Solution- and Solid-Phase Synthesis of Radicicol (Monorden) and Pochonin C

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Abstract: A modular synthesis for pochonin C and radicicol is reported. The two natural products were prepared in seven and eight steps, respectively, from three readily available fragments. Alternative syntheses of these compounds were achieved using a combination of polymer-bound reagents and solid phase reactions. The conformation of the two natural products was studied and compared by using 2D NMR spectroscopy.

Keywords: metathesis · natural products · solid-phase synthesis · total synthesis

Introduction

Monorden (**1**, Figure 1) was first isolated over half a century ago[1] from *Monocillium nordinii* and later reported to have mild sedative activity along with antibiotic activity.[2] The same molecule was independently isolated from *Nectria radicicola* and given the name of radicicol (**1**, Figure 1).[3] The absolute stereochemistry of its three chiral centers was assigned by X-ray crystallography[4] and confirmed by total synthesis.[5,6] The reported biological activity initially attributed to this compound did not arouse much interest until it was reported that radicicol was a tyrosine kinase inhibitor.[7] It was later discovered that the inhibitory effect of radicicol for certain kinases stemmed from the fact that radicicol was an inhibitor of HSP90;[8,9] this molecular chaperone is necessary for the maturation and function of the kinases whose inhibition was originally observed. In the absence of this chaperoning activity, the clients of HSP90 are targeted for degradation by the proteosome.[10,11] The list of HSP90 clients includes notorious oncogenic proteins such as Src, Bcr-Abl, Raf1, ErbB2, Akt and mutated p53. The fact that multiple oncogenic proteins can be shut down by the inhibition of HSP90 has made it an attractive target for chemotherapy.[12] Radicicol (**1**, Figure 1) as well as geldanamycin (**2**, Figure 1) have been reported to be potent inhibitors of HSP90. This renewed interest in radicicol prompted further work on its total synthesis notably by the Lett group[13,14] and the Danishefsky group[15] as well as studies to define the structure–activity relationship of this potential therapeutic.[16–20] Pearl and co-workers showed that despite the lack of structural similarity between radicicol and ATP, radicicol was a competitive ligand for the ATP binding site of HSP90.[21] More recently, a third natural product, novobiocin (**3**, Figure 1), has also been shown to inhibit HSP90, though through a different binding site.[22–24] Structural information about HSP90 has led to the design of inhibitors based on adenosine thus yielding new leads such as compound **4**.[25,26]

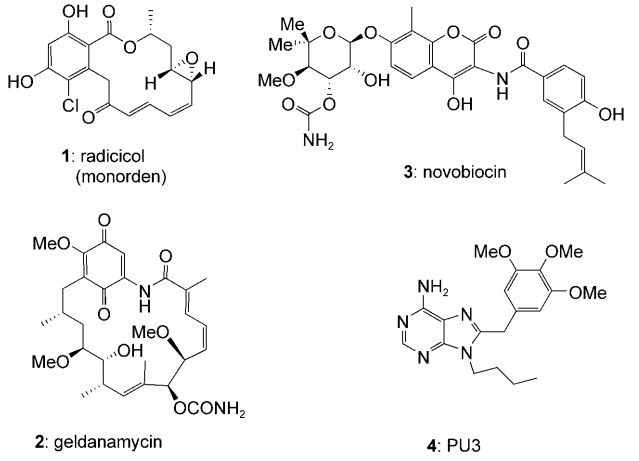

Figure 1. Structure of HSP90 inhibitors.

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author: ^{1}H NMR of synthetic pochonin C (in CD_3OD), synthetic radicicol (in CD_3OD) as well as NOESY spectry of radicicol and pochonin C are included.

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A new family of closely related resocyclic macrolides isolated from the fermentation of *Pochonia chlamydosporia* was recently reported and named pochonin A–F (**5**–**10**, Figure 2).[27] Several members of this family were identified as having activity in a cellular replication assay against the herpes simplex virus (HSV). While radicicol was the most potent inhibitor (0.2–0.8 μM), it was also cytotoxic whereas the closely related pochonin C was less active (6 μM) but was not toxic at that concentration and had the highest selectivity index ($cytotoxicity_{50}/IC_{50}$) amongst the resorcyclides. Our total synthesis of pochonin C[28] clarified the stereochemistry of the chlorine atom at carbon 5 (Figure 2) and established that pochonin C is indeed the product of a formal ring opening of radicicol as suggested by Hellwig et al. in their initial isolation report.[25] Molecular dynamics/minimization of radicicol showed that its lowest energy conformation is the bioactive one and that the epoxide moiety is important to maintain this conformation.[29] This observation can rationalize the difference in activity between pochonin C and radicicol.

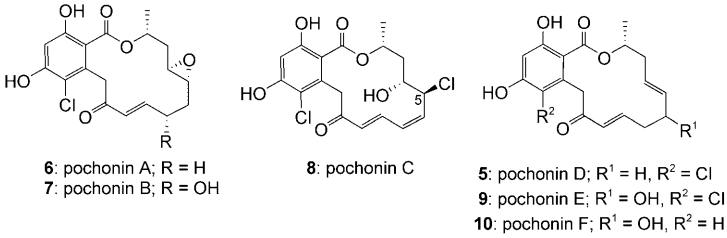


Figure 2. Structure of pochonin deriatives.

Results and Discussion

Our interest in the resorcyclides stems from the observation that several closely related natural products have been reported to be selective inhibitors of different kinases. LL-Z1640-2 is a potent and selective TAK-1 kinase inhibitor for which nor radicicol nor other resorcyclides have been found to be active.[30] Closely related compound LL-783277 is a potent inhibitor of MEK kinase,[31] yet another closely related macrolide, hypothemycin has been reported to inhibit the *ras*-signaling pathway.[32] Although structural information has been reported only for the radicicol-HSP90 interaction wherein radicicol substitutes the adenosine in the ATP-binding pocket,[21] it can be speculated that the kinase inhibition observed with closely related family members stems from the ability of these resorcyclides to act as ATP mimics. This speculation prompted us to develop a diversity-oriented synthesis of the resorcyclides. We have directed our first efforts towards radicicol and the pochonins based on their therapeutic potentials. A major criterion in the development of the synthesis was its amenability to combinatorial synthesis and suitability of the chemistry to prepare analogues extending beyond the diversity of natural resorcyclides. To this end, we developed a strategy that disconnects the macrocycle into three fragments **12**–**14** (Figure 3).[28] It was anticipated that the use of a thioether could not only be important in protecting the α,β-conjugate system (**12**, Figure 3) but also serve as an attachment point to a polystyrene resin. The corresponding selenide (not shown) was also considered as an alternative. At the onset of this work, the stereochemistry of pochonin C's chlorine atom (C5, Figure 3) had not been established. While the *trans* epoxide fragment **14** would be required to reach radicicol, the stereochemistry of both possible diastereoisomers of the C-5 chlorine center of pochonin C would require access to both the *cis* or the *trans* epoxide fragment **14**. For both radicicol and pochonin C, a *cis* olefin would be required as the product of the metathesis reaction. To this end, it was anticipated that the timing of the epoxide opening and thioether elimination could be used to alter the conformational strain and relative equilibrium of the *cis* and *trans* products.

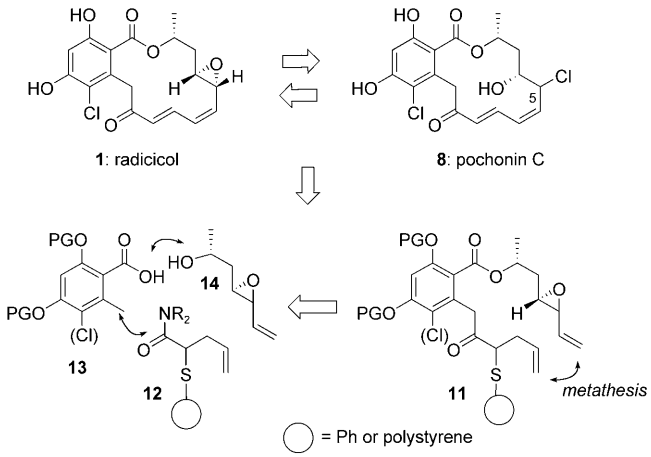
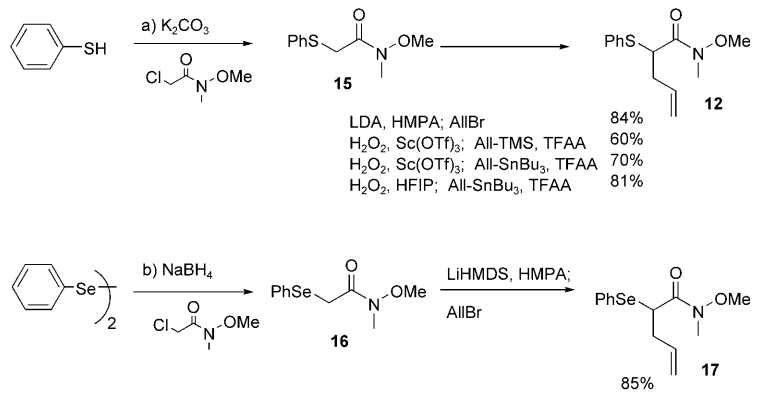


Figure 3. Retrosynthetic analysis of radicicol and pochonin C.

The Weinreb amide fragment **12** was prepared in two steps. First, alkylation of commercially available 2-chloroacetamide with thiophenoxide, or selenophenoxide allowed us to obtain **15** and **16**, respectively (Scheme 1). Both of these products could be allylated smoothly under alkylation conditions (LDA or LiHMDS, HMPA; allyl bromide) to afford products **12** and **17** in good yields. Thioether **15** was also allylated using a Pummerer reaction; oxidation of **15** to the sulfoxide followed by treatment with trifluoroacetic anhydride in the presence of All-$SiMe_3$ or All-$SnBu_3$ afforded the desired product **12** in comparable yield to the alkylation procedure. For the oxidation of thioether **15**, *m*CPBA at −78 °C gave poor results with substantial amount of over oxidation to the sulfone despite incomplete reaction. Oxidation with H_2O_2 in the presence of Lewis acids such as $Sc(OTf)_3$[33] or protic acid such as hexafluoroisopropanol[34] was found to be more reliable. The Pummerer allylation of selenide **16** was found to be less efficient using the same conditions as for **15** except that a Lewis acid is not required in the oxidation with H_2O_2.

Coupling of fragments **13** and **12** was then investigated (Figure 3).[35] To this end, commercially available 2,4-dihydroxytoluate **18** (Scheme 2) was protected with methyl

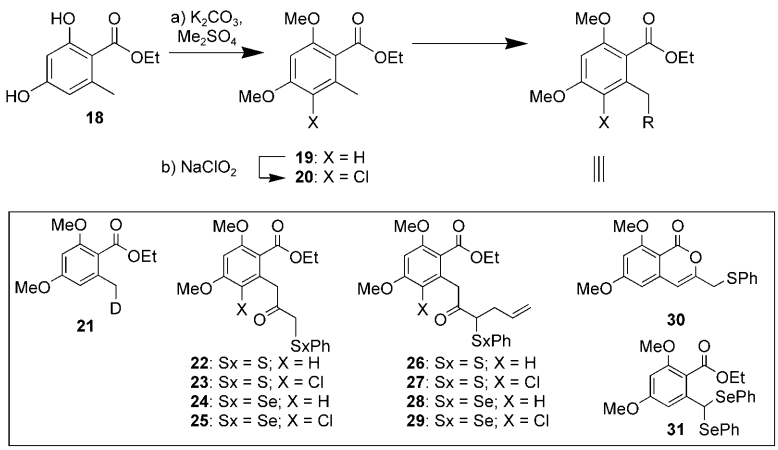


Scheme 1. Synthesis of Weinreb amides **12** and **15**–**17**. a) Thiophenol (1.0 equiv), K_2CO_3 (1.0 equiv), DMF, 23 °C, 2-chloro-*N*-methoxy-*N*-methylacetamide (1.0 equiv), 23 °C, 4 h, 95 %; b) diphenyl diselenide (1.0 equiv), $NaBH_4$ (2.0 equiv), 23 °C, 1.5 h; 2-chloro-*N*-methoxy-*N*-methylacetamide (1.0 equiv), 23 °C, 30 min, 90 %.

amid **15** (entry 4 vs entry 6), it was not the case for the reaction with the allylated 2-seleno Weinreb amide **17** which unexpectedly afforded compound **31** as the only isolable reaction product (entry 8).

The introduction of the allyl group could potentially be carried out after the coupling between the toluate fragment and the Weinreb amide. As shown in Scheme 3, oxidation of **22** with H_2O_2 and catalytic scandium triflate afforded the sulfoxide **32** which was allylated under Pummerer conditions in good yield (trifluoroacetic anhy-

groups to obtain **19** which was subsequently chlorinated to yield **20**. Interestingly, the coupling reaction with **19** required two equivalents of LDA despite the fact that the characteristic deep red color of the toluate anion was obtained with the first equivalent. Deuterium quenching experiments using one equivalent of LDA showed no incorporation of deuterium at the benzylic position (Table 1, entry 1) whereas the use of two equivalents afforded 70 % deuterium incorporation (entry 2). This was attributed to the fact that although the toluate anion is formed with one equivalent of LDA, it was involved in a strong hydrogen bond to the diisopropyl amine and is not accessible to the D_2O nor the Weinreb amide **12** as was previously observed by Seebach et al. for enolates.[36] The use of HMPA only afforded a marginal improvement (entry 3). The coupling of **19** with Weinreb amide **12** or **15** using two equivalents of LDA afforded the desired products in good yield (entries 4 and 7). The coupling could also be carried out with the more congested chlorinated toluate **20** (entry 9), however, only with nonallylated Weinreb amide **15** (entry 9 vs entry 10). It was found to be necessary to keep the reaction at −78 °C to avoid formation of coumarin **30** (entry 5). While the reaction of the anion of toluate **19** with 2-seleno Weinreb amide **16** proceeded as well as with 2-thio Weinreb



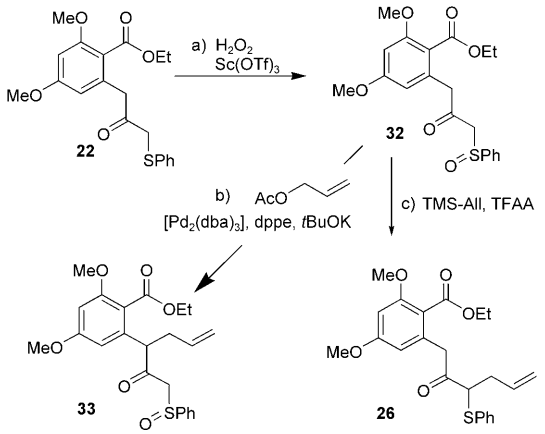
Scheme 2. Deprotonation and reaction toluate of esters **19** and **20**. a) K_2CO_3 (4.0 equiv), Me_2SO_4 (4.0 equiv), acetone, reflux, 4 h, 98 %; b) NH_2SO_3H (3.5 equiv), CH_3CHO (1.0 equiv), $NaClO_2$ (3.25 equiv), THF/H_2O 1:2, 0→23 °C, 20 h, 78 %.

Table 1. Reaction conditions for chlorination of compound **19** or **20**.

	Toluate	Base	Electrophile	Product	Yield [%]
1	**19**	1 equiv LDA, −78 °C	D_2O	**21**	0
2	**19**	2 equiv LDA, −78 °C	D_2O	**21**	70
3	**19**	1 equiv LDA, HMPA, −78 °C	D_2O	**21**	5
4	**19**	2 equiv LDA, −78 °C	**15 (S)**	**22**	88
5	**19**	2 equiv LDA, −78 → 0 °C	**15 (S)**	**30**	84
6	**19**	2 equiv LDA, −78 °C	**16 (Se)**	**24**	90
7	**19**	2 equiv LDA, −78 °C	**12 (AllS)**	**26**	85
8	**19**	2 equiv LDA, −78 °C	**17 (AllSe)**	**31**	45
9	**20 (Cl)**	2 equiv LDA, −78 °C	**15 (S)**	**23**	75
10	**20 (Cl)**	2 equiv LDA, −78 °C	**12 (AllS)**	**27**	0

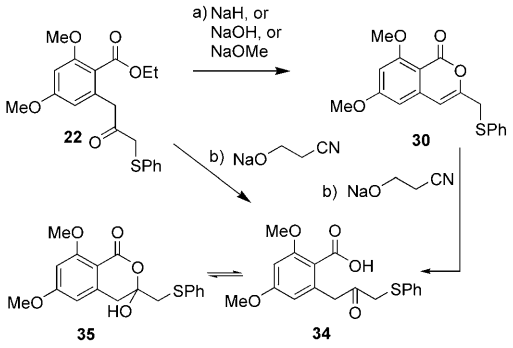
dride, All-$SiMe_3$). Interestingly, alkylation of the ketosulfoxide with a π-ally complex afforded product **33** suggesting that the benzylic position is more nucleophilic than the ketosulfoxide. Nevertheless, cyclization to coumarin **30** was not observed during the reaction.

The propensity of compound **22** to form the coumarin **30** (Scheme 4) is well known and, indeed, treatment of **22** with



Scheme 3. Allylation of ketosulfoxide **32**. a) H_2O_2 (5.0 equiv), $Sc(OTf)_3$ (0.2 equiv), CH_2Cl_2/EtOH 10:1, 23 °C, 3 h, 91 %; b) *t*BuOK (1.0 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.1 equiv), dppe (0.1 equiv), allyl acetate (5.0 equiv), THF, 0→23 °C, 10 min, 84 %; c) All-TMS (5.0 equiv), CH_2Cl_2, −78 °C; TFAA (3.0 equiv), −78 → 23 °C, 80 %.

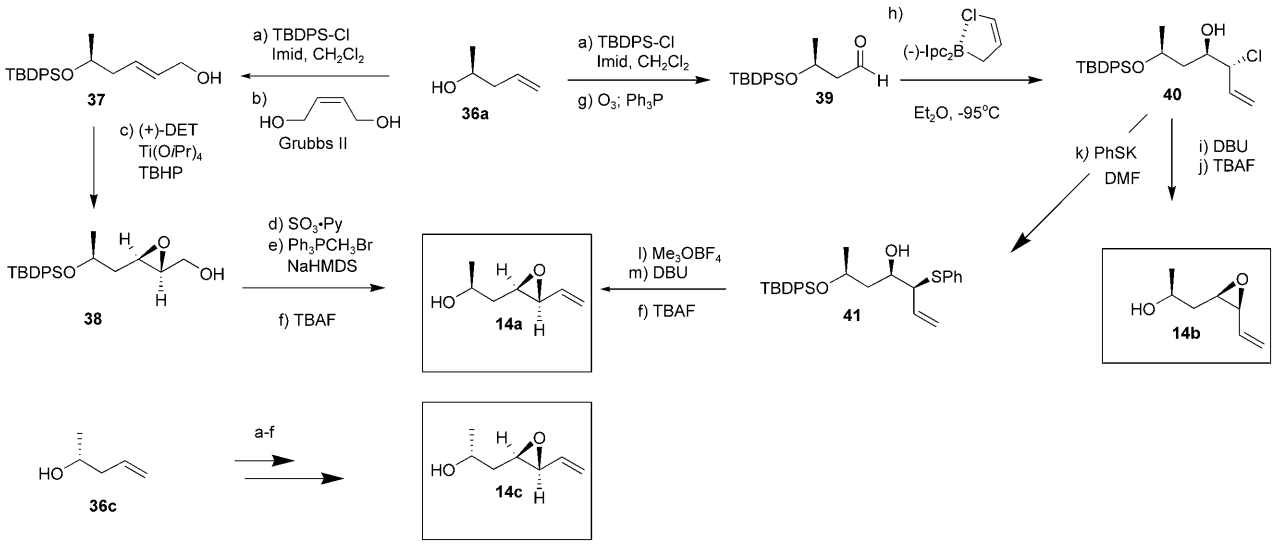
alkoxide or hydroxide led to the rapid formation of coumarin **30** (Scheme 4). We were gratified to find that a hydrolysis of the ester was nevertheless possible using the alkoxide of 3-hydroxypropionitrile which presumably first participates in a transesterification followed by an elimination thus affording the hydrolyzed product as a mixture of hemiketals **34** and **35**. It is noteworthy that this procedure was also effective to hydrolyze the coumarin **30**. Esterification of the acid **34** through activation of the carbonyl led to significant formation of coumarin **30** while esterification under Mitsunobu conditions were not effective presumably due to the fact that the *ortho*-phenol is protected.[37]



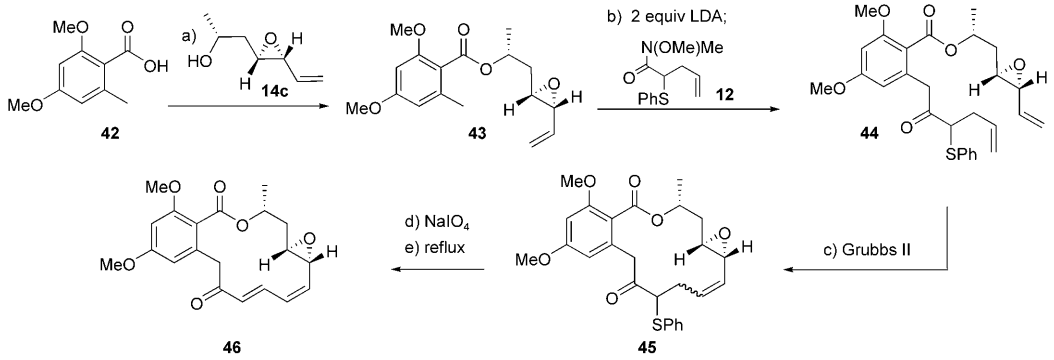
Scheme 4. Hydrolysis of ester **22** and isocoumarin **30**. a) NaH (2.0 equiv), THF, 0 → 23 °C, 10 min, quant.; b) 3-hydroxipropionitrile (10.0 equiv), NaH (4.0 equiv), THF, 0 → 23 °C, 10 min, 93 %.

The last required fragment was alcohol **14**. Access to both the *cis* and *trans* epoxides (**14a** and **b**), was achieved with a divergent strategy starting from commercially available alcohol **36a** (Scheme 5) which was protected with a silyl group (TBDPS) and subjected to an ozonolysis to obtain aldehyde **39** in excellent yield. Treatment of aldehyde **39** with (*Z*)-(γ-chloroallyl)diisopinocampheylborane[38,39] yielded the halohydrin **40** with good diastereoselectivity. Direct oxirane formation with DBU followed by TBAF deprotection of the silyl group afforded the *cis*-epoxide **14b**. Importantly, it was found that the epoxide could be converted back to the chlorohydrin functionality present in pochonin C *stereospecifically*. The corresponding *trans*-epoxide **14a** was obtained by S_N2 displacement of the chloride **40** with thiophenoxide to obtain compound **41** which was activated for oxirane formation by methylation of the sulfur.[40] Treatment with DBU followed by removal of the silyl group afforded the *trans*-epoxide **14a**. Alcohol **14a** could also be reached via a six-step sequence involving silyl protection of alcohol **36a** followed by cross metathesis with an excess of 1,4-butanediol to afford allylic alcohol **37** which was subjected to a Sharpless asymmetric epoxidation as previously reported.[15,41] Importantly the epoxidation reaction required a bulky protecting group on the homoallylic alcohol to obtain high enantiomeric excess, the use of TBS instead of TBDPS led to disappointing results. Oxidation of alcohol **38** followed by a Wittig olefination and deprotection of the silyl protecting group afforded alcohol **14a**. The same sequence starting from alcohol **36c** yielded the diastereomer **14c**.

To test the efficacy of the metathesis reaction in our system, we prepared the open diene **11** (Figure 3) containing all the functional groups present in the natural product. Thus, esterification of alcohol **14c** (Scheme 6) with 2,4-dimethoxytoluyl chloride afforded toluate **43** which was coupled with Weinreb amide **12** to yield the desired open precursor **44** in good yield. Importantly, the potential side reaction of the toluate anion with the epoxide was slow relative to the desired reaction with the Weinreb amide. However, it was found that leaving the toluate anion of **43** at −78 °C for over 20 min led to significant decomposition presumably due to this type of side reactions. Treatment of this open chain diene with Grubbs second-generation catalyst[42,43] in toluene at reflux for 10 minutes (kinetic ring-closure condition)[44] gave the cyclization product **45** in 85 % isolated yield as a mixture of olefin geometry. It is noteworthy that this metathesis was accomplished in the presence of a thioether in β-position to the carbene reactive center which has been reported to poison the catalytic cycle.[45] Oxidation of **45** proved to be challenging as *m*CPBA gave unsatisfactory results and the H_2O_2 in the presence of scandium triflate led to epoxide opening (at the time of this experiment, we were not aware of the HFIP[34] conditions which have proven to be very effective). An acceptable oxidation was achieved with $NaIO_4$ although the reaction was sluggish, never reaching completion despite large excess of oxidant. Isolation of the major oxidation product (there are eight possible products corresponding to a mixture of olefin geometry, stereochemistry of the α-ketosulfoxide center and the sulfoxide itself) and heating to reflux in toluene afforded dimethyl monocillin I[46] **46** very cleanly and in good yield. It was clear from previous attempts[15,47] that the methyl groups on the phenols could not be removed in the presence of the sensitive functionalities of radicicol and pochonin C and that other protecting groups were required. We chose MOM



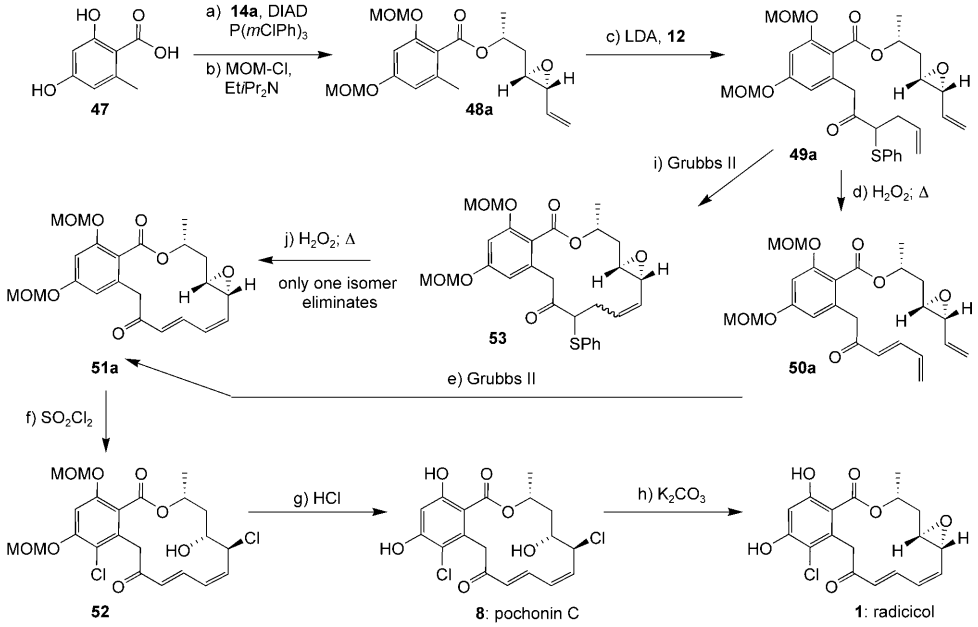
Scheme 5. Stereodivergent synthesis of alcohols **14a–c**. a) *t*BuPh$_2$SiCl (1.1 equiv), Imid (1.7 equiv), CH_2Cl_2, 23 °C, 4 h, 98 %; b) 2-butene-1,4-diol (4 equiv), Grubbs II (10 %), toluene, 80 °C, 12 h, 56 %; c) (+)-DET, Ti(O*i*Pr)$_4$, TBHP, Et_2O, −30 °C, 12 h, 90 %, >93 % *ee*; d) SO_3•Py (1.5 equiv), Et_3N (1.6 equiv), DMSO, 1 h, 90 %; e) Ph_3PCH_3Br, NaHMDS, 0 °C, 80 %; f) TBAF (1.2 equiv), THF, 23 °C, 6 h, 98 %; g) O_3, CH_2Cl_2, −78 °C, 5 min; Ph_3P (1.5 equiv), 23 °C, 2 h, 94 %; h) AllCl (2.0 equiv), LiN*c*Hex (2.0 equiv), (−)-IpcBOMe (1.5 equiv), BF_3OEt_2 (2.5 equiv), −95 °C, 4 h, 68 % (85 % *de*); i) DBU (3.0 equiv), CH_2Cl_2, 0 °C, 8 h, 97 %; j) TBAF (1.2 equiv), THF, 23 °C, 6 h, 98 %; k) thiophenol (4.4 equiv), *t*BuOK (3.3 equiv), 23 °C, 1 h and then, **40** (1.0 equiv), DMF, 0→23 °C, 86 %; l) Me_3OBF_4 (2.0 equiv), CH_2Cl_2, 0→23 °C, 4 h; m) DBU (3.0 equiv), CH_2Cl_2, 0 °C, 4 h, 80 % (two steps).



Scheme 6. Synthesis of dimethyl monocillin. a) Oxalyl chloride (1.0 equiv), DMF (cat), CH_2Cl_2, 0 → 23 °C, 1 h, and then at 0 °C Et_3N (2.0 equiv), **14c** (0.8 equiv), DMAP, 0 → 23 °C, 3 h, 80 %; b) LDA (2.0 equiv), THF, −78 °C, 5 min; **12** (1.0 equiv), THF, −78 °C, 5 min, 75 %; c) Grubbs II (5 % mol), toluene (2 mM), 87 %; d) $NaIO_4$ (1.5 equiv), MeOH, 23 °C, 8 h, 40 %; e) toluene, reflux, 1 h, 80 %.

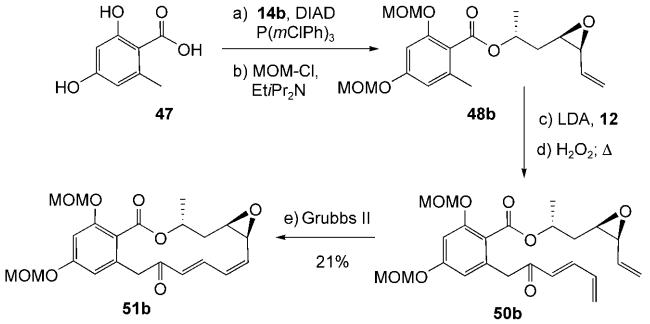
based on their stability to enolate chemistry. The most convergent sequence of assembly of fragment **12**–**14** (Figure 3) requires alcohol **14** to be coupled to benzoic acid **13** prior to coupling to Weinreb amide **12** to avoid protecting group manipulations. As previously discussed, esterification of the 2-hydroxy toluic acid **47** under Mitsunobu or carbodiimide conditions was found to work best with the 2-hydroxy position free.[37] It was found that the acid **47** (Scheme 7) with both *ortho*- and *para*-phenols free could be selectively esterified using a Mitsunobu esterification[48] with tris(3-chlorophenyl)phosphine.[49] This product was then protected with MOM-Cl to afford ester **48a**. The esterification under classical Mitsunobu conditions (Ph_3P, DIAD, CH_2Cl_2, THF or toluene) gave a poor selectivity between the desired esterification and undesired ether formation of the *para*-phenol. Reaction of toluate **48a** using two equivalents of LDA followed by addition of Weinreb amide **12** afforded cyclization precursor **49a** in good yield. Treatment of intermediate **49a** with the second generation Grubbs catalyst in toluene at reflux led to rapid ring closure to obtain the macrocycle **53** as an inseparable mixture of *cis*/*trans* olefins (1:1), according to the previous results with the ring closure of **44**. With the low yield of the $NaIO_4$ oxidation and the inadequacy of *m*CPBA or H_2O_2/$ScOTf_3$, we were gratified to find that thioether **53** could be chemoselectively oxidized with H_2O_2 in hexafluoroisopropanol[34] with no over-oxidation product nor epoxide opening. As this oxidation proceeded in a clean fashion, the elimination could be carried out on the crude sulfoxide which is a mixture of diasteroisomers (two olefin geometry, stereochemistry of the α-ketosulfoxide center and the sulfoxide itself). Interestingly, only the desired *cis*/*trans* product **51a** was obtained despite the fact that the reaction

was done on a mixture of olefins! Presumably, elimination of the sulfoxide proceeded *only* for the compound leading to the desired *trans*/*cis* diene **53**, the *trans*-olefin **53** not being able to adopt the adequate conformation to participate in a 1,2-*syn* elimination of the sulfoxide. While this was convenient, the overall yield was poor. However, the selectivity in the elimination reflects the rigidity of the macrocycle and suggested that carrying out the metathesis on the triene **50a** should lead to the desired *trans*/*cis* diene. Oxidation/elimination of the thioether **49a** followed by RCM in refluxing toluene led indeed exclusively to the desired *trans*/*cis* conjugated diene **51a** within 10 min in excellent yield. It has been shown that the *cis*/*trans* selectivity of the RCM in unsubstituted 14-membered macrocycles is kinetically controlled;[50] however, the high degree of selectivity in the ring closure of **50a** can not be attributed to short reaction time considering the lack of selectivity for the closure of **49a** under the same conditions. There remained to chlorinate the aryl ring and open the epoxide stereospecifically to reach pochonin C. The epoxide could be cleanly opened by using several equivalents of HCl in dioxane while the chlorine atom could be efficiently introduce with hypochloride. However, it was found that both operations could be carried out in a single step by using an excess of the SO_2Cl_2 which generates an equivalent of HCl in situ (no overchlorination of the aromatic ring was observed).[15,51] Final deprotection of the MOMs led to compound **8** which was found to have identical NMR spectra to natural pochonin C.[52] Treatment of compound **8** with K_2CO_3 led to rapid and clean oxirane formation thus yielding compound **1** which was identical to radicicol (Scheme 7).



Scheme 7. Synthesis of pochonin C and radicicol. a) **14a** (1.0 equiv), P(*m*ClPh)$_3$ (2.0 equiv), DIAD (2.0 equiv), toluene, 23 °C, 3 h, 84 %; b) MOMCl (4.0 equiv), Et*i*Pr$_2$N (4.0 equiv), TBAI (cat), DMF, 80 °C, 3 h, 91 %; c) LDA (2.0 equiv), THF, −78 °C; **12** (1.0 equiv), 81 %; d) H_2O_2 (2.0 equiv), $(CF_3)_2CHOH$, 23 °C, 3 h; toluene, 80 °C, 1 h, 92 %; e) Grubbs II (5 % mol), toluene (2 mM), reflux, 10 min, 87 %; f) SO_2Cl_2 (3.0 equiv), Et_2O, 0 °C, 68 %; g) HCl_{conc} (2.5 % in dioxane), 0→23 °C, 1 h, 74 %; h) K_2CO_3 (2.0 equiv) DMF, 23 °C, 1 h, 86 %; i) Grubbs II (5 % mol), toluene (2 mM), reflux, 10 min, 94 %; j) H_2O_2 (2.0 equiv), $(CF_3)_2CHOH$, 23 °C, 3 h; toluene, 80 °C, 1 h, 22 % two steps (85 % based on recovered sulfoxide).

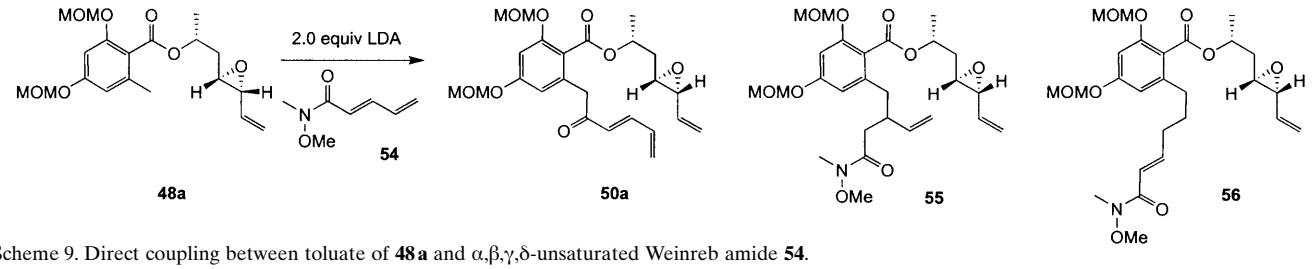
A similar reaction sequence starting from alcohol **14b** (Scheme 8) and toluic acid **47** led to the triene **50b**. Treatment of this compound to the successful metathesis conditions used for **50a** afforded the ring closure product **51b** as the conjugated *trans*/*cis* diene albeit in poor yield (Scheme 8).



Scheme 8. Synthesis of pochonin C and radicicol using the *cis*-epoxide. a) **14b** (1.0 equiv), P(*m*ClPh)$_3$ (2.0 equiv), DIAD (2.0 equiv), toluene, 23 °C, 3 h, 84 %; b) MOMCl (4.0 equiv), Et*i*Pr$_2$N (4.0 equiv), TBAI (cat), DMF, 80 °C, 3 h, 91 %; c) LDA (2.0 equiv), THF, −78 °C; **50b** (1.0 equiv), 81 %; d) H_2O_2 (2.0 equiv), $(CF_3)_2CHOH$, 23 °C, 3 h; toluene, 80 °C, 1 h, 92 %; e) Grubbs II (5 % mol), toluene (2 mM), reflux, 10 min, 21 %.

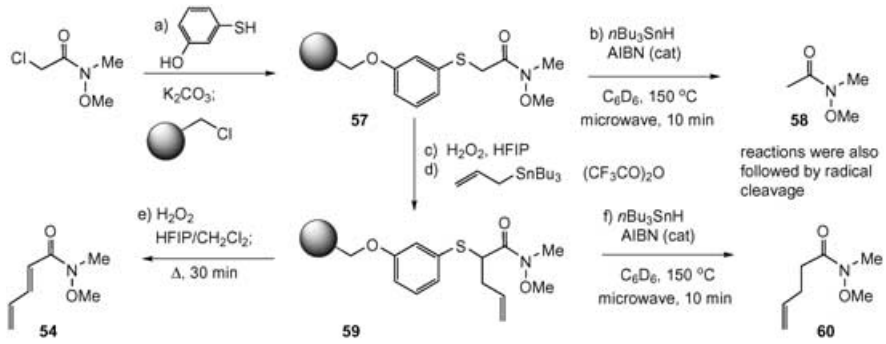
Considering the fact that the metathesis gives better selectivity on triene **50a** rather than diene **49a**, we asked whether it would be possible to carry out the coupling of toluate **48a** directly on the α,β,δ,γ-conjugated Weinreb amide. As shown in Scheme 9, this reaction led to a mixture of desired 1,2-addition **50a** as well as the 1,4-addition **55** and 1,6-addition product **56**. Despite several attempts to favor the 1,2-addition product, we could not obtain more than 30 % yield of **50a** with this reaction. It is interesting to note that similar reactions on simple α,β-conjugate systems rather than conjugated dienes have proved more productive.[29,53]

Solid-phase synthesis of pochonin C and radicicol: Aside from masking the α,β-conjugated system thus providing a protection during the toluate–Weinreb amide coupling step, the thioether was foreseen as a possible attachment point to



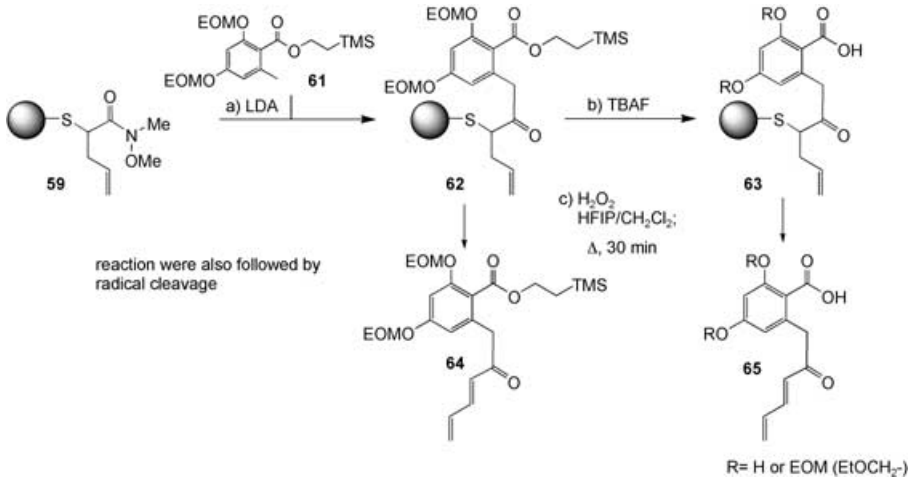
Scheme 9. Direct coupling between toluate of **48a** and α,β,γ,δ-unsaturated Weinreb amide **54**.

a solid phase. As shown in Scheme 10, the polymer-bound equivalent of compound **15** was prepared in one pot by a selective S-alkylation of 3-hydroxythiophenol with 2-chloroacetamide by using one equivalent of base, followed by the addition of Merrifield resin and a second equivalent of base to obtain **57**. By using the same conditions as were developed in solution, the thioether linker of resin **57** was oxidized with H_2O_2 using hexafluoroisopropanol as a Lewis acid. The resulting sulfoxide was activated with trifluoroacetic anhydride in the presence of All-$SnBu_3$ for a Pummerer allylation to obtain resin **59**. The success of this reaction and subsequent reactions could be assessed by taking an aliquot of resin (10 mg) and cleaving the thioether under reductive conditions (Bu_3SnH, AIBN) in deuterated benzene such that the product was analyzed directly by NMR after filtration of the resin. For convenience and speed, the reactions were carried out in a microwave and found to go to completion in 10 min. More importantly, oxidation of resin **59** with H_2O_2 followed by a brief heating afforded compound **54** in 80% yield based on the loading of the Merrifield resin and >95% purity as judged by NMR. The fact that the sulfoxide does not eliminate at room temperature is practical as it allows for washing the resin and performing the elimination in a solvent free of reagents.



Scheme 10. Pummerer rearrangement on solid support. a) 3-mercaptophenol (1.0 equiv), K_2CO_3 (1.0 equiv), 2-chloro-*N*-methoxy-*N*-methylacetamide (1.0 equiv), DMF, 23 °C, 2 h; Merrifield resin (0.6 equiv), K_2CO_3 (2.0 equiv), TBAI, 50 °C, 2 h, 90%; b) nBu_3SnH (5.0 equiv), AIBN (cat), C_6D_6, *hv* (150 °C, 300 W), 10 min; c) H_2O_2 (4.0 equiv), $(CF_3)_2CHOH/CH_2Cl_2$ 1:1, 23 °C, 12 h; d) $AllylSnBu_3$ (5.0 equiv), −78 °C, CH_2Cl_2; then TFAA (3.0 equiv), −78→23 °C; e) H_2O_2 (4.0 equiv), $(CF_3)_2CHOH/CH_2Cl_2$ 1:1, 23 °C, 12 h and then, toluene, 80 °C, 30 min, 80% isolated yield from Merrifield resin; f) nBu_3SnH (5.0 equiv), AIBN (cat), C_6D_6, μΩ (150 °C, 300 W), 10 min.

As shown in Scheme 11, the polymer-bound Weinreb amide **59** was coupled with suitably protected toluic ester **61** to afford the polymer bound product **62**. The calculated yield of the reaction based on the free radical cleavage procedure is 60%; however, using the oxidation/elimination procedure and drying the product in vacuo overnight showed only the desired product **64** as the α,γ-conjugate olefin **54** is volatile enough to be removed. Trying to drive the reaction to completion with more equivalents of toluate anion did not improve the yield. Interestingly, the coupling of the toluate anion with polymer bound Weinreb amide **57** did not proceed at all even though the corresponding reaction in solution is very effective. This was rational-



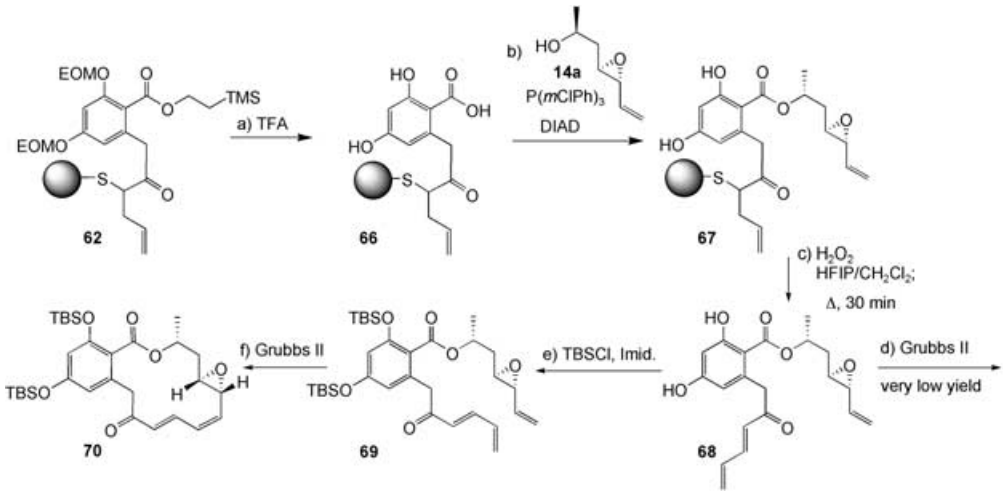
Scheme 11. Coupling of toluate **61** and Weinreb amide **59** on solid support. a) **61** (4.0 equiv), LDA (8.0 equiv), THF, −78 °C, 10 min, and then **60** (1.0 equiv) −78 °C, 4 h; b) TBAF (1.2 equiv), THF, 23 °C, 6 h, >95%; c) H_2O_2 (4.0 equiv), $(CF_3)_2CHOH/CH_2Cl_2$ 1:1, 23 °C, 12 h; toluene, 80 °C, 30 min, 60% from resin **59**.

ized by the fact that the polystyrene environment altered the relative rates of Weinreb amide enolization relatively to the coupling reaction and the less hindered Weinreb amide was enolized rather than participating in the coupling. Likewise, the use of larger excess of reagents did not improve the reactions since the enolized Weinreb amide is simply not reactive towards the coupling. Nevertheless, considering that the elimination product of the unreacted Weinreb amide is volatile, clean product could be obtained anyhow. The TMS ethanol could be selectively removed using TBAF to afford polymer bound acid **63** which is similar to solution intermediate **35** (Scheme 4) and requires the free *ortho*-phenol to be esterified. The *ortho*-MOM could be selectively deprotected with 5% TFA but based on our previous observation that it was possible to achieve a selective Mitsunobu esterification in the presence of both free phenols, we opted to remove the three protecting groups in one operation using 20% TFA, thus yielding the deprotected intermediate **66** (Scheme 12). Esterification of this product according to the same reaction conditions as previously used in solution afforded the polymer bound cyclization precursor which was released from the resin by oxidation–elimination. Disappointingly, this compound did not give good yields in the metathesis ring closure. It has been shown that the presence or absence of a protected *ortho*-phenol in a similar system could affect the outcome of a RCM by virtue of the hydrogen bond to the carbonyl and its impact on the preorganization of the open chain system.[54] However, in this case, the incompatibility stems from the *para*-phenol as the metathesis was very effective when only the *para*-phenol was protected (not shown). Re-protection of the phenols with TBS-Cl afforded product **69** which was an excellent substrate for the metathesis reaction yielding macrocyle **70** in 83%. Compound **70** was converted to radicicol according to known procedures.[6] Conversely, the acid **47** could be esterified with alcohol **14a** by using polymer-bound DEAD (Scheme 13) followed by MOM protection to obtain toluate **48a** which could be used in the subsequent coupling without further purification. Deprotonation of the crude toluate **48a** with LDA and reaction with polymer bound Weinreb amide **59** afforded the polymer bound diene **71**. Oxidation–elimination of compound **71** followed by metathesis afforded compound **51a** which was the same as the one previously obtained in solution. SO_2Cl_2 mediated chlorination/halohydrin formation followed by MOM deprotection thus afforded pochonin C.

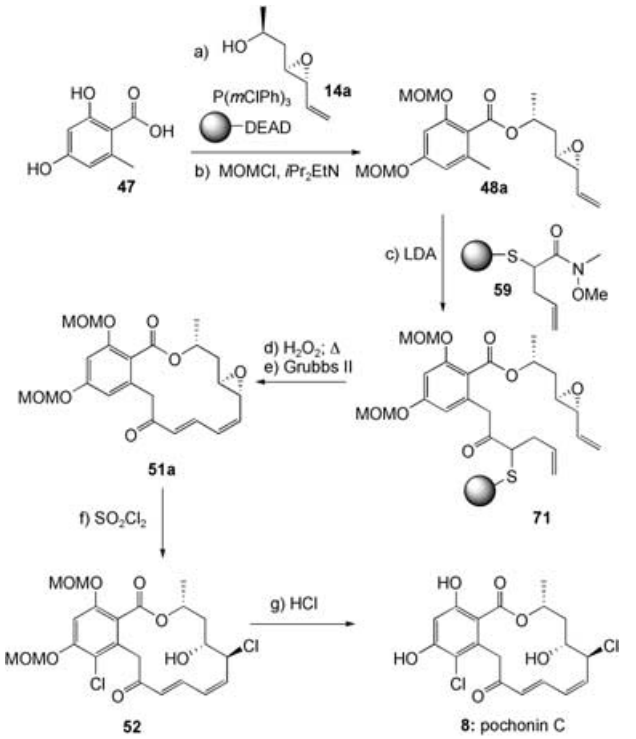
Conformational study of radicicol and pochonin C: The difference in selectivity in the ring closing metathesis reaction between compound **49a** versus **50a** reflects the rigidity of radicicol's macrocyle. NMR analysis of radicicol's conformation in solution (CD_3OD) clearly showed a very well define conformation with strong NOE between the proton of methyl group (C1) and the proton of C8 and C11 in accordance with its conformation bound in the active site of HSP90 (Figure 4).[21] In comparison, pochonin C showed a very different pattern of c with the strong NOE between C1 and C8/C11 clearly absent suggesting a more planar and less organized conformation. The difference in biological activity reported by Hellwig et al.[27] for pochonin C and radicicol may be in part rationalize by the fact that despite the structural similarity of these compounds, they have very different conformations.

Conclusion

A concise and modular synthesis of pochonin C and radicicol has been achieved in seven and eight steps, respectively, from benzoic acid **47**, alcohol **14** and Weinreb amide **12**. The



Scheme 12. Solid support assisted synthesis of TBS protected monocillin **70**. a) TFA (20%), CH_2Cl_2, 1 h, >95%; b) **14a** (4.0 equiv), P(*m*ClPh)$_3$ (4.0 equiv), DIAD (4.0 equiv), CH_2Cl_2, 23°C, 4 h; c) H_2O_2 (4.0 equiv), $(CF_3)_2CHOH/CH_2Cl_2$ 1:1, 23°C, 12 h and then, toluene, 80°C, 12 h, 70% from resin **62**; d) Grubbs II (5% mol), toluene (2 mM), reflux; e) TBSCl (10.0 equiv), Imid. (10.0 equiv), DMF, 12 h, 90%; f) Grubbs II (5% mol), toluene (2 mM), reflux, 83%.



Scheme 13. Polymer-assisted synthesis of pochonin C. a) **14a** (1.0 equiv), P(*m*ClPh)$_3$, (2.0 equiv), PS-DEAD (2.0 equiv, 1.3 mmol g^{-1}), toluene, 23 °C, 3 h, 83 %; b) MOMCl (4.0 equiv), Et*i*Pr$_2$N (4.0 equiv), TBAI (cat), DMF, 80 °C, 3 h, 95 %; c) **48a** (2.0 equiv), LDA (4.0 equiv), THF, −78 °C, 10 min, and then **59** (1.0 equiv) −78 °C, 4 h; d) H_2O_2 (4.0 equiv), $(CF_3)_2CHOH/CH_2Cl_2$ 1:1, 23 °C, 12 h; toluene, 80 °C, 12 h, 53 % (three steps); e) Grubbs II (5 % mol), toluene (2 mM), 120 °C, 10 min, 87 %; f) SO_2Cl_2 (3.0 equiv), Et_2O, 0 °C, 68 %; g) HCl_{conc} (2.5 % in dioxane), 0→23 °C, 1 h, 74 %.

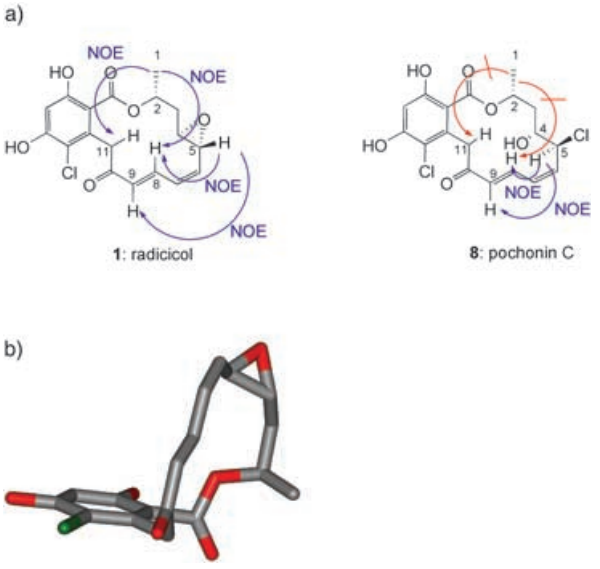


Figure 4. Conformational aspects of radicicol and pochonin C. a) NOE signals observed for radicicol and pochonin C. [Numbering according to pochonin C definition]. b) Conformation of radicicol bound to HSP90 (PDB structure ID 1BGQ).[21]

longest linear sequence is 13 steps for pochonin C and 14 steps for radicicol. The combination of polymer supported reagents and solid phase reactions greatly facilitate the chemistry requiring only two traditional chromatography for the seven steps from the three fragments **47**, **14** and **12**. The two dimensional NMR studies clearly point to the fact that although radicicol and pochonin C are closely related structurally, they are quite different topologically. The topological diversity that is achievable by closely related resorcyclides may explain the different biological activity of closely related compounds. Finally, these synthetic studies add to our knowledge of the scope of the ring closing metathesis by adding a precedent for a very *cis*-selective closure from a triene having four possible RCM products.

Experimental Section

General procedures: All polymer-bound reagents and Merrifield resin were obtained from Novabiochem. The Grubbs catalyst was purchased from Materia Inc. Solid phase reactions were carried on a Quest 210 or round bottom flasks and filtered in fritted funnels. All reactions were carried out under a nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions. Tetrahydrofuran (THF), toluene and diethyl ether (Et_2O) were distilled from sodium/benzophenone, and methylene chloride (CH_2Cl_2) from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially available alumina column (Solv-Tek, Inc., VA). Reactions were monitored by thin layer chromatography (TLC) and preparative thin layer chromatography (PTLC) were carried out on 0.25 mm E. Merck silica gel coated glass plates (60F-254) 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. NMR spectra were recorded on Bruker Advance-400 instruments 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, qt = quintet, m = multiplet, br = broad. IR spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. LC-MS were recorded using an Agilent 1100 HPLC (Supelco C8, 5 cm × 4.6 mm, 5 μm particules column) with a Bruker micro-TOF instrument (ESI) by using 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}. Unless otherwise stated, LDA was prepared at a concentration of 0.566 M by treating a solution of diisopropyamine (1.0 equiv) in THF at −78 °C with *n*-butyllithium (1.0 equiv) and stirred for 30 min at that temperature before used.

Weinreb amide 15: 2-Chloro-*N*-methoxy-*N*-methylacetamide (10.3 g, 74.5 mmol) was added at 23 °C to a solution of thiophenol (7.6 mL, 74.5 mmol) and K_2CO_3 (10.3 g, 74.5 mmol) in dry DMF (40 mL). After 4 h stirring at room temperature, the mixture was quenched by addition of a solution of saturated NH_4Cl_{aq} (50 mL), diluted with Et_2O (50 mL), washed several times with saturated NH_4Cl_{aq} (30 mL) and brine (30 mL) and dried over $MgSO_4$. Concentration under reduced pressure afforded compound **15** (13.4 g, 95 %). R_f = 0.22 (silica gel, EtOAc/hexane 3:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.46 (d, J = 7.6 Hz, 2H), 7.32–7.28 (m, 2H), 7.23–7.19 (m, 1H), 3.84 (s, 2H), 3.70 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.9, 135.8, 129.6, 128.9 (×3), 126.5, 61.4, 35.3, 32.3; IR (film): $\tilde{\nu}_{max}$ = 3059, 2925, 1654, 1584, 1438, 1380, 999, 741, 690 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{10}H_{13}O_2NS$: 234.0559, found 234.0533 [M+Na$^+$].

Weinreb amide 12: $Sc(OTf)_3$ (49 mg, 0.1 mmol) and H_2O_2 (255 μL, 5 mmol) were sequentially added to a solution of compound **15** (211 mg, 1 mmol) in CH_2Cl_2/EtOH (10:1, 5.5 mL). After 3 h stirring at room temperature, the reaction was diluted with EtOAc (10 mL), washed with a saturated aqueous solution of $NaHCO_3/Na_2S_2O_3$ (10:1, 11 mL), dried

over $MgSO_4$ and concentrated under reduced pressure. The crude mixture (206 mg, 0.9 mmol) was then diluted in CH_2Cl_2 (10 mL) and allyltrimethylsilane (723 μL, 4.6 mmol) was added. The resulting solution was cooled down to −78 °C and, trifluoroacetic anhydride (384 μL, 2.7 mmol) was added. After 10 min at −78 °C, the reaction was allowed to warm up to room temperature for 1 h. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–50 % EtOAc/hexane), afforded compound **12** (151 mg, 60 %). R_f = 0.34 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.53–7.51 (m, 2H), 7.35–7.32 (m, 3H), 5.88–5.77 (m, 1H), 5.12 (dd, J = 17.0, 1.8 Hz, 1H), 5.09 (dd, J = 11.2, 1.8 Hz, 1H), 4.21 (br s, 1H), 3.62 (s, 3H), 3.20 (s, 3H), 2.73–2.66 (m, 1H), 2.55–2.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.0, 134.6, 133.7 (×2), 132.9, 128.9 (×2), 128.1, 117.7, 61.4, 46.2, 36.4, 32.4; IR (film): $\tilde{\nu}_{max}$ = 2923, 1660, 1654, 1439, 1379, 990, 739, 697 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{13}H_{17}O_2SNa$: 274.0872, found 274.0812 [M+Na$^+$].

Weinreb amide 16: $NaBH_4$ (237 mg, 6.4 mmol) was added to a solution of diphenyl diselenide (1 g, 3.2 mmol) in EtOH/THF (4:1, 32 mL). The reaction was stirred at room temperature until the mixture turned color from orange to light yellow (~1.5 h). At that time, 2-chloro-*N*-methoxy-*N*-methylacetamide (882 mg, 6.4 mmol) was added to the mixture. The reaction was stirred for 30 min and then quenched with brine (50 mL), extracted with EtOAc (50 mL) and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–30 % EtOAc/hexane), afforded compound **16** (744 mg, 90 %). R_f = 0.17 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.66–7.64 (m, 2H), 7.31–7.30 (m, 3H), 3.76 (s, 2H), 3.70 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.2, 133.0, 129.9, 129.1 (×3), 127.5, 61.3, 32.4, 26.6; IR (film): $\tilde{\nu}_{max}$ = 2935, 1661, 1578, 1478, 1438, 1379, 999, 739, 691 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{10}H_{13}O_2NSeNa$: 282.0004, found 282.9980 [M+Na$^+$].

Weinreb amide 17: A solution of compound **16** (130 mg, 0.5 mmol) in anhydrous THF (5 mL) was treated at −78 °C with LiHMDS (500 μL, 1 M solution, 0.5 mmol). After 10 min at that temperature, HMPA (87 μL, 0.5 mmol) and allyl bromide (43 μL, 0.5 mmol) were sequentially added. The resulting solution was then allowed to warm up to 0 °C and followed by TLC until completion (~1 to 3 h). The reaction mixture was diluted with EtOAc and washed several times with 1 N HCl and brine. The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica gel, 0–30 % EtOAc/hexane gradient) to yield compound **17** (127 mg, 85 %). R_f = 0.44 (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.61 (d, J = 7.0 Hz, 2H), 7.33–7.26 (m, 3H), 5.82–5.71 (m, 1H), 5.08 (d, J = 18.1 Hz, 1H), 5.04 (d, J = 10.5 Hz, 1H), 4.14 (br s, 1H), 3.59 (s, 3H), 3.15 (s, 3H), 2.77–2.69 (m, 1H), 2.54–2.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.6, 135.9 (×2), 135.3, 128.9 (×2), 128.4, 127.6, 117.3, 61.3, 38.8, 36.4, 32.5; IR (film): $\tilde{\nu}_{max}$ = 3073, 2973, 2936, 1658, 1578, 1477, 1438, 1382, 1175, 992, 919, 740, 692 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{13}H_{17}O_2NSeNa$: 322.0317, found 322.0266 [M+Na$^+$].

2,4-Dimethoxy ester 19: A solution of 2,4-dihydroxy ester **18** (980 mg, 5 mmol) and potassium carbonate (2.76 g, 20 mmol) in acetone (20 mL) was treated with dimethyl sulfate (1.89 mL, 20 mmol) and heated for 4 h at reflux. The mixture was then concentrated under vacuum, dissolved in EtOAc (20 mL) and washed with 1 N HCl (2×20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to provide compound **19** (1.10 g, 98 %). R_f = 0.43 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.33 (s, 2H), 4.38 (q, J = 7.0 Hz, 2H), 3.81 (s, 6H), 2.32 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.2, 161.2, 158.1, 138.0, 116.8, 106.6, 96.2, 60.9, 55.9, 55.3, 19.8, 14.3; IR (film): $\tilde{\nu}_{max}$ = 2978, 1724, 1606, 1459, 1267, 1203, 1160, 1098, 1052 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{12}H_{16}O_4Na$: 247.0941, found 247.0872 [M+Na$^+$].

Chlorinated ester 20: Sulfamic acid (300 mg, 3.12 mmol) and acetaldehyde (50 μL, 0.89 mmol) was added to a solution of compound **19** (200 mg, 0.89 mmol) in THF/H_2O (1:2, 15 mL). After cooling down to 0 °C, sodium chlorite (260 mg, 2.90 mmol) was added and the solution was stirred for 20 h at room temperature. The reation was diluted with saturated NH_4Cl_{aq} (20 mL) and extracted with EtOAc (15 mL). The organic layer was then dried over $MgSO_4$ and concentrated under vacuum. Crude ^{1}H NMR indicated 60 % conv. Flash chromatography (silica gel, 0–30 % EtOAc/hexane) afforded compound **20** (108 mg, 78 % based on recovery of the starting material). R_f = 0.49 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.43 (s, 1H), 4.41 (q, J = 7.0 Hz, 2H), 3.95 (s, 3H), 3.87 (s, 3H), 2.35 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.5, 156.4, 155.7, 135.4, 117.9, 114.9, 94.3, 61.3, 56.3, 56.2, 17.4, 14.2; IR (film): $\tilde{\nu}_{max}$ = 2982, 1724, 1594, 1459, 1259, 1211, 1081 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{12}H_{15}O_4ClNa$: 281.0551, found 281.0528 [M+Na$^+$].

Toluate 21: A solution of compound **19** (50 mg, 0.22 mmol) in anhydrous THF (500 μL) was treated at −78 °C with freshly made LDA (777 μL, 0.44 mmol). The resulting mixture was then stirred for 5 min and quenched by addition of a mixture of D_2O/THF (1:1, 1 mL). Upon warming to room temperature, the reaction was diluted with EtOAc (5 mL), washed several times with saturated NH_4Cl_{aq} (4 mL) and brine (4 mL), and dried over $MgSO_4$. Concentration under reduced pressure afforded compound **21**. Crude ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.34 (s, 2H), 4.38 (q, J = 7.2 Hz, 2H), 3.82 (s, 6H), 2.30 (t, J = 2.2 Hz, 2H), 1.39 (t, J = 7.0 Hz, 3H).

Sulfide 22: A solution of compound **19** (100 mg, 0.45 mmol) in anhydrous THF (2 mL) was treated at −78 °C with freshly made LDA (1.6 mL, 0.90 mmol). After 5 min stirring, a solution of compound **15** (95 mg, 0.45 mmol) in THF (0.5 mL) was added dropwise. The resulting mixture was then stirred for 5 min at −78 °C and quenched at this temperature by addition of saturated NH_4Cl_{aq} (5 mL). Upon warming to room temperature, the reaction was diluted with EtOAc (10 mL), washed several times with saturated NH_4Cl_{aq} (8 mL) and brine (8 mL), and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–33 % EtOAc/hexane gradient) afforded compound **22** (147 mg, 88 %). R_f = 0.34 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36–7.33 (m, 2H), 7.31–7.26 (m, 2H), 7.23–7.19 (m, 1H), 6.41 (d, J = 2.3 Hz, 1H), 6.31 (d, J = 2.2 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 3.89 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.78 (s, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 201.8, 167.5, 161.7, 159.1, 134.9, 129.8, 129.4 (×2), 129.0 (×2), 126.7, 116.4, 107.6, 98.0, 61.2, 56.0, 55.4, 46.0, 43.1, 14.2; IR (film): $\tilde{\nu}_{max}$ = 2980, 1718, 1604, 1459, 1204, 1161, 1092, 741, 691 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{20}H_{22}O_5SNa$: 397.1080, found 397.1021 [M+Na$^+$].

Sulfide 23: A solution of compound **20** (100 mg, 0.39 mmol) in anhydrous THF (1 mL) was treated at −78 °C with freshly made LDA (1.37 mL, 0.77 mmol). After 5 min stirring, a solution of compound **15** (82 mg, 0.39 mmol) in THF (0.5 mL) was added dropwise. The resulting mixture was then stirred for 5 min at −78 °C and quenched at this temperature by addition of saturated NH_4Cl_{aq} (5 mL). Upon warming to room temperature, the reaction was diluted with EtOAc (10 mL), washed several times with saturated NH_4Cl_{aq} (8 mL) and brine (8 mL), and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–30 % EtOAc/hexane gradient) afforded compound **23** (119 mg, 75 %). R_f = 0.25 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37 (d, J = 7.6 Hz, 2H), 7.32–7.27 (m, 3H), 6.48 (s, 1H), 4.26 (q, J = 7.0 Hz, 2H), 4.10 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.81 (s, 2H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.4, 166.8, 156.9, 156.7, 135.0, 132.7, 129.4 (×2), 129.1 (×2), 126.7, 117.6, 115.3, 95.8, 61.4, 56.3, 56.3, 43.6, 43.6, 14.1; IR (film): $\tilde{\nu}_{max}$ = 2936, 1719, 1592, 1257, 1212, 1083, 741, 691 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{20}H_{21}O_5ClSNa$: 431.0690, found 431.0624 [M+Na$^+$].

Selenide 24: A solution of compound **19** (95 mg, 0.42 mmol) in anhydrous THF (2 mL) was treated at −78 °C with freshly made LDA (1.5 mL, 0.85 mmol). After 5 min stirring, a solution of compound **16** (109 mg, 0.42 mmol) in THF (0.5 mL) was added dropwise. The resulting mixture was then stirred for 5 min at −78 °C and quenched at this temperature by addition of saturated NH_4Cl_{aq} (5 mL). Upon warming to room temperature, the reaction was diluted with EtOAc (10 mL), washed several times with saturated NH_4Cl_{aq} (8 mL) and brine (8 mL), and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–30 % EtOAc/hexane gradient) afforded compound **24** (161 mg, 90 %). R_f = 0.32 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR

(400 MHz, $CDCl_3$, 25 °C): δ = 7.53–7.52 (m, 2H), 7.29 (m, 3H), 6.41 (s, 1H), 6.33 (s, 1H), 4.33 (q, J = 7.0 Hz, 2H), 3.90 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.68 (s, 2H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.0, 167.5, 161.7, 159.0, 135.0, 133.1 (×2), 129.3 (×2), 129.1, 127.6, 116.6, 107.4, 97.9, 61.2, 56.0, 55.4, 45.9, 35.1, 14.2; IR (film): $\tilde{\nu}_{max}$ = 2937, 1719, 1604, 1272, 1204, 1161, 1097, 1047, 739, 691 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{20}H_{22}O_5SeNa$: 445.0526, found 445.0683 [M+Na$^+$].

Sulfide 26: A solution of compound **19** (100 mg, 0.45 mmol) in anhydrous THF (2 mL) was treated at −78 °C with freshly made LDA (1.58 mL, 0.89 mmol). After 5 min stirring, a solution of compound **12** (112 mg, 0.45 mmol) in THF (0.5 mL) was added dropwise. The resulting mixture was then stirred for 5 min at −78 °C and quenched at this temperature by addition of saturated NH_4Cl_{aq} (5 mL). Upon warming to room temperature, the reaction was diluted with EtOAc (10 mL), washed several times with saturated NH_4Cl_{aq} (8 mL) and brine (8 mL), and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–30 % EtOAc/hexane gradient) afforded compound **26** (157 mg, 85 %). R_f = 0.34 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.39 (m, 2H), 7.32–7.29 (m, 3H), 6.41 (d, J = 2.4 Hz, 1H), 6.31 (d, J = 2.3 Hz, 1H), 5.85–5.75 (m, 1H), 5.12–5.07 (m, 2H), 4.33 (q, J = 7.0 Hz, 2H), 4.08 (d, J = 16.1 Hz, 1H), 3.92 (d, J = 16.1 Hz, 1H), 3.82 (s + m, 4H), 3.78 (s, 3H), 2.58 (ddd, J = 14.9, 7.2, 7.2 Hz, 1H), 2.43 (ddd, J = 14.6, 7.2, 7.2 Hz, 1H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.1, 167.6, 161.4, 158.7, 134.6, 134.3, 133.4 (×2), 131.8, 129.0 (×2), 128.2, 117.6, 116.8, 107.2, 97.9, 61.1, 55.9, 55.3, 54.5, 45.1, 34.0, 14.2; IR (film): $\tilde{\nu}_{max}$ = 2935, 1717, 1604, 1459, 1161, 1096, 1050, 744, 691 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{23}H_{26}O_5SNa$: 437.1393, found 437.1269 [M+Na$^+$].

Isocoumarin 30: A solution of compound **19** (43 mg, 0.19 mmol) in anhydrous THF (1 mL) was treated at −78 °C with freshly made LDA (671 μL, 0.38 mmol). After 5 min stirring, a solution of compound **15** (40 mg, 0.19 mmol) in THF (0.5 mL) was added dropwise. The resulting mixture was then stirred for 10 min at −78 °C and heated up to 0 °C. After 30 min at that temperature, the red color of the solution had disappeared and TLC revealed the formation of isocoumarin **30**. The reaction mixture was warmed up to room temperature, quenched by addition of saturated NH_4Cl_{aq} (5 mL), diluted with EtOAc (10 mL), washed several times with saturated NH_4Cl_{aq} (8 mL) and brine (8 mL) and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–30 % EtOAc/hexane gradient) afforded compound **30** (54 mg, 84 %). R_f = 0.31 (silica gel, EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40 (d, J = 7.0 Hz, 2H), 7.33–7.23 (m, 3H), 6.47 (s, 1H), 6.31 (s, 1H), 6.25 (s, 1H), 3.99 (s, 3H), 3.89 (s + s, 3H + 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 165.4, 163.3, 158.9, 154.1, 141.7, 134.8, 130.6 (×2), 129.1 (×2), 127.1, 104.6, 103.1, 100.2, 98.7, 56.3, 55.6, 36.3; IR (film): $\tilde{\nu}_{max}$ = 2933, 1718, 1663, 1598, 1570, 1458, 1370, 1214, 1164, 742, 690 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{18}H_{16}O_4S$: 329.0842, found 329.0755 [M+H$^+$].

Bis-selenide 31: A solution of compound **19** (196 mg, 1 mmol) in anhydrous THF (4 mL) was treated at −78 °C with freshly made LDA (2 mL, 2 mmol, 1 M in THF). After 5 min stirring, a solution of compound **17** (109 mg, 1 mmol) in THF (1 mL) was added dropwise. The resulting mixture was then stirred for 5 min at −78 °C and quenched at this temperature by addition of saturated NH_4Cl_{aq} (5 mL). Upon warming to room temperature, the reaction was diluted with EtOAc (10 mL), washed several times with saturated NH_4Cl_{aq} (8 mL) and brine (8 mL), and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–30 % EtOAc/hexane gradient) afforded compound **31** (240 mg, 45 %). R_f = 0.45 (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.49 (d, J = 6.5 Hz, 4H), 7.33–7.22 (m, 6H), 6.74 (d, J = 1.6 Hz, 1H), 6.31 (d, J = 1.6 Hz, 1H), 5.82 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H), 3.74 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.1, 161.4, 158.0, 141.4, 136.1, 134.3 (×4), 131.1, 128.9 (×4), 128.0 (×2), 114.8, 105.3, 98.4, 61.2, 56.0, 55.4, 40.1, 14.2; IR (film): $\tilde{\nu}_{max}$ = 2977, 2932, 1731, 1704, 1602, 1267, 1159, 1100, 1045, 737, 688 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{24}H_{24}O_4Se_2Na$: 558.9902, found 558.9874 [M+Na$^+$].

Sulfoxide 32: $Sc(OTf)_3$ (99 mg, 0.2 mmol) and H_2O_2 (257 μL, 5 mmol) were added sequentially to a solution of compound **22** (380 mg, 1 mmol) in CH_2Cl_2/EtOH (10:1, 5.5 mL). After 3 h stirring at room temperature, the reaction was diluted with EtOAc (10 mL), washed with a saturated solution of $NaHCO_3/Na_2S_2O_3$ (10:1, 11 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield compound **32** (355 mg, 91 %). R_f = 0.42 (silica gel, EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.68–7.66 (m, 2H), 7.53–7.52 (m, 3H), 6.42 (d, J = 1.2 Hz, 1H), 6.28 (d, J = 1.8 Hz, 1H), 4.30 (q, J = 7.0 Hz, 2H), 3.92 (d, J = 7.0 Hz, 2H), 3.81 (s, 6H), 3.75 (d, J = 5.3 Hz, 2H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 198.6, 167.4, 162.0, 159.3, 143.3, 134.2, 131.5, 129.4 (×2), 124.2 (×2), 116.1, 107.7, 98.3, 67.4, 61.2, 56.0, 55.5, 49.9, 14.2; IR (film): $\tilde{\nu}_{max}$ = 2944, 1720, 1605, 1275, 1162, 1090, 1047, 750, 691 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{12}H_{15}O_4ClNa$: 281.0551, found 281.0528 [M+Na$^+$].

Sulfoxide 33: In a first flask, a mixture of allylacetate (59.8 μL, 0.55 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (11.4 mg, 0.011 mmol) and dppe (4.4 mg, 0.011 mmol) in THF (1 mL) was stirred for 30 min until the reaction color change from deep purple to orange. In another flask, a solution of compound **32** (46 mg, 0.11 mmol) in THF (1 mL) was sequentially treated at room temperature with tBuOK (13.2 mg, 0.11 mmol) and the palladium solution. After completion of the reaction, as judged by TLC, the solution was diluted with EtOAc (5 mL), washed several times with saturated NH_4Cl_{aq} and brine, and dried over $MgSO_4$. Evaporation of solvents, followed by flash chromatography (silica gel, 0–33 % EtOAc/hexane) afforded compound **33** (43 mg, 84 %) as a mixture of diastereoisomers 1:1. R_f = 0.45 (silica gel, EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.68–7.64 (m, 4H), 7.53–7.49 (m, 6H), 6.42 (s, 1H), 6.38 (s, 1H), 6.21 (s, 1H), 6.14 (s, 1H), 5.63–5.55 (m, 2H), 5.03–4.94 (m, 4H), 4.44–4.35 (m, 4H), 4.08 (d, J = 14.5 Hz, 1H), 4.03 (d, J = 14.0 Hz, 1H), 3.84–3.76 (m, 14H), 3.70 (d, J = 14.0 Hz, 1H), 3.65 (d, J = 14.5 Hz, 1H), 2.80–2.70 (m, 2H), 2.47–2.38 (m, 2H), 1.40–1.36 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 200.2, 199.7, 167.7, 167.6, 161.9, 161.8, 158.5, 158.4, 143.5, 143.2, 136.3, 136.0, 134.8, 134.6, 131.4, 131.1, 129.3 (×2), 129.2 (×2), 124.3 (×2), 124.2 (×2), 117.8, 117.7, 117.2, 117.1, 104.0, 98.2, 98.1, 67.6, 66.9, 61.6, 61.5, 56.9, 56.2, 55.9 (×2), 55.5 (×2), 35.4 (×2), 14.3, (2 $C_{quat.}$ are not visible); HRMS (ESI-TOF): m/z: calcd for $C_{23}H_{26}O_6SNa$: 453.1342, found 453.1363 [M+Na$^+$].

Sulfide 26 from sulfoxide 32: A solution of compound **32** (500 mg, 1.28 mmol) in CH_2Cl_2 (12.8 mL) was treated at −78 °C with allyltrimethylsilane (1.02 mL, 6.40 mmol). After 30 min stirring, trifluoroacetic anhydride (543 μL, 3.84 mmol) was added to the mixture. After 10 min at that temperature, the reaction was warmed up to room temperature. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–30 % EtOAc/hexane), afforded compound **26** (425 mg, 80 %). R_f = 0.34 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.40–7.39 (m, 2H), 7.32–7.29 (m, 3H), 6.41 (d, J = 2.4 Hz, 1H), 6.31 (d, J = 2.3 Hz, 1H), 5.85–5.75 (m, 1H), 5.12–5.07 (m, 2H), 4.33 (q, J = 7.0 Hz, 2H), 4.08 (d, J = 16.1 Hz, 1H), 3.92 (d, J = 16.1 Hz, 1H), 3.82 (s + m, 4H), 3.78 (s, 3H), 2.58 (ddd, J = 14.9, 7.2, 7.2 Hz, 1H), 2.43 (ddd, J = 14.6, 7.2, 7.2 Hz, 1H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.1, 167.6, 161.4, 158.7, 134.6, 134.3, 133.4 (×2), 131.8, 129.0 (×2), 128.2, 117.6, 116.8, 107.2, 97.9, 61.1, 55.9, 55.3, 54.5, 45.1, 34.0, 14.2; IR (film): $\tilde{\nu}_{max}$ = 2935, 1717, 1604, 1459, 1161, 1096, 1050, 744, 691 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{23}H_{26}O_5SNa$: 437.1393, found 437.1269 [M+Na$^+$].

Compounds 34 and 35: A preformed solution of 3-hydroxypropionitrile (77 μL, 1.13 mmol) and sodium hydride (18 mg, 0.45 mmol) in THF (1.5 mL) was added to a solution of compound **22** (37 mg, 0.11 mmol) in THF (1.5 mL) at 0 °C. The reaction was warmed up to room temperature and after stirring for 10 min, was quenched with 1 N HCl (5 mL), diluted with EtOAc (10 mL), washed several times with saturated NH_4Cl_{aq} (2× 5 mL) and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–100 % EtOAc/hexane gradient) afforded a mixture of compounds **34** and **35** (36 mg, 93 %). R_f = 0.51 (silica gel, EtOAc); ^{1}H NMR (400 MHz, $(CD_3)_2CO$, 25 °C): δ = 7.50–7.48 (d, J = 7.6 Hz, 2H), 7.39–7.29 (m, 6H), 7.24–7.20 (m, 2H), 6.63 (d, J = 1.8 Hz, 1H), 6.54 (s, 1H), 6.49 (d, J = 1.8 Hz, 1H), 6.45 (s, 1H), 4.07 (s,

2H), 4.02 (s, 2H), 3.94 (s, 3H), 3.90–3.86 (m, 10H), 3.85 (s, 3H); HRMS (ESI-TOF): *m/z*: calcd for $C_{18}H_{18}O_5SNa$: 369.0767, found 369.0662 [*M*+Na$^+$].

Alcohol 37: A solution of (*S*)-4-penten-2-ol **36a** (228 mg, 2.65 mmol) in anhydrous CH_2Cl_2 (9 mL) at 0 °C was treated with imidazole (306 mg, 4.50 mmol) in one portion. After 10 min stirring, *tert*-butyldiphenylchlorosilane (760 μL, 2.91 mmol) was added dropwise and the reaction was allowed to warm to 23 °C and stirred for 4 h. Then, the reaction mixture was diluted with Et_2O and washed successively with 5% NH_4Cl_{aq} and brine. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (silica gel, hexane) to provide (*S*)-2-(*tert*-butyldiphenylslyloxy)pent-4-ene (0.85 g, 98%). R_f = 0.44 (silica gel, hexane/Et_2O 10:1).

A solution of this compound (287 mg, 1.0 mmol) in toluene (5 mL) was treated at room temperature with but-2-ene-1,4-diol (329 μL, 4.0 mmol). The mixture of both compounds was heated up to 80 °C and Grubbs II catalyst (80 mg, 0.1 mmol) was added once the solution was hot. The reaction was then stirred for 12 h at that temperature. Evaporation of the solvents, followed by flash chromatography (silica gel, 0–33% EtO_2/hexane), afforded compound **37** (199 mg, 56%) and found to be identical to previously reported compound **37**.[15] R_f = 0.50 (silica gel, hexane/Et_2O 5:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.72–7.69 (m, 4H), 7.47–7.39 (m, 6H), 5.63–5.59 (m, 2H), 4.05 (d, *J* = 3.8 Hz, 2H), 3.93 (m, 1H), 2.26–2.17 (m, 2H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 135.9 (×4), 134.6, 134.5, 131.5, 129.6, 129.5, 129.1, 127.6 (×2), 127.5 (×2), 69.4, 63.6, 42.4, 27.1 (×3), 23.1, 19.3; IR (film): $\tilde{\nu}_{max}$ = 3332, 2930, 2857, 1427, 1111, 997 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{22}H_{30}O_2SiNa$: 377.1907, found 377.1932 [*M*+Na$^+$]. (−)-(2*E*,5*S*): $[\alpha]_D^{20}$ = −20.6 (*c* 1.00, $CHCl_3$).

Aldehyde 39: Ozone was bubbled into the cooled solution (−78 °C) of (*S*)-2-(*tert*-butyldiphenylsilyloxy)pent-4-ene (820 mg, 2.52 mmol) in CH_2Cl_2 (40 mL) until it turned blue (~5 min). The reaction was purged with argon and triphenylphosphine (990 mg, 3.78 mmol) was added. The solution was removed from the cold bath and stirred at 23 °C for 2 h. Concentration under reduced pressure and purification by flash chromatography (silica gel, 0–2% Et_2O/hexane gradient) furnished aldehyde **39** (750 mg, 94%). R_f = 0.40 (silica gel, hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.79 (s, 1H), 7.73–7.68 (m, 4H), 7.50–7.38 (m, 6H), 4.43–4.33 (m, 1H), 2.56 (ddd, *J* = 15.8, 5.9, 2.9 Hz, 1H), 2.49 (ddd, *J* = 15.8, 5.9, 2.3 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 202.0, 135.8 (×4), 134.0, 133.6, 129.8, 129.7, 127.7 (×2), 127.6 (×2), 65.7, 52.7, 26.9 (×3), 23.8, 19.2; IR (film): $\tilde{\nu}_{max}$ = 2959, 2930, 2857, 1709, 1428, 1113, 998 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{20}H_{26}O_2SiNa$: 349.1594, found 349.1596 [*M*+Na$^+$]. (−)-(3*S*): $[\alpha]_D^{20}$ = −4.0 (*c* 1.00, $CHCl_3$).

Chlorohydrin 40: To a stirred and cooled (−95 °C, Et_2O, dry ice) mixture of (−)-Ipc$_2$BOMe (5.12 g, 16.2 mmol) and allyl chloride (1.76 mL, 21.6 mmol) in anhydrous Et_2O (78 mL) was added a solution of LiN(*c*-Hex)$_2$ (21.6 mmol) [prepared from dicyclohexylamine (4.3 mL, 21.6 mmol) in THF (20 mL) by deprotonation with *n*BuLi (13.5 mL, 1.6 M in hexane, 21.6 mmol) and stirring at 0 °C for 0.5 h. The mixture was stirred at −95 °C and after 1 hour, $BF_3{\cdot}OEt_2$ (3.19 mL, 27.0 mmol) was slowly added. After stirring 0.5 h, solution of **39** (3.52 g, 10.8 mmol) in anhydrous Et_2O (10 mL) cooled at −95 °C was added dropwise. The mixture was maintained at −95 °C for an additional 2.5 h and quenched by the addition of MeOH (11 mL). Then, 3 M NaOAc (11 mL) and 35% H_2O_2 (6.7 mL) were sequentially added and the reaction was allowed to slowly warm up to room temperature for ~10 h. Then, water was added and the reaction mixture was extracted with Et_2O (3×50 mL). The combined organic layers were sequentially washed with saturated NH_4Cl_{aq}, brine and finally dried over $MgSO_4$. Concentration under reduced pressure and purification by flash chromatography (silica gel, 0–10% Et_2O/hexane gradient) yielded chlorohydrin **40** (2.96 g, 68%). R_f = 0.39 (silica gel, hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.77–7.73 (m, 4H), 7.50–7.41 (m, 6H), 6.01–5.92 (ddd, *J* = 17.0, 10.6, 8.1 Hz, 1H), 5.38 (d, *J* = 16.7 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 4.31 (dd, *J* = 8.3, 5.6 Hz, 1H), 4.27–4.22 (m, 1H), 4.11–4.06 (m, 1H), 3.02 (d, *J* = 3.8 Hz, 1H), 1.73–1.69 (m, 2H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 135.9 (×2), 135.9 (×2), 135.2, 134.0, 133.5, 129.9, 129.8, 127.7 (×2), 127.6 (×2), 118.7, 71.2, 68.0, 67.8, 41.7, 27.0 (×3), 23.2, 19.2; IR (film): $\tilde{\nu}_{max}$ = 3475, 2962, 2951, 2857, 1472, 1428, 1378, 1112 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{23}H_{31}O_2SiClNa$: 425.1674, found 425.1603 [*M*+Na$^+$]. (−)-(2*S*,4*R*,5*R*): $[\alpha]_D^{20}$ = −11.8 (*c* 1.00, $CHCl_3$).

Sulfide 41: A solution of thiophenol (2.3 mL, 22.0 mmol) in anhydrous DMF (100 mL) at room temperature was treated with potassium *tert*-butoxide (1.8 g, 16.4 mmol) and stirred at this temperature for 1 h. The mixture was filtered and added dropwise to a 0 °C solution of halohydrin **40** (2.0 g, 5.0 mmol) in anhydrous DMF (100 mL). The resulting mixture was allowed to warm up to room temperature and stirred until consumption of the starting material (reaction monitored by TLC). The reaction mixture was diluted with Et_2O and washed several times with water and brine. The organic phase was then dried ($MgSO_4$), concentrated under reduced pressure and purified by flash chromatography (silica gel, 0–10% Et_2O/hexane gradient) to provide compound **41** (1.98 g, 86%). R_f = 0.39 (silica gel, hexane/EtOAc 5:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.76–7.72 (m, 4H), 7.51–7.42 (m, 8H), 7.36–7.29 (m, 3H), 5.97–5.88 (m, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 5.06 (d, *J* = 17.2 Hz, 1H), 4.27–4.21 (m, 2H), 3.66 (dd, *J* = 8.5, 4.0 Hz, 1H), 3.07 (d, *J* = 2.7 Hz, 1H), 1.80 (ddd, *J* = 14.0, 10.2, 3.8 Hz, 1H), 1.68 (ddd, *J* = 14.5, 6.4, 2.1 Hz, 1H), 1.67 (d, *J* = 6.4 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 135.9, 134.4, 134.2, 134.1, 133.5, 132.7, 129.8, 129.7, 128.8, 127.7, 127.5, 127.3, 118.1, 69.1, 67.9, 59.3, 42.7, 26.9, 23.1, 19.2; IR (film): $\tilde{\nu}_{max}$ = 3408, 2929, 1472, 1427, 1378, 1111 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{29}H_{36}O_2SiSNa$: 499.2098, found 499.2007 [*M*+Na$^+$]. (−)-(2*S*,4*R*,5*S*): $[\alpha]_D^{20}$ = −14.2 (*c* 1.00, $CHCl_3$).

Alcohol 14a: A solution of the β-hydroxyphenylsulfide **41** (1.30 g, 2.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a cooled (0 °C) and well-stirred suspension of trimethyloxonium tetrafluoroborate (800 mg, 5.5 mmol) in dry CH_2Cl_2 (20 mL). The resulting mixture was stirred at 0 °C for 2 h, warmed to room temperature and stirred until TLC analysis indicated quantitative formation of the sulfonium salt by expense of the starting material (ca. 2–3 h). After re-cooling to 0 °C, the reaction was diluted with CH_2Cl_2 (10 mL) and a solution of DBU (1.2 mL, 8.2 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring at 0 °C for 4 h, water was added and the mixture was quickly partitioned between water and Et_2O. After washing with brine and drying with $MgSO_4$, the organic phase was concentrated under reduced pressure and purified by flash chromatography (silica gel, 0–5% Et_2O/hexane gradient) to yield TBDPS-protected-**14a** (7.8 g, 80% over two steps). R_f = 0.6 (silica gel, hexane/EtOAc 5:1).

*n*Bu$_4$NF (10.74 mL, 1.0 M solution in THF, 10.74 mmol) was added dropwise at 23 °C to a solution of TBDPS-protected-**14a** (3.28 g, 8.95 mmol) in anhydrous THF (85 mL). The reaction was stirred for 6 h and then, concentrated under reduced pressure. Flash chromatography (silica gel, 0–25% Et_2O/hexane gradient) provided alcohol **14a** (1.1 g, 98%). R_f = 0.14 (silica gel, Et_2O/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.50 (ddd, *J* = 17.1, 9.7, 7.5 Hz, 1H), 5.44 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.25 (dd, *J* = 9.7, 1.6 Hz, 1H), 3.98 (m, 1H), 3.18 (dd, *J* = 7.5, 2.2 Hz, 1H), 3.03–3.00 (m, 1H), 1.82 (ddd, *J* = 13.9, 8.1, 4.3 Hz, 1H), 1.58 (ddd, *J* = 14.5, 7.0, 4.3 Hz, 1H), 1.20 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 135.3, 119.5, 65.5, 58.3, 58.0, 40.1, 23.4; IR (film): $\tilde{\nu}_{max}$ = 3413, 2969, 1458, 1408, 1137 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_7H_{12}O_2$: 129.0910, found 129.0716 [*M*+H$^+$]. (+)-(2*S*,4*R*,5*R*): $[\alpha]_D^{20}$ = + 35.4 (*c* 1.00, $CHCl_3$).

Alcohol 14b: Halohydrin **40** (2.96 g, 7.3 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) and treated with a solution of DBU (3.3 mL, 22.0 mmol) in CH_2Cl_2 (15 mL) at 0 °C. Stirring was continued at 0 °C until TLC showed quantitative conversion of the halohydrin (ca. 8 h). The mixture was poured into a saturated $NaHCO_{3aq}$ solution (20 mL), the organic layer separated, and the aqueous phase was extracted with Et_2O (3×20 mL). The combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by flash chromatography (silica gel, 0–5% Et_2O/hexane gradient) to yield compound TBDPS-**14b** (2.6 g, 97%). R_f = 0.58 (silica gel, hexane/EtOAc 5:1).

nBu$_4$NF (10.74 mL, 1.0 M solution in THF, 10.74 mmol) was added dropwise at 23 °C to a solution of compound TBDPS-**14b** (3.28 g, 8.95 mmol) in anhydrous THF (85 mL). The reaction was stirred for 6 h and then, concentrated under reduced pressure. Flash chromatography (silica gel, 0–25% Et$_2$O/hexane gradient) provided alcohol **14b** (1.1 g, 98%). R_f = 0.15 (silica gel, Et$_2$O/hexane 1:3); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 5.76 (ddd, J = 17.2, 10.2, 3.5 Hz, 1H), 5.49 (d, J = 16.7 Hz, 1H), 5.40 (d, J = 10.5 Hz, 1H), 4.15–4.05 (m, 1H), 3.48 (dd, J = 7.0, 2.6 Hz, 1H), 3.34–3.29 (m, 1H), 1.76 (ddd, J = 14.3, 7.6, 4.7 Hz, 1H), 1.68 (ddd, J = 14.0, 7.6, 4.4 Hz, 1H), 1.31 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 132.4, 120.6, 66.2, 56.9, 55.9, 36.7, 23.9; IR (film): $\tilde{\nu}_{max}$ = 3408, 2966, 1452, 1140 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for C$_7$H$_{12}$O$_2$Na: 151.0729, found 151.0426 [M+Na$^+$]. (+)-(2S,4R,5S): $[\alpha]_D^{20}$ = +3.8 (c 0.16, CHCl$_3$).

Alcohol 14c: R_f = 0.16 (silica gel, Et$_2$O/hexane 1:3); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 5.53 (ddd, J = 17.0, 8.8, 8.6 Hz, 1H), 5.43 (d, J = 16.9 Hz, 1H), 5.24 (d, J = 9.4 Hz, 1H), 4.03–3.97 (m, 1H), 3.10 (d, J = 7.6 Hz, 1H), 2.99 (m, 1H), 1.80–1.75 (m, 1H), 1.68 (ddd, J = 14.1, 10.7, 7.0 Hz, 1H), 1.20 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 135.3, 119.4, 66.0, 58.3, 58.2, 40.8, 23.3; IR (film): $\tilde{\nu}_{max}$ = 3408, 2967, 1452, 1144 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for C$_7$H$_{12}$O$_2$Na: 151.0729, found 151.0449 [M+Na$^+$]. (+)-(2R,4R,5R): $[\alpha]_D^{20}$ = +13.1 (c 1.00, CHCl$_3$).

Ester 43: Oxalyl chloride (219 μL, 2.6 mmol) was added at 0 °C to a solution of 2,4-dimethoxy-6-methylbenzoic acid (500 mg, 2.6 mmol) in anhydrous CH$_2$Cl$_2$ (10 mL) and catalytic DMF (10 μL). The solution was then stirred at 25 °C. After 1 h, the reaction was recooled at 0 °C, and treated sequentially with Et$_3$N (798 μL, 5.8 mmol), alcohol **14c** (260 mg, 2.0 mmol) and a solution of DMAP (catalytic amount) in anhydrous CH$_2$Cl$_2$ (3 mL). The reaction was followed by TLC until consumption of the starting material (~3 h). It was then diluted with CH$_2$Cl$_2$ (50 mL), washed with saturated NH$_4$Cl$_{aq}$ (50 mL) and dried over MgSO$_4$. Evaporation of the solvents followed by flash chromatography (silica gel, 0–10% EtOAc/hexane gradient) yielded ester **43** (625 mg, 80%). R_f = 0.33 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 6.34 (s, 2H), 5.64–5.57 (m, 1H), 5.49 (d, J = 17.6 Hz, 1H), 5.39–5.34 (m, 1H), 5.30 (d, J = 10.5 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.18 (d, J = 7.3 Hz, 1H), 3.06–3.03 (m, 1H), 2.32 (s, 3H), 2.09–2.02 (m, 1H), 1.93–1.87 (m, 1H), 1.44 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 167.5, 161.2, 158.0, 137.7, 135.4, 119.0, 116.7, 106.6, 96.1, 69.0, 57.9, 56.9, 55.7, 55.2, 38.0, 19.9, 19.7; IR (film): $\tilde{\nu}_{max}$ = 2977, 1720, 1605, 1459, 1327, 1266, 1202, 1151, 1096, 1051 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for C$_{17}$H$_{22}$O$_5$Na: 329.1359, found 329.1273 [M+Na$^+$]. (−)-(*R*,*R*,*R*): $[\alpha]_D^{20}$ = −22.2 (c 0.46, CHCl$_3$).

Sulfide 44: A solution of compound **43** (150 mg, 0.49 mmol) in anhydrous THF (1 mL) was treated at −78 °C with freshly made LDA (1.78 mL, 0.98 mmol). After 5 min stirring, a solution of compound **12** (123 mg, 0.49 mmol) in THF (0.7 mL) was added dropwise. The resulting mixture was then stirred for 5 min at −78 °C and quenched by addition of saturated NH$_4$Cl$_{aq}$. Upon warming to room temperature, the reaction was diluted with EtOAc, washed several times with saturated NH$_4$Cl$_{aq}$, brine and dried over MgSO$_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–50% EtOAc/cyclohexane gradient) afforded sulfide **44** as a mixture of two diasteroisomers 1:1 (182 mg, 75%). R_f = 0.28 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.39 (brs, 2H), 7.31–7.30 (m, 3H), 6.40 (d, J = 1.2 Hz, 1H), 6.30 (s, 1H), 5.86–5.76 (m, 1H), 5.65–5.58 (m, 1H), 5.48 (d, J = 16.9 Hz, 1H), 5.32–5.27 (m, 2H), 5.12–5.07 (m, 2H), 4.16–3.90 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.85–3.77 (m, 1H), 3.14 (bd, J = 7.0 Hz, 1H), 3.06–3.05 (m, 1H), 2.62–2.55 (m, 1H), 2.47–2.39 (m, 1H), 2.02–1.88 (m, 2H), 1.39 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 202.2, 167.2, 161.6, 158.8, 135.5, 134.9, 134.4, 133.4, 129.0 (×3), 128.3, 128.2, 119.2, 117.7, 116.8, 107.3, 97.9, 69.4, 58.1, 57.0, 55.8, 55.4, 54.8, 45.0, 38.1, 34.1, 19.9; IR (film): $\tilde{\nu}_{max}$ = 2973, 2939, 1713, 1604, 1579, 1459, 1272, 1205, 1161, 1094, 1048, 922, 750, 692 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for C$_{28}$H$_{32}$O$_6$SNa: 519.1812, found 519.1662 [M+Na$^+$].

Macrocycle 45: A 2 mM solution of compound **44** (150 mg, 0.3 mmol) in anhydrous toluene was heated at reflux and treated with 5% mol of Grubbs catalyst, 2nd generation. The reaction mixture was stirred for 10 min at that temperature and quenched quickly by cooling down to −78 °C. The reaction mixture was then filtered through a pad of silica gel, washed with CH$_2$Cl$_2$ and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 0–25% EtOAc/cyclohexane gradient) afforded **45** (123 mg, 87%) as a mixture of diastereoisomers. R_f = 0.22 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 7.57–7.55 (m, 4H), 7.39–7.37 (m, 6H), 6.39 (s, 2H), 6.05 (s, 2H), 5.79–5.72 (m, 2H), 5.26–5.20 (m, 2H), 5.02 (dd, J = 15.8, 8.8 Hz, 2H), 4.01 (d, J = 19.3 Hz, 2H), 3.84–3.77 (m, 2H), 3.82 (s, 6H), 3.79 (s, 6H), 3.65 (d, J = 19.3 Hz, 2H), 3.13 (d, J = 8.8 Hz, 2H), 2.80–2.77 (m, 2H), 2.53–2.30 (m, 8H), 1.36 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 203.0, 167.8, 161.5, 159.1, 135.0, 134.5 (×2), 129.2 (×2), 129.1, 128.9, 128.3, 107.9, 98.0, 70.5, 68.5, 56.8, 55.9, 55.8, 55.4, 54.1, 53.2, 48.4, 37.1, 34.7, 20.4; IR (film): $\tilde{\nu}_{max}$ = 2924, 2854, 1712, 1604, 1459, 1272, 1204, 1162, 1094, 1047, 747, 692 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for C$_{26}$H$_{28}$O$_6$SNa: 491.1499, found 491.1364 [M+Na$^+$].

Bismethyl-monocillin 46: A solution of compound **45** (100 mg, 0.21 mmol) in MeOH (20 mL) was treated with an aqueous solution of NaIO$_4$ (68.5 mg in 200 μL of water, 0.32 mmol). The reaction was stirred for 8 h at room temperature. After extraction with EtOAc (20 mL), the organic phase was washed with saturated NH$_4$Cl$_{aq}$ (20 mL), dried over MgSO$_4$ and the solvents were evaporated under reduced pressure. The major product was isolated by flash chromatography (silica gel, 0–33% EtOAc/hexane) to recover 40 mg (40%) of sulfoxide-**45**. The resulting compound was then dissolved in toluene (10 mL) and heated up to 80 °C for 1 h. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–33% EtOAc/hexane), afforded bismethyl-monocillin **46** (24 mg, 80%), which was found to have identical proton NMR to previously reported compound **46**.[45] R_f = 0.45 (silica gel, hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, CD$_3$OH, 25 °C): δ = 7.33–7.26 (dd, J = 16.0, 11.1 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 6.34 (s, 1H), 6.23 (dd, J = 11.0, 11.0 Hz, 1H), 6.01 (d, J = 16.1 Hz, 1H), 5.90 (d, J = 11.2 Hz, 1H), 5.34–5.30 (m, 1H), 4.27 (d, J = 13.9 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.51 (d, J = 13.7 Hz, 1H), 3.22 (d, 1H, obscured by CD$_3$OD), 3.15–3.11 (m, 1H), 2.46 (d, J = 14.4 Hz, 1H), 1.56–1.52 (m, 1H), 1.51 (d, J = 6.1 Hz, 3H).

Compound 48a: A solution of compound **47** (336 mg, 2.0 mmol), compound **14a** (256 mg, 2.0 mmol) and tris(3-chlorophenyl)phosphine (1.46 g, 4.0 mmol) in anhydrous toluene (5 mL) was treated at room temperature with DIAD (788 μL, 4.0 mmol). After stirring for 3 h, the reaction mixture was diluted with EtOAc and washed several times with saturated NH$_4$Cl$_{aq}$ and brine. The organic phase was dried over MgSO$_4$, concentrated under reduced pressure and purified by flash chromatography (silica gel, 0–10% EtOAc/cyclohexane gradient) to yield compound bis-phenol-**48a** (467 mg, 84%). R_f = 0.31 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 11.84 (s, 1H), 6.29 (d, J = 2.2 Hz, 1H), 6.26 (s, 1H), 6.22 (d, J = 2.2 Hz, 1H), 5.63–5.51 (m, 1H), 5.49 (d, J = 16.1 Hz, 1H), 5.47–5.41 (m, 1H), 5.32 (d, J = 10.2 Hz, 1H), 3.18 (dd, J = 7.0, 1.6 Hz, 1H), 3.02 (m, 1H), 2.52 (s, 3H), 2.10–1.96 (m, 2H), 1.45 (d, J = 5.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, 25 °C): δ = 171.1, 165.4, 160.7, 143.9, 134.8, 120.1, 111.6, 105.4, 101.3, 69.9, 58.4, 57.3, 38.2, 24.6, 20.1; IR (film): $\tilde{\nu}_{max}$ = 2928, 1646, 1448, 1383, 1313, 1260, 1199, 1159, 1106 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for C$_{15}$H$_{18}$O$_5$Na: 301.1046, found 301.1067 [M+Na$^+$]. (−)-(2R,4S,5R): $[\alpha]_D^{20}$ = −15.0 (c 0.48, CHCl$_3$).

To a stirred solution of bis-phenol-**48a** (467 mg, 1.6 mmol) in anhydrous DMF (5.5 mL) at room temperature were added in sequential fashion: diisopropylethylamine (1.06 mL, 6.4 mmol), tetrabutylammonium iodide (catalytic) and chloromethyl methyl ether (486 μL, 6.4 mmol). The resulting solution was heated up to 80 °C and stirred for 4 h at that temperature. The reaction was then allowed to cool down to room temperature, diluted with EtOAc and washed several times with saturated NH$_4$Cl$_{aq}$. The organic phase was dried over MgSO$_4$, concentrated under reduced pressure and purified by flash chromatography (silica gel, 0–50% EtOAc/cyclohexane gradient) to yield compound **48a** (719 mg, 91%). R_f = 0.40 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, CDCl$_3$, 25 °C): δ = 6.69 (d, J = 1.6 Hz, 1H), 6.57 (d, J = 1.6 Hz, 1H), 5.60 (ddd, J = 17.2, 10.2, 7.5 Hz, 1H), 5.49 (dd, J = 17.2, 1.1 Hz, 1H), 5.42–5.36 (m, 1H), 5.30 (dd, J = 10.2, 1.1 Hz, 1H), 5.18 (s, 2H), 5.16 (d, J = 1.1 Hz, 2H),

3.49 (s, 3H), 3.48 (s, 3H), 3.18 (dd, $J=7.0$, 2.2 Hz, 1H), 3.03 (td, $J=5.6$, 2.2 Hz, 1H), 2.32 (s, 3H), 2.00 (ddd, $J=14.5$, 5.9, 5.9 Hz, 1H), 1.90 (ddd, $J=14.5$, 5.4, 5.4 Hz, 1H), 1.45 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.4, 158.6, 155.2, 137.7, 135.3, 119.2, 118.6, 110.6, 101.0, 94.6, 94.2, 69.2, 57.9, 56.9, 56.1, 56.0, 38.1, 19.9, 19.6; IR (film): $\tilde{\nu}_{max}=2933$, 1724, 1607, 1452, 1320, 1268, 1214, 1268, 1148, 1095, 1051, 1025, 926 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{19}H_{26}O_7Na$: 389.1571, found 389.1601 [M+Na$^+$]. (−)-(2*R*,4*S*,5*R*): $[\alpha]_D^{20}$ = −15.3 (*c* 0.51, $CHCl_3$).

Compound 49a: A solution of compound **48a** (366 mg, 1.0 mmol) in anhydrous THF (1 mL) was treated at −78 °C with freshly made LDA (3.8 mL, 2.0 mmol). After 5 min stirring, a solution of compound **12** (251 mg, 1.0 mmol) in THF (0.7 mL) was added dropwise. The resulting mixture was then stirred for 5 min at −78 °C and quenched by addition of a solution of saturated NH_4Cl_{aq}. Upon warming to room temperature, the reaction was diluted with EtOAc, washed several times with saturated NH_4Cl_{aq}, brine and dried over $MgSO_4$. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–10% EtOAc/cyclohexane gradient) afforded compound **49a** (450 mg, 81%) as a mixture of diastereoisomers. $R_f=0.35$ (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta=7.40$–7.35 (m, 4H), 7.33–7.30 (m, 6H), 6.69 (d, $J=2.2$ Hz, 2H), 6.57 (d, $J=2.2$ Hz, 2H), 5.83–5.77 (m, 2H), 5.63–5.44 (m, 4H), 5.35–5.26 (m, 4H), 5.16 (s, 4H), 5.14 (s, 4H), 5.18–5.08 (m, 4H), 4.10 (d, $J=16.1$ Hz, 1H), 4.07 (d, $J=16.6$ Hz, 1H), 4.02 (d, $J=16.5$ Hz, 1H), 3.97 (d, $J=16.1$ Hz, 1H), 3.85–3.77 (m, 2H), 3.48 (s, 6H), 3.46 (s, 6H), 3.13 (dd, $J=7.3$, 2.2 Hz, 2H), 3.08–3.04 (m, 2H), 2.66–2.55 (m, 2H), 2.47–2.39 (m, 2H), 1.96–1.92 (m, 4H), 1.41 (d, $J=6.4$ Hz, 6H).

Compound 50a: A solution of compound **49a** (333 mg, 0.6 mmol) in hexafluoroisopropanol (3 mL) was treated with hydrogen peroxide (35% solution in water, 117 μL, 1.2 mmol) and stirred for 3 h at room temperature. The reaction mixture was diluted in EtOAc, washed with a saturated aqueous solution of $NaHCO_3/Na_2S_2O_3$ (10:1, 11 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was then dissolved in toluene (5 mL) and stirred for 1 h at 80 °C. Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–50% EtOAc/cyclohexane gradient) afforded compound **50a** (249 mg, 92%). $R_f=0.20$ (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.22 (dd, $J=15.6$, 10.7 Hz, 1H), 6.80 (d, $J=2.2$ Hz, 1H), 6.56 (d, $J=2.2$ Hz, 1H), 6.51–6.41 (m, 1H), 6.27 (d, $J=15.6$ Hz, 1H), 5.69 (d, $J=17.2$ Hz, 1H), 5.63–5.55 (m, 2H), 5.48 (dd, $J=17.2$, 1.6 Hz, 1H), 5.34–5.26 (m, 2H), 5.17 (s, 4H), 3.94 (m, 2H), 3.49 (s, 3H), 3.48 (s, 3H), 3.14 (dd, $J=7.5$, 2.1 Hz, 1H), 3.04 (td, $J=5.9$, 2.1 Hz, 1H), 1.99–1.87 (m, 2H), 1.41 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.3, 167.0, 159.1, 156.2, 143.2, 135.4, 135.2, 135.1, 129.2, 126.7, 119.3, 118.5, 111.4, 102.5, 94.8, 94.3, 69.5, 58.1, 56.9, 56.3, 56.2, 45.9, 38.1, 19.9; HRMS (ESI-TOF): m/z: calcd for $C_{24}H_{30}O_8Na$: 469.1833, found 469.1952 [M+Na$^+$].

Compound 51a: A 2 mM solution of compound **50a** (150 mg, 0.34 mmol) in anhydrous toluene was heated at reflux and treated with 5% mol of Grubbs catalyst, 2nd generation (14 mg, 0.017 mmol). The reaction mixture was stirred for 10 min at that temperature and quenched by cooling it down to −78 °C. The reaction mixture was then filtered through a pad of silica gel, washed with CH_2CL_2 and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 0–25% EtOAc/cyclohexane gradient) afforded **51a** (122 mg, 87%). $R_f=0.19$ (silica gel, EtOAc/cyclohexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.68 (dd, $J=16.1$, 11.3 Hz, 1H), 6.75 (d, $J=2.1$ Hz, 1H), 6.59 (d, $J=2.1$ Hz, 1H), 6.26 (dd, $J=11.3$, 11.2 Hz, 1H), 6.05 (d, $J=16.1$ Hz, 1H), 5.84 (dd, $J=10.8$, 4.4 Hz, 1H), 5.42–5.33 (m, 1H), 5.21–5.17 (m, 2H), 5.14 (s, 2H), 3.97 (d, $J=14.0$ Hz, 1H), 3.86 (d, $J=13.4$ Hz, 1H), 3.57 (m, 1H), 3.48 (s, 3H), 3.47 (s, 3H), 3.13–3.10 (ddd, $J=7.5$, 3.7, 2.2 Hz, 1H), 2.47 (dt, $J=14.5$, 4.8 Hz, 1H), 1.73 (ddd, $J=15.0$, 7.5, 3.2 Hz, 1H), 1.59 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.9, 166.8, 159.2, 156.0, 140.2, 136.6, 134.5, 131.8, 130.2, 117.8, 108.7, 102.1, 94.6, 94.3, 69.8, 56.3, 55.8, 54.9, 42.4, 37.1, 29.7, 18.9; IR (film): $\tilde{\nu}_{max}=2923$, 2849, 1719, 1664, 1602, 1461, 1286, 1149, 1027, 920 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{22}H_{26}O_8Na$: 441.1520, found 441.1595 [M+Na$^+$]. (−)-(2*R*,4*S*,5*R*): $[\alpha]_D^{20}$ = −50.0 (*c* 0.11, $CHCl_3$).

Compound 53: A 2 mM solution of compound **49a** (100 mg, 0.18 mmol) in anhydrous toluene was heated at 120 °C and treated with 5% mol of Grubbs catalyst, 2nd generation (8 mg, 0.009 mmol). The reaction mixture was stirred for 10 min at that temperature and quenched quickly by cooling down to −78 °C. The reaction mixture was then filtered through a pad of silica gel, washed with CH_2Cl_2 and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 0–25% EtOAc/hexane gradient) afforded compound **53** (89 mg, 94%) as a mixture of diastereoisomers (epimers and mixture of *cis*/*trans* olefin 1:1). By preparative TLC (silica gel, 50% EtOAc/hexane), it was possible to separate the two epimers: $R_f=0.10$ (silica gel, EtOAc/hexane 1:3); *less polar* epimer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.43 (d, $J=7.0$ Hz, 2H), 7.35–7.26 (m, 3H), 6.73 (d, $J=2.4$ Hz, 1H), 6.19 (d, $J=2.1$ Hz, 1H), 5.88–5.81 (m, 1H), 5.53–5.46 (m, 1H), 5.17–5.13 (m, 1H), 5.15 (d, $J=2.4$ Hz, 2H), 5.07 (d, $J=1.2$ Hz, 2H), 4.23 (d, $J=18.7$ Hz, 1H), 4.00–3.93 (m, 1H), 3.91 (d, $J=18.7$ Hz, 1H), 3.50 (s, 3H), 3.48 (s, 3H), 3.25 (bd, $J=4.1$ Hz, 1H), 2.82–2.77 (m, 1H), 2.57–2.47 (m, 2H), 2.40–2.34 (m, 2H), 1.38 (d, $J=6.2$ Hz, 3H); *more polar* epimer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.57–7.54 (m, 2H), 7.40–7.35 (m, 3H), 6.73 (d, $J=2.0$ Hz, 1H), 6.35 (d, $J=2.0$ Hz, 1H), 5.80–5.71 (m, 1H), 5.25–5.13 (m, 5H), 5.01 (dd, $J=15.5$, 8.9 Hz, 1H), 3.98 (d, $J=19.3$ Hz, 1H), 3.81 (dd, $J=12.1$, 3.6 Hz, 1H), 3.64 (d, $J=19.3$ Hz, 1H), 3.52 (s, 3H), 3.48 (s, 3H), 3.25 (dd, $J=8.8$, 2.3 Hz, 1H), 2.79–2.76 (m, 1H), 2.65–2.50 (m, 2H), 2.44–2.29 (m, 2H), 1.37 (d, $J=6.2$ Hz, 3H).

Compound 52: Neat sulfuryl chloride (7.5 μL, 0.09 mmol) was added to a cooled (0 °C) solution of compound **51a** (13 mg, 0.03 mmol) in Et_2O (1 mL). The reaction was stirred for 1.5 h at 0 °C and then diluted with CH_2Cl_2 (5 mL). The mixture was washed several times with saturated NH_4Cl_{aq} (8 mL) and dried over $MgSO_4$. Removal of the solvents under reduced pressure, followed by flash chromatography (silica gel, 0–33% EtOAc/cyclohexane), afforded compound **52** (10 mg, 68%). $R_f=0.25$ (silica gel, EtOAc/cyclohexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.18 (dd, $J=16.2$, 11.2 Hz, 1H), 7.04 (s, 1H), 6.26 (dd, $J=10.9$, 10.9 Hz, 1H), 6.10 (d, $J=16.4$ Hz, 1H), 5.81 (dd, $J=10.2$, 10.2 Hz, 1H), 5.47 (m, 1H), 5.35–5.12 (m, 5H), 4.11 (d, $J=15.8$ Hz, 1H), 3.92 (d, $J=15.8$ Hz, 1H), 3.55 (s, 3H), 3.53 (s, 3H), 3.55–3.48 (m, 1H), 2.08–2.04 (m, 2H), 1.57 (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.3, 166.7, 159.3, 156.0, 140.8, 137.9, 134.7, 133.2, 131.2, 117.8, 102.0, 95.2, 94.6, 71.9, 69.7, 60.4, 56.7, 56.4, 45.1, 21.0, 18.8, (1$C_{quat.}$ is not visible); IR (film): $\tilde{\nu}_{max}=3075$, 2930, 1685, 1647, 1618, 1571, 1439, 1235, 1147, 1112, 1080, 1017, 942 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{22}H_{26}Cl_2O_8$: 510.9994, found 511.0002 [M+Na$^+$].

Pochonin C (8): A solution of compound **52** (10 mg, 0.02 mmol) in dioxane (5 mL) was treated at 0 °C with HCl_{conc} (125 μL, to reach a 2.5% solution). The reaction was then allowed to warm up to room temperature and stirred for 1 h. The resulting solution was filtered on a pad of silica gel and washed several times with Et_2O. The solvents were removed under reduced pressure and preparative TLC (silica gel, 50% EtOAc/cyclohexane) provided synthetic pochonin C (**8**) (6.3 mg, 74%). Synthetic pochonin C was found to have identical ^{1}H NMR as natural pochonin C (see Supporting Information). $R_f=0.11$ (silica gel, EtOAc/cyclohexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.28 (s, 1H), 8.59 (s, 1H), 7.11 (dd, $J=14.7$, 12.3 Hz, 1H), 6.66 (s, 1H), 6.31 (t, $J=10.4$ Hz, 1H), 6.10 (d, $J=16.1$ Hz, 1H), 5.91 (m, 1H), 5.78 (t, $J=9.9$ Hz, 1H), 5.22 (d, $J=15.8$ Hz, 1H), 4.92 (t, $J=9.1$ Hz, 1H), 3.96 (d, $J=15.8$ Hz, 1H), 3.95 (m, 1H), 2.48 (dd, $J=15.8$, 10.7 Hz, 1H), 2.13 (m, 1H), 1.54 (d, $J=6.4$ Hz, 3H); ^{1}H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 10.58 (s, 1H), 10.13 (s, 1H), 7.12 (dd, $J=16.1$, 11.3 Hz, 1H), 6.56 (s, 1H), 6.27 (t, $J=10.8$ Hz, 1H), 6.04 (d, $J=16.1$ Hz, 1H), 5.78 (t, $J=10.8$ Hz, 1H), 5.46 (d, $J=5.4$ Hz, 1H), 5.28 (m, 1H), 5.10 (dd, $J=9.9$, 4.8 Hz, 1H), 4.05 (d, $J=16.1$ Hz, 1H), 3.99 (m, 1H), 3.60 (d, $J=16.1$ Hz, 1H), 1.87 (m, 2H), 1.37 (d, $J=6.2$ Hz, 3H); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.28 (dd, $J=16.0$, 11.1 Hz, 1H, H_8), 6.53 (s, 1H, H_{15}), 6.25 (dd, $J=10.7$, 10.7 Hz, 1H, H_7), 6.02 (d, $J=16.6$ Hz, 1H, H_9), 5.82 (dd, $J=10.7$, 10.7 Hz, 1H, H_6), 5.47–5.43 (m, 1H, H_2), 5.20 (dd, $J=9.7$, 5.9 Hz, 1H, H_5), 4.27 (d, $J=16.1$ Hz, 1H, H_{11}), 4.03–4.00 (m, 1H, H_4), 3.73 (d, $J=16.1$ Hz, 1H, H_{11}), 2.11 (dd, $J=14.0$, 6.9 Hz, 1H, H_3), 2.00–1.92 (m, 1H, H_3), 1.48 (d, $J=6.4$ Hz, 3H, H_1); ^{13}C NMR (100 MHz, [D$_6$]DMSO, 25 °C): δ = 197.0, 166.5, 155.5, 139.1, 137.0, 133.2, 132.1, 129.9, 115.1, 112.2, 102.9, 71.1,

69.5, 60.8, 44.9, 37.8, 19.0; HMQC 2D (125.77 MHz, CD_3OD, 25 °C): δ = 199.7, 157.1, 141.0, 138.1, 134.6, 132.4, 130.8, 116.2, 114.3, 103.7, 72.6, 70.8, 60.6, 45.7, 38.1, 19.2, ($2C_{quat.}$ are not visible); HRMS (ESI-TOF): *m/z*: calcd for $C_{18}H_{18}Cl_2O_6Na$: 422.9995, found 423.0337 [*M*+Na^+]. (−)-(2*R*,4*S*,5*R*): $[\alpha]_D^{20}$ = −68.3 (*c* 0.06, $CHCl_3$).

Radicicol (1): A solution of compound **8** (5.0 mg, 0.01 mmol) in DMF (500 μL) was treated with K_2CO_3 (4.0 mg, 0.02 mmol) and stirred for 1 h at room temperature. The reaction was then diluted with EtOAc (5 mL) and washed several times with saturated NH_4Cl_{aq} (10 mL). Removal of the solvents and preparative TLC (silica gel, 50% EtOAc/cyclohexane) provided radicicol (**1**) (4.0 mg, 86%). Analisys of synthetic radicicol were found to be identical to the natural ones. R_f = 0.32 (silica gel, EtOAc/cyclohexane 1:1); ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 7.62 (dd, *J* = 16.0, 9.9 Hz, 1H, H_8), 6.48 (s, 1H, H_{15}), 6.26 (dd, *J* = 10.6, 10.6 Hz, 1H, H_7), 6.12 (d, *J* = 16.0 Hz, 1H, H_9), 5.80 (dd, *J* = 10.6, 3.8 Hz, 1H, H_6), 5.42–5.39 (m, 1H, H_2), 4.19 (d, *J* = 16.0 Hz, 1H, H_{11}), 3.95 (d, *J* = 16.4 Hz, 1H, H_{11}), 3.33 (m, 1H, H_5, obscured by CD_3OD), 3.08 (dt, *J* = 7.8, 3.1 Hz, 1H, H_4), 2.44 (dt, *J* = 14.7, 3.4 Hz, 1H, H_3), 1.74 (ddd, *J* = 18.4, 8.5, 3.7 Hz, 1H, H_3), 1.54 (d, *J* = 6.5 Hz, 3H, H_1); ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 198.2, 167.7, 159.0, 158.0, 139.2, 135.5, 133.6, 130.1, 129.4, 102.4, 70.6, 55.4, 55.1, 45.1, 36.3, 17.4, ($2C_{quat.}$ are not visible); HRMS (ESI-TOF): *m/z*: calcd for $C_{18}H_{17}ClO_6Na$: 387.0611, found 387.0795 [*M*+Na^+]. (+)-(2*R*,4*R*,5*R*): $[\alpha]_D^{20}$ = +95.3 (*c* 0.06, $CHCl_3$).

Compound 48b: In a similar manner as that described for compound **48a**, compound **48b** was prepared with a 76% yield in two steps from **47**. *Bis-phenol of **48b***: R_f = 0.30 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.81 (s, 1H), 7.29 (s, 1H), 6.30 (d, *J* = 2.2 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 5.79–5.69 (m, 1H), 5.52 (d, *J* = 16.3 Hz, 1H), 5.45–5.36 (m + s, 3H), 3.47 (m, 1H), 3.27 (m, 1H), 2.55 (s, 3H), 2.02–1.98 (m, 2H), 1.48 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.1, 165.5, 160.3, 143.9, 131.8, 120.9, 111.3, 105.8, 101.3, 70.3, 56.3, 55.3, 34.0, 24.6, 20.1; IR (film): $\tilde{\nu}_{max}$ = 2928, 1646, 1458, 1378, 1314, 1262, 1173, 1098 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{15}H_{18}O_5Na$: 301.1046, found 301.1054 [*M*+Na^+]. (−)-(2*R*,4*S*,5*S*): $[\alpha]_D^{20}$ = −16.9 (*c* 0.55, $CHCl_3$).

*Compound **48b***: R_f = 0.36 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.69 (d, *J* = 1.8 Hz, 1H), 6.57 (d, *J* = 2.4 Hz, 1H), 5.80–5.72 (ddd, *J* = 16.9, 10.5, 7.0 Hz, 1H), 5.51 (d, *J* = 16.9 Hz, 1H), 5.40 (dd, *J* = 10.5, 1.8 Hz, 1H), 5.39–5.33 (m, 1H), 5.17 (s, 2H), 5.16 (s, 2H), 3.49 (s, 3H), 3.48 (s, 3H), 3.48–3.44 (dd, *J* = 7.0, 2.3 Hz, 1H), 3.33–3.29 (m, 1H), 2.32 (s, 3H), 2.02 (ddd, *J* = 14.6, 6.5, 6.4 Hz, 1H), 1.90 (ddd, *J* = 14.6, 5.4, 5.3 Hz, 1H), 1.43 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.5, 158.7, 155.3, 137.7, 132.1, 120.7, 118.7, 110.6, 101.1, 94.6, 94.3, 69.5, 56.4, 56.2, 56.1, 55.3, 34.0, 20.1, 19.7; IR (film): $\tilde{\nu}_{max}$ = 2957, 1724, 1606, 1451, 1267, 1147, 1050, 925 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{19}H_{26}O_7$: 389.1571, found 389.1605 [*M*+Na^+]. (−)-(2*R*,4*S*,5*S*): $[\alpha]_D^{20}$ = −7.9 (*c* 0.33, $CHCl_3$).

Compound 49b: In a similar manner as that described for compound **49a**, compound **49b** was prepared in 81% yield. R_f = 0.36 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.45–7.35 (m, 4H), 7.33–7.28 (m, 6H), 6.78 (d, *J* = 2.2 Hz, 2H), 6.55 (s, 2H), 5.87–5.70 (m, 4H), 5.50 (d, *J* = 17.2 Hz, 2H), 5.38 (d, *J* = 10.2 Hz, 2H), 5.33–5.27 (m, 2H), 5.17 (s, 4H), 5.15 (s, 4H), 5.20–5.09 (m, 4H), 4.12 (d, *J* = 16.6 Hz, 1H), 4.06 (d, *J* = 16.3 Hz, 1H), 4.02 (d, *J* = 14.3 Hz, 1H), 3.98 (d, *J* = 16.6 Hz, 1H), 3.82 (t, *J* = 7.5 Hz, 1H), 3.81 (t, *J* = 7.5 Hz, 1H), 3.49 (s, 6H), 3.48 (s, 6H), 3.45–3.42 (m, 2H), 3.34–3.32 (m, 2H), 2.61–2.55 (m, 2H), 2.47–2.41 (m, 2H), 2.02–1.95 (m, 2H), 1.8 (m, 2H), 1.40 (d, *J* = 6.4 Hz, 6H).

Compound 50b: In a similar manner as that described for compound **50a**, compound **50b** was prepared in 92% yield. R_f = 0.22 (silica gel, hexane/EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.23 (dd, *J* = 15.8, 11.1 Hz, 1H), 6.80 (d, *J* = 1.8 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 1H), 6.45 (m, 1H), 6.27 (d, *J* = 15.8 Hz, 1H), 5.77–5.67 (m, 1H), 5.69 (d, *J* = 16.4 Hz, 1H), 5.57 (d, *J* = 9.4 Hz, 1H), 5.50 (d, *J* = 17.0 Hz, 1H), 5.39 (d, *J* = 9.9 Hz, 1H), 5.33–5.27 (m, 1H), 5.19 (s, 2H), 5.18 (s, 2H), 3.95 (m, 2H), 3.50 (s, 3H), 3.48 (s, 3H), 3.44 (dd, *J* = 6.4, 4.7 Hz, 1H), 3.31 (td, *J* = 10.5, 5.8 Hz, 1H), 2.00–1.94 (m, 1H), 1.84 (ddd, *J* = 14.7, 5.3, 5.3 Hz, 1H), 1.39 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.3, 167.1, 159.1, 156.3, 143.2, 135.3, 135.2, 132.2, 129.2, 126.7, 120.6, 118.5, 111.4, 102.5, 94.8, 94.3, 69.7, 56.3, 56.3, 56.2, 55.3, 46.0, 34.0, 20.0; IR (film): $\tilde{\nu}_{max}$ = 2932, 1718, 1605, 1438, 1275, 1149, 1020, 924 cm^{-1}; HRMS (ESI-TOF): *m/z*: calcd for $C_{24}H_{30}O_8Na$: 469.1833, found 469.1913 [*M*+Na^+]. (−)-(2*R*,4*S*,5*S*): $[\alpha]_D^{20}$ = −2.8 (*c* 0.18, $CHCl_3$).

Compound 51b: In a similar manner as that described for compound **51a**, compound **51b** was prepared in 21% yield. R_f = 0.19 (silica gel, EtOAc/cyclohexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.66 (dd, *J* = 15.8, 10.8 Hz, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 6.58 (d, *J* = 2.1 Hz, 1H), 6.25 (dd, *J* = 9.7, 9.7 Hz, 1H), 6.04 (d, *J* = 15.8 Hz, 1H), 5.83 (dd, *J* = 10.8, 4.3 Hz, 1H), 5.37 (m, 1H), 5.20–5.16 (m, 2H), 5.13 (s, 2H), 3.96 (d, *J* = 13.7 Hz, 1H), 3.85 (d, *J* = 13.7 Hz, 1H), 3.56 (m, 1H), 3.48 (s, 3H), 3.46 (s, 3H), 3.11–3.09 (m, 1H), 2.47 (ddd, *J* = 15.2, 5.1, 4.3 Hz, 1H), 1.71 (ddd, *J* = 15.2, 7.2, 3.0 Hz, 1H), 1.58 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.8, 166.8, 159.2, 156.1, 140.1, 136.6, 132.8, 131.8, 130.2, 114.2, 108.7, 102.1, 94.6, 94.3, 69.8, 56.3, 55.7, 54.9, 42.4, 37.1, 29.7, 18.8; HRMS (ESI-TOF): *m/z*: calcd for $C_{22}H_{26}O_8Na$: 441.1520, found 441.1599 [*M*+Na^+].

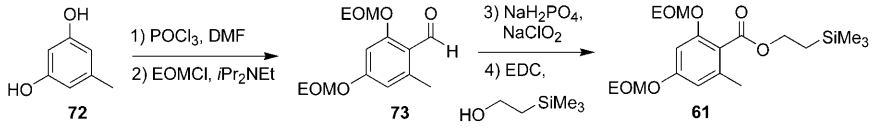
Resin 57: 3-Mercaptophenol (1.63 mL, 16.0 mmol) and K_2CO_3 (2.2 g, 16.0 mmol) were added at 23 °C to a solution of 2-chloro-*N*-methoxy-*N*-methylacetamide (2.2 g, 16.0 mmol) in dry DMF (15 mL). The resulting suspension was stirred at 23 °C for 2 h. After that period of time, the mixture was added to Merrifield resin (10 g, 1.0 mmol g^{-1}) swelled in dry DMF (100 mL), followed by K_2CO_3 (4.4 g, 32.0 mmol) as well as a catalytic amount of TBAI (tetrabutylammonium iodide), and the suspension was heated up to 50 °C. After 2 h at such temperature, the resin was filtered and washed several times: HCl_{aq} (50 mL), MeOH (50 mL), CH_2Cl_2 (50 mL) and Et_2O (50 mL). The resin was dried to constant mass under reduced pressure before use. The final mass gain of 1.72 g indicates an estimate loading of 0.77 mmol g^{-1}. A yield of 90% yield was calculated based on mass gain.

Weinreb amide 58: A catalytic amount of AIBN and nBu_3SnH (104 μL, 0.385 mmol) was added to a suspension of resin **57** (100 mg, 0.77 mmol g^{-1}) in C_6D_6 (1 mL). The resulting mixture was heated up in the microwave (150 °C, 300 W) for 10 min. After that period of time, the solution was directly subjected to a ^{1}H NMR: Crude ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 3.07 (s, 3H), 2.95 (s, 3H), 1.99 (s, 3H).

Resin 59: Resin **57** (10 g, 0.77 mmol g^{-1}) was suspended in a 1:1 mixture of HFIP/CH_2Cl_2 (100 mL, HFIP = hexafluoroisopropanol). To this suspension, H_2O_2 (3 mL, 31 mmol) was added at 23 °C and the resulting mixture was shaken overnight at room temperature. The resulting resin was then filtered, washed using MeOH (100 mL), CH_2Cl_2 (100 mL) and Et_2O (100 mL) and dried to constant mass. This resin was then suspended in dry CH_2Cl_2 (100 mL), cooled down to −78 °C and treated sequentially with allyltributyltin (11.9 mL, 38.4 mmol) and trifluoroacetic anhydride (3.27 mL, 23.1 mmol). After 10 min at that temperature, the reaction was allowed to warm up to room temperature for 1 h and then was filtered and washed several times: HCl_{aq} (100 mL), MeOH (100 mL), CH_2Cl_2 (100 mL) and Et_2O (100 mL) to obtain resin **59**. The resin was dried to constant mass under reduced pressure before use. A yield of 85% was estimated based on the NMR interpretation of **58** relatively to **60** after cleavage under free radical conditions.

α,β,γ,δ-Unsaturated Weinreb amide 54: Resin **59** (1 g) was suspended in a 1:1 mixture of HFIP/CH_2Cl_2 (10 mL). To this suspension H_2O_2 (300 μL, 3 mmol) was added at 23 °C and the resulting mixture was shaken for 12 h. The resulting resin was then filtered, washed with MeOH (100 mL), CH_2Cl_2 (100 mL) and Et_2O (100 mL) followed by toluene. This resin was resuspended in toluene (10 mL) and heated up to 80 °C for 30 min. The resulting mixture was filtrated and washed several times with more toluene. The combined toluene solutions were evaporated giving pure compound **54** (113 mg 80% yield from Merrifield resin). Compound **54** is volatile and can not be dried at 0.1 mmHg for extended time: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.33 (dd, *J* = 15.3, 11.0 Hz, 1H), 6.52 (m, 2H), 5.61 (d, *J* = 16.6 Hz, 1H), 5.48 (d, *J* = 10.2 Hz, 1H), 3.73 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.8, 143.4, 135.1, 124.7, 119.7, 61.7, 32.3; IR (film): $\tilde{\nu}_{max}$ = 2936, 1658, 1598, 1427, 1382, 1181, 1095, 1005 cm^{-1}.

γ,δ-Unsaturated Weinreb amide 60: A catalytic amount of AIBN and nBu$_3$SnH (90 μL, 0.335 mmol) was added to a solution of resin **59** (100 mg, estimated loading 0.67 mmol g^{-1}) in C_6D_6 (1 mL). The resulting mixture was heated up in the microwave (150 °C, 300 Watts) for 10 min. After that period of time, the solution was directly subjected to a ^{1}H NMR: Crude ^{1}H NMR (400 MHz, C_6D_6, 25 °C): δ = 5.97–5.90 (m, 1H), 5.15 (d, J = 17.2 Hz, 1H), 5.06 (d, J = 10.2 Hz, 1H), 3.09 (s, 3H), 2.93 (s, 3H), 2.53 (m, 2H), 2.44–2.42 (m, 2H).



72 **73** **61**

Compound 73: $POCl_3$ (65.8 mL, 706 mmol) was dropped slowly into anhydrous DMF (106 mL) at 0 °C. The resulting solution was then stirred at room temperature for 20 min. A solution of orcinol (21.9 g, 176 mmol) in anhydrous DMF (20 mL) was then added slowly and the reaction mixture was warmed up to 75 °C for 2 h. After cooling down to room temperature, the solution was poured into ice water (500 mL) and neutralized slowly with NaOH pellets. The aqueous solution was extracted several times with Et_2O (3×250 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of solvents, crude ^{1}H NMR indicated 50% conversion. Flash chromatography (silica gel, CH_2Cl_2) afforded 2,4-dihydroxy-6-methylbenzaldehyde (9.6 g, 72% based on recovery of the starting material). R_f = 0.29 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 12.41 (s, 1H), 10.13 (s, 1H), 6.25 (s, 2H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 193.4, 166.3, 165.3, 145.1, 112.9, 110.6, 100.5, 17.3; IR (KBr): $\tilde{\nu}_{max}$ = 3126, 2345, 1621, 1481, 1276, 1232 cm^{-1}.

To a solution of this product (2.9 g, 19 mmol) in anhydrous CH_2Cl_2 (40 mL), were added in a sequential fashion, diisopropylethylamine (14.0 mL, 80 mmol) and chloromethyl ethyl ether (7.42 mL, 80 mmol). The reaction was stirred at room temperature until TLC analysis indicated reaction completion (3 h). The reaction was then diluted with EtOAc (50 mL), washed with saturated NH_4Cl_{aq} (70 mL) and dried ($MgSO_4$). Evaporation of the solvents under reduced pressure afforded bis-EOM-formylated orcinol **73**, used without further purification in the next step. R_f = 0.49 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.54 (s, 1H), 6.76 (s, 1H), 6.55 (s, 1H), 5.33 (s, 2H), 5.28 (s, 2H), 3.81–3.73 (m, 4H), 2.60 (s, 3H), 1.28–1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 190.7, 162.9, 161.9, 144.2, 118.5, 112.2, 100.5, 93.5, 92.7, 64.8, 64.6, 22.2, 15.0, (1C$_{quat.}$ is not visible); IR (KBr): $\tilde{\nu}_{max}$ = 2976, 1676, 1600, 1150 cm^{-1}; ESI-TOF: m/z: calcd for $C_{14}H_{20}NaO_5$: 291; found 291 [M+Na$^+$].

Compound 61: To a solution of compound **73** (4.3 g, 16 mmol) in DMSO (40 mL) at 0 °C, were added slowly in a sequential fashion, $NaH_2PO_4 \cdot H_2O$ (12.5 g, 80 mmol) dissolved in H_2O (25 mL) and $NaClO_2$ (7.3 g, 80 mmol) dissolved in H_2O (25 mL). After stirring for 12 h, the reaction was diluted with Et_2O (80 mL), washed with saturated NH_4Cl_{aq} (70 mL) and dried ($MgSO_4$). Evaporation of the solvents under reduced pressure resulted into the corresponding acid used without further purification in the next step.

To a solution of this acid (3.9 g, 13.2 mmol) dissolved in anhydrous CH_2Cl_2 (40 mL), were added in a sequential fashion, trimethylsilylethanol (3.8 mL, 26.4 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hypochloride (EDC) (2.5 g, 13.2 mmol) and a catalytic amount of dimethylaminopyridine (DMAP). After stirring at room temperature for 30 min, the reaction was diluted with EtOAc (50 mL), washed with saturated NH_4Cl_{aq} (50 mL) and dried ($MgSO_4$). Concentration under reduced pressure, followed by flash chromatography (silica gel, 0–10% EtOAc/cyclohexane) afforded compound **61** (2.6 g, 52% over 3 steps): R_f = 0.60 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.72 (s, 1H), 6.55 (s, 1H), 5.21 (s, 4H), 4.40 (t, J = 9.2 Hz, 2H), 3.75–3.72 (m, 4H), 2.31 (s, 3H), 1.27–1.22 (m, 6H), 1.15–1.10 (m, 2H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.5, 161.5, 158.1, 139.4, 119.7, 111.1, 101.4, 93.2, 92.6, 62.6, 61.5, 15.8 (×2), 13.5, 11.0, 6.4 (×3); IR (film): $\tilde{\nu}_{max}$ = 2954, 2897, 1724, 1607, 1266 cm^{-1}; ESI-TOF: m/z: calcd for $C_{19}H_{32}NaO_6Si$: 407; found 407 [M+Na$^+$].

Resin 62: A solution of compound **61** (1.3 g, 5.4 mmol) in anhydrous THF (20 mL) was treated at −78 °C with freshly prepared LDA (19.1 mL, 10.8 mmol). In a separated flask, resin **59** (2 g, estimated loading of 0.67 mmol g^{-1}, 1.34 mmol) was swelled and cooled to at −78 °C in anhydrous THF (10 mL) and then treated with the solution of compound **61**. The resulting mixture was then stirred for 4 h at −78 °C. After that time, the resin was filtered and washed several times: saturated NH_4Cl_{aq} (30 mL), MeOH (30 mL), CH_2Cl_2 (30 mL) and Et_2O (30 mL). The resin was dried to constant mass under reduced pressure before use.

Compound 64: Resin **62** (250 mg) was suspended in a 1:1 mixture of HFIP/CH_2Cl_2 (1.2 mL). To this suspension H_2O_2 (50 μL, 0.5 mmol) was added at 23 °C and the resulting suspension was shaken for 12 h. The resulting resin was then filtered, washed using MeOH (20 mL), CH_2Cl_2 (20 mL) and Et_2O (20 mL) and toluene. This resin was resuspended in toluene (2.5 mL) and heated up to 80 °C for 30 min. The resulting mixture was filtrated and washed several times with more toluene. The combined toluene solutions were evaporated and dried overnight at 0.1 mmHg to afford pure compound **64** (40 mg, 60% yield from resin **59**): R_f = 0.49 (silica gel, EtOAc/hexane 1:3); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.23 (dd, J = 15.5, 10.8 Hz, 1H), 6.85 (d, J = 1.8 Hz, 1H), 6.56 (d, J = 1.8 Hz, 1H), 6.50–6.41 (m, 1H), 6.27 (d, J = 15.2 Hz, 1H), 5.68 (d, J = 17.0 Hz, 1H), 5.56 (m, 1H), 5.24 (s, 2H), 5.22 (s, 2H), 4.37–4.32 (m, 2H), 3.89 (s, 1H), 3.79–3.70 (m, 4H), 1.27 (t, J = 7.0 Hz, 3H), 1.25 (d, J = 7.0 Hz, 3H), 1.10–1.05 (m, 2H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.4, 167.7, 159.1, 156.4, 143.6, 143.1, 135.2, 129.2, 126.6, 124.1, 111.4, 102.9, 93.8, 93.0, 64.4 (×2), 63.4, 46.1, 17.4, 15.1, 15.0, −1.5 (×3).

Resin 66: Resin **62** (1.5 g, estimated loading 0.34 mmol g^{-1}, 0.51 mmol) was stirred in a mixture CH_2Cl_2/TFA (5:1, 10 mL) for 1 h at room temperature. After that time, the resin was filtered and washed several times: 1 N HCl_{aq} (50 mL), MeOH (50 mL), CH_2Cl_2 (50 mL) and Et_2O (50 mL). The resin was dried to constant mass under reduced pressure before use. LC-MS analysis of the oxidation elimination product showed a complete conversion, therefore giving an estimated yield of >95%.

Resin 67: A solution of resin **66** (1 g, 0.33 mmol, estimated loading 0.33 mmol g^{-1}), compound **14a** (168 mg, 1.32 mmol) and tris(3-chlorophenyl)phosphine (478 mg, 1.32 mmol) in anhydrous CH_2Cl_2 (10 mL) was treated at room temperature with DIAD (260 μL, 1.32 mmol). After stirring for 4 h, the resin was filtered and washed several times: saturated NH_4Cl_{aq} (60 mL), MeOH (60 mL), CH_2Cl_2 (60 mL) and Et_2O (60 mL). The resin was dried to constant mass under reduced pressure before use.

Triene 68: Resin **67** (~1 g, consider loading of 0.34 mmol g^{-1}) was suspended in a 1:1 mixture of HFIP/CH_2Cl_2 (10 mL). To this suspension H_2O_2 (48 μL, 0.5 mmol) was added at 23 °C and the resulting mixture was shaken for 12 h. The resulting resin was then filtered, washed using MeOH (40 mL), CH_2Cl_2 (40 mL) and Et_2O (40 mL) and dried under reduced pressure before used. Then, this resin was suspended in toluene (10 mL) and heated up to 80 °C for 12 h. The resulting mixture was filtrated and washed several times with more toluene. The combined toluene solutions were evaporated giving pure triene **68** (34 mg, 70% from resin **62**). R_f = 0.22 (silica gel, hexane/EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.8 (s, 1H), 7.52 (s, 1H), 7.30 (dd, J = 15.3, 11.5 Hz, 1H), 6.56–6.46 (m, 1H), 6.30–6.28 (m, 1H), 6.25 (s, 1H), 6.11 (d, J = 2.1 Hz, 1H), 5.74 (d, J = 17.2 Hz, 1H), 5.62 (d, J = 10.2 Hz, 1H), 5.59–5.44 (m, 2H), 5.41–5.28 (m, 2H), 4.43 (d, J = 17.7 Hz, 2H), 3.95 (d, J = 17.7 Hz, 2H), 3.10 (dd, J = 7.3, 1.9 Hz, 1H), 2.92–2.88 (m, 1H), 1.97 (dt, J = 14.2, 4.5 Hz, 1H), 1.76 (ddd, J = 14.5, 7.5, 7.5 Hz, 1H), 1.29 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 198.8, 170.2, 165.6, 161.5, 143.9, 138.7, 135.1, 134.8, 129.1, 127.4, 120.0, 113.4, 105.3, 103.0, 70.4, 58.0, 57.4, 49.4, 38.1, 20.0.

Triene 69: A solution of **68** (30 mg, 0.08 mmol) in DMF (1 mL) was treated sequentially at room temperature with imidazole (55 mg, 0.8 mmol) and TBSCl (121 mg, 0.8 mmol). After 12 h stirring at that temperature, the reaction was diluted in Et_2O (5 mL) and washed several times with saturated NH_4Cl_{aq} and brine. Evaporation of the solvents, followed by flash chromatography (silica gel, EtOAc/hexane 1:6), afforded triene **69** (42.2 mg, 90%). R_f=0.15 (silica gel, hexane/EtOAc 6:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.20 (dd, J=15.6, 10.7 Hz, 1H), 6.42 (dt, J=16.6, 10.2 Hz, 1H), 6.30–6.29 (m, 2H), 6.23 (d, J=15.1 Hz, 1H), 5.67 (d, J=16.1 Hz, 1H), 5.57–5.53 (m, 2H), 5.47 (dd, J=17.2, 1.6 Hz, 1H), 5.30–5.24 (m, 2H), 3.80 (d, J=4.3 Hz, 2H), 3.10 (dd, J=7.5, 2.2 Hz, 1H), 2.97 (td, J=5.6, 2.1 Hz, 1H), 1.93 (t, J=5.6 Hz, 2H), 1.43 (d, J=6.4 Hz, 3H), 0.99 (s, 9H), 0.98 (s, 9H), 0.26 (s, 6H), 0.25 (s, 6H).

Macrocycle 70: A 2 mM solution of triene **69** (40 mg, 0.068 mmol) in anhydrous toluene was heated at 120°C and treated with 5% mol of Grubbs catalyst, 2nd generation (3 mg, 0.0034 mmol). The reaction mixture was stirred for 10 min at that temperature and quenched quickly by cooling down to −78°C. Then, the reaction mixture was filtered through a pad of silica gel, washed with CH_2Cl_2 and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 0–25% EtOAc/cyclohexane gradient) afforded **70** (32 mg, 83%). R_f=0.10 (silica gel, hexane/EtOAc 6:1); ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.76 (dd, J=16.4, 11.5 Hz, 1H), 6.30 (d, J=1.6 Hz, 1H), 6.25 (d, J=1.6 Hz, 1H), 6.30–6.20 (m, 1H), 6.03 (d, J=16.1 Hz, 1H), 5.89 (dd, J=10.7, 3.2 Hz, 1H), 5.41–5.33 (m, 1H), 3.93 (d, J=14.0 Hz, 1H), 3.67 (d, J=14.0 Hz, 1H), 3.48 (m, 1H), 3.15–3.11 (m, 1H), 2.51 (dt, J=14.5, 3.5 Hz, 1H), 1.78–1.72 (m, 1H), 1.63 (d, J=6.4 Hz, 3H), 0.98 (s, 9H), 0.97 (s, 9H), 0.27 (s, 6H), 0.25 (s, 6H); HRMS (ESI-TOF): m/z: calcd for $C_{30}H_{46}O_6Si_2$: 559.2906, found 559.2878 [M+H$^+$].

Compound 48a: Polymer-assisted synthesis: A solution of 2,4-dihydroxy-6-methyl-benzoic acid (336 mg, 2.0 mmol), compound **14a** (256 mg, 2.0 mmol) and tris(3-chlorophenyl)phosphine (1.46 g, 4.0 mmol) in anhydrous CH_2Cl_2 (32 mL) was treated at room temperature with polymer-bound DEAD (3.2 g, 1.3 mmol g^{-1}). After stirring for 3 h, the reaction mixture was filtrated on silica and washed with hexane/EtOAc (10:1, 50 mL) and hexane/EtOAc (3:1, 50 mL). The 3:1 mixture was concentrated under reduce pressure to yield bis-phenol-**48a** (460 mg, 83%).

To a stirred solution of bis-phenol-**48a** (460 mg, 1.6 mmol) in anhydrous DMF (10 mL) at room temperature were added in sequential fashion: diisopropylethylamine (1.1 mL, 6.4 mmol), tetrabutylammonium iodide TBAI (catalytic) and chloromethyl methyl ether (500 μL, 6.4 mmol). The resulting solution was heated up to 80°C and stirred for 3 h at that temperature. The reaction was then allowed to cool down to room temperature, diluted with EtOAc and washed several times with saturated NH_4Cl_{aq}. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to provide compound **48a** as a crude (600 mg, >95%).

Resin 71: A solution of crude compound **48a** (500 mg, 1.36 mmol) in anhydrous THF (3 mL) was treated at −78°C with freshly made LDA (4.8 mL, 2.72 mmol). After 5 min stirring at that temperature, the solution was added over resin **59** (380 mg, 0.27 mmol, estimated loading 0.74 mmol g^{-1}) pre-swelled and cooled at −78°C in THF (4 mL). The resulting mixture was then stirred for 4 h at −78°C, and then, the reaction was filtered and washed several times: saturated NH_4Cl_{aq} (30 mL), MeOH (30 mL), CH_2Cl_2 (30 mL) and Et_2O (30 mL). The resin was then dried to constant mass under reduced pressure before use.

Triene 50a from resin 71: Resin **71** (~380 mg) was suspended in a 1:1 mixture of HFIP/CH_2Cl_2 (4 mL). To this suspension H_2O_2 (110 μL, 1.1 mmol) was added at 23°C and the resulting mixture was shaken for 12 h. The resulting resin was then filtered, washed using MeOH (40 mL), CH_2Cl_2 (40 mL) and Et_2O (40 mL) and dried under reduced pressure before used. Then, this resin was suspended in toluene (4 mL) and heated up to 80°C for 12 h. The resulting mixture was filtrated and washed several times with more toluene. The combined toluene solutions were evaporated giving pure compound **50a** (66 mg, 53% after 3 steps).

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[1] P. Delmotte, J. Delmotte-Plaquee, *Nature* **1953**, *171*, 344.
[2] F. McCapra, A. I. Scott, P. Delmotte, J. Delmotte-Plaquee, N. S. Bhacca, *Tetrahedron Lett.* **1964**, 869–875.
[3] R. N. Mirrington, E. Ritchie, C. W. Shoppee, W. C. Taylor, S. Sternhell, *Tetrahedron Lett.* **1964**, 365–370.
[4] H. G. Cutler, R. F. Arrendale, J. P. Springer, P. D. Cole, R. G. Roberts, R. T. Hanlin, *Agric. Biol. Chem.* **1987**, *51*, 3331–3338.
[5] M. Lampilas, R. Lett, *Tetrahedron Lett.* **1992**, *33*, 773–776.
[6] M. Lampilas, R. Lett, *Tetrahedron Lett.* **1992**, *33*, 777–780.
[7] H. J. Kwon, M. Yoshida, Y. Fukui, S. Horinouchi, T. Beppu, *Cancer Res.* **1992**, *52*, 6926–6930.
[8] S. V. Sharma, T. Agatsuma, H. Nakano, *Oncogene* **1998**, *16*, 2639–2645.
[9] T. W. Schulte, S. Akinaga, S. Soga, W. Sullivan, B. Stensgard, D. Toft, L. M. Neckers, *Cell Stress Chaperones* **1998**, *3*, 100–108.
[10] J. S. Isaacs, W. Xu, L. Neckers, *Cancer Cell* **2003**, *3*, 213–217.
[11] D. D. Mosser, R. I. Morimoto, *Oncogene* **2004**, *23*, 2907–2918.
[12] U. Banerji, I. Judson, P. Workman, *Curr. Cancer Drug Targets* **2003**, *3*, 385–390.
[13] I. Tichkowsky, R. Lett, *Tetrahedron Lett.* **2002**, *43*, 3997–4001.
[14] I. Tichkowsky, R. Lett, *Tetrahedron Lett.* **2002**, *43*, 4003–4007.
[15] R. M. Garbaccio, S. J. Stachel, D. K. Baeschlin, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 10903–10908.
[16] S. Soga, L. M. Neckers, T. W. Schulte, Y. Shiotsu, K. Akasaka, H. Narumi, T. Agatsuma, Y. Ikuina, C. Murakata, T. Tamaoki, S. Akinaga, *Cancer Res.* **1999**, *59*, 2931–2938.
[17] T. Agatsuma, H. Ogawa, K. Akasaka, A. Asai, Y. Yamashita, T. Mizukami, S. Akinaga, Y. Saitoh, *Bioorg. Med. Chem.* **2002**, *10*, 3445–3454.
[18] Y. Ikuina, N. Amishiro, M. Miyata, H. Narumi, H. Ogawa, T. Akiyama, Y. Shiotsu, S. Akinaga, C. Murakata, *J. Med. Chem.* **2003**, *46*, 2534–2541.
[19] Z.-Q. Yang, X. Geng, D. Solit, C. A. Pratilas, N. Rosen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2004**, *126*, 7881–7889.
[20] K. Yamamoto, R. M. Garbaccio, S. J. Stachel, D. B. Solit, G. Chiosis, N. Rosen, S. J. Danishefsky, *Angew. Chem.* **2003**, *115*, 1318–1322; *Angew. Chem. Int. Ed.* **2003**, *42*, 1280–1284.
[21] S. M. Roe, C. Prodromou, R. O'Brien, J. E. Ladbury, P. W. Piper, L. H. Pearl, *J. Med. Chem.* **1999**, *42*, 260–266.
[22] B.-G. Yun, W. Huang, N. Leach, S. D. Hartson, R. L. Matts, *Biochem. J.* **2004**, *43*, 8217–8229.
[23] T. Langer, H. Schlatter, H. Fasold, *Cell Biol. Int.* **2002**, *26*, 653–657.
[24] M. G. Marcu, A. Chadli, I. Bouhouche, M. Catelli, L. M. Neckers, *J. Biol. Chem.* **2000**, *275*, 37181–37186.
[25] G. Chiosis, B. Lucas, H. Huezo, D. Solit, A. Basso, N. Rosen, *Curr. Cancer Drug Targets* **2003**, *3*, 371–376.
[26] M. Vilenchik, D. Solit, A. Basso, H. Huezo, B. Lucas, H. He, N. Rosen, C. Spampinato, P. Modrich, G. Chiosis, *Chem. Biol.* **2004**, *11*, 787–797.
[27] V. Hellwig, A. Mayer-Bartschmid, H. Mueller, G. Greif, G. Kleymann, W. Zitzmann, H.-V. Tichy, M. Stadler, *J. Nat. Prod.* **2003**, *66*, 829–837.
[28] S. Barluenga, P. Lopez, E. Moulin, N. Winssinger, *Angew. Chem.* **2004**, *116*, 3549–3552; *Angew. Chem. Int. Ed.* **2004**, *43*, 3467–3470.
[29] E. Moulin, V. Zoete, S. Barluenga, M. Karplus, N. Winssinger, *J. Am. Chem. Soc.* **2005**, *127*, 6999–7004.

[30] J. Ninomiya-Tsuji, T. Kajino, K. Ono, T. Ohtomo, M. Matsumoto, M. Shiina, M. Mihara, M. Tsuchiya, K. Matsumoto, *J. Biol. Chem.* **2003**, *278*, 18485–18490.
[31] W. P. Neumann, J. Pedain, *Tetrahedron Lett.* **1964**, 2461–2465.
[32] H. Tanaka, K. Nishida, K. Sugita, T. Yoshioka, *Jpn. J. Cancer Res.* **1999**, *90*, 1139–1145.
[33] M. Matteucci, G. Bhalay, M. Bradley, *Org. Lett.* **2003**, *5*, 235–237.
[34] K. S. Ravikumar, J.-P. Begue, D. Bonnet-Delpon, *Tetrahedron Lett.* **1998**, *39*, 3141–3144.
[35] P. L. Creger, *J. Am. Chem. Soc.* **1970**, *92*, 1396–1397.
[36] T. Laube, J. D. Dunitz, D. Seebach, *Helv. Chim. Acta* **1985**, *68*, 1373–1393.
[37] A survey of the literature revealed that most Mitsunobu esterification on 2-hydroxybenzoic acid were carried out with the hydroxy group in the 2-position left unprotected. The benefit of this free phenol presumably comes from the hydrogen bond it forms with the acid thereby increasing the acidity of the benzoic acid which is known to accelerate the reaction.
[38] S. Jayaraman, S. Hu, A. C. Oehlschlager, *Tetrahedron Lett.* **1995**, *36*, 4765–4768.
[39] S. Hu, S. Jayaraman, A. C. Oehlschlager, *J. Org. Chem.* **1996**, *61*, 7513–7520.
[40] C. Hertweck, W. Boland, *Eur. J. Org. Chem.* **1998**, 2143–2148.
[41] U. Schlede, M. Nazare, H. Waldmann, *Tetrahedron Lett.* **1998**, *39*, 1143–1144.
[42] A. K. Chatterjee, J. P. Morgan, M. Scholl, R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.
[43] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956.
[44] K. Yamamoto, K. Biswas, C. Gaul, S. J. Danishefsky, *Tetrahedron Lett.* **2003**, *44*, 3297–3299.
[45] A. Fürstner, G. Seidel, N. Kindler, *Tetrahedron* **1999**, *55*, 8215–8230.
[46] R. N. Mirrington, E. Ritchie, C. W. Shoppee, S. Sternhell, W. C. Taylor, *Aust. J. Chem.* **1966**, *19*, 1265–1284.
[47] R. M. Garbaccio, S. J. Danishefsky, *Org. Lett.* **2000**, *2*, 3127–3129.
[48] O. Mitsunobu, *Synthesis* **1981**, 1–28.
[49] D. L. Hughes, R. A. Reamer, J. J. Bergan, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1988**, *110*, 6487–6491.
[50] C. W. Lee, R. H. Grubbs, *Org. Lett.* **2000**, *2*, 2145–2147.
[51] J. A. Elix, S. Norfolk, *Aust. J. Chem.* **1975**, *28*, 1113–1124.
[52] Synthetic pochonin C was found to have identical NMR spectra to natural pochonin D (spectra were kindly provide by Marc Stadler, Bayer Health Care, Wuppertal, Germany).
[53] C. N. Lewis, P. L. Spargo, J. Staunton, *Synthesis* **1986**, 944–946.
[54] E. A. Couladouros, A. P. Mihou, E. A. Bouzas, *Org. Lett.* **2004**, *6*, 977–980.

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