Pergamon

Tetrahedron 54 (1998) 3955–3970

TETRAHEDRON

SOLUTION-PHASE COMBINATORIAL SYNTHESIS: CONVERGENT MULTIPLICATION OF DIVERSITY VIA THE OLEFIN METATHESIS REACTION

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Abstract. The solution-phase synthesis of iminodiacetic acid diamides functionalized with ω-alkenes and their dimerization via the olefin metathesis reaction in the preparation of mixture libraries are detailed. Libraries containing as many as 113,232 compounds prepared from only *N*-BOC-iminodiacetic acid anhydride (**1**), 15 amines, and 4 ω-alkene carboxylic acids illustrate the diversity that may be achieved by a convergent versus divergent combination of a small number of monomer building blocks that provides the multiplication of diversity typically associated with linear library syntheses including peptides, oligonucleotides and sequential template functionalizations. Unlike the divergent synthesis of such libraries which is amenable to solid-phase synthesis techniques, the convergent synthesis is especially well suited for solution-phase synthesis and is precluded by solid-phase techniques since the combining components typically would be on mutually exclusive phases.

Ligand-induced receptor and protein dimerization or oligomerization has emerged as a general mechanism for signal transduction[1] and members of the important receptor superfamilies are activated by such a process. These include protein tyrosine kinase receptors (homo- or heterodimerization),[2] class I cytokine receptors (homo- or heterodimerization),[3] serine/threonine kinase receptors (hetero-oligomerization),[4] and members of the TNF-receptor family (trimerization), Table 1.[5] Within the cytokine receptor superfamily, the most extensively studied examples are the human growth hormone (hGHr),[6] prolactin (PRLr)[7] and erythropoietin receptors (EPOr),[8] which form homodimers upon binding their ligands. Similarly, intracellular signal transduction often proceeds by protein–protein homo- or heterodimerization and important examples include activators of transcription (*e.g.*, Myc–Max dimerization, STAT homo- and heterodimers).[9,10]

Important therapeutic applications may emerge from either the development of agonists or antagonists of such receptor or protein dimerization and representative examples are provided in Table 2 for the cytokine receptor superfamily. Our interest in combinatorial chemistry rested on its potential ability to provide candidate leads for promoting receptor activation by dimerization which to our knowledge had not emerged from screening natural products. This interest in studying receptor activation via dimerization and the potential of utilizing a single approach for the discovery of antagonists and their conversion to agonists[11] was one important element underlying our pursuit of solution-phase combinatorial chemistry at a time when solid-phase techniques were considered most valuable.

Combinatorial chemistry, initially pursued with peptide and oligonucleotide libraries, has undergone rapid development providing a new paradigm for drug discovery.[12] Perhaps as a consequence of the extension from linear peptide and oligonucleotide synthesis, the majority of applications have relied on linear solid-phase synthesis and methodological advances continue to extend common synthetic transformations to polymer-supported versions.[13] A less

0040-4020/98/$19.00
PII: S0040-4020(98)00128-8

Table 1. Class I cytokine receptors

Family	Examples	Activation Characteristics
GH receptor	GHR, EPOR, PRLR, G-CSFR	homodimers
IL-3 receptor	IL-3R, GM-CSFR, IL-5R	heterodimeration with β_c
IL-6 receptor	IL-6R, LIFR, CNTFR, IL-11R	heterodimerization with gp130
IL-2 receptor	IL-2Rα, IL-2Rβ, IL-4R, IL-7R	heterodimerization with IL-2Rγ

Protein–tyrosine kinase receptors activated by dimerization or oligomerization

Family	Examples
PDGF receptor	PDGFR-α, PDGFR-β, SCFR, CSF-R, Fik-2
EGF receptor	EGFR (erbB), erbB-2 (Neu), erbB-3, erbB-4
FGF receptor	FGFR-1, FGFR-2, FGFR-3. FGFR-4
IGF receptor	Insulin R, IGF-1R
HGF receptor	HGFR (Met), MSPR (Ron)
VEGF receptor	Flt-1, Flt-2 (KDR)
Neurotrophin receptor	Trk, TrkB, TrkC
Eph receptor	Eph, Elk, Eck, Cck5, Sek, Eck, Erk

Abbreviations: R, receptor; receptor; CSF, colony-stimulating factor; GH, growth hormone; EPO, erythropoietin; PRL, prolactin; IL, interleukin; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic factor; PDGF, platelet-derived growth factor; SCF, stem cell factor; CSF, colony-stimulating factor; EGF, epidermal growth factor; FGF, fibroblast growth factor, IGF, insulin-like growth factor; HGF, hepatocyte growth factor; MSP, microphage-stimulating protein; VEGF, vascular endothelial growth factor; FN, fibronectin.

Table 2. Approved/potential therapeutic applications of cytokine agonists and antagonists

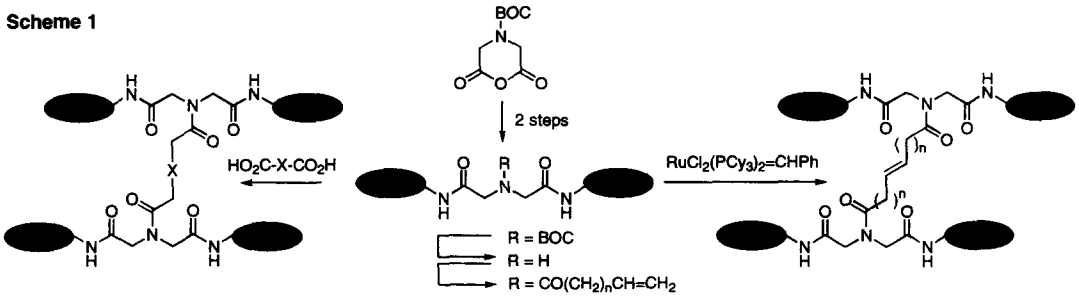
Cytokine	Agonist	Antagonist
EPO	anemias, selective blood donation	cancer, leukemia
TPO	thrombocytopenia	
IL-2	cancer	histoincompatability
IL-3	leukopenia, myeloid reconstitution	leukemia
IL-4	inflammation, cancer	allergy
IL-6	thrombocytopenia	cancer, osteoporosis, inflammation
IL-11	thrombocytopenia	
IL-12	cancer, infections	histoincompatability, autoimmunity
G-CSF	neutropenia, myeloid reconstitution	leukemia
GM-CSF	leukopenia, myeloid reconstitution	leukemia
IFN α/β	cancer, viral infections, autoimmunity	inflammation
IFN γ	chronic granulonatous disease, infections	inflammation, autoimmunity

commonly employed complement is the development of protocols for solution-phase combinatorial synthesis.[14–22] Preceding the disclosure of our own efforts on the development of a multistep solution-phase parallel synthesis of chemical libraries,[20] the single step solution-phase synthesis of mixture libraries was detailed by at least three groups.[15–17] In addition to continued advances in this work, progress in using solution-phase multicomponent reactions for generating combinatorial mixtures,[18,19] the use of resin capture as well as resin scavenger techniques[21] including ion-exchange resins for solid-phase acid-base extractions,[20] fluorous phase extractions,[22] and liquid-phase polymers[23] have been described.

Our efforts focused on the development of a technically non-demanding multistep, solution-phase strategy for the preparation of chemical libraries which relied on the removal of excess reactants and reagents by liquid–liquid or

liquid–solid extractions.[20] The approach was shown to dependably deliver pure individual compounds in large quantities (50–150 mg), and libraries of >1000 individual members were assembled in initial efforts.[20] It has been since implemented on scales producing 50–150 mg of the final materials in formats for the parallel synthesis of individual pure compounds,[20] for modest sized libraries composed of small mixtures[24] (1000–10,000 member libraries, 10–100 compounds/mixture), or combinatorially assembled to provide larger compound libraries[25] (25,000–100,000 member libraries, 10–28,000 compounds/mixture) allowing its compatibility with any screening objective or protocol. Since the libraries are produced on a relatively large scale, they may be repeatedly dispensed for routine screening without depletion of the growing collection. These features along with its technically non-demanding implementation are among its greatest attributes.

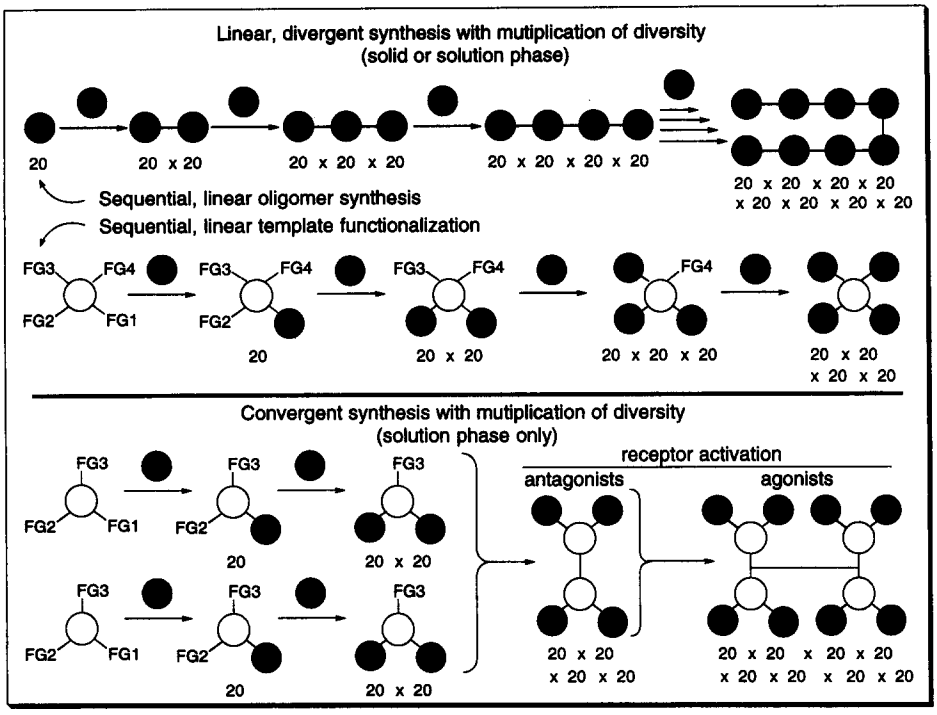
Scheme 1



More recently we disclosed its extension to the preparation of modest sized libraries suitable for probing protein–protein interactions. This entailed the dimerization linkage of iminodiacetic acid diamides using either symmetrical dicarboxylic acids[24] or the olefin metathesis reaction to join and combinatorially randomize the length of a linking tether (Scheme 1).[25] Herein, we provide details of this latter approach, its extension to higher order libraries, and its use in the generation of large combinatorial libraries enlisting a convergent versus divergent approach to the factorial multiplication of the diversity. Unlike the linear divergent synthesis of libraries which is suited for solid-phase synthesis, the convergent synthesis is especially well suited for solution-phase synthesis and would be precluded by solid-phase techniques where the combining components are on mutually exclusive solid-phases.

Developmental Studies. Initial efforts focused on the preparation of a modest sized library to illustrate the approach. It constitutes the dimerization and simultaneous randomization of the length of a linking tether joining two iminodiacetic acid diamides employing the olefin metathesis reaction.[26–28] The reaction sequence requires 4 steps and represents an extension of our solution-phase synthesis of chemical libraries that is especially well suited for establishing an unknown linker length. In addition to the advantages outlined originally,[20] the solution-phase synthesis of the fragments and their convergent linkage would be precluded by conventional solid-phase synthesis techniques.

The precursors for the protypical library of 300 members (600 compounds including *cis/trans* isomers) were assembled from 6 iminodiacetic acid diamides each functionalized with 4 ω-alkene carboxylic acids, Scheme 2. The precursors were assembled in a matrix 6 × 6 × 4 format and only the diagonal 6 iminodiacetic acid diamides were prepared by parallel synthesis and the last reaction was conducted with a mixture of 4 ω-alkene carboxylic acids. As such, the 24 precursors **4** were assembled in 3 parallel steps as 6 mixtures each containing 4 compounds with variations in only



the chain length of the terminal alkene. For the development studies, the selection of the matrix diagonal **AXBX** combination represented in Table 3 was simply a matter of convenience. Each of the 3 steps was conducted in solution employing acid/base extractions[20] to isolate and purify the intermediates providing the desired pure products (≥95% pure) free of contaminants derived from unreacted starting materials, reagents, and reaction byproducts independent of the reaction yields (Table 3). To insure that different coupling rates might not affect the equimolar mixture, the final coupling step of the reaction sequence to produce **4** was conducted with excess **3** (1.5 equiv) for a prolonged reaction time (16 h) to guarantee complete consumption of the stoichiometry limiting carboxylic acid (**C1–C4**).

Prior to implementing the library construction, the protocol for conducting the olefin metathesis reaction was examined with the individual members of the **A1B1C1–C4** sublibrary. The couplings of **A1B1** with CH_2=$CH(CH_2)_nCO_2H$ (n = 1, 2, 3, 4, 7, and 8) provided the corresponding ω-alkene amides (83–100%, Scheme 3). Symmetrical homodimerization of **4** by olefin metathesis was accomplished by treatment with $RuCl_2(PCy_3)_2$=CHPh[27] (0.2–0.25 equiv, $CHCl_3$, reflux, 16 h) and cleanly afforded the homodimers **5** for n = 3, 4, 7, and 8, but worked less effectively for n = 2, and failed to provide the desired product with n = 1. A mixture of *trans* and *cis* double bond isomers was observed (2.2–3.2:1) and although the *trans* isomer predominated, both isomers were produced in significant amounts. Both $RuCl_2(PCy_3)_2$=CHPh and $RuCl_2(PCy_3)_2$=CH-CH=CPh_2 failed to produce comparable results when the reaction was conducted at 25 °C and $Mo(C_{10}H_{12})$ $(C_{12}H_{17}N)[OC(CH_3)(CF_3)_2]_2$ proved too sensitive under the robust reaction conditions. Typically, complete reaction required 0.15–0.25 equiv of the catalyst $RuCl_2(PCy_3)_2$=CHPh and a summary of a study with n = 7 is provided in Scheme 3. The **A1B1C1–C4** homodimer sublibrary was constructed (67%) similarly and

Scheme 2

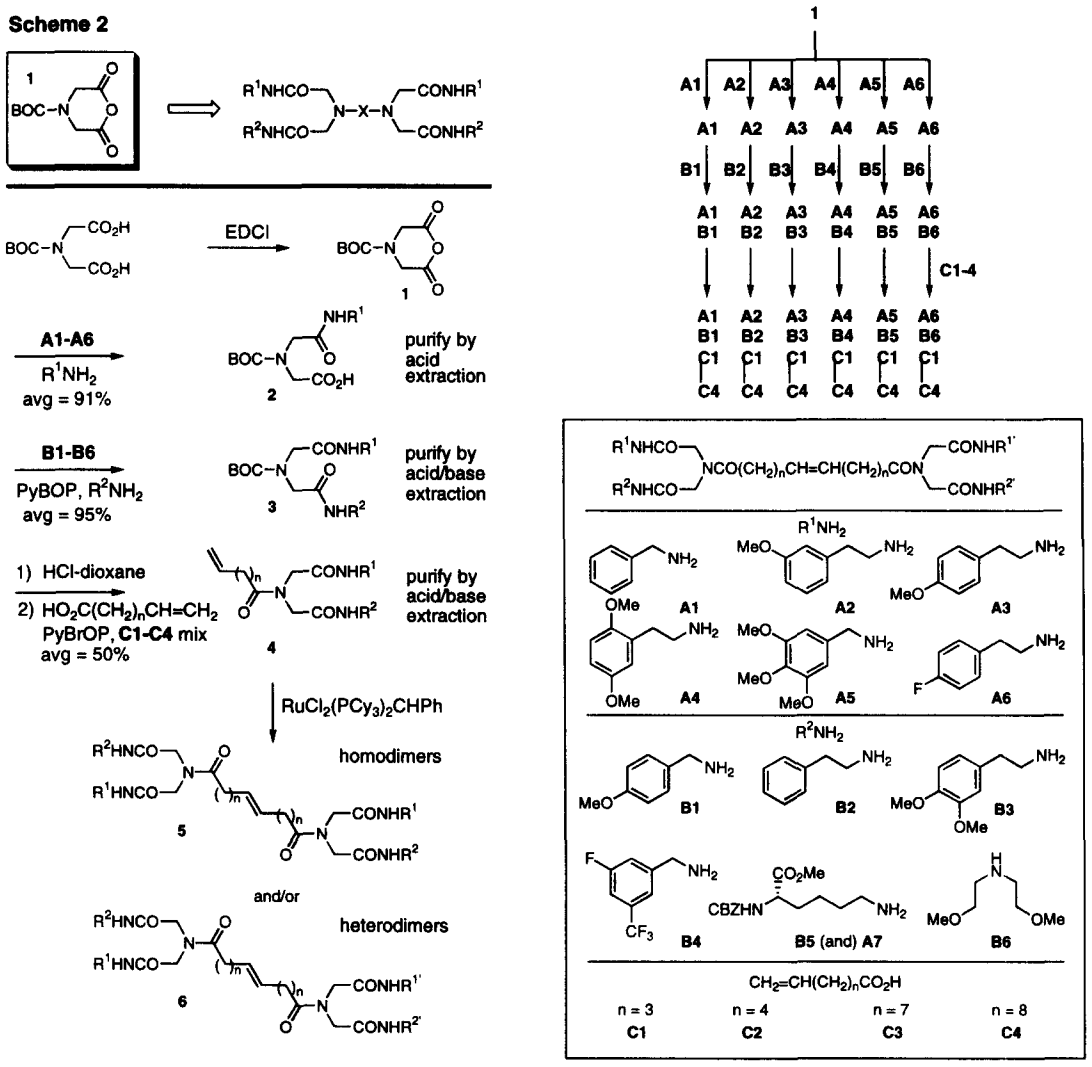


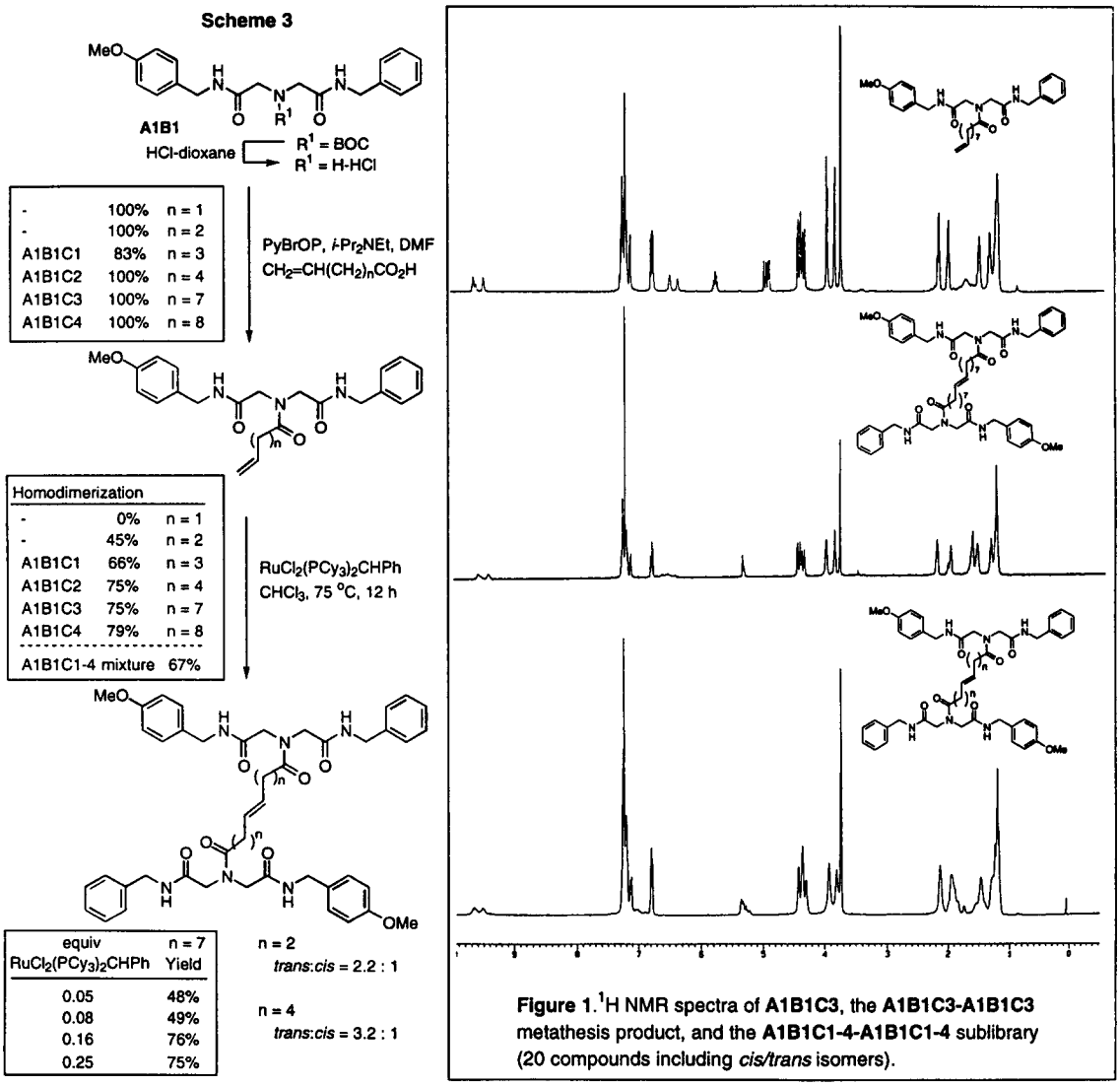
Table 3. Yields (%) of the Library Precursors

2	A1	A2	A3	A4	A5	A6
	93	91	99	88	76	100
3	A1	A2	A3	A4	A5	A6
B1	99					
B2		99				
B3			94			
B4				95		
B5					93	
B6						89
4	A1B1C1-4		A2B2C1-4		A3B3C1-4	
	61		41		53	
	A4B4C1-4		A5B5C1-4		A6B6C1-4	
	52		25		68	

Table 4. Yields (%) of the Sublibrary Reactions

	A1 B1 C1 C4	A2 B2 C1 C4	A3 B3 C1 C4	A4 B4 C1 C4	A5 B5 C1 C4	A6 B6 C1 C4
A1B1C1-C4	67	75	65	51	72	72
A2B2C1-C4	75	64	68	37	71	57
A3B3C1-C4	65	68	42	62	45	68
A4B4C1-C4	51	37	62	42	49	47
A5B5C1-C4	72	71	45	49	51	45
A6B6C1-C4	72	57	68	47	45	55
A1-6B1-6C1-4	62% (600 compounds)					

characterized (^{1}H NMR, MS). The mass spectrum exhibited the molecular ion peaks corresponding to each of the 10 components and the ^{1}H NMR spectrum proved remarkably clear given the potential complexity of the mixture (Figure 1). Clear from these comparisons is the absence of the monomers in the metathesis dimer products as evidenced by the loss of the diagnostic vinyl signals and their replacement by disubstituted olefin signals.



-	100%	n = 1
-	100%	n = 2
A1B1C1	83%	n = 3
A1B1C2	100%	n = 4
A1B1C3	100%	n = 7
A1B1C4	100%	n = 8

Homodimerization		
-	0%	n = 1
-	45%	n = 2
A1B1C1	66%	n = 3
A1B1C2	75%	n = 4
A1B1C3	75%	n = 7
A1B1C4	79%	n = 8
A1B1C1-4 mixture	67%	

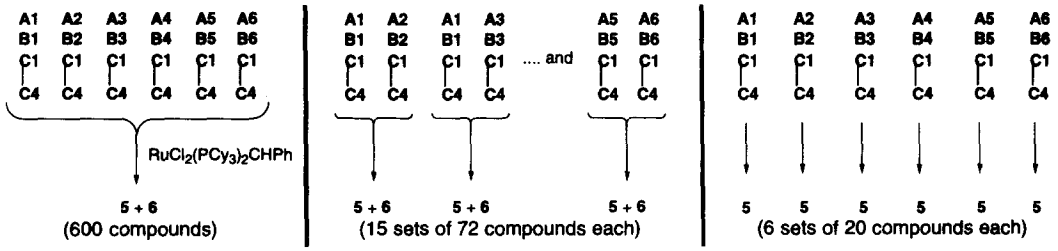
equiv $RuCl_2(PCy_3)_2CHPh$	n = 7 Yield
0.05	48%
0.08	49%
0.16	76%
0.25	75%

Figure 1. ^{1}H NMR spectra of **A1B1C3**, the **A1B1C3-A1B1C3** metathesis product, and the **A1B1C1-4-A1B1C1-4** sublibrary (20 compounds including *cis/trans* isomers).

The library of compounds **5** and **6** construction was accomplished in a single reaction providing a mixture of 600 compounds and by 15 pair-wise combinations (**A1B1C1–4** + **A2B2C1–4**) providing 15 sublibraries of 72 compounds containing two sets of homodimers (**5**) as well as a defined set of heterodimers (**6**) (Figure 2). Finally, the 6 sublibraries

of homodimers containing 20 compounds were assembled in 6 reactions. There was no special significance to this choice of combinations except that each represents a significantly different mixture pool size which can be chosen to accomodate preferences in testing and deconvolution protocols. However, given the ease of conducting the modest number of reactions to generate all three, this protocol does provide a first level deconvolution as well as a multisampling of the same compounds since each homodimer is additionally generated in 5 of the 15 mixtures (indexed mixtures). This provides the opportunity for considerable deconvolution in a first pass assay. Final deconvolution of such mixtures by resynthesis from the individual components of the final precursors (last step) in the modest-sized 20- or 72-membered sublibraries is straightforward. This can be further simplified by hydrogenation of the final library mixtures to provide products containing the saturated hydrocarbon linking chain.

Figure 2



The assemblage of the library of 600 compounds, the 15 homo/heterodimer sublibraries, and the 6 homodimer libraries was conducted (0.2–0.25 equiv $RuCl_2(PCy_3)_2$=CHPh, $CHCl_3$, reflux, 16 h) providing the mixture libraries in 75–23% (50% average, Table 4). The dimer metathesis products **5** and **6** proved to be chromatographically similar to one another and substantially different from the precursors **4**, which in turn behaved similarly. This additional and unanticipated observation provided the opportunity to purify the final products as mixtures, free from any potential starting materials. In our original design, the intention was to conduct the olefin metathesis reaction under conditions where essentially all **4** was consumed. While this proved to be the case, the simple chromatographic separation of the metathesis products from the precursors **4** permitted an additional level of purity control without compromising the mixture integrity. This chromatographic purification was used to remove the metathesis catalyst, its reaction byproducts, any trace amount of remaining reacting monomers and their exchange products with the catalyst. The latter minor byproducts containing a terminating styrene derived from the catalyst proved chromatographically similar to the starting monomers and were readily removed during the chromatographic enrichment. This was employed for the prototypical library generation detailed herein but in practice is unnecessary. Assay of the precursor mixtures **AXBXC1–4** along with the metathesis libraries permits detection of activity due to monomer precursors and that of the styrene-capped monomers could be recognized and addressed upon resynthesis and deconvolution of the the small mixtures.

A Dimer Library. Following the initial studies, the extension of this work to the preparation of full matrix libraries was conducted. The results of a representative library are summarized in Tables 5 and 6 using an expanded version of the library illustrated in Scheme 1 further incorporating N^{α}-CBZ-lysine methyl ester (**A7**) since it emerged from initial screening efforts as a key substituent. To complement rather than simply repeat the initial library, it was also

Table 5. Yields (%) of the Library Precursors

2	A1	A2	A3	A4	A5	A6	A7
	93	91	99	88	76	100	82
3, 4	A1	A2	A3	A4	A5	A6	A7
B1	99, 53	83, 42	100, 87	100, 43	100, 43	92, 39	83, 80
B2	92, 63	99, 68	94, 46	92, 95	95, 46	99, 42	94, 89
B3	95, 66	85, 50	94, 41	92, 86	84, 65	100, 45	86, 82
B4	97, 83	100, 87	100, 75	95, 59	100, 66	100, 46	95, 99
B5	45, 44	45, 52	94, 56	100, 96	90, 61	100, 46	84, 80
B6	72, 88	70, 69	100, 69	88, 83	42, 66	89, 47	73, 70

C1 - C4, n = 2, 4, 7, 9

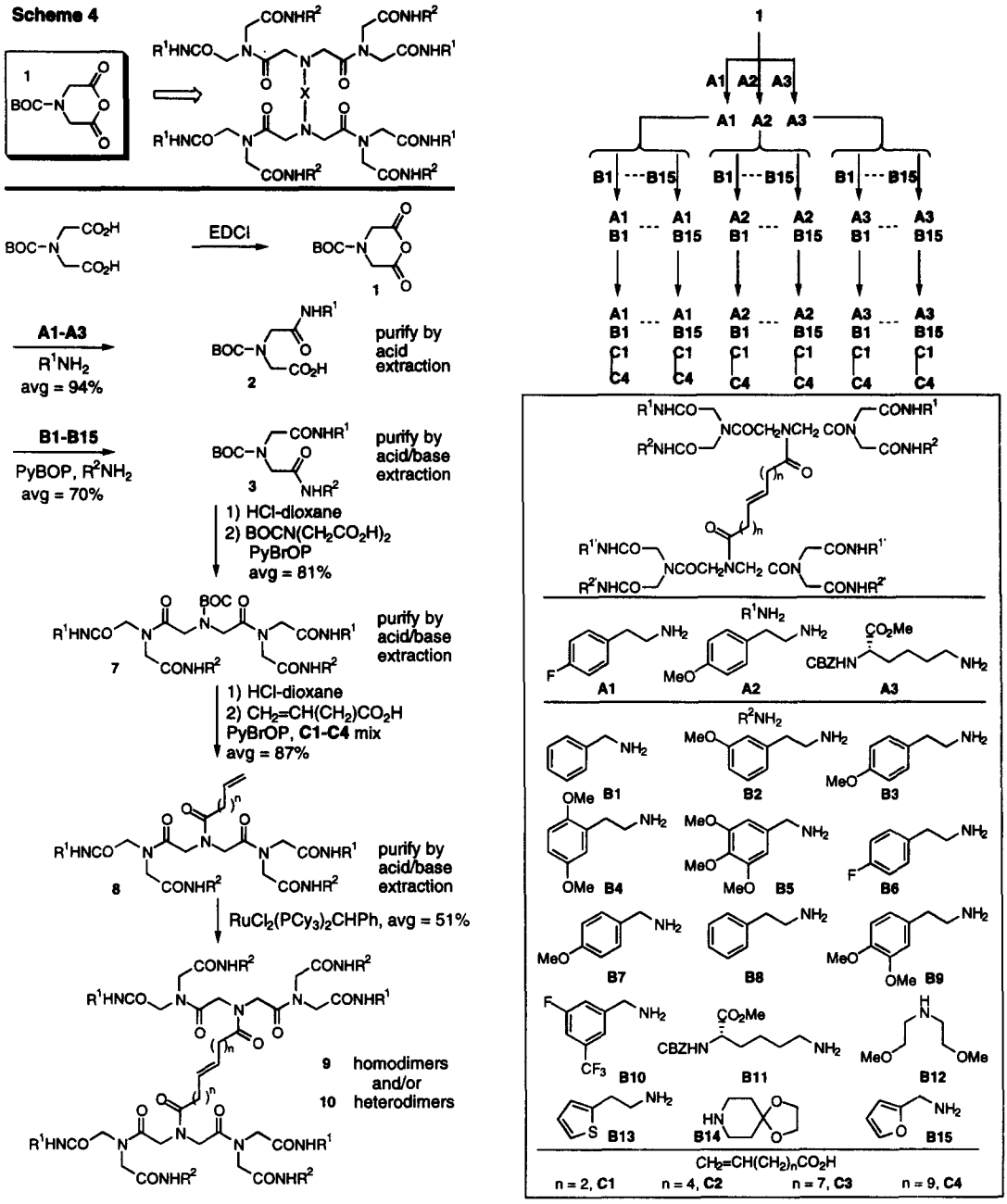
Table 6. Yields (%) of the Sublibrary Reactions

5	A1	A2	A3	A4	A5	A6	A7
B1	43	57	53	46	28	65	40
B2	55	53	41	51	58	57	58
B3	51	28	22	61	35	47	32
B4	30	67	42	47	53	58	15
B5	46	20	20	52	45	65	64
B6	40	48	45	24	36	51	45
A1-7B1-6C1-4			53%	(28,392 compounds)			

conducted with an altered set of 4 ω-alkene carboxylic acids (n = 2, 4, 7, and 9 for **C1–C4**). The library precursors were prepared as outlined in Scheme 1 providing the functionalized iminodiacetic acid diamides in 3 steps with average yields of 88% (step 1), 89% (step 2), and 65% (step 3). Olefin metathesis homodimerization of each of the 42 iminodiacetic acid diamides functionalized with the 4 ω-alkenes (n = 2, 4, 7, 9) provided a library of 840 compounds in a format of 42 mixtures of 20 compounds. In addition, the combinatorial synthesis of the full homo- and heterodimer library consisting of 28,492 compounds was also accomplished in a single step employing an equimolar mixture of the 42 starting materials. Notably, this large compound mixture arises from the use of only **1**, 13 amines, and 4 ω-alkene carboxylic acids statistically combined in all homo- and heterodimerization combinations by the olefin metathesis reaction providing a convergent factorial multiplication of the diversity. Although analogous to the simple multiplication of diversity one achieves in a linear, divergent library synthesis (*e.g.*, repetitive peptide couplings of 20 amino acids), the convergent synthesis also provides the advanced intermediates in a form that permits incorporation from library to library.

This mixture could be generated even more simply in a total of 4 steps by using modestly sized mixtures of reactants at each of the first three steps of the four step synthesis: 7 amines in step 1, 6 amines in step 2, and 4 ω-alkene carboxylic acids in step 3.

Higher Order Libraries. Given the size of the endogenous protein ligands and hormones that promote receptor dimerization, the knowledge that many (*e.g.*, PDGF, CSF-1, SCF) act not as monomers but as dimers in their own right, and the large size of the ligand binding pocket formed upon receptor dimerization created by discontinuous domains of the proteins,[6-8] the simple dimerization of the iminodiacetic acid diamides may only provide antagonists of ligand binding and be of insufficient size to serve as agonists for receptor activation. Given that endogenous ligands themselves are quite large and bind on the cell surface via the extracellular domains of the receptors, larger or higher order structures based on the iminodiacetic acid diamides often may be better suited as potential agonists. Provided they are synthetically readily accessible, such candidate synthetic agonists may prove acceptable since they need not be permeable to the cell for effective activity. In our efforts, we have examined a convergent versus linear protocol that provides tetramers versus dimers of the iminodiacetic acid diamides (Scheme 4). The approach entails the further one-step dimerization to **7** of the iminodiacetic acid diamides with *N*-BOC-iminodiacetic acid followed by *N*-BOC deprotection,



functionalization with ω-alkene carboxylic acids to provide **8**, and subsequent olefin metathesis for further dimerization (**9/10**) with randomization of the length of the linking chain. The results obtained in the first library assembled in this manner are summarized in Scheme 4 and Table 7. For reasons related to screening results, the library was assembled in a 3 × 15 × 4 format providing 42 iminodiacetic acid diamides **3**, each of which contained one of the three best side chains.

These were dimerized in a single step upon treatment with 4 M HCl–dioxane (25 °C, 4 h) followed by coupling with *N*-BOC-iminodiacetic acid (0.33 equiv, 1 equiv PyBrOP, 3 equiv *i*-Pr_2NEt, DMF, 25 °C, 16 h, avg yield = 81%) to provide **7**, an interesting class of iminodiacetic acid diamide dimers for screening in their own right. Subsequent *N*-BOC deprotection (4 M HCl–dioxane, 25 °C, 4 h) and coupling with 4 ω-alkene carboxylic acids (0.67 equiv, 1 equiv PyBrOP, 3 equiv *i*-Pr_2NEt, DMF, 25 °C, 16 h, avg yield = 87%) provided the olefin metathesis precursors **8**. Olefin metathesis homodimerization to **9** (0.2 equiv $RuCl_2(PCy_3)_2CHPh$, $CHCl_3$, reflux, 16 h, avg yield = 51%) of each of the 42 linked iminodiacetic acid diamides functionalized with the 4 ω-alkenes (n = 2, 4, 7, 9) provided a library of 840 compounds in a format of 42 mixtures of 20 compounds. The full homo- and heterodimer library (**9/10**) consisting of 28,392 compounds was prepared in a single step employing an equimolar mixture of the 42 starting materials.

Table 7. Yields (%) of the Olefin Metathesis Tetramer Library

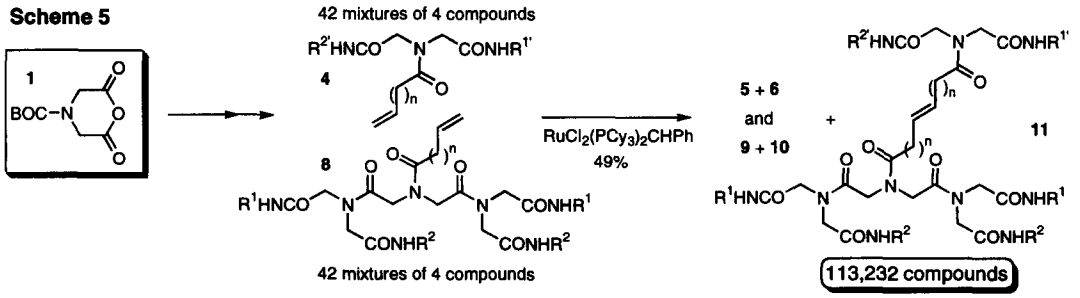
2	**A1**	**A2**	**A3**
	100	99	82
3, 7, 8, 9	**A1**	**A2**	**A3**
B1	70, 95, 96, 53	86, 57, 98 , 66	61, 94, 83, 49
B2	73, 96, 83, 45	77, 100, 81, 54	61, 84, 82, 51
B3	68, 82, 80, 59	83, 100, 68, 57	61, 91, 87, 67
B4	65, 93, 90, 47	87, 100, 87, 65	55, 87, 81, 38
B5	58, 80, 81, 46	72, 100, 88, 46	57, 51, 83, 67
B6	67, 59, 90, 58	–[a]	66, 93, 99, 63
B7	59, 90, 93, 62	74, 89, 95, 38	59, 73, 76, 67
B8	64, 80, 87, 57	74, 91, 96, 66	63, 96, 89, 64
B9	53, 70, 93, 57	71, 31, 94, 45	53, 65, 89, 30
B10	58, 68, 92, 42	75, 100, 96, 43	69, 100, 93, 36
B11	–[a]	–[a]	58, 71, 96, 30
B12	75, 53, 80, 44	64, 77, 91, 44	50, 48, 62, 54
B13	93, 69, 89, 68	93, 69, 97, 51	86, 92, 97, 30
B14	63, 96, 80, 41	74, 75, 60, 78	75, 68, 95, 53
B15	87, 100, 100, 37	91, 78, 87, 34	86, 99, 89, 57
A1-3B1-15C1-4	44%	(28,392 compounds)	

[a]Prepared as A1B3, A3B3, or A3B6

The statistical combination of the precursors **7** with the simultaneous variation in the linking chain length to provide the large library required only *N*-BOC-iminodiacetic acid, 15 amines, and 4 ω-alkene carboxylic acids as starting materials.

In a reaction that highlights beautifully the advantages of the modular convergent construction of the libraries that accompanies the olefin metathesis linkage of the individual monomers, an equimolar mixture of the 42 iminodiacetic acid diamides **4** bearing the 4 ω-alkenes from the initial dimer library and the analogous 42 precursors **8** from the second tetramer library were combined in a single reaction (0.2 equiv cat., $CHCl_3$, reflux, 16 h, 49%) to provide an even larger library of 113,232 compounds composed of all members of the two initial libraries plus all cross metathesis reaction products incorporating 3 versus 2 or 4 iminodiacetic acid diamides (Scheme 5). This convergent library construction employed only **1**, 15 different amines, and 4 ω-alkene carboxylic acids.

Scheme 5



Conclusions. The solution-phase synthesis of prototypical libraries for use in studying receptor and protein homodimerization and heterodimerization were detailed which were derived from the olefin metathesis linkage of

iminodiacetic acid diamide monomers. The iminodiacetic acid diamide derived monomers may be screened in advance as well as alongside the dimer libraries for simple binding and antagonist activity. This further simplifies the extension of the studies to the discovery of agonists where the subsequent homodimer products constitute those potentially suited as agonists of protein homodimerization while the heterodimer products constitute those potentially suited as agonists for dimerization of two different proteins. The convergent dimerization linkage of the immediate precursors to provide the libraries would be precluded by solid-phase synthesis techniques making the solution-phase approach especially valuable. In addition, the use of the olefin metathesis reaction to join and randomize the length of the linking tether provides a direct solution to the rapid generation of a statistically controlled mixture of compounds that is especially well suited for establishing a required linker length within dimer or oligomer libraries. Most importantly, it highlights the use of a convergent synthetic approach to library synthesis that embodies a factorial versus simple multiplication of diversity characteristic of a linear divergent synthesis necessarily employed with solid-phase libraries. The examination of the properties of the libraries detailed herein and their extensions will be disclosed elsewhere.

Experimental

General Procedure for the First Diversification: *N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-methoxyphenyl)ethyl)iminodiacetic Acid Monoamide (Library 1, A3). A mixture of *N*-((*tert*-butyloxy)carbonyl)iminodiacetic acid (4.66 g, 20 mmol) and EDCI (3.8 g, 20 mmol) in 60 mL of anhydrous DMF was stirred for 1 h at 25 °C. 4-Methoxyphenethyl amine (**A3**, 3.0 g, 20 mmol) was added to the resulting solution in four portions (slightly exothermic). The reaction mixture was stirred for 20 h at 25 °C before it was poured into 250 mL of 10% aqueous HCl. The product was extracted into EtAOc (3 × 200 mL) and the combined organic phases were washed with 10% aqueous HCl (2 × 200 mL), saturated aqueous NaCl (2 × 200 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to afford 7.3 g (99%) of the title compound as a white solid: R_f = 0.6 (10% HOAc–EtOAc); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.27 (m, 1H), 7.12 (m, 2H), 6.84 (m, 2H), 3.91, 3.87, 3.83 and 3.80 (four s, 4H), 3.70 (s, 3H), 3.25 (m, 2H), 2.64 (m, 2H), 1.35 and 1.32 (two s, 9H); IR (film) ν_{max} 2976, 2931, 1705, 1635, 1513, 1456, 1393, 1368, 1248, 1164, 1032, 824, 600 cm^{-1}; FABHRMS (NBA–NaI) *m/z* 367.1862 (M + H$^+$, $C_{18}H_{26}N_2O_6$ requires 367.1869).

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-(benzyl)iminodiacetic Acid Monoamide (A1):** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 and 7.13 (two s, 1H, NH), 7.27 (m, 5H), 4.47 (m, 2H), 3.97 (m, 4H), 1.43 and 1.34 (two s, 9H); IR (film) ν_{max} 3292, 2974, 2933, 1708, 1636, 1569, 1456, 1395, 1369, 1251, 1164, 1031, 964, 908, 856, 780, 739, 697 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 455.0599 (M + Cs$^+$, $C_{16}H_{22}N_2O_5$ requires 455.0583).

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(3-methoxyphenyl)ethyl)iminodiacetic Acid Monoamide (A2):** ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.26 (m, 1H), 7.19 (m, 1H), 6.76 (m, 3H), 3.90, 3.87, 3.84 and 3.81 (four s, 4H), 3.73 (s, 3H), 3.32 (m, 2H), 2.69 (q, 2H, J = 10 Hz), 1.35 and 1.32 (two s, 9H); IR (film) ν_{max} 3853, 3744, 3675, 3648, 3294, 2976, 1700, 1653, 1635, 1584, 1559, 1506, 1490, 1457, 1394, 1368, 1259, 1165, 1038, 963, 877, 781, 697 cm^{-1}; FABHRMS (NBA–NaI) *m/z* 367.1860 (M + H$^+$, $C_{18}H_{26}N_2O_6$ requires 367.1869).

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(2,5-dimethoxyphenyl)ethyl)iminodiacetic Acid Monoamide (A4):** ^{1}HNMR ($CDCl_3$, 500 MHz) δ 7.54 and 6.90 (two s, 1H, NH), 6.72 (m, 3H), 3.94 (m, 4H), 3.77 (two s, 3H), 3.74 (two s, 3H), 3.52 (m, 2H), 2.81 (m, 2H), 1.43 and 1.38 (two s, 9H); IR (film) ν_{max} 3307, 2974, 2933, 2831, 1708, 1631, 1503, 1451, 1390, 1364, 1226, 1164, 1041, 979, 928, 908, 877, 856, 805, 780, 733, 708 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 529.0938 (M + Cs$^+$, $C_{19}H_{28}N_2O_7$ requires 545.0951).

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-(3,4,5-trimethoxybenzyl)iminodiacetic Acid Monoamide (A5):** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 and 7.62 (two s, 1H, NH), 6.55 and 6.48 (two s, 2H), 4.37 (m, 2H), 3.96 (m, 4H), 3.82, 3.81, 3.79, and 3.78 (four s, 9H), 1.42, 1.40, and 1.30 (three s, 9H); IR (film) ν_{max} 3293, 2974, 2933, 1702, 1636, 1590, 1508, 1456, 1421, 1390, 1364, 1328, 1236, 1164, 1123, 1005 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 545.0873 (M + Cs$^+$, $C_{19}H_{28}N_2O_8$ requires 545.0900).

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-fluorophenyl)ethyl)iminodiacetic Acid Monoamide (A6):** ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.23 (m, 1H), 7.24 (m, 2H), 7.09 (m, 2H), 3.89, 3.86, 3.82 and 3.80 (four s, 4H), 3.30 (m, 2H), 2.71 (m, 2H), 1.35 and 1.32 (two s, 9H); IR (film) ν_{max} 3852, 3744, 3675, 3648, 3295, 2978, 1700, 1684, 1653, 1635,

1559, 1540, 1510, 1457, 1394, 1368, 1222, 1161, 896, 772 cm^{-1}; FABHRMS (NBA–NaI) *m/z* 355.1661 ($M + H$,$^+$ $C_{17}H_{23}N_2O_5$ requires 355.1669).

General Procedure for the Second Diversification: *N*-((*tert*-Butyloxy)carbonyl)-*N'*-(3,4,5-trimethoxybenzyl)-*N''*-(*N*-α-CBZ-L-lysine Methyl Ester)iminodiacetic Acid Diamide (Library 1, A5B5). The monoamide **A5** (0.237 g, 0.575 mmol) was dissolved in DMF (6 mL) and added to a flask containing *i*-Pr_2NEt (0.223 g, 1.7 mmol) and CBZ-Lys-OCH_3 (**B5**, 0.209 g, 0.632 mmol). PyBOP (0.33 g, 1.73 mmol) was added in portions and the resulting mixture was stirred overnight at 25 °C (16 h). The reaction mixture was poured into 60 mL of 10% aqueous HCl and extraction into EtOAc (3 × 40 mL) followed by washing of the combined organic phases with 10% aqueous HCl (2 × 60 mL), saturated aqueous NaCl (1 × 60 mL), saturated aqueous $NaHCO_3$, (2 × 60 mL) and saturated aqueous NaCl (1 × 60 mL), drying (Na_2SO_4) and evaporation provided 0.355 g (93%) of **A5B5** as an oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.59 and 8.20 (two s, 1H, NH), 7.25 (m, 5H), 6.60 and 6.52 (two s, 2H), 5.54 (apparent d, 1H), 5.08 (apparent d, 2H), 4.38 (m, 3H), 3.88 (m, 13H), 3.32 (s, 3H), 3.25 (m, 2H), 1.80 (m, 2H), 1.74 (m, 2H), 1.68 (m, 2H), 1.38 and 1.29 (two s, 9H); IR (film) ν_{max} 3426, 2995, 1641, 1508 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 821.2398 ($M + Cs^+$, $C_{34}H_{48}N_4O_{11}$ requires 821.2374).

All **AXBX** were similarly characterized providing an assessment of each of the coupling reactions.

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-benzyl-*N''*-(4-methoxybenzyl)iminodiacetic Acid Diamide (A1B1):** ^1H NMR ($CDCl_3$, 500 MHz) δ 8.60 (m, 1H, NH), 8.20 (m, 1H, NH), 7.26 (m, 7H), 6.75 (m, 2H), 4.39 and 4.32 (two s, 4H), 3.75 (m, 7H), 1.32 (s, 9H); IR (film) ν_{max} 3241, 3067, 2974, 2833, 1703, 1656, 1559, 1513, 1452, 1390, 1369, 1246, 1174, 1139, 1031, 959, 897, 846, 744, 697 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 574.1296 ($M + Cs^+$, $C_{24}H_{31}N_3O_5$ requires 574.1318).

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(3-methoxyphenyl)ethyl)-*N''*-(2-phenylethyl)iminodiacetic Acid Diamide (A2B2):** ^1H NMR ($CDCl_3$, 500 MHz) δ 8.40 (m, 1H, NH), 7.80 (m, 1H, NH), 7.21 (m, 6H), 6.78 (m, 3H), 3.76 (apparent two s, 7H), 3.50 (m, 4H), 2.82 (m, 4H), 1.38 (s, 9H); IR (film) ν_{max} 3245, 3070, 2974, 2933, 1704, 1654, 1654, 1585, 1564, 1487, 1452, 1395, 1369, 1256, 1164, 1036, 903, 780, 749, 697 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 601.1611 ($M + Cs^+$, $C_{26}H_{35}N_3O_5$ requires 602.1631).

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-methoxyphenyl)ethyl)-*N''*-(2-(3,4-dimethoxyphenyl)ethyl)iminodiacetic Acid Diamide (A3B3):** ^1H NMR (DMSO-d_6, 400 MHz) δ 8.67 (m, 2H), 7.13 (m, 2H), 6.84 (m, 4H), 6.72 (d, 1H, J = 8.0 Hz), 3.79 and 3.76 (two s, 2H), 3.73 (s, 3H), 3.72 and 3.70 (two s, 2H), 3.70 (s, 6H), 3.33 (m, 4H), 2.65 (m, 4H), 1.31 (two s, 9H); IR (film) ν_{max} 3250, 3074, 2935, 2835, 2056, 1650, 1212, 1571, 1514, 1454, 1417, 1393, 1367, 1301, 1247, 1159, 1141, 1029, 960, 895, 848, 809, 762, 665 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 662.1850 ($M + Cs^+$, $C_{28}H_{39}N_3O_7$ requires 662.1842).

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(2,5-dimethoxyphenyl)ethyl)-*N''*-(3-fluoro-5-(trifluoromethyl)benzyl)iminodiacetic Acid Diamide (A4B4):** ^1H NMR ($CDCl_3$, 500 MHz) δ 9.84 and 9.18 (two t, 1H, NH), 7.25 (m, 3H), 7.09 and 6.59 (two t, 1H, NH), 6.73 (m, 3H), 4.49 (d, 2H, J = 6 Hz) 3.77 (m, 10H), 3.48 (apparent dd, 2H), 2.80 (apparent dd, 2H), 1.35 (s, 9H); IR (film) ν_{max} 3231, 3067, 2974, 2933, 2831, 1703, 1656, 1564, 1503, 1456, 1390, 1364, 1339, 1246, 1221, 1169, 1128, 1092, 1044, 977, 960, 874, 801, 700 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 704.1379 ($M + Cs^+$, $C_{27}H_{33}N_3O_6F_4$ requires 704.1360).

***N*-((*tert*-Butyloxy)carbonyl)-*N'*-(2-(4-fluorophenyl)ethyl)-*N''*-di(2-methoxyethyl)iminodiacetic Acid Diamide (A6B6):** ^1H NMR ($CDCl_3$, 500 MHz) δ 9.20 and 9.96 (two t, 1H, NH), 7.05 (m, 2H), 6.80 (m, 2H), 4.05, 3.92, 3.76, and 3.66 (four s, 4H), 3.38 (m, 8H), 3.17 (m, 6H), 2.68 (m, 2H), 1.27 (s, 9H); IR (film) ν_{max} 3508, 3241, 3077, 2974, 2923, 1702, 1641, 1564, 1508, 1441, 1390, 1364 1251, 1221, 1164, 111, 1010, 964, 928, 892, 826 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 602.1634 ($M + Cs^+$, $C_{23}H_{36}N_3O_6$ requires 602.1642).

General Procedure for the Third Diversification for Library 1, Individual Components: Preparation of *N*-(4-Pentenylcarbonyl)-*N'*-benzyl-*N''*-(4-methoxybenzyl)iminodiacetic Acid Diamide (A1B1C1). The BOC derivative **A1B1** (146 mg, 0.33 mmol) was stirred in a solution of 4 M HCl–dioxane (2.5 mL) at 25 °C for 4 h. Removal of the solvent under N_2 and *in vacuo* gave the deprotected material as a pale yellow solid. The crude amine hydrochloride was dissolved in anhydrous DMF (4.5 mL) and **C1** (25 mg, 0.22 mmol), *i*-Pr_2NEt (173 μL, 0.99 mmol) and PyBrOP (154 mg, 0.33 mmol) were added sequentially. The reaction mixture was stirred for 16 h at 25 °C before being diluted with EtOAc (100 mL) and washed (3 × 100 mL) with acidic saturated aqueous NaCl (20% aqueous HCl/saturated aqueous NaCl: 1/1), saturated aqueous $NaHCO_3$ (2 × 100 mL), saturated aqueous NaCl (100 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide 80 mg (83%) of the **A1B1C1** as an oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.60 (m, 1H, NH), 7.25 (m, 7H), 7.15 (m, 1H, NH), 6.82 (m, 2H), 5.69 (m, 1H), 4.95 (m, 2H), 4.39 (m, 4H), 3.85 (m, 4H), 3.76 (s, 3H), 2.15 (m, 2H), 1.97 (m, 2H), 1.60 (m, 2H); IR (film) ν_{max} 3272, 3067, 2933, 1646, 1554, 1508, 1456, 1246,1174,

1026, 917, 815, 744, 697 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 570.1375 (M + Cs^+, $C_{25}H_{31}N_3O_4$ requires 570.1369).

***N*-(5-Hexenylcarbonyl)-*N'*-benzyl-*N''*-(4-methoxybenzyl)iminodiacetic Acid Diamide (A1B1C2):** ^1H NMR ($CDCl_3$, 500 MHz) δ 9.55 (m, 1H, NH), 7.26 (m, 7H), 6.83 (m, 2H), 6.27 (two s, 1H, NH), 5.75 (m, 1H), 4.95 (m, 2H), 4.44 (m, 4H), 4.03 and 4.01 (two s, 2H), 3.89 and 3.88 (two s, 2H), 3.79 (m, 3H), 2.20 (m, 2H), 1.56 (m, 2H), 1.32 (m, 2H); IR (film) ν_{max} 3272, 3067, 2933, 1646, 1554, 1513, 1456, 1246, 1174, 1031, 641, 821cm^{-1}; FABHRMS (NBA–CsI) *m/z* 584.1535 (M + Cs^+, $C_{26}H_{33}N_3O_4$ requires 584.1535).

***N*-(8-Nonenylcarbonyl)-*N'*-benzyl-*N''*-(4-methoxybenzyl)iminodiacetic Acid Diamide (A1B1C3):** ^1H NMR ($CDCl_3$, 500 MHz) δ 9.65 (m, 1H, NH), 7.25 (m, 7H), 6.84 (m, 2H), 6.32 (two s, 1H, NH), 5.80 (m, 1H), 4.94 (m, 2H), 4.43 (m, 4H), 4.03 (m, 2H), 3.89 (m, 2H), 3.79 (m, 3H), 2.21 (m, 2H), 2.04 (m, 2H), 1.55 (m, 2H), 1.36 (m, 2H), 1.21 (m, 6H); IR (film) ν_{max} 3272, 3067, 2923, 2851, 1656, 1636, 1564, 1549, 1513, 1462, 1246, 1174, 1031 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 626.2006 (M + Cs^+, $C_{29}H_{39}N_3O_4$ requires 626.1995).

***N*-(9-Decenylcarbonyl)-*N'*-benzyl-*N''*-(4-methoxybenzyl)iminodiacetic Acid Diamide (A1B1C4):** ^1H NMR ($CDCl_3$, 500 MHz) δ 9.50 (m, 1H), 7.27 (m, 7H), 6.83 (m, 2H), 6.50 (two s, 1H), 5.81 (m, 1H), 4.96 (m, 2H), 4.43 (m, 4H), 4.01 (apparent d, 2H), 3.88 (broad s, 2H), 3.77 (m, 3H), 2.18 (m, 2H), 2.03 (m, 2H), 1.52 (m, 2H), 1.25 (m, 2H), 1.25 and 1.22 (two s, 8H); IR (film) ν_{max} 3262, 3077, 2923, 2851, 1656, 1641, 1564, 1549, 1513, 1462, 1246, 1174, 1031 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 640.2165 (M + Cs^+, $C_{30}H_{41}N_3O_4$ requires 640.2151).

General Procedure for the Third Diversification of Library 1: Preparation of A2B2C1–4. A stock solution was prepared by diluting a mixture of 2.5 mmol of each ω-alkene carboxylic acid (**C1–C4**) and 45 mmol of *i*-Pr_2NEt to 100 mL in anhydrous DMF. A 4.97 mL sample of this stock solution (0.497 mmol of **CX**) was added to **A2B2**•HCl (0.746 mmol). After the addition of PyBrOP (348 mg, 0.746 mmol), the mixture was stirred for 16 h at 25 °C. Work-up as described provided 102 mg (41%) of the title mixture as a light yellow oil. The ^1H NMR spectrum showed the vinyl protons ($CH=CH_2$) as two multiplets at δ 5.70 and 4.96, respectively. The MS exhibited all the expected molecular ions: ESMS (M + H^+) *m/z* 536, 522, 480, 466.

General Procedure for the Synthesis of Individual Homodimer Sublibrary Entries in Library 1: Preparation of A1B1C1–A1B1C1. A solution of **A1B1C1** (22 mg, 0.050 mmol) and $RuCl_2(PCy_3)_2$=CHPh (10 mg, 0.12 mmol) in $CHCl_3$ (2 mL) was warmed at reflux for 16 h. The solvent was removed *in vacuo* and chromatography (SiO_2, 1.5 × 20 cm, 50–100% EtOAc–hexane and 5% CH_3OH–EtOAc) afforded 14 mg (66%) of **A1B1C1–A1B1C1** as a yellow oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.47 (broad s, 2H, NH), 7.23 (m, 16H, fourteen aromatic and two NH), 6.81 (m, 4H), 5.20 (two br s, 2H), 4.40 (m, 8H), 3.77 (m, 14H), 2.18 (m, 4H), 1.90 (m, 4H), 1.52 (m, 4H); IR (film) ν_{max} 3272, 3067, 2933, 2851, 1651, 1559, 1513, 1456, 1400, 1400, 1303, 1246, 1174, 1026, 1026, 959, 821, 739, 697 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 979.3337 (M + Cs^+, $C_{48}H_{58}N_6O_8$ requires 979.3370).

A1B1C2–A1B1C2: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.60 (m, 2H), 7.26 (m, 16H, fourteen aromatic and two NH), 6.81 (m, 4H), 5.28 (br s, 2H), 4.40 (m, 8H), 3.77 (m, 14H), 2.17 (br s, 4H), 1.94 (br s, 4H), 1.50 (br s, 4H), 1.27 (m, 4H); the *trans*:*cis* ratio was established by ^1H NMR integration (600 MHz, C_6D_6) δ 5.37 and 5.42 (3.2:1); IR (film) ν_{max} 3272, 3067, 2933, 2851, 1652, 1558, 1514, 1456, 1431, 1303, 1249, 1203, 1180, 1133, 1026, 964, 805, 697 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 1007.3638 (M + Cs^+, $C_{50}H_{62}N_6O_8$ requires 1007.3683).

A1B1C3–A1B1C3: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.65 (m, 2H, NH), 7.27 (m, 14H), 6.82 (m, 4H), 6.60 (m, 2H, NH), 5.37 (m, 2H), 4.40 (m, 8H), 4.00 (m, 4H), 3.86 (br s, 4H), 3.78 and 3.77 (two s, 6H), 2.19 (m, 4H), 1.60 (m, 4H), 1.53 (m, 4H), 1.32 (m, 4H), 1.22 (m, 12H); IR (film) ν_{max} 3262, 3056, 2923, 2851, 1662, 1651, 1564, 1513, 1451, 1246, 1174, 1144, 1113, 1026, 959, 892, 856, 821 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 1091.4671 (M + Cs^+, $C_{56}H_{74}N_6O_8$ requires 1091.4622).

A1B1C4–A1B1C4: ^1H NMR ($CDCl_3$, 500 MHz) δ 9.60 (m, 2H, NH), 7.26 (m, 14H), 6.82 (m, 4H), 6.60 (m, 2H, NH), 5.38 (m, 2H), 4.40 (m, 8H), 4.00 (m, 4H), 3.86 (br s, 4H), 3.78 and 3.77 (two s, 6H), 2.19 (m, 4H), 1.97 (m, 4H), 1.52 (m, 4H), 1.32 (m, 4H), 1.22 (m, 16H); IR (film) ν_{max} 3272, 3067, 2923, 1646, 1559, 1513, 1451, 1246, 1174, 1031 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 1119.4985 (M + Cs^+, $C_{58}H_{78}N_6O_8$ requires 1119.4985).

General Procedure for the Synthesis of a Homodimer Sublibrary for Library 1. A solution of **A1B1C1–4** (39 mg, 0.082 mmol) and $RuCl_2(PCy_3)_2$=CHPh (17 mg, 0.021 mmol) in $CHCl_3$ (2 mL) was warmed at reflux for 16 h. The solvent was removed *in vacuo* and chromatography (SiO_2, 1.5 × 20 cm, 50–100% EtOAc–hexane and 5% CH_3OH–EtOAc) afforded 26 mg (67%) of the homodimer sub-library as a yellow oil. The ^1H NMR spectrum exhibited the olefinic protons (CH=CH) as a multiplet at δ 5.35. The MS exhibited all the molecular ions (10 different components with 9 different molecular weights) : ESMS (M + H^+) *m/z* 987, 973, 959, 931, 917, 903, 875, 861, 847.

General Procedure for the Synthesis of a Homodimer/Heterodimer Sublibrary for Library 1. A solution of

A3B3C1–4 (11 mg, 0.020 mmol), **A4B4C1–4** (12 mg, 0.020 mmol), and $RuCl_2(PCy_3)_2$=CHPh (8.2 mg, 0.01 mmol) in $CHCl_3$ (2 mL) was warmed at reflux for 16 h. The solvent was evaporated and chromatography (SiO_2, 1.5 × 20 cm, 50–100% EtOAc–hexane and 5–15% CH_3OH–EtOAc) afforded 14 mg (62%) of the sublibrary as a yellow oil. The ^1H NMR spectrum showed the olefinic protons (CH=CH) as a multiplet at δ 5.35. The MS exhibited all the expected molecular ions (36 different components which have 17 different molecular weights): ESMS (M + H^+) *m/z* 1248, 1234, 1220, 1206, 1192, 1178, 1164, 1150, 1136, 1122, 1108, 1094, 1080, 1066, 1052, 1038, 1024.

General Procedure for Preparation of 7 (Library 2) : *N,N′*-Bis(*N*-(2-(3,4-dimethoxyphenyl)ethyl) carboxamidomethyl)-*N,N′*-bis(*N*-(2-(4-fluorophenyl)ethyl)carboxamidomethyl)-*N′′*-((*tert*-butyloxy)carbonyl)iminodiacetic Acid Diamide (Library 2, 7: A1B9). The Boc derivative **3** (**A1B9** 1.29 g, 2.50 mmol) was stirred in a solution of 4 M HCl–dioxane (13 mL) at 25 °C for 4 h. Removal of the solvent under N_2 and *in vacuo* gave the deprotected material as a pale yellowish solid, which was dissolved in anhydrous DMF (10 mL). *N*-BOC-Iminodiacetic acid (194 mg, 0.83 mmol), *i*-Pr_2NEt (1.30 mL, 7.49 mmol) and PyBrOP (1.16 g, 2.50 mmol) were added sequentially. The reaction mixture was stirred for 16 h at 25 °C before being diluted with EtOAc (100 mL) and washed with 10% aqueous HCl (2 × 100 mL), saturated aqueous $NaHCO_3$ (2 × 100 mL), saturated aqueous NaCl (100 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure to provide 859 mg (100%) of the title substance in oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.90–7.70 (m, 4H, NH), 7.09 (apparent br s, 4H), 6.90 (apparent br s, 4H), 6.71 (apparent br s, 6H), 4.01 (m, 8H), 3.77 (apparent br s, 16H), 3.40 (m, 8H), 2.74 (m, 8H), 1.35 (apparent br s, 9H); IR (film) ν_{max} 3276, 3074, 2939, 1661, 1565, 1509, 1464, 1414, 1369, 1333, 1256, 1236, 1154, 1026, 831, 759 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 1164.3933 (M + Cs^+, $C_{53}H_{67}N_7O_{12}F_2$ requires 1164.3870).

***N,N′*-Bis(*N*-(2-(3-methoxyphenyl)ethyl)carboxamidomethyl)-*N,N′*-bis(*N*-(2-(4-methoxyphenyl)ethyl)carboxamidomethyl)-*N′′*-((*tert*-butyloxy)carbonyl)iminodiacetic Acid Diamide (7: A2B2):** ^1H NMR ($CDCl_3$, 500 MHz) δ 8.90–7.30 (m, 4H, NH), 7.07 (m, 6H), 6.78 (m, 10H), 4.02 (m, 8H), 3.74 (m, 16H), 3.45 (m, 8H), 2.76 (m, 8H), 1.41 (m, 9H); IR (film) ν_{max} 3272, 3076, 2933, 2831, 1662, 1610, 1585, 1513, 1462, 1405, 1364, 1303, 1246, 1164, 1036, 964, 903, 841, 780, 739, 697 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 1128.4125 (M + Cs^+, $C_{53}H_{69}N_7O_{12}$ requires 1128.4059).

***N,N′*-Tetra(*N*-(2-(*N*-α-CBZ-L-lysine Methyl Ester)carboxamidomethyl)-*N′′*-((*tert*-butyloxy)carbonyl) iminodiacetic Acid Diamide (7: A3B11):** ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (m, 20H), 5.80 (m, 4H), 5.07 (d, 8H), 4.28 (m, 4H), 4.10 (m, 24H), 3.20 (m, 8H), 1.70 (m, 8H), 1.40 (m, 25H); IR (film) ν_{max} 3301, 3077, 2944, 2862, 1713, 1656, 1539, 1456, 1436, 1344, 1256, 1215, 1169, 1051, 1031, 913, 846, 780, 739, 697 cm^{-1}; FABHRMS (NBA–NaI) *m/z* 1590.7336 (M + Na^+, $C_{77}H_{105}N_{11}O_{24}$ requires 1590.7232).

General Procedure for the Preparation of 8 (Library 2): A1B13C1–4. A stock solution was prepared through diluting a mixture of 2.5 mmol of each ω-alkene carboxylic acid (**C1–C4**) and 45 mmol of *i*-Pr_2NEt to 100 mL of anhydrous DMF. A 0.591 mL sample of this stock solution (0.0591 mmol of **CX**) was added to **A1B13**•HCl (0.887 mmol) followed by PyBrOP (41.3 mg, 0.887 mmol) and the mixture was stirred at 25 °C for 16 h. Work-up as described above provided 50 mg (88%) of the title substance as a light yellow oil. The ^1H NMR spectrum shows the vinyl protons (CH=CH_2) as two multiplets at δ 5.70 and 4.96, respectively. The MS exhibited all the expected molecular ions: ESMS (M + Na^+) *m/z* 1027, 998, 956, 928.

A1B4C1–4: The ^1H NMR spectrum shows the vinyl protons (CH=CH_2) as two multiplets at δ 5.70 and 4.96, respectively. The MS exhibited all the expected molecular ions: ESMS (M + Na^+) *m/z* 1159, 1131, 1089, 1061.

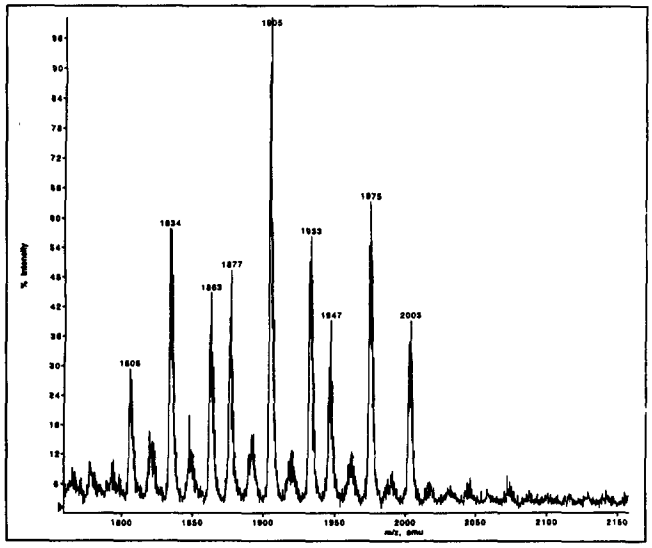


Figure 3. ESMS of the tetramer homodimer sublibrary (**9**) derived from **A1B13C1-C4** (10 components with 9 different molecular weights)

A3B14C1–4: The ^{1}H NMR spectrum shows the vinyl protons (CH=CH_2) as two multiplets at δ 5.70 and 4.96, respectively. The MS spectrum exhibited all the expected molecular ions: ESMS (M + Na^+) *m/z* 1369, 1341, 1299, 1271.

General Procedure for the Synthesis of a Homodimer Sublibrary for Library 2 (Tetramers). A solution of **A1B13C1–4** (36 mg, 0.038 mmol), and $RuCl_2(PCy_3)_2$=CHPh (6.2 mg, 0.0075 mmol) in $CHCl_3$ (3 mL) was warmed at reflux for 16 h. The solvent was evaporated and chromatography (SiO_2, 1.5 × 20 cm, 50–100% EtOAc–hexanes and 5–25% CH_3OH–EtOAc) afforded 24 mg (68%) of the sublibrary as a yellow oil. The ^{1}H NMR spectrum shows the olefinic protons (CH=CH) as a broad singlet at δ 5.30. The MS exhibited all the expected molecular ions (10 different components which have 9 different molecular weights): ESMS (M + Na^+) *m/z* 2003, 1975, 1947, 1933, 1905, 1877, 1863, 1834, 1806 (Figure 3).

Acknowledgments. We gratefully acknowledge that the financial support of the work was provided by Johnson and Johnson and The Skaggs Institute for Chemical Biology.

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