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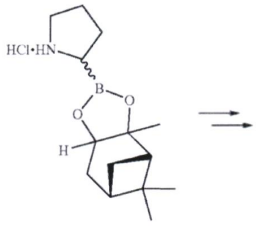
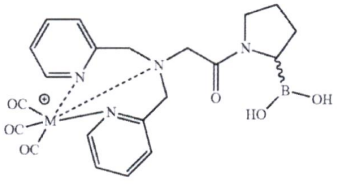


(2-(±)-1001

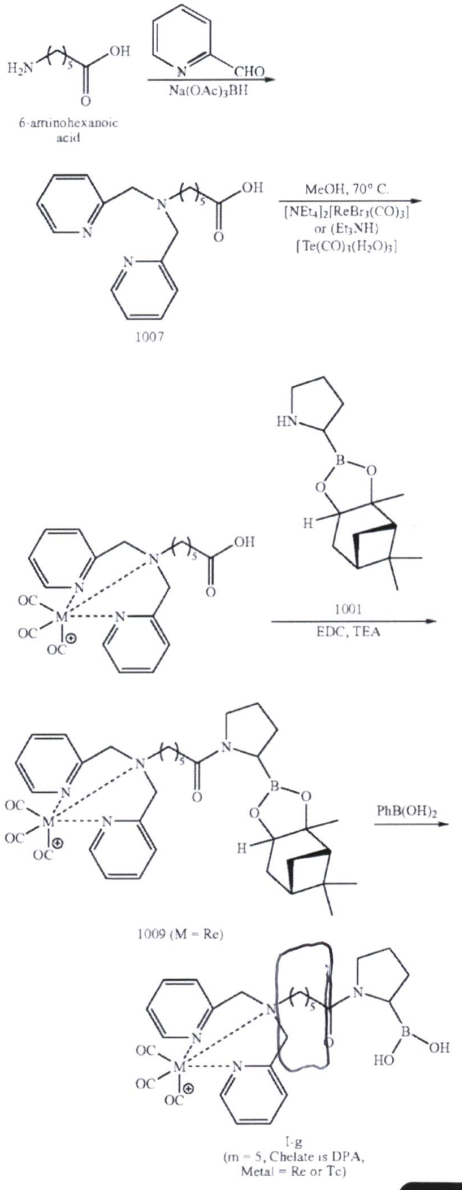


(2-(±)-I-a

[0127] The syntheses can be accomplished by reductive amination of the borane-protected boronoproline 1003 with two equivalents of the appropriate aldehyde (e.g. 2-pyridinecarboxaldehyde) using sodium triacetoxyborohydride as the reducing agent. The free ligands thus obtained may then be complexed with the desired metal followed by removal of borane protection group to afford the desired metal complex I-a. Similarly, compounds of Formula I-a with U=P(O)(OPh)$_2$, CO_2H or CN can be prepared when diphenyl pyrrolidin-2-ylphosphonate, proline or pyrrolidine-2-carbonitrile is used as a starting material, respectively. The borane-protected boronoproline 1003 can be prepared from the corresponding compound 1001 via standard peptide formation. One skilled in the art would readily utilize any appropriate chiral or non-chiral borane-protecting groups to prepare compound 1001 in racemic or enantiomeric form according to the known procedures (see examples in Coutts et al., *J. Med. Chem.* 1996, 39(10), 2087-2094). Compounds of Formula I-a in racemic or enantiomeric form can then be prepared accordingly.

[0128] Scheme 3 illustrates the synthesis of functionalized proline-$M^+(CO)_3$ complex (e.g. U $B(OH)_2$) from a preformed $M^+(CO)_3$ ligand. The synthetic route utilizes the preformed chelate and enantiomerically rich boronoproline 1001 as the starting materials to prepare the boronoproline $M(CO)_3$ Dpa analog (1-g, wherein m=5, Chelate is Dpa, Metal=Re or Tc). Compounds of Formula I-g in racemic form can be prepared utilizing a non-chiral starting material, e.g. a racemate analog of compound 1001.

Scheme 3: Synthesis of boronoproline-$M^+(CO)_3$ complex from preformed $M^+(CO)_3$ ligand



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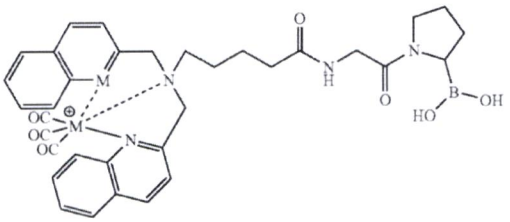
[0129] Similarly, compounds of Formula I-g with U=P(O)$(OPh)_2$, CO_2H or CN can be prepared where diphenyl pyrrolidin-2-ylphosphonate, proline or pyrrolidine-2-carbonitrile is used as a starting material, respectively.

[0130] Scheme 3 can be utilized to synthesize functionalized proline-$M^+(CO)_3$ complexes to explore the effect of more significant variations of the distance of the metal chelator from the proline moiety by incorporating a tether into these structures. The tether may comprise a simple alkyl chain as shown, a PEG $(CH_2CH_2O)_n$, a polyethylene amine $((CH_2CH_2NH)_n)$, or the like. Terminal aminoalkanoic acids (such as (β-alanine, 4-aminobutanoic acid, 5-aminopentanoic acid, 6-aminohexanoic acid and the 8-aminooctanoic acid) or amino-PEG-acids $(NH_2—(CH_2CH_2O)_n—CH_2—COOH$, e.g. 2-(2-(3-aminopropoxy)ethoxy)acetic acid) may be utilized as tethers, according to some embodiments.

[0131] According to some embodiments, glycine and/or other appropriate amino acid can be incorporated as a linker, as well as an additional binding moiety to afford seprase inhibitors. Scheme 4 illustrates synthesis of boronoproline-$Re^+(CO)_3$ or $Tc^+(CO)_3$ complexes having the structure as represented by Formula I-b and I-c. Lysine is used to prepare compounds of Formula I with additional amine moiety in the linkers.



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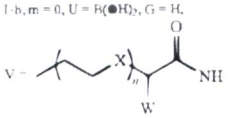
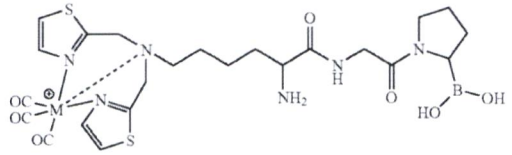
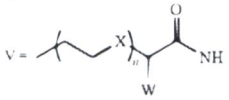
I-b, m = 0, U = B(OH)$_2$, G = H,



wherein W = H, X = CH_2, n = 1



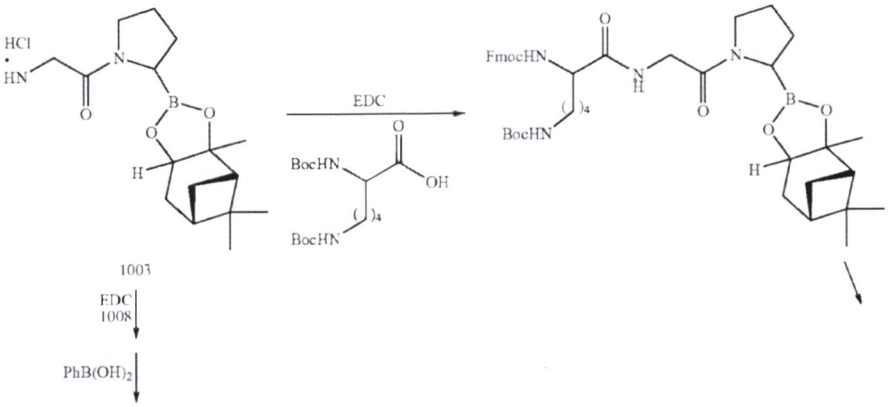
I-c, m = 1, U = B(OH)$_2$,
Chelate is bis(thiazol-2-ylmethyl)amine
G = H,



wherein W = NH, X = CH_2, n = 1

[0132] The molecules in this class may be prepared from the corresponding compound 1003, as illustrated in Scheme 4. The complexes of Formula I-b can be prepared from protected lysine utilized standard peptide coupling chemistry. The complexes of Formula I-c are prepared from the appropriate terminal aminoalkanoic acids. Similarly, by employing suitable borane-protecting groups, one can prepare the corresponding racemic compound (from the non-chiral borane-protecting starting material) or the enantiomer (from the chiral-protecting starting material in opposite chirality).

Scheme 4: Synthesis of functionalized proline-$M^+(CO)_3$ Complex utilizing amino acid linker



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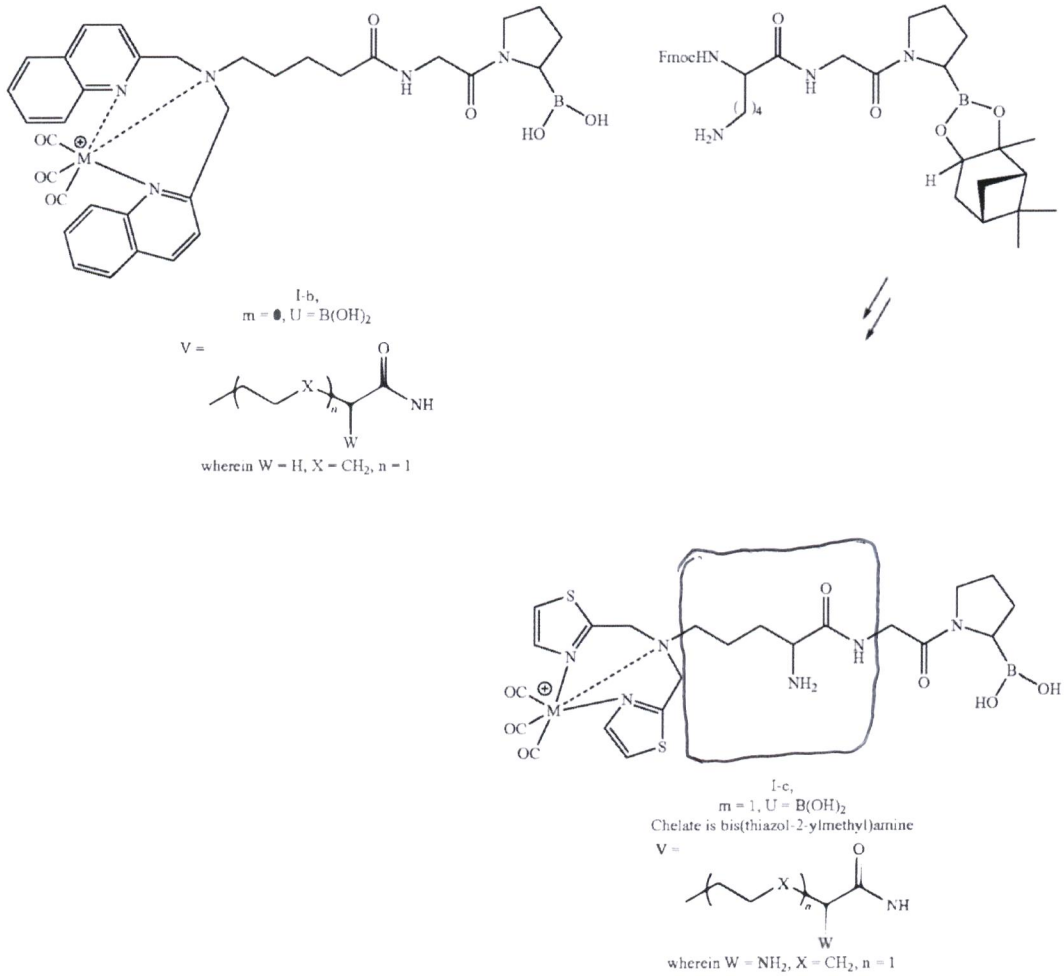

[0133] The above reaction scheme is applicable to any modification of the tether by incorporation of heteroatoms into the tether chain. This may have additional benefits on the affinity as well as the selectivity for seprase. Incorporation of heteroatoms into the tether such as oxygen can take advantage of the commercially availability of a variety of short polyethylene glycol (PEG) diamines that can be readily incorporated into the complexes. One of ordinary skilled in the art would also readily apply other chelates to prepare functionalized proline-$M^{+}(CO)_3$ complexes.

[0134] The general synthesis of the N-substituted benzamide glycineboronoproline analogs is shown below in Scheme 5. The synthesis of the glycineboronoproline intermediate has been previously described (Simon J. C. et al. *J. Med. Chem.* 1996, 39, 2087-2094). The two step synthesis from compound 1003 (or its racemic or enantiomeric analogs) involves an amide formation and deprotection steps. Similarly, compounds of Formula II with $U=P(O)(OPh)_2$, CO_2H or CN can be prepared when diphenyl pyrrolidin-2-ylphosphonate, proline or pyrrolidine-2-carbonitrile is used as a starting material, respectively to afford the corresponding compound 1003 analogs via the glycine coupling steps as described before. Alternatively, compound 1001 may be used to couple with glycine-linked N-substituted benzamide for the preparation of compound of general Formula IV.