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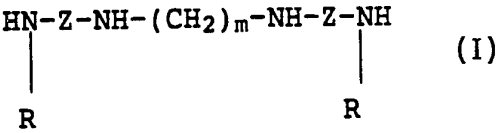

(I)

(57) Abstract

The present invention relates to treating CMV infections with polyamine compounds of formula (I) wherein Z is a saturated or branched chain (C_2-C_6) alkylene moiety; m is 7 or 8; each R group independently is hydrogen, a C_1-C_6 saturated or unsaturated hydrocarbyl, or -$(CH_2)_x$-(Ar)-X wherein Ar is phenyl or napthyl, X is H, C_1-C_6 alkoxy, halogen C_1-C_4 alkyl, wherein x is an integer 0, 1, or 2; with the proviso that both R groups cannot be hydrogen; or said compounds of formula (I) can be a pharmaceutically acceptable acid addition salt thereof.

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POLYAMINE DERIVATIVES AS ANTI-CYTOMEGALOVIRAL AGENTS

BACKGROUND OF THE INVENTION

Human cytomegalovirus (CMV) infections occur in a range of severity, from a passive silent infection without consequences to diseases that are manifested by fever, hepatitis, pneumonitis, and after congenital or neonatal infection may result in severe brain damage, stillbirth, or perinatal death.

Cytomegalovirus infections frequently occur through out life, with the incidence of seropositivity most frequent in the elderly. Intrauterine infection with CMV has a high frequency of infection, with CMV the leading cause of congenital viral infection, occurring in about 0.4 to 2.2% of all births. CMV infections can have serious effects in diseases in immunocompromised patients with a high frequency of morbidity and mortality, and is the major cause of sight-threatening infections in AIDS patients.

CMV is ubiquitously transmitted in all populations. However, risk to CMV infections varies considerably in different geographic areas. Infected individuals may transmit the virus in urine, saliva, cervical secretions, semen, feces, milk, or infected blood and organs.

Molecular analysis of the DNA of CMV isolates reveals minor strain-specific differences that are useful markers in epidemiological investigation. CMV is highly host-specific and cannot be propagated in laboratory animals or in most non-human cell cultures. Therefore, experiments designed to be predictive of CMV activity generally are restricted to human cell lines that have resident the CMV virus or have become infected with CMV.

It is well known that aliphatic polyamines, such as spermine and spermidine, play a role in cell growth and proliferation. These naturally occurring polyamines are found in animal cells and are produced in a biosynthetic pathway involving putrescine as a precursor. Putrescine is formed by a decarboxylation of ornithine by ornithine decarboxylase (ODC) and this is a highly regulated stage in the biosynthesis of spermidine and spermine.

The first indication that polyamines may have a role in certain viral function was discovered when putrescine and spermidine were found to be present in the bacteriophage T2. Later the polyamines, putrescine and spermidine, were found in other viruses, including human cytomegalovirus, poxvirus, vaccinia virus, and human type 5 adenovirus to name a few. However, the fact that polyamines are present in several animal viruses does not directly indicate a role for polyamines in viral replication. Unusually, CMV infection of cells in vitro is antagonised by inhibition of ODC by specific inhibitors of the enzyme (Tyms et al., J. Antimicrobial Chemotherapy 22, 403-427 1988).

The human cytomegaloviruses are a subgroup of agents within the herpes group of viruses, all of which have the propensity for remaining latent in man. No specific therapy is generally available for CMV infections. Although ganciclovir and foscovir are both licensed for use against some infections in the immunocompromised host, both

compounds can induce major side effects. It is a feature of the present invention that the CMV agents afford less cell and/or tissue toxicity compared to other agents in use.

CMV, compared to other herpes viruses, herpes simplex type 1 and type 11 and varicella-zoster virus, is relatively resistant to the action of acyclovir. Research in this area is primarily focused toward identifying agents which would be therapeutically effective in humans. A further feature of the present invention is that the compounds described herein provide a CMV agent that selectively acts against CMV compared to other Herpes viruses.

It has now been found that certain polyamine derivatives are effective therapeutic agents when used against cell cultures infected with CMV. An object of the present invention is the use of the describe polyamine derivatives as therapeutic agents against CMV.

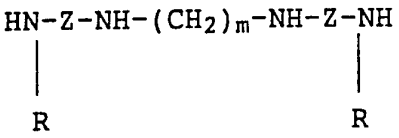
SUMMARY OF THE INVENTION AND DETAILED DESCRIPTION

Synthesis of compounds of the present invention as anticancer agents has been described in part in U.S. Patent Application 07/602,530 which is herein incorporated by reference. Synthesis of compounds of the present invention as antiprotozoal agents has been described in part in U.S. Patent Application 07/840,575 which is herein incorporated by reference. Synthesis of compounds of the present invention as potentiating cell-mediated immunity has been described in part in U.S. Patent Application 07/856,818 which is herein incorporated by reference.

This invention relates to methods of use of certain polyamine derivatives in the treatment of patients

suffering from CMV disease states and to pharmaceutical compositions containing these polyamine derivatives.

More specifically, this invention relates to a method for the treatment of patients suffering from CMV infections which comprises administering a therapeutically effective amount of a compound of the formula (I): wherein Z is a



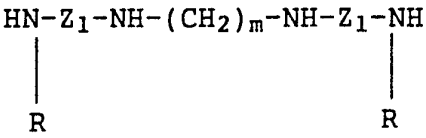
(I)

(C_2-C_6) saturated or branched chain alkyl moiety; m is 7 or 8; each R group independently is hydrogen, a C_1-C_6 saturated or unsaturated hydrocarbyl, or $-(CH_2)_x-(Ar)-X$ wherein Ar is phenyl or napthyl, X is H, C_1-C_6 alkoxy, halogen C_1-C_4 alkyl, wherein x is an integer 0, 1, or 2; with the proviso that both R groups cannot be hydrogen; or said compounds of formula I can be a pharmaceutically acceptable acid addition salt thereof.

As a further aspect of the present invention, it has been found that compounds of formulae (I) provide an anti-CMV effect in patients in need thereof. Compounds of formuale I generally produce effective treatment without similar delayed toxicity effects produced by other agents.

The present invention relates to the use of novel compounds of the formula (I) for CMV infections, or more specifically to the novel compounds of formula (Ia) and (Ib).

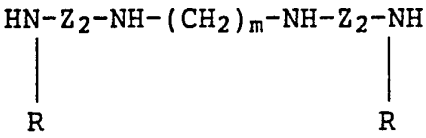
The novel compounds of formula (Ia) are of the formula:



(Ia)

wherein Z_1 is a branched chain (C_2-C_6) alkyl moiety; m is 7 or 8; and each R group independently is hydrogen, a C_1-C_6 saturated or unsaturated hydrocarbyl, or $-(CH_2)_x-(Ar)-X$ wherein Ar is phenyl or napthyl, X is H, C_1-C_6 alkoxy, halogen C_1-C_4 alkyl, wherein x is an integer 0, 1, or 2; with the proviso that both R groups cannot be hydrogen; or said compounds of formula Ia can be a pharmaceutically acceptable acid addition salt thereof.

The novel compounds of formula (Ib) are of the formula:



(Ib)

wherein Z_2 is a straight chain (C_2-C_6) alkyl moiety; m is 7 or 8; each R group independently is hydrogen, a C_1-C_6 saturated or unsaturated hydrocarbyl, or $-(CH_2)_x-(Ar)-X$ wherein Ar is phenyl or napthyl, X is H, C_1-C_6 alkoxy, halogen C_1-C_4 alkyl, wherein x is an integer 0, 1, or 2; with the proviso that both R groups cannot be hydrogen; or said compounds of formula Ib can be a pharmaceutically acceptable acid addition salt thereof.

The center alkylene moiety of compounds of the formula (I) is a saturated, straight-chain hydrocarbyl radical comprising 7 or 8 carbon atoms, i.e., "$(CH_2)_7$" or "$(CH_2)_8$". As used herein, the term "Z" is understood to mean a saturated hydrocarbylene radical of straight (Z_2) or branched-chain configuration (Z_1) comprising 2 to 6 carbon

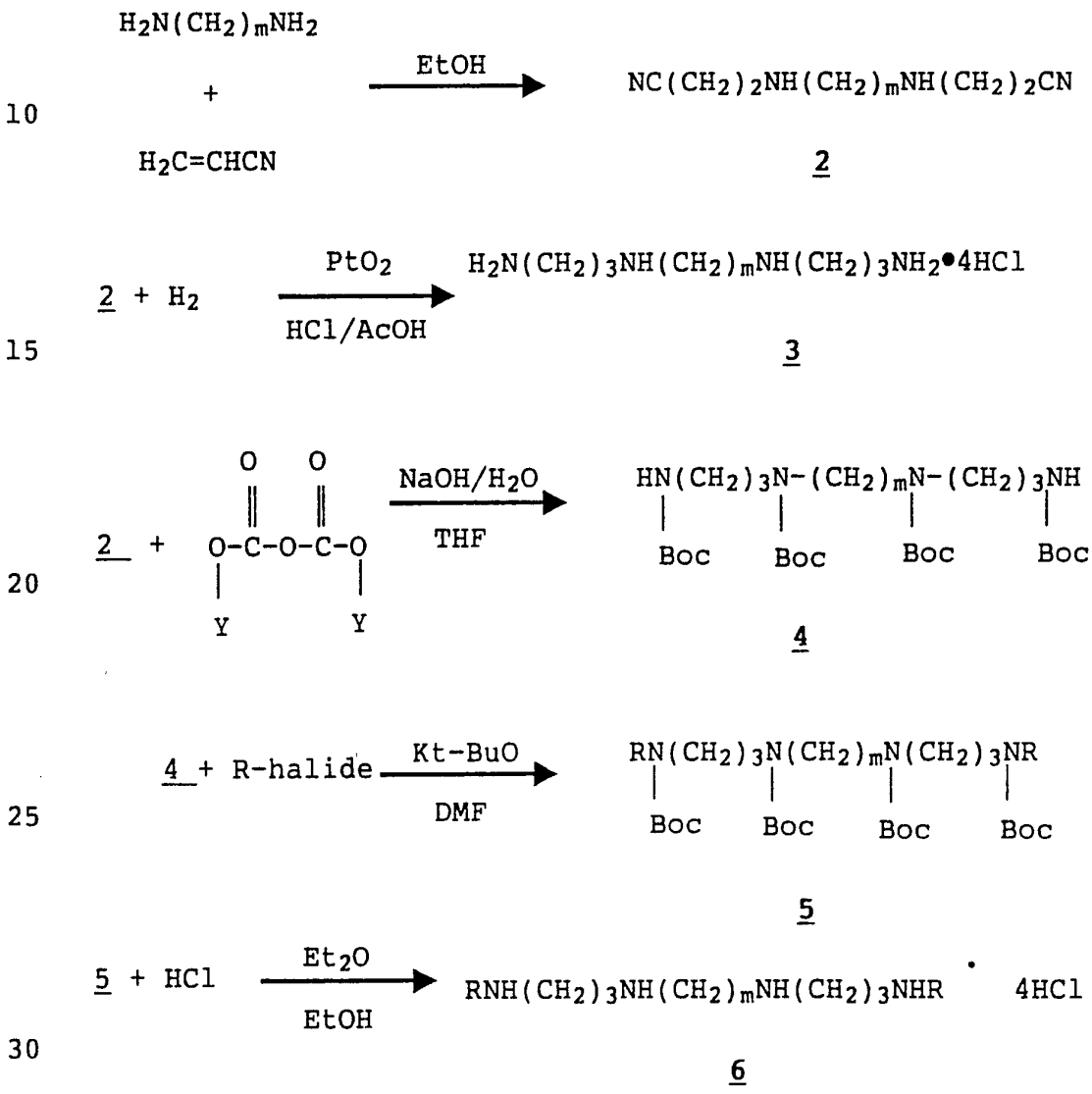
atoms including, but not limited to, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2(CH_2)_2CH_2-$, $-CH_2(CH_2)_3CH_2-$, $-CH_2(CH_2)_4CH_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$ and the like. In those instances where R is an unsaturated hydrocarbyl moiety, such compounds include straight, branched, or cyclized hydrocarbyl moieties such as $-CH_2CH=CH_2$, $-CH_2CH_2CH=CH_2$, $-CH_2CH\equiv CH$, and $-CH_2CH=C=CH_2$.

Compounds of the formula (I) can be used according to the present invention as pharmaceutically acceptable acid addition salts thereof. The term "pharmaceutically acceptable acid addition salt" encompasses both organic and inorganic acid addition salts including, for example, those prepared from acids such as hydrochloric, hydrofluoric, sulfuric, sulfonic, tartaric, fumaric, hydrobromic, glycolic, citric, maleic, phosphoric, succinic, acetic, nitric, benzoic, ascorbic, p-toluenesulfonic, benzenesulfonic, naphthalenesulfonic, propionic, and the like. The hydrochloric acid addition salts are preferred. The selection and preparation of pharmaceutically acceptable non-toxic acid addition salts are within the ability of one of ordinary skill in the art utilizing procedures and techniques well known and appreciated in the art.

In general, the compounds of formula (I) may be prepared by chemical reactions analogously known in the art. The choice of any specific route of preparation is dependent upon a variety of factors. For example, general availability and cost of the reactants, applicability of certain generalized reactions to specific compounds, and so forth, are all factors which are fully understood by those of ordinary skill in the art and all contribute to the choice of synthesis in the preparation of any specific compound embraced by formula (I).

A preferred route for the synthesis of compounds of the formula (I) wherein Z is $-CH_2CH_2CH_2-$, but also applicable by analogy for other compounds of formula (I) wherein Z is an alkyl-substituted propyl group (such as $-CH(CH_3)CH_2CH_2-$), is presented in Reaction Scheme A.

Reaction Scheme A



wherein m is 7 or 8, R is as defined in formula (I) except when R is $X-(Ar)-(CH)_x$, x cannot be zero. In reaction scheme A Boc is the t-butoxycarbonyl protecting group, and Y is tert-butyl.

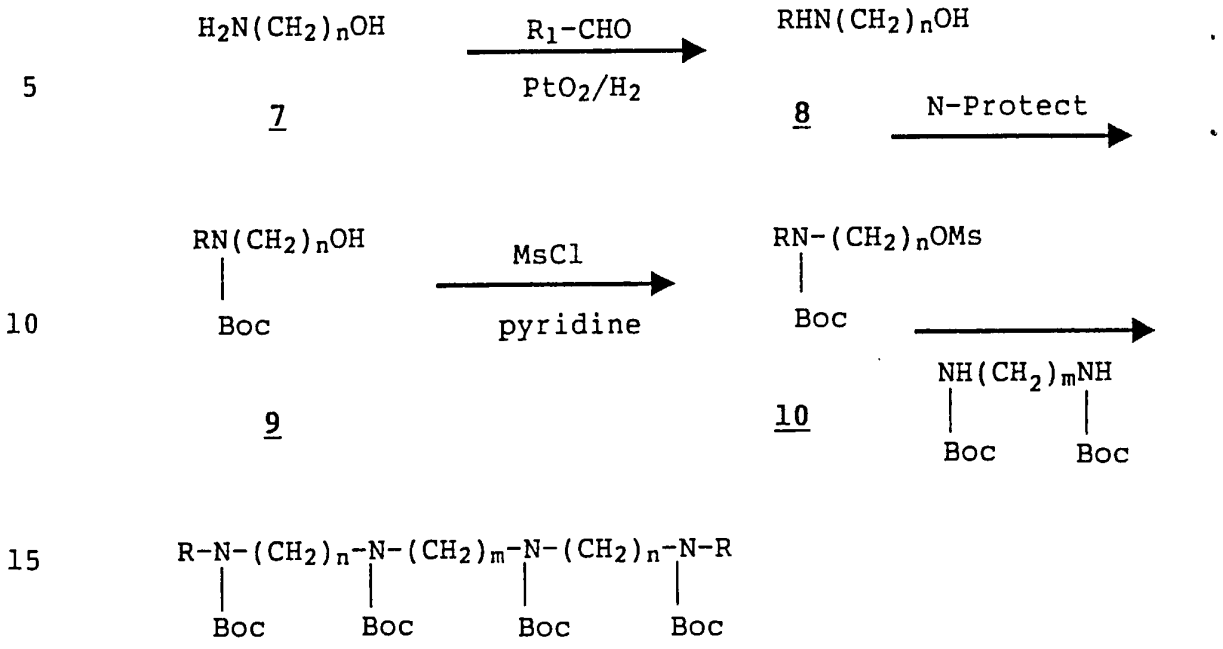
The initial step of this process entails an N-alkylation of the appropriate diamine with 2 equivalents of acrylonitrile by heating reactants, either in a suitable solvent or neat, according to standard conditions well known in the art. The resulting cyano derivatives (2) are chemically reduced by reaction with hydrogen in the presence of a catalyst (PtO_2) in a suitable solvent, such as acetic acid containing 8 equivalents of hydrochloric or hydrobromic acid, to produce the resulting hydrohalic salts according to standard procedures well known in the art. Of course, other reducing systems, e.g., reduction with lithium aluminum hydride, may also be utilized to produce compounds of formula (3). Following the preparation of these compounds the hydrohalic salts are neutralized with base and the nitrogen atoms are protected, preferably with di-t-butyldicarbonate according to standard operating conditions well known in the art. The tetra N-protected amines (4) are alkylated by reacting (4) with the appropriate alkyl halides (chloro or bromo) in the presence of potassium butoxide according to standard alkylation procedures well known in the art. When it is desired to provide compounds of the formula (I) wherein both R groups are the same, about 3 equivalents of the alkyl halide is reacted. When it is desired to provide compounds of the formula (I) wherein the R groups are not the same, monosubstitution of compounds of formula (4) is effected by reacting about 1 to about 1.5 equivalents of the alkyl halide with subsequent isolation of the monosubstituted compound according to standard procedures well known in the art and optionally further reacting the monosubstituted

compound with the desired different alkyl halide. Following alkylation the N-protective groups of compound (5) are removed by standard procedures, e.g., treatment with acid, preferably HCl, in the presence of a suitable solvent or solvent system, e.g., diethyloxide in ethanol, to obtain the desired products (6).

Alternatively, compounds of formula (3) and their otherwise prepared homologs may be subjected to a reductive alkylation using an appropriate aldehyde. The reduction is effected by hydrogenation in the presence of PtO_2 or sodium cyanoborohydride according to well known procedures. This procedure does not generally require protection of the nitrogen atoms of the intermediates.

A preferred route for the preparation of compounds of formula (I) wherein Z is $-CH_2(CH_2)_2CH_2-$, but which is also applicable by analogy to those compounds wherein Z is any straight chain, is presented in Reaction Scheme B.

Reaction Scheme B



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wherein m is 7 or 8, n is an integer 2 to 6 describing a straight chain alkylene moiety, Boc is the t-butoxycarbonyl protecting group, R is as defined in formula (I), Ms is mesyl and R_1 is hydrogen, methyl or ethyl.

This synthesis is initiated by reductive alkylation techniques well known in the art using an amino alcohol (7) and an appropriate aldehyde to form R- substituted amino alcohols (8). The nitrogen atom is protected, preferably with di-t-butyldicarbonate, according to standard operating conditions well known in the art, to yield the N-protected amino alcohols (9) which are converted to their mesylates (10) by known reaction conditions, e.g., reaction with mesylchloride in the presence of pyridine, preferably in a solvent such as CH_2Cl_2.

The mesylate is subjected to alkylation with an N-protected diamine (i.e., $BocNH(CH_2)_mNHBoc$) in the presence of potassium t-butoxide in a solvent such as DMF. The so-produced tetra N-protected tetramines (11) are deprotected as in Scheme A. In essence the foregoing reductive alkylation, N-protection, mesylation, alkylation and deprotection procedures all employ techniques and reaction conditions which are well known in the art.

In those instances wherein it is desired to prepare compounds of formula (I) wherein Z is $-CH_2-CH_2-$, it is preferred to employ Reaction Scheme C to obtain the necessary intermediates (14) which could be subjected to the alkylation procedures discussed above in Scheme A wherein m is 7 or 8.

Reaction Scheme C

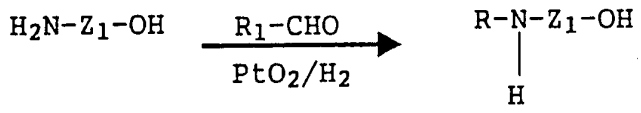
$$H_2NCH_2CH_2NH_2 + Br(CH_2)_mBr \longrightarrow H_2N(CH_2)NH(CH_2)_mNH(CH_2)_2NH_2$$

12 13 14

The foregoing N-alkylation entails the reaction of an appropriate dihaloalkane (13) with excess quantities (10x) of ethylene diamine (12) by heating the reactants at reflux temperatures in a suitable solvent, e.g., ethanol. Preparation of the final products bearing the desired R substituents on the terminal nitrogen atoms of the intermediates (14) may be effected by N-protection, alkylation with the appropriate alkyl halide, and deprotection in an analogous manner to that described for Reaction Scheme A. Preferably, the alkylation can be carried out by the reductive alkylation procedures without N-protection as alternatively described for Reaction Scheme A.

In general, compounds of the formula (Ia) can be prepared in an analogous manner to that described in Reaction Scheme D.

Reaction Scheme D



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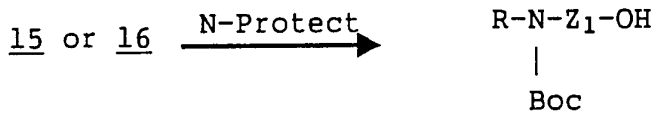

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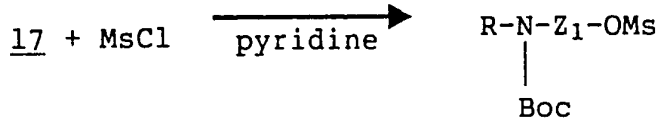

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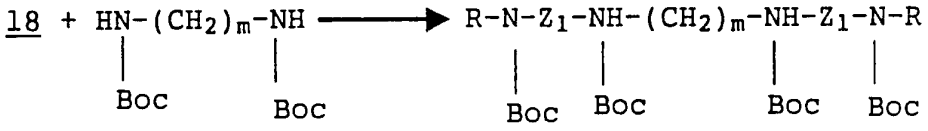

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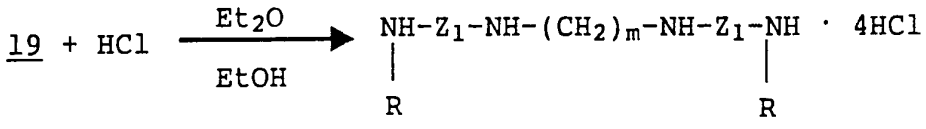

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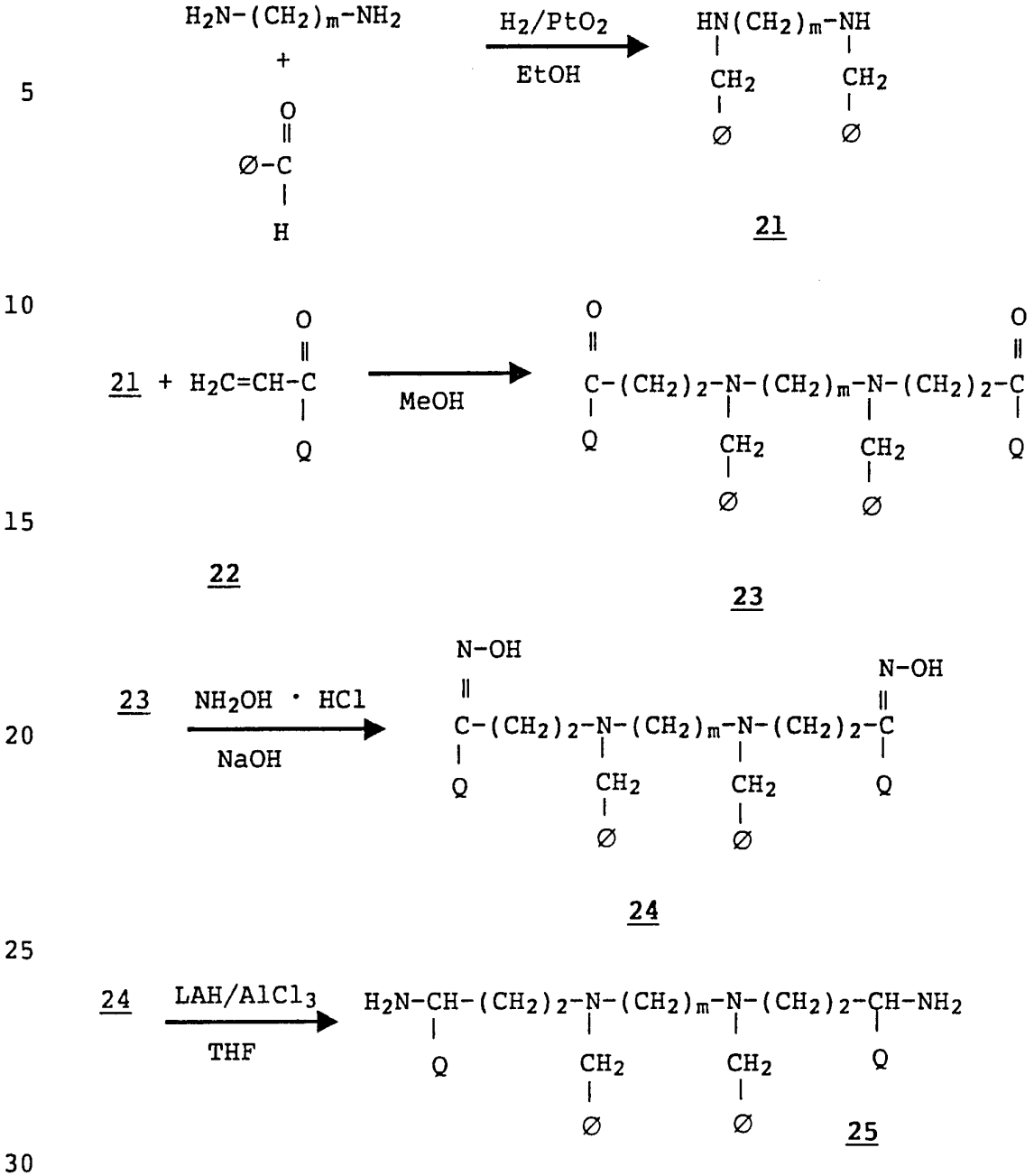
wherein m is 7 or 8, R and Z_1 are as generically defined for formula (Ia), and R_1 is hydrogen.

The appropriate primary amino alcohol (15) containing a branched chain hydrocarbyl moiety (i.e., Z_1) is prepared by standard procedures well known in the art. If desired, the primary amine can at this point be converted to a secondary amine (16), by a reductive alkylation with the appropriate aldehyde. The amino alcohol is reacted as described in Reaction Scheme A by standard conditions well known in the art to effect protection of the amines with an appropriate N-protecting group such as Boc (17). The mesylates of the N-protected amino alcohols (18) are prepared and are alkylated with the appropriate N-protected diamine (i.e., $BocNH(CH_2)_mNHBoc$) using standard procedures well known in the art as discussed for Reaction Scheme B. The so-produced tetra N-protected tetramines (19) are deprotected as in Scheme A to yield compounds of the formula (Ia). In essence, the foregoing reductive alkylation, N-protection, mesylation, alkylation and deprotective procedures all employ techniques and reaction conditions which are well known in the art.

Where it is desired to provide a compound of the formula (Ia) wherein each R group is not the same, the substituted mesylates (18) are prepared separately and monoalkylation of the appropriate N-protected diamine (i.e., $BocNH(CH_2)_mNHBoc$) is effected by reacting the diamine with about 1.0 to 1.5 equivalents of one of the mesylates (18) with subsequent isolation of the monosubstituted compound and optionally further reacting the monosubstituted compound with the desired differently substituted mesylate (18).

In those instances in which it is desired to prepare compounds of the formula (Ia) wherein Z_1 is an alkyl-substituted propylene group such as *-CH(Q)CH_2CH_2- wherein Q is a saturated alkyl radical comprising 1 to 3 carbon atoms of straight or branched chain configuration, Reaction Scheme E can be used to obtain intermediates of the formula (25) which can be subjected to alkylation of the N-terminal groups in a manner analogous to that described in Reaction Scheme A prior to de-protection,

Reaction Scheme E



wherein m is 7 or 8, Ø is phenyl, and Q is as defined above.

The initial step of the process entails a reductive alkylation wherein the appropriate diamine is reacted with hydrogen gas and 2 equivalents of benzaldehyde in the presence of a catalyst such as PtO_2 to yield the N-protected

diamine (21) under standard conditions well known in the art. The N-protected diamine (21) is then alkylated with 2 equivalents of the appropriate vinyl ketone (22) in a suitable solvent such as methanol using standard techniques. The resulting N-substituted diamine (23) is further reacted under standard conditions with hydroxylamine hydrochloride in the presence of base such as NaOH in a suitable solvent such as ethanol/water. The resulting oximes (24) are reduced to the corresponding N-protected di-primary amines (25) by reaction with lithium aluminum hydride (LAH) in the presence of $AlCl_3$ in a suitable solvent such as THF according to standard procedures. The N-protected di-primary amines (25) can be further alkylated with an appropriate aldehyde prior to deprotection in a manner analogous to that described for Reaction Scheme A.

Compounds of formula (Ia) wherein Z_1 is *-$CH(CH_3)CH_2CH_2$- or *-$CH(C_2H_5)CH_2CH_2$- are generally preferred in their end-use application. Compounds of formula (Ia) wherein each R group is the same moiety are also preferred. Compounds of formula (Ia) wherein each R group is methyl or ethyl are particularly preferred.

Of course, it is appreciated that in those instances wherein a compound of formula (Ia) possesses one or more chiral centers, the individual stereoisomers as well as mixtures of stereoisomers are included within the scope of the present invention. For example, the following compounds are specifically included within the scope of formula (I) and (Ia):

(R,R)-N,N'-bis[3-(methylamino)butyl]-1,7-diaminoheptane

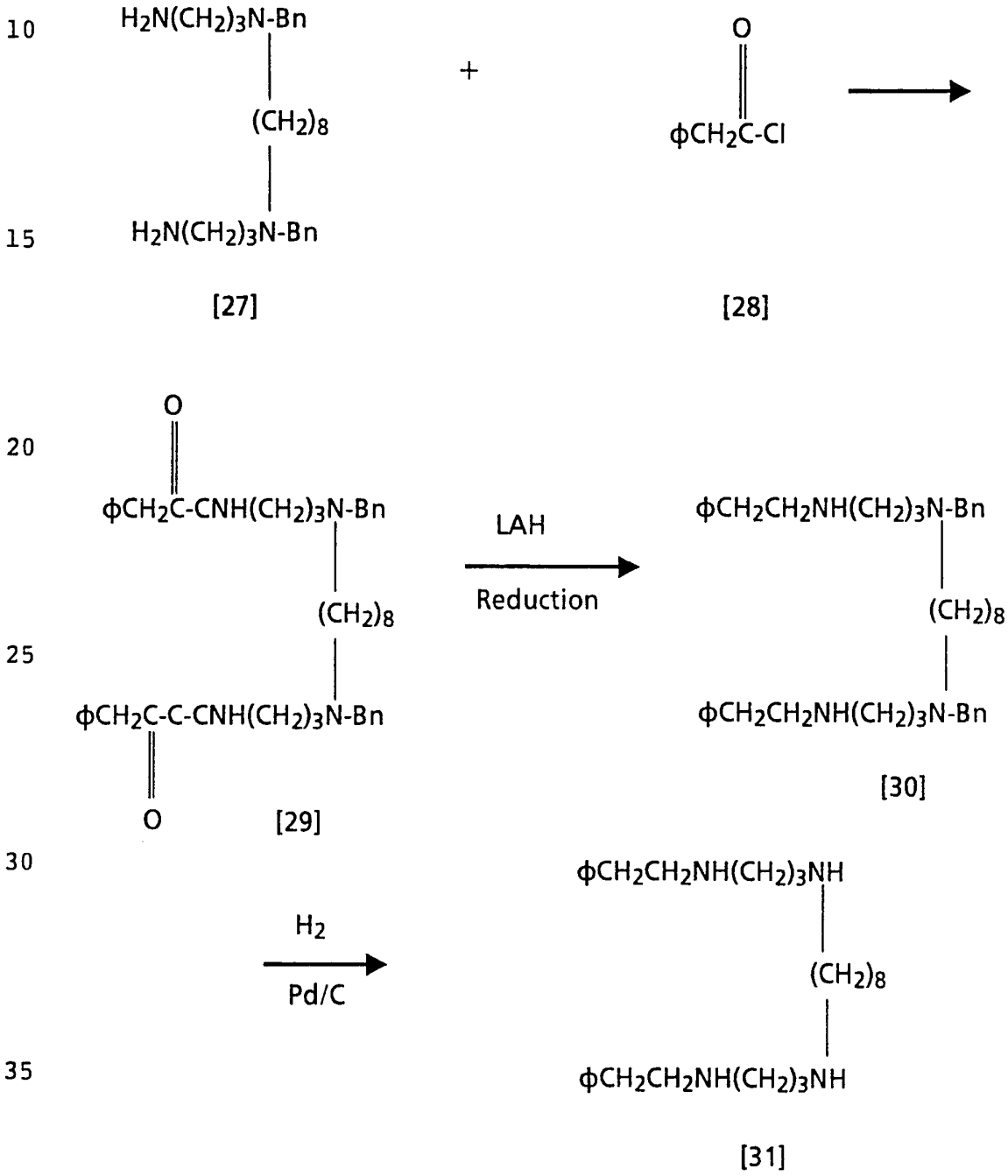
(S,S)-N,N'-bis[3-(methylamino)butyl]-1,7-diaminoheptane

(R,S)-N,N'-bis[3-(methylamino)butyl]-1,7-diaminoheptane.

A preferred method for preparing compounds of formula [I] wherein -(CH)x-(Ar)-X represents phenethyl or

naphthylethyl, particularly wherein Z is 3 and m is 8, is the reaction of an aroylchloride according to the method depicted in Reaction Scheme F wherein depicted in Scheme F Bn is benzyl, Φ is phenyl, and LAH is lithium aluminum hydride.

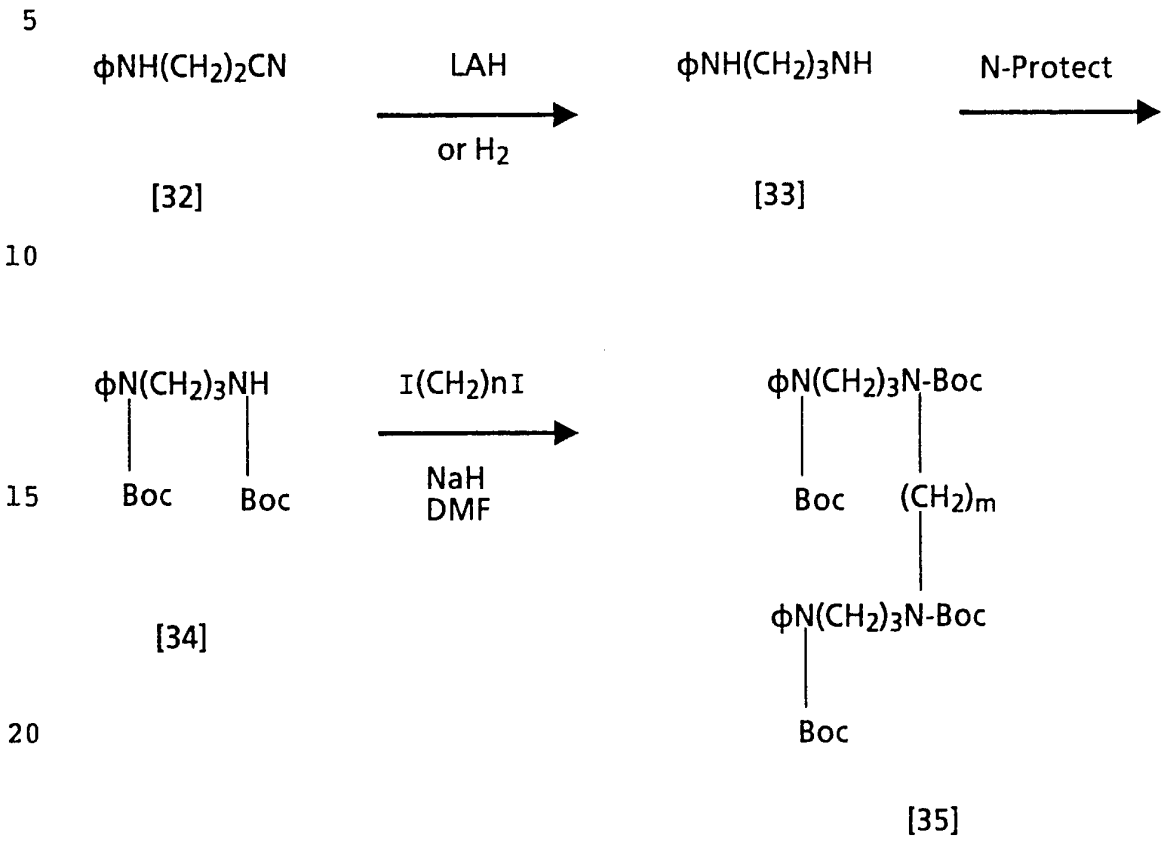
REACTION SCHEME F



As stated above, the foregoing reaction is a preferred method for the preparation of one particular compound which entails N-alkylation of a partially protected intermediate [27] with an arylacetyl chloride [28] in the presence of triethylamine, using an inert solvent, to form an amide [29] which is chemically reduced, preferably with LAH, and the resulting product [30] is catalytically de-benzylated (H_2Pd/C) to form the desired end product [31]. These steps entail reaction techniques and procedures well known in the art. Of course the same reaction scheme can be applied for the preparation of other compounds of formula [I]; adoption of the technique being with the usual caveats well understood by those of ordinary skill in the art.

In those instances wherein -(CH)x-(Ar)-X represents an aromatic moiety (X-phenyl or X-naphthyl) which is attached directly to the terminal nitrogen atoms (i.e., x is zero) then such compounds may be prepared according to the general reactions of Reaction Scheme G.

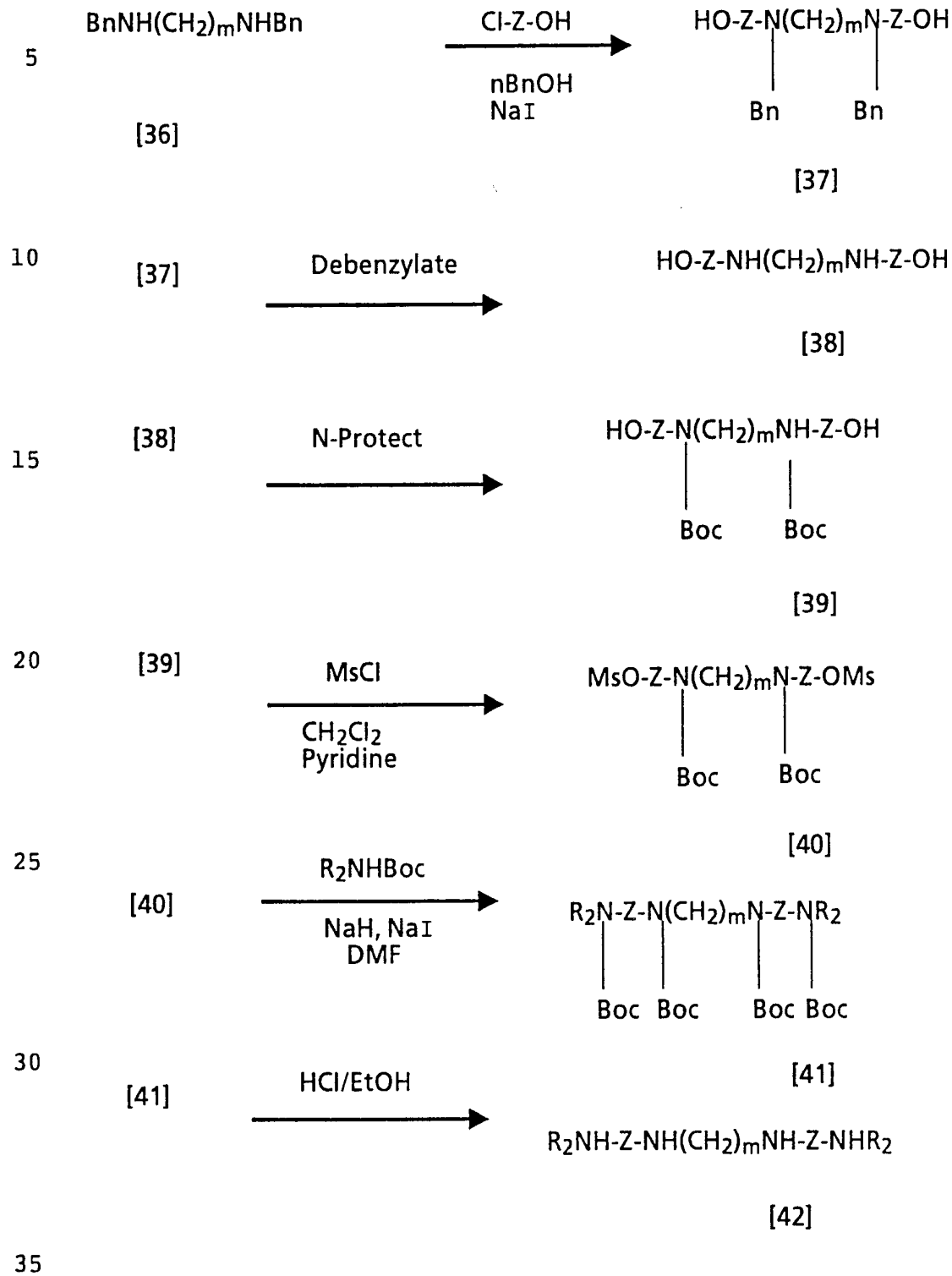
REACTION SCHEME G



The foregoing reaction scheme depicts the preparation of compounds wherein Ar is phenyl, the first step of which is a LAH reduction effected according to procedures published is the art (Bul. Soc. Chim. Fr., Part 2, 165-7 (1979)). Of course this reaction scheme can be expanded to include napthyl and X-substituted intermediates which will not be adversely affected by the reaction conditions. Preferably the N-protection uses the t-butoxycarbonyl protecting groups which are put on and taken off according to standard techniques already mentioned hereinabove. The N-protected compounds are alkylated by reaction with an appropriate dihaloalkane using standard and well known procedures.

In those instances wherein it is desired to prepare compounds of formula [I] which contain an unsaturated hydrocarbyl moiety, i.e., acetylenic, allenic, or allylic moiety-containing compounds, it is preferred to use the techniques of Reaction Scheme H wherein as shown R_2 is an appropriate unsaturated hydrocarbyl moiety, Bn is benzyl, MsCl is methanesulfonyl chloride, and Boc is the t-butoxycarbonyl protecting group.

REACTION SCHEME H



In the foregoing reaction a dibenzylated diamine [36] is N-alkylated by a simple displacement reaction to form compounds [37] which are sequentially benzylated [38] and N-protected. These steps are effected according to well known and standard procedures. The resulting bishydroxyamino-alkanes [39] are mesylated and the mesylates [40] are alkylated with two equivalents of an N-protected amine bearing an appropriate unsaturated hydrocarbyl moiety, e.g., N-(t-butoxycarbonyl)-2,3-butadienylamine. A so-obtained tetra protected tetramine [41] is then readily de-protected to produce the desired compounds [42].

In those instances wherein it is desired to convert an alkylthio substituent to one of its higher oxidation states the alkyl thioether is treated with a peracid according to known conditions. Suitable oxidizing agents are H_2O_2 and $NaIO_4$, but meta-chloroperoxybenzoic acid is preferred. In effecting the oxidation to a sulfinyl derivative 1 molar equivalent (per alkylthioether moiety) is used and 2 molar equivalents of the peracid will yield the sulfonyl derivatives. The oxidations are effected at temperatures of about 0oC to room temperature in solvents which themselves are not susceptible to oxidation. Preferred solvents are CH_2Cl_2, $CHCl_3$, acetic acid, and ethyl acetate.

The foregoing reaction scheme I depicts a method of preparation of the compounds of formula I. In scheme I the following abbreviations are used: Ts is a tolunesulfonyl substituent, DEAD is diethyl azodicarboxylate, THF is tetrahydrofuran, TFA is trifluoroacetic acid, and Boc is the t-butoxycarbonyl protecting group. It is intended that the reaction scheme is illustrative, and not limiting, of the chemistry depicted, wherein it is understood the reaction scheme can be expanded to include variations of m, Z, and R as defined in formula I. For instance, the reaction scheme can be expanded to include the variations

of Ts protecting group by various other arylsulfonyl groups beside toluenesulfonyl, such as mesitylenesulfonyl, benzylsulfonyl and the like.

Initial step (a), of scheme I, is the formation of compound [44] by reaction of N-t-butyloxycarbonyl-p-tolunesulfonamide with a chloroalkyl alcohol in the presence of triphenylphosphine (TPP) and DEAD to form the compound of [44]. Reactions involving step (a) is especially preferred to step (g) when Z=4.

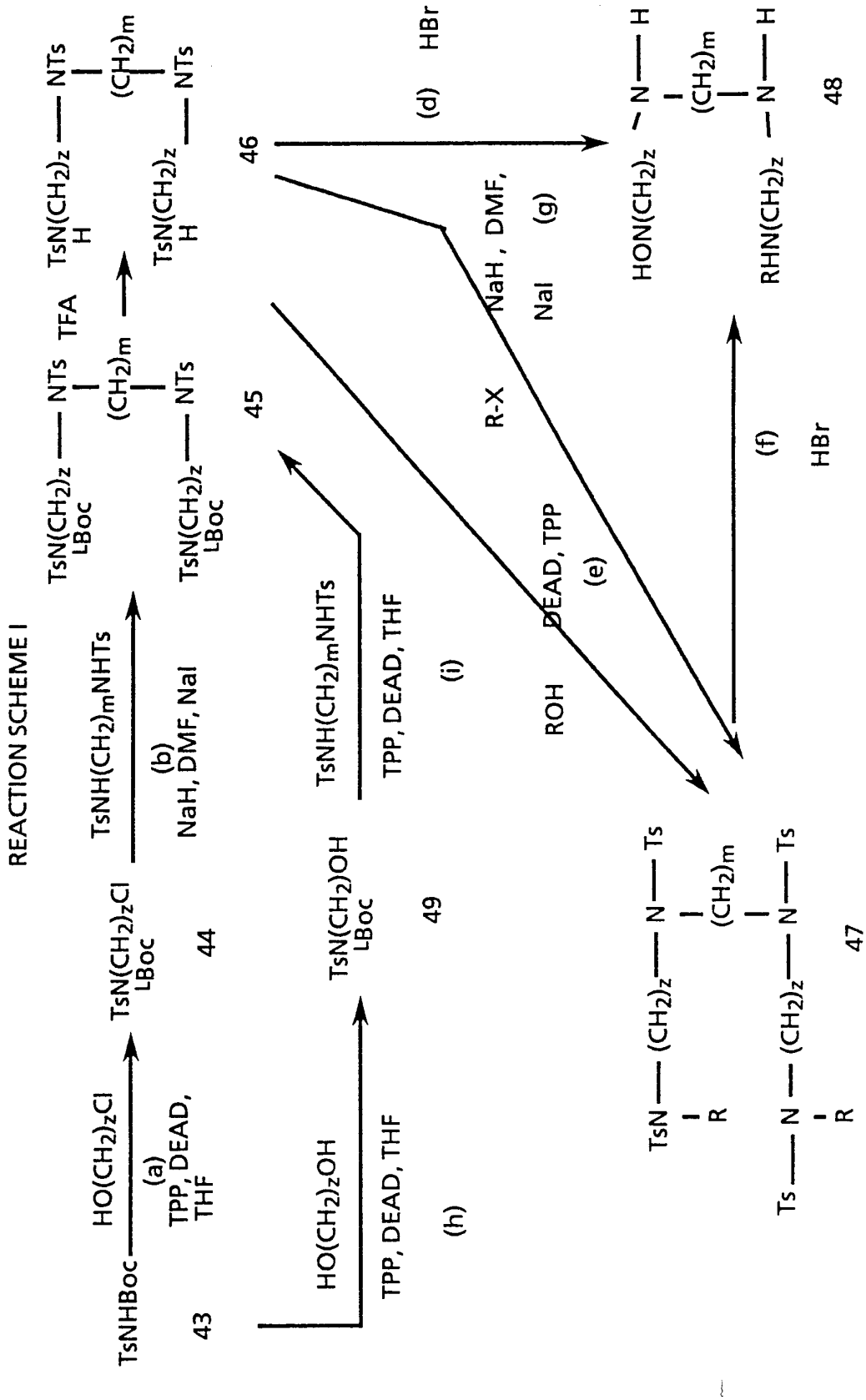
Step (b) involves the reaction of two equivalents of Compound [44] with a suitably protected diaminoalkane, e.g., as shown a di-tolsyl protected alkylydiamine ($TsNH(CH_2)mNHTs$) can be used to form intermediate [45].

An alternative route (step (g)) for forming intermediate [45] can be accomplished by reaction [43] with the approximately 1 equivalent of the alkyldiol shown in the presence of TPP and DEAD in a suitable solvent, such as THF to form intermediate [49]. Intermediate [49] can then be reacted with a protected diaminoalkane, e.g., as shown, the ditosyl protected alkyldiamine ($TsNH(CH_2)mNHTs$), to form intermediate [45]. This route of synthesis, step (g), is suitable in those instance when Z is not 4.

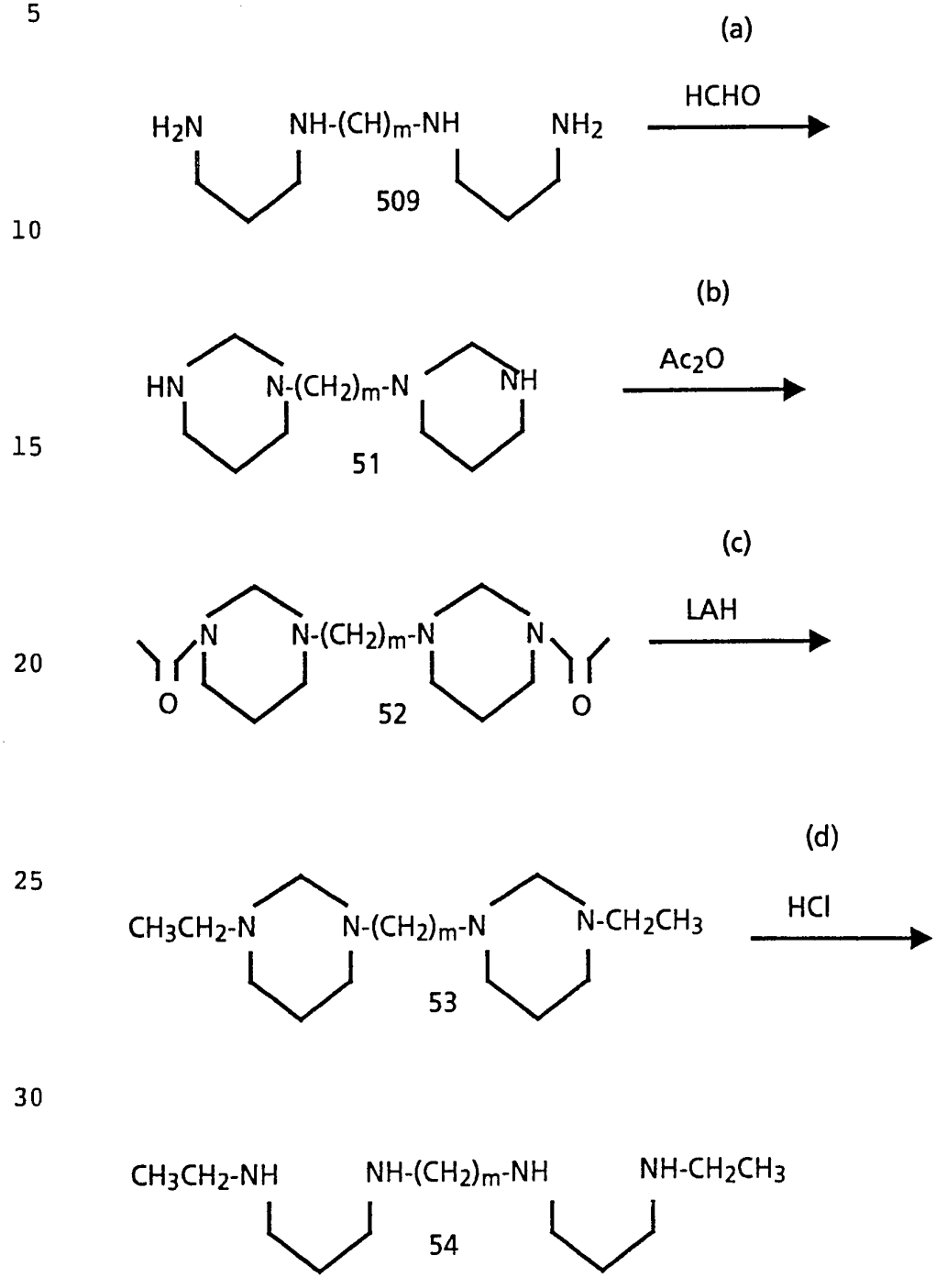
Further reaction of compound [45] can occur by deprotection of the Boc protecting groups with a suitable acid, as for example with trifluoroacetic acid in an aprotic solvent to form intermediate [46]. Further deprotection with a stronger acid, e.g. HBr, can be used to form structures of compound [48] where in the substituted R group is hydrogen. Rather than a two step treatment of acid by steps (c) and (d), the more general route of deprotection would be to directly treat [45] with a strong acid, e.g. HBr, to directly form [48] wherein R is hydrogen.

Optional substitution of compound [48] wherein R is desired to be other than hydrogen, can be accomplished in either of two ways. First, compounds of formula [45] can be reacted with a R-alkyl alcohol in the presence of TPP and DEAD in an appropriate solvent (step e). Alternatively, intermediate [46] can be reacted with a R-alkyl halide in the presence of hydride ion and sodium iodide to give the compound of formula [47]. Compounds of formula [47] can then be deprotected upon treatment with acid, to form the compounds of formula [48], wherein R is other than hydrogen.

REACTION SCHEME I



REACTION SCHEME J



The foregoing reaction scheme J depicts the preparation of N,N'-Bis[3-(ethylamino)propyl]1,7-heptanediamine

tetrahydrochloride. Of course, certain parts of the reaction scheme can be expanded to include the variations of m and R of formula I, however, Z is generally limited to being propyl, wherein Z is 3. The R group introduced in scheme J is shown as ethyl, but the reaction scheme is not limited only to ethyl derivatives but may include those R groups of formula I to form corresponding R substituted derivatives.

The initial step (a) of scheme J is a protection of the nitrogens of formula [50] by reaction with aqueous HCHO using standard and well known procedures to give the corresponding diaza ring systems in compound [51].

In step (b) the N-protected amines [51] are alkylated by reacting with the appropriate acid anhydride according to standard alkylation procedures known to those skilled in the art. When it is desired to provide compounds of the formula (I) wherein both R groups are the same, about 3-6 equivalents of the acid anhydride is reacted. When it is desired to provide compounds of the formula (I) wherein the R groups are not the same, monosubstitution of compounds of formula [52] is effected by reacting about 1 to about 1.5 equivalents of the acid anhydride with subsequent isolation of the monosubstituted compound according to standard procedures well known in the art and optionally further reacting the monosubstituted compound with the desired different acid anhydride or alkyl or aryl halide.

The resulting acetylated derivatives of [52] are then chemically reduced (step c) by reaction with lithium aluminum hydride in anhydrous conditions according to standard procedures well known in the art. Of course, other reducing systems, e.g., reduction with H_2 and PtO_2, may also be utilized under appropriate conditions to produce compounds of formula [53].

Following reduction, the N-protective groups of compound [53] are removed by standard procedures, e.g., treatment with acid, preferably HCl, in the presence of a suitable solvent or solvent system, to obtain the desired products of formula [54].

As is well known in the art of pharmaceutical inventions wherein generic classes of compounds are involved, certain specific compounds are more effective in their end use applications than other members of the generic class. The following compounds are preferred in the method of use described by the present invention:

1,18-Bis[(phenyl)methyl]-1,5,14,18-tetraazaoctadecane•4HCl,
1,20-Bis[(phenyl)methyl]-1,16,15,20-tetraazaeicosane•4HCl,
N,N'-Bis(3-aminobutyl)-1,8-octanediamine,
N,N'-Bis(3-ethylamino)butyl]-1,7-diaminoheptane tetrahydrochloride,
1,4,13,16-tetra(t-butoxycarbonyl)-1,4,13,16tetraazahexadecane,
1,18-Bis[(2-phenyl)ethyl]-1,5,14,18-tetraazaoctadecane•4HCl,
1,18-Bis(phenyl)-1,5,14,18-tetraazaoctadecane,
1,18-Bis(2,3-butadienyl)-1,5,14,18-tetraazaoctadecane tetrahydrochloride.

Especially preferred are the following compounds:
3,7,15,19-tetraazaheneicosane tetrahydrochloride,
3,17-dimethyl-2,6,14,18-tetraazanonadecane tetrahydrochloride, and
4,16-dimethyl-2,6,14,18-tetraazanonadecane tetrahydrochloride.

Based upon standard laboratory experimental techniques and procedures well known and appreciated by those skilled in the art, as well as upon comparisons with compounds of known usefulness, the compounds of formula (I) can be used in the treatment of patients suffering disease states for CMV infections.

Of course, one skilled in the art will recognize that not every compound of formula (I) will be effective against each of the CMV disease states, and that selection of the most appropriate compound is within the ability of one of ordinary skill in the art and will depend on a variety of factors including assessment of results obtained in standard animal tumor models.

As used herein, the term "patient" refers to a warm-blooded animal such as a mammal which is afflicted with a neoplastic disease state. It is understood that dogs, cats, rats, mice, horses, bovine cattle, sheep, and humans are examples of animals within the scope of the meaning of the term.

The term "cytomegaloviral infection" as used herein refers to an abnormal state or condition characterized by an active or latent CMV infection or state whenever the patient has virus residing active or dormant in the patients tissues, fluids, or body cavities.

Treatment of a patient afflicted with a CMV disease state comprises administering to such patient an amount of a compound of the formula (I) which is therapeutically effective in controlling the symptomatic and/or associated viral states of CMV beyond that expected in the absence of such treatment.

As used herein, "controlling CMV infection" refers to slowing, interrupting, arresting or stopping a CMV infection and does not necessarily indicate a total elimination of the virus. It is believed that the prolonged survivability of a patient with the instant compounds indicates control of a CMV infection.

In effecting treatment of a patient afflicted with a CMV infection or prophylatic treatment to prevent infection a compound of formula (I) can be administered parenterally in any manner which makes (I) bioavailable in effective amounts including for example, by intraperitoneal (i.p.), subcutaneous (s.c.), or intravenous (i.v.) injection. Administration by intravenous injection is preferred.

A therapeutically effective dose or amount can readily be determined by the attending diagnostician and is a function of a number of factors including, but not limited to, the species of mammal, its size, age and general health, the specific CMV infection involved, the stage of the CMV infection, the compound selected and mode of administration, the bioavailability characteristics of the preparation administered, the dose regimen selected, and use of concomitant medication. The correct amount for any specific situation can be readily determined by those skilled in the art using conventional range finding techniques and analogous results observed under other circumstances. A therapeutically effective amount of (I) will vary from about 1 milligram per kilogram of body weight per day (mg/kg/day) to about 500 mg/kg/day and preferably will be about 5 mg/kg/day to about 50 mg/kg/day. It is believed that compounds of the formula (I) administered at the above doses to a patient suffering from a CMV infection are therapeutically effective in controlling the growth of one or more disease states a patient may have so as to prolong the survivability of the

patient beyond that expected in the absence of such treatment.

Another embodiment of the present invention relates to pharmaceutical compositions for parenteral administration for compounds of the formula (I). These pharmaceutical compositions comprise a therapeutically effective amount of one or more compounds of the formula (I) in an admixture with one or more pharmaceutically acceptable excipients, Such compositions are prepared in conventional manner well known in the art of pharmaceutical science. The amounts of the active ingredient(s) in a unit dosage form and the dosage regimen are adjusted to provide a sustained pharmacologic effect at the dose regimen selected.

Pharmaceutically acceptable excipients are substances that are chemically inert to the active compound(s) and have no detrimental side effects or toxicity to mammals under the conditions of use. Suitable excipients include solvents such as water, alcohol, and propylene glycol, surface active agents, suspending agents, lubricants, flavors, colorants, and the like. Such carriers and excipients are known to those in the art and are disclosed, for example, in texts such as Remington's Pharmaceutical Manufacturing, 13th Edition, Mack Publishing Co., Easton, PA (1965).

Injectable dosage forms of a solution or suspension of (I) can be prepared, for example, in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid such as water and oils with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative of oils which can be employed in these preparations are those of petroleum, animal, vegetable or synthetic origin, for example, peanut oil, soybean oil and mineral oil. In general, water, saline, aqueous dextrose and related sugar solution

ethanols and glycols such as propylene glycol or polyethylene glycol are preferred liquid carriers, particularly for injectable solutions.

As is well known in the art of pharmaceutical inventions wherein generic classes of compounds are involved, certain subgeneric and certain specific compounds are more efficient in their end-use applications than other members of the generic class. In this invention, those compounds wherein Z is $-CH_2CH_2CH_2-$ or $-CH(CH_3)CH_2CH_2-$ are most preferred. In all instances it has been shown that the symmetrical compounds are preferred. Compounds for which each R is independently methyl or ethyl are preferred for this method of use and compounds for which both R groups are methyl or both R groups are ethyl are preferred. Compounds for which both R groups are the same moiety are generally preferred. Further compounds of formula I may have m = to 7 or 8

The following compounds are preferred in the method of use described by the present invention:

N,N'-bis[3-(methylamino)butyl]-1,7-diaminoheptane;

N,N'-bis[3-(ethylamino)propyl]-1,7-diaminoheptane (MDL28,314);

N,N'-bis[3-(methylamino)propyl]-1,7-diaminoheptane;

N,N'-bis[3-(methylamino)-2-(methyl)propyl]-1,7-diaminoheptane.

Amongst the listed compounds, and the respective substituent which are structurally part their of may be used to form a more preferred grouping of compounds.

For instance, of the compounds listed, N,N'-bis[3-(ethylamino)propyl]-1,7-diaminooctane and N,N'-bis[3-(ethylamino)propyl]-1,7-diaminoheptane are most preferred.

In order to illustrate the preparation of compounds of formulas (Ia) and (Ib), the following examples are provided. The examples are illustrative only and are not intended to limit the invention in any way. All temperatures are in degrees Celsius and the following abbreviations are used: (g) is grams, (mol) is moles, (ml) is milliliters, (l) is liters, (lb/in^2) is pounds per square inch, (TLC) is thin layer chromatography, (THF) is tetrahydrofuran, (DMF) is dimethylformamide, (mp) is melting point, (mm/Hg) is pressure expressed as millimeters of mercury, (bp) is boiling point.

CHEMICAL EXAMPLES

EXAMPLE 1

N,N-Bis((3-methylamino)propyl)-1,8-octanediamine tetrahydrochloride

Step A: N,N'-Bis(2-(cyano)ethyl)-1,8-octanediamine

Dissolve 14.4 g (0.1 mol) of 1,8-diaminooctane and 14.5 ml (0.22 mol) of acrylonitrile in 100 ml of ethanol and reflux overnight. Remove the solvent at reduced pressure. Analysis showed the title compound to be >98% pure.

Step B: N,N'-Bis(3-(amino)propyl)1,8-octanediamine tetrahydrochloride

Combine 14.4 g (0.057 mol) of the product of Step A, 200 ml of acetic acid, 30 ml of conc. HCl, and 1.2 g PtO_2 and treat the mixture with H_2 at 45 lbs/in^2 in a shaker flask until H_2 is no longer being reacted. Filter the mixture and remove the solvent at reduced pressure. 22.5 g of the title compound is obtained after purification. (R_f is 0.17 for TLC on silica gel developed with 40% conc. ammonia/methanol).

Step C: 1,5,14,18-Tetra(t-butoxycarbonyl)-1,5,14,18-tetraazaoctadecane

Combine 22.5 g (0.052 mol) of the product of Step B with 8.83 g (0.22 mol) of NaOH, 100 ml H_2O and 500 ml THF and stir until a homogenous solution is obtained. To this solution add 48.13 g (0.22 mol) of di-t-butyldicarbonate and stir the resulting mixture overnight. Pour the mixture into 1 l. of ethyl acetate, separate the organic layer, and dry over anhydrous $MgSO_4$. Remove the solvent at reduced pressure. Purify the residue by flash chromatography (silica gel), eluting with 25% ethyl acetate/hexane to yield 13.5 g of the title compound (R_f is 0.28 for TLC on silica gel developed with 25% ethyl acetate/hexane).

Step D: 1,18-Bis(methyl)-1,5,14,18-tetra(t-butoxycarbonyl)-1,5,14,18-tetraazoctadecane

Combine 4.3 g (0.0068 mol) of the product of Step C, 0.94 ml (0.015 mol) of iodomethane, 1.69 g (0.015 mol) of potassium t-butoxide, and 15 ml DMF and stir overnight. Remove the solvent at reduced pressure and dissolve the residue in 500 ml ethyl acetate and 200 ml of H_2O. Wash the organic layer with 100 ml H_2O (2x) and dry over anhydrous $MgSO_4$. Remove the solvent at reduced pressure and purify the residue by flash chromatography (silica gel), eluting with 20% ethyl acetate/hexane to yield 4.4 g of the title compound (R_f is 0.20 for TLC on silica gel developed with 20% ethyl acetate/hexane.)

Step E: N,N'-Bis(3-(methylamino)propyl)-1,8-octanediamine tetrahydrochloride

Dissolve 4.4 g (0.0065 mol) of the product of Step D in 3 ml ethanol and treat the solution with 50 ml of 2N HCl in diethyl ether stirring overnight. Filter the resulting mixture and crystallize the residue from methanol/isopropanol/water (20/60/20,v/v/v) at reduced temperature. Filter and dry the product at 79°C over P_2O_5 at 0.1 mmHg to yield 2.08 g of the title compound (mp >300°C). Elemental analysis: calculated, C-44.44, H-9.79, N-12.86, Cl-32.80; Found C-44.44, H-9.82, N-12.95,.

EXAMPLE 2

N,N'-Bis(3-(ethylamino)propyl)-1,8-octanediamine tetrahydrochloride

Step A: 1,18-Bis(ethyl)-1,5,14,18-tetra(t-butoxy-carbonyl)-1,5,14-18-tetraazaoctadecane

Combine 9.5 g (0.0144 mol) of the product of Step C in Example 1, 2.91 g (0.026 mol) of potassium t-butoxide, and 45 ml of DMF and cool to 0°C. Add 2.1 ml (0.026 mol) of iodoethane and stir at 0°C for 4 hours. Allow the mixture to warm slowly to room temperature and stir overnight. Remove the solvent at reduced pressure and partition the residue between 1400 ml ethyl acetate and 200 ml H_2O. Wash the organic layer with 100 ml H_2O (2x) and dry over anhydrous $MgSO_4$. Remove the solvent under reduced pressure and purify the residue by flash chromatography (silica gel) eluting with 20% ethyl acetate/hexane to yield 3.3 g of the title compound (R_f is 0.26 for TLC on silica gel developed with 20% ethyl acetate/hexane.)

Step B: N,N'-Bis(3-(ethylamino)propyl)-1,8-octanediamine tetrahydrochloride hemihydrate

Dissolve 3.3 g (0.0046 mol) of the product of Step A in 7 ml ethanol and treat with 70 ml of 2 N HCl in diethyl ether stirring overnight. Filter the mixture and dry the residue at 70°C at reduced pressure to yield 1.95 g of the title compound, mp >300°C. Elemental analysis: Calculated, C-46.09, H-10.10, N-11.95, Cl-30.24; Found C-46.23, H-9.94, N-12.11, Cl-29.99.

EXAMPLE 3

N-(3-Aminopropyl)-N'-(3-(ethylamino)propyl)-1,8-octanediamine tetrahydrochloride

Step A: 1-Ethyl-1,5,14,18-tetra-(t-butoxycarbonyl)-1,5,14,18-tetraazaoctadecane

Follow the procedure described in Step A of Example 2 to yield 2.5 g of the title compound after flash chromatography (R_f is 0.17 for TLC on silica gel developed with 20% ethyl acetate/hexane).

Step B: N-(3-Aminopropyl)-N'-(3-(ethylamino)propyl)-1,8-octanediamine tetrahydrochloride

Dissolve 2.5 g (0.0036 mol) of the product of Step A in 5 ml of ethanol and treat with 60 ml of 2 N HCl in diethyl ether stirring overnight. Filter the mixture and dry the residue to yield 1.35 g of the title compound, mp >300°C. Elemental analysis: Calculated, C-43.54, H-9.82, N-12.69, Cl-32.13; Found, C-43.43, H-9.60, 9.55; N-12.60, 12.62; Cl-32.30.

EXAMPLE 4

N,N'-Bis[3-(methylamino)butyl]-1,7-diaminoheptane tetrahydrochloride

Step A: N,N'-Bis[(phenyl)methyl]-1,7-heptanediamine

Combine 1,7-diaminoheptane (65.0 g, 0.5 mol), benzaldehyde (106 gm, 1 mol) and platinum oxide (PtO_2)[2.0 g] in ethanol (800 ml) and treat the mixture with hydrogen gas (45 lb/in^2) until the uptake of gas ceases. Remove the catalyst by filtration and remove the solvent in vacuo. Purify the residue by bulb to bulb distillation to yield 99.4 g of the title compound (bp 191-195°C @ 1.0 mm/Hg).

Step B: N,N'-Bis[(3-oxo)butyl]-N,N'-bis[(phenyl)methyl] -1,7-diaminoheptane

Dissolve N,N'-bis[(phenyl)methyl]-1,7-heptanediamine (9.3 g, 0.03 mol) in methanol (120 ml) and while stirring the mixture introduce methyl vinyl ketone (5.6 ml, 0.066 mol) in a stream of nitrogen gas. Stir the mixture for 18 hours to yield the title compound.

Step C: N,N'-Bis[(3-hydroxyimino)butyl]-N,N'-bis[(phenyl) methyl]-1,7-diaminoheptane

Cool the reaction mixture obtained in step B to 0°C and to this mixture add a solution of hydroxylamine hydrochloride (4.38 g, 0.063 mol) and sodium bicarbonate (5.54 g, 0.066 mol) in water (40 ml). Stir the mixture at 0°C for 30 minutes and then stir at ambient temperature for 2 hours. Remove the solvent in vacuo and partition the residue between water (200 ml) and dichloromethane (200 ml). Wash the aqueous layer 3 times with 200 ml of dichloromethane each time. Combine the organic layers and dry over anhydrous $MgSO_4$. Remove the solvent in vacuo to yield 14.4 g of the title compound. Rf is 0.53 for TLC on silica gel developed with ethyl acetate.

Step D: N,N'-Bis[3-(amino)butyl]-N,N'-bis[(phenyl) methyl]-1,7-diaminoheptane

Add a solution of N,N'-bis[(3-hydroxyimino)butyl]-N,N'-bis[(phenyl)methyl]-1,7-diaminoheptane (14.4 g, 0.03 mol) in THF (70 ml) to a mixture of lithium aluminum hydride (5.8 g, 0.15 mol) in THF (250 ml) and reflux the mixture overnight. Cool the mixture and quench slowly with water (5.8 ml), followed by 15% NaOH (5.8 ml), followed by water (17.4 ml). Filter the mixture and wash the filtrate 3 times with 100 ml of THF each time. Combine the organic layers and remove the solvent in vacuo to obtain 13.4 g of the title compound as a clear viscous oil. Rf is 0.33 for TLC on silica gel developed with 4% conc. ammonia in methanol.

Step E: 2,16-Bis(methyl)-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane

Combine N,N'-bis[3-(amino)butyl]-N,N'-bis[(phenyl)methyl]-1,7-diaminoheptane (13.4 g, 0.029 mol), Pearlman's Catalyst (2.0 g) and ethanol (90 ml) and treat the mixture with hydrogen gas at 45 lb/in^2 until gas uptake ceases. Remove the catalyst by filtration and remove the solvent in vacuo to obtain 7.7 g of N,N'-bis[3-(amino)butyl]-1,7-diaminoheptane (Rf is 0.37 for TLC on silica gel developed with 40% conc. ammonia in methanol). Dissolve the residue in dichloromethane (90 ml) and treat the mixture with di-t-butyldicarbonate (26.2 g, 0.12 mol) for 3 hours. Remove the solvent in vacuo and purify the residue by flash chromatography on silica gel eluting with 25% ethyl acetate in hexane to yield 17.1 g of the title compound as a clear oil. Rf is 0.35 for TLC on silica gel developed with 25% ethyl acetate in hexane.

Step F: 1,2,16,17-Tetramethyl-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane

Combine 2,16-bis(methyl)-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane (8.5 g, 0.0126 mol) and sodium hydride (60% in oil)[1.21 g, 0.03 mol] in DMF (75 ml) and stir until hydrogen evolution ceases. To this mixture add methyl iodide (1.88 g, 0.03 mol) and stir for 2 hours. Remove the solvent in vacuo and partition the residue between ethyl acetate (400 ml) and water (200 ml). Dry the organic layer over anhydrous $MgSO_4$ and remove the solvent in vacuo. Purify the residue by flash chromatography on silica gel eluting with 22% ethyl acetate in hexane to yield 3.8 g of the title compound as a clear oil. Rf is 0.22 for TLC on silica gel developed with 20% ethyl acetate in hexane.

Step G: N,N'-Bis[3-(methylamino)butyl]-1,7-diaminoheptane tetrahydrochloride

Add 1N HCl in methanol (50 ml) to 1,2,16,17-tetramethyl-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane (3.8 g, 0.0054 mol) and stir overnight. Remove the solvent in vacuo and recrystallize the residue two times from methanol/acetonitrile (40/60, v/v) to yield 0.74 g of the title compound as a white solid (mp 238-9 °C). Rf is 0.31 for TLC on silica gel developed with 40% conc. ammonia in methanol.

EXAMPLE 5

N,N'-Bis[3-(ethylamino)butyl]-1,7-diaminoheptane tetrahydrochloride

Step A: 1,17-Diethyl-2,16-dimethyl-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane

Combine 2,16-bis(methyl)-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane (8.5 g, 0.0126 mol), made as described in Example 5, and sodium hydride (60% in oil)[1.21 g, 0.03 mol] in DMF (75 ml) and stir until hydrogen evolution ceases. To this mixture add ethyl iodide (4.68 g, 0.03 mol) and stir for 2 hours. Remove the solvent in vacuo and partition the residue between ethyl acetate (400 ml) and water (200 ml). Dry the organic layer over anhydrous $MgSO_4$ and remove the solvent in vacuo. Purify the residue by flash chromatography on silica gel eluting with 22% ethyl acetate in hexane to yield 3.9 g of the title compound as a clear oil. Rf is 0.31 for TLC on silica gel developed with 20% ethyl acetate in hexane.

Step B: N,N'-Bis[3-(ethylamino)butyl]-1,7-diaminoheptane tetrahydrochloride

Add 1N HCl in methanol (50 ml) to 1,17-diethyl-2,16-dimethyl-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane (3.9 g, 0.0054 mol) and stir overnight. Remove the solvent in vacuo and recrystallize the residue two times from methanol/acetonitrile (40/60, v/v) to yield 0.90g of the title compound as a white solid (mp 249-50 °C). Rf is 0.56 for TLC on silica gel developed with 40% conc. ammonia in methanol.

EXAMPLE 6

N,N'-Bis[3-(ethylamino)propyl]-1,7-heptanediamine

Steps A and B: 1,5,13,17-Tetraazaheptadecane tetrahydrochloride

Prepare the title compound by the method of Israel et al., J. Med. Chem. 7, 710 (1964).

Step C: 1,5,13,17-Tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane

Combine 1,5,13,17-tetraazaheptadecane tetrahydrochloride (3.9 gm, 0.01 mol) and sodium hydroxide (1.76 gm, 0.44 mol) in water (44 ml) and stir until homogeneous. To this mixture add di-t-butyldicarbonate (9.6 gm, 0.044 mol) in THF (88 ml) and stir for 3 hours. Dilute the mixture with ethyl acetate (EtOAc) [300 ml] and separate the organic layer. Dry the organic layer over anhydrous $MgSO_4$ and evaporate *in vacuo* to obtain a viscous oil. Purify the residue by flash chromatography (silica gel) eluting with 25% EtOAc/hexane to yield 3.0 gm of the title compound. R_f is 0.20 on silica gel plates eluted with 25% EtOAc/hexane.

Step D: 3,7,15,19-Tetra(t-butoxycarbonyl)-3,7,15,19-tetraazaheneicosane

Combine 1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane (3.0 gm, 0.0046 mol) and sodium hydride (50% in oil) [0.45 gm, 0.011 mol] in DMF (9 ml) and stir the mixture until hydrogen evolution ceases. Add ethyl iodide (0.9 ml, 0.011 mol) and stir the mixture for 18 hours. Evaporate the DMF *in vacuo* and partition the residue between ethyl acetate (600 ml) and water (200 ml). Separate the organic layer, dry the organic layer over

anhydrous $MgSO_4$ and evaporate *in vacuo*. Purify the residue by flash chromatography (silica gel) eluting with 20% EtOAc/hexane to yield 1.68 gm of the title compound. R_f is 0.5 on silica gel plates eluted with 25% EtOAc/hexane.

Step E: N,N'-Bis[3-(ethylamino)propyl]-1,7-heptanediamine
Treat 3,7,15,19-tetra(t-butoxycarbonyl)-3,7,15,19-tetraazaheneicosane (1.68 gm, 0.0024 mol) with HCl in methanol (50 ml, 1.0 N) and stir overnight. Filter the mixture and recrystallize the title compound from methanol/water (20:80, v/v) to yield 0.5 gm of the title compound. R_f is 0.39 on silica gel plates eluted with 40% ammonia (concentrated) in methanol; mp 322-23°C with degradation.

EXAMPLE 7

1,18-Bis[(phenyl)methyl]1,5,14,18-tetraazaoctadecane•4HCl

Step A: N,N'-Bis-[2,2'-bis(cyano)ethyl]-1,8-diamino-octane
Dissolve 28.8 gm (0.2 mol) of 1,8 diaminooctane in 250 ml of EtOH. Add 27 ml (0.41 mol) of acrylonitrile and gently reflux the mixture overnight. Remove the solvent at reduced pressure. Analysis shows desired material to be >95% pure.

Step B: 1,5,14,18-Tetraazaoctadecane tetrahydrochloride
Combine 50.0 gm of the product of Example 1, 2.0 gm PtO_2, 133 ml of conc. HCl at 45 lbs./sq. in. in a shaker flask until hydrogen is no longer taken up. Filter the resulting mixture, evaporate the solvent and triturate the product with 1 liter of EtOH. Filter and dry the product to obtain 51.6 gm of the title compound, Rf is 0.17 (silica gel plates eluted with 40% conc. NH_3/CH_3OH).

Step C: 1,5,14,18-Tetra(t-butoxycarbonyl)-1,5,14,18-tetraazaoctadecane

Treat 28.0 gm (0.069 mol) of the product of Step B with 10.99 gm (0.274 mol) of NaOH in 120 ml H_2O. When a homogenous solution is obtained add 65.7 gm (0.307 mol) of di-t-butyldicarbonate in 750 ml of THF and stir the resulting mixture for 16 hours. Separate the layers, remove and wash (2x) the aqueous layer with 500 ml CH_2Cl_2. Combine and dry ($MgSO_4$) the organics, filter and evaporate (invacuo) the solvents and flash chromatograph the residue (silica gel), eluting with 25% EtOAc/hexane to yield 30.2 g of the desired product. Rf is 0.33 on silica gel plates eluted with 25% EtOAc/hexane).

Step D: 1,18,-Bis[(phenyl)methyl]-1,5,14,18-tetra(t-butoxycarbonyl)-1,5,14,18-tetraazaoctadecane

Dissolve 20.0 gm (0.03 mol) of the product from Step C in 30 ml DMF and treat with 7.5 gm (0.067 mol) KtBuO and 7.96 ml (0.067 mol) BnBr, with stirring for 18 hours. Evaporate the volatiles (0.5 mm and 45°C) and take up the resulting residue in 1400 ml of EtOAc and water-wash (2x, 500 ml). The organic layer is then dried ($MgSO_4$) and the solvent is evaporated (in vacuo). Flash chromatography on silica gel eluted with 20% EtOAc/hexane yields 12.4 gm (50%) of desired product as a clear viscous oil. Rf is .42 (silica gel plates eluted with 25% EtOAc/hexane).

Step E: 1,18-Bis-[(phenyl)methyl]-1,5,14,18-tetraaza-octadecane•4HCl

Dissolve 12.4 g (0.0147 mol) of the product of Step D in 14.7 ml of anhydrous EtOH and treat with 160 ml of 2N HCl in Et_2O with stirring overnight. Filter, wash the filter cake with Et_2O, and dry to obtain 7.2 gm of the desired compound, mp >300°C. Rf is 0.24 (from silica gel eluted with 10% conc. NH_3/CH_3OH).

EXAMPLE 8

1,20-Bis[(phenyl)methyl]-1,16,15,20-tetraazaeicosane•4HCl

Step A: N,N'-Bis(t-butoxycarbonyl)-1,8-octanediamine

Dissolve 10.8 gm (0.075) of diaminooctane in 200 ml CH_2Cl_2 and 100 ml CH_3OH, add 32.7 gm (0.156 mol) of di-t-butyldicarbonate and stir the mixture overnight. Evaporate, *in vacuo*, and crystallize the residue from hexane to obtain 20.2 gm of the desired compound, mp 96-97°C.

Step B: 4-[[(Phenyl)methyl]amino]-butan-1-ol

Combine 4-amino-butan-1-ol (8.9 gm - 0.1 mol), benzaldehyde (10.6 gm - 0.1 mol), EtOH (100 ml) and PtO_2 (0.3 gm), and hydrogenate the mixture at 45 lbs./sq.in. until H2 is no longer taken up. Filter, evaporate the solvent (*in vacuo*) to yield 17.7 gm of the desired compound. Rf is 0.70 (eluted from silica gel with 10% conc. NH3/CH30H).

Step C: 4-[N-(t-butoxycarbonyl)-N-[(phenyl)methyl]amino] butan-1-ol

Combine the butanol of Step B (17.7 g - 0.1 mol) and di-tbutyldicarbonate in 100 ml of CH_2Cl_2 and stir the mixture overnight. Evaporate off the solvents, in vacuo, and flash chromatography of the residue, eluting from silica gel with 25% EtOAc/hexane to obtain the desired compound. Rf is .27 (silica gel plates eluted with 20% EtOAc/hexane).

Step D: 4-[N-(t-butoxycarbonyl)-N-[(phenyl)methyl]-amino]-1nethansulfonyl butane

Cool (ice-bath) a mixture containing the product of Step C (21.8 gm - 0.078 mol), 250 ml CH_2Cl_2 and 9.7 ml pyridine (0.12 mol), add in a dropwise fashion (20 minutes) mesylchloride (6.65 ml - 0.086 mol) in 6.6 ml CH_2Cl_2 and allow the mixture to warm to room temperature, stirring the mixture for 2 hours. Pour the resulting mixture into 200 ml CH_2Cl_2, wash with 500 ml 0.5 N HCl, saturated NaHCO3, dry over MgS04, evaporate (*in vacuo*) and flash chromatograph

eluting from the silica gel with 25% EtOAc/hexane to obtain 10.7 g of desired product, Rf is).36 (silica gel plates eluted with 25% EtOAc/hexane).

Step E: 1,20-Bis[(phenyl)methyl]-1,16,15,20-tetra-(t-butoxycarbonyl)-1,6,15,20-tetraazaeicosane

Admix the products of Step A (5.16 gm - 0.015 mol) and of Step D of this example (10.7 g - 0.032 mol), Kt-BuO (3.92 gm), NaI 0.2 gm), and 60 ml DMF and stir the mixture for 72 hours at room temperature. Evaporate the solvent (*in vacuo*), take up the residue in 600 ml EtOAc and wash (2x) with 200 ml water. Dry the organic layer ($MgSO_4$), evaporate the solvents, and flash chromatograph the viscous residue on silica gel eluting with 20% EtOAc/hexane to obtain the desired product, Rf is 0.22 (silica gel plates eluted with 20% EtOAc/hexane).

Step F: 1,20-Bis[(phenyl)methyl]-1,6,15,20-tetraeicosane•4 HCl

Dissolve the product of Step E (4.7 gm) (0.0054 mol) in 5 ml EtOH and treat with 54 ml of 2N HCl in EtO_2, stir the mixture overnight, filter and recrystallize to so-obtained solids from isopropanol/water. Cool, filter and dry the desired product, mp >300°C, Rf is 0.47 (eluted from silica with 10% conc. NH_3/CH_3OH).

EXAMPLE 9

N,N'-Bis(3-aminobutyl)-1,8-Octanediamine

Step A: N,N'-Bis((phenyl)methyl)-1,8-octanediamine

Combine 14.4 g (0.1 mol) of 1,8-octanediamine, 20.3 ml (0.2 mol) of benzaldehyde, 0.3 g PtO_2 and 150 ml ethanol and treat the mixture with H_2 at 45 lb/in^2 in a shaker flask until no more gas is taken up. Remove the catalyst by filtration and remove the solvent at reduced pressure to yield the title compound.

Step B: N,N'Bis((3-oxo)butyl)-N,N'-bis((phenyl)methyl)-1,8octanediamine

Dissolve the product obtained in Step A in 1400 ml of methanol and introduce 21.6 of methyl vinyl ketone on a stream of N_2 gas. Stir for 16 hours to yield the title compound.

Step C: N,N'-Bis((3-hydroxyimino)butyl)-N,N'-Bis-((phenyl)methyl)-1,8-octanediamine

Combine 18.07 g hydroxylamine hydrochloride, 10.4 g of NaOH and 40 ml of H_20 and add to the solution obtained in Step B. Reflux the mixture for 3 hours, then cool and evaporate the solvent. Pour the reaction mixture into 300 ml of ethyl acetate and wash with 300 ml H_20. Wash the aqueous layer with 300 ml of ethyl acetate (2x). Combine the organic layers and dry over anhydrous $MgSO_4$. Remove the solvent at reduced pressure. Purify the product by flash chromatography (silica gel), eluting with ethyl acetate to yield 34.8 g of the title compound (Rf is 0.42 for TLC on silica gel developed with ethyl acetate).

Step D: N,N'-Bis((3-amino)butyl)-N,N'-Bis((phenyl)-methyl)-1,8-octanediamine

Add 34.8 g of the product of Step C in 100 ml THF to 12.10 g (0.310 mol) of lithium aluminum hydride in 540 ml THF and reflux the mixture while stirring overnight. Cool the mixture and slowly add 15 ml H_20 followed by 45 ml 1N NaOH and stir the mixture for 6 hours. Filter the mixture to remove a white granular precipitate and remove the solvent at reduced pressure. Subject the residue to short path distillation to yield 17.0 g of the title compound (bp 230-235°C at 0.1 mmHg).

Step E: N,N'-Bis((3-amino)butyl)-1,8-octanediamine

Combine 5.0 g (0.01 mol) of the product of Step D, 0.5 g of 20% $Pd(OH)_2$ on carbon (Pearlman's Catalyst), and 50 ml or ethanol and treat the mixture with H_2 at 45 lb/in2 in a

shaker flask until no more gas is taken up. Remove the catalyst by filtration and remove the solvent at reduced pressure. Subject the residue to short path distillation to yield 1.59 g of the title compound (bp 145-148°C at 0.012 mmHg).

EXAMPLE 10

N,N'-Bis[3-(methylamino)butyl]-1,7-diaminoheptane tetrahydrochloride

Step A: N,N'-Bis[(phenyl)methyl]-1,7-heptanediamine

Combine 1,7-diaminoheptane (65.0 g, 0.5 mol), benzaldehyde (106 gm, 1 mol) and platinum oxide (PtO_2)[2.0 g] in ethanol (800 ml) and treat the mixture with hydrogen gas (45 lb/in_2) until the uptake of gas ceases. Remove the catalyst by filtration and remove the solvent in vacuo. Purify the residue by bulb to bulb distillation to yield 99.4 g of the title compound (bp 191-195°C @ 1.0 mm/Hg).

Step B: N,N'-Bis[(3-oxo)butyl]-N,N'-bis[(phenyl)methyl]-1,7- diaminoheptane

Dissolve N,N'-bis[(phenyl)methyl]-1,7-heptanediamine (9.3 g, 0.03 mol) in methanol (120 ml) and while stirring the mixture introduce methyl vinyl ketone (5.6 ml, 0.066 mol) in a stream of nitrogen gas. Stir the mixture for 18 hours to yield the title compound.

Step C: N,N'-Bis[(3-hydroxyimino)butyl]-N,N'-bis[(phenyl) methyl]-1,7-diaminoheptane

Cool the reaction mixture obtained in step B to 0°C and to this mixture add a solution of hydroxylamine hydrochloride (4.38 g, 0.063 mol) and sodium bicarbonate (5.54 g, 0.066 mol) in water (40 ml). Stir the mixture at 0°C for 30 minutes and then stir at ambient temperature for 2 hours. Remove the solvent in vacuo and partition the residue between water (200 ml) and dichloromethane (200 ml). Wash the aqueous layer 3 times with 200 ml of dichloromethane

each time. Combine the organic layers and dry over anhydrous $MgSO_4$. Remove the solvent in vacuo to yield 14.4 g of the title compound. Rf is 0.53 for TLC on silica gel developed with ethyl acetate.

Step D: N,N'-Bis[3-(amino)butyl]-N,N'-bis[(phenyl) methyl]-1,7-diaminoheptane

Add a solution of N,N'-bis[(3-hydroxyimino)butyl]-N,N'bis[(phenyl)methyl]-1,7-diaminoheptane (14.4 g, 0.03 mol) in THF (70 ml) to a mixture of lithium aluminum hydride (5.8 g, 0.15 mol) in THF (250 ml) and reflux the mixture overnight. Cool the mixture and quench slowly with water (5.8 ml), followed by 15% NaOH (5.8 ml), followed by water (17.4 ml). Filter the mixture and wash the filtrate 3 times with 100 ml of THF each time. Combine the organic layers and remove the solvent in vacuo to obtain 13.4 g of the title compound as a clear viscous oil. Rf is 0.33 for TLC on silica gel developed with 4% conc. ammonia in methanol.

Step E: 2,16-Bis(methyl)-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane

Combine N,N'-bis[3-(amino)butyl]-N,N'-bis[(phenyl)methyl]-1,7diaminoheptane (13.4 g, 0.029 mol), Pearlman's Catalyst (2.0 g) and ethanol (90 ml) and treat the mixture with hydrogen gas at 45 lb/in2 until gas uptake ceases. Remove the catalyst by filtration and remove the solvent in vacuo to obtain 7.7 g of N,N'-bis[3-(amino)butyl]-1,7-diaminoheptane (Rf is 0.37 for TLC on silica gel developed with 40% conc. ammonia in methanol). Dissolve the residue in dichloromethane (90 ml) and treat the mixture with di-t-butyldicarbonate (26.2 g, 0.12 mol) for 3 hours. Remove the solvent in vacuo and purify the residue by flash chromatography on silica gel eluting with 25% ethyl acetate in hexane to yield 17.1 g of the title compound as a clear oil. Rf is 0.35 for TLC on silica gel developed with 25% ethyl acetate in hexane.

Step F: 1,2,16,17-Tetramethyl-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane

Combine 2,16-bis(methyl)-1,5,13,17-tetra(t-butoxycarbonyl) 1,5,13,17-tetraazaheptadecane (8.5 g, 0.0126 mol) and sodium hydride (60% in oil)[1.21 g, 0.03 mol] in DMF (75 ml) and stir until hydrogen evolution ceases. To this mixture add methyl iodide (1.88 g, 0.03 mol) and stir for 2 hours. Remove the solvent in vacuo and partition the residue between ethyl acetate (400 ml) and water (200 ml). Dry the organic layer over anhydrous $MgSO_4$ and remove the solvent in vacuo. Purify the residue by flash chromatography on silica gel eluting with 22% ethyl acetate in hexane to yield 3.8 g of the title compound as a clear oil. Rf is 0.22 for TLC on silica gel developed with 20% ethyl acetate in hexane.

Step G: N,N'-Bis[3-(methylamino)butyl]-1,7-diaminoheptane tetrahydrochloride

Add 1N HCl in methanol (S0 ml) to 1,2,16,17-tetramethyl-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane (3.8 g, 0.0054 mol) and stir overnight. Remove the solvent in vacuo and recrystallize the residue two times from methanol/acetonitrile (40/60, v/v) to yield 0.74 9 of the title compound as a white solid (mp 238-9 °C). Rf is 0.31 for TLC on silica gel developed with 40% conc. ammonia in methanol.

EXAMPLE 11

N,N'-Bis[3-(ethylamino)butyl]-1,7-diaminoheptane tetrahydrochloride

Step A: 1,17-Diethyl-2,16-dimethyl-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane

Combine 2,16-bis(methyl)-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane (8.5 g, 0.0126 mol), made as described in Example 5, and sodium hydride (60% in

oil)[1.21 g, 0.03 mol] in DMF (75 ml) and stir until hydrogen evolution ceases. To this mixture add ethyl iodide (4.68 g, 0.03 mol) and stir for 2 hours. Remove the solvent in vacuo and partition the residue between ethyl acetate (400 ml) and water (200 ml). Dry the organic layer over anhydrous $MgSO_4$ and remove the solvent in vacuo. Purify the residue by flash chromatography on silica gel eluting with 22% ethyl acetate in hexane to yield 3.9 g of the title compound as a clear oil. Rf is 0.31 for TLC on silica gel developed with 20% ethyl acetate in hexane.

Step B: N,N'-Bis[3-(ethylamino)butyl]-1,7-diaminoheptane tetrahydrochloride

Add 1N HCl in methanol (50 ml) to 1,17-diethyl-2,16-dimethyl-1,5,13,17-tetra(t-butoxycarbonyl)-1,5,13,17-tetraazaheptadecane (3.9 g, 0.0054 mol) and stir overnight. Remove the solvent *in vacuo* and recrystallize the residue two times from methanol/acetonitrile (40/60, v/v) to yield 0.90g of the title compound as a white solid (mp 249-50 °C). Rf is 0.56 for TLC on silica gel developed with 40% conc. ammonia in methanol.

EXAMPLE 12

1,4,13,16-Tetra(t-butoxycarbonyl)-1,4-13,16-tetraazahexadecane

Combine 4.75 gm 1,8-dibromooctane (0.017 mol), 20 ml EtOH and 9.32 ml of ethylene diamine and reflux the mixture overnight. Cool and treat the mixture with 1.4 gm NaOH. Evaporate off the solvent and triturate the residue with CH_2Cl_2 (200 ml 2x), filter. Treat the filtrate with 66.6 gm of di-t-butyldicarbonate and stir the mixture overnight. Remove the solvent and subject the residue to flash chromatography, eluted with 25% EtOAc/hexane to yield the desired product. Rf is 0.64 eluted from silica gel with 50% EtOAc/hexane.

The foregoing may be bis-N-alkylated and the product deprotected by methods analogous to Steps D and E of Example 7 to produce desired compounds of the Formula $R'HN(CH_2)_2N(CH_2)_8N(CH_2)_2NHR'$, e.g., 1,16-Bis[(phenyl)methyl]-1,4,13,16-tetraazahexadecane•4 HCl.

EXAMPLE 13

1,18-Bis[(2-phenyl)ethyl]-1,5,14,18-tetraazaoctadecane•4HCl

Step A: 1,18-Bis[[(phenyl)methyl]carbonyl]-5,14-bis-[(phenyl)methyl]-1,5,14,18-tetraazaoctadecane

Chill a solution of 5,14-bis[(phenyl)methyl]-1,5,14,18-tetraazaoctadecane (2.2 g, 5 mmole) and triethylamine (2 g, 20 mmole) in chloroform (100 ml) in an ice bath. Add a solution of phenylacetyl chloride (2.3 g, 15 mmole) in chloroform (10 ml) dropwise. Remove the ice bath and stir the mixture at ambient temperature for 18 hours. Extract the reaction mixture with aqueous sodium bicarbonate, dry the organic layer and evaporate. Chromatograph the residue on a flash silica gel column (ethyl acetate) to give 3 g of the desired product as a thick oil.

Step B: Add a solution of the product of Step A in THF (150 ml) dropwise to a suspension of LAH (0.5 g) in THF (500 ml). Stir the mixture for 48 hours at ambient temperature. Decompose the excess reducing agent by dropwise addition of 1 ml of water, 1 ml of 15% NaOH then 3 ml of water. Filter the mixture and evaporate the filtrate. Take the residue up in ethanol (100 ml) and add anhydrous HCl gas to convert the product, 1,18-bis[(phenyl)ethyl]-5,14-bis-[(phenyl)methyl]1,5,14,18-tetraazaoctadecane, to its tetrahydrochloride salt. Hydrogenate this product in ethanol (150 ml) in the presence of Pearlman's catalyst (0.3 g) at 43 psi on a Parr hydrogenation apparatus for 24 hours. Filter off the catalyst and evaporate the filtrate. Crystallize the residue from 2-propanol to give the product 1,18-bis-[(phenyl)ethyl]-1,5,14,18-tetraazaoctadecane tetrahydrochloride salt hemihydrate, mp 228-231°C.

EXAMPLE 14

1,18-Bis(phenyl)-1,5,14,18-tetraazaoctadecane

Step A: N-(Phenyl-N,N'-bis(t-butoxycarbonyl)propanediamine

Cool 200 ml of anhydrous Et_2O in an ice bath and add lithium aluminum hydride (8.74 gm -0.23 mol). Add, in a dropwise fashion over 30 minutes, 3-anilinopropionitrile (14.6 gm) in 50 ml of Et_2O, remove the ice bath, and reflux the resulting mixture overnight. Sequentially add 8.7 ml of water, 1.5 g of NaOH (in 10 ml of water) and 25 ml of water. Filter the resulting ppt, rinse with 200 ml of Et_2O and remove the solvent, in vacuo, and treat the resulting N-(phenyl) propanediamine with 43.6 g of di-t-butyldicarbonate in 600 ml of CH_2Cl_2. After stirring overnight, evaporate off the solvent and subject the residue to flash chromatography from silica gel eluting with 17% EtOAc/hexane to produce the desired compound. Rf is 0.50 (eluted from silica gel with 25% EtOAc/hexane).

Step B: 1,18-Bis(phenyl)-1,5,14,18-tetra(t-butoxycarbonyl)-1,5,14,18-tetraazaoctadecane

Stir a mixture containing the product of Step A (13.0 gm), diiodooctane 3.70 gm) and 4.14 g of potassium t-butoxide in 200 ml of DMF for about 16 hours. Evaporate the solvent at 0.5 mm and 45°C, take up the residue in 800 ml of EtOAc. Wash (2x) with 300 ml of water, dry ($MgSO_4$) and remove the solvent *in vacuo*. Subject the so-obtained viscous oil to flash chromatography, eluting with 15% EtOAc from silica gel to yield 5.7 g of the desired product. Rf of 0.36 (eluted from silica gel with EtOAc/hexane). Remove the N-boc protecting groups according to the procedure of Step E of Example 7 to produce the title compound of this example as its hydrochloride salt. mp 264-267°C.

EXAMPLE 15

1,18-Bis(2,3-butadienyl)-1,5,14,18-tetraazaoctadecane tetrahydrochloride

Step A: N-(t-Butoxycarbonyl)propargylamine

In a dropwise fashion, add propargylamine (25 gm) in 25 ml of CH_2Cl_2 to a stirring mixture of di-t-butyldicarbonate (99.18 gm) in 900 ml of CH_2Cl_2. After 2 hours, remove the solvent, in vacuo, to obtain 70 gm of the desired N-protected propargylamine.

Step B: N-(t-Butoxycarbonyl)-2,3-butadienylamine

Reflux a mixture containing N-(t-butoxycarbonyl)-propargylamine (70 gm), 93.5 ml of 32% formaldehyde, 76.4 ml of diisopropylamine, 19.66 gm of cuprous bromide and 860 ml of p-dioxane for 12 hours. Cool and dilute the resulting mixture with 3000 ml of Et_2O, wash with 500 ml of water, 1000 ml acetic acid, 500 ml of water (2x), 200 ml sat'd. sodium chloride, dry ($MgSO_4$) and evaporate in vacuo. Flash chromatograph the residue eluting from silica gel with 10% Et_2O/hexane to yield 40.8 g of the desired

compound. Rf is 0.31 (eluted from silica gel with 10% EtOAc/hexane).

Step C: N,N-Bis[(phenyl)methyl]-1,8-diaminooctane

Combine 14.4 gm of diaminooctane, 20.3 ml of benzaldehyde and 0.66 gm of Pt_2O in 100 ml of ethanol. Treat the resulting mixture with hydrogen at 45 lbs./sq.in. until no further hydrogen is taken up. Filter, evaporate the solvent (in vacuo), and distill the rendered material to obtain 25.5 gm of the desired product, bp 185-190°C at 0.1 mm.

Step D: 1,18-Bis(hydroxy)-5,14-bis[(phenyl)methyl]-5,14-diazaoctadecane

Reflux a mixture containing 25.5 g of the product of Step C, 13.2 ml of 3-chloro-1-hydroxy-propane, 50.4 gm of Na_2CO_3 and 1.19 gm of sodium iodide in 40 ml of n-butanol for 18 hours. Cool the mixture and pour into 700 ml of ethylacetate, wash with water, dry over MgSO4 and remove the solvent (in vacuo) to obtain a residue which upon distillation yields 30.0 gm of the desired product, bp 250-252°C at 0.1 mm.

Step E: 1,18-Bis(hydroxy)-5,14-diazaoctadecane

Hydrogenate a mixture containing 3.0 gm of the product of Step D, 30 ml of AcOH and 0.6 gm of palladium oxide at 45 lbs./sq.in. until no further hydrogen is taken up. Filter and remove the solvent (in vacuo) to yield 1.77 gm of the desired product, Rf is 0.37 (eluted from silica gel with 10% conc. NH_3/CH_3OH)-.

Step F: 1,18-Bis(hydroxy)-5,14-bis-(t-butoxycarbonyl)-5,14-diazaoctadecane

Stir a mixture containing 1.77 gm of the product of Step E, 2.97 gm (0.0136 mol) of di-t-butyldicarbonate, 3 ml of triethylamine and 50 ml of CH_2Cl_2 overnight. Dilute the mixture with 200 ml of CH_2Cl_2, wash with 200 ml of 0.5N HCl, and then 100 ml of sat'd NaCl, dry (over $MgSO_4$) and remove the solvent (in vacuo). Flash chromatograph the residue, eluting from silica gel with 75% EtOAc to obtain the desired product, Rf 0.29, (eluted from silica gel with 75% EtOAc/hexane).

Step G: 1,18-Bis(methanesulfonyl)-5,14-bis(t-butoxycarbonyl)- 5,14-diazaoctadecane

Cool to 0°C a mixture containing 3.0 gm of the product of Step F, 3.3 ml of triethylamine and 70 ml of CH_2Cl_2. In a dropwise fashion add 1.22 ml of mesylchloride in 10 ml of CH_2Cl_2 and stir the resulting mixture at 0°C for 1½ hours. Pour the mixture into 100 ml of CH_2Cl_2, wash with 200 ml of 1N AcOH, 100 ml of water, 100 ml of sat'd sodium bicarbonate, dry over $MgSO_4$ and remove the solvent *in vacuo*. Flash chromatograph the residue, eluting from silica gel with 60% EtOAc/hexane to obtain 3.5 gm of the desired product. Rf is 0.39.

Step H: 1,18-Bis(2,3-butadienyl)-1,5,14,18-tetra-(t-butoxycarbonyl)-1,5,14,18-tetraazaoctadecane

Combine a mixture containing 3.5 gm of the product of Step G, 1.74 gm of sodium iodide, 0.51 gm of hexane washed sodium hydride (60% in oil) in 12 ml of DMF with 2.16 gm of N-(tbutoxycarbonyl)-2,3-butandienylamine (i.e., the product of Step B) and allow the resulting mixture to stand for 2 hours. Remove the solvent (in vacuo), add 350 ml of ethyl acetate to the residue, wash with 50 ml of water (4x), 100 ml sat'd sodium chloride and dry over $MgSO_4$. Remove the solvents (in vacuo) and flash chromatograph the residue

from silica gel eluting with 30% EtOAc/hexane to yield 0.5 gm of the desired product, as a viscous oil. Rf is 0.39 (eluting from silica gel with 25% EtOAc/hexane).

Step I: 1,18-Bis(2,3-butadienyl)-1,5,14,18-tetraazaoctadecane•4HCl

Dissolve 0.5 gm of the product of Step H in 2 ml of EtOH and while stirring treat the mixture with 10 ml of 2N HCl in Et_2O. Stir the resulting mixture overnight, filter and dry the solids (in vacuo) to obtain 0.22 gm of the desired product, mp 283-284°C dec.

EXAMPLE 16

N,N'-Bis[3-(ethylamino)propyl]-1,7-heptanediamine tetrahydrochloride (MDL 28314QA)

Step A: 1,7-Bis(hexahydropyrimidin-1-yl)heptane (MDL 102533)

A solution of N,N'-bis(3-aminopropyl)-1,7-heptanediamine 4HCI (MDL 26752QA, 10.0 g, 25.6 mmol)[4] in 1 N NaOH (103 mL, 4 eq) was cooled to 5°C (ice-water bath) and aqueous HCHO (37 wt%, 3.8 mL, 50.8 mmol) was added in one portion. The solution was stirred for 1 h at 0-5°C and then 1 h at room temperature. The reaction solution was extracted with CH_2CI_2 (3 x 100 mL). The extracts were combined, dried (K_2CO_3) and concentrated to give crude MDL 102533 (6.9 g, 100%) as a light yellow solid. This material was used without further purification. Purification of a sample by flash chromatography using eluant A gave analytically pure MDL 102533 as a white solid: mp 52-55°C; TLC (eluant B) R_f 0.46; ^1H NMR ($CDCI_3$) δ 1.3 (m, 6), 1.46 (br pentet, 4), 1.61 (pentet, 4, J=5.5 Hz), 1.7 (br s, 2, NH), 2.21 (dd, 4, J=7.6, 8.6 Hz), 2.56 (br t, 4, J=4.8 Hz), 2.81 (t, 4, J=5.5 Hz), 3.37 (s, 4); ^{13}C NMR ($CDCI_3$) δ 26.79, 27.05, 27.58, 29.39, 45.07, 53.12, 55.66, 69.84; mass spectrum (Cl/CH_4),

m/z(rel intensity) 270(21), 269(100), 97(18), 83(19), 79(14).

Anal. Calcd for $C_{15}H_{32}N_4$ (268.45): C, 67.11; H, 12.02; N, 20.87. Found: C, 66.65; H, 12.85; N, 20.69.

Step B: 1,7-Bis(3-acetylhexahydropyrimidin-1-yl)heptane (MDL 44868)

A stirred solution of crude bis(hexahydropyrimidine) MDL 102533 (5.0 g, 18.7 mmol) in EtOAc (40 mL), Et_3N (7.6 g, 75 mmol) and Ac_2O (7.6 g, 75 mmol) was heated at reflux for 8 h under N_2. The reaction solution was cooled and concentrated (50°/10 mm). The concentrate was partitioned in CH_2Cl_2 (75 mL) and 1 N NaOH (40 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 75 mL). The CH_2Cl_2 layers were combined, dried (K_2CO_3) and concentrated to give crude MDL 44868 (7.2 g, 110%) as an orange oil. This material was used without further purification. Purification of a sample by flash chromatography using eluant C gave analytically pure MDL 44868 as a colorless oil: TLC (eluant C) R_f, 0.35; ^1H NMR[5] ($CDCl_3$) δ 1.3 (m, 6), 1.5 (m, 4), 1.63/1.70 (overlapping, complex pentets, 4, J=5.6/5.6 Hz), 2.09/2.11 (s, 6), 2.4 (m, 4), 2.72/2.73 (two overlapping t, 4, J=6.3/6.3 Hz), 3.48/3.60 (t, 4, J=5.6/5.6 Hz), 4.04/4.23 (s, 4); ^{13}C NMR ($CDCl_3$) δ 20.99, 21.12, 23.00, 23.06, 23.40, 26.99, 27.21, 29.16, 41.45, 45.96, 51.71, 51.82, 52.21, 53.37, 53.46, 62.46, 62.54, 67.78; mass spectrum (Cl/CH_4), m/z(rel intensity) 381(21), 354(28), 353(100), 351(10).

Anal. Calcd for $C_{19}H_{36}N_4O_2$ (352.52): C, 64.74; H, 10.29; N, 15.89. Found: C, 63.13; H, 10.59; N, 15.52.

Step C: 1,7-Bis(3-ethylhexahydropyrimidin-1-yl)heptane (MDL 45692)

A solution of crude bis(acetylhexahydropyrimidine) MDL 44868 (2.0 g, 5.7 mmol) in anhydrous THF (40 mL) was added to a stirred suspension of LAH (0.85 g, 22.7 mmol) in anhydrous THF (60 mL) under N_2. The reaction mixture was heated at reflux for 16 h and then allowed to cool to room temperature. The reaction mixture was stirred vigorously and quenched by the cautious addition of saturated aqueous Na_2SO_4 (5 mL) at room temperature. It was necessary to stir the mixture for 16 h to ensure total quench. The mixture was filtered (Celite) and the filter cake was washed with THF (3 x 10 mL). The filtrate and washings were combined and concentrated, the residue was dissolved in CH_3CN (50 mL) and was concentrated again to give crude MDL 45692 (1.69, 87%) as a yellow oil. This material was used without further purification. Purification of a sample by flash chromatography using eluant D gave analytically pure MDL 45692 as a light yellow oil: TLC (eluant D) R_f 0.56; 1 H NMR ($CDCI_3$) δ 1.07 (t, 6, J=7.2 Hz), 1.3 (m 6), 1.46 (br pentet, 4, J=6.3 Hz), 1.67 (pentet, 4, J=5.6 Hz), 2.30 (overlapping dd, 4, J=7.6, 7.6 Hz), 2.39 (q, 4, J=7.2 Hz), 2.4-2.5 (m, 8), 3.08 (br s, 4); ^{13}C NMR ($CDCl_3$) δ 12.23, 23.67, 27.10, 27.42, 29.39, 49.00, 52.03, 52.44, 55.38, 76.13; mass spectrum (Cl/CH_4), m/z(rel intensity) 353(16), 326(22), 325(100), 324(57), 323(94).

Anal. Calcd for $C_{19}H_{40}N_4$ (324.56): C, 70.31; H, 12.42; N, 17.26. Found: C, 69.50; H, 12.75; N, 16.70.

Step D: N,N'-Bis[3-(ethylamino)propyl]-1,7-heptanediamine tetrahydrochloride (MDL 28314QA)

To a stirred solution of crude bis(ethylhexahydropyrimidine) MDL 45692 (0.50 g, 1.5 mmol) in MeOH (20 mL), conc. HCl (5 mL) was added in one portion. The reaction solution was heated at reflux for 3 h, using a nitrogen sweep to remove HCHO/MeOH distillate (MDL 28314QA precipitated from the reaction solution shortly after heating began). The loss in reaction volume was periodically adjusted to the original level by addition of MeOH. The reaction mixture was allowed to cool to room temperature and then was filtered. The solid was washed with MeOH (2 x 5 mL) and air-dried to give MDL 28314QA (0.40 g, 58%) as an off-white solid. Recrystallization from H_2O (0.8 mL) and i-PrOH (2.9 mL) gave pure MDL 28314QA (0.32 g, 80% recovery) as a white solid: mp 313°C (dec); TLC (eluant E) R_f 0.39; ^1H NMR (D_2O) δ 1.30 (t, 6, J=7.3 Hz), 1.4 (m, 6), 1.70 (br pentet, 4, J=7.3 Hz), 2.1 (m, 4), 3.1 (m, 4), 3.13 (q, 4, J=7.3 Hz), 3.15 (m, 8); ^{13}C NMR (D_2O) δ 13.30, 25.50, 28.21, 28.25, 30.48, 45.87, 46.71, 47.17, 50.61; mass spectrum (Cl/CH_4), m/z(rel intensity) 329(17), 302(21), 301(100), 300(22), 299(30), 197(8), 159(6), 75(10).

Anal. Calcd for $C_{17}H_{40}N_4$ 4HCl (446.38): C, 45.74; H, 9.94; N, 12.55; Cl, 31.77. Found: C, 45.49; H, 10.48; N, 12.33; Cl, 31.20.

EXAMPLE 17

1,6,14,19-Tetraazanonadecane Tetrahydrobromide

Step A: N-t-Butyloxycarbonyl-N-4-chlorobutyl-p-toluenesulfonamide

A solution of DEAD (17.4 g, 0.1 mole) in THF (20 ml) was added dropwise to a solution of 25 (27.1 g, 01. mole), triphenylphosphine (26.2 g, 0.1 mole) and 4-chloro-1-butanol (10.8 g, 0.1 mole) distilled to remove HCl) in THF (600 ml). After 4 hours at ambient temperature the mixture was evaporated and the residue was chromatographed (toluene) to give the product (29.4 g, 81%) as an oil. IR (film) 2980, 1728, 1456, 1394, 1356, 1292, 1256, 1186, 1156, 1088, 10000, 814, 772, 722, 674, 598, 576 and 546 cm-1. NMR (CDCl3) 1.35 (s, 9H), 1.8-2.0 (m, 4H), 2.45 (s, 3H), 3.6 (t, J=7.5 Hz, 2H), 3.86 (t, J=7.5 Hz, 2H), 7.33 (J=7.5 Hz) and 7.78 (d, J=7.5 Hz, 2H). MS (CI/CH4) 362 (M + H). Anal Calcd for $C_{16}H_{24}ClNO_4S$ 1/8 toluene: C, 54.28; H, 6.75; N, 3.75. Found: C, 54.39; H. 694; N, 3.70.

Step B: 1,7-bis-p-Toluenesulfonamidoheptane

A mixture of dichloromethane (600 ml), aqueous sodium bicarbonate (600 ml) and 1,7-diaminoheptane (25 g, 0.19 mole) was stirred while p-toluenesulfonyl chloride (109 g, 0.57 mole) was added in portions over 1 hour. The layers were separated, the organic layer was extracted with 1N HCl and evaporated. The residue was triurated with toluene to give the product (58g, 70%) as a white solid mp. IR (KBr) 3256, 2942, 2864, 1430, 1328, 1306, 1160, 1094, 1078, 808, 706, 668, 578, 552 and 522 cm-1. NMR (DMSO-d6) 1.1-1.2 (m, 6H), 1.25-1.3 (m, 4H), 2.4 (s, 6H), 2.6-2.7 (m, 4H), 7.37 (d, J=7.5 Hz, 4H), 7.45 (t, J=7.5 Hz, 2H) and 7.75 (d, J=7.5 Hz, 4H). MS (CI/CH4) 439 (M + H). Anal. Calcd for $C_{21}H_{30}N_2O_4S_2$: C, 57.50; H, 6.89; N, 6.39. Found: C, 57.87; H, 7.13; N, 6.20.

Step C: 1,6,14,19-Tetraaza-1,19-bis-t-butyloxycarbonyl-1,6,14,19-tetra-p-tol-uenesulfonylnonadecane

Sodium hydride (0.8 g, 16.8 mmol, 50% mineral oil dispersion) was added in portions to a solution of 27 (3 g, 8.4 mmol) in DMF (300 mL) and the mixture was stirred for 1 h at ambient temperature. Sodium iodide (0.1) and a solution of 26 (5.2 g, 16.8 mmol) in DMF (50 mL) were added and the mixture was heated at 55 C for 18 h. The mixture was cooled, methanol (10 mL) was added to decompose any unreacted sodium hydride, and the mixture was evaporated to dryness. Dichloromethane (300 mL) and water (300 mL) were added, the organic layer was separated, dried and evaporated. Chromatography (toluene/ethyl acetate 6/1) gave the product (4.4 g, 51%) as a thick oil. IR (film) 2980, 2934, 1726, 1458, 1394, 1348, 1306, 1286, 1258, 1186, 1156, 1090, 1006, 814, 756, 722, 674, 654, 598, 576 and 548 cm-1. NMR (CDCL3) 1.25 (s, 6H), 1.32 (s, 18H), 1.42-1.153 (m, 4H), 1.55-1.65 (m, 4H), 1.7-1.8 (m, 4H), 2.55 and 2.56 (s,together 12H), 3.02-3.18 (m, 8H), 4.82 (t, J=7.5 Hz, 4H), 7.25-7.35 (m, 8H), 7.68 (d, J=7.5 Hz, 4H) and 7.77 (d, J=7.5 Hz, 4H). MS (FAB) 1089 (M+). Anal: Calcd for $C_{53}H_{76}N_4O_{12}S_4$, C, 58.42; H, 7.03; N, 5.14. Found: C,60.50: H,7.25; N, 5.08.

Step D: 1,6,14,19-Tetraaza-1,6,14,19-tetra-p-toluenesulfonylnonadecane

A solution of 28 (20 g, 18 mmol) in a mixture of dichloremethane (500 mL) and TFA (20 mL) was stirred overnight at ambient temperature. The mixture was evaporated, toluene (400 mL) was added and the mixture was evaporated to dryness. The residue was chromatographed (toluene/ethyl acetate 3/1) to give the product (14.3 g, 89%) as an oil. IR (film) 3286, 2936, 2864, 1598, 1454, 1426, 1330, 1306, 1290, 1268, 1158, 1092, 1040, 816, 736, 704, 656, 570 and 550 cm-1. NMR (CDCL3) 1.25 (s, 6H), 1.45-1.6 (m, 12H), 2.42 (s, 12H), 2.86-2.95 (m, 4H), 3.0-3.1 (m, 8H), 4.88 (t, J=7.5 Hz, 2H), 7.15-7.3 (m, 8H), 7.43

(D, J=7.5 Hz, 4H) and 7.72 (d, J=7.5 Hz, 4H). MS (CI/CH4) 889 (M + H). Anal: Calcd for $C_{43}H_{60}N_4O_8S_4$ 3/4 toluene: C, 60.38; H, 7.15; N, 5.70. Found: C, 60.48; H, 7.17; N, 5.57.

Step E: 1,6,14,19-Tetraazanonadecane Tetrahydrobromide

A solution of 29 (12.2 g, 13.7 mmol) in 48% aq HBr (500 mL) was heated in a 100 C oil bath for 24 h, cooled and evaporated to dryness. The residue was recrystallized (ethanol/H20) to give the product (5.2 g, 63%) as a white solid, mp 303 C. IR (KBr) 2952, 2874 and 2810 cm-1. NMR (D20) 1.4 (s, 6H), 1.6-1.85 (m, 12H) and 3.0-3.1 (m, 12H). MS (CI/CH4) 273 (M + H). Anal: Calcd for $C_{15}H_{36}N_4$ 4HBr:C, 30.22; H, 6.76; N, 9.40. Found: C, 30.60; H, 6.90; N, 9.09.

Test compound numbers relate to the following compounds:

MDL19,190 = NH=C(NH2)-N=C(CH3)-CH=N-NH-C(NH2)=NH
2,2'-(1-methyl-1,2-ethanediylidene)-bis[hydrazinecarboximidamide], (methyl-glyoxal bis(guanylhydrazone))

MDL27,393 = CH3CH2-NH-(CH2)3-NH-(CH2)8-NH-(CH2)3-NH-CH2CH3
N,N'-Bis(3-(ethylamino)propyl)-1,8-octanediamine

MDL27,616 = ΦCH2-NH-(CH2)3-NH-(CH2)3-NH-CH2Φ
N-(phenylmethyl)-N'[3-[(phenylmethylamino)propyl]-1,3-propanediamine

MDL27,695 =ΦCH2-NH-(CH2)3-NH-(CH2)7-NH-(CH2)3-NH-CH2Φ
1,18-Bis[(phenyl)methyl]1,5,14,18-tetraazaoctadecane

MDL28,314 =CH3CH2-NH-(CH2)3-NH-(CH2)7-NH-(CH2)3-NH-CH2CH3
N,N'-Bis(3-(ethylamino)propyl)-1,7-heptanediamine

MDL28,454 =CH3CH2CH2-NH-(CH2)3-NH-(CH2)7-NH-(CH2)3-NH-CH2CH2CH
N,N'-bis[3-(propylamino)propyl]-1,7-diaminoheptane

gaciclovir = 9-[(2-ydroxy-1-hydroxymethylethoxy)-methyl]guanine

BIOLOGICAL EXAMPLES

EXAMPLE 18: ANTIVIRAL ACTIVITY

The antiviral effects of, polyamine analogues was determined by a standard plaque reduction assay as described by Tyms et al. (J. Antimicrobial Chemotherapy 8, 65-72, 1981). Monolayers of human embryo fibroblasts (MRC-5 strain) were formed in the presence or absence of varying concentrations of compound and infected with CMV strain AD169 or Towne (100 pfu/10^5 cells) in the presence or absence of compound and incubated in the presence or absence of compound for ten days at 37°C. For incubation post infection, cell monolayers were overlaid in maintenance medium (Eagles MEM with 2% bovine fetal calf serum) which contained 0.5% agarose, and fixed and stained with methylene blue at the appropriate time (7-10 days post infection). From the percent reduction in plaque formation compared to untreated controls, a dose response plot was made and the 50% inhibitory concentration (IC50) determined. A range of IC50 values for various polyamine analogues are shown in Table A. The preferred compound,

MDL27,393, consistently gave IC50 values about 10 pmoles/litre when cells were also pre-exposed to compound prior to infection. Using these protocols, the IC50 values for MDL 27,393 were about 100,000 lower than those recorded for the current therapies for CMV infections, ganciclovir and foscovir (Table B).

With similar protocols using MRC-5 cells (Table C) infected with HSV type 1 (17i strain) but using a three day post-infection incubation period, IC50 values for MDL27,393 (TABLE C1) and MDL28,314 (TABLE C2) were between 1-10 µmoles/litre with the pre-post treatment protocol. No antiviral activity was observed in MRC-5 cells even at 100 µM with treatment post-infection only. In vero cells (simian origin) treatment with MDL 27,393 (≤100 µM), pre-post or post-only, failed to inhibit the growth of HSV-1 (strain 17i). This was evidence that the activity of the analogues was related to cellular or virus specific events involved in CMV but not HSV replication.

Natural polyamines putrescine, spermidine or spermine when presented to infected cells, as described in the above protocol, failed to inhibit CMV growth at concentrations < 10µM moles/litre.

Similar experiments were carried out with the same pretreatment protocol as above but at high multiplicity infection (approximately 10^5/pfu/10^5 cells): monolayers were maintained in the absence of agarose in the maintenance medium. Production of progeny virus and the synthesis of "late" viral proteins were measured as previously described Tyms et al (J. Gen. Virol, 68, 1563-1573, 1987). Virus production was inhibited by the preferred compound, MDL27,393, by 90% at 1 nmoles/litre and 95% at 10nmoles/litre with a corresponding reduction in the synthesis of the three major "late" viral proteins the major capsid protein (153KD) tegument protein (69KD) and a

DNA-binding protein (51KD). This was confirmed in experiments in which numbers of CMV infected cells expressing the "late" antigens under these conditions, identified by a specific monoclonal antibody to a late protein, were shown to be reduced. These results were interpreted to mean that the production of infectious progeny virus in infected cells was curtailed which limited the spread of infection in cell monolayers when infected at low multiplicity of infection. This was considered due to an interference with the synthesis of CMV "late" viral proteins by the preferred compound.

EXAMPLE 19: CYTOTOXICITY

MRC-5 cells were seeded at low plating density and grown in the presence or absence of the preferred compound, MDL 27,393, or MDL 28,314 and cell numbers were determined at five days postseeding. The results showed that growth of these cells was not inhibited at concentrations of 0.5 µmoles/litre or less although the time to confluency of the monolayers was longer compared to untreated controls at concentrations between 1 and 5 µmoles/litre (data not shown).

On the basis of these results the therapeutic window, for the preferred compound MDL 27,393, established by the amount of compound required to inhibit virus growth by 50% compared to the concentration required to inhibit cell growth by 50%, was greater than 10,000.

TABLE A

ANTIVIRAL EFFECT OF NATURAL POLYAMINES AGAINST CMV INFECTION

REF: PA219

Conc µM	Spermine	Mean % VC	Spermidine	Mean % VC	DHPG	Mean % VC
100	45, 52, 0	47%	99, 91	93%	0, 0	0%
10	106, 107, 0	100%	99, 92	96%	10, 17	12%
1	- As VC -	100%	- As VC -	100%	68, 67	57%
0.1	- As VC -	100%	- As VC -	100%	106, 95	91%
0.01	- As VC -	100%	- As VC -	100%	- As VC -	100%
VC	103, 99, 105	100%	103, 99, 105	100%	106, 129, 99	100%

Plaque reduction assay - Towne strain grown in MRC-5 cells

TABLE B

ANTIVIRAL EFFECT OF POLYAMINE ANALOGUES AGAINST CMV INFECTION

Compound	IC_{50} Values Pre/Post	Post only
MDL 27,393	<O.lnM	<100nM
MDL 28,314	10nM	100nM
MDL 27,484	<1nM	100nM
MDL 29,587	<lOOnM	1µM
MDL 27,666	1nM	<1µM
MDL 27,667	10nM	>1µM
MDL 27,394	<10nM	<1µM
Ganciclovir	1µM	<10µM

Plaque reduction assay - Towne strain grown in MRC-5 cells.

TABLE C

EFFECT OF POLYAMINE ANALOGUES AGAINST HSV TYPE II INFECTION:

REF: PA 241

MDL 27, 393: TABLE C1

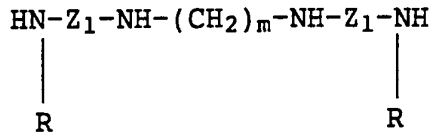
Conc µM	Pre/Post	Mean % VC	Post	Mean % VC
100	0, 0, 0	0%	68, 71, 71	77%
10	16, 17, 20	19%	91, 90, 92	100%
1	30, 27, 30	32%	As VC	100%
0.1	49, 50, 61	59%	As VC	100%
$1x10^{-2}$	75, 71, 60	76%	As VC	100%
$1x10^{-3}$	81, 63, 70	78%	As VC	100%
$1x10^{-4}$	65, 80, 80	81%	As VC	100%
VC	95, 87, 91	100%	90, 89, 92	100%

MDL 28, 314: TABLE C2

Conc µM	Pre/Post	Mean % VC	Post	Mean % VC
100	0, 0, 0	0%	90, 76, 82	81%
10	24, 20, 15*	22%	As VC	100%
1	58, 65, 51	64%	As VC	100%
0.1	63, 65, 59	69%	As VC	100%
$1x10^{-2}$	78, 71, 60	77%	As VC	100%
$1x10^{-3}$	- As VC -	100%	As VC	100%
$1x10^{-4}$	- As VC -	100%	As VC	100%
VC	87, 97, 89	100%	103, 99, 105	100%

WHAT IS CLAIMED:

1. A method of inhibiting a cytomegaloviral infection which comprises administering to a patient in need thereof an effective antiviral amount of a compound of the formula:



wherein Z_1 is a branched chain (C_2-C_6) alkylene moiety; m is 7 or 8; and each R group independently is hydrogen, a C_1-C_6 saturated or unsaturated hydrocarbyl, or $-(CH_2)_x-(Ar)-X$ wherein Ar is phenyl or napthyl, X is H, C_1-C_6 alkoxy, halogen C_1-C_4 alkyl, wherein x is an integer 0, 1, or 2; with the proviso that both R groups cannot be hydrogen; or said compounds of formula I can be a pharmaceutically acceptable acid addition salt thereof..

2. A compound of Claim 1 wherein the compound is N,N'-Bis(3-(ethylamino)propyl)-1,8-octanediamine.

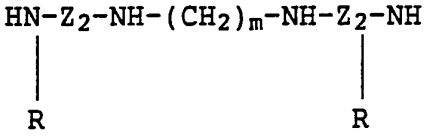
3. A compound of Claim 1 wherein the compound is 1,18-Bis[(phenyl)methyl]1,5,14,18-tetraazaoctadecane.

4. A compound of Claim 6 wherein the compound is N,N'-Bis(3-(ethylamino)propyl)-1,7-heptanediamine.

5. A compound of Claim 6 wherein the compound is N,N'-bis[3-(propylamino)propyl]-1,7-diaminoheptane.

6. A pharmaceutical composition according to claim 4 which further comprises an effective amount of a polyamine oxidase inhibitor as an additional ingredient.

7. A method for the treatment of patients suffering from a CMV disease state which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of the formula:



wherein Z_2 is a saturated chain (C_2-C_6) alkylene moiety; m is 7 or 8; each R group independently is hydrogen, a C_1-C_6 saturated or unsaturated hydrocarbyl, or $-(CH_2)_x-(Ar)-X$ wherein Ar is phenyl or napthyl, X is H, C_1-C_6 alkoxy, halogen C_1-C_4 alkyl, wherein x is an integer 0, 1, or 2; with the proviso that both R groups cannot be hydrogen; or said compounds of formula I can be a pharmaceutically acceptable acid addition salt thereof.

8. A compound of Claim 1 wherein the compound is N,N'-Bis(3-(ethylamino)propyl)-1,8-octanediamine.

9. A compound of Claim 1 wherein the compound is 1,18-Bis[(phenyl)methyl]1,5,14,18-tetraazaoctadecane.

10. A compound of Claim 6 wherein the compound is N,N'-Bis(3-(ethylamino)propyl)-1,7-heptanediamine.

11. A compound of Claim 6 wherein the compound is N,N'-bis[3-(propylamino)propyl]-1,7-diaminoheptane.

INTERNATIONAL SEARCH REPORT

Interr. ...nal Application No
PCT/US 93/08517

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/13 A61K31/135

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)
IPC 5 A61K

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP,A,0 399 519 (MERRELL DOW PHARM. INC.) 28 November 1990 see the whole document ---	1,3,7,9 1,7
X	ANTICANCER RES. vol. 10, no. 5A , 1990 pages 1281 - 1288 N.J. PRAKASH ET AL. 'Antitumor activity of a novel synthetic polyamine analogue, N,N'-Bis-[3-(ethylamino)-propyl]-1-7-heptane diamine: Potentiation by polyamine oxidase inhibitors'	4,6,10
Y	see the whole document --- -/--	1,7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"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

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 1994	03. 02. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	**Authorized officer** Krautbauer, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J. MED. CHEM. vol. 34, no. 8 , 1991 pages 2414 - 2420 M.L. EDWARDS ET AL. 'Synthesis and DNA-binding properties of polyamine analogues' see the whole document	2-5,8-11
Y	JOURNAL OF VIROLOGY vol. 50, no. 1 , 1984 pages 145 - 154 W. GIBSON ET AL. 'D,L-alpha-Difluoromethylornithine inhibits Human Cytomegalovirus replication' see the whole document	1,7
Y	BIOCHEM. J. vol. 257, no. 3 , 1989 pages 769 - 774 A.J. BITONTI ET AL. 'Regulation of polyamine biosynthesis in rat hepatoma (HTC) cells by a bisbenzyl polyamine analogue' see abstract	1,7
Y	J. MED. VIROL. vol. 34, no. 4 , 1991 pages 212 - 216 J.R. CLARKE ET AL. 'Polyamine biosynthesis in cells infected with different clinical isolates of Human Cytomegalovirus' see abstract	1,7
Y	NATURE vol. 297, no. 5868 , 1982 pages 690 - 691 A.S. TYMS ET AL. 'Inhibitors of polyamine biosynthesis block human cytomegalovirus replication' see the whole document	1,7
Y	LIFE CHEM. REP. vol. 9 , 1991 pages 179 - 183 A.S.TYMS ET AL 'An association between polyamine biosynthesis and symptomatic infection with human cytomegalovirus' see the whole document	1,7
2 A	R. BERKOW ET AL. 'THE MERCK MANUAL' 1987 , MERCK SHARP & DOHME RESEARCH LAB. , RAHWAY, N.J. see page 180 - page 183	1,7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08517

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claim 1 and 7 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☒ Claims Nos.: 1,6,7
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
For further information please see annex.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Box I.2:

The Markush formulas of claims 1 and 7 are too broad and inconcise to be searched as such. The search had therefore to be restricted to the compounds explicitely mentioned in the claims. These compounds themselves and their use in the treatment of cytomegaloviral infection have been searched, including the general inventive idea of the invention. The expression "polyamine oxidase inhibitor" is too inconcise as to make a complete search possible; restriction of the search to the general inventive idea in this case.
Claims searched completely: 2-5,8-11.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten ...nal Application No
PCT/US 93/08517

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0399519	28-11-90	AU-B-	628174	10-09-92
		AU-A-	5517190	29-11-90
		JP-A-	3005420	11-01-91