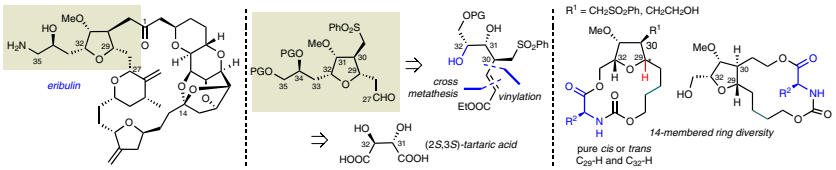
Synthesis S. Konda et al. Special Topic

Stereoselective Synthesis of the C27–C35 Eribulin Fragment and Its Utilization in Building Structurally Diverse Macrocycles

Saidulu Konda
Mahender Khatravath
Naveen Kumar Mallurwar
Pallavi Rao
Shivashankar Sripelly
Javed Iqbal*
Prabhat Arya*

Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India
prabhata@drils.org
prof.javediqbal@gmail.com
www.prabhatarya.org



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Abstract A practical and scalable stereoselective synthesis of the western substituted tetrahydrofuran ring C27–C35 fragment of eribulin was developed by using (2*S*,3*S*)-tartaric acid as a cheap starting material that was converted into an intermediate through a stereoselective vinylation and cross-metathesis as the key steps. A regio- and stereoselective intramolecular oxy-Michael cyclization or an iodocyclization reaction finally provided the required western tetrahydrofuran ring fragment and its related isomeric analogues. These key fragments were further utilized in obtaining several types of macrocyclic derivatives for exploration of their biological properties. The simplicity of our present approach has the potential to be considered for large-scale syntheses of key fragments of eribulin and related analogues.

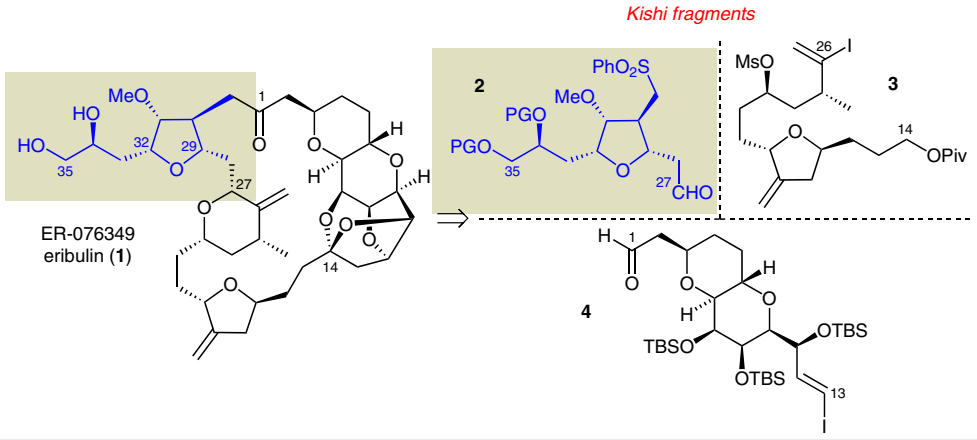
Key words halichondrins, eribulin, medicinal chemistry, macrocycles, natural products, stereoselective synthesis

The marathon efforts by Kishi and co-workers,[1–6] Phillips and co-workers,[7–11] and others[12,13] toward the synthesis of members of the halichondrin family of marine natural products led to the development of eribulin (**1**),[12,14–20] a drug for treating metastatic breast cancer, approved by the FDA in 2010 and marketed by Eisai Co., Ltd. (Tokyo) as Halaven. Eribulin is a nontaxane microtubule-dynamics inhibitor that functions through novel binding interactions with tubulin as a target.[20–22] Its precise mechanism of action is still not clear, and several groups are working toward its elucidation. It appears that the binding site for eribulin in tubulin differs from that of several known anticancer drugs such as paclitaxel or the vinca alkaloids.[21] Eribulin binds to an interdimer interface or to a β-tubulin subunit and, in doing so, inhibits the microtubular growth phase of microtubular dynamics instability in interphase cells without any effect on the shortening of the microtubules.[20] Furthermore, it also promotes centromere spindle relaxation without affecting the rate of microtubule stretching. In the case of eribulin-treated human lymphoma and prostate cancer, several biochemical apoptosis-related studies that included examinations of cytochrome c release from mitochondria, activation of caspase-3 and caspase-9, cleavage of poly(ADP-ribose) polymerase, and phosphorylation of Bcl-2 were also undertaken to understand the biological effects of eribulin.[16,23]

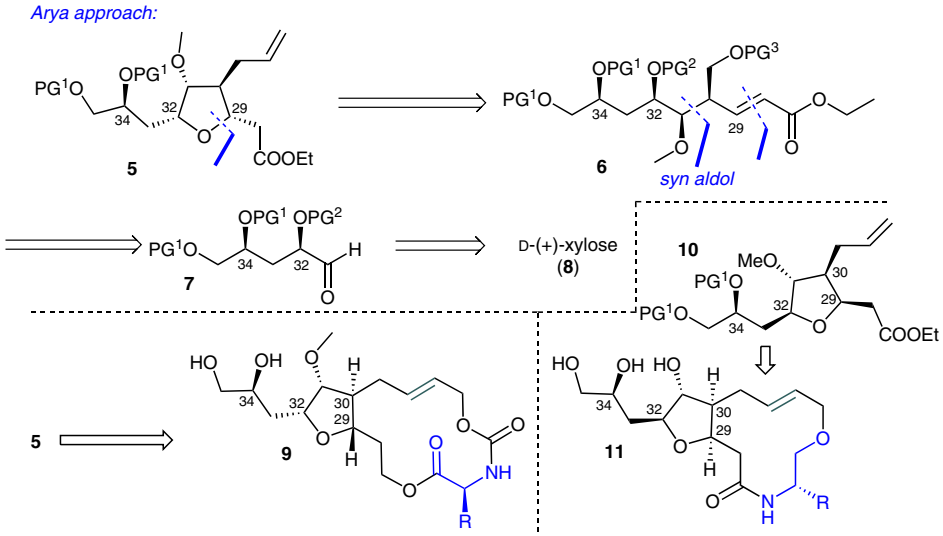
Shown in Scheme 1 are the three key fragments of eribulin, according to Kishi:[3,24,25] **2** (the western tetrahydrofuran ring), **3**, and **4**. Over the years, serious efforts have been made to develop practical and viable approaches for the large-scale synthesis of these fragments, which eventually led to a total synthesis of eribulin.

We previously reported a stereoselective synthesis of the tetrahydrofuran **5** (Scheme 2), an analogue of the western tetrahydrofuran ring fragment of eribulin.[26] The key reactions in our approach were a chiral auxiliary-based *syn*-aldol reaction to give vinylic ester **6** from aldehyde **7**, and a regio- and stereoselective oxy-Michael reaction that led to the required fragment **5**. This approach also permitted a synthesis of the isomeric compound **10** in which a diastereomeric analogue of **7** was used in the *syn*-aldol reaction (not shown in the scheme). Aldehyde **7** and its diastereomeric derivative were synthesized from D-(+)-xylose. Finally, the furan ring fragment **5** and its isomeric derivative **10** were used in syntheses of the 14-membered macrocycle **9** and the 12-membered macrocycle **11**, respectively, with the aim of exploring the biological properties of these products.

In a continuation of our interest in obtaining a series of various macrocyclic compounds containing the western tetrahydrofuran ring fragment, we describe our next-generation synthesis plan and its execution. Our first goal was to develop a practical and scalable stereoselective synthesis of several forms of the western furan ring fragment (for ex-



Scheme 1 Eribulin (**1**) and its three key fragments, according to Kishi

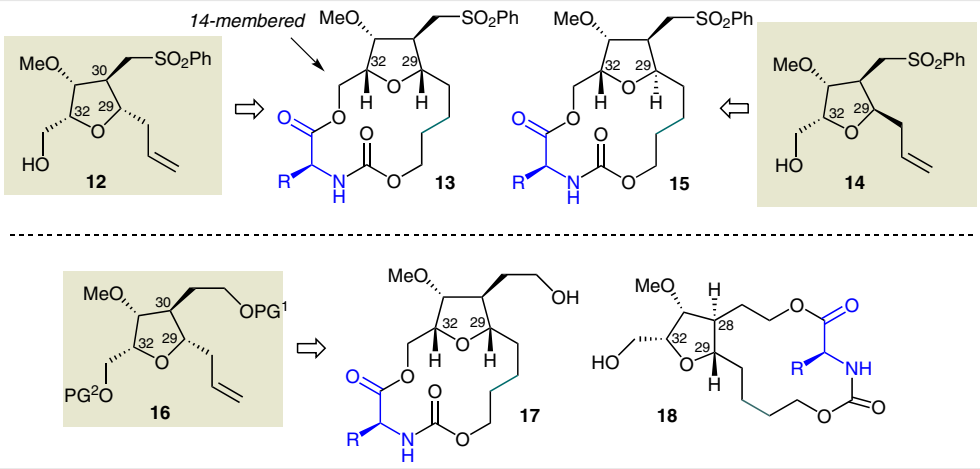


Scheme 2 Arya's approach to the western furan ring fragment **5**, and the synthesis of the 14- and 12-membered macrocyclic compounds **9** and **11** from **5** and **10**, respectively

ample, **12**, **14**, and **16**; Scheme 3) by using commercially available (2*S*,3*S*)-tartaric acid as a cheap starting material. If we could develop a synthetic route to these three analogues, we then planned to obtain various types of macrocyclic compounds as follows: (i) synthesis of 14-membered rings through the ring-closing metathesis approach (see **13** and **15**) from the two isomeric starting materials **12** and **14**, and (ii) a modular synthesis of two different 14-membered ring derivatives **17** and **18** from **16**. There is growing interest in developing practical methods for synthesizing various natural-product-inspired macrocyclic compounds because of their attractive features, which include dynamic preorganization, the ability to interact with several binding sites, and enhanced cell permeation.[26–32]

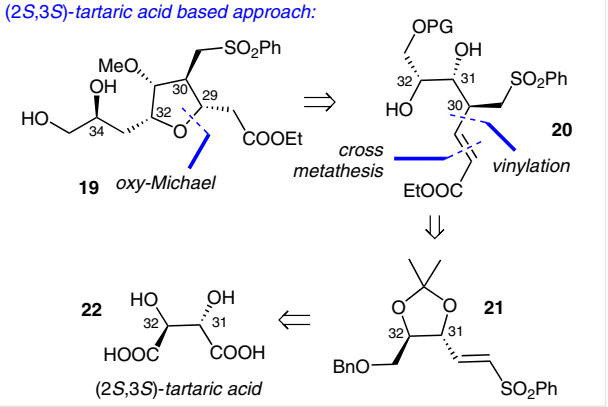
In the past few years, our group has reported the development of several methods for synthesizing diverse sets of macrocyclic compounds.[26,34–39] The long-term goal of our current study is to assemble a macrocyclic chemical toolbox consisting of compounds originating from substructures of eribulin to permit the exploration of their biological properties in several challenging targets related to protein–protein interactions and deregulated signaling pathways.

Our synthesis plan for obtaining fragment **12** and its two analogues **14** and **16** from (2*S*,3*S*)-tartaric acid is shown in Scheme 4. As demonstrated in our first approach,[26] ester **19** can be obtained from the vinyl ester **20** through a regio- and stereoselective oxy-Michael reaction. We envisioned a synthesis of **20** from the dioxolane **21** in two key steps: cross-metathesis and stereoselective vinyla-



Scheme 3 Plan to obtain several macrocyclic compounds from three analogues of the western furan ring fragments **12**, **14**, and **16**

tion. The dioxolane **21** can be easily obtained from (2*S*,3*S*)-tartaric acid (**22**). A key attraction of this approach is its use of **22** as a cheap chiral starting material.



Scheme 4 Plan to obtain **19** from (2*S*,3*S*)-tartaric acid (**22**)

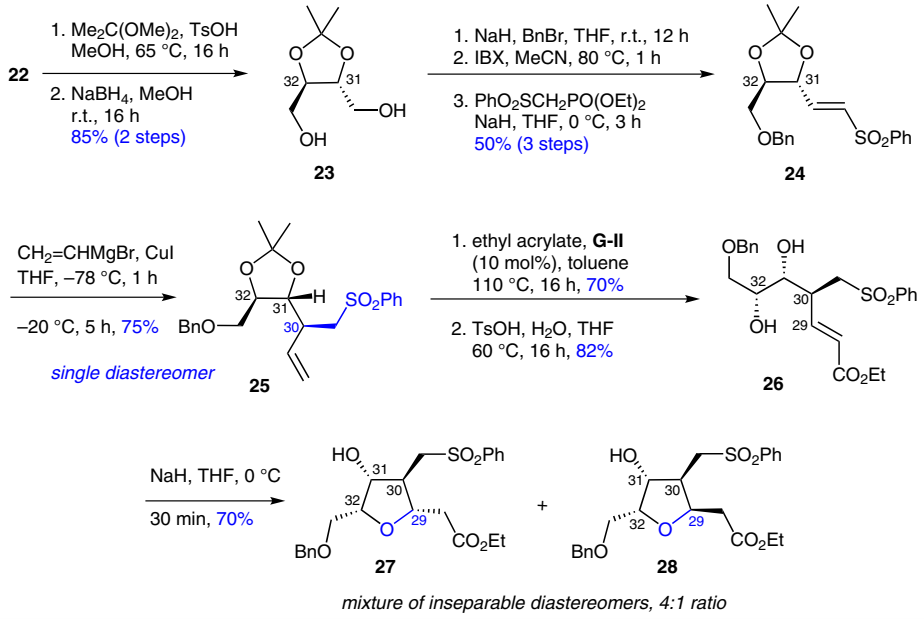
(2*S*,3*S*)-Tartaric acid (**22**) was converted into the diol **23** in two steps (Scheme 5). Subsequent oxidation of **23** followed by two-carbon homologation gave dioxolane **24**. Vinylation of **24** gave vinylic derivative **25** as a single diastereomer; the absolute stereochemistry at C-30 was assigned following cyclization. Cross-metathesis and removal of the acetonide group gave diol **26** in high yield. Treatment of **26** with NaH in THF at 0 °C resulted in an intramolecular oxy-Michael reaction to give the two inseparable products **27** and **28** in a 4:1 diastereomeric ratio. Complete stereochemical assignments for these products were made at a later stage (see compounds **29** and **30**).

The 4:1 diastereomeric mixture of **27** and **28** was subjected several simple transformations to give the tetrahydrofurans **29** (major) and **30** (minor) as separable compounds (Scheme 6). Details of the stereochemical assignment of **29** and **30** are provided in the Supporting Information. Tetrahydrofuran **29** was subjected to several simple reactions to complete the synthesis of the diol **33**. Overall, the current approach is simple and practical in nature; for example, by starting from 100 grams of (2*S*,3*S*)-tartaric acid, we can easily prepare 5 grams of **33** within a short period. The method therefore has the potential to be accepted as a process synthesis of **33**.

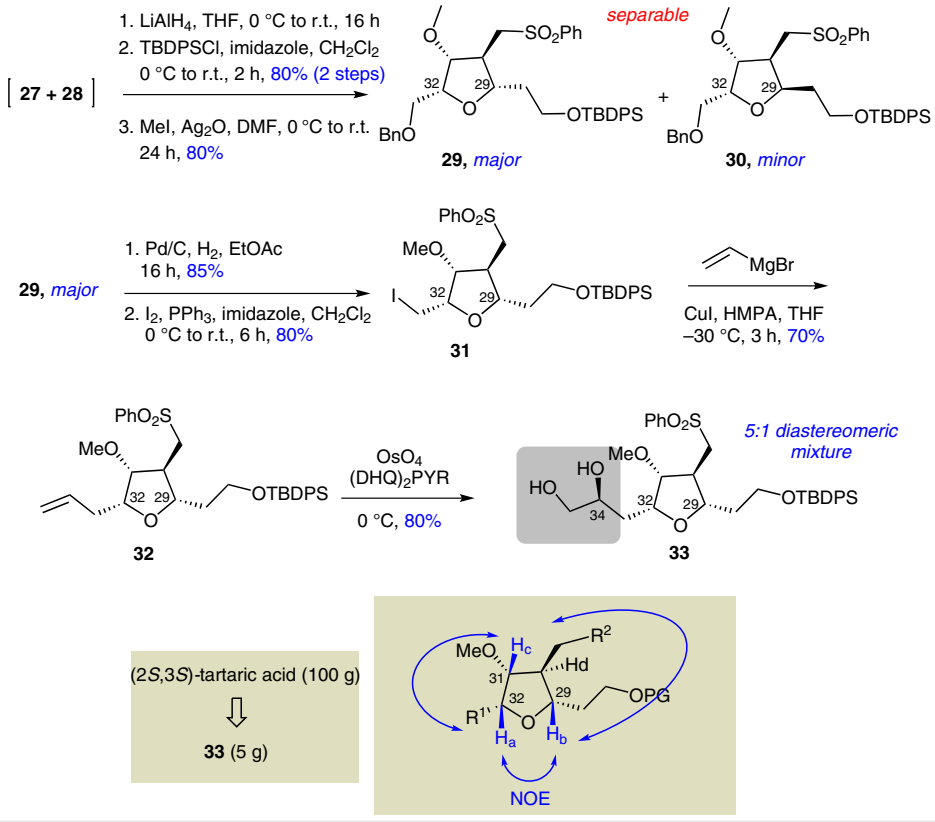
As an alternative to the oxy-Michael approach, we developed the iodocyclization-based strategy shown in Scheme 7. The precursor **35** needed for our iodocyclization strategy was obtained from dioxolane **36** or **37**, both of which can be obtained from (2*S*,3*S*)-tartaric acid.

Compound **25** (Scheme 8) was subjected to acetonide removal and then treated with iodine to give the iodo compounds **38** and **39** as a mixture of two separable diastereomers. Details of the stereochemical assignment are provided in the Supporting Information. To test the iodocyclization reaction on **44**, we used dioxolane **40** as a starting material, easily obtained from diol **23** (see the Supporting Information). Grignard vinylation of **40** gave stereoisomeric products **41** in a 13:1 ratio; these were then converted into the corresponding separable lactones **42** (major) and **43** (minor). The vinyl derivative **44** was obtained from the major lactone **42** in three steps. Iodocyclization of **44** gave the tetrahydrofuran **45** as a single diastereomer. At this stage, the configuration of **45** was thoroughly assigned by one- and two-dimensional NMR studies (see Supporting Information). In addition, iodo compounds **39** and **40** were also easily converted into the corresponding derivatives **46** and **47**, useful as key precursors for completing the synthesis of several macrocycles.

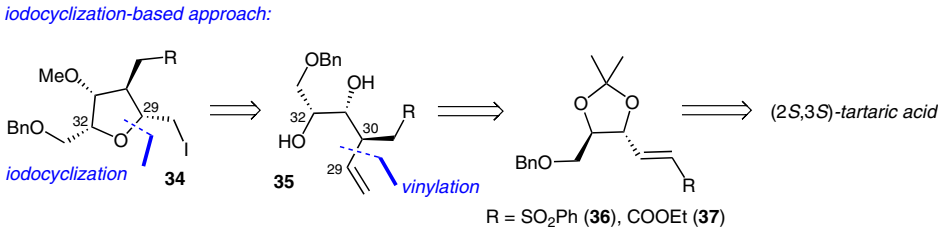
The syntheses of various 14-membered-ring-based macrocyclic compounds from tetrahydrofurans **46**, **47**, and **48** are shown in Scheme 9. A three-step sequence consisting of debenzylation, coupling with various *N*-allyloxycarbonyl-protected amino acids, and ring-closing metathesis with the Grubbs second-generation catalyst gave macrocy-



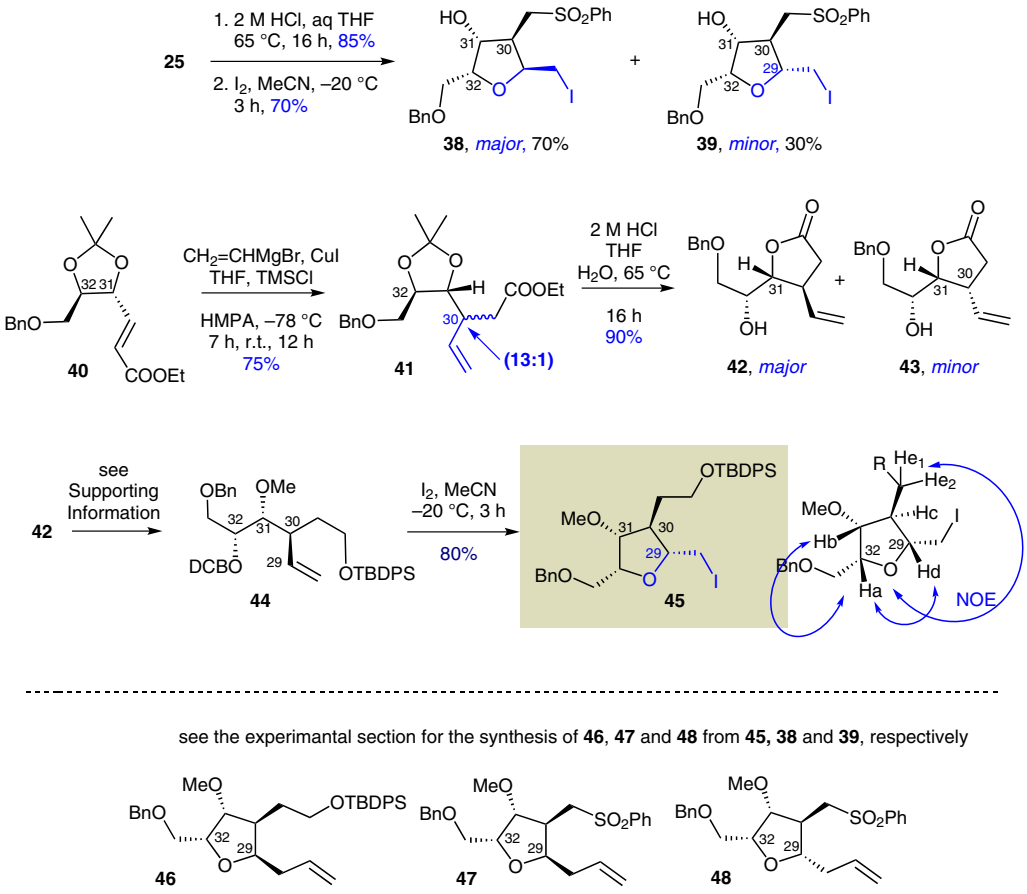
Scheme 5 Furan ring formation; IBX = 2-iodoxybenzoic acid; **G-II** = Grubbs second-generation catalyst



Scheme 6 Completion of the synthesis of Kishi's western furan ring fragment; $(DHQ)_2PYR$ = (8a,9*R*,8′′′a,9′′′*R*)-9,9′-[(2,5-diphenylpyrimidine-4,6-diyl)bis(oxy)]bis(6′-methoxy-10,11-dihydrocinchonan)



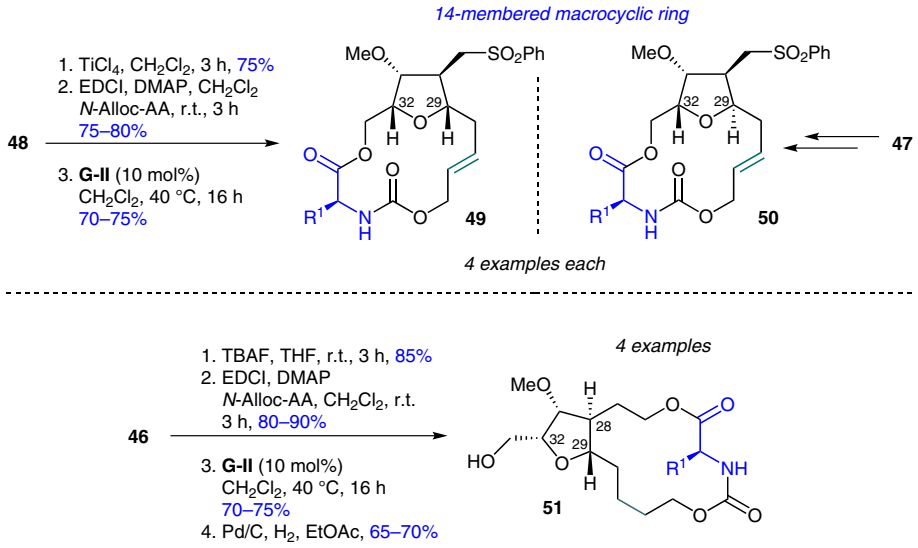
Scheme 7 Our planned iodocyclization approach



Scheme 8 Iodocyclization approach to **45**, **46**, and **47**

cles **49** smoothly from **48**. The formation of the 14-membered macrocyclic ring is independent of the choice of the amino acid moiety, and it produced a single double-bond isomer (the *trans*-olefin). A similar approach led to the synthesis of 14-membered macrocyclic compounds **50** and **51** from **47** and **46**, respectively.

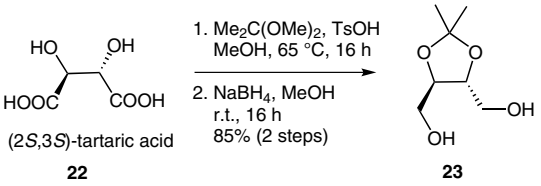
To summarize, scalable stereoselective syntheses of the key western tetrahydrofuran ring fragment-based compounds **45**, **46**, and **47** were achieved in a manner that permitted their large-scale preparation in a time-efficient way. The use of (2*S*,3*S*)-tartaric acid in the preparation of these key intermediates is attractive in making our approach acceptable as a process synthesis. Compounds **45**–**47** were also used in syntheses of several 14-membered macrocycles. Biological evaluation of the compounds generated in this program is in progress, and the results of these studies will be made available in due course.



Scheme 9 Syntheses of various macrocycles; *N*-Alloc-AA = *N*-allyloxycarbonyl amino acid

All reactions were carried out in flame-dried glassware under N_2. TLC was carried out on aluminum sheets coated with silica gel 60F254 (Merck, 1.05554); spots were visualized by UV irradiation at 254 nm or by staining with aq basic $KMnO_4$ or ceric ammonium molybdate. Flash column chromatography was performed on silica gel (Merck, 60A; 230–400 mesh). Commercially available reagents were used as supplied or were distilled before use. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer at the frequencies indicated. Where indicated, NMR peaks were assigned by COSY or NOESY experiments. All chemical shifts are referenced to residual solvent as an internal standard. Mass spectra and LC/MS were recorded by using electron impact, chemical ionization, or electrospray ionization techniques on an Agilent 6430 Triple-Quadrupole spectrometer. HPLC was carried out on Agilent 1200 series equipment. All reactions were performed in oven-dried glassware. DMF, CH_2Cl_2, and THF were dried by standard procedures immediately before use. Acetone was distilled under an inert atmosphere from K_2CO_3. DMF and CH_2Cl_2 were distilled from CaH_2 under N_2. THF were distilled over Na under N_2. All solvents were removed by evaporation under reduced pressure.

Synthesis of Fragment 33



Scheme 10

[(4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl]dimethanol (23)

To a stirred solution of (2*S*,3*S*)-tartaric acid (**22**; 100 g) in MeOH (20 mL) were added a catalytic amount of TsOH and 2,2-dimethoxypropane (2 equiv). The mixture was refluxed for 16 h until the starting material was consumed (TLC), then concentrated under reduced pressure and purified by column chromatography (hexanes–EtOAc, 9:1) to give **22.1** as a colorless liquid.

This was dissolved in MeOH (100 mL), and $NaBH_4$ (2 equiv) was added in a portionwise manner at 0 °C. After 16 h, the mixture was concentrated and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give **23** as a colorless liquid; yield: 92 g (85%). This was used directly in the next step.

Molecular formula: $C_7H_{14}O_4$; R_f = 0.5 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.05–4.00 (m, 2 H), 3.85–3.80 (m, 2 H), 3.75–3.70 (m, 2 H), 2.35–2.30 (m, 2 H), 1.45 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 139.9, 137.4, 133.5, 131.1, 129.3, 128.4, 127.8, 127.7, 127.7, 110.4, 79.0, 73.6, 69.0, 26.8, 26.5.

Scheme 11

(4*R*,5*R*)-4-[(Benzyloxy)methyl]-2,2-dimethyl-5-[(*E*)-2-(phenylsulfonyl)vinyl]-1,3-dioxolane (24)

NaH (1 equiv) was added in a portionwise manner to a stirred solution of diol **23** (92 g) in THF (100 mL) at 0 °C. BnBr (1 equiv) was then added and, after 12 h, the reaction was quenched with H_2O. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 8:2) to give **23.1** as a colorless liquid; yield: 98 g.

Compound **23.1** (98 g) was dissolved in MeCN (100 mL) and 2-iodoxybenzoic acid (IBX; 2 equiv) was added. The mixture was then refluxed at 80 °C for 1 h. When all the starting material was consumed (TLC),

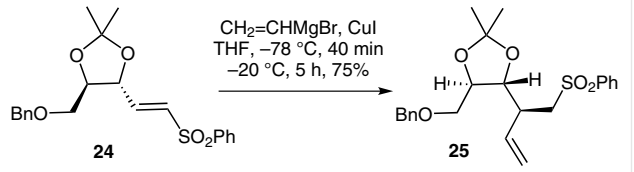
the mixture was filtered through Celite and concentrated under reduced pressure to provide crude **23.2** as a pale-yellow liquid; yield: 98 g. This was used directly in the next step.

A solution of the crude **23.2** (98 g) in THF was added to a Wittig ylide, freshly prepared from $PhO_2SCH_2PO(OEt)_2$ and NaH at 0 °C, and the mixture was stirred at 0 °C for 2 h. The reaction was then quenched with H_2O and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 8:2) to give a white solid; yield: 110 g (50%, 3 steps); molecular formula: $C_{21}H_{24}O_5S$; R_f = 0.4 (hexanes–EtOAc, 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.83 (m, 2 H), 7.60 (t, *J* = 7.20 Hz, 1 H), 7.51 (t, *J* = 7.70 Hz, 2 H), 7.37–7.25 (m, 5 H), 6.96 (dd, *J* = 14.95, 4.09 Hz, 1 H), 6.61 (dd, *J* = 14.96, 1.64 Hz, 1 H), 4.61–4.51 (m, 2 H), 4.48 (ddd, *J* = 8.36, 4.07, 1.64 Hz, 1 H), 3.95–3.89 (m, 1 H), 3.62 (dq, *J* = 10.30, 4.88 Hz, 2 H), 1.40 (s, 3 H), 1.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.2, 139.9, 137.5, 133.5, 131.2, 129.3, 128.5, 127.9, 127.7, 110.4, 79.1, 73.7, 69.1, 26.8, 26.6.

MS (ES+): *m/z* = 389.2 [M + 1].



Scheme 12

(4*R*,5*R*)-4-[(Benzyloxy)methyl]-2,2-dimethyl-5-{(1*S*)-1-[(phenylsulfonyl)methyl]prop-2-en-1-yl}-1,3-dioxolane (25)

CH_2=CHMgBr (37 mL, 38.1 mmol) was added dropwise to a stirred solution of CuI (1.8 g, 9.538 mmol) in anhyd THF (10 mL) at –78 °C, and the mixture was stirred at –78 °C for 10 min. A solution of sulfone **24** (3.7 g, 9.538 mmol) in THF (2 mL) was added dropwise over 20 min, and the mixture was stirred at –78 °C to –20 °C for 40 min and at –20 °C for 5 h. When the reaction was complete, it was quenched with a 1:1 aq soln of NH_4Cl and NH_4OH at –20 °C, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 9:1) to give a colorless oil; yield: 1.45 g (75%); molecular formula: $C_{23}H_{28}O_5S$; R_f = 0.35 (hexanes–EtOAc, 8:2).

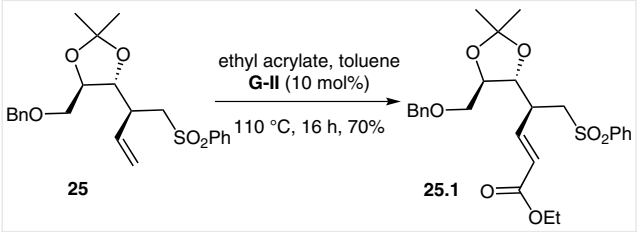
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.31 Hz, 2 H), 7.67–7.58 (m, 1 H), 7.54 (d, *J* = 7.70 Hz, 2 H), 7.37–7.26 (m, 4 H), 5.53–5.41 (m, 1 H), 5.14 (s, 1 H), 5.04 (d, *J* = 11.00 Hz, 1 H), 4.54 (s, 2 H), 3.97–3.91 (m, 1 H), 3.73 (s, 1 H), 3.60–3.50 (m, 2 H), 3.49–3.41 (m, 1 H), 3.20–3.11 (m, 1 H), 2.82–2.72 (m, 1 H), 1.35 (s, 3 H), 1.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 137.8, 134.8, 133.6, 129.4, 129.2, 128.4, 128.1, 127.7, 127.3, 119.4, 109.5, 79.0, 78.2, 73.3, 70.4, 57.2, 43.5, 27.1, 27.1.

MS (ES+): *m/z* = 417.1 [M + 1].

Ethyl (2*E*,4*S*)-4-{(4*R*,5*R*)-5-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-5-(phenylsulfonyl)pent-2-enoate (25.1)

To a stirred solution of dioxolane **25** (1 g, 2.403 mmol) in toluene (50 mL) were added the Grubbs second-generation catalyst (**G-II**; 101 mg, 0.120 mmol) and ethyl acrylate (1.27 mL, 12.015 mmol), and the mixture was refluxed for 16 h. When the reaction complete, the mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 8:2) to give a light-yellow oil; yield: 780 mg (70%); molecular formula: $C_{26}H_{32}O_7S$; R_f = 0.5 (hexanes–EtOAc, 8:2).

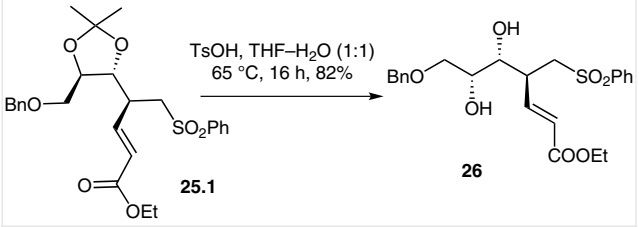


Scheme 13

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.86 (m, 2 H), 7.65 (t, *J* = 7.2 Hz, 1 H), 7.55–7.52 (m, 2 H), 7.39–7.29 (m, 5 H), 6.58 (dd, *J* = 9.60, 15.60 Hz, 1 H), 5.84 (d, *J* = 15.60 Hz, 1 H), 4.54 (s, 2 H), 4.15 (q, *J* = 7.40 Hz, 2 H), 3.95–3.85 (m, 2 H), 3.58 (dd, *J* = 2.80, 15.60 Hz, 1 H), 3.50 (t, *J* = 4.37 Hz, 2 H), 3.25 (dd, *J* = 9.60, 14.40 Hz, 1 H), 3.04–2.96 (m, 1 H), 1.37 (s, 3 H), 1.34 (s, 3 H), 1.30–1.28 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.3, 143.8, 139.3, 137.6, 133.8, 129.3, 128.4, 128.1, 127.7, 127.6, 124.9, 109.9, 78.6, 78.1, 73.5, 70.2, 60.5, 56.3, 40.9, 31.9, 30.0, 29.7, 27.0, 22.7, 14.2.

MS (ES+): *m/z* = 489.2 [M + 1].



Scheme 14

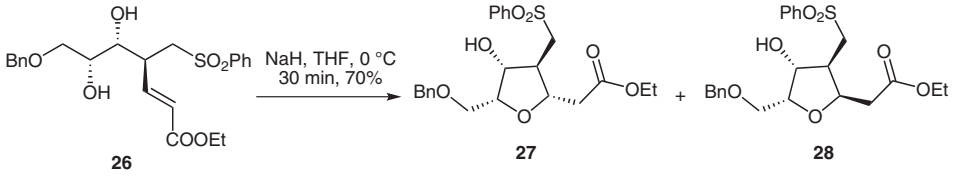
Ethyl (2*E*,4*S*,5*R*,6*R*)-7-(Benzyloxy)-5,6-dihydroxy-4-[(phenylsulfonyl)methyl]hept-2-enoate (26)

TsOH (281 mg, 1.639 mmol) was added to a stirred solution of dioxolane **25.1** (780 mg, 1.639 mmol) in THF–H_2O (1:1; 20 mL), and the mixture was refluxed for 16 h until all the starting material was consumed (TLC). The mixture was then extracted with EtOAc (3 × 50 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 5:5) to give a white solid; yield: 588 mg (82%); molecular formula: $C_{23}H_{28}O_7S$; R_f = 0.2 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88–7.86 (m, 2 H), 7.62 (t, *J* = 7.41 Hz, 1 H), 7.55–7.52 (m, 2 H), 7.38–7.27 (m, 5 H), 6.58 (dd, *J* = 15.60, 9.57 Hz, 1 H), 5.85 (d, *J* = 15.60 Hz, 1 H), 4.52 (s, 2 H), 4.14 (q, *J* = 7.15 Hz, 2 H), 3.77 (dd, *J* = 14.16, 2.40 Hz, 1 H), 3.72 (t, *J* = 4.06 Hz, 1 H), 3.58 (d, *J* = 4.83 Hz, 2 H), 3.52 (d, *J* = 7.94 Hz, 1 H), 3.21 (dd, *J* = 14.16, 9.20 Hz, 1 H), 3.16–3.08 (m, 1 H), 2.97–2.91 (br s, 1 H), 2.63–2.56 (br s, 1 H), 1.27 (t, *J* = 7.13 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): 165.5, 144.4, 137.1, 133.7, 129.3, 128.6, 128.1, 127.9, 125.2, 110.0, 73.8, 73.0, 72.6, 68.7, 60.5, 56.6, 41.0, 14.2.

MS (ES+): *m/z* = 449.3 [M + 1].



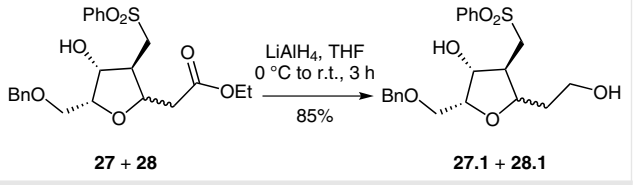
Scheme 15

Ethyl {(2*R*,3*R*,4*R*,5*R*)- and {(2*S*,3*R*,4*R*,5*R*)-5-[(Benzyloxy)methyl]-4-hydroxy-3-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}acetate (27 and 28)

60% NaH (21 mg, 0.892 mmol) was added to a stirred solution of ester **26** (400 mg, 0.892 mmol) in anhyd THF (15 mL) at 0 °C, and the mixture was stirred for 30 min. When the reaction was complete, it was quenched with H_2O and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 3:7) to provide an inseparable mixture of the isomers **27** and **28** as a white gummy liquid; yield: 360 mg (70%); molecular formula: $C_{23}H_{28}O_7S$; R_f = 0.3 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.88 (m, 2 H), 7.67 (t, *J* = 7.45 Hz, 1 H), 7.58–7.54 (m, 2 H), 7.38–7.26 (m, 5 H), 4.62–4.48 (m, 2.6 H), 4.24–4.18 (m, 1 H), 4.11 (q, *J* = 7.14 Hz, 2 H), 4.03 (dd, *J* = 11.92, 5.52 Hz, 0.68 H), 3.94 (dd, *J* = 9.59, 4.66 Hz, 0.68 H), 3.79–3.65 (m, 2.2 H), 3.26 (d, *J* = 6.99 Hz, 1.3 H), 3.23–3.15 (m, 1 H), 2.87–2.76 (m, 1.5 H), 2.71–2.65 (m, 1 H), 2.59–2.50 (m, 0.8 H), 2.48–2.44 (m, 0.5 H), 1.23 (t, *J* = 9.6 Hz, 3 H).

MS (ES+): *m*/*z* = 449.7 [M + 1].



Scheme 16

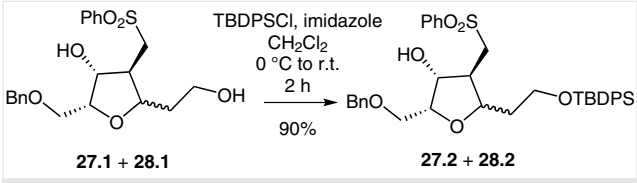
(2*R*,3*R*,4*R*,5*R*)- and (2*R*,3*R*,4*R*,5*S*)-2-[(Benzyloxy)methyl]-5-(2-hydroxyethyl)-4-[(phenylsulfonyl)methyl]tetrahydrofuran-3-ol (27.1 and 28.1)

$LiAlH_4$ (43 mg, 1.138 mmol) was added to a stirred solution of **27** + **28** (340 mg, 0.7589 mmol) in anhyd THF (15 mL) at 0 °C and the mixture was stirred for 3 h. The reaction was quenched with sat. aq NaOH (2 mL), and the mixture was filtered through Celite and concentrated under reduced pressure to give a colorless liquid; yield (**27.1** + **28.1**): 260 mg (85%). This was used directly in the next reaction.

Molecular formula: $C_{21}H_{26}O_6S$; R_f = 0.2 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.89 (m, 2 H), 7.70–7.64 (m, 1 H), 7.58–7.54 (m, 2 H), 7.37–7.27 (m, 5 H), 4.59–4.44 (m, 3 H), 4.29 (t, *J* = 4.40 Hz, 0.7 H), 4.22 (q, *J* = 7.14 Hz, 0.3 H), 4.00 (q, *J* = 5.20 Hz, 0.7 H), 3.80–3.69 (m, 5 H), 3.24–3.12 (m, 2 H), 2.73 (br s, 2 H), 2.67–2.62 (m, 1 H), 2.47–2.41 (m, 2 H), 1.95—1.79 (m, 1.6 H), 1.67–1.51 (m, 0.8 H).

MS (ES+): *m*/*z* = 407.3 [M + 1].



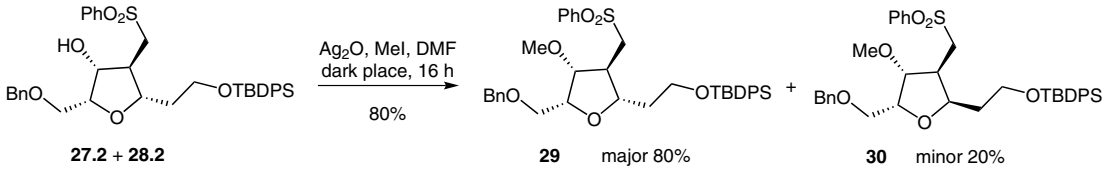
Scheme 17

(2*R*,3*R*,4*R*,5*R*)- and (2*R*,3*R*,4*R*,5*S*)-2-[(Benzyloxy)methyl]-5-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-4-[(phenylsulfonyl)methyl]tetrahydrofuran-3-ol (27.2 and 28.2)

To a stirred solution of **27.1** + **28.1** (200 mg, 0.492 mmol) in anhyd CH_2Cl_2 (10 mL) at 0 °C were added imidazole (100 mg, 1.479 mmol) and TBDPSCl (0.15mL, 0.5911 mmol), and the mixture was stirred at r.t. for 3 h. When the reaction was complete it was quenched with H_2O and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 7.5:2.5) to give a gummy liquid; yield (**27.2** + **28.2**): 280 mg (90%); molecular formula: $C_{37}H_{44}O_6SSi$; R_f = 0.5 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.23 Hz, 2 H), 7.68–7.60 (m, 5 H), 7.56–7.51 (m, 2 H), 7.44–7.27 (m, 11 H), 4.61–4.52 (m, 2 H), 4.51–4.41 (m, 0.7 H), 4.37 (t, *J* = 4.80 Hz, 1 H), 4.11 (q, *J* = 4.80 Hz, 0.3 H), 3.97 (q, *J* = 4.80 Hz, 0.7 H), 3.81–3.66 (m, 5 H), 3.23–3.11 (m, 2 H), 2.60–2.54 (m, 0.7 H), 2.33–2.25 (m, 1 H), 1.91–1.81 (m, 1 H), 1.76–1.61 (m, 1.3 H), 1.03–1.01 (m, 9 H).

MS (ES+): *m*/*z* = 645.1 [M + 1].



Scheme 18

(2-{(2*R*,3*S*,4*R*,5*R*)- and (2-{(2*S*,3*S*,4*R*,5*R*)-5-[(Benzyloxy)methyl]-4-methoxy-3-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}ethoxy)(*tert*-butyl)diphenylsilane5-[(Benzyloxy)methyl]-4-methoxy-3-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}ethoxy)(*tert*-butyl)diphenylsilane (29 and 30)

To a stirred solution of **27.2** + **28.2** (120 mg, 0.1863 mmol) in anhyd DMF (15 mL) at 0 °C were added Ag_2O (243 mg, 0.931 mmol) and MeI (0.12mL, 1.863 mmol), and the mixture was stirred at r.t. for 48 h in darkness. When the reaction was complete, the mixture was filtered through Celite and extracted sequentially with EtOAc (20 mL) and cold water (3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 8:2) to give **29** as a colorless liquid (yield: 85 mg), and **30** as a white solid (yield: 10 mg); combined yield: 90%.

29

Molecular formula: $C_{38}H_{46}O_6SSi$; R_f = 0.6 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.78 Hz, 2 H), 7.66–7.63 (m, 5 H), 7.53 (t, *J* = 7.72 Hz, 2 H), 7.46–7.25 (m, 11 H), 4.57 (dd, *J* = 41.73, 12.20 Hz, 2 H), 4.01 (d, *J* = 3.68 Hz, 1 H), 3.96–3.91 (m, 1 H), 3.80–3.64 (m, 5 H), 3.39 (s, 3 H), 3.17–3.06 (m, 2 H), 2.55–2.48 (m, 1 H), 1.97 (dt, *J* = 13.61, 6.57 Hz, 1 H), 1.74 (dt, *J* = 13.61, 6.57 Hz, 1 H), 1.02 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 139.5, 138.1, 135.5, 133.9, 133.8, 133.6, 129.6, 129.4, 128.3, 127.8, 127.7, 127.6, 85.5, 80.8, 80.7, 73.4, 68.4, 60.8, 57.8, 43.9, 37.9, 26.8, 19.1.

MS (ES+): *m/z* = 659.2 [M + 1]

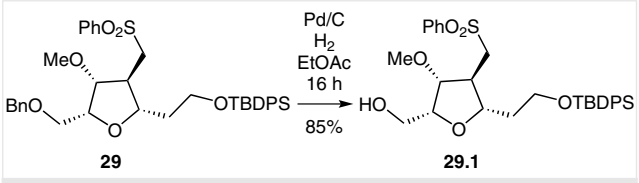
30

Molecular formula: $C_{38}H_{46}O_6SSi$; R_f = 0.65 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 7.69 Hz, 2 H), 7.67–7.60 (m, 5 H), 7.55 (t, *J* = 7.76 Hz, 2 H), 7.44–7.25 (m, 11 H), 4.55 (dd, *J* = 41.73, 12.20 Hz, 2 H), 4.35–4.24 (m, 3 H), 3.74–3.64 (m, 2 H), 3.62–3.51 (m, 2 H), 3.37 (s, 3 H), 3.15 (dd, *J* = 14.26, 3.23 Hz, 1 H), 2.85 (dd, *J* = 14.20, 10.61 Hz, 1 H), 2.72–2.65 (m, 1 H), 1.67–1.58 (m, 2 H), 1.03 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 139.7, 138.3, 135.5, 133.9, 133.7, 129.6, 129.4, 128.3, 127.8, 127.7, 127.6, 127.5, 84.5, 78.6, 75.7, 73.3, 68.9, 61.2, 58.0, 53.2, 41.2, 33.2, 26.8, 19.2.

MS (ES+): *m/z* = 659.2 [M + 1].



Scheme 19

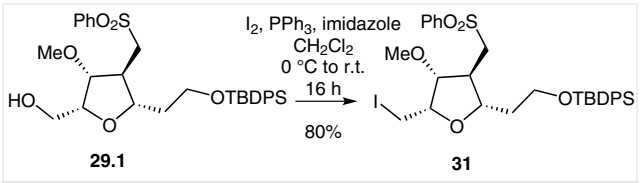
{(2*R*,3*R*,4*S*,5*S*)-5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methanol (29.1)

To a stirred solution of tetrahydrofuran **29** (160 mg) in anhyd EtOAc (15 mL) was added Pd/C (20 mg) and the mixture was stirred for 24 h under H_2 (1 atm). The mixture was then filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 6:4) to give a colorless gummy liquid; yield: 118 mg (85%); molecular formula: $C_{31}H_{40}O_6SSi$; R_f = 0.3 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.83 Hz, 2 H), 7.67–7.63 (m, 5 H), 7.55 (t, *J* = 7.72 Hz, 2 H), 7.46–7.34 (m, 6 H), 4.11 (br s, 1 H), 3.87–3.70 (m, 6 H), 3.43 (s, 3 H), 3.16–3.11 (m, 2 H), 2.57–2.52 (m, 1 H), 2.20 (br s, 1 H), 1.93 (dt, *J* = 13.68, 5.80 Hz, 1 H), 1.79 (dt, *J* = 13.13, 12.77, 5.84 Hz, 1 H), 1.01 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 139.5, 135.5, 133.9, 133.7, 133.6, 129.6, 129.4, 127.8, 127.7, 127.6, 86.5, 81.0, 80.5, 61.5, 60.7, 57.9, 57.6, 44.2, 37.7, 26.8, 19.2.

MS (ES+): *m/z* = 569.2 [M + 1].



Scheme 20

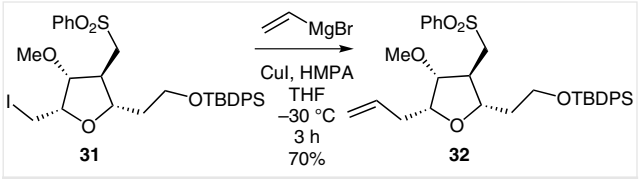
***tert*-Butyl(2-{(2*S*,3*S*,4*R*,5*S*)-5-(iodomethyl)-4-methoxy-3-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}ethoxy)diphenylsilane (31)**

To a stirred solution of the tetrahydrofuran **29.1** (50 mg, 0.088 mmol) in anhyd CH_2Cl_2 (10 mL) at r.t. were added PPh_3 (115 mg, 0.440 mmol) and imidazole (29 mg, 0.440 mmol). The mixture was cooled to 0 °C, I_2 (110 mg, 0.440 mmol) was added, and the mixture was stirred for 16 h until the starting material was consumed (TLC). The reaction was then quenched with sat. aq $Na_2S_2O_3$, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 9.5:0.5) to give a white solid; yield: 45 mg (80%); molecular formula: $C_{31}H_{39}IO_5SSi$; R_f = 0.2 (hexanes–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.98 Hz, 2 H), 7.67–7.63 (m, 5 H), 7.55 (t, *J* = 7.76 Hz, 2 H), 7.44–7.34 (m, 6 H), 4.05–4.02 (m, 1 H), 4.01–3.98 (m, 1 H), 3.87 (td, *J* = 8.03, 5.05 Hz, 1 H), 3.79–3.67 (m, 2 H), 3.45 (s, 3 H), 3.32 (t, *J* = 8.78 Hz, 1 H), 3.21 (dd, *J* = 9.41, 5.73 Hz, 1 H), 3.12 (d, *J* = 6.99 Hz, 2 H), 2.61 (dd, *J* = 12.01, 6.62 Hz, 1 H), 1.91 (td, *J* = 13.67, 6.85 Hz, 1 H), 1.76 (td, *J* = 13.19, 6.15 Hz, 1 H), 1.01 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 139.5, 135.5, 133.9, 129.6, 129.5, 127.8, 127.6, 84.9, 82.2, 81.6, 60.6, 58.0, 57.8, 43.7, 38.2, 29.7, 26.8, 19.2.

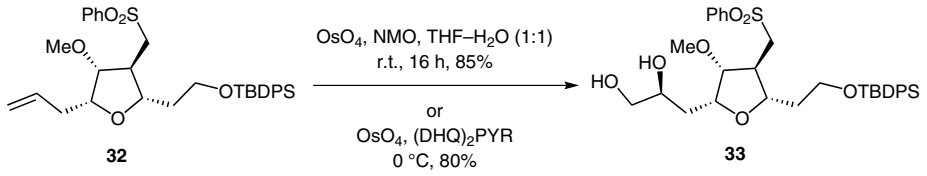
MS (ES+): *m/z* = 679.1 [M + 1].



Scheme 21

(2-{(2*S*,3*S*,4*R*,5*R*)-5-Allyl-4-methoxy-3-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}ethoxy)(*tert*-butyl)diphenylsilane (32)

To a stirred solution of iodide **31** (25 mg, 0.0368 mmol) in anhyd THF (2 mL) at 23 °C were added CuI (3 mg, 0.0184 mmol) and HMPA (0.07 mL, 0.368 mmol). The mixture was cooled to –30 °C and CH_2=CHMgBr (1 M in THF; 0.11 mL, 0.11 mmol) was added dropwise. The mixture was stirred for 3 h at –30 °C and then the reaction was quenched with sat. aq NH_4Cl solution. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by col-



Scheme 22

umn chromatography (hexanes–EtOAc, 7:3) to give a colorless oil; yield: 15 mg (70%); molecular formula: $C_{33}H_{42}O_5SSi$; R_f = 0.2 (hexanes–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 2 H), 7.70–7.64 (m, 4 H), 7.62–7.59 (m, 1 H), 7.55–7.49 (m, 2 H), 7.46–7.36 (m, 6 H), 5.58–5.48 (m, 2 H), 5.25–5.16 (m, 3 H), 4.04 (dd, *J* = 6.11, 3.16 Hz, 1 H), 3.98 (dd, *J* = 4.90, 2.53 Hz, 1 H), 3.88–3.80 (m, 2 H), 3.31–3.29 (m, 2 H), 3.22 (s, 3 H), 2.27–2.21 (m, 2 H), 1.77–1.73 (m, 2 H), 1.02 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 139.7, 135.6, 135.5, 134.9, 133.6, 133.5, 133.3, 129.7, 129.2, 128.0, 127.8, 127.7, 118.4, 110.0, 81.2, 70.6, 62.2, 56.6, 52.8, 42.7, 37.3, 31.9, 29.7, 29.6, 29.3, 26.9, 26.8, 22.7, 19.1, 14.1.

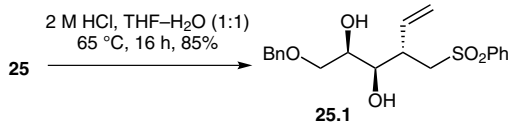
MS (ES+): *m*/*z* = 579.3 [M + 1].

(2*S*)-3-{(2*R*,3*R*,4*S*,5*S*)-5-(2-{[*tert*-Butyl(diphenyl)silyl]oxy}ethyl)-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}propane-1,2-diol (33)

To a stirred solution of vinyl compound **32** (5 mg, 0.086 mmol) in 1:1 THF–H_2O (1 mL) at r.t. was added *N*-methylmorpholine *N*-oxide (0.023 mL, 0.198 mmol), OsO_4 (0.1 M in *t*-BuOH; 0.08 mL, 0.00172 mmol), and $(DHQ)_2PYR$ (0.07 mg, 1 mol%), and the mixture was stirred for 16 h. When the starting material was completely consumed, $Na_2S_2O_3$ (2 mg in 2 mL H_2O) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 5:5) to give a colorless oil:[4] yield: 4 mg (80%); molecular formula: $C_{33}H_{44}O_7SSi$; R_f = 0.2 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.91 Hz, 2 H), 7.68–7.65 (m, 5 H), 7.59 (t, *J* = 7.68 Hz, 2 H), 7.49–7.40 (m, 6 H), 4.08–4.02 (m, 1 H), 3.98–3.75 (m, 5 H), 3.68–3.64 (m, 2 H), 3.49–3.45 (m, 1 H), 3.42 (s, 3 H), 3.14–3.06 (m, 1 H), 2.72–2.65 (m, 1 H), 2.10–1.85 (m, 3 H), 1.82–1.68 (m, 3 H), 1.06 (s, 9 H).

MS (ES+): *m*/*z* = 613.2 [M + 1].



Scheme 23

Synthesis of Fragments 38 and 39

(2*R*,3*R*,4*S*)-1-(Benzyloxy)-4-[(phenylsulfonyl)methyl]hex-5-ene-2,3-diol (25.1)

2 M aq HCl (1 mL) was added to a stirred solution of sulfone **25** (1 g, 2.87 mmol) in THF–H_2O (1:1), and the mixture was refluxed for 16 h until the starting material was consumed (TLC). The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 5:5) to give a light-yellow solid; yield: 760 mg (85%); molecular formula: $C_{20}H_{24}O_5S$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.89 (m, 2 H), 7.66–7.62 (m, 1 H), 7.57–7.53 (m, 2 H), 7.39–7.29 (m, 5 H), 5.65–5.56 (m, 1 H), 5.17–5.11 (m, 2 H), 4.54 (s, 2 H), 3.89–3.84 (m, 1 H), 3.71 (dd, *J* = 14.31, 2.97 Hz, 1 H), 3.62–3.58 (m, 2 H), 3.50–3.46 (m, 1 H), 3.19 (dd, *J* = 14.30, 8.94 Hz, 1 H), 2.96 (dq, *J* = 18.00, 2.80 Hz, 1 H), 2.31–2.16 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9, 137.3, 135.8, 133.6, 129.2, 128.6, 128.1, 127.8, 119.4, 73.2, 73.0, 68.4, 57.2, 42.5, 28.1.

MS (ES+): *m*/*z* = 393.2 [M + 17].

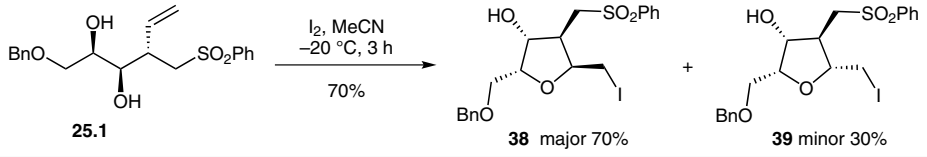
(2*R*,3*R*,4*R*,5*S*)- and (2*R*,3*R*,4*R*,5*R*)-2-[(Benzyloxy)methyl]-5-(iodomethyl)-4-[(phenylsulfonyl)methyl]tetrahydrofuran-3-ol (38 and 39)

Diol **25.1** (1 g, 2.645 mmol) was dissolved in MeCN (20 mL) in round-bottomed flask, and a solution of I_2 (1 g, 3.968 mmol) in MeCN (2 mL) was added slowly at –20 °C. The mixture was stirred for 3 h at –20 °C until the reaction was complete. The reaction was then quenched with sat. aq $Na_2S_2O_3$ and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 8:2) to give **38** as white solid (yield: 600 mg) and **39** as a colorless liquid (yield: 250 mg); combined yield: 70%.

38

Molecular formula: $C_{20}H_{23}IO_5S$; R_f = 0.3 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.56 Hz, 2 H), 7.68 (t, *J* = 7.41 Hz, 1 H), 7.58 (t, *J* = 7.67 Hz, 2 H), 7.39–7.28 (m, 5 H), 4.72 (br s, 1 H), 4.61–4.50 (m, 3 H), 4.33 (q, *J* = 5.60 Hz, 1 H), 3.74 (d, *J* = 4.24 Hz, 2 H), 3.29–3.21 (m, 2 H), 3.19–3.03 (m, 3 H), 2.76–2.68 (m, 1 H).



Scheme 24

^{13}C NMR (100 MHz, $CDCl_3$): 138.5, 137.2, 134.1, 129.5, 128.5, 128.1, 127.8, 78.4, 78.2, 75.6, 73.9, 69.4, 53.0, 45.3, 3.6.

MS (ES+): *m/z* = 502.8 [M + 1].

39

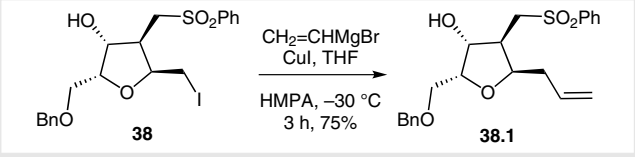
Molecular formula: $C_{20}H_{23}IO_5S$; R_f = 0.2 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.17 Hz, 2 H), 7.70 (t, *J* = 7.01 Hz, 1 H), 7.61 (t, *J* = 7.72 Hz, 2 H), 7.41–7.30 (m, 5 H), 4.60 (s, 2 H), 4.44 (t, *J* = 4.37 Hz, 1 H), 4.10 (q, *J* = 4.78 Hz, 1 H), 3.83–3.77 (m, 2 H), 3.77–3.72 (m, 1 H), 3.47 (dd, *J* = 10.31, 5.73 Hz, 1 H), 3.38 (dd, *J* = 10.28, 5.54 Hz, 1 H), 3.32–3.22 (m, 2 H), 2.53–2.45 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): 138.6, 137.5, 134.2, 129.6, 128.5, 128.2, 127.9, 127.8, 81.7, 79.8, 77.8, 73.8, 68.8, 58.0, 48.2, 29.7, 8.4.

MS (ES+): *m/z* = 502.8 [M + 1].

Synthesis of Macrocycles 50a–d



Scheme 25

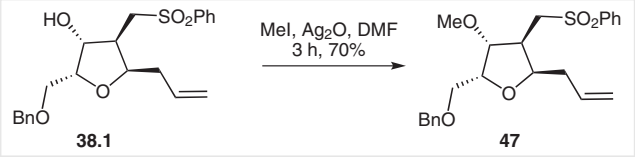
(2*R*,3*R*,4*R*,5*R*)-5-Allyl-2-[(benzyloxy)methyl]-4-[(phenylsulfonyl)methyl]tetrahydrofuran-3-ol (38.1)

To a stirred solution of compound **38** (500 mg, 0.793 mmol) in anhyd THF (5 mL) were added CuI (75 mg, 0.396 mmol) and HMPA (1.41 mL, 7.93 mmol) at 23 °C. The mixture was cooled to –30 °C and CH_2=CHMgBr (1 M in THF; 2.3 mL, 2.37 mmol) was added dropwise. The mixture was stirred for 3 h at –30 °C and then the reaction was quenched with sat. aq NH_4Cl. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 7:3) to give a white solid; yield: 300 mg (75%); molecular formula: $C_{22}H_{26}O_5S$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.87 (m, 2 H), 7.64–7.61 (m, 1 H), 7.54 (t, *J* = 7.60 Hz, 2 H), 7.38–7.27 (m, 5 H), 5.66–5.55 (m, 1 H), 5.16–5.10 (m, 2 H), 4.53 (d, *J* = 1.45 Hz, 2 H), 3.86–3.84 (m, 1 H), 3.70 (dd, *J* = 14.29, 2.98 Hz, 1 H), 3.62–3.57 (m, 2 H), 3.48 (d, *J* = 8.72 Hz, 1 H), 3.18 (dd, *J* = 14.30, 8.84 Hz, 1 H), 2.95 (dq, *J* = 8.88, 2.89 Hz, 1 H), 2.16–1.61 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.0, 137.4, 135.8, 133.6, 129.1, 128.5, 128.0, 127.8, 119.3, 73.7, 73.2, 73.0, 68.4, 57.2, 42.4.

MS (ES+): *m/z* = 402.8 [M + 1].



Scheme 26

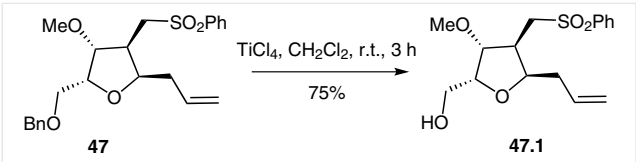
(2*R*,3*S*,4*R*,5*R*)-2-Allyl-5-[(benzyloxy)methyl]-4-methoxy-3-[(phenylsulfonyl)methyl]tetrahydrofuran (47)

Ag_2O (2 equiv) and MeI (5 equiv) were added to a stirred solution of sulfone **38.1** (320 mg) in DMF (20 mL) in darkness and the mixture as stirred for 16 h at r.t. The mixture was then filtered through Celite and the filtrate was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 9:1) to give a white solid; yield: 240 mg (70%); molecular formula: $C_{23}H_{28}O_5S$; R_f = 0.6 (hexanes–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.84 (m, 2 H), 7.63–7.59 (m, 1 H), 7.52 (t, *J* = 7.59 Hz, 2 H), 7.36–7.27 (m, 5 H), 5.75–5.62 (m, 1 H), 5.13–5.06 (m, 2 H), 4.51 (s, 2 H), 3.62–3.52 (m, 3 H), 3.44–3.39 (m, 1 H), 3.37–3.36, (m, 6 H), 3.30 (dd, *J* = 6.52, 3.21 Hz, 1 H), 3.21 (dd, *J* = 14.28, 10.09 Hz, 1 H), 3.05–2.98 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.0, 137.7, 136.8, 133.4, 129.0, 128.3, 128.0, 127.7, 118.2, 82.6, 80.1, 73.4, 68.4, 60.7, 58.6, 56.8, 41.1, 29.6.

MS (ES+): *m/z* = 417.2 [M + 1].



Scheme 27

{(2*R*,3*R*,4*S*,5*R*)-5-Allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methanol (47.1)

$TiCl_4$ (0.14 mL, 1.329 mmol) was added to a stirred solution of sulfone **47** (250 mg, 0.664 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred for 3 h at r.t. When the starting material was completely consumed, the reaction was quenched with sat. aq NH_4Cl and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (hexanes–EtOAc, 5:5) to give a colorless oil; yield: 150 mg (75%); molecular formula: $C_{16}H_{22}O_5S$; R_f = 0.35 (hexanes–EtOAc, 5:5).

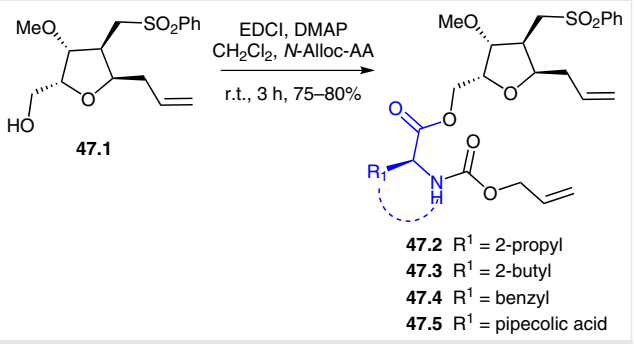
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.87 (m, 3 H), 7.63 (t, *J* = 7.43 Hz, 1 H), 7.54 (t, *J* = 7.55 Hz, 2 H), 5.73 (dt, *J* = 17.16, 8.85 Hz, 1 H), 5.11–5.06 (m, 2 H), 3.75 (dd, *J* = 11.52, 5.02 Hz, 1 H), 3.67 (dd, *J* = 11.53, 4.41 Hz, 1 H), 3.49 (dd, *J* = 14.40, 2.93 Hz, 1 H), 3.42 (d, *J* = 7.78 Hz, 6 H), 3.32 (dt, *J* = 9.56, 9.31, 4.49 Hz, 2 H), 3.22 (dd, *J* = 14.38, 9.47 Hz, 1 H), 3.04–2.97 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 137.0, 133.6, 129.1, 128.0, 118.0, 83.6, 81.5, 60.9, 60.4, 58.5, 56.6, 40.7, 30.9, 29.6.

MS (ES+): *m/z* = 327.1 [M + 1].

Dienes 47.2–47.5; General Procedure

To a stirred solution of alcohol **47.1** (30 mg) in CH_2Cl_2 (20 mL) were added EDCI (2 equiv), DMAP (2 equiv), and the appropriate *N*-allyloxycarbonyl amino acid (2 equiv). The mixture was stirred for 3 h at r.t. until the starting material was completely consumed and then the reaction was quenched with H_2O and the mixture was extracted with CH_2Cl_2. The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (hexanes–EtOAc, 7:3).



Scheme 28

{(2*R*,3*R*,4*S*,5*R*)-5-Allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methyl (2*S*)-2-{[(Allyloxy)carbonyl]amino}-3-methylbutanoate (47.2)

Colorless oil; yield: 32.78 mg (75%); molecular formula: $C_{25}H_{35}NO_8S$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.87 (m, 2 H), 7.64–7.60 (m, 1 H), 7.55–7.52 (m, 2 H), 5.94–5.84 (m, 1 H), 5.74–5.63 (m, 1 H), 5.34–5.17 (m, 3 H), 5.10 (dd, *J* = 13.83, 2.73 Hz, 2 H), 4.55 (d, *J* = 5.57 Hz, 2 H), 4.29–4.19 (m, 3 H), 3.55–3.45 (m, 2 H), 3.40–3.38 (m, 6 H), 3.25–3.18 (m, 2 H), 3.06–3.01 (m, 1 H), 2.18–2.09 (m, 1 H), 0.97 (d, *J* = 6.84 Hz, 3 H), 0.89 (d, *J* = 6.87 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 156.0, 140.0, 136.4, 133.6, 132.5, 129.1, 128.0, 118.6, 117.8, 82.3, 79.0, 65.8, 63.7, 60.5, 59.0, 58.9, 56.7, 40.9, 31.1, 19.0, 17.5.

MS (ES+): *m*/*z* = 510.3 [M + 1].

{(2*R*,3*R*,4*S*,5*R*)-5-Allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methyl 2-{[(Allyloxy)carbonyl]amino}-3-methylpentanoate (47.3)

Colorless oil; yield: 36.57 mg (76%); molecular formula: $C_{26}H_{37}NO_8S$; R_f = 0.5 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.69 Hz, 2 H), 7.63 (t, *J* = 7.39 Hz, 1 H), 7.54 (t, *J* = 7.71 Hz, 2 H), 5.95–5.84 (m, 1 H), 5.75–5.63 (m, 1 H), 5.34–5.18 (m, 3 H), 5.11 (dd, *J* = 13.59, 2.64 Hz, 2 H), 4.55 (d, *J* = 5.43 Hz, 2 H), 4.34–4.19 (m, 3 H), 3.56–3.45 (m, 2 H), 3.41–3.39 (m, 5 H), 3.25–3.17 (m, 2 H), 3.08–3.02 (m, 1 H), 1.83–1.79 (m, 2 H), 1.46–1.35 (m, 1 H), 1.23–1.12 (m, 1 H), 0.94–0.89 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 155.9, 140.0, 136.4, 133.6, 132.5, 129.1, 128.0, 118.6, 117.9, 82.3, 79.0, 65.8, 63.7, 60.5, 59.0, 58.3, 56.7, 40.9, 37.8, 30.9, 29.6, 24.9, 15.5, 11.5.

MS (ES+): *m*/*z* = 524.6 [M + 1].

{(2*R*,3*R*,4*S*,5*R*)-5-Allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methyl (2*S*)-2-{[(Allyloxy)carbonyl]amino}-3-phenylpropanoate (47.4)

Colorless oil; yield: 39.98 mg (78%); molecular formula: $C_{29}H_{35}NO_8S$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.97 Hz, 2 H), 7.65–7.61 (m, 1 H), 7.54 (t, *J* = 7.57 Hz, 2 H), 7.32–7.21 (m, 4 H), 7.13 (t, *J* = 8.01 Hz, 2 H), 5.91–5.81 (m, 1 H), 5.69–5.48 (m, 1 H), 5.31–5.04 (m, 5 H), 4.60–4.52 (m, 3 H), 4.29–4.06 (m, 2 H), 3.81–3.64 (m, 1 H), 3.57–3.26 (m, 4 H), 3.24–2.93 (m, 5 H), 2.16 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 155.6, 139.8, 136.0, 133.7, 132.5, 129.2, 128.7, 128.1, 128.0, 127.2, 119.6, 119.0, 117.9, 81.6, 72.3, 69.0, 65.9, 64.4, 60.6, 58.9, 57.5, 56.6, 54.9, 42.5, 41.2, 38.2.

MS (ES+): *m*/*z* = 558.2 [M + 1].

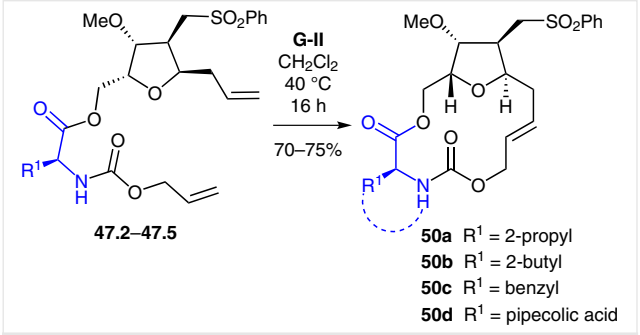
1-Allyl 2-({(2*R*,3*R*,4*S*,5*R*)-5-allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methyl) (2*S*)-Piperidine-1,2-dicarboxylate (47.5)

Colorless oil; yield: 38.38 mg (80%); molecular formula: $C_{26}H_{35}NO_8S$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.43 Hz, 2 H), 7.62 (t, *J* = 7.34 Hz, 1 H), 7.53 (t, *J* = 7.57 Hz, 2 H), 5.96–5.81 (m, 1 H), 5.73–5.61 (m, 1 H), 5.34–5.07 (m, 4 H), 4.95–4.82 (m, 1 H), 4.58–4.56 (m, 2 H), 4.31 (dd, *J* = 11.36, 5.87 Hz, 1 H), 4.24–4.14 (m, 1 H), 4.13–3.98 (m, 1 H), 3.56–3.43 (m, 2 H), 3.38–3.36 (m, 6 H), 3.26–3.16 (m, 2 H), 3.06–3.04 (m, 2 H), 2.24–2.14 (m, 1 H), 1.85–1.57 (m, 2 H), 1.50–1.35 (m, 1 H), 1.28–1.20 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 156.2, 140.0, 136.4, 133.6, 132.7, 129.1, 128.0, 118.7, 117.4, 82.3, 78.9, 66.2, 63.4, 60.6, 58.9, 56.8, 54.2, 41.8, 41.7, 41.0, 26.6, 24.6, 20.6.

MS (ES+): *m*/*z* = 522.2 [M + 1].



Scheme 29

Macrocycles 50a–d; General Procedure

G-II (10 mol%) was added to a stirred solution of the appropriate diene **47.2**–**47.5** (30 mg) in CH_2Cl_2 (100 mL), and the mixture was stirred for 16 h at 40 °C until the starting material was completely consumed. The mixture was then concentrated under reduced pressure and the residue was purified by column chromatography (hexanes–EtOAc, 5:5).

(1*R*,5*S*,13*R*,14*S*,15*R*)-5-Isopropyl-15-methoxy-14-[(phenylsulfonyl)methyl]-3,8,16-trioxa-6-azabicyclo[11.2.1]hexadec-10-ene-4,7-dione (50a)

Colorless oil; yield: 20.4 mg (72%); molecular formula: $C_{23}H_{31}NO_8S$; R_f = 0.2 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 7.47 Hz, 2 H), 7.67–7.62 (m, 1 H), 7.56 (d, *J* = 7.72 Hz, 2 H), 5.88–5.82, (m, 1 H), 5.75–5.64 (m, 1 H), 5.30–5.22 (m, 1 H), 5.13–5.09 (m, 2 H), 4.57 (br s, 2 H), 4.33–4.19, (m, 3 H), 3.54–3.48 (m, 1 H), 3.42–3.40 (m, 5 H), 3.25–3.19 (m, 2 H), 3.10–3.02 (m, 1 H), 2.20–2.10 (m, 1 H), 0.98 (d, *J* = 6.80 Hz, 3 H), 0.90 (d, *J* = 6.56 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 155.9, 140.0, 136.4, 133.6, 129.2, 128.1, 128.0, 118.7, 82.3, 78.9, 64.6, 63.7, 60.5, 59.0, 56.7, 53.4, 40.9, 31.9, 31.1, 29.7, 29.6, 29.3, 22.7.

MS (ES+): *m*/*z* = 482.3 [M + 1].

(1*R*,13*R*,14*S*,15*R*)-5-*sec*-Butyl-15-methoxy-14-[(phenylsulfonyl)methyl]-3,8,16-trioxa-6-azabicyclo[11.2.1]hexadec-10-ene-4,7-dione (50b)

Colorless oil; yield: 21 mg (74%); molecular formula: $C_{24}H_{33}NO_8S$; R_f = 0.25 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.61 (m, 1 H), 7.57–7.52 (m, 2 H), 7.38–7.37 (m, 1 H), 7.33–7.30 (m, 1 H), 5.76–5.64 (m, 1 H), 5.37–5.24 (m, 1 H), 5.18–5.10 (m, 2 H), 4.73 (d, *J* = 6.16 Hz, 1 H), 4.38–4.19 (m, 3 H), 3.55–3.46 (m, 2 H), 3.44–3.38 (m, 5 H), 3.24–3.19 (m, 2 H), 3.11–3.02 (m, 1 H), 1.94–1.82 (m, 1 H), 1.75–1.70 (m, 2 H), 0.96–0.89 (m, 6 H).

MS (ES+): *m*/*z* = 496.3 [M + 1].

(1*R*,5*S*,13*R*,14*S*,15*R*)-5-Benzyl-15-methoxy-14-[(phenylsulfonyl)methyl]-3,8,16-trioxa-6-azabicyclo[11.2.1]hexadec-10-ene-4,7-dione (50c)

Colorless oil; yield: 19.4 mg (70%); molecular formula: $C_{27}H_{31}NO_8S$; R_f = 0.1 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.84 (m, 2 H), 7.70–7.60 (m, 1 H), 7.56–7.53 (m, 2 H), 7.34–7.28 (m, 3 H), 7.18–7.17 (m, 2 H), 6.02–5.38 (m, 2 H), 5.05–4.25 (m, 4 H), 3.76–3.38 (m, 5 H), 3.33–2.74 (m, 5 H), 2.35–1.58 (m, 5 H).

MS (ES+): *m*/*z* = 530.6 [M + 1].

(4*R*,5*R*,6*S*,7*R*,18a*S*)-5-methoxy-6-[(phenylsulfonyl)methyl]-4,5,6,7,8,11,16,17,18,18a-decahydro-3*H*-4,7-epoxypyrido[1,2-*c*][1,6,3]dioxazacyclopentadecine-1,13(15*H*)-dione (50d)

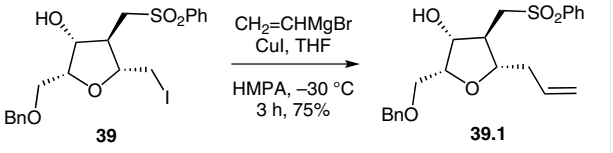
Colorless oil; yield: 20.4 mg (72%); molecular formula: $C_{24}H_{31}NO_8S$; R_f = 0.2 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 7.43 Hz, 2 H), 7.64 (t, *J* = 7.43 Hz, 1 H), 7.54 (t, *J* = 7.61 Hz, 2 H), 5.99–5.53 (m, 2 H), 4.84–4.55 (m, 1 H), 4.45–3.75 (m, 4 H), 3.52–2.97 (m, 12 H), 2.91–2.75 (m, 1 H), 2.25 (d, *J* = 13.73 Hz, 1 H), 1.86–1.66 (m, 4 H), 1.45–1.41 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 143.4, 133.8, 129.3, 128.0, 128.0, 127.9, 110.0, 102.7, 84.9, 82.3, 62.1, 56.5, 36.8, 31.9, 31.4, 29.7, 25.7, 24.2, 22.7, 20.4, 14.1.

MS (ES+): *m*/*z* = 494.1 [M + 1].

Synthesis of Macrocycles 49a–d



Scheme 30

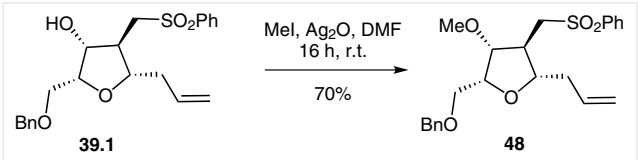
(2*R*,3*R*,4*R*,5*S*)-5-Allyl-2-[(benzyloxy)methyl]-4-[(phenylsulfonyl)methyl]tetrahydrofuran-3-ol (39.1)

CuI (75 mg, 0.396 mmol) and HMPA (1.41 mL, 7.93 mmol) were added to a stirred solution of iodide **39** (500 mg, 0.793 mmol) in anhyd THF (5 mL) at 23 °C. The mixture was cooled to –30 °C and CH_2=CHMgBr (2.4 mL, 2.4 mmol) was added dropwise. The mixture was stirred for 3 h at –30 °C and then the reaction was quenched with sat. aq NH_4Cl. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 7:3) to give a white solid; yield: 300 mg (75%); molecular formula: $C_{22}H_{26}O_5S$; R_f = 0.5 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.87 (m, 2 H), 7.66–7.60 (m, 1 H), 7.53 (dd, *J* = 10.40, 4.69 Hz, 2 H), 7.38–7.26 (m, 5 H), 5.66–5.55 (m, 1 H), 5.17–5.08 (m, 2 H), 4.53 (d, *J* = 1.57 Hz, 2 H), 3.87–3.84 (m, 1 H), 3.70 (dd, *J* = 14.31, 3.01 Hz, 1 H), 3.61–3.55 (m, 2 H), 3.47 (dd, *J* = 8.72, 1.37 Hz, 1 H), 3.18 (dd, *J* = 14.32, 8.86 Hz, 1 H), 2.95 (dd, *J* = 8.91, 2.88 Hz, 1 H), 2.28 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.0, 137.4, 135.8, 133.6, 129.1, 128.5, 128.0, 127.8, 119.3, 73.7, 73.2, 73.0, 68.4, 57.2, 42.4.

MS (ES+): *m*/*z* = 403.3 [M + 1].



Scheme 31

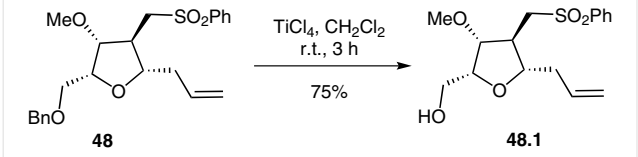
(2*S*,3*S*,4*R*,5*R*)-2-Allyl-5-[(benzyloxy)methyl]-4-methoxy-3-[(phenylsulfonyl)methyl]tetrahydrofuran (48)

To a stirred solution of tetrahydrofuran **39.1** (320 mg) in DMF (20 mL) were added Ag_2O (2 equiv) and MeI (5 equiv) in a dark environment. The mixture was stirred for 16 h at r.t., then filtered through Celite. The filtrate was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 9:1) to give a colorless oil; yield: 250 mg (70%); molecular formula: $C_{23}H_{28}O_5S$; R_f = 0.6 (hexanes–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.85 (m, 2 H), 7.64–7.60 (m, 1 H), 7.53 (t, *J* = 7.56 Hz, 2 H), 7.38–7.27 (m, 5 H), 5.66–5.54 (m, 1 H), 5.14–5.10 (m, 2 H), 4.54–4.48 (m, 2 H), 3.71 (dd, *J* = 14.25, 2.66 Hz, 1 H), 3.61 (dq, *J* = 9.93, 5.15 Hz, 2 H), 3.52–3.35 (m, 6 H), 3.16 (dd, *J* = 14.24, 9.31 Hz, 2 H), 2.97 (dq, *J* = 9.08, 2.52 Hz, 1 H), 2.57 (d, *J* = 7.96 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): 140.0, 137.8, 136.8, 133.5, 129.1, 129.1, 128.4, 128.1, 128.0, 127.8, 127.7, 118.3, 82.0, 80.0, 73.4, 68.4, 60.8, 58.7, 56.8, 41.2.

MS (ES+): *m*/*z* = 416.8 [M + 1].



Scheme 32

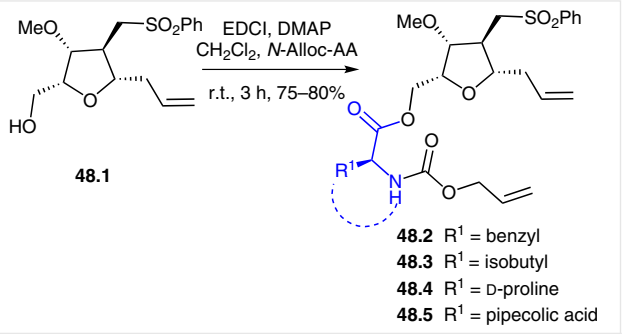
{(2*R*,3*R*,4*S*,5*S*)-5-Allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methanol (48.1)

To a stirred solution of sulfone **48** (250 mg, 0.664 mmol) in CH_2Cl_2 (100 mL) was added $TiCl_4$ (0.14 mL, 1.329 mmol), and the mixture was stirred for 3 h at r.t. until all the starting material was consumed. The reaction was then quenched with sat. aq NH_4Cl and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography (hexanes–EtOAc, 5:5) to give a colorless oil; yield: 150 mg (75%); molecular formula: $C_{16}H_{22}O_5S$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.85 (m, 2 H), 7.64–7.60 (m, 1 H), 7.56–7.51 (m, 2 H), 5.71 (td, *J* = 17.19, 8.92 Hz, 1 H), 5.10–5.05 (m, 2 H), 3.05–2.95 (m, 1 H), 3.77–3.69 (m, 1 H), 3.69–3.62 (m, 1 H), 3.49 (dd, *J* = 14.40, 2.90 Hz, 1 H), 3.41–3.38 (m, 5 H), 3.31 (dt, *J* = 9.41, 4.35 Hz, 2 H), 3.22 (dd, *J* = 14.39, 3.02–3.95 (m, 1 H), 9.59 Hz, 1 H), 2.17 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9, 136.9, 133.6, 129.2, 128.0, 118.1, 83.5, 81.4, 60.9, 60.5, 58.5, 56.6, 40.8, 29.7.

MS (ES+): *m/z* = 327.2 [M + 1].



Scheme 33

Dienes 48.2–48.5; General Procedure

To a stirred solution of sulfone **48.1** (30 mg) in CH_2Cl_2 (20 mL) were added EDCI (2 equiv), DMAP (2 equiv), and the appropriate *N*-allyloxycarbonyl amino acid (2 equiv), and the mixture was stirred for 3 h at r.t. until all the starting material was consumed. The reaction was quenched with H_2O and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 7:3) to provide give a colorless oil.

{(2*R*,3*R*,4*S*,5*S*)-5-Allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methyl (2*S*)-2-{[(Allyloxy)carbonyl]amino}-3-phenylpropanoate (48.2)

Colorless oil; yield: 36.9 mg (72%); molecular formula: $C_{29}H_{35}NO_8S$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 7.23 Hz, 2 H), 7.65–7.61 (m, 1 H), 7.56–7.52 (m, 2 H), 7.34–7.21 (m, 4 H), 7.13 (s, 1 H), 5.92–5.82 (m, 1 H), 5.71–5.59 (m, 1 H), 5.31–5.16 (m, 3 H), 5.15–5.08 (m, 2 H), 4.62 (dd, *J* = 14.26, 6.35 Hz, 1 H), 4.54 (d, *J* = 5.56 Hz, 3 H), 4.20 (d, *J* = 5.91 Hz, 2 H), 3.50 (dd, *J* = 14.15, 2.50 Hz, 1 H), 3.37–3.35 (m, 3 H), 3.33 (s, 3 H), 3.24–3.01 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 155.5, 140.0, 136.4, 135.5, 133.6, 132.5, 129.3, 129.3, 129.2, 128.7, 128.0, 127.3, 118.7, 117.9, 110.0, 82.2, 78.8, 65.9, 64.0, 60.5, 59.0, 56.8, 54.8, 40.9, 38.2, 29.7, 29.6.

MS (ES+): *m/z* = 558.2 [M + 1].

{(2*R*,3*R*,4*S*,5*S*)-5-Allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methyl (2*S*)-2-{[(Allyloxy)carbonyl]amino}-4-methylpentanoate (48.3)

Colorless oil; yield: 34.6 mg (72%); molecular formula: $C_{26}H_{37}NO_8S$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.86 (m, 2 H), 7.66–7.60 (m, 1 H), 7.55–7.52 (m, 2 H)5.95–5.82 (m, 1 H), 5.74–5.51 (m, 1 H), 5.33–5.24 (m, 1 H), 5.22–5.07 (m, 4 H), 4.54–4.53 (m, 2 H), 4.37–4.28 (m, 1 H), 4.28–4.22 (m, 1 H), 4.19–4.09 (m, 1 H), 3.68 (dd, *J* = 14.24, 2.42 Hz, 1 H), 3.55–3.32 (m, 5 H), 3.26–3.12 (m, 2 H), 3.07–2.94 (m, 1 H), 2.47–2.42 (m, 1 H), 1.74–1.47 (m, 4 H), 0.92 (dd, *J* = 6.41, 1.66 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 155.9, 140.0, 136.0, 133.6, 132.5, 129.2, 128.0, 119.6, 117.8, 81.7, 72.3, 69.1, 65.9, 64.1, 60.7, 58.9, 57.5, 56.5, 52.5, 42.5, 41.2, 29.7, 24.7, 22.8, 21.7, 14.1.

MS (ES+): *m/z* = 524.6 [M + 1].

1-Allyl 2-({(2*R*,3*R*,4*S*,5*S*)-5-allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methyl) (2*R*)-Pyrrolidine-1,2-dicarboxylate (48.4)

Colorless oil; yield: 34 mg (73%); molecular formula: $C_{25}H_{33}NO_8S$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.88 (m, 2 H), 7.63–7.61 (m, 2 H), 7.59–7.51 (m, 2 H), 5.98–5.80 (m, 1 H), 5.63–5.53 (m, 1 H), 5.35–5.05 (m, 4 H), 4.61–4.54 (m, 2 H), 4.41–4.15 (m, 3 H), 3.62–3.35 (m, 7 H), 3.25–3.13 (m, 2 H), 3.06–2.98 (m, 1 H), 2.42–2.13 (m, 2 H), 2.01–1.90 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 154.7, 136.0, 132.7, 129.1, 128.0, 118.8, 117.4, 81.9, 72.2, 68.9, 66.0, 60.5, 58.8, 56.6, 46.4, 42.6, 41.3, 30.9, 29.7, 24.5, 24.4, 23.5.

MS (ES+): *m/z* = 508.1 [M + 1].

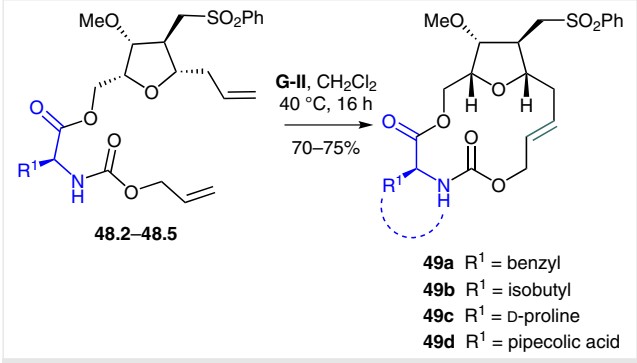
1-Allyl 2-({(2*R*,3*R*,4*S*,5*S*)-5-allyl-3-methoxy-4-[(phenylsulfonyl)methyl]tetrahydrofuran-2-yl}methyl) (2*S*)-Piperidine-1,2-dicarboxylate (48.5)

Colorless oil; yield: 34 mg (73%); molecular formula: $C_{26}H_{35}NO_8S$; R_f = 0.3 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.88 (m, 2 H), 7.72–7.51 (m, 3 H), 5.99–5.81 (m, 1 H), 5.73–5.49 (m, 1 H), 5.41–5.05 (m, 4 H), 4.95–4.84 (m, 1 H), 4.58–4.57 (m, 2 H), 4.35–4.17 (m, 2 H), 4.10–3.99 (m, 2 H), 3.72–3.31 (m, 4 H), 3.28–2.89 (m, 3 H), 2.26–1.98 (m, 3 H), 1.69–1.66 (m, 3 H), 1.24–1.20 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 139.7, 135.9, 132.7, 129.2, 129.1, 128.0, 119.6, 117.4, 110.0, 81.7, 72.3, 66.2, 63.5, 57.4, 56.5, 54.5, 54.3, 53.1, 41.8, 41.2, 29.6, 29.6, 26.6, 24.6, 22.6, 20.6, 20.6, 20.6, 14.1.

MS (ES+): *m/z* = 522.2 [M + 1].



Scheme 34

Macrocycles 49a–d; General Procedure

G-II (10 mol%) was added to a stirred solution of the appropriate diene **48.2–48.5** (30 mg) in CH_2Cl_2 (100 mL), and the mixture was stirred for 16 h at 40 °C until the starting material was completely

consumed. The mixture was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes–EtOAc, 5:5) to provide give a colorless oil.

(1*R*,5*S*,13*S*,14*S*,15*R*)-5-Benzyl-15-methoxy-14-[(phenylsulfonyl)methyl]-3,8,16-trioxa-6-azabicyclo[11.2.1]hexadec-10-ene-4,7-dione (49a)

Colorless oil; yield: 21.9 mg (75%); molecular formula: $C_{27}H_{31}NO_8S$; R_f = 0.2 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.84 (m, 2 H), 7.65–7.61 (m, 1 H), 7.56–7.52 (m, 2 H), 7.34–7.27 (m, 3 H), 7.18 (d, *J* = 6.73 Hz, 2 H), 5.72–5.63 (m, 1 H), 5.58–5.49 (m, 1 H), 4.98–4.90 (m, 1 H), 4.76–4.67 (m, 1 H), 4.42–4.27 (m, 1 H), 4.12–4.02 (m, 1 H), 3.73–3.63 (m, 2 H), 3.40–3.34 (m, 3 H), 3.26–3.10 (m, 4 H), 2.99–2.87 (m, 4 H), 1.61 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 155.8, 133.6, 129.2, 129.0, 128.9, 128.9, 128.1, 127.5, 114.1, 113.8, 83.3, 59.1, 56.9, 56.4, 36.5, 31.9, 29.7, 22.7, 14.1.

MS (ES+): *m/z* = 530.1 [M + 1].

(1*R*,5*S*,13*S*,14*S*,15*R*)-5-Isobutyl-15-methoxy-14-[(phenylsulfonyl)methyl]-3,8,16-trioxa-6-azabicyclo[11.2.1]hexadec-10-ene-4,7-dione (49b)

Colorless oil; yield: 19.9 mg (75%); molecular formula: $C_{24}H_{33}NO_8S$; R_f = 0.25 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.87 (m, 2 H), 7.65–7.61 (m, 1 H), 7.57–7.53 (m, 2 H), 5.79–5.54 (m, 2 H), 5.20–4.99 (m, 1 H), 4.91 (d, *J* = 5.99 Hz, 1 H), 4.86–4.78 (m, 1 H), 4.72 (dd, *J* = 12.92, 6.22 Hz, 1 H), 4.12–4.06 (m, 1 H), 4.03–3.99 (m, 1 H), 3.82 (dd, *J* = 14.23, 2.19 Hz, 1 H), 3.61–3.55 (m, 1 H), 3.47 (m, 3 H), 3.23–3.12 (m, 2 H), 2.83–2.73 (m, 1 H), 2.09–2.02 (m, 1 H), 1.76–1.45 (m, 4 H), 0.95–0.90 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 155.8, 140.1, 133.6, 133.6, 129.7, 129.2, 128.0, 128.0, 122.0, 114.0, 74.5, 63.3, 58.7, 57.2, 54.4, 40.1, 39.6, 29.7, 24.8, 22.7, 21.6.

MS (ES+): *m/z* = 496.3 [M + 1].

(4*R*,5*R*,6*S*,7*S*,17a*S*)-5-Methoxy-6-[(phenylsulfonyl)methyl]-4,5,6,7,8,11,15,16,17,17a-decahydro-1*H*,3*H*-4,7-epoxypyrrolo[1,2-*c*][1,6,3]dioxazacyclopentadecine-1,13-dione (49c)

Colorless oil; yield: 20.4 mg (72%); molecular formula: $C_{23}H_{29}NO_8S$; R_f = 0.1 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.83 (m, 2 H), 7.66–7.61 (m, 1 H), 7.59–7.51 (m, 2 H), 5.03–4.89 (m, 1 H), 4.79–4.71 (m, 1 H), 4.63–4.40 (m, 1 H), 4.36–4.04 (m, 2 H), 3.70–3.35 (m, 7 H), 3.27–3.13 (m, 1 H), 3.04–2.88 (m, 1 H), 2.78–2.57 (m, 1 H), 2.36–2.19 (m, 1 H), 2.09–1.82 (m, 3 H), 1.77–1.55 (m, 2 H), 6.00–5.78 (m, 1 H), 5.76–5.40 (m, 2 H).

MS (ES+): *m/z* = 480.6 [M + 1].

(4*R*,5*R*,6*S*,7*S*,18a*S*)-5-Methoxy-6-[(phenylsulfonyl)methyl]-4,5,6,7,8,11,16,17,18,18a-decahydro-3*H*-4,7-epoxypyrido[1,2-*c*][1,6,3]dioxazacyclopentadecine-1,13(15*H*)-dione (48d)

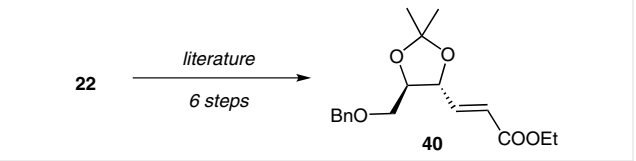
Colorless oil; yield: 20.6 mg (73%); molecular formula: $C_{24}H_{31}NO_8S$; R_f = 0.1 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87–7.85 (m, 2 H), 7.65–7.61 (m, 1 H), 7.56–7.52 (m, 2 H), 5.85–5.44 (m, 2 H), 5.16–4.62 (m, 3 H), 4.54–4.42 (m, 1 H), 4.23–3.78 (m, 3 H), 3.64 (d, *J* = 2.11 Hz, 1 H), 3.51–3.35 (m, 5 H), 3.27–3.13 (m, 2 H), 3.00–2.83 (m, 2 H), 2.34–2.07 (m, 1 H), 1.79–1.60 (m, 4 H), 1.49–1.38 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 142.7, 133.6, 129.1, 128.1, 128.1, 128.0, 110.0, 63.2, 57.0, 55.4, 41.3, 31.9, 29.7, 29.6, 29.6, 29.3, 26.0, 24.3, 24.3, 24.3, 24.2, 22.7, 20.4, 14.1.

MS (ES+): *m/z* = 494.1 [M + 1].

Synthesis of Fragment 46



Scheme 35

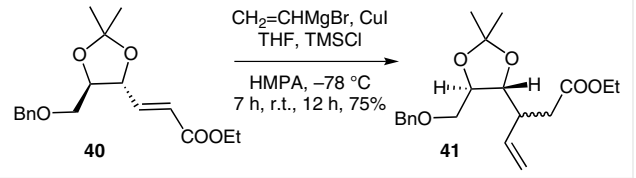
Ethyl (2*E*)-3-{(4*R*,5*R*)-5-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (40)

Triethyl phosphonoacetate (23.6 mL, 119.047 mmol) was added dropwise to a stirred solution of 60% NaH (2.85 g, 119.047 mmol) in anhyd THF over 30 min at 0 °C, and the mixture was stirred at 0 °C for 30 min. Aldehyde **23.2** (10 g, 39.682 mmol) was added slowly and the mixture was stirred for 2 h at 0 °C until the reaction was complete (TLC). The reaction was then quenched with H_2O, and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 9:1) to give a yellowish liquid; yield: 11.2 g (90%); molecular formula: $C_{18}H_{24}O_5$; R_f = 0.5 (hexanes–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 6.90 (dd, *J* = 15.63, 5.6 Hz, 1 H), 6.10 (dd, *J* = 15.64, 1.20 Hz, 1 H), 4.64–4.56 (m, 2 H), 4.45–4.41 (m, 1 H), 4.21 (q, *J* = 7.2 Hz, 2 H), 3.98–3.94 (m, 1 H), 3.64 (d, *J* = 4.80 Hz, 2 H), 1.46 (s, 3 H), 1.44 (s, 3 H), 1.30 (t, *J* = 7.20 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 144.0, 137.6, 128.4, 127.7, 127.6, 122.5, 110.1, 79.5, 73.6, 69.2, 60.5, 26.9, 26.6, 14.20.

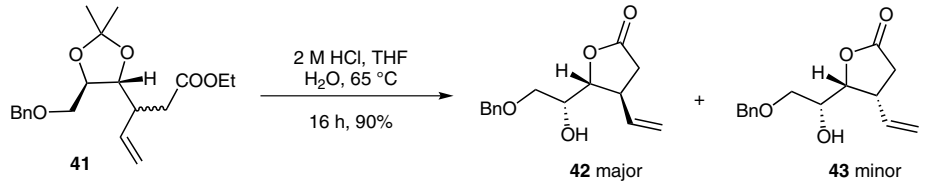
MS (ES+): *m/z* = 337.1 [M + 17].



Scheme 36

Ethyl (3*S*)-3-{(4*R*,5*R*)-5-[(Benzyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}pent-4-enoate (41)

CH_2=CHMgBr (8.1 mL, 8.12 mmol) was added dropwise to a stirred solution of CuI (77 mg, 4.062 mmol) in anhyd THF (10 mL) at –78 °C, and the mixture was stirred at –78 °C for 40 min. TMSCl (1 mL, 8.12 mmol) and a solution of ester **40** (1.3 g, 4.062 mmol) in THF (2 mL) were added dropwise over 20 min, followed by HMPA (2.8 mL, 16.24 mmol). The mixture was stirred at –78 °C for 7 h and then at r.t. for 12 h until the reaction was complete. The reaction was quenched with a 1:1 aq solution of NH_4Cl and NH_4OH at –78 °C, and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 9:1) to give a colorless oil; yield: 990 mg (75%); molecular formula: $C_{20}H_{28}O_5$; R_f = 0.5 (hexanes–EtOAc, 9:1).



Scheme 37

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 5.53 (td, *J* = 17.20, 17.20 Hz, 1 H), 5.14 (d, *J* = 17.20 Hz, 1 H), 5.03 (dd, *J* =10.29, 1.19 Hz, 1 H), 4.58 (s, 2 H), 4.14–4.06 (m, 2 H), 4.02–3.96 (m, 1 H), 3.74 (t, *J* = 7.66 Hz, 1 H), 3.59 (dd, *J* = 10.52, 2.98 Hz, 1 H), 3.48 (dd, *J* = 10.52, 5.95 Hz, 1 H), 2.78–2.68 (m, 2 H), 2.37–2.28 (m, 1 H), 1.40 (s, 6 H), 1.23 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): 172.2, 138.0, 136.3, 128.3, 127.7, 118.0, 109.2, 79.4, 78.8, 73.3, 70.6, 60.3, 45.1, 36.7, 27.2, 14.2.

MS (ES+): *m/z* = 349.3 [M + 1].

(4*S*,5*R*)- and (4*R*,5*R*)-5-[(1*R*)-2-(Benzyloxy)-1-hydroxyethyl]-4-vinyldihydrofuran-2(3*H*)-one (42 and 43)

2 M aq HCl (1 mL) was added to a stirred solution of ester **41** (1 g, 2.87 mmol) in 1:1 THF–H_2O (20 mL), and the mixture was refluxed for 16 h until the starting material was consumed (TLC). The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (8:2 hexanes–EtOAc) to give **42** (yield: 650 mg) and **43** (yield: 50 mg) in 13:1 ratio (total yield: 90%).

42

Molecular formula: $C_{15}H_{18}O_4$; R_f = 0.3 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 5 H), 5.79–5.70 (m, 1 H), 5.22–5.14 (m, 2 H), 4.59–4.52 (m, 2 H), 4.23 (dd, *J* = 7.6, 2.00 Hz, 1 H), 3.91–3.88 (m, 1 H), 3.64–3.56 (m, 2 H), 3.30 (p, 1 H), 2.80 (dd, *J* = 17.60, 9.20 Hz, 1 H), 2.42 (dd, *J* = 17.60, 9.20 Hz, 1 H), 2.32 (d, *J* = 6.00 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): 175.7, 137.5, 136.0, 128.5, 127.9, 127.8, 118.0, 83.4, 73.5, 71.1, 69.4, 41.0, 34.9.

MS (ES+): *m/z* = 279.7 [M + 17].

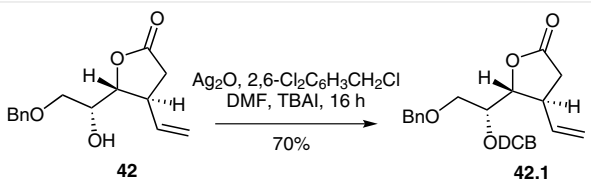
43

Molecular formula: $C_{15}H_{18}O_4$; R_f = 0.5 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H), 5.68–5.59 (m, 1 H), 5.37 (d, *J* = 3.60 Hz, 1 H), 5.34 (d, *J* = 2.80 Hz, 1 H), 4.54 (s, 2 H), 4.34 (dd, *J* = 9.60, 2.40 Hz, 1 H), 3.88 (bt, 1 H) 3.68–3.57 (m, 3 H), 1.90–1.83 (m, 1 H), 1.74–1.67 (m, 1 H), 1.66–1.62 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): 176.0, 137.8, 136.8, 136.6, 132.9, 130.2, 128.4, 128.4, 127.7, 117.3, 83.4, 76.1, 73.6, 69.1, 67.0, 40.6, 34.9.

MS (ES+): *m/z* = 279.7 [M + 17].



Scheme 38 DCB = 2,4-dichlorobenzyl

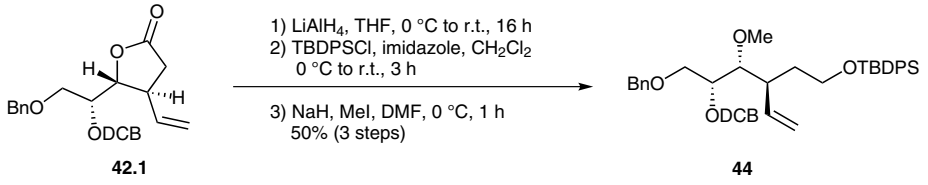
(4*S*,5*R*)-5-{(1*R*)-2-(Benzyloxy)-1-[(2,6-dichlorobenzyl)oxy]ethyl}-4-vinyldihydrofuran-2(3*H*)-one (42.1)

To a stirred solution of alcohol **42** (1.2 g, 4.58 mmol) in anhyd DMF (10 mL) were added Ag_2O (1.8 g, 6.87 mmol), TBAI (3.38 g, 9.16 mmol), and 2,6-dichlorobenzyl chloride (1.78 g, 9.16 mmol) under an inert atmosphere, and the mixture was stirred for 48 h in darkness. When the reaction was complete, the mixture was filtered through Celite and extracted with EtOAc (30 mL) and cool H_2O (15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 9:1) to provide give a colorless oil; yield: 1.35 g (70%); molecular formula: $C_{22}H_{22}Cl_2O_4$; R_f = 0.5 (hexanes–EtOAc, 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.30 (m, 7 H), 7.21 (dd, *J* = 8.67, 7.40 Hz, 1 H), 5.71 (dt, *J* = 17.10, 10.16, 8.37 Hz, 1 H), 5.09–4.95 (m, 2 H), 4.83 (d, *J* = 10.50 Hz, 1 H), 4.62–4.53 (m, 2 H), 4.40 (dd, *J* = 6.80, 1.60 Hz, 1 H), 3.88 (dd, *J* = 8.82, 4.85 Hz, 1 H), 3.75–3.67 (m, 2 H), 3.17 (m, 1 H), 2.77 (dd, *J* = 17.60, 9.00 Hz, 1 H), 2.37 (dd, *J* = 17.60, 9.00 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): 176.0, 137.8, 136.8, 136.6, 132.9, 130.3, 128.5, 128.4, 127.8, 117.4, 83.4, 76.1, 73.6, 69.1, 67.1, 40.7, 34.9.

MS (ES+): *m/z* = 437.6 [M + 17].



Scheme 39

(3*S*,4*R*,5*R*)-6-(Benzyloxy)-5-[(2,4-dichlorobenzyl)oxy]-3-vinylhexane-1,4-diol (42.2)

$LiAlH_4$ (312 mg, 8.21 mmol) was added in a portionwise manner to a stirred solution of tetrahydrofuranone **42.1** (2.3 g, 5.476 mmol) in anhyd THF (20 mL) at 0 °C. After 16 h, the reaction was quenched with 1 M aq NaOH and the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and product **42.2** was used directly in the next reaction.

Molecular formula: $C_{22}H_{26}Cl_2O_4$; R_f = 0.4 (hexanes–EtOAc, 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 7 H), 7.22–7.16 (m, 1 H), 5.66–5.57 (m, 1 H), 5.07–4.96 (m, 3 H), 4.83–4.80 (m, 1 H), 4.61–4.53 (m, 2 H), 3.79–3.66 (m, 4 H), 3.60–3.53 (m, 2 H), 2.47 (dq, *J* = 8.77, 4.41 Hz, 1 H), 2.27 (s, 3 H), 2.01–1.91 (m, 1 H), 1.62–1.53 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): 139.4, 137.8, 136.8, 133.2, 130.0, 128.4, 128.2, 127.7, 127.6, 116.9, 74.2, 73.6, 70.2, 66.5, 60.9, 44.7, 33.9, 30.8 (4 are overlapping signals).

MS (ES+): *m*/*z* = 425.1 [M + 1].

(2*R*,3*R*,4*S*)-1-(Benzyloxy)-4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-2-[(2,4-dichlorobenzyl)oxy]hex-5-en-3-ol (42.3)

Crude product **42.2** (2.93 g, 6.896 mmol) was dissolved in anhyd CH_2Cl_2 (20 mL), and imidazole (1.4 g, 20.688 mmol) and TBDPSCl (2.2 mL, 8.275 mmol) were added at 0 °C. The mixture was then stirred for 3 h until the reaction was complete. The reaction was quenched with H_2O, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 9.6:0.4) to give a colorless oil; yield: 3.42 g (75%); molecular formula: $C_{38}H_{44}Cl_2O_4Si$; R_f = 0.5 (hexanes–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 6.99 Hz, 4 H), 7.43–7.28 (m, 13 H), 7.21–7.15 (m, 1 H), 5.53 (td, *J* = 17.39, 9.82 Hz, 1 H), 5.05–4.93 (m, 3 H), 4.86–4.81 (m, 1 H), 4.60–4.54 (m, 2 H), 3.80–3.59 (m, 4 H), 3.53 (t, *J* = 7.80 Hz, 1 H), 2.61–2.51 (m, 1 H), 2.45 (d, *J* = 7.71 Hz, 1 H), 2.10–2.02 (m, 1 H), 1.61 (s, 1 H), 1.54–1.43 (m, 1 H), 1.03 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 139.1, 138.1, 136.9, 135.6, 135.2, 134.8, 134.0, 133.9, 133.5, 135.6, 130.0, 129.7, 129.5, 128.4, 127.7, 127.7, 127.6, 127.6, 117.2, 74.1, 73.6, 70.5, 66.8, 61.8, 43.8, 33.0, 26.9, 26.6, 19.2, 19.0.

MS (ES+): *m*/*z* = 663.1 [M + 1].

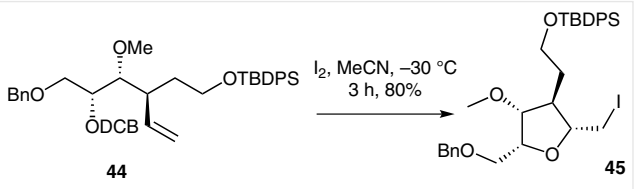
[((3*S*)-3-{(1*R*,2*R*)-3-(Benzyloxy)-2-[(2,4-dichlorobenzyl)oxy]-1-methoxypropyl}pent-4-en-1-yl)oxy](*tert*-butyl)diphenylsilane (44)

Alcohol **42.3** (2.5 g, 4.7 mmol) was dissolved in DMF (20 mL), and NaH (177 mg, 0.177 mmol) was added slowly at 0 °C. MeI was added at 0 °C and, after 1 h, the reaction was quenched with H_2O. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 9.5:0.5) to give a colorless oil; yield: 1.8 g (50%, 3 steps); molecular formula: $C_{39}H_{46}Cl_2O_4Si$; R_f = 0.6 (hexanes–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.67 (m, 5 H), 7.45–7.27 (m, 12 H), 7.17–7.11 (m, 1 H), 5.56 (td, *J* = 17.08, 9.58 Hz, 1 H), 5.00–4.93 (m, 2 H), 4.86 (q, *J* = 10.21 Hz, 2 H), 4.55 (s, 2 H), 3.75–3.57 (m, 5 H), 3.42 (s, 3 H), 3.25 (dd, *J* = 7.57, 1.83 Hz, 1 H), 2.68 (dt, *J* = 10.09, 2.06 Hz, 1 H), 2.04–1.93 (m, 1 H), 1.52–1.41 (m, 1 H), 1.04 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 139.4, 138.2, 137.0, 135.6, 134.1, 134.1, 133.7, 129.8, 129.5, 128.3, 128.3, 127.8, 127.6, 127.5, 116.8, 83.7, 78.6, 73.5, 69.2, 67.0, 62.0, 60.7, 41.9, 32.7, 26.9, 19.2.

MS (ES+): *m*/*z* = 677.7 [M + 1].



Scheme 40

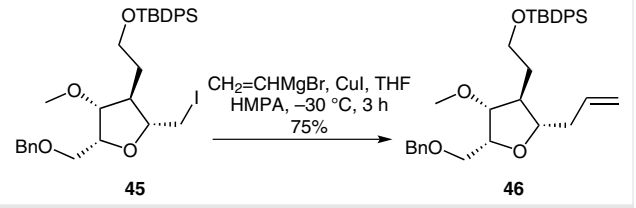
(2*R*,3*R*,4*R*,5*R*)-2-[(Benzyloxy)methyl]-4-(2-{[*tert*-butyl(diphenyl)silyl]oxy}ethyl)-5-(iodomethyl)tetrahydrofuran-3-ol (45)

A soln of I_2 (1 g, 3.9 mmol) in MeCN (50 mL) was added dropwise to stirred solution of alkene **44** (1.8 g, 3.3 mmol) in MeCN (50 mL) at –30 °C. After 3 h, sat. aq $Na_2S_2O_3$ was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 9:1) to give a colorless oil; yield: 1.45 g (80%); molecular formula: $C_{32}H_{41}IO_4Si$; R_f = 0.5 (hexanes–EtOAc, 9.5:0.5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.68 (m, 4 H), 7.46–7.32 (m, 11 H), 4.58 (dd, *J* = 43.23, 12.13 Hz, 2 H), 4.10 (td, *J* = 6.65, 4.58 Hz, 1 H), 3.80 (dt, *J* = 6.69, 3.73 Hz, 1 H), 3.76–3.69 (m, 3 H), 3.64 (dd, *J* = 10.05, 6.74 Hz, 1 H), 3.56 (dd, *J* = 4.00, 1.09 Hz, 1 H), 3.29–3.28 (m, 2 H), 3.24 (s, 3 H), 2.51–2.44 (m, 1 H), 1.70–1.62 (m, 1 H), 1.57–1.50 (m, 1 H), 1.07 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 138.2, 135.6, 135.5, 134.8, 133.5, 135.5, 129.8, 129.7, 129.6, 128.3, 127.8, 127.7, 127.6, 86.2, 84.3, 81.2, 73.4, 69.1, 61.6, 57.0, 45.2, 35.2, 29.7, 26.9, 26.5, 19.2, 9.8.

MS (ES+): *m*/*z* = 645.1 [M + 1].



Scheme 41

(2-{(2*S*,3*S*,4*R*,5*R*)-2-Allyl-5-[(benzyloxy)methyl]-4-methoxytetrahydrofuran-3-yl}ethoxy)(*tert*-butyl)diphenylsilane (46)

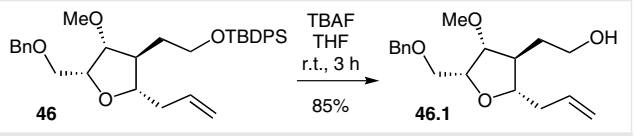
To a stirred solution of iodide **45** (500 mg, 0.793 mmol) in anhyd THF (5 mL) were added CuI (75 mg, 0.396 mmol) and HMPA (1.41 mL, 7.93 mmol) at 23 °C. The mixture was cooled to –30 °C and CH_2=CHMgCl (2.4 mL, 2.4 mmol) was added dropwise. The reaction mixture was stirred for 3 h at –30 °C, and then the reaction was quenched with sat. aq NH_4Cl. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 7:3) to give a colorless oil; yield: 320 mg (75%); molecular formula: $C_{34}H_{44}O_4Si$; R_f = 0.3 (hexanes–EtOAc, 9.5:0.5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 6.68 Hz, 4 H), 7.43–7.28 (m, 11 H), 5.69–5.57 (m, 1 H), 5.08–5.01 (m, 2 H), 4.55 (s, 2 H), 3.92–3.85 (m, 1 H), 3.77–3.69 (m, 2 H), 3.65 (m, 2 H), 3.57–3.49 (m, 2 H), 3.44 (s, 3 H), 3.17 (dd, *J* = 6.80, 2.64 Hz, 1 H), 2.68–2.61 (m, 1 H), 2.38–2.35 (m, 1 H), 1.56–1.44 (m, 1 H), 1.98–1.88 (m, 1 H), 1.07 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): 134.1, 133.3, 130.8, 129.2, 124.8, 123.7, 123.0, 123.0, 122.8, 112.3, 78.5, 68.6, 66.9, 65.4, 57.1, 55.5, 37.5, 28.0, 22.2, 22.1, 14.5.

MS (ES+): *m/z* = 544.8 [M + 1].

Synthesis of Macrocycles 46.2.1–46.5.1



Scheme 42

2-{(2*S*,3*S*,4*R*,5*R*)-2-Allyl-5-[(benzyloxy)methyl]-4-methoxytetrahydrofuran-3-yl}ethanol (46.1)

To a stirred solution of silyl ether **46** (500 mg) in THF (50 mL) was added TBAF (2 equiv), and the mixture was stirred for 3 h at r.t. until the starting material was completely consumed. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 5:5) to give a colorless oil; yield: 245 mg (85%); molecular formula: $C_{18}H_{26}O_4$; R_f = 0.5 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 5.71–5.59 (m, 1 H), 5.10–5.08 (m, 2 H), 4.58–4.49 (m, 2 H), 3.71–3.64 (m, 1 H), 3.64–3.53 (m, 3 H), 3.49–3.43 (m, 4 H), 3.41 (s, 3 H), 3.18 (dd, *J* = 7.98, 3.05 Hz, 1 H), 2.62–2.53 (m, 1 H), 1.97–1.86 (m, 2 H), 1.57–1.46 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.4, 137.9, 128.4, 127.7, 117.0, 78.9, 74.5, 73.5, 71.5, 70.0, 60.9, 58.4, 45.2, 34.2.

MS (ES+): *m/z* = 307.1 [M + 1].

Dienes 46.2–46.5; General Procedure

To a stirred solution of alcohol **46.1** (60 mg, 0.196 mmol, 1 equiv) in CH_2Cl_2 (30 mL) were added EDCI (0.392 mmol, 2 equiv), DMAP (0.392 mmol, 2 equiv), and the appropriate *N*-allyloxycarbonyl amino acid (0.392 mmol, 2 equiv). The mixture was stirred for 3 h at r.t. until all the starting material was consumed. The reaction was then quenched with H_2O and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 7:3).

2-{(2*S*,3*S*,4*R*,5*R*)-2-Allyl-5-[(benzyloxy)methyl]-4-methoxytetrahydrofuran-3-yl}ethyl (2*S*)-2-{[(Allyloxy)carbonyl]amino}-3-phenylpropanoate (46.2)

Colorless oil; yield: 92 mg (85%); molecular formula: $C_{31}H_{39}NO_7$; R_f = 0.5 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.23 (m, 8 H), 7.12 (d, *J* = 6.79 Hz, 2 H), 5.93–5.83 (m, 1 H), 5.59–5.46 (m, 1 H), 5.32–5.03 (m, 6 H), 4.66–4.50 (m, 6 H), 4.23–4.17 (m, 1 H), 4.08–4.01 (m, 1 H), 3.68 (dd, *J* = 9.95, 5.29 Hz, 1 H), 3.60 (dd, *J* = 9.96, 4.76 Hz, 1 H), 3.46–3.41 (m, 4 H), 3.10 (dq, *J* = 13.95, 6.01 Hz, 2 H), 2.49 (d, *J* = 7.42 Hz, 1 H), 2.38 (dq, *J* = 10.68, 10.48, 3.09 Hz, 1 H), 2.22–2.11 (m, 1 H), 1.79 (br s, 1 H), 1.56–1.47 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 155.5, 138.3, 137.9, 135.8, 132.6, 129.3, 128.6, 128.4, 127.8, 127.8, 127.7, 127.1, 118.1, 117.8, 78.6, 74.3, 73.6, 69.9, 65.8, 64.0, 58.4, 54.8, 44.9, 38.2, 29.2.

MS (ES+): *m/z* = 538.1 [M + 1].

2-{(2*S*,3*S*,4*R*,5*R*)-2-Allyl-5-[(benzyloxy)methyl]-4-methoxytetrahydrofuran-3-yl}ethyl (2*S*)-2-{[(allyloxy)carbonyl]amino}-4-methylpentanoate (46.3)

Colorless oil; yield: 57.8 mg (88%); molecular formula: $C_{28}H_{41}NO_7$; R_f = 0.4 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 5 H), 5.90 (ddd, *J* = 22.68, 10.81, 5.61 Hz, 1 H), 5.56 (td, *J* = 17.13, 9.94 Hz, 1 H), 5.34–5.25 (m, 1 H), 5.21–5.01 (m, 4 H), 4.58–4.52 (m, 4 H), 4.35 (dt, *J* = 8.86, 5.33 Hz, 1 H), 4.20–4.15 (m, 1 H), 4.07–3.98 (m, 1 H), 3.66–3.57 (m, 2 H), 3.48–3.41 (m, 4 H), 3.40 (s, 3 H), 3.16 (dd, *J* = 8.35, 2.50 Hz, 1 H), 2.56 (dt, *J* = 11.30, 3.00 Hz, 1 H), 2.12–2.02 (m, 1 H), 1.74–1.46 (m, 4 H), 0.94–0.92 (m, 6 H).

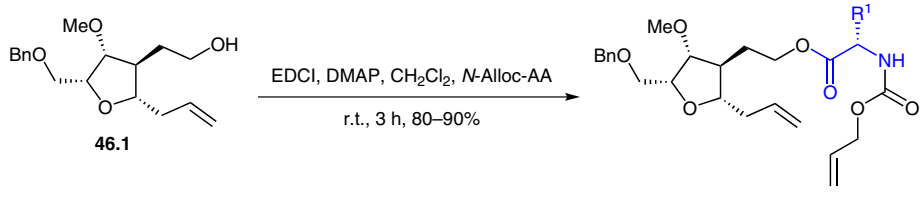
^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 155.8, 138.5, 138.0, 132.6, 128.4, 127.7, 117.7, 117.7, 83.3, 79.8, 73.4, 68.8, 65.7, 63.9, 60.8, 58.8, 52.5, 43.1, 41.9, 28.8, 24.7, 22.8, 21.9.

MS (ES+): *m/z* = 504.3 [M + 1].

2-{(2*S*,3*S*,4*R*,5*R*)-2-Allyl-5-[(benzyloxy)methyl]-4-methoxytetrahydrofuran-3-yl}ethyl 2-(2*S*)-{[(Allyloxy)carbonyl]amino}-3-methylpentanoate (46.4)

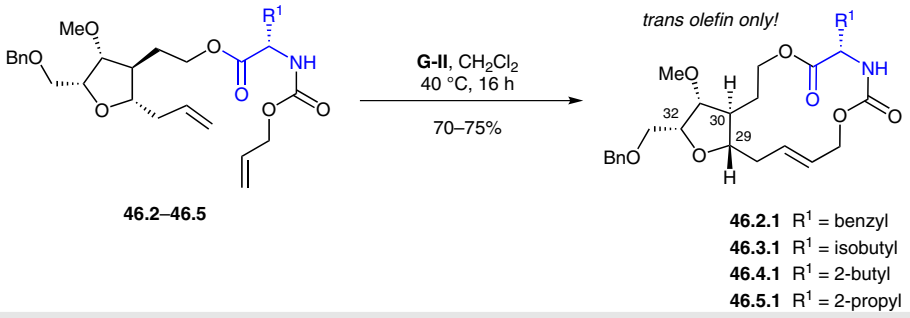
Colorless oil; yield: 48.4 mg (82%); molecular formula: $C_{28}H_{41}NO_7$; R_f = 0.45 (hexanes–EtOAc, 7:3).

^{1}H NMR (100 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 5.90 (ddd, *J* = 22.71, 10.88, 5.64 Hz, 1 H), 5.52 (dt, *J* = 19.80, 6.80 Hz, 1 H), 5.35–5.25 (m, 2 H), 5.24–5.02 (m, 4 H), 4.59–4.51 (m, 5 H), 4.31–427 (m, 1 H), 4.21–4.16 (m, 2 H), 4.10–4.04 (m, 1 H), 3.67 (dd, *J* = 9.94, 5.29 Hz, 1 H),



46.2 R^1 = benzyl
46.3 R^1 = isobutyl
46.4 R^1 = 2-butyl
46.5 R^1 = 2-propyl

Scheme 43



Scheme 44

3.60 (dd, *J* = 9.94, 4.79 Hz, 1 H), 3.46–3.40 (m, 5 H), 2.47 (d, *J* = 7.76 Hz, 1 H), 2.44–2.35 (m, 1 H), 2.27–2.16 (m, 1 H), 1.58–1.47 (m, 1 H), 1.44–1.37 (m, 1 H), 1.21–1.11 (m, 1 H), 0.92–0.88 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 155.9, 138.3, 137.9, 132.7, 128.4, 127.8, 127.8, 127.7, 127.6, 118.1, 117.8, 78.6, 74.2, 73.6, 69.9, 65.8, 63.7, 58.4, 44.9, 38.0, 29.2, 24.9, 15.4, 11.6.

MS (ES+): *m/z* = 504.1 [M + 1].

2-{(2*S*,3*S*,4*R*,5*R*)-2-Allyl-5-[(benzyloxy)methyl]-4-methoxytetrahydrofuran-3-yl}ethyl (2*S*)-2-{[(Allyloxy)carbonyl]amino}-3-methylbutanoate (46.5)

Colorless oil; yield: 34.4 mg (86%); molecular formula: $C_{27}H_{39}NO_7$; R_f = 0.5 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 5 H), 5.90 (qd, *J* = 10.79, 5.62 Hz, 1 H), 5.57 (td, *J* = 17.05, 9.92 Hz, 1 H), 5.33–5.25 (m, 2 H), 5.23–5.17 (m, 1 H), 5.12–5.06 (m, 2 H), 4.59–4.50 (m, 4 H), 4.28–4.16 (m, 2 H), 4.06–4.00 (m, 1 H), 3.85 (dt, *J* = 6.29, 1.98 Hz, 1 H), 3.54–3.44 (m, 2 H), 3.42 (s, 3 H), 3.12 (dd, *J* = 7.97, 2.02 Hz, 1 H), 2.51 (dt, *J* = 10.99, 3.06 Hz, 1 H), 2.27 (br s, 1 H), 2.19–2.10 (m, 1 H), 2.09–2.00 (m, 2 H), 1.60–1.50 (m, 1 H), 0.95 (d, *J* = 6.84 Hz, 3 H), 0.87 (d, *J* = 6.86 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 156.1, 137.9, 132.7, 128.4, 127.8, 118.1, 117.8, 82.8, 73.4, 71.5, 69.9, 65.8, 63.6, 60.7, 58.9, 43.2, 31.3, 28.8, 19.0, 17.4.

MS (ES+): *m/z* = 490.2 [M + 1].

Macrocycles 46.2.1–46.5.1; General Procedure

To a stirred solution of the appropriate diene **46.2**–**46.5** (85 mg) in CH_2Cl_2 (100 mL) was added **G-II** (10 mol%). The mixture was stirred for 16 h at 40 °C until all the material was consumed. It was then concentrated under reduced pressure, and the residue was purified by column chromatography (hexanes–EtOAc, 5:5).

(2*R*,3*R*,3a*S*,8*S*)-8-Benzyl-2-[(benzyloxy)methyl]-3-methoxy-2,3,3a,4,5,8,9,12,15,15a-decahydrofuro[3,2-*i*][1,6,3]dioxazacyclotetradecine-7,10-dione (46.2.1)

Colorless oil; yield: 24.8 mg (75%); molecular formula: $C_{29}H_{35}NO_7$; R_f = 0.5 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 8 H), 7.15–7.10 (m, 2 H), 5.77 (br s, 1 H), 5.57 (dt, *J* = 17.2, 10.0 Hz, 1 H), 5.28–5.20 (m, 1 H), 5.12–5.06 (m, 2 H), 4.65–4.57 (m, 1 H), 4.54–4.50 (m, 4 H), 4.23–4.15 (m, 1 H), 4.00 (dd, *J* = 7.75, 2.87 Hz, 1 H), 3.88–3.81 (m, 1 H), 3.54–3.45 (m, 2 H), 3.42 (s, 3 H), 3.14–3.02 (m, 3 H), 2.51–2.44 (m, 1 H), 2.39–2.24 (m, 1 H), 2.05–1.94 (m, 1 H), 1.57–1.48 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 155.4, 137.9, 135.7, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 128.4, 128.3, 128.1, 127.8, 127.8, 127.7, 127.1, 118.1, 82.8, 73.4, 71.5, 69.9, 64.6, 63.9, 60.8, 54.7, 43.2, 38.3, 29.7, 29.7, 28.8.

MS (ES+): *m/z* = 510.3 [M + 1].

(2*R*,3*R*,3a*S*,8*S*)-2-[(Benzyloxy)methyl]-8-isobutyl-3-methoxy-2,3,3a,4,5,8,9,12,15,15a-decahydrofuro[3,2-*i*][1,6,3]dioxazacyclotetradecine-7,10-dione (46.3.1)

Colorless oil; yield: 23.1 mg (82%); molecular formula: $C_{26}H_{37}NO_7$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.28 (m, 5 H), 5.86–5.64 (m, 2 H), 4.90–4.64 (m, 2 H), 4.53 (s, 2 H), 4.25–4.09 (m, 2 H), 3.73–3.54 (m, 4 H), 3.46–3.37 (m, 8 H), 3.17–3.08 (m, 1 H), 2.67–2.54 (m, 1 H), 2.07–2.00 (m, 1 H), 1.80–1.55 (m, 3 H), 0.95–0.90 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 141.5, 137.9, 128.4, 127.8, 127.8, 125.0, 110.0, 82.4, 82.4, 73.5, 68.8, 61.1, 58.9, 54.3, 45.8, 29.7, 24.8.

MS (ES+): *m/z* = 476.3 [M + 1].

(2*R*,3*R*,3a*S*,8*S*)-2-[(Benzyloxy)methyl]-8-*sec*-butyl-3-methoxy-2,3,3a,4,5,8,9,12,15,15a-decahydrofuro[3,2-*i*][1,6,3]dioxazacyclotetradecine-7,10-dione (46.4.1)

Colorless oil; yield: 26.4 mg (72%); molecular formula: $C_{26}H_{37}NO_7$; R_f = 0.4 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 3.67 (dd, *J* = 9.93, 5.31 Hz, 1 H), 3.61 (dd, *J* = 9.93, 4.79 Hz, 1 H), 5.84 (br s, 1 H), 5.52 (dt, *J* = 17.20, 9.60 Hz, 1 H), 5.29–5.25 (m, 1 H), 5.15–5.04 (m, 2 H), 4.56–4.53 (m, 4 H), 4.29 (dd, *J* = 8.81, 4.86 Hz, 1 H), 4.22–4.16 (m, 1 H), 4.13–4.04 (m, 1 H), 3.49–3.40 (m, 3 H), 2.48–2.35 (m, 2 H), 2.27–2.18 (m, 1 H), 1.92–1.82 (m, 1 H), 1.61–1.49 (m, 5 H), 0.93–0.89 (m, 6 H).

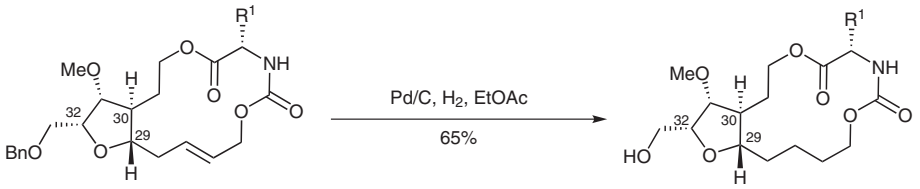
^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 155.8, 137.9, 137.9, 128.4, 128.2, 127.8, 127.8, 118.2, 82.8, 73.4, 71.5, 69.9, 64.6, 63.5, 60.7, 58.3, 43.2, 38.0, 28.8, 24.9, 15.5, 11.6.

MS (ES+): *m/z* = 476.1 [M + 1].

(2*R*,3*R*,3a*S*,8*S*)-2-[(Benzyloxy)methyl]-8-isopropyl-3-methoxy-2,3,3a,4,5,8,9,12,15,15a-decahydrofuro[3,2-*i*][1,6,3]dioxazacyclotetradecine-7,10-dione (46.5.1)

Colorless oil; yield: 31.4 mg (74%); molecular formula: $C_{25}H_{35}NO_7$; R_f = 0.5 (hexanes–EtOAc, 5:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 5.84 (br s, 1 H), 5.57 (td, *J* = 17.09, 9.92 Hz, 1 H), 5.28 (d, *J* = 7.57 Hz, 1 H), 5.15–5.06 (m, 2 H), 4.63–4.49 (m, 4 H), 4.29–4.15 (m, 2 H), 4.04 (td, *J* = 10.70,



46.4.1 - R^1 = 2-butyl
46.5.1 - R^1 = 2-propyl

51a - R^1 = 2-butyl
51b - R^1 = 2-propyl

Scheme 45

8.39 Hz, 1 H), 3.88–3.84 (m, 1 H), 3.54–3.45 (m, 2 H), 3.44 (s, 3 H), 3.13 (dd, *J* = 7.93, 1.74 Hz, 1 H), 2.51 (dt, *J* = 10.84, 3.05 Hz, 1 H), 2.20–1.99 (m, 3 H), 1.60–1.50 (m, 1 H), 0.87 (d, *J* = 6.76 Hz, 3 H), 0.95 (d, *J* = 6.82 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 156.0, 137.8, 128.4, 127.8, 118.2, 82.8, 73.4, 71.5, 69.9, 64.6, 63.6, 60.8, 59.0, 43.2, 31.3, 29.7, 28.8, 19.0, 17.5.

MS (ES+): *m/z* = 462.3 [M + 1].

Macrocycles 51a and 51b; General Procedure

To a stirred solution of the appropriate macrocycle **46.4.1** or **46.5.1** (35 mg) in EtOAc (10 mL) was added Pd catalyst (10 mol%), and the mixture was stirred for 16 h under H_2 (1 atm). When the starting material was completely consumed, the mixture was filtered through Celite and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes–EtOAc, 6:4).

(2*R*,3*R*,3a*S*)-8-*sec*-Butyl-2-(hydroxymethyl)-3-methoxydodecahydrofuro[3,2-*i*][1,6,3]dioxazacyclotetradecine-7,10-dione (51a)

Colorless oil; yield: 15.5 mg (65%); molecular formula: $C_{19}H_{33}NO_7$; R_f = 0.1 (hexanes–EtOAc, 3:7).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40 (d, *J* = 8.63 Hz, 1 H), 4.32–4.21 (m, 2 H), 4.15–4.04 (m, 3 H), 3.67–3.64 (m, 2 H), 3.57–3.52 (m, 1 H), 3.48 (s, 3 H), 3.18 (br s, 1 H), 1.84–1.78 (m, 2 H), 1.68–1.59 (m, 4 H), 1.54–1.36 (m, 4 H), 1.00–0.85 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 156.5, 82.6, 72.4, 64.8, 64.3, 63.8, 60.8, 58.4, 38.5, 37.8, 31.9, 29.7, 28.2, 25.5, 25.0, 23.7, 15.5, 11.5.

MS (ES+): *m/z* = 388.1 [M + 1].

(2*R*,3*R*,3a*S*)-2-(Hydroxymethyl)-8-isopropyl-3-methoxydodecahydrofuro[3,2-*i*][1,6,3]dioxazacyclotetradecine-7,10-dione (51b)

Colorless oil; yield: 18.4 mg (65%); molecular formula: $C_{18}H_{31}NO_7$; R_f = 0.1 (hexanes–EtOAc, 3:7).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.42–5.34 (m, 1 H), 4.30–4.09 (m, 6 H), 3.72–3.63 (m, 2 H), 3.59–3.52 (m, 1 H), 3.48 (s, 3 H), 3.19–3.17 (m, 1 H), 2.94–2.76 (m, 1 H), 2.18–2.08 (m, 1 H), 1.89–1.76 (m, 1 H), 1.74–1.36 (m, 8 H), 0.97–0.91 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 156.6, 82.6, 72.4, 63.9, 59.2, 38.6, 33.8, 31.9, 29.7, 28.2, 25.5, 23.7, 22.7, 19.1, 17.7, 14.1, 11.7.

MS (ES+): *m/z* = 374.3 [M + 1].

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