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Diversity-Oriented Synthesis of Pochonins and Biological Evaluation against a Panel of Kinases

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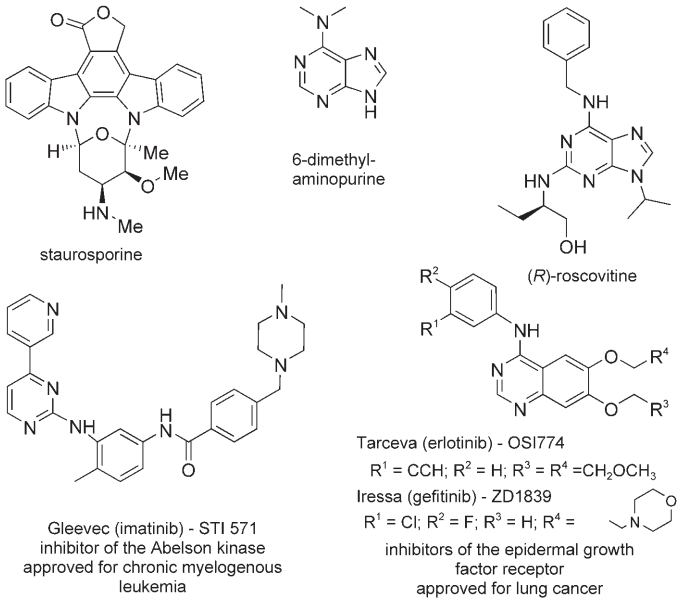
Abstract: Pochonins A–F were recently characterized as six new members of the naturally occurring family of 14-membered resorcylic acid lactones. As there are a high number of ATPase and kinase inhibitors among natural resorcylic lactones, a library based on the pochonin scaffold, with five points of diversity, was prepared which includes diversity beyond that of the natural analogues. The library was synthesized by using solid-supported reagents amenable to automation. Testing the library for its inhibition against a panel of 24 kinases at 10 μM afforded a >14% hit rate. These results demonstrate the potential of the resorcylides towards the inhibition of therapeutically relevant kinases.

Keywords: Bergerat fold · combinatorial chemistry · kinase inhibitors · organic synthesis · pochonin

Introduction

Modulation of protein activity through phosphorylation/dephosphorylation of a serine, threonine or tyrosine residue by the action of kinases and phosphatases is at the center of the majority of signal transduction mechanisms.[1] Small molecule inhibitors, such as 6-dimethylaminopurine and staurosporine, were instrumental in understanding the importance of such phosphorylation mechanisms and shed light on the biological function of kinases. Kinases bind to ATP with a K_m of 0.1–10 μM, and transfer the γ-phosphate group selectively to a specific residue of a given protein. The core domain of kinases, consisting of the ATP-binding site with the residues involved in phosphotransfer reaction, are highly conserved throughout the kinome.[2] This led to the speculation that inhibitors targeting this highly conserved ATP-binding pocket would not only have to compete with ATP present at high concentration (mM), but would necessarily lack selectivity. The discovery that modified purines, such as (*R*)-roscovitine were potent and fairly selective inhibitors[3] challenged that notion and inspired the synthesis of combinatorial libraries around the purine scaffold[4,5] yielding important leads.[6,7]



Nevertheless, designing selective kinase inhibitors or targeted libraries remains challenging. From a chemical biology perspective, the ability to knock down a specific kinase activity with a cell-permeable small molecule is an attractive approach to deconvolute the role of specific kinases within complex signaling networks. Furthermore, it has become increasingly apparent that the biological function of kinases is often regulated by their conformation, which is in turn dic-

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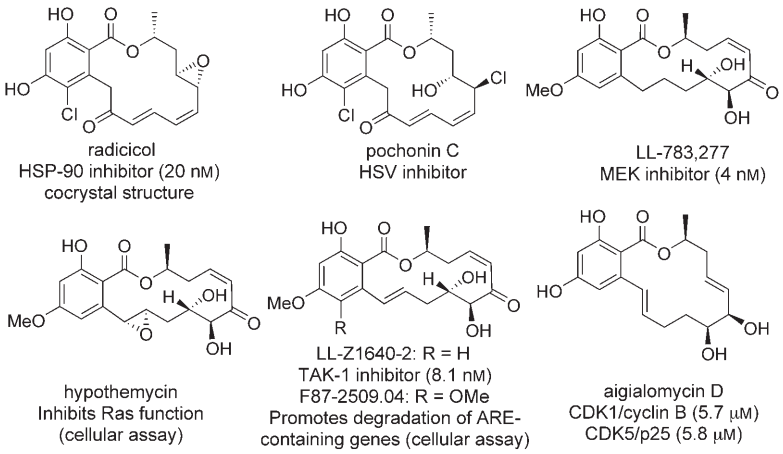
tated by their phosphorylation level and intra- as well as intermolecular associations. Small molecule inhibitors have the potential to discriminate between the different conformations of a given kinase which would provide a means to dissect their respective functions. From a therapeutic perspective, imbalance in the phosphorylation/dephosphorylation equilibrium is at the source of numerous oncogenic processes and inhibition of kinases has emerged as one of the most promising avenues for chemotherapy.[8] Three kinase inhibitors, gleevec, which inhibits Abl, iressa, and tarceva, which both inhibit EGFR, have already been approved for treatment and herald a new era of highly targeted chemotherapy.

Given the challenge of developing selective kinase inhibitors, radicicol caught our attention as it has been shown to be a highly potent competitive ligand for the HSP90's ATP-binding pocket while being highly selective for it.[9] HSP90 is an ATPase rather than a kinase, and its ATP-binding pocket has a Bergerat fold,[10,11] which is distinct from kinases' ATP-binding pockets. However, literature search for other resorcylic macrolides with the same skeletons as radicicol revealed that closely related analogues are inhibitors of kinases but not HSP90. Indeed, LL-Z1640-2 was found to be a potent and selective inhibitor of TAK1 kinase for which radicicol and other resorcylides were not active.[12–15] Closely related LL-783,227, in which one of the olefins has been reduced, is a potent inhibitor of MEK kinase.[15] Compound F87-2509.04 was found to induce degradation of mRNA containing AU-rich elements (ARE)[16] and hypothemycin was found to inhibit the Ras-mediated cellular signaling.[17] We have recently shown that aigialomycin D is a CDK inhibitor.[18] Interestingly, pochonin C which is closely related to radicicol was found to inhibit Herpes Simplex Virus (HSV) replication with a significant therapeutic window, whereas it is a poor HSP90 inhibitor.[19] While radicicol and pochonin C are structurally very similar, they have very different conformations in solution which can rationalize their different biological activities.[20] Although structural information has been reported only for the radicicol-HSP90 interaction, wherein radicicol substitutes the adenosine in the ATP-binding pocket, it can be speculated that the kinase inhibitors amongst the resorcylides exert their effect also by competing for the ATP-binding pocket. It was anticipated that a library extending beyond the natural resorcylides would lead to new kinase and ATPase inhibitors.[21–23]



Results and Discussion

The library was envisioned to stem from five points of diversity around the resorcylic macrolide scaffold as shown in Figure 1; modifications of the *para* phenol (R^1, a number of natural resorcylides bear a methyl group at that position),

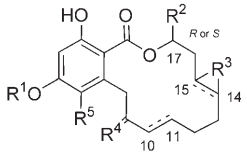


Figure 1. General structure of the library.

the group on C17 (R^2, both stereochemistry are present in natural resorcylides; however, only with a methyl substituent), the C14–C15 olefin (R^3), the C9 carbonyl (R^4), the olefin C10–C11, and the meta position on the aryl ring (R^5, a number of natural resorcylides bear a chlorine at that position). An important consideration in the design of the chemistry used to elaborate the molecular diversity of this scaffold was that a maximum number of steps should be carried out on the solid phase or by using polymer-bound reagents,[24,25] so as to minimize traditional chromatography. The assembly of the macrocycle relied on the chemistry developed for the synthesis of pochonin D.[26] Thus, commercially available benzoic acid **1** (Scheme 1) and its chlorinated analog **2** (the chlorine atom was introduced on acid **1** prior to esterification by using HClO generated in situ by the oxidation of acetaldehyde with $NaClO_2$/sulfamic acid)[26] were esterified with fifteen different homoallylic alcohols by using polymer-supported DEAD to yield esters **3** in excellent purity. The homoallylic alcohols that are not commercially available were obtained in their enantiomerically pure form either by enzymatic resolution[27,28] of the racemic alcohol or by means of Brown allylation of the corresponding aldehyde.[29] The products **3** were then protected with ethoxymethylene chloride[30] (EOM-Cl) in the presence of Hunig's base to obtain the corresponding protected toluic

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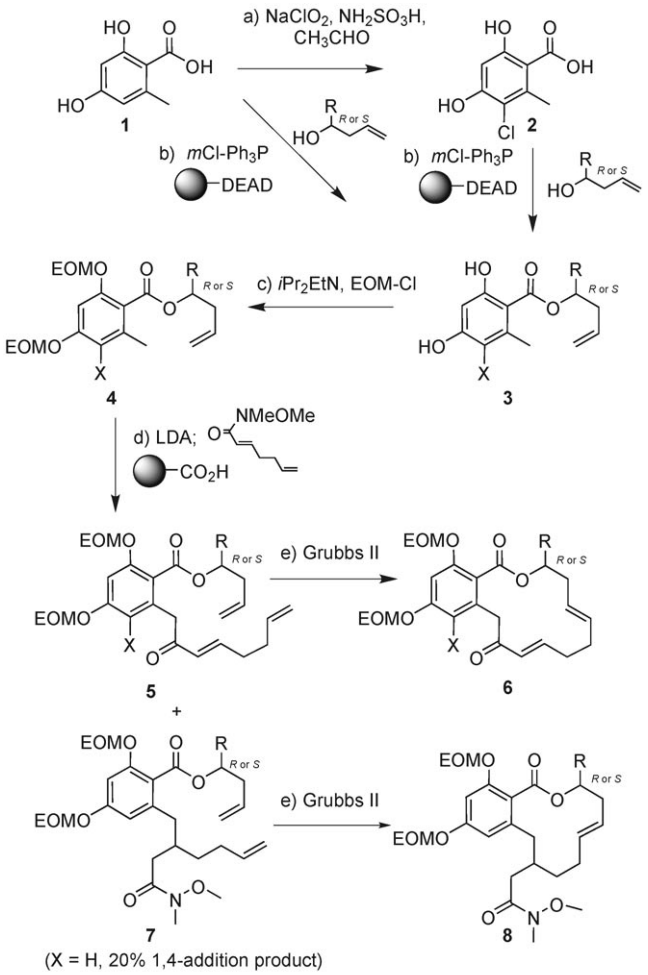
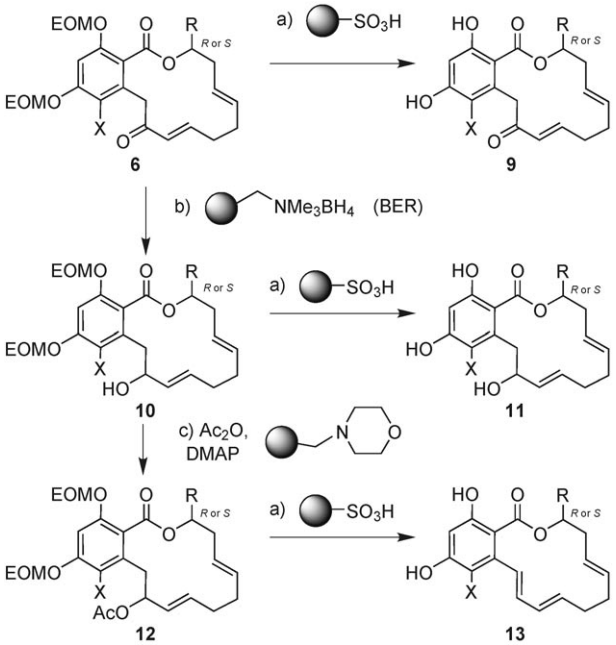


Scheme 1. Synthesis of macrocyles **6** and **8**: a) $NaClO_2$ (5.0 equiv), NH_2SO_3H (5.0 equiv), CH_3CHO (1.0 equiv), THF/H_2O 5:1, 0 °C, 0.5 h, 92 %; b) PS-DEAD (2.5 equiv, 1.3 mmol g^{-1}), alcohol (1.0 equiv), P(*m*ClPh)$_3$ (2.0 equiv), CH_2Cl_2, 23 °C, 0.5 h, 60–80 %; c) *i*Pr_2EtN (4.0 equiv), EOMCl (4.0 equiv), TBAI (cat.), DMF, 80 °C, 5 h, 80–90 %; d) LDA (2.0 equiv), THF, −78 °C, Weinreb amide (1.0 eq), 10 min, Amberlite IRC-50 (20 equiv, 10.0 mmol g^{-1}); e) Grubbs II (10 % mol), toluene (2 mM), 80 °C, 12 h, 60–85 % after two steps. PS-DEAD = ethoxycarbonylazocarboxymethyl polystyrene, Grubbs II = ruthenium[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine), LDA = lithium diisopropylamide, EOM = methoxymethylene; TBAI = tetrabutylammonium iodide.

esters **4**, which could be used in the subsequent carbon-acylation reaction without further purification.

Deprotonation of the toluic esters **4** by using two equivalents of LDA, followed by addition of the α,β-unsaturated Weinreb amide, previously prepared by solid-phase chemistry,[26] afforded acylation products **5**. The reaction was quenched with a polymer-bound acid which also sequestered all the diisopropyl amine. We had previously noted that this reaction could lead to some level of 1,4-conjugate addition rather than desired 1,2-addition.[20] While the bulky chlorine present in pochonin D suppresses this reaction, compounds lacking the aryl chloride afforded 20 % of the conjugate addition products **7**. Nevertheless, the crude mixtures of these reactions were used in the subsequent cyclization step. Unfortunately, compounds **4** bearing a furyl or pyridyl side chain did not afford clean products in the acylation reaction. The trienes then underwent ring-closing metathesis by using Grubbs second-generation catalyst[31,32] under thermodynamic conditions,[33] affording the desired 14-membered macrocycles. In the cases in which the metathesis reactions were carried out with a mixture of **5** and **7**, the corresponding 12-membered-ring product **8** was obtained in addition to **6** as a separable mixture. All successful reaction sequences were purified by standard chromatography at this stage yielding the macrocycles **6** and **8** in 30–60 % and 8–10 % overall yield, respectively, from **1**.

Macrocycles **6** were then used as the starting point for further diversifications. Deprotection of the EOM groups of **6** by using sulfonic acid resin afforded compounds **9** in pure form and excellent yields after simple filtration of the resin and evaporation of the solvents (Scheme 2). The 12-membered-ring products **8** were deprotected as smoothly (not shown). As expected, EOM deprotections under acid catalysis were slower for the chlorinated analogues and had to be monitored as prolonging the reaction times could lead to conjugate additions (vide infra). Treatment of **6** with reducing agents led to either carbonyl reduction with DIBAL or mixtures of carbonyl and 1,4-reduction with $NaBH_4$. It is known that using a noncoordinating counter ion for borohy-



Scheme 2. Deprotection and synthesis of the reduced ketone analogues. a) PS-TsOH (10.0 equiv, 3.2 mmol g^{-1}), MeOH, 40 °C, 4 h, >90 %; b) BER resin (1.0 equiv, 2.5 mmol g^{-1}), MeOH, 0 °C, 12 h, ~60 %; c) Ac_2O (1.2 equiv), PS-NMM (1.2 equiv, 3.20 mmol g^{-1}), DMAP (0.05 equiv), DMF, 23 °C, 0.5 h, ~80 %. BER resin = borohydride exchange resin, PS-TsOH = sulfonic acid resin MP, DIBAL = diisobutylaluminum hydride, DMAP = dimethylaminopyridine, PS-NMM = morpholinomethyl polystyrene.

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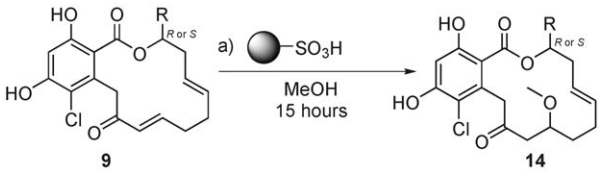
dride can favor the carbonyl reduction and this was most conveniently achieved by using a polymer-supported quaternary ammonium borohydride known as borohydride exchange resin (BER).[34,35] Thus, ketones **6** could be reduced with BER-resin to obtain both diastereoisomers of **10** in ~60% yield. Deprotection of the EOMs with sulfonic acid resin under regular conditions afforded compounds **11**. Acetylation of the reduced intermediates **10** by using PS-NMM/Ac_2O yielded compounds **12** which led to elimination upon deprotection to afford trienes **13** as a mixture of olefin geometries.

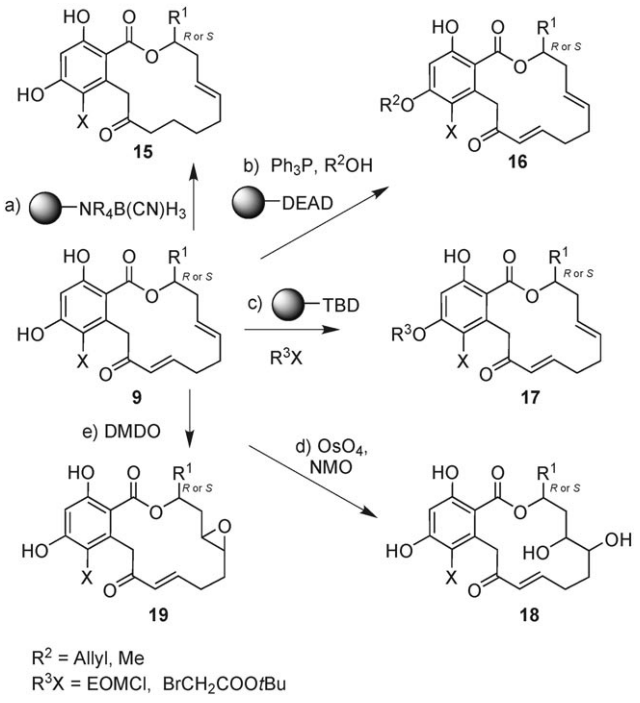
As we observed that prolonged exposure of resorcylides **6** to methanol in the presence of sulfonic acid resin led to conjugate addition, we asked whether this reaction could be driven to completion cleanly. We found that phenol **9** (Scheme 3) could be quantitatively converted to product **14** in 15 h. This product could obviously be obtained directly from **6** under the same conditions.



Scheme 3. Synthesis of analogues **14** by conjugate addition. a) PS-TsOH (10.0 equiv, 3.2 mmol g^{-1}), MeOH, 40 °C, 15 h, 80%; PS-TsOH = sulfonic acid resin.

Compounds **9** were also used as starting points for further diversifications (Scheme 4). Thus, treatment of **9** with polymer-bound cyanoborohydride afforded the 1,4-reduction products **15** in moderate yields. The more acidic *para*-hydroxyl groups of **9** were substituted by either Mitsunobu reaction using polymer bound DEAD or alkylation using a polymer-bound base to afford compounds with general structure **16** and **17**, respectively. Oxidation with OsO_4 afforded the dihydroxylation products **18** as a mixture of isomers as well as the products corresponding to the dihydroxylation of the conjugate olefin (product not shown). Treatment of **9** with freshly prepared dimethyldioxirane led to the selective epoxidation of the nonconjugated olefin as a mixture of diastereoisomers of pochonin A analogues **19**. We have recently shown[36] that higher diastereoselectivity may be obtained for pochonin A if the phenols are protected with TBS; however, this was not found to be necessary for the purpose at hand.

It is interesting to note that the conjugated olefin proved to have different reactivity depending on the presence or absence of the chlorine atom on the aryl ring. While the EOM deprotection of compound **6** in which X = Cl and R = Me could be carried out with HCl in dioxane, treatment of the corresponding compound **6** in which X = H and R = Me with the same conditions led to the conjugate addition of the chlorine ion during the deprotections affording compound **20** (Scheme 5). The difference in reactivity may be attributed to the different conformation of these compounds.



Scheme 4. Derivatization of compounds **9**. a) PS-TMABH_3CN (2.0 equiv, 3.5 mmol g^{-1}), CH_2Cl_2/AcOH (10:1), 23 °C, 4 h, ~50%; b) PPh_3 (2.0 equiv), R^2OH (2.0 equiv), PS-DEAD (2.0 equiv, 1.3 mmol g^{-1}), CH_2Cl_2, 23 °C, 8 h, ~60%; c) R^3X (0.9 equiv), PS-TBD (2.0 equiv, 2.9 mmol g^{-1}), CH_2Cl_2, 23 °C, 3 h, ~90%; d) OsO_4 (0.1 equiv), NMO (1.0 equiv), acetone/H_2O 10:1, 23 °C, 1 h, >70%; e) DMDO (1.2 equiv, 0.04 M in acetone), CH_3CN, 0 °C, 30 min, >90%. DMDO = dimethyldioxirane, NMO = 4-methylmorpholine *N*-oxide, PS-TBD = TBD-methyl polystyrene, PS-TMABH_3CN = (polystyrylmethyl)trimethylammonium cyanoborohydride.

It is conceivable that the differences in conformation affect the level of conjugation between the olefin and the adjacent carbonyl group. Nevertheless, the β-chlorine could be cleanly eliminated in the presence of polymer-bound base to recover the conjugate compound **9**.

While evaluating protecting groups for the phenols, we noticed that dihydropyran, in the presence of a strong acid, such as sulfonic acid, led to electrophilic aromatic substitution rather than phenol protection.[37] Applying these conditions to compounds **9** (Scheme 5) afforded **21** as a separable mixture of diastereoisomers.

The formation of oxime proved to be sluggish on compounds with unprotected phenols. However, compounds **6** (X = H, Scheme 5) protected with EOM groups underwent smooth oxime formation with nine different hydroxyl amines to obtain compounds **22** as *E*/*Z* mixtures with variable ratios. EOM deprotection of **22** with sulfonic acid resin in methanol followed by treatment with sulfonic acid resin in dichloromethane in the presence of dihydropyran afforded oximes **23** bearing a pyran substitution on the aromatic ring as a mixture of diastereoisomers. For the case in which the side chain contains an acid ($R^2X = OCH_2COOH$), the deprotection of the EOM with the sulfonic acid resin in

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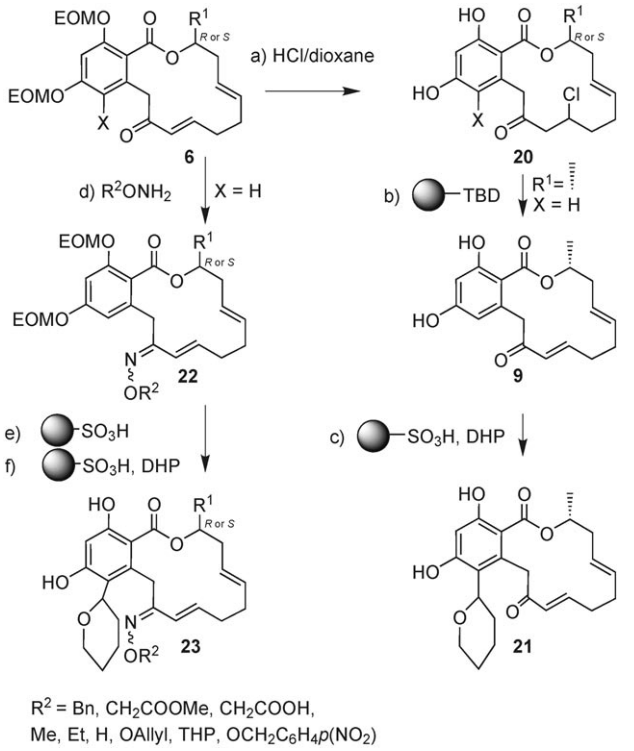
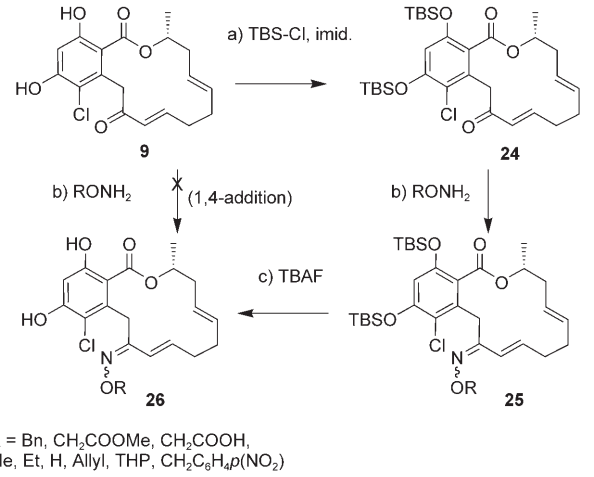


Scheme 5. Derivatization of macrocycles **6**: a) 2.5% HCl/dioxane, 23°C, 3 h, >75%; b) PS-TBD (0.5 equiv, 2.6 mmol g^{-1}), CH_2Cl_2, 23°C, 8 h, ~90%; c) PS-TsOH (1.0 equiv, 3.2 mmol g^{-1}), DHP (1.0 equiv), CH_2Cl_2, 23°C, 5 h, ~80%; d) R^2XNH_2.HCl (5.0 equiv), pyridine/AcOH 5:1, 40°C, 12 h, ~90%; e) PS-TsOH (10 equiv, 3.2 mmol g^{-1}), MeOH, 40°C, 4 h, ~80%; f) PS-TsOH (cat., 3.2 mmol g^{-1}), DHP (1.0 equiv), CH_2Cl_2, 23°C, 5 h, ~70%. DHP = dihydropyran.



Scheme 6. Oxime formation with compounds **9** (R = Me, X = Cl): a) TBS-Cl (5.0 equiv), imidazole (5.0 equiv), DMF, 23°C, 3 h, ~90%; b) R^2ONH_2.HCl (5.0 equiv), Py/AcOH 5:1, 40°C, 12 h, ~90%; c) TBAF (2.5 equiv), THF, 23°C, 2 h, ~80%. TBAF = tetrabutylammonium fluoride, TBS-Cl = *tert*-butyldimethylsilyl chloride.

methanol was accompanied by esterification of the carboxylate. Finally, all attempts of oxime formation on the chlorinated analogues with or without EOM-protecting groups generated mostly the corresponding 1,4-addition of the hydroxylamines (Scheme 6). To our surprise, when pochonin D was protected with a TBS groups, (**24**, Scheme 6) the formation of the desired oxime **25** was the only product observed under the same reaction conditions. Deprotection of the TBS groups was then achieved by using TBAF to obtain oxime **26**. This difference of reactivity is presumably due to the level of conjugation between the olefin and the carboxylate which in turn is a product of the conformation of the macrocycle. It is not so surprising that a bulky-protecting group on the *ortho* phenol has a pronounced impact on the macrocycle conformation as compared to the phenol which forms a hydrogen bond to the carbonyl. Such effects have already been documented to affect the outcome of ring-closing-metathesis reactions[38] and epoxidation diastereoselectivity.[36] It should be noted that a number of oxime derivatives of radicicol have been reported in the literature[39–41] leading to the discovery that some oximes dramatically improve the affinity of derivatized radicicol for HSP90.[42]

While not all permutations of the five points of diversity were pursued, a total of 113 compounds were prepared (Figure 2). A representative subset of the library (84 compounds) was tested for its inhibition in a panel of 24 kinase (AKT1, ARK5, Aurora-A, Aurora-B, B-RAF-VE, CDK2/CycA, CDK4/CycD1, CK2-α1, FAK, EPHB4, ERB2, EGF-R, IGF1-R, SRC, VEGF-R2, VEGF-R3, FLT3, INS-R, MET, PDGFR-β, PLK1, SAK, TIE2, COT) at 10 μM. Significantly, twelve compounds showed more than 50% inhibition which represents a >14% hit rate for a kinase. Interestingly, pochonin D, A, and radicicol which have been shown to be powerful inhibitors of HSP90 did not show significant activity against this panel of kinases. Nine compounds were selected to calculate IC_{50} against each of the 24 kinases (Table 1). In this more detailed analysis, radicicol showed only very mild activity against VGFR-R2 with no inhibition for the twenty three other kinases. Several pochonin analogues showed a well-defined pattern of activity against therapeutically relevant enzymes, such as Src (8 μM for A2), Aurora A (12 μM for A3), and IGF1-R (11 μM for A5). Importantly, the compounds that were found to be kinase inhibitors were not inhibitors of HSP90 (data not shown) and are not indiscriminate ATP-surrogates.

HSP90s ATPase pocket targeted by radicicol and pochonin D has a specific fold that is present in a superfamily which includes functionally diverse proteins, such as DNA topoisomerase II, helicase, MutL, and histidine kinases (Bergerat fold).[10,11] In fact, it has been shown that radicicol does inhibit other members of this family albeit with lower affinity.[43,44] While the pochonin library described herein will certainly contain some compounds that are good inhibitors of enzymes bearing a Bergerat fold, we wished to evaluate whether modification around the pochonin scaffold could retune the selectivity of these compounds from HSP90 inhibitors to kinase inhibitors. The fact that more than fourteen percent of the compounds showed a kinase inhibition of greater than 50% at 10 μM clearly supports the hypothesis that resorcylides are a good scaffold for kinase inhibition.

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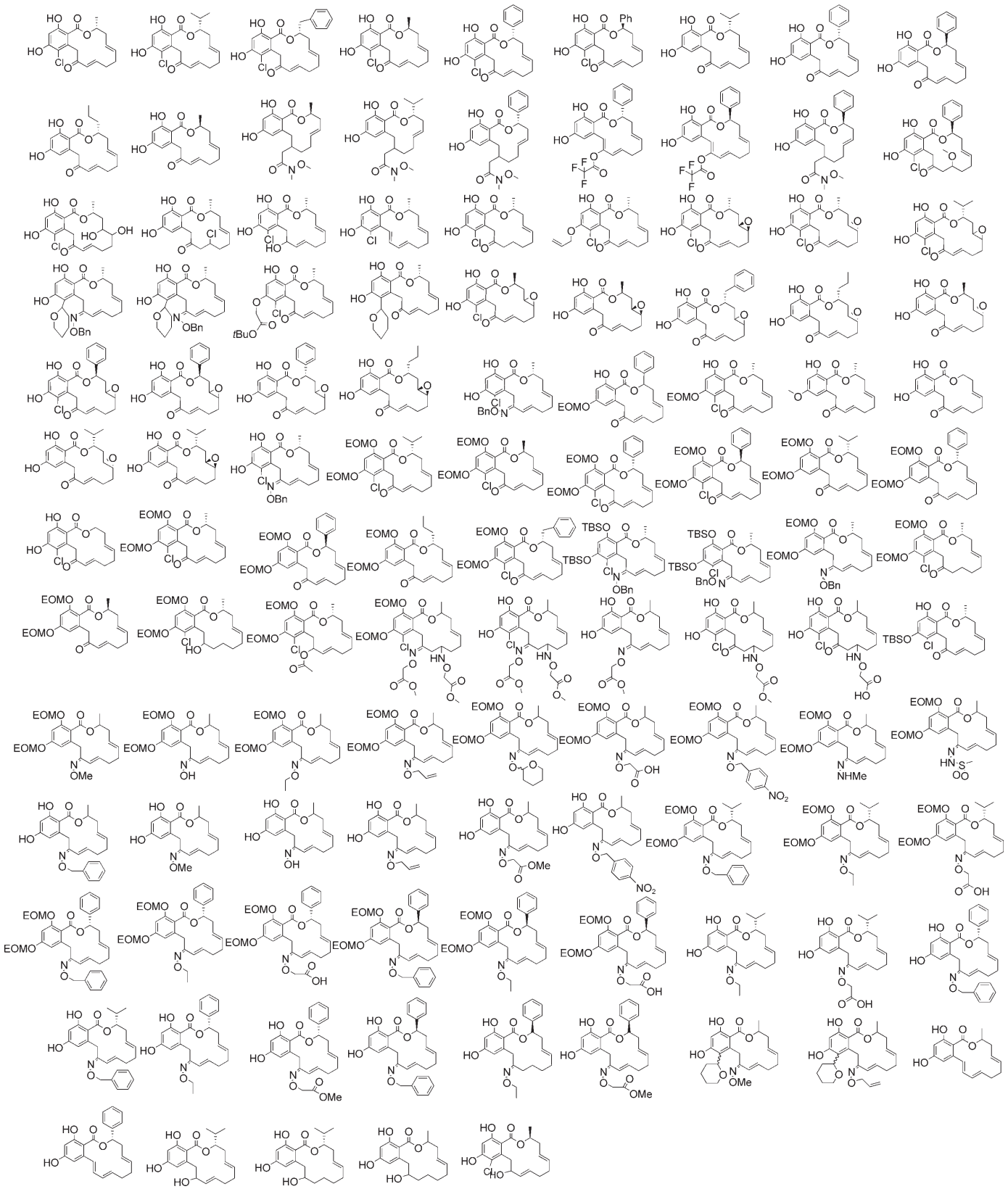

Figure 2. Structures of the pochonin library.

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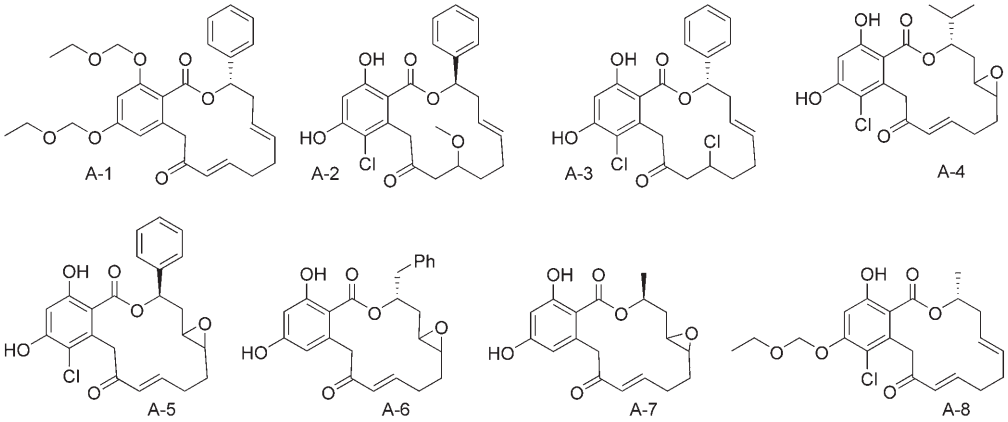
Table 1. Inhibitory activity (IC_{50}; μM) and structure of selected pochonin analogues in a panel of 24 kinase assays (blanks represent an $IC_{50} > 50$ μM).



	AKT1	ARK5	Aurora A	Aurora B	B-RAF-VE	CDK2/CycA	CDK4/CycD1	CK2-α1	FAK	EPHB4	ERBB2	EGF-R
radicicol												
A1												
A2			14	16			50		14	16	16	33
A3			12	14			30		9	40	24	16
A4			30	36			48		37			24
A5			47		50		45		38	49		22
A6				16			37		34	40		16
A7												32
A8												

	IGF1-R	SRC	VEGF-R2	VEGF-R3	FLT3	INS-R	MET	PDGFR-β	PLK1	SAK	TIE2	COT
radicicol			49								72	
A1	23	11										
A2	16	8	19	40	23	36	32			17	16	
A3	19	14	20	19	23	44	29			25	15	
A4	13	12	30	31	45					19		
A5	11	12	19	31						20		
A6	21	20	25	34	44		36			17	25	
A7												
A8												

Conclusion

The synthesis of a library based on the pochonin macrolides by using predominantly polymer-supported reagents has been achieved. The synthetic methods that were developed are amenable to automated synthesis. Screening of this library for kinase inhibition yielded a number of leads for therapeutically important kinases including Src, EGFR, and Aurora A and B. Importantly, the promising kinase leads that were identified were not HSP90 inhibitors and showed diverse selectivity profiles for kinase inhibition amongst 24 tested kinases. These results demonstrate the potential of resorcylides for selective kinase inhibition.

Experimental Section

General techniques: All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Anhydrous solvents were obtained by passing them through a commercially available alumina column (Innovative technology, VA). Substituted polystyrene resins (100–200 mesh, 1% DVB) were purchased from Novabiochem or Aldrich. Reactions were monitored by TLC carried out on 0.25 mm E. Merck silica-gel plates (60F-254) by using UV light as visualizing agent and 10% ethanolic phosphomolybdic acid or vanillin solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash-column chromatography. PTLC (preparative thin layer chromatography) was carried out on 0.25 mm E. Merck silica-gel plates. NMR spectra were recorded on Bruker Advance-400 instrument and calibrated by using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. LCMS were recorded by using an Agilent 1100 HPLC with a Bruker micro-TOF instrument (ESI). Unless other wise stated, a Supelco C8 (5 cm × 4.6 mm, 5 μm particles) column was used with a linear elution gradient from 100% H_2O (0.5% HCO_2H) to 100% MeCN in 13 min at a flow rate of 0.5 mL min^{-1}.

General procedure for the synthesis of compounds 4: A solution of acid **1** or **2** (1.0 equiv), homoallylic alcohol (1.0 equiv), and tris(3-chlorophenyl)phosphine (2.0 equiv) in anhydrous dichloromethane (0.05 M) was treated at room temperature with PS-DEAD (2.5 equiv, 1.3 mmol g^{-1}). After stirring for 30 min, the reaction mixture was filtered on silica and washed with hexane/EtOAc (10:1, 100 mL) and hexane/EtOAc (3:1, 100 mL). The 3:1 mixture was concentrated under reduce pressure to yield compound **3** (60–80%). Without further purification, compound **3** (1.0 equiv) and tetrabutylammonium iodide (catalytic amount) were dissolved in DMF (0.15 M) and treated with diisopropylethylamine (4.0 equiv) and (chloromethyl)ethyl ether (4.0 equiv). After stirring overnight at 80 °C, the reaction mixture was diluted with EtOAc and washed several times with a saturated NH_4Cl solution. The organic phase was

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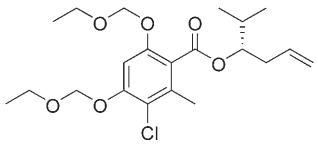
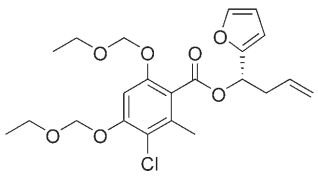
dried over $MgSO_4$ and concentrated under reduce pressure to yield compounds **4** (80–90%).

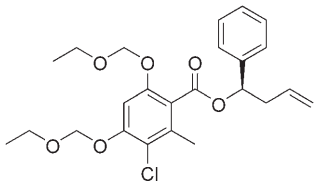
Selected examples of compounds 4: ^{1}H NMR ($CDCl_3$, 400 MHz, 25°C): δ=7.04 (s, 1H), 5.89 (ddt, J=17.0, 10.5, 7.0 Hz, 1H), 5.31 (s, 2H), 5.21



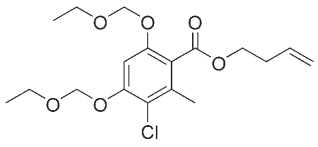
(s, 2H), 5.22–5.06 (m, 3H), 3.79 (q, J=7.0 Hz, 2H), 3.72 (q, J=7.0 Hz, 2H), 2.48–2.44 (m, 2H), 2.36 (s, 3H), 2.01 (qd, J=12.4, 7.0 Hz, 1H), 1.25 (t, J=7.0 Hz, 3H), 1.23 (t, J=7.0 Hz, 3H), 1.02 (d, J=6.4 Hz, 3H), 1.01 ppm (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C): δ= 167.3, 154.0, 152.9, 134.8, 134.1, 120.4, 117.5, 117.1, 101.5, 93.9, 93.4, 79.0, 64.6, 64.3, 35.6, 30.8, 18.4, 17.6, 17.5, 15.0 ppm (×2); HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{31}O_6ClNa$: 437.1701 $[M+Na]^+$; found: 437.1574.



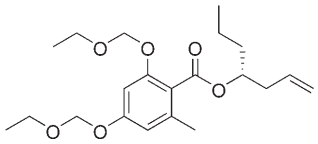
^{1}H NMR ($CDCl_3$, 400 MHz, 25°C): δ=7.43 (d, J=1.8 Hz, 1H), 6.98 (s, 1H), 6.45 (d, J=2.9 Hz, 1H), 6.38 (dd, J=3.5, 1.8 Hz, 1H), 6.18 (t, J= 7.0 Hz, 1H), 5.83 (ddt, J=17.3, 10.5, 7.0 Hz, 1H), 5.30 (s, 2H), 5.20 (dd, J=17.3, 1.6 Hz, 1H), 5.14 (s, 2H), 5.11 (dd, J=10.5, 1.6 Hz, 1H), 3.77 (q, J=7.0 Hz, 2H), 3.65 (q, J=7.0 Hz, 2H), 2.88–2.82 (m, 2H), 2.26 (s, 3H), 1.24 (t, J=7.0 Hz, 3H), 1.20 ppm (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C): δ=166.6, 154.2, 153.0, 151.9, 142.5, 135.1, 132.7, 118.3, 110.2, 109.0, 101.6, 101.1, 93.8, 93.4, 68.9, 64.6, 64.3, 36.7, 17.2, 15.0 ppm (×2), one quartenary carbon is not visible; HRMS (ESI): m/z: calcd for $C_{22}H_{27}O_7ClNa$: 461.1338 $[M+Na]^+$; found: 461.1215.



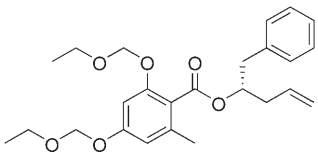
^{1}H NMR ($CDCl_3$, 400 MHz, 25°C): δ=7.46–7.44 (m, 2H), 7.40–7.33 (m, 3H), 7.01 (s, 1H), 6.09 (dd, J=7.9, 5.6 Hz, 1H), 5.83 (ddt, J=17.3, 10.2, 7.0 Hz, 1H), 5.31 (s, 2H), 5.18–5.10 (m, 2H), 5.11 (s, 2H), 3.79 (q, J= 7.0 Hz, 2H), 3.61 (q, J=7.0 Hz, 2H), 2.79 (ddd, J=15.0, 7.3, 7.3 Hz, 1H), 2.67 (ddd, J=15.1, 7.2, 7.2 Hz, 1H), 2.25 (s, 3H), 1.25 (t, J=7.0 Hz, 3H), 1.19 ppm (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C): δ= 166.7, 154.2, 153.1, 139.7, 135.1, 133.3, 128.3 (×2), 128.0, 126.8, 126.8 (×2), 119.9, 118.1, 101.6, 93.9, 93.5, 76.3, 64.6, 64.3, 40.5, 17.4, 15.0, 14.9 ppm; HRMS (ESI): m/z: $C_{24}H_{29}O_6ClNa$: 471.1545 $[M+Na]^+$; found: 471.1421.



^{1}H NMR ($CDCl_3$, 400 MHz, 25°C): δ=6.99 (s, 1H), 5.88–5.78 (m, 1H), 5.27 (s, 2H), 5.18 (s, 2H), 5.17–5.07 (m, 2H), 4.36 (t, J=6.7 Hz, 2H), 3.74 (q, J=7.0 Hz, 2H), 3.69 (q, J=7.0 Hz, 2H), 2.51–2.46 (m, 2H), 2.31 (s, 3H), 1.22–1.18 ppm (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C): δ= 167.3, 154.2, 153.0, 135.0, 133.9, 119.9, 117.2, 117.1, 101.7, 93.8, 93.6, 64.5, 64.3, 64.3, 33.0, 17.4, 14.9 ppm (×2); HRMS (ESI-TOF): m/z: calcd for $C_{18}H_{26}O_6Cl$: 373.1412 $[M+H]^+$; found: 373.1364.



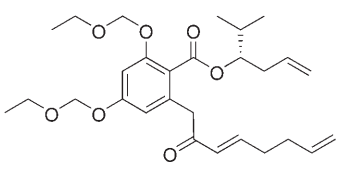
^{1}H NMR ($CDCl_3$, 400 MHz, 25°C): δ=6.74 (d, J=1.2 Hz, 1H), 6.56 (s, 1H), 5.93–5.83 (m, 1H), 5.20 (ddt, J=16.9, 9.9, 7.0 Hz, 1H), 5.21 (s, 2H), 5.20 (s, 2H), 5.16–5.08 (m, 2H), 3.72 (q, J=7.0 Hz, 4H), 2.45 (t, J= 6.4 Hz, 2H), 2.31 (s, 3H), 1.68–1.39 (m, 4H), 1.23 (t, J=7.0 Hz, 3H), 1.22 (t, J=7.0 Hz, 3H), 0.96 ppm (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C): δ=167.9, 158.6, 155.3, 137.4, 133.9, 118.9, 117.5, 110.4, 101.0, 93.2, 93.0, 73.9, 64.2 (x 2), 38.7, 35.7, 19.7, 18.5, 15.0, 15.0, 13.9 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{21}H_{32}O_6Na$: 403.2096 $[M+Na]^+$; found: 403.2017.



^{1}H NMR ($CDCl_3$, 400 MHz, 25°C): δ=7.34–7.25 (m, 5H), 6.75 (s, 1H), 6.54 (s, 1H), 5.94 (ddt, J=17.0, 9.9, 7.0 Hz, 1H), 5.48 (tt, J=6.4, 6.4 Hz, 1H), 5.22 (s, 2H), 5.18–5.14 (m, 4H), 3.74 (q, J=7.0 Hz, 2H), 3.70 (q, J= 7.0 Hz, 2H), 3.05 (dd, J=14.0, 7.0 Hz, 1H), 2.95 (dd, J=14.0, 6.4 Hz, 1H), 2.48–2.45 (m, 2H), 2.11 (s, 3H), 1.25 (t, J=7.3 Hz, 3H), 1.23 ppm (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25°C): δ=167.8, 158.7, 155.4, 137.6, 137.5, 133.7, 129.5 (×2), 128.4 (×2), 126.5, 118.7, 117.9, 110.5, 101.1, 93.3, 93.0, 74.6, 64.3, 64.3, 39.8, 37.8, 19.4, 15.1, 15.0 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{25}H_{32}O_6ClNa$: 451.2130 $[M+Na]^+$; found: 451.2084.

General procedure for the synthesis of compounds 5 and 7: A solution of compound **4** (1.0 equiv) in anhydrous THF (0.2 M) was treated at −78°C with freshly made LDA (2.0 equiv). Immediately after, the α,β-unsaturated Weinreb amide[21] was added to the cooled solution (1.0 equiv). The resulting mixture was then stirred for 10 min at −78°C and quenched by addition of Amberlite resin (20 equiv). Upon warming up to room temperature, the reaction was filtered through a pad of silica and washed with EtOAc. Concentration under reduced pressure afforded the desired compound **5**. This compound was used directly in the metathesis reaction without any further purification. When X=H, 20% of the corresponding 1,4-addition compound was observed and a fraction of the mixture was purified for characterization of compounds **5** and **7** (silica gel, 0–20% EtOAc/cyclohexane gradient).

Selected examples of compounds 5: ^{1}H NMR ($CDCl_3$, 400 MHz, 25°C): δ=6.91 (dt, J=15.8, 6.7 Hz, 1H), 6.87 (d, J=1.8 Hz, 1H), 6.53 (d, J= 1.8 Hz, 1H), 6.19 (d, J=15.8 Hz, 1H), 5.91–5.77 (m, 2H), 5.23 (s, 2H), 5.22 (s, 2H), 5.15–5.00 (m, 5H), 3.87 (s, 2H), 3.73 (q, J=7.0 Hz, 4H), 2.45–2.40 (m, 2H), 2.35–2.29 (m, 2H), 2.25–2.20 (m, 2H), 2.00–1.92 (m,



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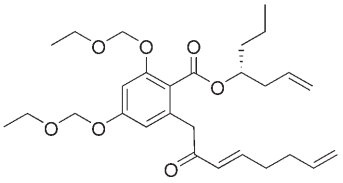
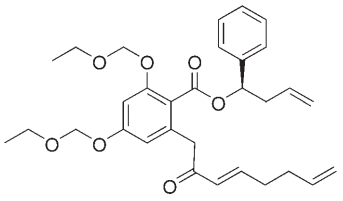
1H), 1.24 (t, $J=7.0$ Hz, 6H), 1.00 (d, $J=2.3$ Hz, 3H), 0.98 ppm (d, $J=3.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta=196.3$, 167.6, 159.0, 156.2, 147.1, 137.0, 135.0, 134.4, 129.5, 118.7, 117.2, 115.5, 111.0, 102.3, 93.3, 93.0, 78.8, 64.4, 64.3, 45.4, 35.8, 32.0, 31.7, 30.8, 18.5, 17.4, 15.0 ppm (×2); HRMS (ESI-TOF): m/z: calcd for $C_{28}H_{40}O_7Na$: 511.2666 $[M+Na]^+$; found: 511.2521.

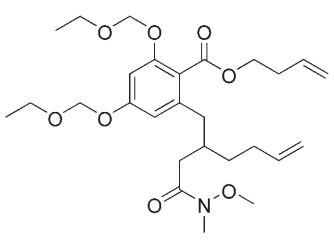


^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=6.89$ (dt, $J=15.4$, 6.7 Hz, 1H), 6.83 (d, $J=1.2$ Hz, 1H), 6.51 (d, $J=1.8$ Hz, 1H), 6.17 (d, $J=15.8$ Hz, 1H), 5.90–5.73 (m, 2H), 5.20 (s, 2H), 5.19 (s, 2H), 5.16–5.12 (m, 2H), 5.06 (2×d, $J=11.1$ Hz, 2H), 4.99 (d, $J=11.1$ Hz, 1H), 3.85 (s, 2H), 3.71 (q, $J=7.0$ Hz, 2H), 3.69 (q, $J=7.0$ Hz, 2H), 2.40 (dd, $J=6.4$, 6.4 Hz, 2H), 2.30 (ddd, $J=7.2$, 7.2, 7.0 Hz, 2H), 2.21 (ddd, $J=6.9$, 6.8, 6.6 Hz, 2H), 1.66–1.53 (m, 2H), 1.52–1.34 (m, 2H), 1.22 (t, $J=6.4$ Hz, 3H), 1.20 (t, $J=6.7$ Hz, 3H), 0.92 ppm (t, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta=196.1$, 167.4, 159.0, 156.1, 147.1, 137.0, 134.9, 134.0, 129.5, 118.7, 117.5, 115.5, 111.0, 102.3, 93.3, 93.0, 74.2, 64.3, 64.3, 45.4, 38.6, 35.6, 32.0, 31.7, 18.4, 15.0, 15.0, 13.9 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{28}H_{40}O_7Na$: 511.2672 $[M+Na]^+$; found: 511.2714.



^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=7.44$–7.42 (m, 2H), 7.39–7.29 (m, 3H), 6.85 (d, $J=1.8$ Hz, 1H), 6.78 (dt, $J=15.8$, 6.4 Hz, 1H), 6.53 (s, 1H), 6.06 (d, $J=16.4$ Hz, 1H), 6.01 (t, $J=7.0$ Hz, 1H), 5.86–5.74 (m, 2H), 5.21 (s, 2H), 5.15 (s, 2H), 5.13–5.01 (m, 4H), 3.80 (d, $J=16.4$ Hz, 1H), 3.76 (d, $J=16.4$ Hz, 1H), 3.72 (q, $J=7.0$ Hz, 2H), 3.65 (q, $J=7.0$ Hz, 2H), 2.79 (ddd, $J=14.0$, 7.0, 7.0 Hz, 1H), 2.65 (ddd, $J=14.6$, 7.0, 7.0 Hz, 1H), 2.29–2.17 (m, 4H), 1.23 (t, $J=7.0$ Hz, 3H), 1.20 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta=196.1$, 167.2, 159.0, 156.2, 147.1, 137.0, 134.9, 133.9, 129.5, 128.2 (×2), 127.8, 126.9 (×2), 118.7, 117.6, 115.5, 111.2, 102.6, 93.4, 93.0, 71.1, 64.4, 64.3, 45.4, 40.2, 32.0, 31.7, 19.4, 15.0, 14.9 ppm; HRMS (ESI): m/z: calcd for $C_{31}H_{38}O_7Na$: 545.2510 $[M+Na]^+$; found: 545.2346.

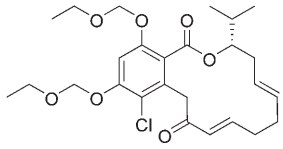
Selected example of compounds 7: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=6.72$ (s, 1H), 6.57 (s, 1H), 5.89–5.71 (m, 2H), 5.20–5.16 (m, 4H), 5.12–



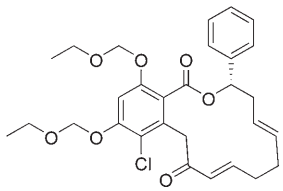
4.90 (m, 4H), 4.33 (t, $J=6.8$ Hz, 2H), 3.69 (2×q, $J=7.0$ Hz, 4H), 3.57 (s, 3H), 3.13 (s, 3H), 2.69–2.64 (m, 1H), 2.53–2.45 (m, 4H), 2.32 (m, 2H), 2.08–2.03 (m, 2H), 1.19 (t, $J=6.8$ Hz, 6H), 1.01 ppm (t, $J=6.5$ Hz, 2H); HRMS (ESI-TOF): m/z: calcd for $C_{27}H_{42}O_8N$: 508.2905 $[M+H]^+$; found: 508.2873.

General procedure for the metathesis reaction: A solution of crude **5** (or mixture of **5** and **7** in which X = Cl), in anhydrous toluene (2 mM) was treated with Grubbs second-generation catalyst (0.10 equiv) and heated at 80 °C for 12 h. The reaction was cooled down to room temperature and the mixture was filtered through a pad of silica gel, washed with CH_2Cl_2 followed by a mixture EtOAc/cyclohexane 1:1, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 0–25 % EtOAc/cyclohexane gradient) afforded compounds **6** or **8** (60–85 % over two steps):

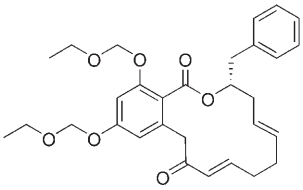
Selected examples of compounds 6: $[\alpha]_D^{25}=+21.3$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=7.14$ (s, 1H), 6.72–6.66 (m, 1H),



5.88 (d, $J=15.2$ Hz, 1H), 5.33–5.17 (m, 6H), 4.92–4.88 (m, 1H), 4.21 (d, $J=17.0$ Hz, 1H), 3.92 (d, $J=17.0$ Hz, 1H), 3.79–3.67 (m, 4H), 2.33–2.17 (m, 5H), 2.07–1.96 (m, 2H), 1.23 (t, $J=7.0$ Hz, 3H), 1.21 (t, $J=7.0$ Hz, 3H), 1.00 ppm (d, $J=5.8$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta=195.7$, 167.1, 154.7, 154.4, 147.4, 133.7, 131.2, 128.8, 128.4, 119.7, 118.0, 102.7, 93.9, 93.5, 80.0, 64.8, 64.5, 44.1, 32.3, 31.2, 30.7, 30.6, 18.3, 17.2, 15.0, 14.9 ppm; HRMS (ESI): m/z: calcd for $C_{26}H_{35}O_7ClNa$: 517.1964 $[M+Na]^+$; found: 517.1844.



$[\alpha]_D^{25}=-40.4$ ($c=0.79$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=7.49$–7.47 (m, 2H), 7.40–7.29 (m, 3H), 7.10 (s, 1H), 6.84–6.77 (m, 1H), 5.98 (d, $J=15.2$ Hz, 1H), 5.78 (d, $J=8.8$ Hz, 1H), 5.44–5.30 (m, 4H), 5.15 (d, $J=7.0$ Hz, 1H), 5.05 (d, $J=6.8$ Hz, 1H), 4.07 (d, $J=17.0$ Hz, 1H), 3.90 (d, $J=17.0$ Hz, 1H), 3.80 (d, $J=7.0$ Hz, 2H), 3.60–3.51 (m, 2H), 2.68–2.62 (m, 1H), 2.50–2.47 (m, 1H), 2.38–2.29 (m, 2H), 2.14–2.02 (m, 2H), 1.25 (t, $J=7.0$ Hz, 3H), 1.17 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta=195.7$, 166.7, 154.8, 154.2, 147.3, 140.7, 133.3, 132.1, 128.5, 128.3 (×2), 128.2, 127.9, 127.7, 126.7 (×2), 120.1, 118.1, 102.9, 93.9, 93.4, 77.4, 64.8, 64.4, 44.5, 40.5, 30.7, 15.0, 14.9 ppm; HRMS (ESI): m/z: calcd for $C_{29}H_{33}O_7ClNa$: 551.1680 $[M+Na]^+$; found: 551.1807.



$[\alpha]_D^{25}=-24.1$ ($c=0.33$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=7.39$–7.33 (m, 4H), 7.31–7.27 (m, 1H), 6.82 (s, 1H), 6.82–6.75 (m, 1H), 6.63 (s, 1H), 6.02 (d, $J=16.4$ Hz, 1H), 5.35–5.29 (m, 2H), 5.27–5.20 (m, 5H), 4.16 (d, $J=14.6$ Hz, 1H), 3.79–3.70 (m, 4H), 3.52 (d, $J=14.6$ Hz,

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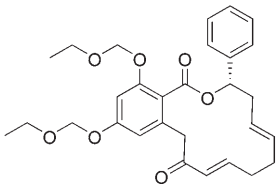
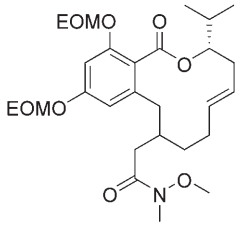
1H), 3.37 (dd, $J=13.4$, 4.1 Hz, 1H), 2.78 (dd, $J=13.5$, 9.4 Hz, 1H), 2.37–2.12 (m, 5H), 2.06–2.02 (m, 1H), 1.26 (t, $J=7.0$ Hz, 3H), 1.24 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta=197.6$, 167.8, 159.2, 156.5, 149.0, 137.3, 135.5, 131.8, 129.9, 129.5 (×2), 128.6 (×2), 128.4, 126.7, 118.1, 109.9, 102.3, 93.5, 93.1, 75.8, 64.6, 64.4, 44.4, 41.0, 36.2, 31.0, 30.6, 15.0 ppm (×2); HRMS (ESI): m/z: calcd for $C_{30}H_{36}O_7Na$: 531.2359 $[M+Na]^+$; found: 531.2350.



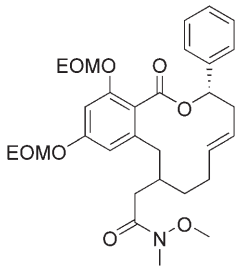
$[\alpha]_D^{25}=-108.3$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=7.56$–7.54 (m, 2H), 7.41–7.29 (m, 3H), 6.89–6.82 (m, 1H), 6.78 (d, $J=2.3$ Hz, 1H), 6.61 (d, $J=1.8$ Hz, 1H), 6.06 (d, $J=16.4$ Hz, 1H), 5.98 (dd, $J=11.7$, 2.4 Hz, 1H), 5.53–5.51 (m, 2H), 5.20 (d, $J=7.0$ Hz, 1H), 5.17 (d, $J=6.4$ Hz, 1H), 5.07 (d, $J=7.0$ Hz, 1H), 4.96 (d, $J=7.0$ Hz, 1H), 4.20 (d, $J=14.6$ Hz, 1H), 3.73–3.68 (m, 2H), 3.54–3.45 (m, 3H), 2.71–2.66 (m, 1H), 2.55–2.51 (m, 1H), 2.38–2.32 (m, 2H), 2.23–2.06 (m, 2H), 1.22 (t, $J=7.0$ Hz, 3H), 1.14 ppm (t, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta=197.6$, 167.4, 159.3, 156.6, 149.0, 140.8, 135.6, 132.2, 129.9, 128.5, 128.2 (×2), 127.9, 126.9 (×2), 117.9, 109.9, 102.3, 93.2, 93.0, 76.6, 64.4, 64.3, 44.4, 40.5, 31.0, 30.6, 15.0, 14.9 ppm; HRMS (ESI): m/z: calcd for $C_{29}H_{34}O_7Na$: 517.2197 $[M+Na]^+$; found: 517.2062.

Selected examples of compounds 8: Mixture of four diastereoisomers; ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=6.77$ (s, 1H), 6.52 (s, 0.5H), 6.46



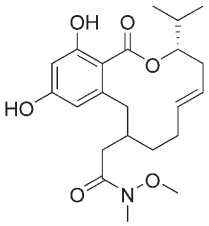
(s, 0.5H), 5.59–5.37 (m, 2H), 5.21–5.18 (m, 4H), 5.09–4.92 (m, 1H), 3.75–3.70 (m, 4H), 3.53–3.48 (m, 3H), 3.38–3.34 (m, 1H), 3.19–3.10 (m, 3H), 2.65–2.47 (m, 3H), 2.29–2.04 (m, 6H), 1.89–1.72 (m, 2H), 1.31–1.20 (m, 6H), 1.06–0.96 ppm (m, 6H); HRMS (ESI-TOF): m/z: calcd for $C_{28}H_{43}O_8NNa$: 544.2881 $[M+Na]^+$; found: 544.2907.

Mixture of four diastereoisomers; ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=$ 7.51–7.42 (m, 2H), 7.38–7.31 (m, 3H), 6.73–6.70 (m, 1H), 6.60–6.49 (m, 1H), 6.45–6.31 (m, 1H), 5.73–5.39 (m, 2H), 5.23–5.00 (m, 4H), 3.75–3.69 (m, 2H), 3.56–3.34 (m, 6H), 3.19–3.09 (m, 3H), 2.66–2.08 (m, 8H), 1.31–1.19 (m, 5H), 1.10–1.04 ppm (m, 3H); HRMS (ESI-TOF): m/z: calcd for $C_{31}H_{41}O_8NNa$: 578.2724 $[M+Na]^+$; found: 578.2715.



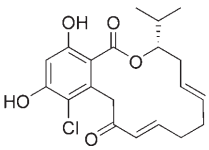
General procedure for EOM deprotection to generate deprotected compounds 8 and 9: PS-TsOH (10.0 equiv, 3.2 mmol g^{-1}) was added to a solution of the corresponding compound **6** or **8** (1.0 equiv) in MeOH (0.03 M) and the resulting suspension was shaken at 40 °C for 1 to 4 h. After this time, the reaction mixture was filtered and the methanolic solution concentrated under reduced pressure. Purification by flash chromatography (silica gel, 0–20% EtOAc/cyclohexane gradient) afforded the corresponding deprotected compound **8** or **9** (>90%).

Selected example of deprotected compounds 8: Mixture of four diastereoisomers: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=11.54$ (s, 1H), 6.33 (d, $J=2.3$ Hz, 1H), 6.25 (s, 1H), 5.53–5.51 (m, 1H), 5.44–5.41 (m, 1H), 5.11–

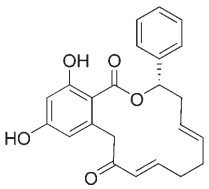


5.08 (m, 1H), 4.01 (d, $J=11.7$ Hz, 2H), 3.45 (s, 3H), 3.11 (s, 3H), 2.83–2.73 (m, 1H), 2.68–2.59 (m, 1H), 2.27–2.20 (m, 1H), 2.10–1.87 (m, 6H), 1.82–1.72 (m, 1H), 1.01–0.94 ppm (m, 6H), *para*-phenol not detected; HRMS (ESI-TOF): m/z: calcd for $C_{22}H_{31}O_6NNa$: 428.2044 $[M+Na]^+$; found: 428.2109.

Selected examples of compounds 9: $[\alpha]_D^{25}=-35.6$ ($c=0.52$ in $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz, 25 °C): $\delta=12.31$ (s, 1H), 6.83 (s, 1H), 6.74–



6.67 (m, 1H), 5.84 (br s, 1H), 5.82 (d, $J=15.8$ Hz, 1H), 5.03–4.95 (m, 1H), 4.88–4.86 (m, 1H), 4.76–4.70 (m, 1H), 4.40 (d, $J=17.6$ Hz, 1H), 4.15 (d, $J=17.5$ Hz, 1H), 2.40–2.34 (m, 1H), 2.22–2.18 (m, 1H), 1.87–1.65 (m, 4H), 1.53–1.48 (m, 1H), 0.92 (d, $J=6.4$ Hz, 3H), 0.66 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (C_6D_6, 100 MHz, 25 °C): $\delta=193.7$, 164.2, 156.8, 145.8, 137.2, 131.8, 129.3, 126.3, 115.3, 107.9, 103.6, 82.1, 46.4, 33.3, 30.9, 30.7, 28.8, 20.1, 18.5, 18.3 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{20}H_{23}ClO_5Na$: 401.1126 $[M+Na]^+$; found: 401.1170.



$[\alpha]_D^{25}=-10.3$ ($c=0.25$ in $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz, 25 °C): $\delta=$ 12.0 (br s, 1H), 7.32–7.29 (m, 3H), 7.19–7.15 (m, 2H), 6.86–6.79 (m, 1H), 6.51 (d, $J=2.4$ Hz, 1H), 6.27–6.25 (m, 1H), 6.11 (d, $J=2.4$ Hz, 1H), 6.02 (d, $J=15.8$ Hz, 1H), 5.49 (s, 1H), 5.17–5.10 (m, 1H), 4.97–4.90 (m, 1H), 4.40 (d, $J=16.4$ Hz, 1H), 3.97 (d, $J=17.2$ Hz, 1H), 2.83–2.76 (m, 1H), 2.45–2.38 (m, 1H), 1.89–1.78 (m, 2H), 1.67–1.58 ppm (m, 2H); ^{13}C NMR (C_6D_6, 100 MHz, 25 °C): $\delta=196.5$, 169.6, 166.1, 161.3, 146.0, 140.5, 138.8, 132.1, 130.0, 128.6 (×2), 127.3, 126.6 (×2), 126.3, 112.2, 105.9, 103.0, 77.1, 48.6, 38.4, 30.9, 30.3 ppm; HRMS (ESI): m/z: calcd for $C_{23}H_{22}O_5Na$: 401.1359 $[M+Na]^+$; found: 401.1271.

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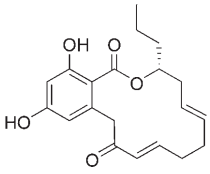
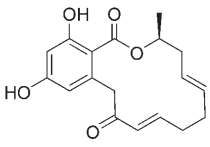
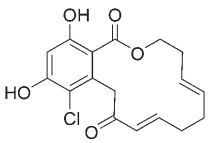
$[\alpha]_D^{25} = +21.6$ ($c = 0.36$ in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta =$ 12.43 (s, 1H), 6.74 (d, $J = 1.7$ Hz, 1H), 6.73–6.65 (m, 1H), 6.48 (d, $J =$ 1.7 Hz, 1H), 5.92 (d, $J = 15.8$ Hz, 1H), 5.12–5.00 (m, 2H), 4.91–4.80 (m, 1H), 4.19 (d, $J =$ 17.0 Hz, 1H), 3.84 (d, $J = 16.4$ Hz, 1H), 2.77 (m, 1H), 2.64–2.57 (m, 1H), 2.01–1.97 (m, 1H), 1.89–1.70 (m, 3H), 1.61–1.56 (m, 2H), 1.30–1.21 (m, 2H), 0.90 ppm (t, $J = 6.7$ Hz, 3H), *para*-phenol not detected; ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): $\delta = 197.5$, 169.9, 165.6, 160.6, 147.5, 140.2, 131.9, 129.5, 127.0, 112.8, 106.1, 102.9, 76.2, 48.7, 35.7, 34.3, 31.1, 29.7, 19.4, 13.8 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{20}H_{25}O_5$: 345.1697 $[M+H]^+$; found: 345.1739.



$[\alpha]_D^{25} = -45.1$ ($c = 0.27$ in $CHCl_3$); ^1H NMR (CD_3OD, 400 MHz, 25 °C): $\delta =$ 6.78–6.71 (m, 1H), 6.29 (d, $J = 2.4$ Hz, 1H), 6.22 (d, $J = 2.0$ Hz, 1H), 5.87 (d, $J = 15.5$ Hz, 1H), 5.37–5.23 (m, 3H), 4.01 (d, $J = 17.2$ Hz, 1H), 3.92 (d, $J = 17.0$ Hz, 1H), 2.67–2.61 (m, 1H), 2.29–2.15 (m, 5H), 1.31 ppm (d, $J = 6.4$ Hz, 3H), phenols not detected; ^{13}C NMR (CD_3OD, 100 MHz, 25 °C): $\delta = 198.5$, 169.8, 164.2, 162.3, 148.4, 139.1, 131.6, 129.6, 127.3, 111.7, 101.7, 72.0, 47.7, 36.8, 30.8, 30.7, 17.4 ppm, one quartenary carbon is not detected; HRMS (ESI-TOF): m/z: calcd for $C_{18}H_{20}O_5Na$: 339.1203 $[M+Na]^+$; found: 339.1141.

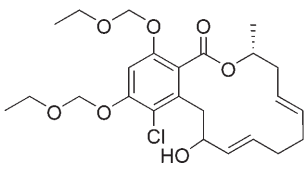


^1H NMR (CD_3OD, 400 MHz, 25 °C): $\delta = 6.74$–6.68 (m, 1H), 6.48 (s, 1H), 5.86 (d, $J = 15.2$ Hz, 1H), 5.31–5.25 (m, 2H), 4.39 (t, $J = 5.3$ Hz, 2H), 4.27 (s, 2H), 2.43–2.40 (m, 2H), 2.25 ppm (m, 4H), phenols not detected; ^{13}C NMR (CD_3OD, 100 MHz, 25 °C): $\delta = 196.9$, 170.1, 161.9, 158.1, 147.8, 135.9, 130.9, 130.2, 129.9, 115.2, 107.3, 102.4, 65.9, 46.2, 31.3, 30.9, 30.5 ppm; HRMS (ESI): m/z: calcd for $C_{17}H_{18}O_5Cl$: 337.0837 $[M+H]^+$; found: 337.0797.



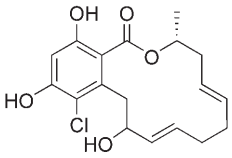
General procedure for the synthesis of compounds 10: BER-resin (borohydride on Amberlite, 1.0 equiv, 2.5 mmol g^{-1}) was added to a solution of the corresponding compound **6** (1.0 equiv) in MeOH (0.03 M) at 0 °C and the reaction was stirred over 12 h. The reaction was then filtered and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 0–20% EtOAc/cyclohexane gradient) afforded **10** (~60%) as a mixture of two diastereoisomers 1:1.

Selected example of compounds 10: ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta = 7.05$ (s, 1H), 6.99 (s, 1H), 5.64–5.57 (m, 2H), 5.54–5.53 (m, 2H), 5.49–5.35 (m, 7H), 5.31–5.28 (m, 4H), 5.24–5.16 (m, 4H), 5.13–5.08 (m, 1H), 4.68 (m, 1H), 4.56 (m, 1H), 3.81–3.69 (m, 8H), 3.25 (dd, $J = 13.9$, 8.0 Hz, 1H), 3.19 (dd, $J = 13.7$, 4.8 Hz, 1H), 3.11 (dd, $J = 13.5$, 10.1 Hz, 1H), 2.90 (dd, $J = 13.9$, 5.12 Hz, 1H, 35), 2.35 (m, 9H), 2.09–1.95 (m, 1H), 1.80–1.70 (m, 2H), 1.39 (d, $J = 2.9$ Hz, 3H), 1.37 (d, $J = 3.2$ Hz, 3H), 1.24 ppm (2 × q, $J = 6.9$, 5.0 Hz, 12H; 35+35′); HRMS (ESI): m/z: $C_{24}H_{33}ClO_7Na$: 491.1807 $[M+Na]^+$; found: 491.1729.



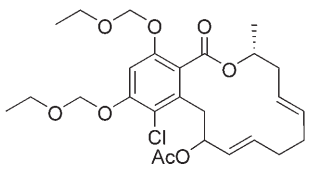
General procedure for the synthesis of compounds 11: PS-TsOH (10.0 equiv, 3.2 mmol g^{-1}) was added to a solution of the corresponding compound **10** (1.0 equiv) in MeOH (0.02 M) and the suspension was shaken at 40 °C for 4 h. The reaction mixture was then filtered and the methanolic solution concentrated under reduced pressure. Purification by preparative TLC (silica gel, 25% EtOAc/cyclohexane) afforded **11** (~90%) as a mixture of two diastereoisomers 1:1.

Selected example of compounds 11: ^1H NMR ($(CD_3)_2CO$, 400 MHz): $\delta =$ 12.30 (s, 2H), 11.43 (s, 2H), 6.75 (s, 2H), 6.00 (br dd, $J = 6.4$, 6.2 Hz, 1H), 5.97 (br dd, $J = 6.4$, 6.2 Hz, 1H), 5.97 (br d, $J = 6.7$ Hz, 1H), 5.77 (br d, $J =$ 6.7 Hz, 1H), 5.57–5.48 (m, 4H), 5.18–5.14 (m, 2H), 4.32–4.10 (m, 2H), 3.38–3.28 (m, 3H), 3.02 (dd, $J = 16.1$, 10.5 Hz, 1H), 2.41–2.09 (m, 12H), 1.11 ppm (d, $J = 6.2$ Hz, 6H), alcohols not detected; HRMS (ESI): m/z: calcd for $C_{18}H_{21}ClO_5Na$: 375.0970 $[M+Na]^+$; found: 375.1029.



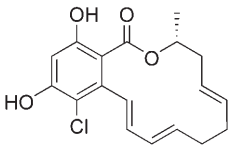
General procedure for the synthesis of compounds 12: Ac_2O (1.2 equiv), morpholinomethyl polystyrene (1.2 equiv, 3.2 mmol g^{-1}), and DMAP (0.05 equiv) were added to a solution of the corresponding compound **10** (1.0 equiv) in DMF (0.02 M) at 23 °C and the mixture was stirred for 30 min, followed by TLC until consumption of the starting material. Then, the resin was filtered and the organic phase was concentrated under reduced pressure. Purification by PTLC (silica gel, 20% EtOAc/cyclohexane) afforded corresponding compound **12** (~80%) as a mixture of two diastereoisomers 1:1.

Selected examples of compounds 12: ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta = 7.04$ (s, 1H), 7.01 (s, 1H), 5.86 (dd, $J = 15.0$, 6.9 Hz, 1H), 5.67 (dd, $J =$ 12.4, 6.2 Hz, 1H), 5.60–5.54 (m, 4H), 5.48 (dd, $J = 7.2$, 7.2 Hz, 1H), 5.41–5.34 (m, 3H), 5.32–5.30 (m, 4H), 5.28–5.23 (m, 2H), 5.21 (dd, $J = 11.0$, 6.7 Hz, 2H), 5.17 (dd, $J = 11.8$, 6.9 Hz, 2H), 3.81–3.69 (m, 8H), 3.43 (dd, $J = 14.2$, 7.5 Hz, 1H), 3.23–3.15 (m, 2H), 2.85 (dd, $J = 13.9$, 5.4 Hz, 1H), 2.30–2.17 (m, 8H), 2.12 (s, 3H), 2.06 (s, 3H), 1.95–2.00 (m, 4H), 1.39 (2 × d, $J = 5.6$ Hz, 6H), 1.24 ppm (m, 12H); HRMS (ESI): m/z: calcd for $C_{26}H_{35}ClO_8Na$: 533.1913 $[M+Na]^+$; found. 533.1864.



General procedure for the synthesis of compounds 13: PS-TsOH (10.0 equiv, 3.2 mmol g^{-1}) was added to a solution of corresponding compound **12** (1.0 equiv) in MeOH (0.02 M) and the suspension was shaken at 40 °C for 4 h. After this time, the reaction mixture was filtered and the methanolic solution concentrated under reduced pressure. Purification by PTLC (silica gel, 20% EtOAc/cyclohexane) afforded compounds **13** (~60% yield).

Selected example of compounds 13: Mixture of diastereoisomers 2:1; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 12.6$ (s, 1H), 12.12 (s, 0.5H), 6.93 (d, $J =$ 8.7 Hz, 0.5H), 6.66 (s, 1H), 6.64 (s, 0.5H), 6.62–6.60 (m, 1H), 6.10–6.05 (m, 3H), 5.47–5.33 (m, 5H), 2.60–2.53 (m, 1.5H), 2.26–2.02 (m, 7.5H), 1.44 (d, $J = 6.2$ Hz, 1.5H), 1.43 ppm (d, $J = 6.4$ Hz, 3H), *para*-phenol not



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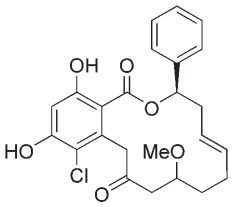
detected; HRMS (ESI) *m/z*: calcd for $C_{18}H_{19}ClO_4Na$: 357.0864 $[M+Na]^+$; found: 357.0898.

General procedure for the preparation of compounds 14: To a solution of corresponding compound **6** (1.0 equiv) in methanol (0.03 M) was added sulfamic acid resin (10.0 equiv) and the suspension was stirred for 15 h at 40 °C. The reaction was then filtered and the resin washed several times with CH_2Cl_2. Concentration under reduced pressure followed by purification on PTLC (Hexane/EtOAc 1:1) afforded desired compounds **14** as a mixture of diastereoisomers (2:1).

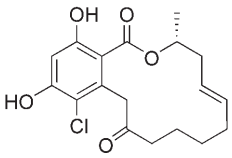
Selected example of compounds 14: ^{1}H NMR (C_6D_6, 400 MHz, 25 °C): δ = 12.28 (s, 0.4H), 11.91 (s, 0.6H), 7.21–7.11 (m, 5H), 6.62 (s, 1H), 6.03–6.01 (m, 1H), 5.58 (br s, 1H), 5.38–5.33 (m, 1H), 5.27–5.20 (m, 1H), 4.76



(d, J = 17.5 Hz, 0.6H), 4.02 (d, J = 17.0 Hz, 0.4H), 4.18 (d, J = 18.1 Hz, 0.6H), 4.09 (d, J = 17.0 Hz, 0.4H), 3.87 (br s, 0.4H), 3.81 (br s, 0.6H), 3.15 (s, 1.8H), 3.12 (s, 1.2H), 2.83–2.78 (m, 1H), 2.45–2.30 (m, 2H), 2.18–2.16 (m, 1H), 2.02–1.97 (m, 2H), 1.79–1.72 ppm (m, 2H); HRMS (ESI-TOF): *m/z*: calcd for $C_{24}H_{25}O_6ClNa$: 467.1232 $[M+Na]^+$; found: 467.1366.

General procedure for the synthesis of compounds 15: (Polystyrylmethyl)trimethylammonium cyanoborohydride (2.0 equiv, 3.5 mmol g^{-1}) was added to a solution of corresponding compound **9** (1.0 equiv) in CH_2Cl_2/AcOH 10:1 (0.08 M) at 23 °C and the reaction was monitored by TLC until the starting material had been consumed (4 h). Then, the resin was filtered and the organic phase was concentrated under reduced pressure. Purification by PTLC (silica gel, 30% EtOAc/cyclohexane) afforded compounds **15** (50–60%).

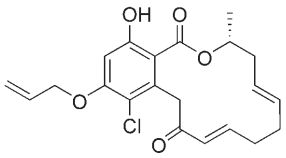
Selected example of compounds 15: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.75 (s, 1H), 6.65 (s, 1H), 5.48 (m, 2H), 5.49 (ddt, J = 6.1, 3.5, 2.9 Hz, 1H), 4.53 (d, J = 17.5 Hz, 1H), 4.04 (d, J = 17.7 Hz, 1H), 2.61–2.54 (m,



2H), 2.48–2.28 (m, 3H), 2.19–2.14 (m, 1H), 2.08–1.99 (m, 1H), 1.72–1.61 (m, 3H), 1.41 ppm (d, J = 6.4 Hz, 3H), *para*-phenol not detected; HRMS (ESI): *m/z*: calcd for $C_{18}H_{21}ClO_5Na$: 375.0970 $[M+Na]^+$; found: 375.1050.

General procedure for the synthesis of compounds 16: The corresponding alcohol (2.0 equiv), triphenylphosphine (2.0 equiv), and ethoxycarbonylazocarboxymethyl polystyrene (2.0 equiv, 1.3 mmol g^{-1}) were added to a solution of corresponding compound **9** (1.0 equiv) in THF (0.05 M) in a sequential manner. The reaction mixture was shaken at room temperature for 8 h, and then the resin was filtered and the filtrates were directly purified by PTLC (silica gel, 10% EtOAc/cyclohexane) to afford a mixture of compound **16** along with the bisallylated product (78%).

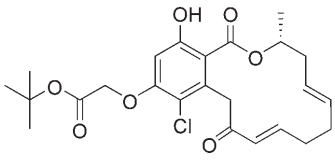
Selected example of compounds 16: Mixture with the corresponding bisallylated compound 1:1; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.83 (s, 1H), 6.82 (ddd, J = 15.7, 8.2, 4.6 Hz, 1H), 6.72–6.65 (m, 1H), 6.46 (s, 1H), 6.41 (s, 1H), 6.09–5.98 (m, 3H), 5.82 (d, J = 15.7 Hz, 1H), 5.46–5.16 (m, 8H), 4.57–4.54 (m, 3H), 4.51–4.49 (m, 3H), 4.19 (d, J = 17.5 Hz, 1H), 4.11 (d, J = 14.6 Hz, 1H), 3.78 (d, J = 17.0 Hz, 1H), 3.51 (d, J = 14.2 Hz, 1H),



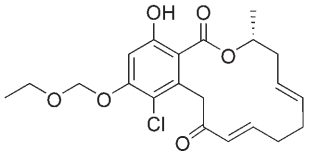
2.76–2.69 (m, 1H), 2.38–2.05 (m, 11H), 1.42 (d, J = 6.2 Hz, 3H), 1.35 ppm (d, J = 6.3 Hz, 3H); monoallylated compound: HRMS (ESI): *m/z*: calcd for $C_{21}H_{23}ClO_5Na$ 413.1132 $[M+Na]^+$; found: 413.1103; bisallylated compound: HRMS (ESI): *m/z*: calcd for $C_{24}H_{27}ClO_5Na$: 453.1449 $[M+Na]^+$; found: 453.1422.

General procedure for the synthesis of compounds 17: TBD-methyl polystyrene (2.0 equiv, 2.9 mmol g^{-1}) and the corresponding alkyl bromide or chloride ($BrCH_2COO$*t*Bu, EOMCl, 0.9 equiv) were added to a solution of the corresponding compound **9** (1.0 equiv) in CH_2Cl_2 (0.05 M) at 23 °C and the mixture was shaken for 3 h. The resin was then filtered and the filtrates were concentrated under reduced pressure. Purification by PTLC (silica gel, 30% EtOAc/cyclohexane) afforded corresponding compound **17** (>90%).

Selected examples of compounds 17: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 11.84 (s, 1H), 6.69 (m, 1H), 6.41 (s, 1H), 5.76 (d, J = 15.0 Hz, 1H), 5.43



(m, 1H), 5,26 (ddd, J = 15.0, 9.1, 4.8 Hz, 1H), 5.18–5.11 (m, 1H), 4.65 (s, 2H), 4.33 (d, J = 17.7 Hz, 1H), 4.16 (d, J = 17.5 Hz, 1H), 2.65–2.58 (m, 1H), 2.37–2.34 (m, 2H), 2.25–2.21 (m, 1H), 2.12–2.01 (m, 2H), 1.53 (s, 9H), 1.34 ppm (d, J = 6.5 Hz, 3H); HRMS (ESI): *m/z*: calcd for $C_{24}H_{29}ClO_7Na$: 487.1494 $[M+Na]^+$; found: 487.1498.



^{1}H NMR (C_6D_6, 400 MHz, 25 °C): δ = 11.76 (s, 1H), 6.86 (s, 1H), 6.70 (dt, J = 14.9, 7.3 Hz, 1H), 5.77 (d, J = 15.8 Hz, 1H), 5.46–5.42 (m, 1H), 5.37 (s, 2H), 5.30–5.19 (m, 2H), 4.34 (d, J = 17.6 Hz, 1H), 4.16 (d, J = 18.1 Hz, 1H), 3.80 (q, J = 7.0 Hz, 2H), 2.66–2.59 (m, 1H), 2.37–2.34 (m, 2H), 2.26–2.21 (m, 1H), 2.13–2.06 (m, 2H), 1.34 (d, J = 6.4 Hz, 3H), 1.27 ppm (t, J = 7.0 Hz, 3H); HRMS (ESI): *m/z*: calcd for $C_{21}H_{25}O_6ClNa$: 431.1237 $[M+Na]^+$; found: 431.1257.

General procedure for the synthesis of compounds 18: OsO_4 (0.1 equiv) followed by NMO (1.0 equiv) was added to a solution of compound **9** (1.0 equiv) in acetone/H_2O 10:1 (0.05 M) at 23 °C and the mixture was stirred for 1 h. The crude mixture was filtered through a plug of silica, concentrated, and purified by PTLC (silica gel, 30% EtOAc/cyclohexane) to afford **18** (>70%) as a mixture of two diastereoisomers 1:1.

Selected example of compounds 18: ^{1}H NMR (CD_3OD, 400 MHz): δ = 7.19 (m, 1H), 6.89–6.81 (m, 1H), 6.52 (s, 1H), 6.47 (s, 1H), 6.20 (d, J = 16.1 Hz, 1H), 6.04 (d, J = 15.6 Hz, 1H), 5.54–5.49 (m, 1H), 5.43–5.36 (m, 1H), 4.50 (d, J = 17.7 Hz, 1H), 4.46 (d, J = 17.7 Hz, 1H), 4.39 (d, J = 17.2 Hz, 1H), 4.07 (d, J = 17.2 Hz, 1H), 3.80–3.64 (m, 2H), 3.51–3.46 (m, 2H), 2.62–2.58 (m, 2H), 2.39–2.30 (m, 2H), 2.27–2.18 (m, 2H), 2.08–2.98 (m, 2H), 2.00–1.85 (m, 4H), 1.44 ppm (d, J = 6.4 Hz, 6H), phenols and al-

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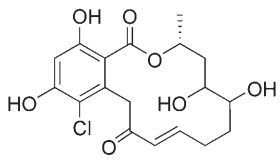
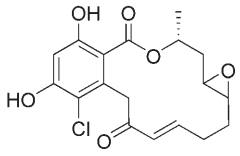


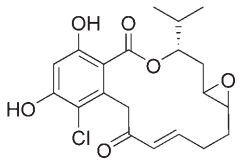
cohol not detected; HRMS (ESI) m/z: calcd for $C_{18}H_{21}ClO_7Na$: 407.0868 $[M+Na]^+$; found: 407.1031.

General procedure for the synthesis of compounds 19: Freshly made DMDO (1.2 equiv, 0.04 M in acetone) was added to a solution of compound **9** (1.0 equiv) in CH_3CN (0.03 M) at 0 °C and the mixture was stirred for 30 min. After evaporation of the solvents under reduced pressure, purification by PTLC (silica gel, 30% EtOAc/cyclohexane) afforded epoxides **19** (>90%) as a mixture of two diastereoisomers (1:1 to 3:1).

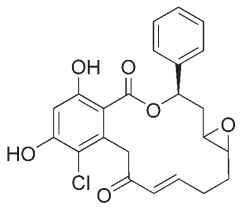
Selected example of compounds 19: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=$ 11.84 (s, 2H), 6.94–6.82 (m, 2H), 6.69 (s, 1H), 6.66 (s, 1H), 6.23 (d, $J=$



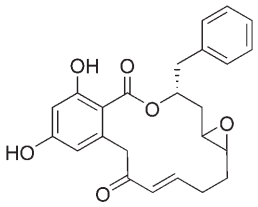
17.1 Hz, 1H), 6.11 (dd, $J=13.2$, 1.6 Hz, 1H), 5.39 (tdd, $J=7.5$, 3.2, 2.7 Hz, 1H), 5.32 (m, 1H), 4.53 (d, $J=17.7$ Hz, 2H), 4.27 (d, $J=17.7$ Hz, 2H), 2.79–2.76 (m, 1H), 2.74–2.69 (m, 1H), 2.58 (m, 1H), 2.56 (m, 1H), 2.47–2.24 (m, 8H), 2.13–2.08 (m, 1H), 2.05–2.03 (m, 1H), 1.91 (dd, $J=$ 4.3, 4.3 Hz, 1H), 1.87 (dd, $J=4.3$, 4.3 Hz, 1H), 1.51 (d, $J=6.4$ Hz, 3H), 1.35 ppm (d, $J=6.4$ Hz, 3H), *para*-phenol not detected; HRMS (ESI): m/z: calcd for $C_{18}H_{19}ClO_6Na$: 389.0762 $[M+Na]^+$; found: 389.0724.



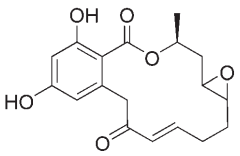
^{1}H NMR (C_6D_6, 400 MHz, 25 °C): $\delta=11.56$ (2×s, 2H), 6.92–6.82 (m, 2H), 6.71 (s, 1H), 6.67 (s, 1H), 6.20 (m, 3H), 6.06 (d, $J=15.8$ Hz, 1H), 5.11 (brs, 1H), 5.94 (m, 1H), 4.46 (2×d, $J=18.1$ Hz, 2H), 4.20 (2×d, $J=$ 18.1 Hz, 2H), 2.72–2.70 (m, 2H), 2.53–2.48 (m, 4H), 2.38–2.35 (m, 3H), 2.25–2.13 (m, 5H), 1.84–1.77 (m, 2H), 1.05–1.01 (m, 6H), 0.91–0.88 (m, 3H), 0.86–0.84 ppm (m, 3H), *para*-phenol not detected; HRMS (ESI): m/z: calcd for $C_{20}H_{23}O_6ClNa$ 417.1075 $[M+Na]^+$; found: 417.1128.



^{1}H NMR (C_6D_6, 400 MHz, 25 °C): $\delta=11.80$ (2×s, 2H), 7.43–7.18 (m, 10H), 7.03–6.95 (m, 2H), 6.69 (s, 1H), 6.61 (s, 1H), 6.30 (d, $J=16.4$ Hz, 1H), 6.21 (d, $J=15.8$ Hz, 1H), 6.15–6.10 (m, 1H), 6.03 (d, $J=11.1$ Hz, 1H), 4.84 (2×d, $J=18.1$ Hz, 2H), 4.41 (2×d, $J=17.6$ Hz, 2H), 2.68–2.60 (m, 4H), 2.41–2.27 (m, 8H), 1.83–1.76 ppm (m, 4H), *para*-phenol not detected; HRMS (ESI): m/z: calcd for $C_{23}H_{21}O_6ClNa$: 451.0919 $[M+Na]^+$; found: 451.1028.



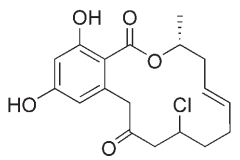
Major isomer; ^{1}H NMR (C_6D_6, 400 MHz, 25 °C): $\delta=11.94$ (s, 1H), 7.36–7.28 (m, 5H), 6.95–6.88 (m, 1H), 6.42 (s, 1H), 6.22 (s, 1H), 6.11 (d, $J=$ 15.8 Hz, 1H), 5.47 (m, 1H), 5.41 (brs, 1H), 4.43 (d, $J=17.5$ Hz, 1H), 3.56 (d, $J=17.6$ Hz, 1H), 3.19 (dd, $J=13.7$, 6.0 Hz, 1H), 3.03 (dd, $J=13.7$, 7.9 Hz, 1H), 2.87 (brs, 1H), 2.70–2.28 (m, 4H), 2.03–1.93 ppm (m, 2H), *para*-phenol not detected; HRMS (ESI): m/z: calcd for $C_{24}H_{24}O_6Na$: 431.1465 $[M+Na]^+$; found: 431.1578.



^{1}H NMR (C_6D_6, 400 MHz, 25 °C): $\delta=11.98$ (s, 1H), 6.91–6.83 (m, 1H), 6.43 (d, $J=2.3$ Hz, 1H), 6.24 (d, $J=2.4$ Hz, 1H), 6.11 (d, $J=15.8$ Hz, 1H), 5.35 (brs, 1H), 5.29 (m, 1H), 4.52 (d, $J=17.5$ Hz, 1H), 3.63 (d, $J=$ 17.5 Hz, 1H), 2.77 (m, 2H), 2.57–2.52 (m, 2H), 2.46–2.27 (m, 2H), 2.14–2.10 (m, 1H), 1.93–1.88 (m, 1H), 1.48 ppm (d, $J=6.4$ Hz, 3H); other isomer: ^{1}H NMR (C_6D_6, 400 MHz, 25 °C): $\delta=11.67$ (s, 1H), 6.89–6.83 (m, 1H), 6.40 (d, $J=2.4$ Hz, 1H), 6.24 (d, $J=2.9$ Hz, 1H), 6.21 (d, $J=$ 16.4 Hz, 1H), 5.37 (brs, 1H), 5.22 (m, 1H), 4.20 (d, $J=17.0$ Hz, 1H), 4.06 (d, $J=17.0$ Hz, 1H), 2.74 (m, 2H), 2.57–2.20 (m, 4H), 1.80–1.76 (m, 1H), 1.68–1.60 (m, 1H), 1.37 ppm (d, $J=6.4$ Hz, 3H), *para*-phenol not detected; HRMS (ESI): m/z: calcd for $C_{18}H_{20}O_6Na$: 355.1152 $[M+Na]^+$; found: 355.1249.

General procedure for the preparation of macrocycles 20: HCl (concd, 20 equiv) was added to a solution of compound **6** (1.0 equiv) in dioxane (0.05 M) at 23 °C, and the mixture was stirred for 3 h. After this time, the reaction was filtered through a plug of silica gel, the solvents evaporated under reduced pressure, and purified by PTLC (silica gel, 30% EtOAc/cyclohexane) to afford compound **20** (>75%) as a mixture of two diastereoisomers 1:1.

Selected examples of compounds 20: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=$ 12.11 (s, 1H), 11.78 (s, 1H), 6.51 (s, 1H), 6.43 (s, 1H), 6.41 (d, $J=2.4$ Hz, 1H), 6.37 (d, $J=2.7$ Hz, 1H), 6.21 (d, $J=2.4$ Hz, 1H), 6.11 (d, $J=2.4$ Hz,



1H), 5.59–5.51 (m, 3H), 5.40–5.32 (m, 3H), 4.54 (d, $J=17.2$ Hz, 1H), 4.42 (d, $J=17.2$ Hz, 1H), 3.60 (d, $J=17.2$ Hz, 1H), 3.45 (d, $J=17.0$ Hz, 1H), 3.28 (dd, $J=18.5$, 9.4 Hz, 1H), 3.11 (dd, $J=13.7$, 6.2 Hz, 1H), 3.07 (dd, $J=13.4$, 4.6 Hz, 1H), 2.76 (dd, $J=19.0$, 6.2 Hz, 1H), 2.62 (ddd, $J=$ 15.5, 8.8, 4.0 Hz, 1H), 2.54 (ddd, $J=15.3$, 6.2, 3.2 Hz, 1H), 2.40–2.26 (m,

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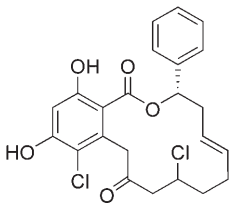
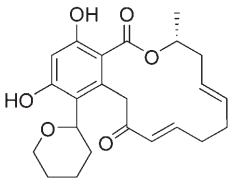
4H), 2.25–2.13 (m, 4H), 2.03–1.91 (m, 2H), 1.42 (d, $J=6.4$ Hz, 3H), 1.40 ppm (d, $J=6.4$ Hz, 3H), *para*-phenol not detected; HRMS (ESI): m/z: calcd for $C_{18}H_{21}ClO_5Na$: 375.0970 $[M+Na]^+$; found: 375.0928.



^{1}H NMR (C_6D_6, 400 MHz, 25 °C): $\delta=11.76$ (s, 0.5H), 11.36 (s, 0.5H), 7.40–7.29 (m, 5H), 6.65 (s, 0.5H), 6.62 (s, 0.5H), 6.18 (t, $J=5.8$ Hz, 1H), 6.14 (s, 0.5H), 6.12 (s, 0.5H), 5.67–5.62 (m, 1H), 5.55–5.49 (m, 1H), 4.93 (d, $J=18.1$ Hz, 0.5H), 4.80 (d, $J=17.1$ Hz, 0.5H), 4.58–4.56 (m, 1H), 4.38 (d, $J=18.1$ Hz, 0.5H), 4.18 (d, $J=17.1$ Hz, 0.5H), 3.33–3.27 (m, 1H), 3.10 (dd, $J=18.4$, 3.8 Hz, 0.5H), 2.84–2.68 (m, 2.5H), 2.42–2.32 (m, 2H), 2.23–2.17 (m, 1H), 2.13–2.04 ppm (m, 1H), *para*-phenol not detected; HRMS (ESI-TOF): m/z: calcd for $C_{23}H_{22}O_5Cl_2Na$: 471.0737 $[M+Na]^+$; found: 471.0754.

Elimination of β-Cl from compound 20: PS-TBD (51 mg, 2.6 mmol g^{-1}) was added to a solution of compound **20** (95 mg, 270 μmol) in CH_2Cl_2 (5 mL) at 23 °C, and the mixture was stirred for 8 h. After that time, the reaction was filtered, the solvents were evaporated under reduced pressure, and the remaining residue was purified by flash chromatography (silica gel, 0–30% EtOAc/cyclohexane gradient) to afford **9** (X = Cl, R = Me, 84 mg, 98%).

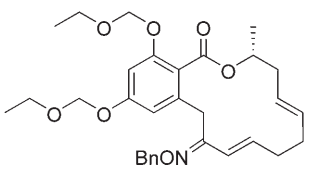
Macrocycle 21: DHP (3.7 μL, 40.8 μmol) and PS-TsOH (12.7 mg, 40.8 μmol, 3.2 mmol g^{-1}) were added to a solution of compound **9** (X = Cl, R = Me, 12.9 mg, 40.8 μmol) in CH_2Cl_2 (1 mL) at 23 °C, and the mixture was stirred for 5 h. After this time, the reaction was filtered and the solvents were evaporated under reduced pressure. Purification by PTLC (silica gel, 30% EtOAc/cyclohexane) afforded **21** (13.8 mg, 85%) as a mixture of two diastereoisomers.



^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=12.33$ (s, 1H), 12.11 (s, 1H), 9.45 (s, 1H), 9.40 (s, 1H), 6.67, (m, 2H), 6.28 (2×s, 2H), 5.83 (d, $J=13.2$ Hz, 1H), 5.79 (d, $J=12.9$ Hz, 1H), 5.35–5.30 (m, 3H), 5.27–5.22 (m, 3H), 5.06 (br d, $J=8.2$ Hz, 2H), 4.10 (d, $J=17.5$ Hz, 2H), 3.90–3.85 (m, 1H), 3.80–3.76 (m, 1H), 3.65 (d, $J=17.7$ Hz, 2H), 3.57–3.52 (m, 2H), 3.46–3.41 (m, 2H), 2.77–2.71 (m, 3H), 2.53–2.49 (m, 3H), 2.36–2.29 (m, 4H), 2.24–1.56 (m, 12H), 1.31 (d, $J=6.4$ Hz, 3H), 1.28 ppm (d, $J=6.4$ Hz, 3H); HRMS (ESI): m/z: $C_{23}H_{28}O_6Na$: 423.1778 $[M+Na]^+$; found: 423.1778.

General procedure for the synthesis of compounds 22: The corresponding hydroxylamine (5.0 equiv) was added to a solution of corresponding compound **6** (1.0 equiv) in pyridine/AcOH (5:1, 0.03 M) and the mixture was heated up to 40 °C. After stirring overnight, the solvents were evaporated under reduced pressure with silica gel. Elution of the compound over a short path of silica gel with a mixture of 30% EtOAc/cyclohexane afforded after evaporation **22** (~99%) as a mixture of two diastereoisomers *cis*/*trans*).

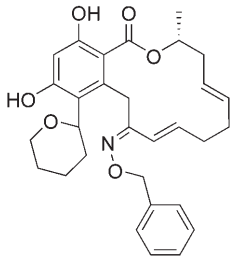
Selected example of compounds 22: ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=$ 7.50–7.25 (m, 10H), 6.82 (s, 1H), 6.75 (s, 1H), 6.66 (s, 1H), 6.48 (s, 1H), 6.24–6.11 (m, 2H), 6.11–6.05 (m, 2H), 5.45–5.38 (m, 4H), 5.34–5.31 (m,



14H), 4.50 (d, $J=17.2$ Hz, 1H), 3.38–3.65 (m, 8H), 3.60 (d, $J=17.1$ Hz, 1H), 3.54 (d, $J=17.1$ Hz, 1H), 3.24 (d, $J=17.2$ Hz, 1H), 2.48–2.36 (m, 4H), 2.17–2.21 (m, 2H), 2.04–2.11 (m, 2H), 1.95–1.83 (m, 2H), 1.62–1.51 (m, 2H), 1.49 (d, $J=6.4$ Hz, 6H), 1.20–1.32 ppm (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=168.02$, 167.85, 159.08, 158.83, 157.23, 155.55, 155.36, 154.19, 140.75, 138.23, 138.19, 137.75, 136.93, 136.74, 132.32, 132.28, 128.34 (×2), 128.31 (×2), 128.18, 128.09 (×2), 127.99 (×2), 127.71, 127.63, 125.50, 118.82, 118.56, 118.34, 108.84, 108.50, 101.72, 101.68, 93.49, 93.44, 93.12 (×2), 77.21, 76.02, 75.88, 71.18, 70.99, 64.47, 64.45, 64.33, 64.31, 39.99, 39.96, 34.87, 32.42, 32.31, 31.63, 31.09, 28.86, 20.25, 20.19, 15.04 (×2), 14.98 ppm (×2); HRMS (ESI): m/z: calcd for $C_{31}H_{39}NO_7Na$: 560.2619 $[M+Na]^+$; found: 560.2627.

General procedure for the synthesis of compounds 23: PS-TsOH (10.0 equiv, 3.2 mmol g^{-1}) was added to a solution of compound **22** (1.0 equiv) in MeOH (0.02 M) and the suspension was shaken at 40 °C for 4 h. After this time, the reaction mixture was filtered and the methanolic solution concentrated under reduced pressure. The crude product obtained was submitted without further purification to the next step. Thus DHP (1.0 equiv) and PS-TsOH (cat, 3.2 mmol g^{-1}) were added to a solution of this crude in CH_2Cl_2 (0.02 M) at 23 °C, and the mixture was stirred for 5 h. After this time, the mixture was filtered, the solvents were evaporated under reduced pressure, and the remaining residue was purified by PTLC (silica gel, 30% EtOAc/cyclohexane) to afford two different diastereoisomers 1:1 of **23** (~65%).

Selected examples of compounds 23: Less polar diastereoisomers; ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=9.25$ (s, 1H), 9.24 (s, 1H), 7.46–



7.33 (m, 10H), 6.29 (s, 1H), 6.26 (s, 1H), 6.07–6.02 (m, 2H), 5.75 (d, $J=$ 15.8 Hz, 1H), 5.69 (d, $J=15.8$ Hz, 1H), 5.44–5.38 (m, 6H), 5.23 (s, 4H), 5.03 (d, J = 8.8 Hz, 2H), 4.34–4.13 (m, 6H), 3.69–3.63 (m, 2H), 2.70–2.67 (m, 2H), 2.30–2.16 (m, 6H), 2.08–1.94 (m, 8H), 1.73–1.65 (m, 8H), 1.42 (t, $J=6.4$ Hz, 3H), 1.39 ppm (t, $J=7.0$ Hz, 3H); HRMS (ESI): m/z: calcd for $C_{30}H_{35}NO_6Na$: 528.2357 $[M+Na]^+$; found: 528.2562.

More polar diastereoisomers: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): $\delta=$ 11.61 (s, 1H), 9.27 (s, 1H), 7.41–7.33 (m, 5H), 6.62 (d, $J=16.4$ Hz, 1H), 6.47 (s, 1H), 6.15–6.07 (m, 1H), 5.50–5.38 (m, 3H), 5.16 (s, 2H), 5.04 (d, $J=10.5$ Hz, 1H), 4.30 (d, $J=15.2$ Hz, 1H), 4.24 (d, $J=10.5$ Hz, 1H), 3.84 (d, $J=15.2$ Hz, 1H), 3.66 (t, $J=11.4$ Hz, 1H), 2.71–2.65 (m, 1H), 2.28–2.08 (m, 6H), 1.73–1.64 (m, 5H), 1.38 ppm (t, $J=7.0$ Hz, 3H); HRMS (ESI): m/z: calcd for $C_{30}H_{35}NO_6Na$: 528.2357 $[M+Na]^+$; found: 528.2494.

Macrocycle 24: TBSCl (53.6 mg, 356 μmol) and imidazole (23.6 mg, 356 μmol) were added to a solution of pochonin D (**9**, X = Cl and R = Me, 25 mg, 71.2 μmol) in DMF (5 mL) and the mixture was stirred for 3 h at room temperature. Purification by column chromatography (silica gel, 0–30% EtOAc/cyclohexane gradient) afforded after evaporation **24** (40 mg, 98%).

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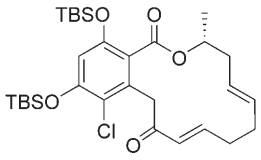
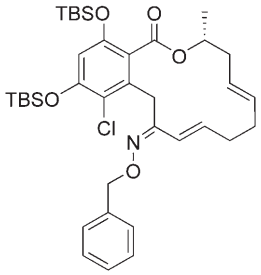


^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 6.71 (dt, J = 15.3, 7.3 Hz, 1H), 6.45 (s, 1H), 5.81 (d, J = 15.3 Hz, 1H), 5.25 (s, 2H), 5.04–5.03 (m, 1H), 3.89 (d, J = 17.4 Hz, 1H), 3.57 (d, J = 17.4 Hz, 1H), 2.31–2.04 (m, 6H), 1.35 (d, J = 6.4 Hz, 3H), 1.03 (s, 9H), 0.99 (s, 9H), 0.28–0.24 ppm (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ = 195.8, 166.8, 152.9, 151.7, 146.5, 132.7, 131.9, 128.6, 126.8, 122.8, 119.7, 110.7, 71.9, 45.6, 38.5, 30.9, 25.7 (×4), 25.6 (×4), 18.7, 18.3, −4.1 (×2), −4.4 ppm (×2); HRMS (ESI): m/z: calcd for $C_{30}H_{47}ClO_5Si_2Na$: 601.2543 $[M+Na]^+$; found: 601.2568.

General procedure for compounds 25: The corresponding hydroxylamine (5.0 equiv) was added to a solution of compound **24** (1.0 equiv) in pyridine/AcOH (5:1, 250 μL), and the mixture was heated up to 40 °C. After stirring overnight, the solvents were evaporated under reduced pressure, and filtration through silica gel with a mixture of 30% EtOAc/cyclohexane afforded after evaporation two isomers of **25** (~90%).

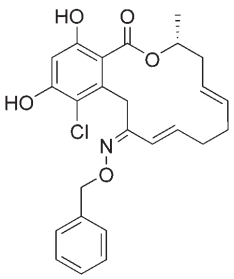
Selected example of compounds 25: *cis* Oxime: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.42 (br d, J = 6.4 Hz, 2H), 7.36 (br dd, J = 7.5, 6.9 Hz, 2H),



7.34–7.32 (m, 1H), 6.52 (d, J = 16.1 Hz, 1H), 6.38 (s, 1H), 6.18–6.10 (m, 1H), 5.36–5.32 (m, 2H), 5.16 (br s, 2H), 4.99–4.95 (m, 1H), 3.79–3.76 (m, 2H), 2.40–1.99 (m, 6H), 1.45 (d, J = 6.2 Hz, 3H), 1.03 (s, 9H), 0.99 (s, 9H), 0.28 (s, 3H), 0.26 (s, 3H), 0.20 ppm (s, 6H); *trans* oxime: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.44 (br d, J = 6.5 Hz, 2H), 7.37 (br dd, J = 7.6, 6.9 Hz, 2H), 7.33–7.31 (m, 1H), 6.41 (s, 1H), 6.04–5.97 (m, 1H), 5.48 (br d, J = 15.0 Hz, 1H), 5.29–5.27 (m, 1H), 5.22 (br s, 2H), 5.00–4.95 (m, 1H), 3.98–3.89 (m, 2H), 2.39–2.02 (m, 6H), 1.37 (d, J = 5.9 Hz, 3H), 1.04 (s, 9H), 0.99 (s, 9H), 0.28 (s, 3H), 0.27 (s, 3H), 0.23 (s, 3H), 0.22 ppm (s, 3H).

General procedure for compounds 26: TBAF (2.5 equiv, 1 M solution in THF) was added to a solution of corresponding compound **25** (1.0 equiv) in THF, and the mixture was stirred at room temperature for 2 h. The solvents were then evaporated under reduced pressure, and filtration on silica gel with a mixture of 30% EtOAc/cyclohexane afforded after evaporation, compounds **26** in >85% yield.

cis: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 11.52 (s, 1H), 7.45–7.34 (m, 5H), 6.64 (s, 1H), 6.09–6.02 (m, 2H), 5.34–5.25 (m, 4H), 5.18–5.08 (m, 2H), 4.33 (d, J = 17.0 Hz, 1H), 4.15 (d, J = 17.6 Hz, 1H), 2.65–2.59 (m, 1H), 2.27–2.14 (m, 3H), 2.04–2.00 (m, 1H), 1.88–1.83 (m, 1H), 1.30 ppm (t, J = 6.4 Hz, 3H); HRMS (ESI): m/z: calcd for $C_{25}H_{26}ClNO_5Na$: 478.1392 $[M+Na]^+$; found: 478.1372.



trans: ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 11.73 (s, 1H), 7.32–7.26 (m, 5H), 6.64 (s, 1H), 6.50 (d, J = 16.4 Hz, 1H), 6.06–5.98 (m, 2H), 5.43–5.24 (m, 3H), 4.91 (s, 2H), 4.22 (s, 2H), 2.61–2.55 (m, 1H), 2.46–2.33 (m, 2H), 2.20–2.02 (m, 3H), 0.98 ppm (t, J = 6.4 Hz, 3H); HRMS (ESI): m/z: calcd for $C_{25}H_{26}ClNO_5Na$: 478.1392; found: 478.1522 $[M+Na]^+$.

Kinase assay: All protein kinases were expressed in Sf9 insect cells as human recombinant GST-fusion proteins or His-tagged proteins by means of the baculovirus expression system. Kinases were purified by affinity chromatography using either GSH-agarose (Sigma) or Ni-NTH-agarose (Qiagen). The purity of each kinase was checked by SDS-PAGE/silver staining and the identity of each kinase was verified by western blot analysis with kinase-specific antibodies or by mass spectroscopy. For measuring the enzymatic activity of the protein kinases a proprietary protein kinase assay (^{33}PanQinase® Activity Assay) was used. All kinase assays were performed in 96-well FlashPlates from Perkin–Elmer/NEN (Boston, MA, USA) in a 50 μL reaction volume by using a Beckman-Coulter/Sagian robotic system. The reaction cocktail was pipetted in four steps in the following order: 1) 20 μL of assay buffer, 2) 5 μL of ATP solution (in H_2O), 3) 5 μL of test compound (in 10% DMSO), and 4) 10 μL of substrate/10 μL of enzyme solution (premixed). The assay for all kinases contained HEPES-NaOH (60 mM), $MgCl_2$ (pH 7.5, 3 mM), $MnCl_2$ (3 mM), Na-orthovanadate (3 μM), DTT (1.2 mM), PEG_{20000} (50 μg mL^{-1}), [γ-^{33}P]-ATP (1 μM, ca. 5×10^5 cpm per well). The final DMSO concentration was 1% in all assays. The reaction cocktails were incubated at 30 °C for 80 minutes. The reaction was stopped with H_3PO_4 (50 μL, 2% v/v). Plates were aspirated and washed two times with H_2O (200 μL) and NaCl (200 μL, 0.9% w/v). Incorporation of $^{33}P_i$ was determined with a microplate scintillation counter (Microbeta, Wallac).

For each concentration of the test compounds residual activities (in %) were calculated relative to control values without test compounds for each kinase assay. With the set of residual activities (in %) obtained for each test compound in a particular kinase assay, IC_{50} values were calculated by using Quattro Workflow V2.0.1.3 (Quattro Research GmbH, Munich, Germany; www.quattro-research.com). The mathematical model used was "sigmoidal response (variable slope)" with parameters "top" fixed at 100% and "bottom" at 0%.

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