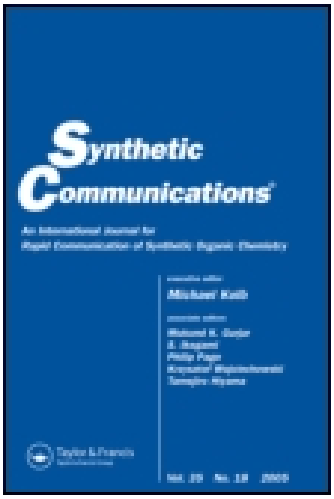


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# General Route for the Preparation of Diverse 17-Membered Macrocycles Based on RCM and Examination of the E/Z Selectivity

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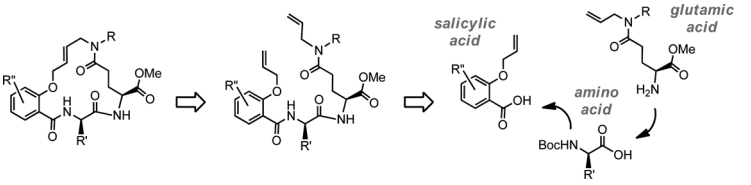
# GENERAL ROUTE FOR THE PREPARATION OF DIVERSE 17-MEMBERED MACROCYCLES BASED ON RCM AND EXAMINATION OF THE *E*/*Z* SELECTIVITY

**Thilo J. Heckrodt and Rajinder Singh**
*Department of Medicinal Chemistry, Rigel Pharmaceuticals, South San Francisco, California, USA*

## GRAPHICAL ABSTRACT




**Abstract** *A convergent, general synthetic route to 17-membered macrocycles was developed to support biological evaluation and structure–activity relationship (SAR) studies during phenotypic screening for immunology targets. A series of amide coupling reactions led to a ring-closing metathesis (RCM) precursor that was cyclized using Grubbs' catalysts. It was found that the reaction formed the macrocyclic products in a 3:1 ratio of* E/Z *isomers. Moreover, it was shown that a number of similarly substituted RCM precursors undergo cyclization to produce the geometric* E/Z *isomers in roughly the same 3:1 ratio. The remarkable independence of the* E/Z *outcome from the substitution pattern of the RCM precursor makes this synthetic approach generally applicable. Separation of the* E/Z *isomers was achieved by preparative high-performance liquid chromatography and allowed biological profiling of the geometric isomers. Reactive groups in the macrocycle were utilized for late-stage modifications in the fashion of diversity-orientated synthesis (DOS), yielding analogs for SAR studies.*

**Keywords** Diversity-orientated synthesis (DOS); *E*/*Z* isomers; Grubbs' catalyst; macrocycles; ring-closing metathesis (RCM)

## INTRODUCTION

Drugs based on macrocyclic compounds play important roles in modern medicine. The inherent features of macrocycles often make them particularly well-suited as pharmaceuticals (e.g., increased stability, decreased conformational flexibility, low number of rotatable bonds can favor high oral bioavailability). Current macrocyclic

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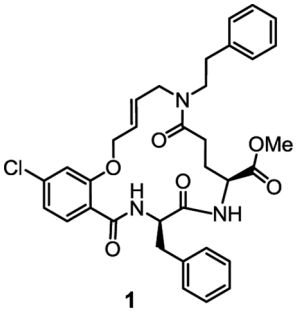



**Figure 1.** Seventeen-membered macrocycle **1**.



drugs are almost exclusively derived from natural sources and are either identical (e.g., rapamycin) or closely related (e.g., temsirolimus) to naturally occurring macrocycles.[1] However, several synthetic macrocycles unrelated to natural products are now under active preclinical and clinical development.[2] In particular, several macrocyclic hepatitis C virus (HCV) protease inhibitors have entered clinical trails.[2b–e]

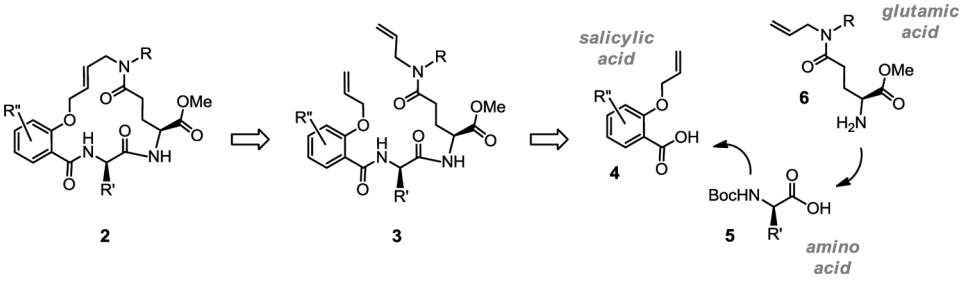
During a high-throughput screening (HTS) campaign we became interested in fully synthetic macrocycles that showed activity against immunology targets. To gain access to larger quantities for biological evaluation and initial structure–activity relationship (SAR) studies, we developed a synthetic route to this compound class.

Compound **1** is an example of the macrocycles that were targeted for further biologic evaluation (Fig. 1). The scaffold is a 17-membered triamide featuring a salicylic acid–based aromatic moiety on the left-hand side, an amino acid at the bottom, a glutamic methyl ester on the right-hand side, and an olefinic linker at the top.

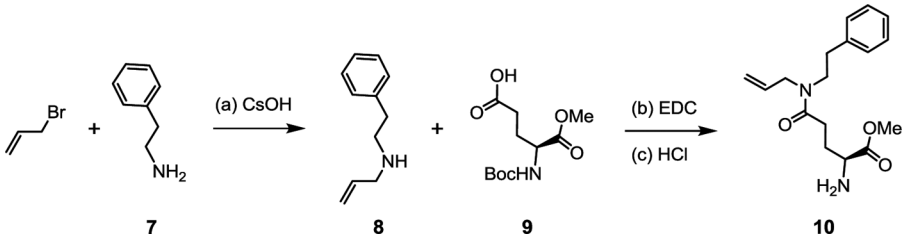
## RESULTS AND DISCUSSION

This article describes our synthetic approach to 17-membered macrocycles utilizing ring-closing metathesis and studies the $E/Z$ selectivity of the ring-closing metathesis (RCM) reaction for this system.

Retrosynthetic disconnection of the macrocyclic scaffold **2** leads to the diolefinic RCM precursor **3** (Scheme 1). Intermediate **3** can be obtained by a sequence of




**Scheme 1.** Retrosynthetic analysis.




7 8 9 10

**Scheme 2.** Synthesis of glutamic ester derivative **10**. Reagents and conditions: (a) $CsOH(H_2O$ (0.1 eq), 4 Å MS, DMF, −20 °C to rT, 12 h, 52%; (b) EDC (1.5 eq), HOBt (1.5 eq), $Et_3N$ (2.0 eq), DCM, rT, 10 h; (c) HCl (4 M in dioxane), MeOH, rT, 1 d, 92% over two steps, (EDC = *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide, HOBt = 1-hydroxybenzotriazole).

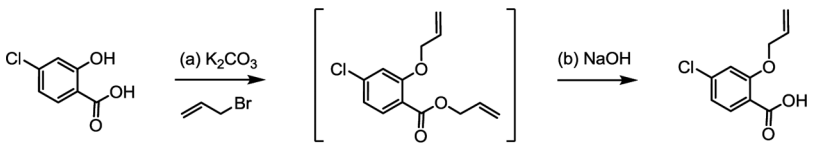


amidations first coupling glutamic acid derivative **6** to protected amino acid **5** and subsequently forming an amide bond with salicylic acid derivative **4**.

The synthesis of glutamic ester derivative **10** starts with the monoallylation of phenylethylamine **7**. This highly exothermic monoallylation reaction proved to be capricious, and most reactions evaluated also gave significant amounts of the diallylated by-product. Using $CsOH \cdot H_2O$ as base[3] in combination with low temperature gave satisfactory yields of the desired monoallylated phenylethyl amine product after column chromatography. Secondary amine **8** was then coupled with Boc-protected (*S*)-glutamic amino methyl ester **9** under standard *N*-ethyl-*N*′-(3-dimethylaminopropyl)-carbodiimide (EDC) conditions. Subsequent deprotection with 4 M HCl furnished the desired intermediate **10** (Scheme 2).

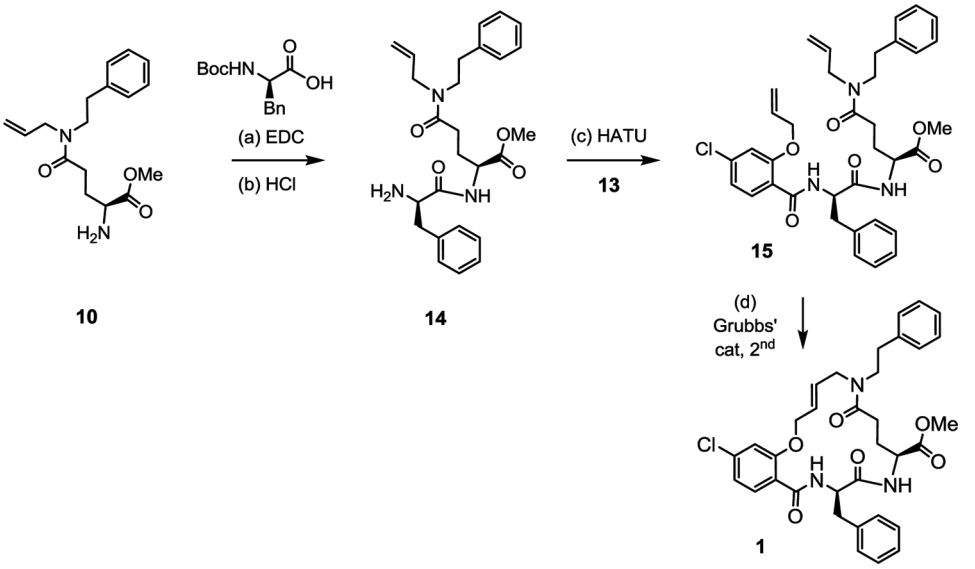
Salicylic acid derivative **13** was obtained by a two-step sequence. Starting material **11** was diallylated to give intermediate **12**, which was subsequently hydrolyzed to the acid **13**. This procedure turned out to be more efficient than selective monoallylation with 1 equivalent of allyl bromide (Scheme 3).

The free primary amine of glutamic ester **10** was coupled with Boc-protected (*R*)-phenylalanine and subsequently deprotected under acidic conditions to yield amide **14**. Final assembly of the RCM precursor **15** was achieved using *O*-(7-azabenzo-triazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) to connect salicylic acid **13** with fragment **14**. Although the employment of first-generation Grubbs' catalyst produced the desired macrocycle **1**, it was found that faster conversion and greater yields were obtained with the use of second-generation Grubbs' catalyst.[4] Special addition protocols such as slow addition via syringe pump were not required (Scheme 4).




11 12 13

**Scheme 3.** Monoallylation of salicylic acid **11**. Reagents and conditions: (a) allyl bromide (4.0 eq), $K_2CO_3$ (3.0 eq), $Cs_2CO_3$ (0.1 eq), acetone, reflux, 8 h; (b) NaOH (1.2 eq) $H_2O$/EtOH 1:1, rT, 10 h, 94% over two steps.

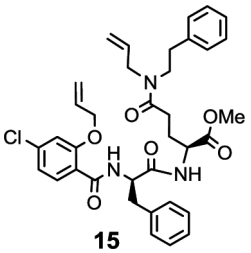
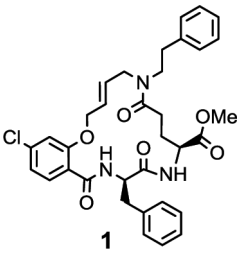
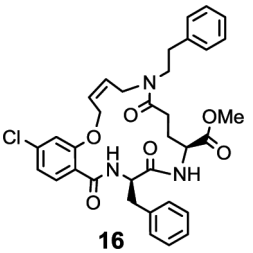
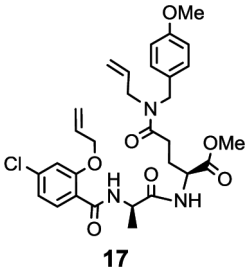
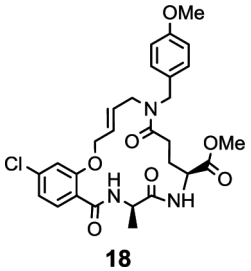
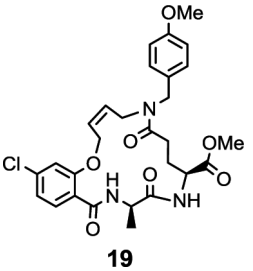
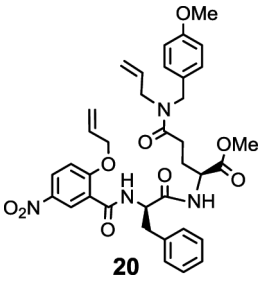
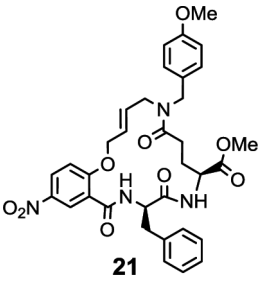
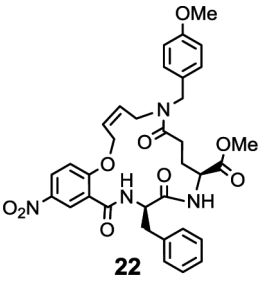
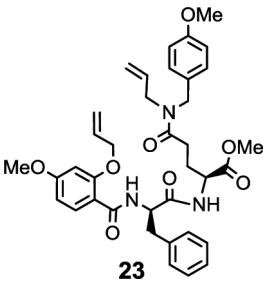
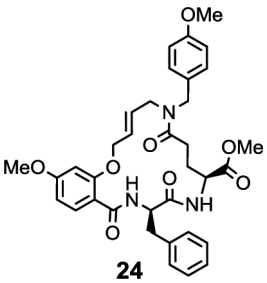
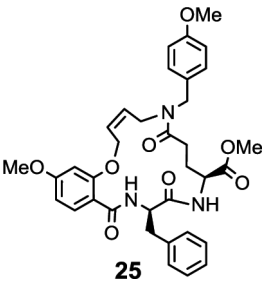



**Scheme 4.** Synthesis of the RCM precursor and ring closure. Reagents and conditions: (a) Boc-(*R*)-phenylalanine (1.0 eq), EDC (1.5 eq), HOBt (1.5 eq), $Et_3N$ (2.0 eq), DCM, rT, 12 h; (b) HCl (4 M in dioxane), MeOH, rT, 8 h, 71% over two steps; (c) **13** (1.0 eq), HATU (1.2 eq), TEA (2.2 eq), DMF, rT, 14 h, 73%; (d) Grubbs' catalyst 2 (0.08 eq), DCM, rT, 8 h, 89% (mixture of *E*/*Z* isomers) [HATU = *O*-(7-azabenzo-triazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate, TEA = triethylamine].

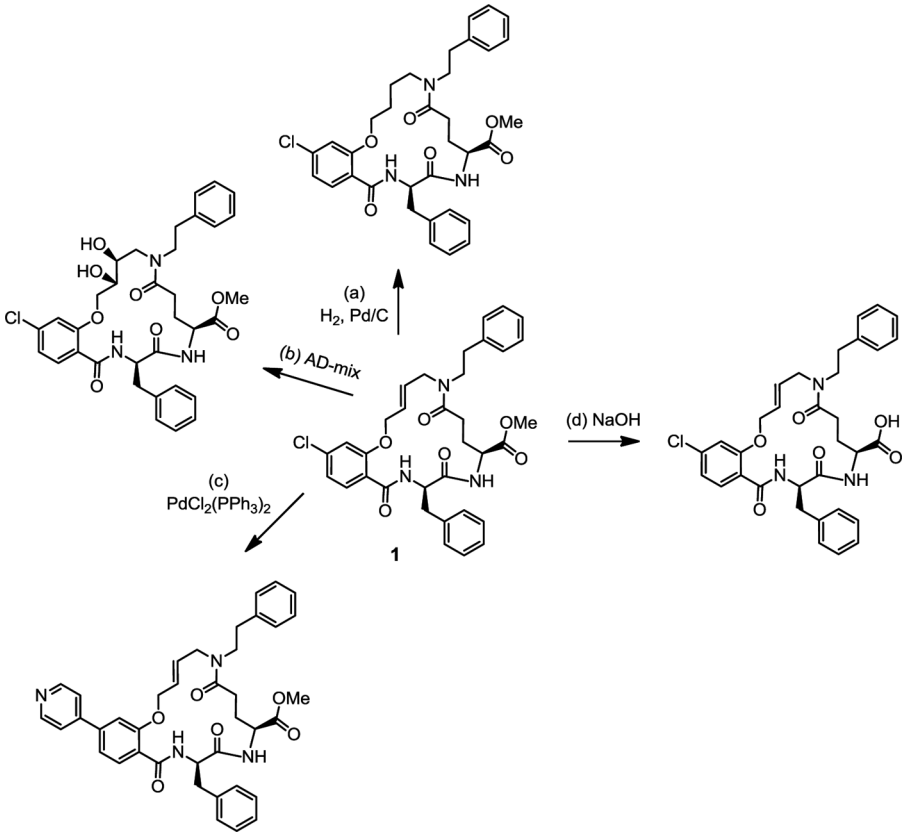
The product of the RCM reaction was observed as a single spot on thin-layer chromatography (TLC) and isolated by flash chromatography. However, analysis of the purified product by (high performance liquid chromatography) (HPLC) revealed that a 78/22 mixture of *E*/*Z* isomers had been formed in the RCM reaction.[5] The *E*/*Z* isomers were readily separated by preparative HPLC and further analyzed by $^1$H NMR. The main isomer was assigned as the *E*-isomer based on the large coupling constant ($J = 15.3$ Hz) indicative for a *trans* double-bond geometry. We subsequently subjected a few more similarly substituted RCM precursors (Table 1, compounds **17**, **20**, and **23**; prepared using the synthetic route as described) to the same metathesis conditions and found that the *E*/*Z* ratio of the products was fairly independent of the substitution pattern (Table 1). In all four examples, the *E*/*Z* ratio was in the same range (E/Z $\approx$ 3/1). It was possible to separate the *E*/*Z* isomers by preparative HPLC in all cases. Some of the *E*-isomers (compounds **18**, **21**, and **24**) were commercially available from AnalytiCon (Potsdam, Germany) as part of a screening library. The main isomers observed in the RCM reaction gave an exact match in retention time on HPLC compared to the commercial *E*-isomers purchased from AnalytiCon [e.g., for compound **18**, *E*-isomer: $t_R$(Rigel) = 10.70 min vs. $t_R$(AnalytiCon) = 10.70 min]. (HPLC was performed on an Agilent Zorbax SB-C18.2.1 × 50-mm (5μm) column.) These findings further confirmed the assignment of the double-bond geometry.

To further take advantage of the products obtained in the complexity-generating macrocyclization process, we envisioned postmacrocyclization functionalizations in the fashion of diversity-orientated synthesis (DOS). Hence, the HPLC-purified macrocyclic *E*-isomer **1** was subjected to a number of late-stage manipulations to gain access

**Table 1.** $E/Z$ ratio of RCM products

| Entry | RCM precursor | E-isomer | $E/Z$ ratio | Z-isomer |
|---|---|---|---|---|
| A |  **15** |  **1** | 78/22 |  **16** |
| B |  **17** |  **18** | 68/32 |  **19** |
| C |  **20** |  **21** | 72/28 |  **22** |
| D |  **23** |  **24** | 73/27 |  **25** |

to analogs for SAR studies. Functional groups and sites of reactivity were exploited for the following transformations: (a) the double bond was hydrogenated using palladium on charcoal as catalyst, (b) the olefin was dihydroxylated with Sharpless' AD-mix-α,[6] (c) the aromatic chloride was used as a handle for a microwave-assisted




**Scheme 5.** Late-stage modifications to access analogs for SAR studies. Reagents and conditions: (a) $H_2$, Pd/C (10 wt%); (b) AD-mix-α (1.4 g/mmol), $^t$Bu-OH, $H_2O$, 0 °C to rT, 58%; (c) *p*-Pyr-B(OH)$_2$ (2.0 eq), $PdCl_2(PPh_3)_2$ (0.1 eq), $Na_2CO_3$ (1.2 eq), DME/EtOH/$H_2O$ 7:3:2, 15 min, microwave, 150 °C, 19%; (d) NaOH (1.5 eq), MeOH/$H_2O$ 1:1, rT, 12 h, 94%.

Suzuki–Miyaura coupling[7] to generate a biaryl moiety, and (d) the methyl ester was hydrolyzed to the carboxylic acid (Scheme 5).

In summary, we developed a synthetic entry into the described class of 17-membered macrocycles using a sequence of amide couplings followed by a RCM reaction to obtain the final product. In all four cases, the RCM reaction yielded the products as a mixture of $E/Z$ isomers in a ratio of about three to one. Reactive groups in the macrocycle were used for a number of late-stage modifications to yield analogs for SAR studies.

## EXPERIMENTAL

All moisture-sensitive reactions were carried out under nitrogen. Anhydrous solvents were purchased from Aldrich. All other solvents were HPLC grade. Column chromatography was performed with EMD Merck silica gel (0.040–0.63 μm, 240–400 mesh) under the low pressure of 5–10 psi. Flash chromatography was carried

out on a Teledyne Isco CombiFlash Rf flash system with variable solvent gradients. TLC analysis was performed with E. Merck silica-gel 60-F254 plates. NMR spectra were recorded on a Varian Mercury VX 300-MHz spectrometer. NMR spectra measured in $CDCl_3$ solutions were referenced to the residual $CHCl_3$ signal ($^1H$, $\delta = 7.26$; $^{13}C$, $\delta = 77.0$); spectra measured in dimethylsulfoxide (DMSO-$d_6$) were referenced to the residual DMSO signal ($^1H$, $\delta = 2.50$; $^{13}C$, $\delta = 39.50$). $^1H$ and $^{13}C$ shifts are given in ppm (s = singlet, d = doublet, t = triplet, q = quadruplet, quin = quintet, m = multiplet, br s = broad signal). Coupling constants, *J*, are given in hertz (Hz). Mass spectra were measured on a Waters Micromass ZQ or ZMD instrument. Accurate mass measurements (HRMS) were obtained using an Acquity ultra performance liquid chromatography (UPLC) system with PDA, ELSD, and LCT Premier XE mass spectrometer (time of flight). Monitored wavelength was 254 nm. Mass analysis was performed in extended W-mode using leucine enkephalin as reference lock mass, 556.2771 Da for positive ion, and 554.2615 Da for negative ion. Samples were initially prepared in methanol at 1 mg/mL and diluted as necessary to remove dead time artifacts. Column: Acuity UPLC, BEH18, 1.7 μm, 2.1 × 50 mm, solvents: A = water 0.05% formic acid, B = acetonitrile 0.05% formic acid, flow rate: 0.735 mL/min, and gradient: 95% A, 5% B to 100% B in 4 min.



### Amine 8

This compound was synthesized using a modified procedure described by Salvatore et al.[3] Phenylethylamine (50.0 g, 413 mmol), $CsOH \cdot H_2O$ (6.93 g, 41.3 mmol), and activated 4-Å molecular sieves (20 g) were combined with dry dimethylformamide (DMF, 300 ml) and stirred at room temperature for 30 min. The mixture was cooled to −20 °C using a NaCl/ice bath. Then allyl bromide (50.0 g, 423 mmol) was added very slowly dropwise. The reaction mixture was allowed to warm to room temperature overnight. Most of the solvent was removed in vacuo, and saturated $NaHCO_3$ (400 ml) was added to the crude product. The mixture was extracted with $Et_2O$ (3 ×), the combined organic layers were dried over $MgSO_4$, and solvents were evaporated under reduced pressure. Analysis by TLC (3% MeOH [2 M $NH_3$] in $CHCl_3$] and HPLC showed that the mono- and di-allylated products had been formed in roughly the same amounts. The desired product was isolated by flash chromatography eluting with 3% MeOH [2 M $NH_3$] in $CHCl_3$. Monoallylated compound **8** was obtained in 52% yield (34.5 g) in form of a pale yellow oil.

$^1H$ NMR (300 MHz, DMSO) δ 7.28–7.10 (m, 5H), 5.96–5.65 (m, 1H), 5.11 (d, $J = 17.2$ Hz, 1H), 5.00 (d, $J = 10.2$ Hz, 1H), 3.15 (d, $J = 5.8$ Hz, 2H), 2.70 (s, 4H), 1.60 (s br, 1H) ppm; MS (ESI) (*m*/*z*): 162 $[M + H]^+$, 146, 119.

### Amide 10

Boc-protected (*S*)-glutamic methyl ester **9** (2.73 g, 10.4 mmol), ethylene dichloride (EDC; 3.00 g, 15.7 mmol), HOBt (2.11 g, 15.7 mmol), and $Et_3N$ (2.9 ml, 20.8 mmol) were dissolved in dry DCM (150 ml). The mixture was stirred for 15 min, and allyl amine **8** was subsequently added to the reaction mixture. Stirring was continued overnight at room temperature. The reaction mixture was then concentrated in vacuo and further purified by flash chromatography eluting with

chloroform/methanol (20/1). The Boc-protected amide was obtained in form of a clear yellowish oil in 94% yield (3.95 g).

$^1$H NMR (300 MHz, DMSO) δ 7.35–7.12 (m, 5H), 5.87–5.59 (m, 1H), 5.11 (d, $J = 11.5$ Hz, 1H), 5.04 (d, $J = 10.5$ Hz, 1H), 4.06–3.91 (m, 1H), 3.85 (d, $J = 19.7$ Hz, 2H), 3.60 (s, 3H), 3.44–3.29 (m, 2H), 2.75 (m, 2H), 2.43–2.20 (m, 2H), 1.90 (m, 1H), 1.72 (m, 1H), 1.34 (d, $J = 7.2$ Hz, 9H) ppm; MS (ESI) ($m/z$): 405 $[M + H]^+$, 349, 305.

The product from this reaction was dissolved in methanol (100 ml), and HCl (20 ml, 4 M in dioxane) was added via syringe. The mixture was stirred at room temperature until analysis by TLC showed complete conversion (1 d). After neutralizing with 1 M NaOH (80 ml), the mixture was extracted with $Et_2O$ (2 ×) and EtOAc (2 ×). The combined organic layers were dried over $Na_2SO_4$, and solvents were removed under reduced pressure to give 2.91 g (98%) amide **10**.

### Acid 13

Salicylic acid **11** (30.0 g, 174 mmol) and allyl bromide (84.1 g, 696 mmol) were dissolved in acetone (500 ml). $K_2CO_3$ (72.1 g, 522 mmol) and $Cs_2CO_3$ (5.67 g, 17.4 mmol) were added, and the reaction mixture was refluxed for 8 h. Salts were filtered off, and the acetone was removed under reduced pressure. Excess allyl bromide was removed by applying high vacuum to the rotary evaporator. The yellowish crude oil was dissolved in ethanol (250 ml), and 2 M NaOH (104 ml, 208 mmol) was added. The mixture was stirred overnight at room temperature and then acidified (ice-bath cooling) using concentrated HCl. Acid **13** was precipitated by adding ice water and keeping the flask in the refrigerator for several hours. The product was obtained in form of a solid and collected by filtration (34.7 g, 94%).

$^1$H NMR (300 MHz, DMSO) δ 7.65 (d, $J = 8.3$ Hz, 1H), 7.16 (s, 1H), 7.03 (d, $J = 8.3$ Hz, 1H), 6.12–5.88 (m, 1H), 5.46 (d, $J = 17.3$ Hz, 1H), 5.23 (d, $J = 10.6$ Hz, 1H), 4.64 (d, $J = 4.7$ Hz, 2H) ppm; $^{13}$C NMR (75 MHz, DMSO) δ 167.13, 158.52, 137.90, 133.56, 132.94, 120.87, 117.81, 114.64, 69.59 ppm; MS (ESI) ($m/z$): 213 $[M + H]^+$, 195, 167, 157.

### Amide 14

Boc-(*R*)-phenylalanine (2.48 g, 9.35 mmol), EDC (2.69 g, 14.0 mmol), HOBt (1.89 g, 14.0 mmol), and $Et_3N$ (2.60 ml, 18.7 mmol) were dissolved in dry DCM (150 ml). The mixture was stirred for 30 min, and glutamic amino methyl ester **10** (2.84 g, 9.35 mmol) was subsequently added to the reaction mixture. Stirring was continued overnight at room temperature. The reaction mixture was then concentrated in vacuo and further purified by flash chromatography eluting with chloroform/methanol (40/1). The Boc-protected amide was obtained in form of a pale yellow oil in 78% yield (4.02 g).

$^1$H NMR (300 MHz, DMSO) δ 8.35 (d, $J = 7.6$ Hz, 1H), 7.33–7.07 (m, 10H), 6.87 (d, $J = 8.7$ Hz, 1H), 5.73 (tdt, $J = 15.8$, 10.4, 5.3 Hz, 1H), 5.09 (m, 2H), 4.25 (m, 2H), 3.89 (d, $J = 5.2$ Hz, 1H), 3.80 (d, $J = 4.0$ Hz, 1H), 3.61 (s, 3H), 3.37 (d, $J = 6.5$ Hz, 2H), 2.99–2.84 (m, 1H), 2.83–2.61 (m, 3H), 2.24 (m, 2H), 1.92 (td, $J = 13.8$, 6.3 Hz, 1H), 1.84–1.66 (m, 1H), 1.27 (s, 9H) ppm; $^{13}$C NMR (75 MHz, DMSO) δ 172.83, 172.34, 171.53, 171.11, 139.84, 139.18, 129.82, 129.41, 129.24,

129.01, 128.57, 126.79, 117.18, 116.69, 79.89, 78.66, 56.25, 52.62, 50.65, 47.88, 38.67, 35.09, 34.31, 28.91, 27.54 ppm; MS (ESI) ($m/z$): 552 $[M + H]^+$, 496, 452.

The product from this reaction was dissolved in methanol (120 ml), and HCl (20 ml, 4 M in dioxane) was added via syringe. The mixture was stirred at room temperature until analysis by TLC showed complete conversion (1 d). After neutralization with 1 M NaOH (80 ml), the mixture extracted with $Et_2O$ (2 ×) and EtOAc (2 ×). The combined organic layers were passed though a plug of $MgSO_4$ to remove residual water, and solvents were removed under reduced pressure to furnish 2.99 g (91%) amide **14**.

### RCM Precursor 15

Salicylic acid **13** (0.735 g, 3.45 mmol), HATU (1.57 g, 4.14 mmol), and $Et_3N$ (1.05 ml, 7.59 mmol) were dissolved in dry DMF (50 ml). The mixture was stirred for 30 min, and compound **14** (1.56 g, 3.45 mmol) was subsequently added to the reaction mixture. Stirring was continued overnight at room temperature. The reaction mixture was then concentrated in vacuo and further purified by flash chromatography, eluting with chloroform/methanol (30/1). The desired amide **15** was obtained in form of a pale yellow oil in 73% yield (1.63 g).

$^1$H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, $J = 7.8$ Hz, 1H), 8.08 (dd, $J = 7.8$, 3.8 Hz, 1H), 7.35–7.04 (m, 11H), 6.99 (d, $J = 8.8$ Hz, 1H), 6.87 (s, 1H), 5.92 (m, 1H), 5.62 (m, 1H), 5.33 (dd, $J = 17.2$, 9.8 Hz, 2H), 5.12 (dd, $J = 18.4$, 10.6 Hz, 2H), 4.95 (m, 1H), 4.55 (m, 4H), 4.32 (m, 1H), 3.67 (s, 3H), 3.51–3.33 (m, 3H), 3.21 (d, $J = 6.8$ Hz, 2H), 2.78 (m, 3H), 2.38–2.07 (m, 1H), 2.06–1.83 (m, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.19, 171.79, 171.05, 167.44, 164.42, 157.22, 139.24, 138.73, 138.25, 136.93, 133.54, 132.86, 131.64, 129.51, 128.95, 128.71, 127.00, 126.50, 121.83, 119.77, 116.94, 113.68, 70.65, 55.17, 52.63, 51.12, 48.69, 38.26, 35.20, 34.39, 29.30, 27.17 ppm; MS (ESI) ($m/z$): 646 $[M + H]^+$, 305.

### Macrocycles 1 and 16

The product **15** (758 mg, 1.17 mmol) from this reaction was dissolved in dry DCM (200 ml, $c \approx 0.006$ mol/L); the solution was degassed and flushed with $N_2$ (3 ×). Grubbs' II catalyst (80.0 mg, 0.091 mmol) dissolved in dry DCM (20 ml) was added dropwise over a period of 5 min. Stirring was continued for 8 h at room temperature. The clear, peach-colored solution turned blackish within a couple of hours. Water (30 ml) was added to deactivate the catalyst; the organic layer was separated and filtered through a plug of $MgSO_4$. Solvents were removed under reduced pressure, and the crude product was purified by column chromatography eluting with chloroform/methanol (30/1). The product (dark oil, 644 mg, 89%) was obtained as a mixture of $E/Z$-isomers in a ratio of 78/22 (determined by LCMS). The geometric isomers were separated by preparative HPLC to allow spectroscopic characterization. The final compounds were obtained in the form of white solids.

**Macrocycle 1 (*E*-Isomer).** $^1$H NMR (300 MHz, DMSO) δ 8.30 (d, $J = 8.8$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.32–7.05 (m, 11H), 5.63 (d, $J = 15.3$ Hz, 1H), 5.44 (d, $J = 15.3$ Hz, 1H), 4.84 (d, $J = 3.7$ Hz, 1H), 4.59 (s, 1H), 4.55–4.46 (m, 1H), 4.45–4.25

(m, 2H), 4.09–3.95 (m, 1H), 3.66 (d, $J = 7.3$ Hz, 1H), 3.62 (s, 3H), 3.24 (dd, $J = 13.7$, 5.3 Hz, 1H), 3.05 (dd, $J = 13.0$, 6.6 Hz, 1H), 2.96 (dd, $J = 13.3$, 4.5 Hz, 1H), 2.70 (s, 2H), 2.14 (d, $J = 13.2$ Hz, 2H), 1.94–1.69 (m, 2H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.49, 171.59, 170.24, 164.12, 157.26, 139.24, 139.14, 136.56, 133.44, 130.51, 130.37, 128.96, 128.71, 128.60, 127.15, 126.56, 124.18, 121.93, 119.62, 112.83, 69.18, 53.92, 53.01, 52.29, 49.06, 48.66, 37.30, 34.20, 28.49, 28.07 ppm; MS (ESI) ($m/z$): 618 $[M + H]^+$; HRMS (TOF MS ES+) $m/z$ calcd. for $C_{34}H_{36}ClN_3O_6$: 618.2371; found: 618.2319.

**Macrocycle 16 (*Z*-Isomer).** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, $J = 4.0$ Hz, 1H), 8.31 (d, $J = 8.3$ Hz, 1H), 8.18 (d, $J = 8.5$ Hz, 1H), 7.36–7.17 (m, 10H), 7.04 (d, $J = 8.5$ Hz, 1H), 6.98 (s, 1H), 5.62–5.47 (m, 2H), 5.04 (td, $J = 8.3$, 4.8 Hz, 1H), 4.81 (t, $J = 9.5$ Hz, 1H), 4.56 (dd, $J = 14.4$, 9.8 Hz, 1H), 4.49–4.41 (m, 1H), 4.32 (s, 1H), 3.77 (s, 3H), 3.52 (m, 2H), 3.20 (dd, $J = 14.5$, 4.6 Hz, 1H), 3.07 (m, 2H), 2.85 (t, $J = 7.3$ Hz, 2H), 2.38–2.10 (m, 2H), 2.03 (dd, $J = 16.1$, 6.0 Hz, 1H), 1.88 (dd, $J = 13.5$, 5.5 Hz, 1H) ppm; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 172.90, 172.61, 171.99, 164.55, 158.05, 138.91, 137.79, 137.40, 134.06, 130.33, 129.65, 129.16, 128.89, 128.69, 127.29, 126.90, 124.78, 122.00, 119.26, 113.51, 64.19, 55.11, 53.12, 52.27, 51.49, 45.01, 38.55, 35.57, 28.88, 23.23 ppm; MS (ESI) ($m/z$): 618 $[M + H]^+$; HRMS (TOF MS ES+) $m/z$ calcd. for $C_{34}H_{36}ClN_3O_6$: 618.2371; found: 618.2315.

### Additional Data for Macrocycles in Table 1

**Macrocycle 18 (*E*-Isomer).** $^1$H NMR (300 MHz, DMSO) δ 8.34 (d, $J = 7.7$ Hz, 1H), 8.24 (d, $J = 7.7$ Hz, 1H), 7.77 (d, $J = 8.3$ Hz, 1H), 7.27 (s, 1H), 7.20–7.03 (m, 3H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.97–5.69 (m, 2H), 4.84–4.57 (m, 3H), 4.53 (dd, $J = 14.4$, 7.1 Hz, 1H), 4.36 (t, $J = 9.3$ Hz, 1H), 4.15–3.88 (m, $J = 37.3$ Hz, 2H), 3.71 (s, 3H), 3.60 (s, 4H), 2.40–2.07 (m, 4H), 1.91–1.68 (m, 1H), 1.34 (d, $J = 7.0$ Hz, 3H) ppm; $^{13}$C NMR (75 MHz, DMSO) δ 172.52, 171.78, 163.98, 159.04, 157.42, 137.42, 132.78, 130.61, 129.90, 129.78, 126.64, 122.19, 121.46, 114.44, 113.97, 100.15, 69.69, 55.69, 52.63, 51.98, 49.72, 48.11, 47.90, 28.36, 26.83, 19.15 ppm; MS (ESI) ($m/z$): 558 $[M + H]^+$, 333; HRMS (TOF MS ES+) $m/z$ calcd. for $C_{28}H_{32}ClN_3O_7$: 558.2007; found: 558.1954.

**Macrocycle 19 (*Z*-Isomer).** $^1$H NMR (300 MHz, DMSO) δ 8.66–8.49 (m, 1H), 8.41 (d, $J = 7.9$ Hz, 1H), 7.98 (t, $J = 8.1$ Hz, 1H), 7.64 (d, $J = 8.3$ Hz, 1H), 7.27 (s, 1H), 7.20–7.03 (m, 3H), 6.94–6.80 (m, 2H), 5.98–5.81 (m, 1H), 5.72 (dd, $J = 11.2$, 5.9 Hz, 1H), 5.45 (dd, $J = 11.5$, 5.8 Hz, 1H), 4.72 (s, 2H), 4.54–4.36 (m, 3H), 4.19 (dd, $J = 16.1$, 9.1 Hz, 1H), 4.09–4.00 (m, 1H), 3.71 (s, 3H), 3.59 (s, 3H), 2.41–2.25 (m, 2H), 2.13–1.92 (m, 2H), 1.27 (d, $J = 7.1$ Hz, 3H) ppm; $^{13}$C NMR (75 MHz, DMSO) δ 173.51, 172.85, 172.49, 171.97, 164.92, 159.07, 157.19, 136.88, 132.08, 130.46, 129.95, 129.09, 124.89, 123.72, 121.49, 114.50, 65.25, 55.69, 52.98, 52.57, 50.13, 48.89, 45.20, 29.31, 25.98, 18.44 ppm; MS (ESI) ($m/z$): 558 $[M + H]^+$; HRMS (TOF MS ES+) $m/z$ calcd. for $C_{28}H_{32}ClN_3O_7$: 558.2007; found: 558.1947.

**Macrocycle 21 (*E*-Isomer).** $^1$H NMR (300 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.82 (d, $J = 6.9$ Hz, 1H), 8.37 (d, $J = 9.1$ Hz, 1H), 7.28–7.22 (m, $J = 3.1$ Hz, 4H), 7.14

(d, $J = 8.6$ Hz, 1H), 7.08 (d, $J = 9.2$ Hz, 1H), 6.82 (d, $J = 8.7$ Hz, 2H), 6.44 (d, $J = 7.2$ Hz, 1H), 5.82–5.65 (m, 2H), 5.21 (d, $J = 14.6$ Hz, 1H), 5.05 (d, $J = 6.3$ Hz, 1H), 4.77 (t, $J = 12.5$ Hz, 2H), 4.55 (dd, $J = 10.4$, 5.9 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.74–3.64 (m, 1H), 3.54–3.37 (m, 2H), 3.33–3.22 (m, 1H), 2.60–2.45 (t, $J = 11.7$ Hz, 2H), 2.37–2.15 (m, 1H), 2.06 (d, $J = 17.8$ Hz, 1H), 1.90–1.70 (m, 2H) ppm; MS (ESI) ($m/z$): 645 $[M + H]^+$, 333; HRMS (TOF MS ES+) $m/z$ calcd. for $C_{34}H_{36}N_4O_9$: 645.2560; found: 645.2487.

**Macrocycle 24 (*E*-Isomer).** $^1$H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, $J = 7.8$ Hz, 2H), 8.20 (d, $J = 8.8$ Hz, 1H), 7.29–7.16 (m, 5H), 7.13 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.6$ Hz, 2H), 6.63 (dd, $J = 8.8$, 2.1 Hz, 1H), 6.52 (d, $J = 7.1$ Hz, 1H), 6.46 (s, 1H), 5.56 (d, $J = 14.1$ Hz, 1H), 5.13 (d, $J = 14.6$ Hz, 1H), 4.57 (dd, $J = 10.8$, 4.4 Hz, 1H), 4.43 (dd, $J = 15.6$, 7.6 Hz, 1H), 4.36 (dd, $J = 10.7$, 6.2 Hz, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.70–3.56 (m, 1H), 3.55–3.42 (m, 1H), 3.39 (dd, $J = 14.3$, 3.6 Hz, 1H), 3.24 (d, $J = 5.4$ Hz, 1H), 2.90 (s br, 2H), 2.62–2.38 (m, 1H), 2.17–2.01 (m, 1H), 1.97–1.68 (m, 2H) ppm; MS (ESI) ($m/z$): 630 $[M + H]^+$, 333; HRMS (TOF MS ES+) $m/z$ calcd. for $C_{35}H_{39}N_3O_8$: 630.2816; found: 630.2776.

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