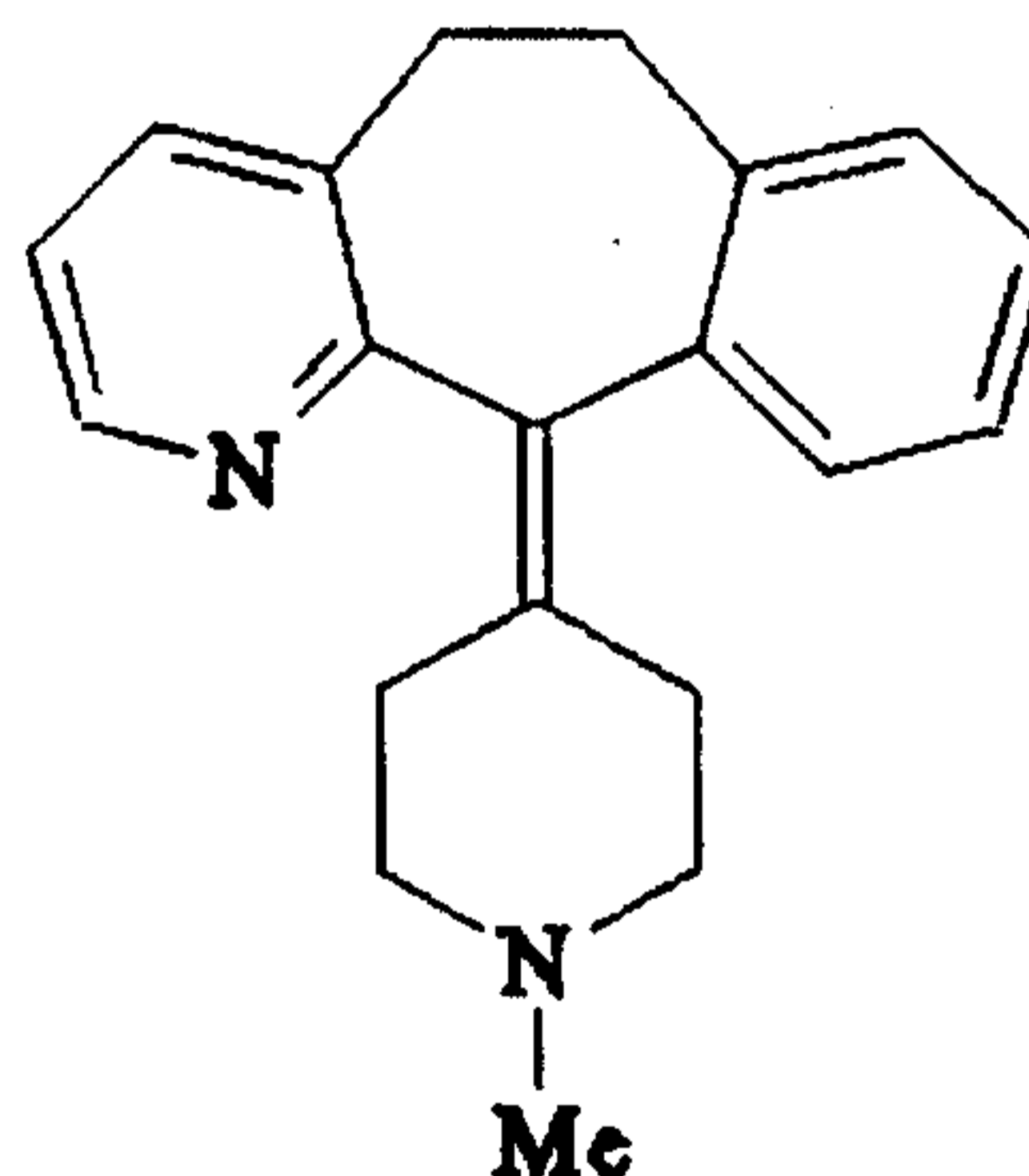
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20

LORATADINE

25



30

AZATADINE

35

 The presence of the chlorine atom at the 8-position makes the chemistry of loratadine uniquely problematical

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and reductive preparations are ineffective because of the removal of chlorine at the 8-position.

5 US-A-3,326,924 (Villani et al) discloses processes for preparing various aza-dibenzo[a,d]-cycloheptene derivatives which involve production of a tricyclic ketone which is reacted with a Grignard reagent derived from 4-chloro-N-methyl piperidine. Dehydration gives the N-methyl product. The process is, however, hindered by the amount up to 30% of 1,6-addition product which is 10 generated in the Grignard reaction causing problems in yield and purification. US-A-4,282,233 (Villani) discloses the preparation of loratadine from the product of the above reaction by demethylation/carboethoxylation.

15 A synthetic route to loratadine is disclosed in US-A-4,659,716 (Villani et al), US-A-4,731,447 (Schumacher et al), US-A-4,873,335 (Schumacher et al) and Journal of Organic Chemistry, 1989, Vol 54,2242-2244 (Schumacher et al.) which involves alkylation of the dianion of the t- 20 butylamide of 2-cyano-3-methyl-pyridine, re-generation of the nitrile, Grignard reaction, cyclisation with HF/BF₃ and demethylation/ carboethoxylation. This process is, however, hampered by the need to use hazardous organometallic reagents (LDA or butyl lithium) and a super-acid environment of liquid HF and BF₃ gas. 25

Cid et al have reported (Tetrahedron, 1988, Vol 44, 6197-6200) that cross coupling reactions between a tricyclic ketone and a cyclic ketone can take place using low valent titanium to give biphenylmethylenepiperidines or cyproheptadine. The process suffers from the disadvantages that low valent titanium has to be 30 generated using lithium metal which is hazardous on industrial scale and by the need to use about 12 equivalents of titanium reagent to prevent the reaction stopping at the diol stage. 35

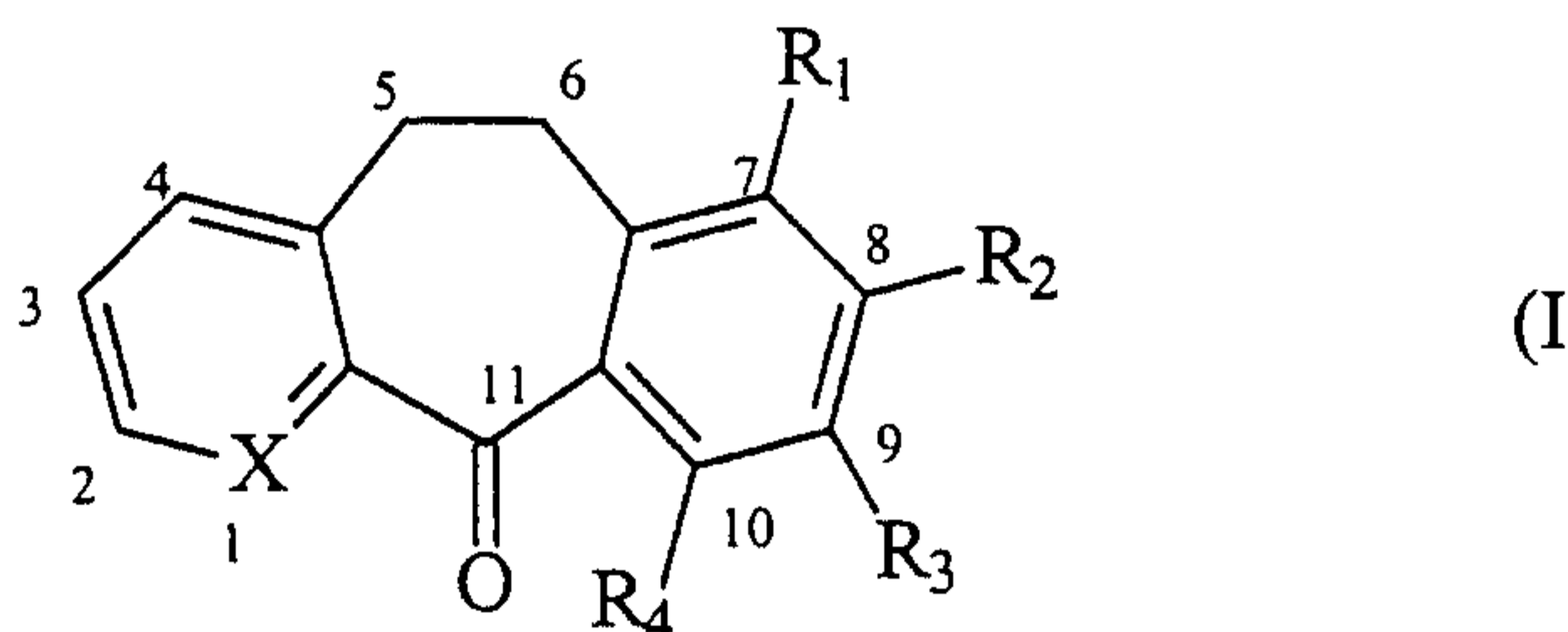
In general there exists a need for improved processes for preparing 10,11-dihydro-5H-dibenzo[a,d]-

cycloheptenes which use less hazardous materials and provide improved yields and selectivity, particularly on industrial scale production. The present invention seeks to provide such an improved process.

5 It has now surprisingly been found that hetero-coupling of a tricyclic aromatic ketone with an aliphatic cyclic ketone in the presence of low valent titanium gives a high yield of unsaturated coupled product with only traces of homo-coupled ketones.
 10 Typically, the low valent titanium is present as titanium (II) and only a slight excess of titanium reagent is required.

Thus viewed from one aspect the present invention provides a process for preparing 5,6-dihydro-11H-
 15 dibenzo[a,d]cyclohept-11-enes comprising reacting a dibenzosuberone or an aza derivative thereof with an aliphatic ketone in the presence of low valent titanium, ie. Ti(O), Ti(I) or Ti(II) wherein said low valent titanium is generated by zinc. Preferably the low
 20 valent titanium consists essentially of Ti(II).

Preferably the dibenzosuberone or aza derivative thereof compound is of formula I:



30

(wherein:

X denotes nitrogen or CH;

and R¹, R², R³ and R⁴ which may be the same or
 35 different independently denote hydrogen or a halogen (eg. F, Cl or Br)).

Preferably the dibenzosuberone compound is one in which R² denotes a halogen (eg. chloro) and R¹, R³ and R⁴

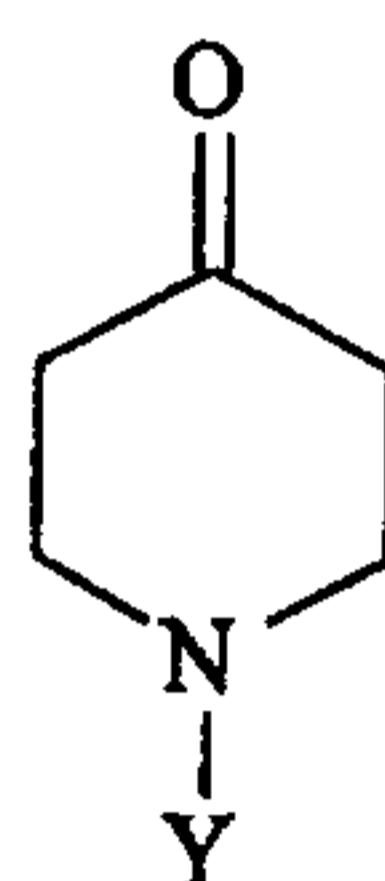
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denote hydrogen and particularly preferably in which in addition X is nitrogen.

In further embodiments, X which is nitrogen may be at the 2, 3 or 4 position as defined in formula I.

5 Preferably the aliphatic ketone is cyclic and particularly preferably is an optionally N-substituted piperidone compound, for example a compound of formula II:

10



(wherein:

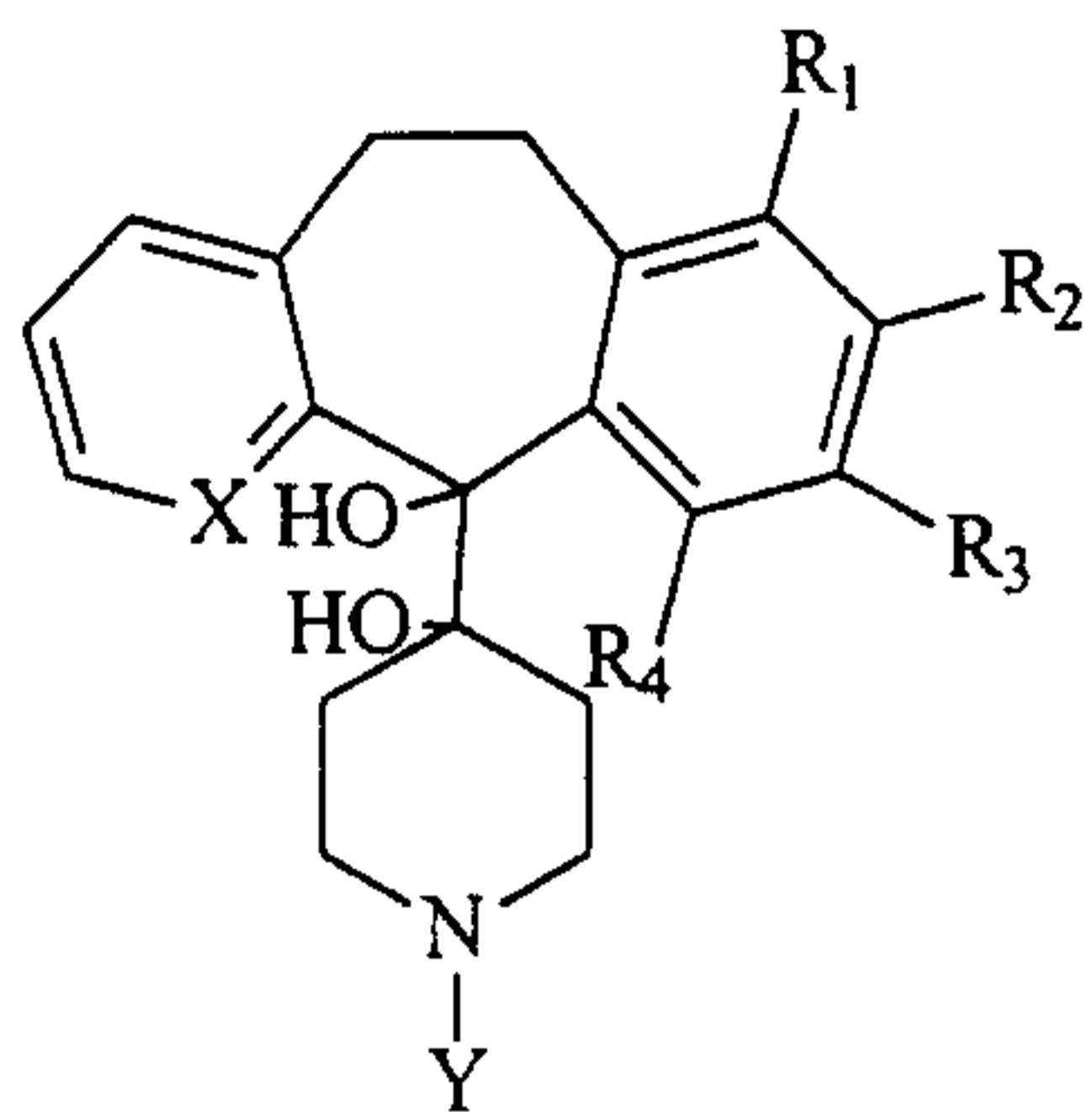
15 Y denotes hydrogen, lower alkyl (eg C₁₋₆-alkyl), CO₂R⁵, SO₂R⁵, CON(R⁵)₂, SO₂N(R⁵)₂, CO₂COR⁵ or a N-protecting group; and

R⁵ is hydrogen, a C₁₋₁₂-alkyl (preferably C₁₋₆-alkyl) group optionally substituted by one or more amino or
 20 C₁₋₆-alkylamino groups, a phenyl group optionally substituted by one or more halo or C₁₋₆-alkyl groups, a C₇₋₁₂-phenylalkyl group optionally substituted at the phenyl by one or more halo or C₁₋₆-alkyl groups, 2-piperidyl, 3-piperidyl or piperidyl substituted at the
 25 nitrogen atom by a C₁₋₄-alkyl group); and the salts thereof.

Preferably the piperidone is one in which Y is the group CO₂Et.

30 The reaction proceeds via an intermediate diol which, if desired, may be isolated by conducting the reaction at a lower temperature. The olefin may be prepared from the intermediate diol in a subsequent step in a conventional manner.

35 The diol intermediate itself is novel and forms a further aspect of the invention. Thus the present invention provides a compound of formula III:

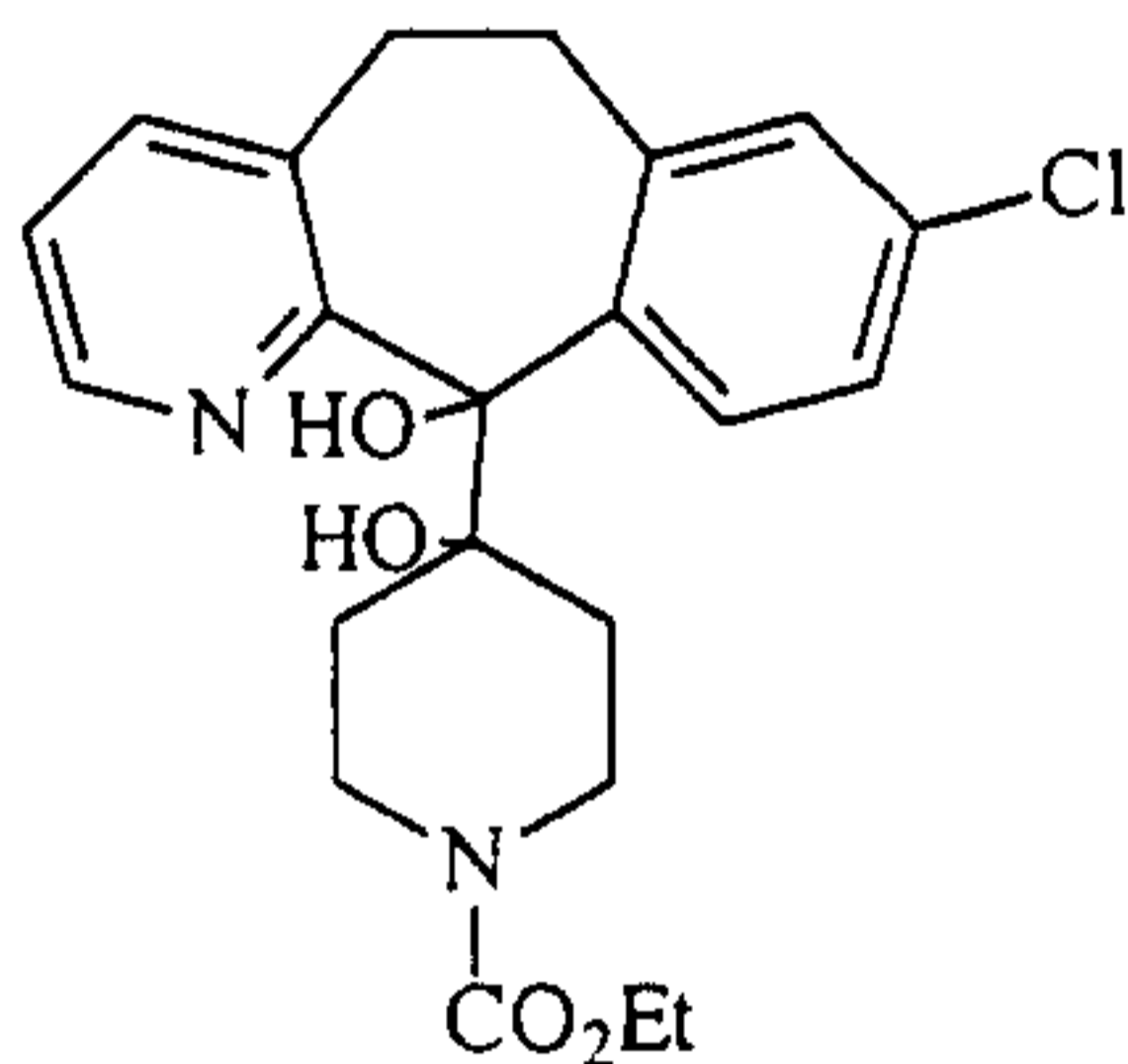


(III)

5

(wherein R_1 , R_2 , R_3 , R_4 , X and Y are as defined
 10 hereinbefore).

The preferred compound is:



15

20 The dibenzosuberone and aliphatic ketone reagents
 are preferably reacted in substantially equimolar
 quantities; however an excess of either reagent can be
 tolerated, eg. the two reagents may be present in molar
 ratios of from 1:2 to 2:1, preferably 1.5:1 to 1:1.5,
 25 especially preferably 1.1:1 to 1:1.1.

Low valent titanium may be prepared *in situ*, using
 zinc eg. by reaction of a Ti(III) or Ti(IV) compound or
 complexes thereof with zinc. In one preferred
 embodiment of the method according to the invention, a
 30 combination of titanium (IV) chloride or a complex
 thereof and zinc is used to generate low valent
 titanium. This embodiment has the advantage that zinc is
 relatively cheap and safe to use on an industrial scale.
 A combination of titanium (III) chloride and zinc may be
 35 used with equal success.

In accordance with the invention, Zn and Ti may be conveniently used in molar ratios of 4:1 to 1:1, preferably 3:1 to 2:1.

Typically, a slight molar excess of titanium reagent is used over the amount of ketone present, although a larger excess may be used if desired.

The titanium reagent is preferably used at a molar ratio of from 0.5:1 to 6:1, preferably 1.5:1 to 4:1, particularly 2:1 to 3:1 relative to the dibenzosuberone.

The reaction may be conveniently conducted in etherial solvents such as for example tetrahydrofuran, dioxane and dimethoxyethane which are commonly used in coupling reactions involving titanium. Nevertheless ethyl acetate, iso-propyl acetate, t-butylacetate, DMF and acetonitrile are equally effective for this purpose. Tetrahydrofuran is preferred.

The reaction temperature may be conveniently in the range -10°C to the reflux temperature of the chosen solvent, but is preferably 100°C or less, especially 20 to 60°C . To prepare the diol the reaction temperature is preferably below 10°C .

As noted above, Y may represent an N-protecting group and suitable groups includes acetyl, benzoyl, ethoxycarbonyl, t-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxy benzyl or 2,4-methoxybenzyl groups. The optional subsequent cleavage of a N-protecting group may for example be carried out by conventional means eg. hydrolytically, hydrogenolytically or in the presence of an oxidising agent or acid. Further examples of N-protecting groups and appropriate deprotection reactions are described in the literature (see for example McOmie, "Protecting groups in organic chemistry", Plenum, 1973 and Greene, "Protective groups in organic synthesis", Wiley Interscience 1981).

The process according to the invention is typically carried out at elevated temperature (eg. under reflux)

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for at least one hour, preferably 1-4 hours, particularly preferably 1-2 hours and at ambient pressure.

The process according to the invention provides a yield of a 10,11-dihydro-5H-dibenzo[a,d]cyclo-heptene typically in excess of 60% and often 80% or more.

The invention is illustrated in a non-limiting fashion by the following examples in which all ratios and percentages are by weight unless otherwise stated:

EXAMPLE 1

Preparation of ethyl 4-(5,6-dihydro-11H-benzo[5,6]cycloheptan)-piperylidene-1-carboxylate

A mixture of 4-carboethoxypiperidone (5.64g, 33 mmole) and dibenzosuberone (6.24g, 30 mmole) are dissolved in tetrahydrofuran (82 ml) under a nitrogen atmosphere. Zinc (8.83g, 135 mmole) is added and the mixture cooled to 0°C. Titanium tetrachloride (7.4 ml, 67.5 mmole) is added over 15 minutes so that the temperature does not exceed 30°C. The mixture is then heated at reflux for about 1.5 hours.

About 50 ml of THF is removed by distillation under reduced pressure and the residue is partitioned between toluene (100 ml) and 2M HCl (100 ml). The layers are separated and the aqueous phase extracted with a further 100 ml toluene. The combined organic phase is washed with 50 ml 10% potassium carbonate solution and dried over magnesium sulphate.

Removal of the solvent and chromatography of the residue (10.3g) on silica gel using ether:dichloromethane (5:95) gives 9.3g (89%) product at constant weight as a viscous oil which crystallises on standing to give a solid (MP 87-90°C).

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EXAMPLE 2**Preparation of ethyl 4-(5,6-dihydro-11H-benzo[5,6]cycloheptan)-piperylidene-1-carboxylate**

5 A mixture of 4-carboethoxypiperidone (3.8g, 22 mmole) and dibenzosuberone (4.4g, 20 mmole) are dissolved in ethyl acetate (50 ml). Zinc (6.4g, 100 mmole) is added and the mixture cooled to 0°C. Titanium tetrachloride (4.9 ml, 45 mmole) is added over about 5
10 minutes so that the temperature stays below 15°C. (If required, the diol may be isolated at this stage by addition to water.) The reaction is heated to reflux for 2 hours. The mixture is allowed to cool and 75 ml 2M HCl is added. The aqueous phase is extracted with a
15 further 50 ml ethyl acetate. The combined organic phase is washed with 50 ml 10% potassium carbonate solution and dried over magnesium sulphate.

 The solvent is removed to constant weight under vacuum to give 6.8g crude product which is contaminated
20 with a small amount of deoxygenated tricycle.

EXAMPLE 3**Preparation of Loratadine**

25 8-Chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-one (2.45g, 10 mmole) (see J. Heterocyclic Compounds, vol. 8, 1971, page 73) and 4-carboethoxypiperidone (1.8g, 10 mmole) are dissolved in 30 ml tetrahydrofuran. Zinc (5g, 78 mmole) is added and
30 the mixture cooled to 0°C. Titanium tetrachloride (3 ml, 27 mmole) is added over about 10 minutes. The mixture is then heated at reflux for 1 hour. The mixture is added to 100 ml water and 50 ml toluene. Most of the aqueous phase is separated and the organic
35 phase is washed with 20 ml ammonium hydroxide solution.

 The mixture is filtered through celite and the celite washed with a further 50 ml toluene. The organic

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phase is separated and dried over magnesium sulphate.

The solvent is removed and the residue (3.75 g) is crystallised from butyl ether to give 2.5g loratadine (68%). HPLC shows the product to be >98% pure.

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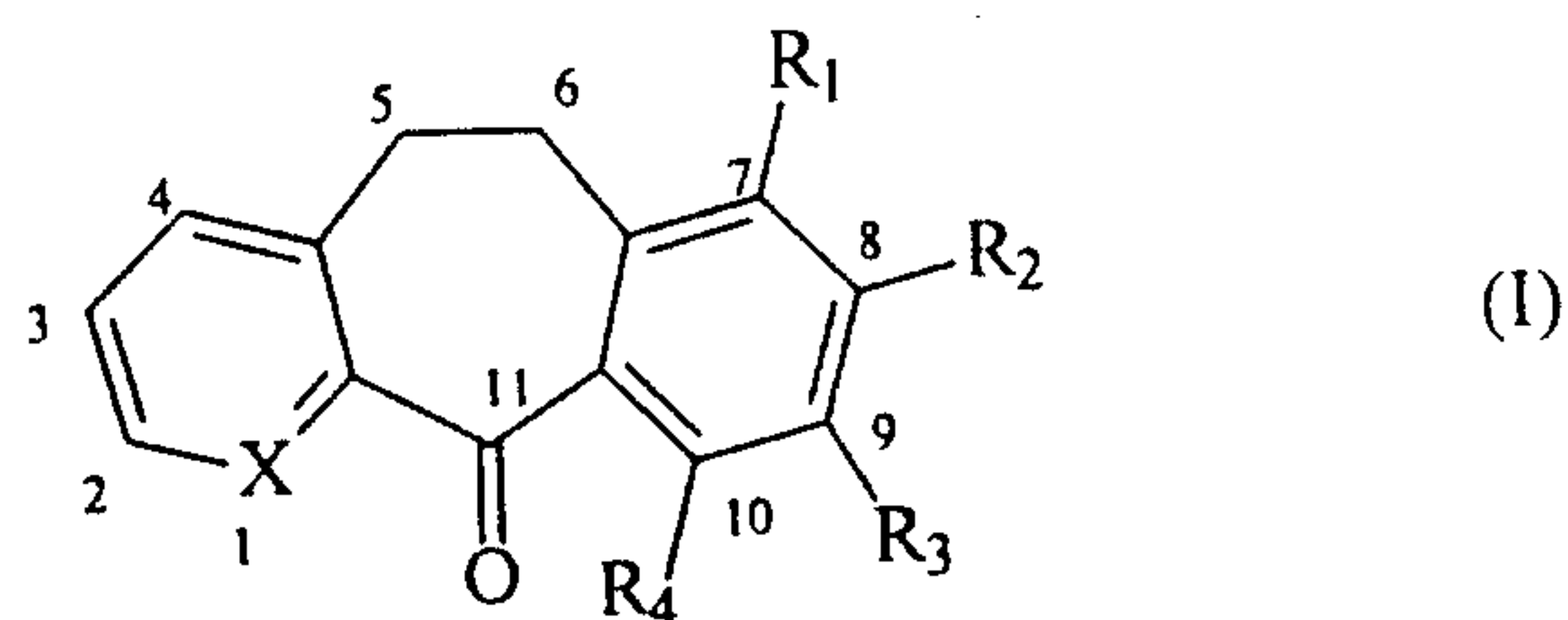
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CLAIMS:

1. A process for preparing 5,6-dihydro-11H-dibenzo[a,d]cyclohept-11-enes comprising reacting a dibenzosuberone or an aza derivative thereof of formula I:

5



(wherein:

X denotes nitrogen or CH;

10

and R¹, R², R³ and R⁴ which may be the same or different independently denote hydrogen or a halogen);

with a cyclic aliphatic ketone in the presence of low valent titanium wherein said low valent titanium is generated by zinc.

15

2. A process as claimed in claim 1 wherein R² is a halogen.

3. A process as claimed in claim 1 or 2 wherein R¹, R³ and R⁴ denote hydrogen.

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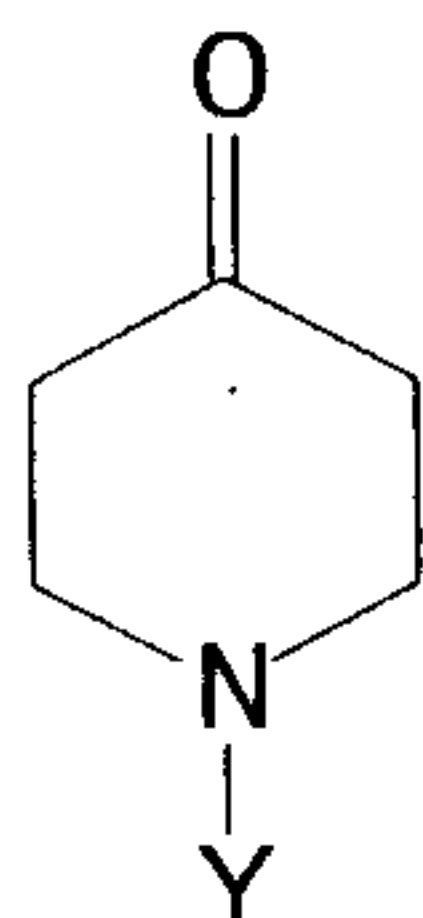
4. A process as claimed in any one of claims 1, 2, or 3 wherein X is nitrogen.

5. A process as claimed in any one of claims 1 to 4 wherein said cyclic aliphatic ketone is an optionally N-substituted piperidone.

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6. A process as claimed in claim 5 wherein said piperidone is of formula II:



5

(wherein:

Y denotes hydrogen, lower alkyl, CO_2R^5 , SO_2R^5 , $\text{CON}(\text{R}^5)_2$, $\text{SO}_2\text{N}(\text{R}^5)_2$, CO_2COR^5 or a N-protecting group; and

10 R^5 is hydrogen, a C_{1-12} -alkyl group optionally substituted by one or more amino or C_{1-6} -alkylamino groups, a phenyl group optionally substituted by one or more halo or C_{1-6} -alkyl groups, a C_{7-12} -phenylalkyl group optionally substituted at the phenyl by one or more halo or C_{1-6} -alkyl
 15 groups, 2-piperidyl, 3-piperidyl or piperidyl substituted at the nitrogen atom by a C_{1-4} -alkyl group) and the salts thereof.

7. A process as claimed in claim 6 wherein Y is CO_2Et .

8. A process as claimed in any one of claims 1 to 7 wherein Ti is present in a molar ratio range 1.5:1 to 4:1
 20 relative to the dibenzosuberone.

9. A process as claimed in claim 8 wherein Ti is present in a molar ratio range 2:1 to 3:1 relative to the dibenzosuberone.

10. A process as claimed in any one of claims 1 to 9
 25 wherein said low valent titanium consists essentially of Ti(II).

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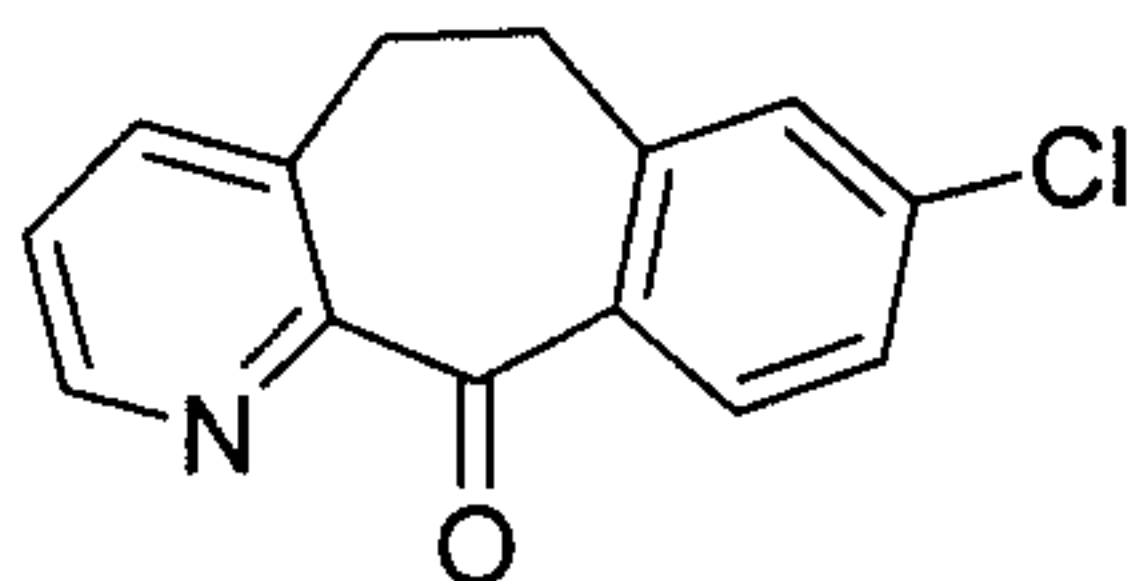
11. A process as claimed in any one of claims 1 to 10 wherein low valent titanium is prepared *in situ*.

12. A process as claimed in claim 11 wherein low valent titanium is prepared by reacting a Ti(III) or Ti(IV) compound
5 or complex with said zinc.

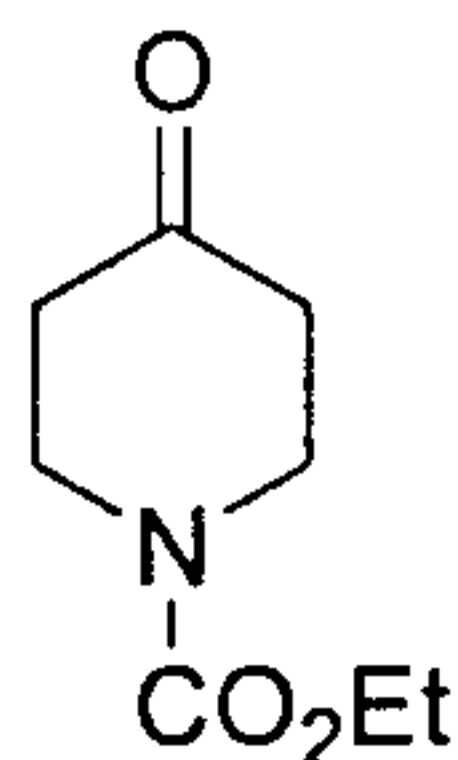
13. A process as claimed in claim 12 wherein said titanium compound is titanium(III) chloride or titanium(IV) chloride or a complex thereof.

14. A process for preparing loratadine, which comprises
10 reacting 8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]-11-one with 1-ethoxycarbonyl-4-piperidone in the presence of low valent titanium, wherein said low valent titanium is generated by zinc.

15. A process according to any one of claims 1 to 13,
15 wherein the aza derivative of dibenzosuberone is of formula:



16. A process according to claim 15, wherein the cyclic aliphatic ketone is of formula:



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