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(54) Titre : PREPARATION DE COMPLEXES DE MONO- ET 1,7-BIS N-HYDROXYALKYL-CYCLENE ET DE SEL DE LITHIUM

(54) Title: PRODUCTION OF MONO AND 1,7-BIS-N-HYDROXYALKYL-CYCLENE AND LITHIUM SALT COMPLEXES

(57) Abrégé/Abstract:
The invention relates to processes for mono- and 1,7-bis-N-β-hydroxyalkylation of cyclenes, the corresponding mono- and 1,7-bis-N-β-hydroxyalkyl-1,4,7,10-tetraazacyclododecane-Li-salt complexes as intermediate products in the process and the use of the N-(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7,10-tetraazacyclododecane-LiCl complex for the production of gadobutrol [Gd complex of N-(1-hydroxy-methyl-2, 3-dihydroxypropyl)-1,4,7-triscarboxymethyl-1,4,7,10-tetraazacyclododecane].

Abstract

The invention relates to processes for mono- and 1,7-bis-N-ß-hydroxyalkylation of cyclenes, the corresponding mono- and 1,7-bis-N-ß-hydroxyalkyl-1,4,7,10-tetraazacyclododecane-Li-salt complexes as intermediate products in the process and the use of the N-(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7,10-tetraazacyclododecane-LiCl complex for the production of gadobutrol [Gd complex of N-(1-hydroxy-methyl-2,3-dihydroxypropyl)-1,4,7-triscarboxymethyl-1,4,7,10-tetraazacyclododecane].

WO 98/55467 PCT/DE98/01523

PRODUCTION OF MONO- AND 1,7-BIS N-HYDROXYALKYL-CYCLENE AND LITHIUM SALT COMPLEXES

The invention relates to the process for mono- and 1,7-bis-N-ß-hydroxyalkylation of cyclene, the corresponding N-ß-hydroxyalkyl-1,4,7,10-tetraazacyclododecane-lithium-salt complexes as intermediate products in the process, and the use of the complexes for the production of gadobutrol [Gd complex of N-(1-hydroxy-methyl-2,3-dihydroxypropyl)-1,4,7-triscarboxymethyl-1,4,7,10-tetraazacyclododecane] and analogs.

Mono-substituted and di-substituted N-ß-hydroxyalkyl-1,4,7,10-tetraazacyclododecanes are valuable intermediate stages in the production of NMR diagnostic agents (see DE A1 36 25 417, EP 545 511 A2 and EP 0 448 191 A1). The synthesis of these compounds is done by reacting 1,4,7,10-tetraazacyclododecane (cyclene) with epoxides, whereby a mixture of mono-, bis- and tris-alkylated products that is statistical and difficult to separate is produced (WO93/24469). By using a large excess of the expensive polyazamacrocycle, mainly the monoalkylated product can be produced, but the separation from the excess starting material is also a problem, especially in the case of production on an industrial scale (quantities of over 50 kg).

The known methods for the production of N-ß-hydroxyalkyl-1,4,7,10-tetraazacyclododecanes requires selective protection of the three nitrogen atoms by reaction with DMF-dimethylacetal,

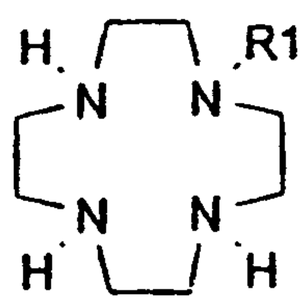
with boranes (H. Bernard et al. Tetrahedron Lett. 1991, 639) or with Cr or Mo-carbonyl complexes (J.-J. Yaouanc et al., Chem. Commun. 1991, 206); these steps are followed by functionalization of the fourth nitrogen atom and subsequent cleavage of the protective group. These methods are very expensive to implement and difficult to use on an industrial scale.

The process for monoalkylation of polyazamacrocycles that is described in US PS 5,064,633 is limited to the use of α-halocarboxylic acid derivatives and cannot be used for reaction with epoxides for the production of the desired substituted N-ß-hydroxyalkyl-1,4,7,10-tetraazacyclododecanes.

The regioselective formylation of monoalkylated cyclene derivatives was described by P. Anelli et al. (J. Chem. Soc., Chem. Commun. 1991, 1317), and the production of 1,7-disubstituted cyclene derivatives by reaction with chloroformic acid esters was described in J. Chem. Soc., Chem. Commun. 1995, 185.

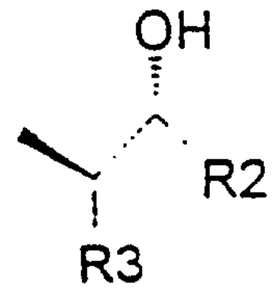
An object of the invention is to provide a process that ensures direct mono- and 1,7-bis-N-ß-hydroxyalkylation of cyclene and avoids expensive and multistage protection of the cyclene.

The invention provides a process for the production of compounds of general formula I



(I)

in which

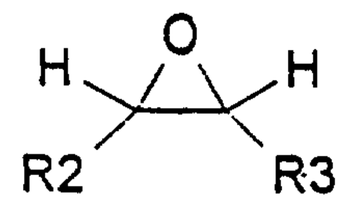
R1 means the group 

and in which within R^1, radicals R^2 and R^3, independently of one another, in each case stand for a hydrogen atom or form a 4-, 5-, 6- or 7-membered cycloalkyl ring, which optionally can be interrupted by 1 to 3 oxygen atom(s) or a C_1-C_{12} alkyl radical, which optionally is substituted with 1 to 3 C_1-C_6 alkyl groups or 1 to 3 hydroxy groups, for example, hydroxymethyl, hydroxyethyl, methyl, ethyl, propyl, butyl, whereby the hydroxy radicals that are present are optionally present in protected form,

by reaction of 1,4,7,10-tetraazacyclododecane,

optionally in the form of a salt,

are reacted with an epoxide of formula II,

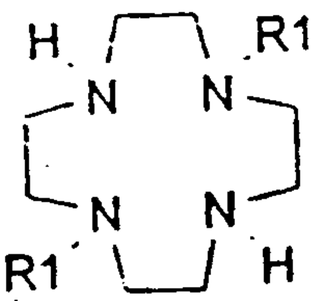


(II)

in which R^2 and R^3 have the above-indicated meanings, with 0.8-1.1 mol, preferably with 0.9-1.0 mol of lithium salt, such as, for example, lithium chloride at temperatures of between 40-150°C, and the reaction mixture that is obtained optionally is worked up in aqueous form.

Further objects of the invention are achieved by a process

for the production of the compounds of general formula III



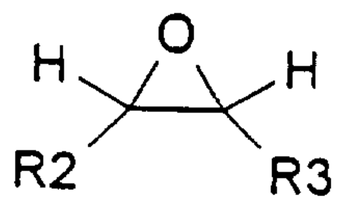
(III)

The compounds of general formula (III) can be produced in a way that is similar to that of the compounds of general formula (I), with the difference that more than 1.11 mol, preferably 1.5-3.0 mol, of lithium salt (lithium chloride) is added. Radicals R^1 have the same meaning as within the compounds of general formula (I).

By adding different quantities of lithium salt (for example lithium chloride), the selectivity of the alkylation can be controlled. When 1 mol of cyclene is converted with up to 1.1 mol of lithium salt, the monoalkylated product with its low proportion of 1,4-disubstituted product is obtained at up to 80%. If more than 1.11 mol, preferably 2 and more lithium salt per mol of cyclene is used in the reaction, the 1,7-disubstituted product is obtained at over 80% if more than 2 mol of epoxide of general formula (III) is used. If the quantity of epoxide is increased, for example to over 5 to 10 mol per mol of cyclene, the selectivity of the reaction to the 1,7-disubstituted product is preserved.

The following epoxides of general formula II are

advantageous for the reaction in the process according to the invention:



(II)

R^2 and R^3 in the meaning of hydrogen, methyl, propyl, butyl or higher alkyl, which optionally can be substituted by one or more hydroxyl groups, R^2 and R^3 together form a 4-, 5-, 6- or 7-membered ring, which can be interrupted by 1-3 oxygen atoms, and especially advantageous are cyclopentene, cyclohexene, cycloheptene-epoxide, ethylene oxide, propylene oxide, 1,2-butene oxide or 4,4-dimethyl-3,5,8-trioxabicyclo[5,1,0]octane.

The crude products that are thus obtained and that over 80% consist of the desired mono-N-ß- and 1,7-bis N-ß-hydroxyalkyl-1,4,7,10-tetraazacyclododecane in the form of lithium complexes can be used directly for the production of NMR contrast media.

As lithium salts, chlorides, bromides, iodides, perchlorates, or trifluoroacetates can be used. As solvents, dimethylformamide, dimethoxyethane, diethylene glycol-dimethyl ether, toluene or alcohols, such as, e.g., isopropanol or mixtures of these solvents can be used. The process according to the invention is carried out at temperatures of between 40 and 150°C, preferably in the temperature range of 80-140°C, and the reaction time is 20-50 hours.

The invention also includes the lithium complexes of the compounds of general formulas (I) and (III); the latter are obtained by direct crystallization of the reaction product. If the reaction mixture is worked up with the addition of water, the free compounds of general formulas (I) and (III) are obtained.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is the x-ray formulae for Example 1 and FIG. 2 is the x-ray formulae for Example 2.

The invention is explained by the examples below:

Example 1:

N-(6-Hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7,10-tetraazacyclododecane LiCl complex

20 g (116.16 mmol) of 1,4,7,10-tetraazacyclododecane, 4.85 g (116.16 mmol) of LiCl and 19.17 g (133.58 mmol) of 4,4-dimethyl-3,5,8-trioxabicyclo[5,1,0]octane are dissolved in 30 ml of isopropanol and refluxed for 22 hours. Then, the reaction mixture is concentrated by evaporation in a vacuum, and the crude product that is obtained (45.26 g) from 150 ml of MTB-ether is crystallized. 33.9 g (82% of theory) of N-(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7,10-tetraazacyclododecane, LiCl complex, is obtained as white crystals. Melting point 197-199°C. ^{1}H-NMR (DMSO-d_6): 3.65-3.40 m (5H, CH_2-O, CH-O); 2.80-2.35 m (17 H, CH_2-N, CH-N), 1.23 s, (6H, CH_3). (X-Ray: Fig. 1).

Example 2:

1,7-Bis((6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7,10-tetraazacyclododecane LiCl complex

10 g (58.08 mmol) of 1,4,7,10-tetraazacyclododecane, 4.85 g (116.16 mmol) of LiCl and 40.0 g (278.4 mmol) of 4,4-dimethyl-

3,5,8-trioxabicyclo[5,1,0]octane are suspended in 40 ml of isopropanol and refluxed for 60 hours. Then, the reaction mixture is mixed with 30 ml of isopropanol and cooled slowly to 0°C. The crystals that are obtained are suctioned off, washed with 30 ml of methyl-tert-butyl ether and dried in a vacuum. 20.7 g (71% of theory) of 1,7-bis(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7,10-tetraazacyclododecane LiCl complex is obtained as white crystals.

Flash point 262-265°C. ^{1}H-NMR (CD_3OD): 3.75-3.45 m (10H, CH_2-O, CH-O); 2.97-2.30 m (18 H, CH_2-N, CH-N), 1.29 s (12H, CH_3).

X-ray: Fig. 2.

Example 3:

N-(6-Hydroxycyclohehyl)-1,4,7,10-tetraazacyclododecane LiCl complex:

1 g (5.8 mmol) of 1,4,7,10-tetraazacyclododecane, 0.24 g (5.8 mmol) of LiCl and 0.65 g (6.7 mmol) of cyclohexene oxide (7-oxabicyclo[4.1.0]heptane) are dissolved in 2.5 ml of isopropanol and refluxed for 18 hours. Then, the reaction mixture is concentrated by evaporation in a vacuum. The crude product is crystallized from methyl-tert-butyl ether. 0.95 g (52% of theory) of N-(6-hydroxycyclohehyl)-1,4,7,10-tetraazacyclododecane LiCl complex is obtained as colorless crystals. Melting point 130-135°C. ^{1}H-NMR (DMSO-d_6): 3.50-3.45 m (1H, CH-O); 2.75-2.30 m (17 H, CH_2-N, CH-N), 2.00-1.57 m (4H, CH_2-CH_2); 1.30-1.08 m (4H, CH_2-CH_2).

Example 4:

1,7-Bis(6-hydroxycyclohexyl)-1,4,7,10-tetraazacyclododecane LiCl complex:

10 g (58.08 mmol) of 1,4,7,10-tetraazacyclododecane, 4.85 g (116.16 mmol) of LiCl and 56.5 g (580.0 mmol) of cyclohexene oxide (7-oxabicyclo[4.1.0]heptane) are suspended in 20 ml of isopropanol and refluxed for 20 hours. Then, the reaction mixture is mixed with 30 ml of isopropanol and slowly cooled to 0°C. The crystals that are obtained are suctioned off, washed with 30 ml of methyl-tert-butyl ether and dried in a vacuum. 19.5 g (82% of theory) of 1,7-bis(6-hydroxycyclohexyl)-1,4,7,10-tetraazacyclododecane LiCl complex is obtained as white crystals. Melting point 170-178°C.

^{1}H-NMR (DMSO-d_6 80°C): 3.48-3.25 m (2H, CH-O); 2.85-2.20 m (18H, CH_2-N, CH-N), 2.03-1.50 m (8H, CH_2-CH_2); 1.30-1.00 m (8H, CH_2-CH_2). MS (FAB): 369 $[M+H]^+$.

Example 5:

Gd Complex of N-(1-hydroxymethyl-2,3-dihydroxypropyl)-1,4,7-triscarboxymethyl-1,4,7,10-tetraazacyclododecane

The crude product that is obtained from Example 1 is dissolved in 50 ml of water and mixed at 70°C with a solution of 38.41 g (406.56 mmol) of chloroacetic acid and 16.26 g (406.56 mmol) of NaOH in 45 ml of water. The reaction mixture is stirred for 6 hours at 65°C, and during this, the pH is kept at 11.0 with NaOH. Then, it is acidified with concentrated HCl to pH 1.5, and the reaction mixture is concentrated by evaporation in a vacuum.

The residue is taken up with 500 ml of methanol, and the undissolved salts are filtered off. The filtrate is concentrated by evaporation, dissolved in 500 ml of water, mixed with 18.91 g (52.27 mmol) of gadolinium oxide and stirred for 2 hours at 100°C. Then, it is made neutral with LiOH, and the water is concentrated by evaporation in a vacuum. The residue is crystallized from ethanol/water. 60.92 g of crystalline crude product is obtained. The product is dissolved in 2 l of water and liberated of ionic contaminants by treatment with 500 ml of Amberlite™ IRA 67 and 500 ml of IRC 50. Then, the solution is concentrated by evaporation, and the residue is recrystallized from EtOH/water.

40.74 g (58% of theory, relative to the feed material) of the Gd complex of N-(1-hydroxy-methyl-2,3-dihydroxypropyl)-1,4,7-triscarboxymethyl-1,4,7,10-tetraazacyclododecane is obtained. The crude product that is thus obtained can be reacted to gadobutrol without further purification steps analogously to the instructions contained in DE 42 18 744 A1.

Example 6:

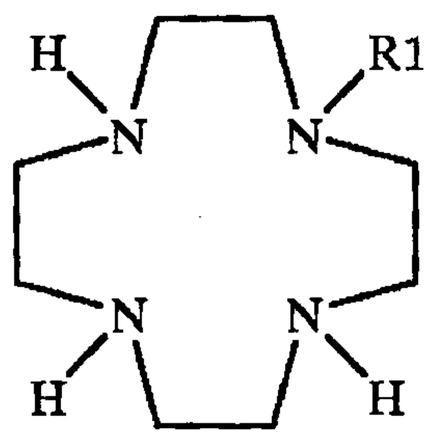
N-(6-Hydroxycyclohehyl)-1,4,7,10-tetraazacyclododecane:

1 g (5.8 mmol) of 1,4,7,10-tetraazacyclododecane, 0.24 g (5.8 mmol) of LiCl and 0.65 g (6.7 mmol) of cyclohexene oxide (7-oxabicyclo[4.1.0]heptane) are dissolved in 2.5 ml of isopropanol and refluxed for 18 hours. Then, the reaction mixture is concentrated by evaporation in a vacuum. The crude product is taken up in 10 ml of chloroform and extracted with 5 ml of water.

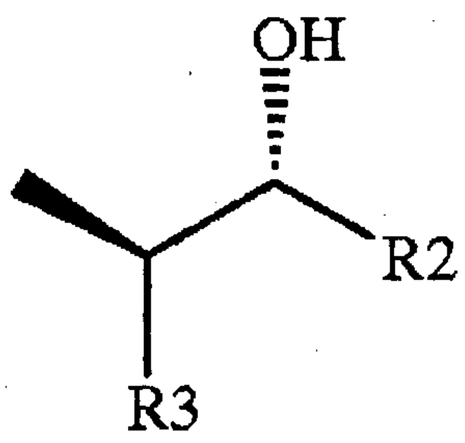
The organic phase is concentrated by evaporation. 1.25 g (79% of theory) of N-(6-hydroxycyclohehyl)-1,4,7,10-tetraazacyclododecane is obtained as a colorless oil.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

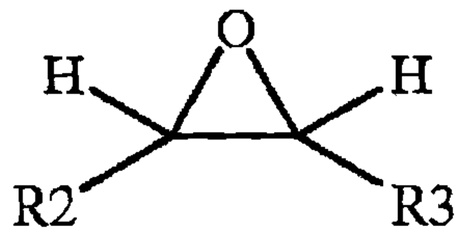
1. A process for the production of a compound of formula I:



wherein R1 is:



and R2 and R3 are, independently of one another, a hydrogen atom; or together with the carbon atoms to which they are bonded form a 4-, 5-, 6- or 7-membered cycloalkyl ring which optionally is interrupted by 1 to 3 oxygen atoms; or a C_1-C_{12} alkyl radical which optionally is substituted with 1 to 3 C_1-C_6 alkyl groups or 1 to 3 hydroxy groups;
wherein the optionally present hydroxyl radicals are optionally present in protected form;
the process comprising:
reacting 1,4,7,10-tetraazacyclododecane, optionally in the form of a salt, with an epoxide of formula II:

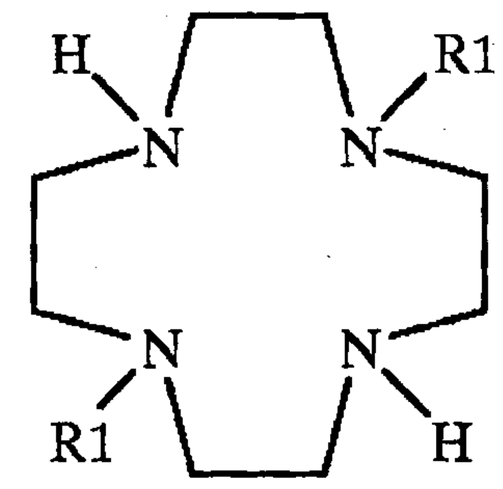


(II)

in which R2 and R3 have the above-indicated meanings, in the presence of 0.8-1.1 mol of lithium salt relative to one mol of cyclene at a temperature of from 40-150° C; and working up the reaction in aqueous form.

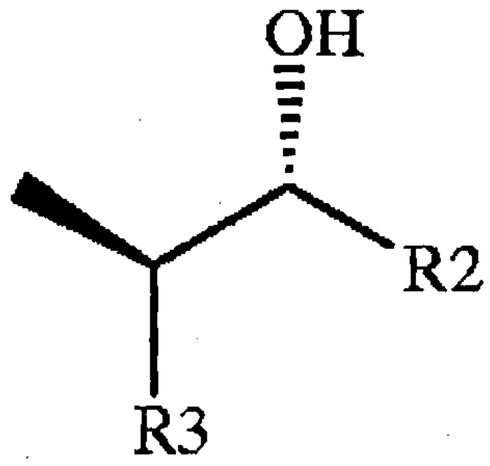
2. The process of claim 1, wherein 0.9-1.0 mol of lithium salt is present in the reaction.

3. A process for the production of a compound of formula III:



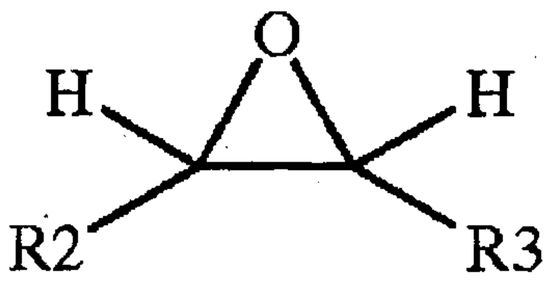
(III)

wherein R1 is:



and R2 and R3 are, independently of one another, a hydrogen atom; or together with the carbon atoms to which they are bonded form a 4-, 5-, 6- or 7-membered cycloalkyl ring

which optionally is interrupted by 1 to 3 oxygen atoms; or a C_1-C_{12} alkyl radical which optionally is substituted with 1 to 3 C_1-C_6 alkyl groups or 1 to 3 hydroxy groups;
wherein the optionally present hydroxy radicals are optionally present in protected form;
the process comprising:
reacting 1,4,7,10-tetraazacyclododecane, optionally in the form of a salt, with an epoxide of formula II:

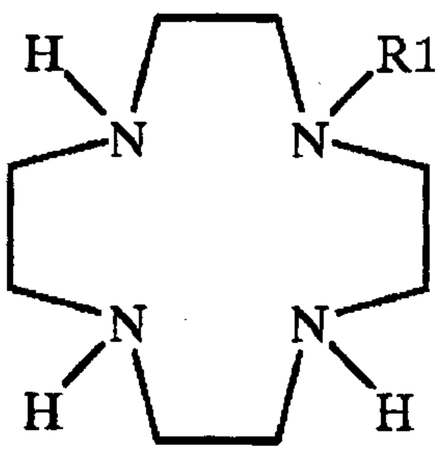


(II)

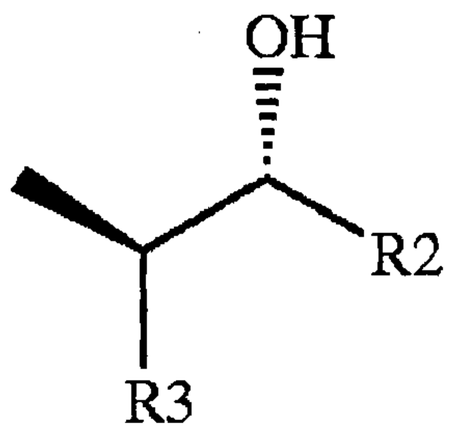
in which R2 and R3 have the above-indicated meanings, in the presence of more than 1.11 mol of lithium salt relative to 1 mol of cyclene at a temperature of from 40-150° C; and working up the reaction in aqueous form.

4. The process of claim 3, wherein 2.0-3.0 mol of lithium salt is present in the reaction.

5. A lithium complex of a compound of formula I:

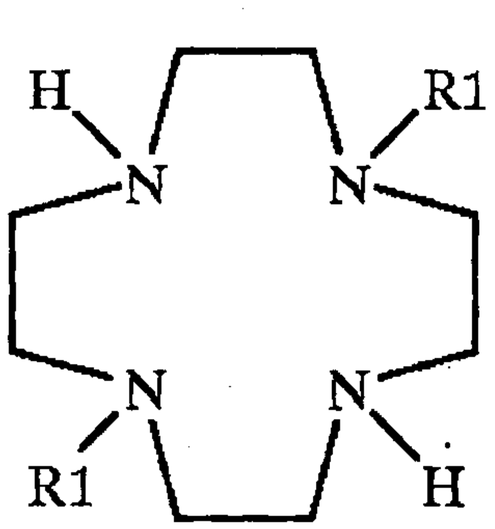


wherein R1 is:

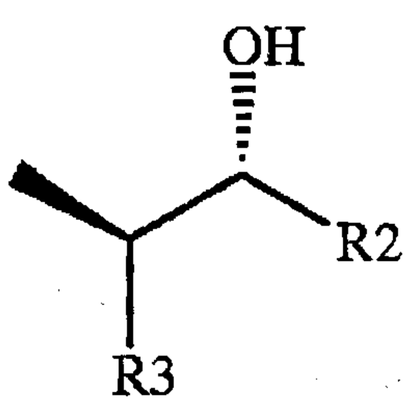


and R2 and R3 are, independently of one another, a hydrogen atom; or together with the carbon atoms to which they are bonded form a 4-, 5-, 6- or 7-membered cycloalkyl ring which optionally is interrupted by 1 to 3 oxygen atoms; or a C_1-C_{12} alkyl radical, which optionally is substituted with 1 to 3 C_1-C_6 alkyl groups or 1 to 3 hydroxy groups.

6. A lithium complex of a compound of formula III:



wherein R1 is:



and R2 and R3 are, independently of one another, a hydrogen atom; or together with the carbon atoms to which they are

bonded form a 4-, 5-, 6- or 7-membered cycloalkyl ring which optionally is interrupted by 1 to 3 oxygen atoms; or a C_1-C_{12} alkyl radical, which optionally is substituted with 1 to 3 C_1-C_6 alkyl groups or 1 to 3 hydroxy groups.

7. A complex of claim 6 which is a 1,7-bis(6-hydroxycyclohexyl)-1,4,7,10-tetraazacyclododecane LiCl complex, or a 1,7-bis((6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7,10-tetraazacyclododecane LiCl complex.

8. A complex of claim 5 which is an N-(6-hydroxycyclohexyl)-1,4,7,10-tetraazacyclododecane LiCl complex, or an N-(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7,10-tetraazacyclododecane LiCl complex.

9. Use of the lithium complex as defined in claim 5 for preparing gadobutrol or an analog thereof.

10. Use of the lithium complex as defined in claim 6 for preparing gadobutrol or an analog thereof.

11. Use of the N-(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)-1,4,7,10-tetraazacyclododecane-LiCl complex as defined in claim 5 for preparing the Gd complex of N-(1-hydroxymethyl-2,3-dihydroxypropyl)-1,4,7-triscarboxymethyl-1,4,7,10-tetraazacyclododecane.

12. The process of claim 1 or 2, wherein the lithium salt is a lithium chloride, bromide, iodide, perchlorate or trifluoroacetate.

13. The process of claim 1 or 2, wherein the lithium salt is lithium chloride.

14. The process of claim 1 or 2, wherein the epoxide is cyclopentane-epoxide, cyclohexane-epoxide, cycloheptene-epoxide, ethylene oxide, propylene oxide, 1,2-butene oxide, or 4,4-dimethyl-3,5,8-trioxabicyclo[5,1,0]octane.

15. The process of claim 1 or 2, wherein the temperature is from 80-140° C.

16. The process of claim 1 or 2, wherein the mono-N-β-substituted compound of formula (I) is selectively obtained with a yield of over 80%.

17. The process of claim 3 or 4, wherein the lithium salt is a lithium chloride, bromide, iodide, perchlorate or trifluoroacetate.

18. The process of claim 3 or 4, wherein the lithium salt is lithium chloride.

19. The process of claim 3 or 4, wherein the epoxide is cyclopentane-epoxide, cyclohexane-epoxide, cycloheptene-epoxide, ethylene oxide, propylene oxide, 1,2-butene oxide, or 4,4-dimethyl-3,5,8-trioxabicyclo[5,1,0]octane.

20. The process of claim 3 or 4, wherein the temperature is from 80-140° C.

21. The process of claim 3 or 4, wherein the 1,7-disubstituted compound of formula (III) is selectively obtained with a yield of over 80%.

Fig. 1

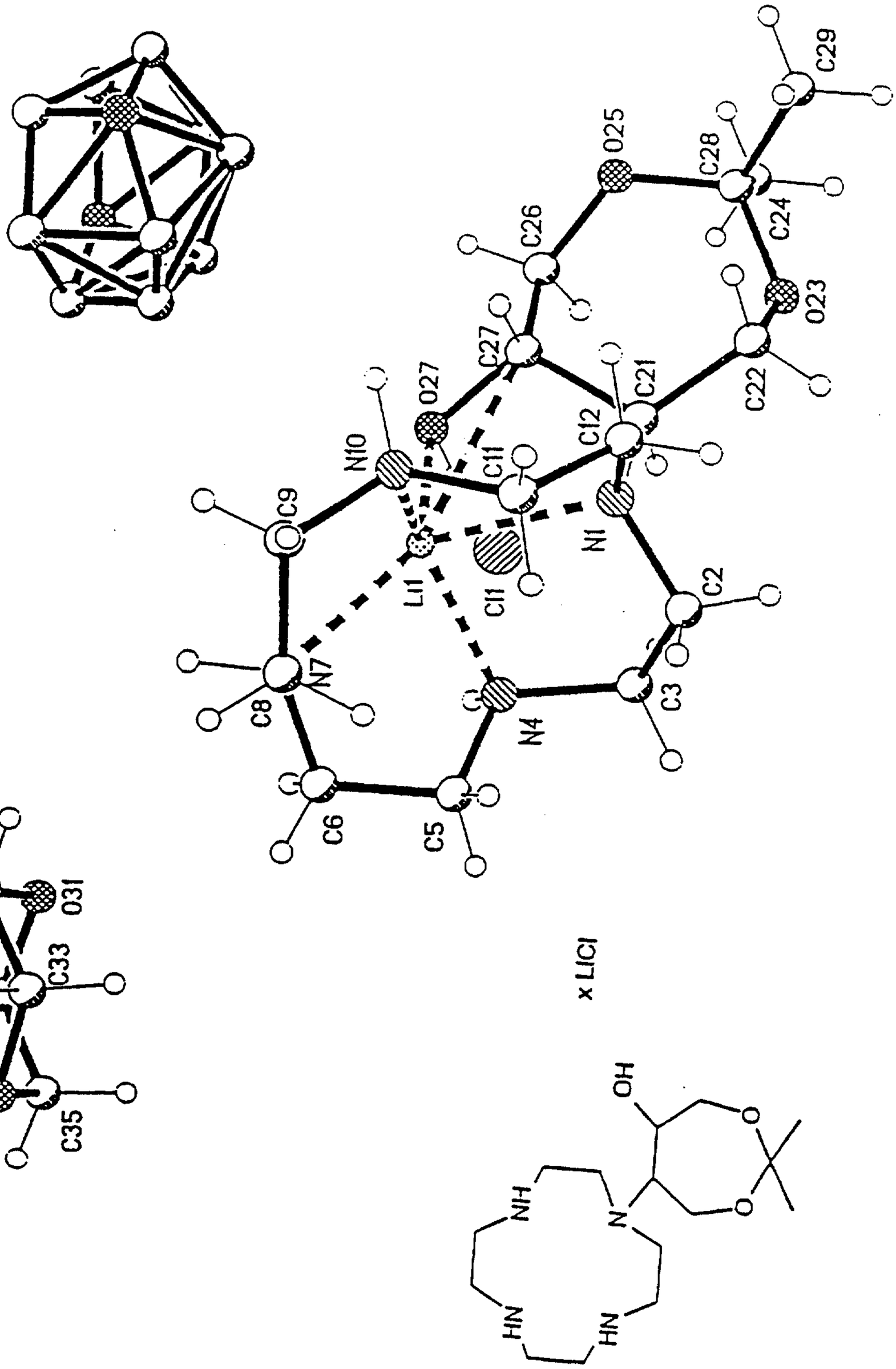

C29
025
C28
C26
C24
023
C27
C22
027
C21
C12
N10
C11
C9
N1
Li1
Cl1
C2
N7
C8
C3
N4
C6
C5
C32
031
C36
C33
034
C35
TCHX76/2 in P2(1)/c
x LiCl
OH
NH
N
HN
HN

Fig. 2