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Synthesis of Diverse Macrocyclic Peptidomimetics Utilizing Ring-Closing Metathesis and Solid-Phase Synthesis

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The synthesis of a range of highly functionalized peptidomimetic macrocycles has been accomplished using ring-closing metathesis and enyne tandem cross-metathesis−ring-closing metathesis reactions. This approach gives access to rigidified macrocycles modeled on the structures of cyclic peptides and designed to be biologically stable. The potential for peripheral functionalization of these templates has been demonstrated using Diels−Alder reactions, palladium(0) coupling reactions, and amide formation both in the solution phase and using polymer-supported syntheses.

Introduction

Research on site-specific mutation of proteins involved in biologically important protein−protein interactions shows that the key residues for binding are often non-contiguous and grouped in areas of the molecules that are 15−30 Å across. Molecules that can span such distances usually contain long highly flexible chains whose orientation to maximize binding is entropically disfavored. Peptide chemistry and early combinatorial chemistry have generally focused on the solid-phase assembly of linear chains of building blocks. However, the conformational restrictions imposed within cyclic peptides make them useful probes for the investigation of biologically important systems.[1] Small cyclic peptides containing four to six amino acids have indeed the ability to display key pharmacophoric groups in well-defined three-dimensional orientation. Although these peptides are less susceptible to proteolysis, their linkages may still be labile in vivo. Peptidomemetics are generally designed with the aim of retaining or increasing the biological activity of the parent peptide while reducing metabolic degradation. The incorporation of all carbon bridging units into cyclic peptidomemetics can infer increased metabolic stability and conformational rigidity.[2] We were interested in producing novel small macrocyclic compounds of 15−18 ring size by using other building blocks besides α amino acids and other reactions besides amide bond construction. The new desired pharmacophore template should contain some rigidifying elements but should not be totally rigid, thus ensuring low entropy while enabling some relaxation into binding conformations. Pendant groups should be attached to the template to allow varied orientation in space. The assembly of the ring system should be short (<10 steps), divergent to enable combinatorial synthesis, and amenable to solid supported synthesis for ease of handling of large numbers of analogues. Computational analysis of the non-peptide-based macrocycles of basic structures **1** and **2** (Figure 1) revealed that the conformational rigidity imposed by the aromatic rings and the trans alkene moiety should give the desired receptor binding. We therefore envisioned that these novel potential pharmacophores would provide a basic scaffold for the facile attachment of diverse peripheral functionalities in addition to the hydrogen bond donor and acceptor units already present.

The use of the ring-closing metathesis reaction[3] for the elaboration of macrocyclic ring systems has been developed by Fürstner[4] and rapidly adopted by other groups.[5] Such macrocyclization reactions are noted for their mild reaction conditions, wide functional group tolerance, and the preference for cyclization over intermolecular side reactions.[3−4] We have ourselves recently employed alkene cross-metathesis and ring-closing metathesis for the

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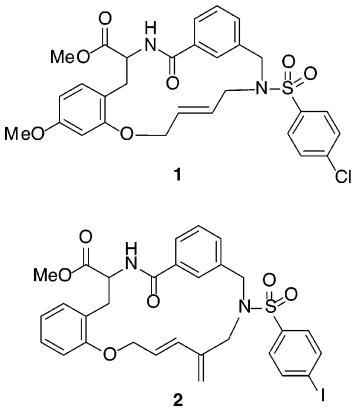
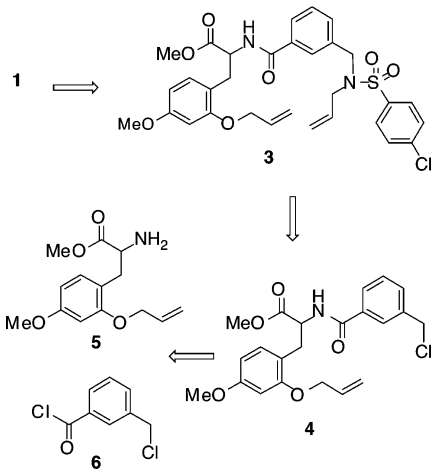


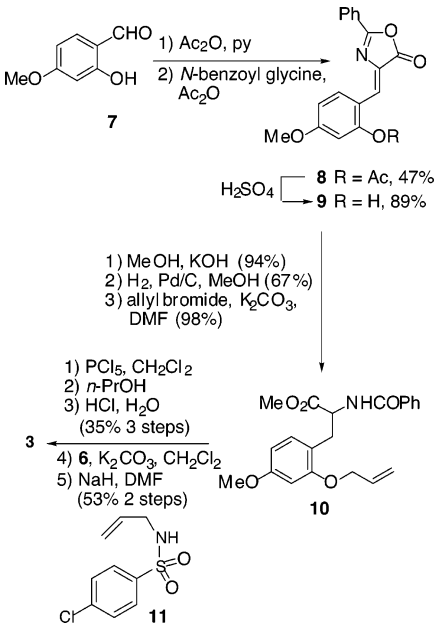
FIGURE 1. Target macrocyclic templates.

elaboration of delicate bioactive molecules such as β-lactams,[6] glycosphingolipids,[7] macrocyclic coronanes,[8] and hydroxyvitamin D_2 derivatives.[9] Consequently, we viewed macrocyclization by this method as crucial in our synthetic planning. Herein, we report the synthesis of macrocycles **1** and **2** and demonstrate the potential of the enhancement of diversity of **2** by functionalization of the diene, ester, and iodide groups using both solution-phase and polymer-supported parallel synthesis.

SCHEME 1. Retrosynthetic Analysis of Macrocycle 1



SCHEME 2. Synthesis of Metathesis–Macrocyclization Precursor 3



Results and Discussion

Synthesis of Macrocycles 1 and 2. We initially sought to synthesize the macrocycle **1** using the retrosynthetic plan outlined in Scheme 1. This route should be flexible and allow for access to a diverse set of macrocyclic compounds by simple variation in the amino acid and sulfonamide units. We considered that macrocyclization using a ring-closing metathesis reaction of diene **3** should provide the target cyclic peptidomimetic **1**. In turn, diene **3** should be available from amine **5** and acid chloride **6** via the amide **4** and *N*-alkylation.

The synthesis of racemic diene **3**, which is outlined in Scheme 2, utilized standard amino acid chemistry and hydrogenation of an intermediate dehydro-α-amido ester. Aldehyde **7** was condensed with acetic anhydride and *N*-benzoylglycine to provide the oxazolone **8**.[10] Deacetyl-

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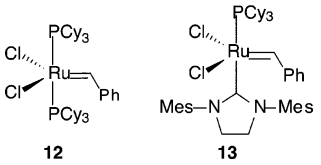
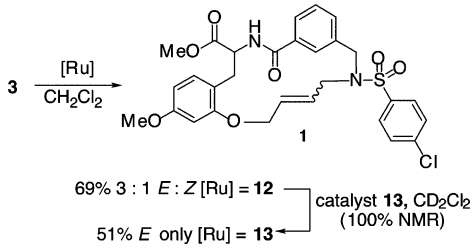


FIGURE 2. Catalysts employed for macrocyclization of **3**.

SCHEME 3. Ring-Closing Metathesis of Diene 3



ation and methanolysis gave the corresponding dehydro-α-amido ester, which was hydrogenated over palladium on carbon and *O*-allylated to provide benzamide **10**. Deacylation of amide **10** by formation of the imino chloride and imidate and hydrolysis[11] gave the corresponding primary amine. This was directly acylated using the acid chloride **6** and *N*-alkylated using the sulfonamide **11**[12] to produce the target diene **3**.

With precursor **3** in hand, its macrocyclization using the ruthenium catalysts **12** and **13** (Figure 2) under various high dilution conditions was examined (Scheme 3).[4,8] Using catalyst **12**,[13] the optimum procedure was found to be the slow syringe pump additions of the catalyst **12** to a solution of the diene **3** in dichloromethane at reflux. Under these conditions, the macrocyclic alkene **1** was formed in 69% yield as a mixture of cis and trans isomers (3:1). Using the second-generation Grubbs catalyst **13**,[14] the macrocyclization was accomplished under milder conditions and gave the macrocyclic amide **1** (51%), which was isolated solely as the trans isomer. Furthermore, when the 3:1 mix of isomers was allowed to further react with catalyst **13** (5 mol %), rapid and total isomerization to the trans isomer was observed. Such isomerization is consistent with reversible ring-closing metathesis with this catalyst.[15]

With the elaboration of the 16-membered macrocycle **1** successfully accomplished, attention was directed toward the second target macrocycle **2**, which would provide a versatile template for further late structural variation at the three points of diversity shown in Figure 3.

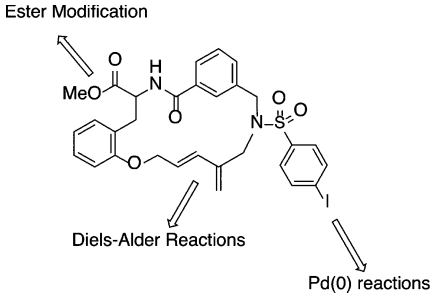
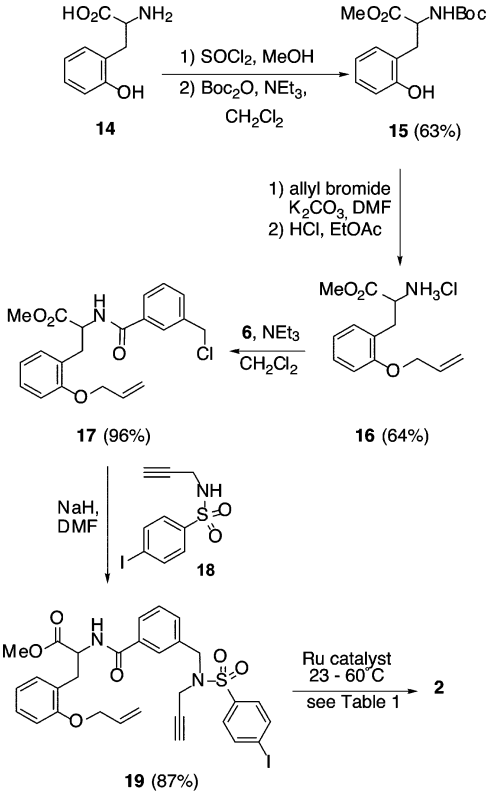


FIGURE 3. Projected late-stage diversification of scaffold **2**.

SCHEME 4. Synthesis of Macrocyclic Peptoid 2



The synthesis of the enyne **19** and its subsequent macrocyclization reaction to provide the second macrocyclic peptoid **2** are outlined in Scheme 4. Racemic *o*-tyrosine **14** was converted into the amine hydrochloride **16** by sequential esterification, Boc protection,[16] and *O*-allylation. Subsequent acylation using acid chloride **6** gave amide **17**, which was *N*-alkylated using the sulfonamide **18** to provide the enyne **19**. The requisite sulfonamide reagent **18** was, in turn, synthesized from 2-propynylamine and 4-iodobenzenesulfonyl chloride.

We have exploited the use of enyne metathesis[3a,17−19] for the preparation of a diverse range of 6-, 7-, and 8-membered mono-, bi-, and tricyclic β-lactams in the past, and with precursor **19** in hand, we anticipated that such a ring closing enyne metathesis should provide the target macrocycle **2**.[6b,20] These studies on the key enyne

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TABLE 1. Optimization of the Tandem Enyne Metathesis−Cross-Metathesis Macrocyclization To Provide 2[a]

entry	catalyst	solvent	*T* (°C)	ethylene	% **23**	% **2**
1	**12**	PhMe	60	no	0	<5
2	**12**	CH_2Cl_2	40	no	0	<5
3	**12**	CH_2Cl_2	40	yes	0	<5
4	**21**	CH_2Cl_2	40	no	0	0
5	**20**	PhMe	60−80	no	0	<5
6	**20**	CH_2Cl_2	reflux	no	0	<5
7	**20**	PhMe	60	yes	10 (32)[b]	15
8	**20**	CH_2Cl_2	reflux	yes	30	25
9	**20**	CH_2Cl_2	23	yes	25 (45)[b]	10
10[c]	**20**	$(CH_2Cl)_2$	40	yes	32	27
11	**22**	$(CH_2Cl)_2$	40	yes	22 (60)[b]	12
12	**13**	CH_2Cl_2	40	no	<5 (65)[c]	<5
13	**13**	$(CH_2Cl)_2$	23	yes	35[d]	56 (78)[e]
14	**13**	$(CH_2Cl)_2$	40	yes	30	44

[a] Reaction time was 24 h, ethylene bubbling continued until **19** was fully consumed (TLC), 10% catalyst employed. [b] Percent of recovered starting material. [c] 1 equiv of Ti(O*i*-Pr)$_4$ added. [d] **23** recycled once to give a further 22% of **2**. [e] Overall yield.

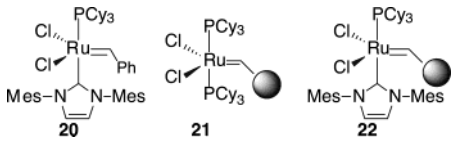

FIGURE 4. Additional catalysts examined for macrocyclization of enyne **19**.

macrocyclization[19] using the ruthenium catalysts **12**, **13**, and **20** and the boomerang supported catalysts **21** and **22** are summarized in Table 1 and Figure 4. The Grubbs catalyst **12** or its boomerang equivalent **21** were almost completely inactive in catalyzing the crucial macrocyclization reaction (entries 1−4).[13,21] The addition of ethylene[22] proved beneficial for macrocyclization reactions using the catalyst **20**[23] and led to efficient conversion of enyne **19** to triene **23** and diene **2** (entries 5−9) while the addition of the mild Lewis acid titanium tetraisopropoxide[24] (entry 10) or the use of the polymer-supported version of the catalyst **22**[25] (entry 11) had little effect.

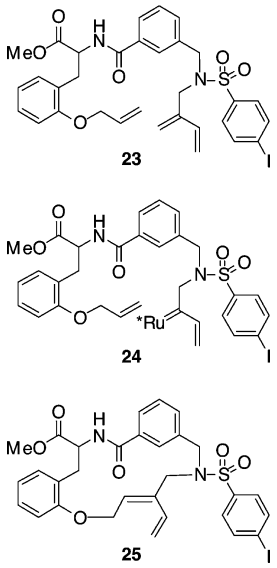

FIGURE 5.

Much to our delight, complete consumption of enyne **19** was observed after only 4 h reaction at room temperature using catalyst **13** (entries 12−14),[14] after which time ethylene addition was discontinued. After a further 24 h reaction, the products triene **23** and diene **2** were separated. The side product triene **23** was subsequently recycled to afford a further amount of macrocyclic product **2** (78% yield after one recycle). Increasing the reaction temperature had a deleterious effect on the yield, and the conditions employed in entry 13 were therefore used for the synthesis of diene **2** on a multigram scale. Significantly, **2** was isolated as the *E*-isomer and none of the cis alkene isomer was detected.

On the basis of these results, it is reasonable to suggest that the formation of diene **2** proceeds via the intermediacy of triene **23**. Intermediate **23** may have arisen either from an initial crossed enyne metathesis reaction between **19** and ethylene or from diene **25** and ring-opening metathesis with ethylene (Figure 5). Interestingly, none of the typical enyne product **25** was isolated. For this reason, we favor the higher probability of macrocyclization taking place through the formation of carbene **24**, which undergoes rapid metathesis with ethylene to provide triene **23.** A subsequent slower ring-closing metathesis of the allyl ether residue with the diene moiety in **23** occurs to provide the macrocycle **2**.[28] The formation of 1,3-dienes from alkynes has precedent,[19b,26] as have reactions that proceed via tandem ROM−RCM processes.[27] During the course of our studies, Shair and Lee have reported similar macrocyclization protocols.[29]

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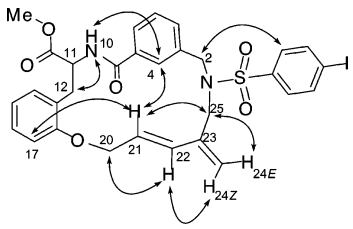

FIGURE 6. NMR conformational studies of macrocycle **2**.

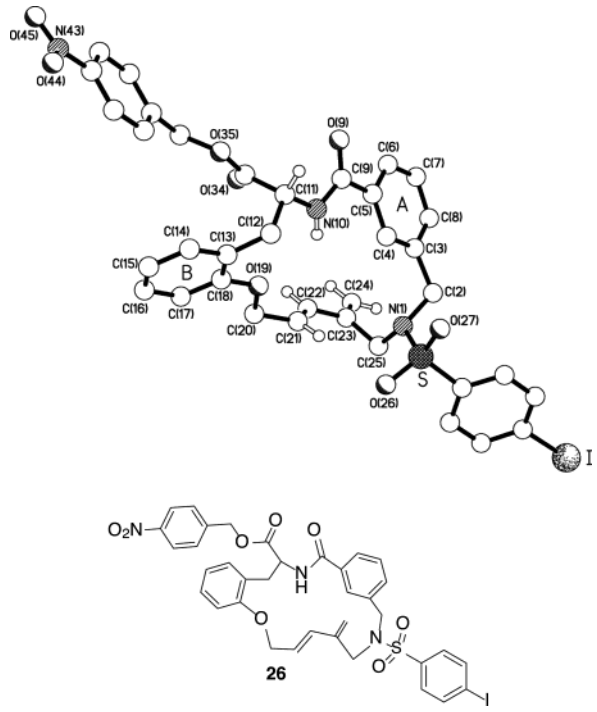

FIGURE 7. X-ray crystal structure of **26**.

The constitution and conformation of the macrocyclic product **2** in solution were confirmed by 2-D high field (750 MHz) NMR studies (Figure 6). Hence, the observation of an ROE between 24*Z*-H and 22-H, but not to 21-H, as well as an NOE from 21-H to 25-H clearly established the orientation of the double bond as the one depicted in Figure 6. This orientation was expected due to the steric interactions, which would have been involved between 21-H and 24*Z*-H in the alternative orientation. Many ROE's, such as the transannular ROE observed between 21-H and 4-H, can be used as restraints in molecular modeling for generating preferred conformations. Furthermore, local regions of conformational preference could be identified, such as the coupling between 12′-H and 11-H ($^3J_{11-12'} = 2.5$ Hz), indicating a preferred gauche orientation between these two protons. Interestingly, these NMR studies could not exclude the presence of a given low percentage conformation in fast dynamic exchange in solution. The cyclic nature of **2** combined with the NMR restraints observed could be further exploited to determine the possible low energy conformations of the macrocycle.

The solid-state structure of **2** was determined from a single-crystal X-ray study of the corresponding 4-nitrobenzyl ester **26** and is illustrated in Figure 7. The central 17-membered macrocycle has a distinctly puckered and self-filling conformation with its two phenyl rings, A and B, inclined by ca. 71°. The amide group is rotated by ca. 20° out of the plane of ring A and the olefinic group by ca. 63° out of that of ring B. A perhaps unusual feature of the macrocycle geometry is the coplanarity of the olefinic and vinylic groups [the torsional twist about C(22)−C(23) is 179°]. This geometry, however, does not give rise to any apparent delocalization, the C(22)−C(23) bond length being typical of a C(sp^2)−C(sp^2) single bond and the overall pattern of bonding does not differ significantly from that observed in other cyclic systems where these two groups are appreciably rotated with respect to each other.[30] Although the amide and olefinic groups are steeply inclined to each other (ca. 71°) the distance from the amide N(10)−H hydrogen atom to the C(21)═C(22) bond is too long for any N−H···π interaction [the shortest contact is to C(21) at 3.2 Å]. Indeed the only potential transannular interaction is an N−H···O hydrogen bond to O(19), but although the N···O distance of 2.99 Å is reasonable, the H···O distance (2.41 Å) is on the long side for any appreciable bonding interaction.

With the macrocyclic template **2** accessible in sufficient quantities, its further diversification using both solution- and solid-phase chemistry was examined.

Functionalization of Macrocycle 2 in the Solution Phase. As outlined in Figure 3, macrocycle **2** has three key functional groups that are available for modification and library synthesis: the diene, the ester, and the aryl iodide. Diels−Alder reactions with the diene unit were initially investigated (Scheme 5). Pleasingly, cycloaddition of diene **2** with *N*-phenylmaleimide **27** and tetracyanoethylene provided adducts **28** (60%) and **31** (52%). No apparent influence of the remote amino acid derived chiral center was observed and both **28** and **31** were obtained as 1:1 mixtures of endo-diastereoisomers. The structures of these adducts were confirmed by 1- and 2-D NMR studies. The aryl iodide functionality was appropriate for palladium(0) catalyzed transformations. Thus, the Diels−Alder adduct **28** was allowed to react under Suzuki coupling[31] with 3-nitrobenzeneboronic acid **29** to afford the corresponding biphenyl **30** (76%). One of the diastereoisomers of the adduct **30** was separated by chromatography and subsequent crystallization and shown to be the endo isomer by NOE analysis. Surprisingly, although the Suzuki coupling reaction of iodide **28** proceeded uneventfully, the parent diene **2** failed to undergo a similar coupling under a variety of conditions. This was possibly due to binding of the diene unit to a palladium(0) intermediate, thereby disfavoring catalytic turnover. The ester group in macrocycle **2** was readily transformed into the carboxylic acid **32** (87%) and subsequently coupled to glycine methyl ester hydrochloride **35** to afford the dipeptide **33** (58%). The resultant

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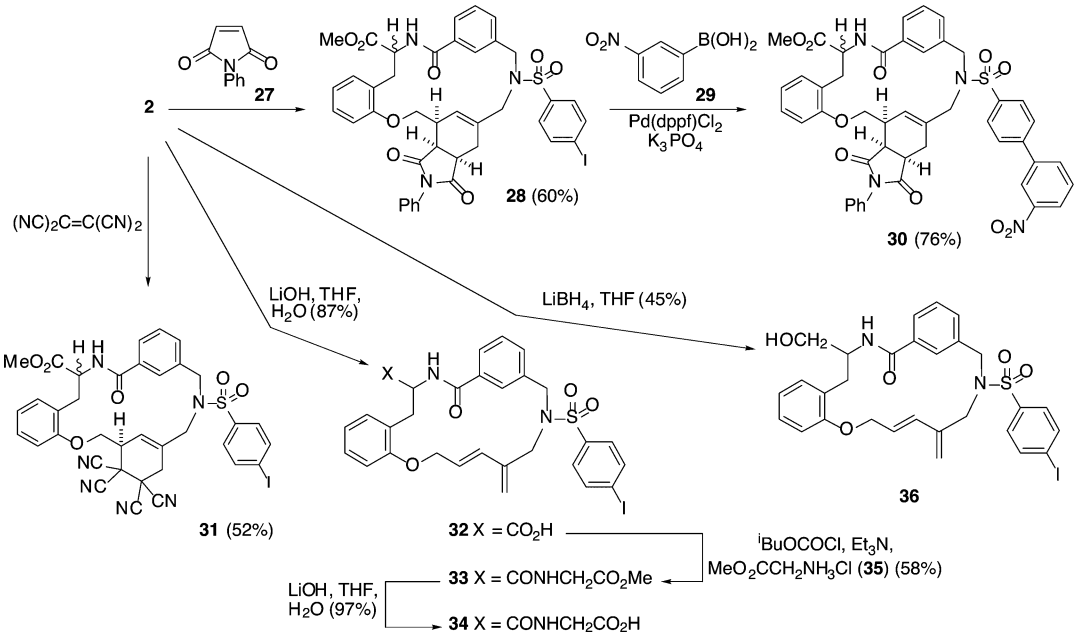
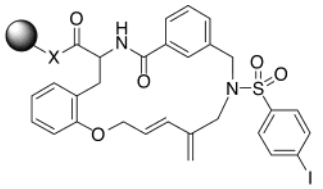
SCHEME 5. Diversification of the Macrocyclic Template in the Solution Phase



ester **33** was in turn saponified to provide **34**, thereby constituting a single amino acid extension of the macrocyclic scaffold and exploiting a further point of diversity. Reduction of ester **2** to its corresponding alcohol **36** was also readily carried out using lithium borohydride albeit in modest unoptimized yield (45%). Having demonstrated that all three key diversification reactions of the macrocyclic template **2** were possible, attention was directed toward related solid-supported syntheses.

Diversification of the Macrocycle 2 Using Solid-Supported Synthesis. Carboxylic acid **32** was immobilized onto Wang resin using coupling conditions[32] with 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole in the presence of *N*-methylimidazole. This gave resin **37** with a modest loading level (0.41 mmol/g) (Figure 8). In



37 X = O, Wang resin, 0.41 mmol.g^{-1}
38a X = NHCH$_2$CO$_2$, Wang resin, 0.33 mmol.g^{-1}
38b X = NHCH$_2$CO$_2$, Wang resin, 0.54 mmol.g^{-1}
39 X = NH, Rink resin, 0.32 mmol.g^{-1}

FIGURE 8. Immobilization of the macrocyclic template on solid support.

contrast, carbodiimide-coupling reactions proved ineffective as a method of attachment to the Wang resin, presumably due to steric hindrance suppressing the reactivity of the intermediate. Representative Diels–Alder reactions were carried out on resin **37** using a 10-fold excess of dienophile and subsequent mild cleavage from the support using trifluoroacetic acid in dichloromethane (1:9). This provided the Diels–Alder products **40**, **41**, and **43** in excellent yields and reasonable purities (Figure 9). In this manner, cycloadducts **40**, **41**, and **43**

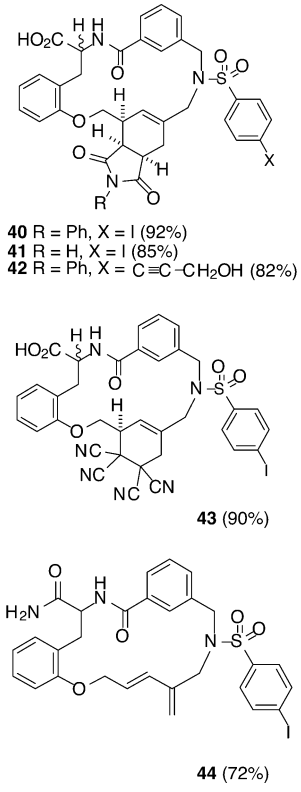


FIGURE 9. Diversification of the macrocyclic template by solid-phase synthesis.

were obtained as 1:1 mixtures of diastereoisomers as established by ^{1}H NMR spectroscopy. As a representative example of palladium(0)-catalyzed coupling of the aryl iodide, a Sonogashira coupling reaction[33] was successfully undertaken. Thus, the resin **37** was allowed to react with the dienophile *N*-phenylmaleimide followed by 2-propyn-

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1-ol in the presence of $Pd(PPh_3)_2Cl_2$ and copper(I) iodide. Subsequent cleavage using trifluoroacetic acid gave alkyne **42** in excellent overall yield.

The potential for further solid-phase diversification of the macrocyclic template was demonstrated by converting acid **32** into acid **34** and subsequently coupling the latter to Wang resin to provide resin **38a**. More conveniently, acid **32** was directly linked to commercial preloaded glycine-Wang resin through a peptide coupling reaction using PyBop and HOBt, which gave resin **38b** with a superior loading.[34] In the same way, the carboxylic acid **32** was immobilized on commercial RINK amide resin to provide resin **39**. Subsequent cleavage of resins **38b** and **39** using trifluoroacetic acid gave acid **34** (65%) and amide **44** (72%) in good yields and purities, indicating that these resins are suitable for further solid-phase synthesis.

Conclusion

In conclusion, we have demonstrated the power of ring-closing metathesis in the synthesis of polyfunctional macrocyclic peptoid alkenes and dienes. Both 16- and 17-membered ring systems were prepared, respectively, using a diene RCM and an enyne tandem CM-RCM process. The diversification of diene **2** was accomplished using solution and solid-phase synthesis and thereby demonstrated the potential to prepare libraries of analogues of this template.

Experimental Section

Methyl *N*-(3-(*N*-(2-Propen-1-yl)(4-chlorophenyl)sulfonamidomethyl)benzoyl)-*O*-methyl-2-(2-propen-1-yloxy)-tyrosinate (3). K_2CO_3 (33 mg, 0.24 mmol) and chloride **6** (34 μL, 0.24 mmol) were added to amine **5** (60 mg, 0.24 mmol) in dry CH_2Cl_2 (6 mL). The mixture was stirred at room temperature for 20 h, filtered through Celite, and rotary evaporated. Chromatography (CH_2Cl_2/EtOAc 9:1) gave amide **4** (81 mg, 81%) as a colorless oil: $R_f = 0.51$ (CH_2Cl_2/EtOAc 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.74 (m, 4H), 7.05−7.10 (m, 2H), 6.46−6.49 (m, 2H), 6.00−6.09 (m, 1H), 5.54 (dd, J = 17.3, 1.0 Hz, 1H), 5.30 (d, J = 10.0 Hz, 1H), 4.87 (q, J = 6.5 Hz, 1H), 4.57−4.61 (m, 4H), 3.80 (s, 3H), 3.77 (s, 3H), 3.21 (d, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 166.6, 160.1, 156.8, 137.9, 132.8, 131.7, 131.6, 128.9, 127.3, 127.0, 117.8, 117.3, 105.2, 100.1, 69.4, 55.4, 54.4, 52.3, 45.6, 31.6; MS (CI) m/z 418 $(M + H)^+$, 384, 379, 366, 313, 256; HRMS (CI) calcd for $C_{22}H_{25}ClNO_5$ $(M + H)^+$ 418.1427, found 418.1421. The crude amide **4** was used directly in the next step without further purification. Allylamine (3.75 mL, 50 mmol) was added to 4-$ClC_6H_4SO_2Cl$ (10.6 g, 50 mmol) and K_2CO_3 (6.91 g, 50 mmol) in CH_2Cl_2 (60 mL). After the mixture was stirred for 3 h, H_2O (13 mL) and 10% aqueous HCl (25 mL) were added. The organic phase was separated, successively washed with 10% aqueous HCl, saturated $NaHCO_3$, and H_2O, dried ($MgSO_4$), and rotary evaporated to give a yellow solid which was recrystallized from PhMe to give sulfonamide **11**[12] (6.7 g, 58%) as colorless needles: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 5.67−5.80 (m, 1H), 5.12−5.23 (m, 2H), 4.57 (br s, 1H), 3.62−3.67 (m, 2H). NaH (7.5 mg, 0.19 mmol) was added to sulfonamide **11** (65 mg, 0.28 mmol) in dry DMF (1 mL) and the mixture was stirred until homogeneous. Chloride **4** (78 mg, 0.19 mmol) in DMF (2 mL) was added dropwise and stirring continued for 20 h. The mixture was poured into H_2O (10 mL), extracted with CH_2Cl_2 (20 mL), and the combined organic extracts were rotary evaporated. The resultant oily residue was chromatographed (hexanes/EtOAc 2:1) to yield amide **3** (76 mg, 66%) as a colorless foam: $R_f = 0.34$ (hexanes/EtOAc 1:1); IR 1740, 1657, 1605 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 7.33−7.76 (m, 6H), 7.03−7.08 (m, 2H), 6.47−6.50 (m, 2H), 6.01−6.09 (m, 1H), 5.40−5.50 (m, 3H), 5.29 (dd, J = 10.5, 1.0 Hz, 1H), 5.04−5.11 (m, 2H), 4.86 (q, J = 6.5 Hz, 1H), 4.59 (d, J = 5.0 Hz, 2H), 4.37 (s, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.20 (d, J = 5.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 166.7, 160.1, 157.4, 139.2, 138.8, 136.3, 134.4, 132.9, 131.62, 131.55, 129.5, 128.8, 128.6, 127.3, 126.4, 120.1, 117.8, 117.2, 105.3, 105.3, 100.1, 69.4, 55.4, 54.3, 52.3, 50.0, 49.8, 31.7; MS (CI) m/z 630 $(M + NH_4)^+$, 613 $(M + H)^+$; HRMS (FAB) calcd for $C_{31}H_{34}ClN_2O_7S$ $(M + H)^+$ 613.1800, found 613.1795.

Methyl 17-((4-Chlorophenyl)sulfonyl)-9-methoxy-2-oxo-12-oxa-3,17-diazatricyclo(17.3.1.0^{6,11}]trieicosa-1(23),6,8,10,14,19,21-heptaene-4-carboxylate (1). (a) Synthesis Using Catalyst 12. Separate solutions of Grubbs catalyst **12** (2.7 mg, 0.0003 mmol) in CH_2Cl_2 (3 mL) and diene **3** (50 mg, 0.82 mmol) in CH_2Cl_2 (3 mL) were added over 5 h via syringe pumps to CH_2Cl_2 (30 mL) at reflux. Reflux was maintained for an additional 24 h when the mixture was rotary evaporated. The residue was chromatographed (hexanes/EtOAc 1:1) to yield macrocycle **1** (33 mg, 69%) as a chromatographically inseparable 3:1 mixture of trans and cis isomers as a white solid. Data for major (trans) isomer: mp 131−135 °C; R_f = 0.32 (hexanes/EtOAc 1:1); IR 1730, 1643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.0 Hz, 1H), 7.52−7.58 (m, 3H), 7.42−7.44 (m, 2H), 7.36 (d, J = 6.5 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 6.45 (dd, J = 8.5, 2.0 Hz, 1H), 6.35 (d, J = 2.0 Hz, 1H), 5.46 (dt, J = 15.5, 6.0 Hz, 1H), 5.80 (dt, J = 15.5, 6.5 Hz, 1H), 4.74 (dt, J = 9.5, 3.0 Hz, 1H), 4.58 (d, J = 14.0 Hz, 1H), 4.45 (dd, J = 12.0, 6.5 Hz, 1H), 4.31 (dd, J = 13.0, 6.0 Hz, 1H), 4.40 (d, J = 14.0 Hz, 1H), 3.80−3.88 (m, 1H), 3.76 (s, 3H), 3.74−3.76 (m, 1H), 3.70 (s, 3H), 3.17 (dd, J = 14.0, 9.5 Hz, 1H), 3.07 (dd, J = 14.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 167.7, 160.1, 156.8, 139.5, 135.1, 134.6, 132.5, 132.4, 130.8, 129.7, 129.5, 129.1, 128.6, 128.2, 128.1, 127.1, 117.4, 105.3, 99.5, 68.5, 55.6, 55.4, 52.4, 52.2, 50.4, 31.6; MS (CI) m/z 585 $(M + H)^+$; HRMS (CI) calcd for $C_{29}H_{30}ClN_2O_7S$ $(M + H)^+$ 585.1462, found 585.1473. **(b) Synthesis Using Catalyst 13.** Catalyst **13** (28 mg, 0.033 mmol) in CH_2Cl_2 (10 mL) was added to diene **3** (87 mg, 0.16 mmol) in CH_2Cl_2 (70 mL). After overnight stirring at room temperature, the mixture was rotary evaporated and the residue was chromatographed (hexanes/EtOAc 1:1) to yield macrocycle **1** (49 mg, 51%) as a white solid. ^{1}H and ^{13}C NMR spectra were consistent with the product **1** consisting solely of the trans isomer. **(c) *Z* to *E* Isomerization of Macrocycle 1 Using Catalyst 13.** Catalyst **13** (0.6 mg, 0.0007 mmol) in CD_2Cl_2 (0.7 mL) was added to macrocycle **1** (E/Z = 3:1) (8.5 mg, 0.015 mmol) in an NMR tube. ^{1}H NMR spectra were recorded periodically and complete isomerization to the trans isomer was observed to have taken place after 2 h.

Methyl *N*-(3-(*N*-(2-Propyn-1-yl)(4-iodophenyl)sulfonamidomethyl)benzoyl)(2-(2-propen-1-yloxy)phenyl)alaninate (19). Using the same procedure as for the synthesis of **3**, **19** (327 mg, 87%) was obtained as a colorless foam: R_f = 0.56 (hexanes/EtOAc 1:1); IR 1734, 1658 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.93 (m, 2H), 7.60−7.68 (m, 4H), 7.51−7.54 (m, 1H), 7.39−7.41 (m, 1H), 7.16−7.36 (m, 3H), 6.95−

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6.97 (m, 2H), 6.01−6.10 (m, 1H), 5.41−5.48 (m, 1H), 5.26−5.28 (m, 1H), 4.80−4.91 (m, 1H), 4.64−4.66 (m, 2H), 4.37 (s, 2H), 3.92 (s, 2H), 3.76 (s, 3H), 3.28 (d, J = 6.5 Hz, 2H), 2.05 (t, J = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 166.7, 156.4, 138.4, 138.3, 135.1, 134.6, 133.0, 132.0, 131.3, 129.3, 129.0, 128.8, 127.5, 127.0, 125.1, 121.4, 117.7, 112.4, 100.5, 75.6, 74.9, 69.4, 54.3, 52.4, 49.7, 35.9, 32.2; MS (FAB) m/z 673 $(M + H)^+$; HRMS (FAB) calcd for $C_{30}H_{30}IN_2O_6S$ $(M + H)^+$ 673.0869, found 673.0858. Anal. Calcd for $C_{30}H_{29}IN_2O_6S$: C, 53.58; H, 4.35; N, 4.17. Found: C, 53.38; H, 4.45; N, 4.26.

Methyl 18-((4-Iodophenyl)sulfonyl)-16-methylidene-2-oxo-12-oxa-3,18-diazatricyclo[18.3.1.0^{6,11}]tetraeicosa-1(24),6,8,10,14,20,22-heptaene-4-carboxylate (2). Ethylene was bubbled through catalyst **13** (52 mg, 0.060 mmol) in $ClCH_2CH_2Cl$ (40 mL). After 15 min, **19** (0.40 g, 0.60 mmol) in $ClCH_2CH_2Cl$ (40 mL) was added. Maintaining ethylene bubbling, the mixture was stirred for 4 h at room temperature until enyne **19** was consumed (TLC). The ethylene bubbling was stopped, the mixture stirred for a further 24 h and filtered through silica. Rotary evaporation and chromatography (hexanes/EtOAc 2:1) gave **2** (228 mg, 56%) as a white solid and **23** (145 mg, 35%) as an oil. Triene **23** (145 mg, 0.21 mmol) in $ClCH_2CH_2Cl$ (10 mL) was allowed to react with catalyst **13** (18 mg, 0.021 mmol) in $ClCH_2CH_2Cl$ (10 mL), and the mixture was stirred under N_2 for 24 h to afford a further amount of macrocycle **2** (90 mg, 22%, 78% overall yield) after chromatography. Triene **23**: R_f = 0.55 (hexanes/EtOAc 1:1); IR 1737, 1652, 1522 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2H), 7.41−7.62 (m, 3H), 7.14−7.35 (m, 6H), 6.87−7.09 (m, 3H), 6.18 (dd, J = 18.0, 11.0 Hz, 1H), 5.99−6.08 (m, 1H), 5.44 (d, J = 1.5 Hz, 1H), 5.40 (d, J = 1.5 Hz, 1H), 5.26−5.30 (m, 2H), 4.89−5.06 (m, 2H), 4.60 (dd, J = 3.5, 1.0 Hz, 2H), 4.28−4.35 (m, 2H), 3.97 (d, J = 15.5 Hz, 1H), 3.89 (d, J = 15.5 Hz, 1H), 3.75 (s, 3H), 3.25 (d, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 166.6, 156.5, 139.5, 139.1, 138.4, 136.5, 136.0, 133.9, 133.0, 131.4, 131.3, 128.7, 128.6, 128.5, 127.2, 126.2, 125.0, 121.3, 119.1, 117.7, 115.6, 112.2, 100.0, 69.3, 54.0, 52.3, 51.0, 49.6, 32.3; MS (FAB) m/z 701 $(M + H)^+$, 400, 267; HRMS (FAB) calcd for $C_{32}H_{34}IN_2O_6S$ $(M + H)^+$ 701.1182, found 701.1207. Diene **2**: mp 119−122 °C (EtOAc); R_f = 0.40 (hexanes/EtOAc 1:1); IR 1739, 1653, 1497 cm^{-1}; ^{1}H NMR (750 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 6.5 Hz, 1H), 7.24−7.29 (m, 2H), 7.19 (dd, J = 7.5, 2.0 Hz, 1H), 7.14−7.17 (m, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.55 (dt, J = 16.0, 6.5 Hz, 1H), 6.19 (d, J = 16.0 Hz, 1H), 5.18 (s, 1H), 5.11 (s, 1H), 4.76−4.81 (m, 1H), 4.51−4.53 (m, 2H), 4.21 (br d, J = 13.5 Hz, 1H), 4.14 (d, J = 13.5 Hz, 1H), 4.12 (br d, J = 13.5 Hz, 1H), 3.84 (d, J = 13.5 Hz, 1H), 3.69 (s, 3H), 3.33 (dd, J = 14.5, 9.0 Hz, 1H), 3.30 (dd, J = 14.5, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 168.4, 156.3, 139.2, 138.6, 137.2, 136.6, 135.0, 134.1, 131.8, 130.9, 128.8, 128.5, 128.3, 127.8, 126.5, 126.0, 125.4, 123.3, 121.5, 111.6, 100.6, 69.5, 55.7, 53.4, 52.4, 52.1, 32.12; MS (FAB) m/z 673 $(M + H)^+$, 495, 371; HRMS (FAB) calcd for $C_{30}H_{30}IN_2O_6S$ $(M + H)^+$ 673.0869, found 673.0870. Anal. Calcd for $C_{30}H_{29}IN_2O_6S$: C, 53.58; H, 4.35; N, 4.17. Found: C, 53.49; H, 4.17; N, 4.06. On a larger scale, ethylene was bubbled through catalyst **13** (260 mg, 0.31 mmol) in $ClCH_2CH_2Cl$ (250 mL). After 25 min, **19** (3.50 g, 5.20 mmol) in $ClCH_2CH_2Cl$ (250 mL) was added. Maintaining ethylene bubbling, the mixture was stirred for 5.5 h at room temperature until enyne **19** was consumed (TLC). The ethylene bubbling was stopped, and the mixture was stirred for a further 24 h and filtered through silica. Rotary evaporation and chromatography (hexanes/EtOAc 2:1) gave **2** (1.28 g, 37%) as a white solid and **23** (1.74 g, 48%) as an oil. Triene **23** (1.74 g, 2.48 mmol) in $ClCH_2CH_2Cl$ (100 mL) was allowed to react with catalyst **13** (100 mg, 0.12 mmol) in $ClCH_2CH_2Cl$ (100 mL), and the mixture was stirred under N_2 for 24 h to afford a further amount of macrocycle **2** (870 mg, 25%, 62% overall yield) after chromatography.

Methyl (1*S*,24*R*,28*S*)-20-((4-Iodophenyl)sulfonyl)-13,25,27-trioxo-26-phenyl-3-oxa-12,20,26-triazapentacyclo-[20.6.1.1^{14,18}.0^{4,9}.0^{24,28}]triaconta-4,6,8,14(30),15,17,22(29)-heptaene-11-carboxylate (28). *N*-Phenylmaleimide **27** (72 mg, 0.42 mmol) and diene **2** (190 mg, 0.28 mmol) in $ClCH_2CH_2Cl$ (0.5 mL) were heated at 40 °C for 48 h. Rotary evaporation and chromatography (hexanes/EtOAc 1:1) gave imide **28** (140.7 mg, 60%), a 1:1 mixture of diastereoisomers, as a white solid: mp 145−150 °C (hexanes−EtOAc); R_f = 0.25 (hexanes/EtOAc 1:1); IR 1738, 1642 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92−7.95 (m, 2H), 7.74−7.87 (m, 2H), 7.60 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.35−7.50 (m, 5H), 7.16−7.26 (m, 4H), 6.98−7.12 (m, 3H), 5.98 (br s, 0.5H), 5.78 (br s, 0.5 H), 5.15−5.18 (m, 0.5H), 4.41−4.64 (m, 1.5H), 4.27−4.38 (m, 1H), 4.00−4.12 (m, 1.5H), 3.73 (s, 1.5H), 3.70−3.73 (m, 0.5H), 3.67 (s, 1.5H), 3.30−3.40 (m, 4.5H), 3.14−3.27 (m, 1H), 3.04 (dd, J = 14.0, 1.5 Hz, 0.5H), 2.85 (br s, 0.5H), 2.64 (d, J = 15.5 Hz, 0.5H), 2.54 (d, J = 15.0 Hz, 0.5H), 2.20 (br s, 0.5H), 1.80−1.85 (m, 0.5 H), 1.06−1.11 (m, 0.5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 177.6, 176.2, 176.1, 172.2, 171.2, 167.9, 166.6, 157.3, 156.8, 139.5, 138.7, 137.9, 136.9, 136.7, 136.5, 135.3, 134.6, 134.0, 132.7, 132.1, 131.9, 131.6, 131.5, 130.7, 130.0, 129.7, 129.6, 129.3, 129.2, 129.1, 128.92, 128.86, 128.75, 128.6, 128.5, 128.1, 127.0, 126.9, 126.3, 126.2, 123.3, 122.7, 100.4, 100.2, 117.5, 114.4, 73.4, 71.5, 56.0, 55.8, 54.1, 53.3, 53.1, 52.4, 52.2, 42.0, 41.7, 39.9, 37.3, 36.8, 32.6, 31.1, 26.8, 26.0; MS (FAB) m/z 846 $(M + H)^+$, 786, 663, 557, 551; HRMS (FAB) calcd for $C_{40}H_{37}IN_3O_8S$ $(M + H)^+$ 846.1346, found 846.1381.

Methyl (1*S*,24*R*,28*S*)-20-((3′-Nitro-4-biphenylyl)sulfonyl)-13,25,27-trioxo-26-phenyl-3-oxa-12,20,26-triazapentacyclo[20.6.1.1^{14,18}.0^{4,9}.0^{24,28}]triaconta-4,6,8,14(30),-15,17,22(29)-heptaene-11-carboxylate (30). Iodide **28** (140.7 mg, 0.17 mmol), $Pd(dppf)Cl_2$ (7 mg, 0.0083 mmol), K_3PO_4 (106 mg, 0.50 mmol) and 3-nitrophenylboronic acid **29** (33.6 mg, 0.18 mmol) in dry degassed DME (1.2 mL) were allowed to react at room temperature for 24 h. H_2O (5 mL) and CH_2Cl_2 (20 mL) were added, and the organic layer was separated, dried (Na_2SO_4), and rotary evaporated. Chromatography (hexanes/EtOAc 1:1) gave imide **30** (103.0 mg, 76%), a 1:1 mixture of diastereoisomers, as a white solid: mp 148−150 °C (hexanes−EtOAc); R_f = 0.15 (hexanes/EtOAc 1:1); IR 1741, 1705, 1525 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 7.5 Hz, 1H), 8.27−8.30 (m, 1H), 7.95−8.03 (m, 3H), 7.81−7.86 (m, 3H), 7.75 (d, J = 7.5 Hz, 0.5H), 7.66−7.71 (m, 1H), 7.53 (d, J = 7.5 Hz, 0.5H), 7.36−7.50 (m, 4.5H), 7.17−7.32 (m, 4.5H), 7.08−7.14 (m, 1H), 6.97−7.05 (m, 2H), 5.99 (br s, 0.5H), 5.81 (br s, 0.5H), 5.14−5.18 (m, 0.5H), 4.69−4.72 (m, 1H), 4.51−4.56 (m, 1H), 4.41 (t, J = 10.5 Hz, 0.5H), 4.31 (dd, J = 10.0, 3.0 Hz, 0.5H), 4.27 (d, J = 9.5 Hz, 0.5H), 4.11−4.19 (m, 1H), 4.05 (d, J = 14.5 Hz, 0.5H), 3.79 (d, J = 14.5 Hz, 0.5H), 3.73 (s, 1.5H), 3.67 (s, 1.5H), 3.53 (d, J = 14.5 Hz, 0.5H), 3.42 (dd, J = 14.0, 3.0 Hz, 0.5H), 3.28−3.29 (m, 2H), 3.14−3.25 (m, 1.5H), 3.04 (d, J = 13.5 Hz, 0.5H), 2.87 (br s, 0.5H), 2.64 (d, J = 15.5 Hz, 0.5H), 2.54 (d, J = 14.5 Hz, 0.5H), 2.20 (br s, 0.5H), 1.80−1.86 (m, 0.5H), 1.06−1.16 (m, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 177.6, 176.2, 176.1, 172.2, 171.2, 167.9, 166.7, 157.2, 156.8, 148.8, 143.2, 143.1, 140.9, 140.8, 139.7, 138.2, 137.0, 136.8, 136.4, 135.4, 134.5, 133.9, 133.24, 133.19, 132.7, 132.2, 131.9, 131.6, 131.5, 130.2, 130.1, 129.9, 129.7, 129.6, 129.3, 129.2, 129.1, 128.9, 128.8, 128.7, 128.4, 128.2, 128.1, 128.03, 127.99, 127.1, 127.0, 126.9, 126.3, 126.2, 123.3, 123.2, 122.7, 122.3, 117.7, 114.4, 73.4, 71.5, 56.1, 55.9, 54.1, 53.4, 53.0, 52.4, 52.2, 51.4, 42.0, 41.7, 39.9, 39.8, 37.3, 36.8, 32.6, 32.1, 26.8, 26.0; MS (FAB) m/z 841 $(M + H)^+$, 663; HRMS (FAB) calcd for $C_{46}H_{41}N_4O_{10}S$ $(M + H)^+$ 841.2543, found 841.2515. Recrystallization from hexanes and EtOAc gave one diastereoisomer of imide **30** (29 mg, 21%) as colorless crystals: mp 147−149 °C (hexanes−EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (t, J = 2.0 Hz, 1H), 8.30 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 7.81−8.00 (m, 3H), 7.81−7.87 (m, 4H), 7.70 (t, J = 8.0 Hz, 1H), 7.43−7.50 (m, 3H), 7.35−7.40 (m, 2H), 7.17−7.23 (m, 4H), 7.08

(dd, J = 7.5, 1.5 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.00 (br s, 1H), 5.20 (m, 1H), 4.71 (d, J = 14.5 Hz, 1H), 4.41 (t, J = 10.5 Hz, 1H), 4.32 (dd, J = 10.5, 3.0 Hz, 1H), 4.18 (d, J = 13.5 Hz, 1H), 3.73 (d, J = 14.5 Hz, 1H), 3.67 (s, 3H), 3.43 (dd, J = 17.5, 3.0 Hz, 1H), 3.35 (d, J = 13.5 Hz, 1H), 3.15−3.21 (m, 3H), 2.70 (d, J = 15.5 Hz, 1H), 2.20 (br s, 1H), 1.06−1.16 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 176.2, 171.2, 166.6, 157.3, 148.8, 143.2, 140.9, 138.7, 138.2, 137.0, 136.8, 134.0, 133.2, 132.7, 131.9, 131.5, 130.2, 130.0, 129.4, 129.1, 128.9, 128.8, 128.22, 128.19, 128.1, 127.1, 126.9, 126.3, 123.3, 122.3, 117.6, 73.4, 56.1, 54.1, 53.4, 52.1, 41.7, 39.9, 37.3, 32.6, 26.8.

18-((4-Iodophenyl)sulfonyl)-16-methylidene-2-oxo-12-oxa-3,18-diazatricyclo[18.3.1.0^{6,11}]tetraeicosa-1(24),6,8,-10,14,20,22-heptaene-4-carboxylic Acid (32). Aqueous LiOH (1 M; 0.094 mL, 0.095 mmol) was added to ester **2** (58.1 mg, 0.086 mmol) in THF (1 mL). After 4 h at room temperature, the mixture was neutralized with 1 M HCl and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and rotary evaporated to give carboxylic acid **32** (49.0 mg, 87%) as a white solid: mp 215−220 °C dec; IR 1722, 1671, 1650, 1581 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.06 (d, J = 8.5 Hz, 2H), 7.70−7.76 (m, 3H), 7.56−7.60 (m, 1H), 7.49 (d, J = 6.0 Hz, 1H), 7.20−7.32 (m, 4H), 7.07 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.63 (dt, J = 16.0, 6.5 Hz, 1H), 6.24 (d, J = 16.0 Hz, 1H), 5.34 (s, 1H), 5.11 (s, 1H), 4.52−4.68 (m, 3H), 4.20−4.34 (m, 2H), 4.06 (d, J = 9.0 Hz, 2H), 3.33 (dd, J = 14.0, 5.0 Hz, 1H), 3.25 (dd, J = 14.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.5, 168.4, 157.4, 140.7, 139.6, 138.8, 138.3, 136.0, 135.2, 132.5, 130.7, 130.1, 129.5, 128.8, 127.8, 127.0, 126.9, 126.7, 123.9, 122.0, 112.7, 101.0, 71.2, 56.6, 53.9, 52.9, 32.6; MS (FAB) m/z 659 (M + H)$^+$, 391; HRMS (FAB) calcd for $C_{29}H_{28}IN_2O_6S$ (M + H)$^+$ 659.0713, found 659.0733. Anal. Calcd for $C_{29}H_{27}IN_2O_6S$: C, 52.90; H, 4.13; N, 4.25. Found: C, 52.98; H, 4.02; N, 4.30.

Methyl *N*-((18-((4-Iodophenyl)sulfonyl)-16-methylidene-2-oxo-12-oxa-3,18-diazatricyclo[18.3.1.0^{6,11}]tetraeicosa-1(24),6,8,10,14,20,22-heptaen-4-yl)carbonyl)glycinate (33). Et_3N (5 μL, 0.037 mmol) was added to acid **32** (29 mg, 0.034 mmol) in CH_2Cl_2 (0.3 mL). After 15 min, isobutyl chloroformate (5 μL, 0.037 mmol) in CH_2Cl_2 (0.1 mL) was added dropwise at −15 °C, and the mixture was stirred at this temperature for 30 min. Et_3N (6 μL, 0.041 mmol) and $MeO_2CCH_2NH_3Cl$ **35** (4.3 mg, 0.034 mmol) were successively added, and the reaction mixture was allowed to warm to room temperature overnight. H_2O (1 mL) and CH_2Cl_2 (10 mL) were added, and the organic layer was separated, dried (Na_2SO_4), and rotary evaporated. The residual solid was chromatographed (hexanes/EtOAc 2:1) to yield amide **33** (15 mg, 58%) as a white solid: mp 95−98 °C (hexanes−EtOAc); R_f = 0.35 (hexanes/EtOAc 1:1); IR 1745, 1655, 1522 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.51−7.55 (m, 4H), 7.19−7.29 (m, 4H), 6.91−6.97 (m, 3H), 6.51 (dt, J = 16.0, 6.0 Hz, 1H), 6.18 (d, J = 16.0 Hz, 1H), 5.18 (s, 1H), 5.15 (s, 1H), 4.65−4.70 (m, 1H), 4.56 (dd, J = 12.5, 6.0 Hz, 1H), 4.46 (dd, J = 12.5, 6.5 Hz, 1H), 4.21 (d, J = 15.5 Hz, 1H), 3.93−4.06 (m, 5H), 3.69 (s, 1H), 3.43 (dd, J = 14.0, 10.0 Hz, 1H), 3.18 (dd, J = 14.0, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.0, 169.0, 156.2, 139.2, 138.6, 137.1, 136.7, 134.5, 133.6, 132.1, 131.4, 128.8, 128.6, 128.4, 127.8, 126.4, 125.9, 123.37, 123.36, 121.7, 111.7, 100.7, 69.6, 57.2, 53.2, 52.3, 52.1, 41.2, 31.6; MS (FAB) m/z 730 (M + H)$^+$, 641, 613; HRMS (FAB) calcd for $C_{32}H_{33}IN_3O_7S$ (M + H)$^+$ 730.1084, found 730.1117.

(4-Nitrophenyl)methyl 18-((4-Iodophenyl)sulfonyl)-16-methylidene-2-oxo-12-oxa-3,18-diazatricyclo-[18.3.1.0^{6,11}]-tetraeicosa-1(24),6,8,10,14,20,22-heptaene-4-carbox-ylate (26). 1-Methylimidazole (13 μL, 0.16 mmol) was added to acid **32** (57 mg, 0.086 mmol) in CH_2Cl_2 (1 mL). Upon complete dissolution of **32**, 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (25 mg, 0.084 mmol) and 4-nitrobenzyl alcohol (8.6 mg, 0.056 mmol) were added. After 24 h, CH_2Cl_2 (20 mL) was added, and the mixture was washed successively with 1 M NaOH (10 mL), 1 M HCl (10 mL), and H_2O (10 mL), dried (Na_2SO_4), and rotary evaporated. The product was chromatographed (hexanes/EtOAc 2:1) to give ester **26** (35 mg, 52%) as a white solid: mp 120−122 °C (hexanes−EtOAc); R_f = 0.45 (hexanes/EtOAc 1:1); IR 1746, 1657, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.5 Hz, 2H), 7.67 (d, J = 8.0 Hz, 1H), 7.62−7.64 (m, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.23−7.28 (m, 2H), 7.12 (t, J = 6.0 Hz, 2H), 6.93 (d, J = 8.5 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.63 (dt, J = 16.0, 6.5 Hz, 1H), 6.11 (d, J = 16.0 Hz, 1H), 5.04−5.30 (m, 4H), 4.82−4.87 (m, 1H), 4.51 (d, J = 6.5 Hz, 2H), 4.12 (dd, J = 7.0, 3.0 Hz, 2H), 3.99 (d, J = 4.5 Hz, 2H), 3.29−3.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 168.7, 156.2, 147.6, 142.9, 139.1, 138.7, 137.0, 136.8, 134.9, 134.4, 131.9, 130.7, 129.0, 128.8, 128.4, 128.3, 127.7, 126.3, 125.9, 125.1, 123.8, 123.5, 121.5, 111.6, 100.7, 69.8, 65.2, 56.1, 53.8, 52.5, 32.2; MS (FAB) m/z 794 (M + H)$^+$, 391; HRMS (FAB) calcd for $C_{36}H_{33}IN_3O_8S$ (M + H)$^+$ 794.1033, found 794.1056. Anal. Calcd for $C_{36}H_{32}IN_3O_8S$: C, 54.48; H, 4.06; N, 5.29. Found: C, 54.57; H, 3.97; N, 5.16. Crystal data: $C_{36}H_{32}N_3O_8SI\cdot0.5C_4H_8O_2$, M = 837.7, triclinic, $P\bar{1}$ (no. 2), a = 9.0425(14) Å, b = 9.2131(10) Å, c = 23.544(3) Å, α = 90.965(14)°, β = 95.791(12)°, γ = 95.601(14)°, V = 1941.4(4) Å^3, Z = 2, D_c = 1.433 g cm^{-3}, μ(Cu Kα) = 7.46 mm^{-1}, T = 183 K, colorless blocks; 5756 independent measured reflections, F^2 refinement, R_1 = 0.101, wR_2 = 0.254, 4132 independent observed absorption corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 120°], 502 parameters.

Resin 37. 1-Methylimidazole (15 μL, 0.19 mmol) and carboxylic acid **32** (30 mg, 0.046 mmol) in CH_2Cl_2 (0.5 mL) were added to 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (14 mg, 0.047 mmol), and the resulting mixture was added to Wang resin (26 mg, 0.58 mmol/g, 0.015 mmol). The mixture was shaken under an argon atmosphere for 24 h, washed alternately with CH_2Cl_2 (3×) and MeOH (3 ×), and dried overnight at 40 °C in vacuo. The excess carboxylic acid could be recovered from the washings by chromatography (CH_2Cl_2/AcOH 1:4). The loading of resin **37** was determined by weight increase to be approximately 0.41 mmol/g. A portion of the starting carboxylic acid was cleaved from the resin by shaking the beads in TFA in CH_2Cl_2 (1:9) for 10 min. The resin was filtered off, and the filtrate was rotary evaporated to yield **32** (>95% recovered yield) with spectroscopic data identical to that obtained for the starting material.

(1*S*,24*R*,28*S*)-20-((4-Iodophenyl)sulfonyl)-13,25,27-trioxo-26-phenyl-3-oxa-12,20,26-triazapentacyclo-[20.6.1.1^{14,18}.0^{4,9}.0^{24,28}]triaconta-4,6,8,14(30),15,17,22(29)-heptaene-11-carboxylic Acid (40). A mixture of resin **37** (50.1 mg, 0.062 mmol) and *N*-phenylmaleimide **27** (107 mg, 0.62 mmol) in $ClCH_2CH_2Cl$ (1.0 mL) was shaken at 40 °C for 48 h. The resin was filtered off, washed alternately with CH_2Cl_2 (3×) and MeOH (3×), and dried overnight at 40 °C in vacuo. The carboxylic acid product was cleaved from the resin by shaking the beads with TFA (0.2 mL) in CH_2Cl_2 (2 mL) for 10 min. The resin was filtered off, and the filtrate was rotary evaporated to yield crude acid **40** (13 mg, 92%), a 1:1 mixture of diastereoisomers, as a white solid: mp 190−198 °C dec; IR 1722, 1633 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.04−8.07 (m, 2H), 7.64−7.82 (m, 4H), 7.52−7.62 (m, 0.5H), 7.45−7.52 (m, 1H), 7.31−7.44 (m, 6H), 7.15−7.19 (m, 3.5H), 7.11 (d, J = 8.0 Hz, 0.5H), 6.98 (t, J = 7.5 Hz, 0.5H), 6.31 (br s, 0.5H), 5.85 (br s, 0.5H), 4.97−5.00 (m, 0.5H), 4.69 (d, J = 15.0 Hz, 0.5H), 4.60 (dd, J = 10.5, 2.5 Hz, 0.5H), 4.41−4.56 (m, 1.5H), 4.31 (dd, J = 9.5, 3.0 Hz, 0.5H), 4.25 (d, J = 15.0 Hz, 0.5H), 4.16 (d, J = 13.5 Hz, 0.5H), 4.10 (d, J = 14.0 Hz, 0.5H), 3.88 (d, J = 15.0 Hz, 0.5H), 3.36−3.56 (m, 3.5H), 3.21−3.33 (m, 1H), 3.11 (dd, J = 13.5, 2.5 Hz, 1H), 2.44−2.60 (m, 1.5H), 1.94−2.31 (m, 1H), 1.08−1.14 (m, 0.5H); ^{13}C NMR (125 MHz, acetone-d_6) δ 178.9, 177.4, 173.0, 172.3, 167.55, 167.48, 167.1, 167.0, 158.43, 158.38, 141.3, 139.6, 139.5, 139.4, 138.6, 137.3, 136.5, 135.5, 135.4, 133.6, 132.9, 133.0, 132.4, 132.1, 131.7, 131.6, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 129.2, 129.05, 129.00, 128.8,

128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 127.74 127.71, 122.9, 118.0, 115.5, 100.6, 100.4, 74.4, 72.7, 56.9, 54.9, 54.7, 53.8, 53.5, 51.4, 42.9, 42.7, 41.01, 40.98, 38.0, 37.4, 32.9, 32.3, 27.5, 26.7; MS (ES^+) *m*/*z* 854 $(M + Na)^+$, 832 $(M + H)^+$.

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Supporting Information Available: Full experimental conditions and characterization data for **8**, **9**, methyl (*Z*)-2-benzamido-3-(2-hydroxy-4-methoxyphenyl)propenoate, methyl 2-benzamido-3-(2-hydroxy-4-methoxyphenyl)propanoate, **10**, **5**, methyl 3-(2-hydroxyphenyl)-2-aminopropanoate hydrochloride, **15**, methyl 2-((*tert*-butyloxycarbonyl)amino)-3-(2-(2-propen-1-yloxy)phenyl)propanoate, **16**−**18**, **31**, **34**, **36**, and **41**−**44**. Copies of ^1H and ^{13}C spectra for **1**−**3**, **23**, **28**, **30**, **31**, **33**, **34**, **36**, **40**−**44** and methyl 3-(2-(2-propen-1-yloxy)phenyl)-2-*tert*-butyloxycarbonylaminopropanoate. COSY, ROESY, and HMQC spectra for **2**; NOESY, COSY, and HMQC spectra for **30**; and X-ray crystallographic data for **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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