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Total synthesis of (−)-salicylihalamide A and related congeners

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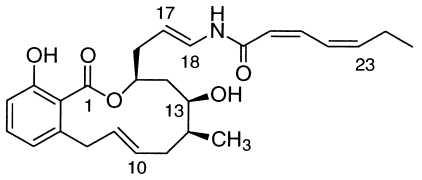
Dedicated to Professor Yoshito Kishi, on the occasion of the 2001 Tetrahedron Prize, with admiration and respect for his many seminal contributions to chemistry

Abstract—A concise, highly efficient total synthesis of (−)-salicylihalamide A (**1**), a novel marine sponge metabolite, has been achieved. Key features of the synthetic strategy include a highly *E*-selective ring-closing metathesis to construct the 12-membered salicylihalamide A macrocycle and a practical method for installation of the labile ene-hepta-(*Z*,*Z*)-dienamide side chain involving *N*-acylation of enecabarmate **5**, the latter derived from the corresponding α,β-unsaturated carboxylic acid **28** via acyl azide formation and thermal Curtius rearrangement. Two structurally simplified analogs (**3** and **4**) were also prepared which displayed significant, but attenuated cell growth inhibitory activity against several human tumor cell lines. © 2002 Published by Elsevier Science Ltd.

1. Introduction

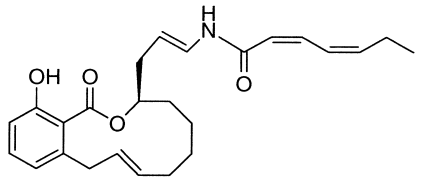
Salicylihalamides A and B (**1** and **2**; Fig. 1) comprise a novel class of secondary metabolites isolated by Boyd and co-workers[1] in 1997 from the marine sponge *Haliclona*. Detailed NMR studies revealed that salicylihalamide A (**1**) possesses a medium-sized salicylate macrolide, in conjunction with a novel dienylenamide sidechain. The absolute configuration, 12*S*, 13*R*, 15*S*, was secured by De Brabander and co-workers[2] in conjunction with their syntheses of both (+) and (−)-salicylihalamides A (**1**).[3] Salicylihalamide A (**1**) displays potent cytotoxicity in the NCI 60-cell line human tumor assay, with a mean GI_{50} value of 15 nM.[1] The COMPARE pattern-recognition analysis[4] revealed that the mean-graph profiles do not correlate with any of the profiles of known antitumor agents within the NCI database, thereby suggesting a novel mechanism of action. Recent pharmacological studies however do indicate that salicylihalamide A selectively inhibits mammalian vacuolar-type (H^+)-ATPase (V-ATPase).[5] Unfortunately, further biological studies directed at defining the mode of action of (−)-salicylihalamide A (**1**) have been significantly hampered by the limited availability of material from natural sources.

Since the discovery of the salicylihalamides, a growing number of structurally related, bioactive metabolites have been isolated and characterized, including the apicularens,[6] the lobatamides,[7] the oximidines,[8] CJ-12950,[9] and CJ-13357,[9] all of which share the salicylic acid moiety and a similar highly unsaturated enamide side chain common to the salicylihalamides. In the case of the apicularens, the side chains are identical with those of the

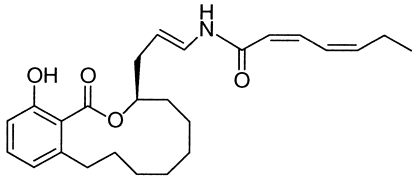


(–)-Salicylihalamide A (**1**): 17(E)

(–)-Salicylihalamide B (**2**): 17(Z)



(–)-**3**



(–)-**4**

Figure 1.

Keywords: salicylihalamide; total synthesis; macrocycles; metathesis; Curtius rearrangement.

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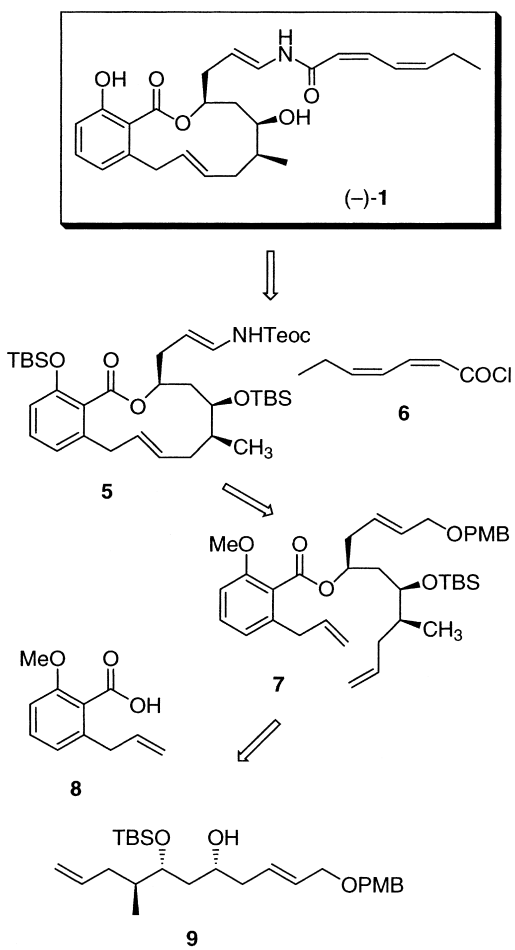
salicylihalamides, while those of other members terminate in various *O*-methyl oximes.

The unprecedented highly unsaturated enamide side chain of the salicylihalamides, in conjunction with both the potent cytotoxicities and their scarcity, has engendered considerable interest within the synthetic community, including successful total syntheses by De Brabander,[2] Labrecque,[10] Snider,[11] Fürstner,[12] and our group.[13] In addition, a number of synthetic approaches towards the ring system[14] and strategic procedures for construction of the labile enamide side chain[15] have been disclosed. Herein, we describe a full account of our total synthesis of the naturally occuring enantiomer of (−)-salicylihalamide A (**1**), in conjunction with the preparation of two functionally simplified analogs (**3** and **4**). We have previously communicated the synthesis of the unnatural enantiomer, (+)-salicylihalamide A.[13] Evaluation of the biological activities of (−)-salicylihalamide A (**1**) and the analogs (**3** and **4**) is also presented.

2. Result and discussions

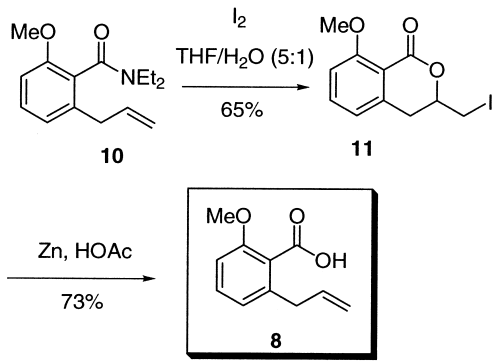
2.1. Total synthesis of (−)-salicylihalamide A

From the retrosynthetic perspective, we reasoned that the sensitive enamide side chain would best be installed at a late stage of the synthesis via *N*-acylation of an advanced enecarbamate (**3**) with (*Z*,*Z*)-dienyl chloride **6** (Scheme 1).[16] For the construction of the macrocycle, we envisioned ring closing metathesis (RCM).[17] Although at the outset of this synthetic venture, ring closing metatheses had been used to form 12-member macrolactones,[17] the high *E*-selectivity could not be assured. Mitsunobu esterification[18] of alcohol **9** and *O*-methyl-6-allylsalicylic acid **8** would provide **7**, the requisite diene substrate for the metathesis process.



Scheme 1.

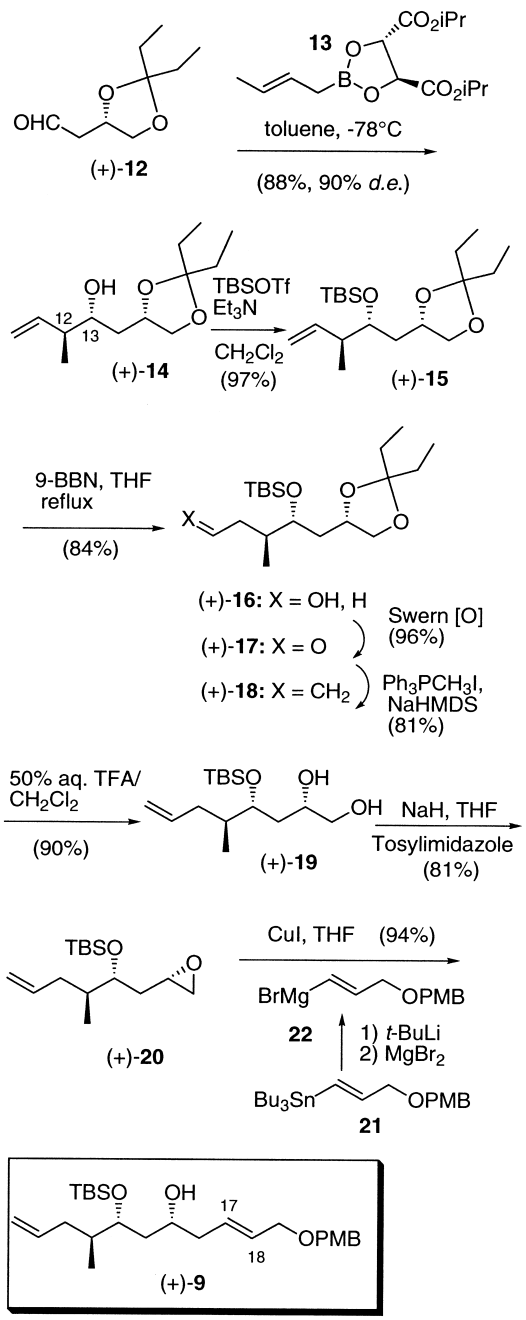
The synthesis of salicylic acid **8** was achieved as described in Scheme 2. Exposure of known amide **10**[19] (available in two steps from *O*-methyl salicylic acid chloride) to iodine in THF/H_2O (5:1) furnished iodolactone **11**, which in turn was converted to acid **8** by treatment with zinc in acetic acid.[20]



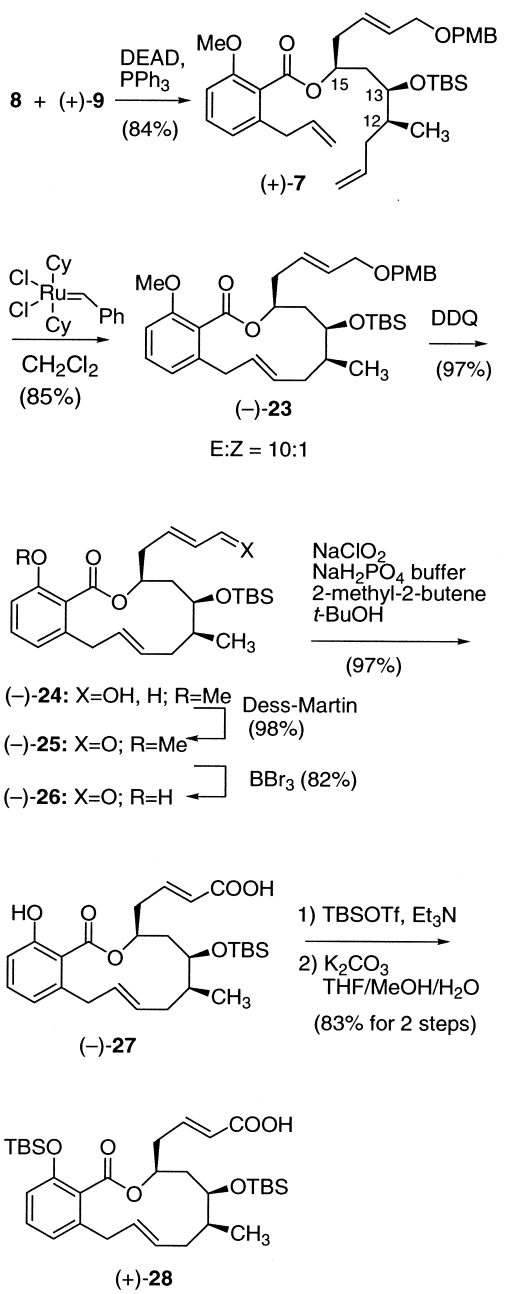
Scheme 2.

Our point of departure for the required coupling partner alcohol **9** (Scheme 3), was known aldehyde (+)-**12**,[21] readily prepared from natural *S*-malic acid in three steps. Roush crotylboration[22] furnished alcohol (+)-**14** (90% de), which was protected as the *tert*-butyldimethylsilyl ether (+)-**15**. A three-step homologation involving hydroboration,[23] Swern oxidation[24] and Wittig methylenation.[25] led to olefins (+)-**18**. Exposure to aqueous trifluoroacetic acid[26] then furnished diol (+)-**19**, which was converted to the terminal epoxide (+)-**20** exploiting the Kishi epoxide protocol.[27] Treatment of the latter with vinyl Grignard **22** in presence of a catalytic amount of CuI afforded secondary alcohol (+)-**9**.[28] The required Grignard reagent (**22**) was prepared from the known vinyltin **21**[29] by transmetalation with *n*-BuLi[30] and treatment with $MgBr_2$.[31] Interestingly, attempts to open epoxide (+)-**20** with a variety of higher order cuprates[32] derived from the corresponding vinyl lithium failed to furnish (+)-**9**. From the synthetic perspective, it is noteworthy that this sequence results in introduction of the future *C*(17) and *C*(18) enamide carbons.

Esterification of acid **8** with alcohol (+)-**9** exploiting the Mitsunobu protocol[18] then furnished the olefin metathesis substrate (+)-**7**, possessing the required stereogenic centers at C(12, 13 and 15) for (−)-salicylihalamide A (**1**) (Scheme 4). Pleasingly, treatment of (+)-**7** (0.008 M in CH_2Cl_2) with the Grubbs catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$ (10 mol%) generated the salicylihalamide macrolide (−)-**23** as a mixture of double bond isomers (ca. 10:1), favoring the desired *E*-congener. Similar ring-closing metathesis selectivities were observed by De Brabander[2] and Labrecque[10] in their total syntheses of (−)-salicylihalamide A (**1**).



Scheme 3.

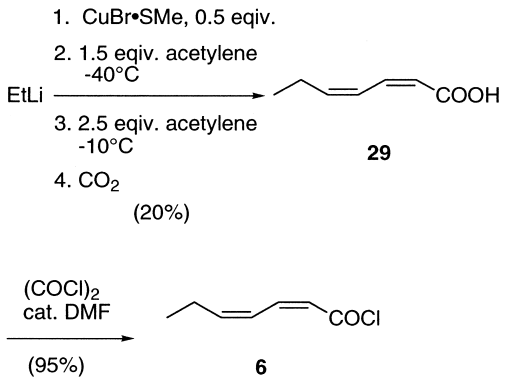


Scheme 4.

Although RCM-based macrocyclizations are known to be reversible processes and usually provide *E*,*Z*-mixtures, often favoring the thermodynamically more stable isomer,[33] De Brabander and co-workers have demonstrated that the highly *E*-selective RCM in the case of salicylihalamide macrolactone skeleton employing the first generation Grubbs catalyst derives from kinetic control.[2]

Continuing with elaboration of the (−)-salicylihalamide A (**1**), attempts to achieve removal of the anisole methyl and PMB moieties in one step using various Lewis acid[34] (i.e., BBr_3, BCl_3, TMSI) failed, furnishing instead allylic halide by-products. The PMB protecting group could however be removed with DDQ to provide primary allylic alcohol (−)-**24**, which in turn was oxidized to enal (−)-**25** via the Dess–Martin protocol.[35] Treatment of enal (−)-**25** with BBr_3[34] then cleanly removed the anisole methyl to provide phenol (−)-**26**. Subsequent oxidation afforded acid (−)-**27**, which in turn was converted to acid (+)-**28** after silylation of both the *C*(3) hydroxyl and acid moieties with TBSOTf (Et_3N) and base-mediated saponification.[36]

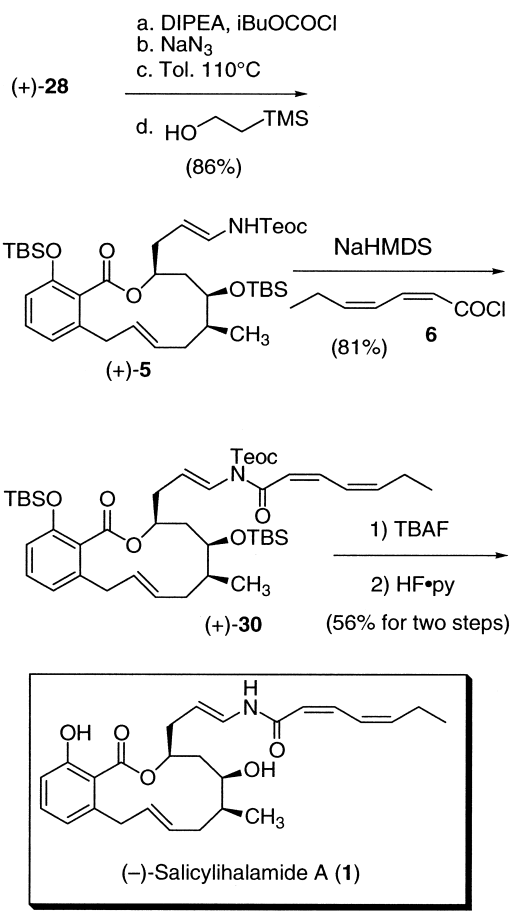
In anticipation of the *N*-acylation tactic to install the salicylihalamide side chain, we turned to the synthesis of acid chloride **6** (Scheme 5). Following the procedure of Taylor and co-workers[37] for the synthesis of the closely related *Z*,*Z*-nonadienoic acid, ethyl lithium (prepared by lithium–halogen exchange between *t*-BuLi and ethyl iodide) was treated sequentially with the $CuBr{\cdot}SMe_2$ complex (0.5 equiv.) and acetylene (1.5 equiv., introduced



Scheme 5.

as a measured volume of gas) at −40°C to generate the corresponding (*Z*)-alkenyl cuprate. Introduction of an additional 2.5 equiv. of acetylene at −10°C resulted in the addition of the (*Z*)-alkenyl cuprate to acetylene. The resulting *Z*,*Z*-dienylcuprate was then trapped with carbon dioxide to furnish dienyl acid **29** as a single isomer, albeit in only 20% overall yield. Preparation of acid chloride **6** then proceeded in a straightforward manner upon treatment with oxalyl chloride in the presence of a catalytic amount of DMF.

With ample quantities of both **6** and (+)-**28** in hand, the stage was set to incorporate the enamide side chain. Towards this end, exposure of (+)-**28** (Scheme 6) to



Scheme 6.

Hünig's base, *i*-BuOCOCl and then aqueous NaN_3 á la Weinstock,[38] followed by warming to effect the facile Curtius rearrangement and capture of the resultant isocyanate with 2-(trimethylsilyl)-ethanol furnished enecarbamate (+)-**5** in excellent overall yield (86%). *N*-acylation then proceeded smoothly via exposure of (+)-**5** to NaHMDS, followed by acid chloride **6** to yield (+)-**30**.[16] From the synthetic perspective, this stepwise procedure proved to be an efficient, practical method for incorporation of the salicylihalamide side chain. The Teoc and the aryl TBS protecting groups were then removed by treatment with TBAF. Interestingly, the secondary TBS ether proved quite resistant. In the end, the secondary TBS moiety was removed by treatment with HF·py in THF and pyridine (3:1), as described by De Brabander,[2] to afford (−)-salicylihalamide A (**1**), possessing spectra and chiroptic properties identical in all respects to those reported of the natural product [e.g., ^{1}H (500 MHz), ^{13}C NMR (125 MHz), IR, HRMS and $[\alpha]_D^{25}=-22.8°$ (*c* 0.11, MeOH); lit.[1] $[\alpha]_D^{25}=-35°$ (*c* 0.70, MeOH)].

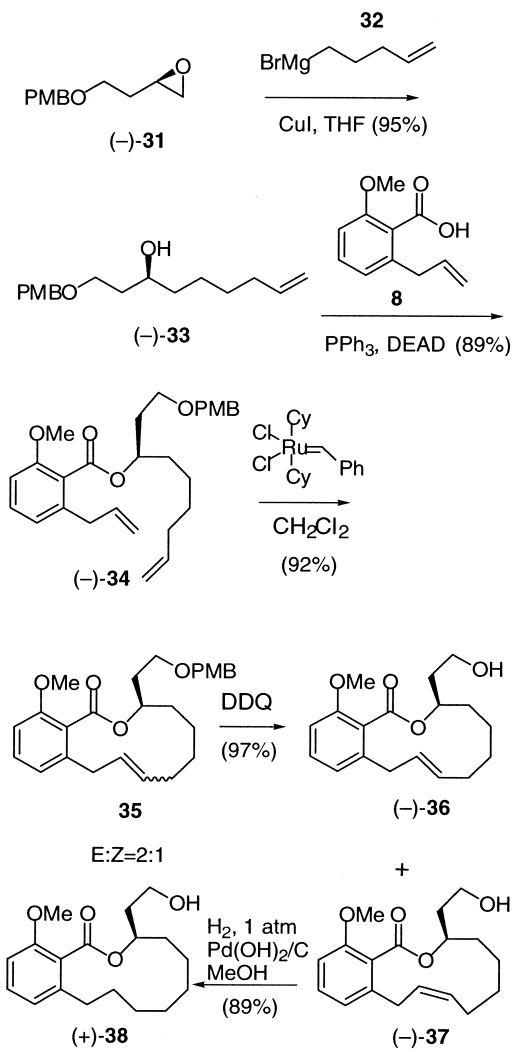
2.2. Analogs of the salicylihalamide A

The first study on the structure–activity relationships (SAR) of (−)-salicylihalamide A (**1**), reported recently by De Brabander and co-workers,[2] revealed that the characteristic *N*-acyl enamine functionality is essential for activity, and as they propose may lead to covalent bond with the putative binding protein via a protonation/addition reaction sequence.[39] Interestingly, analogs lacking the enoyl functionality also displayed significant cell growth inhibitory activity.

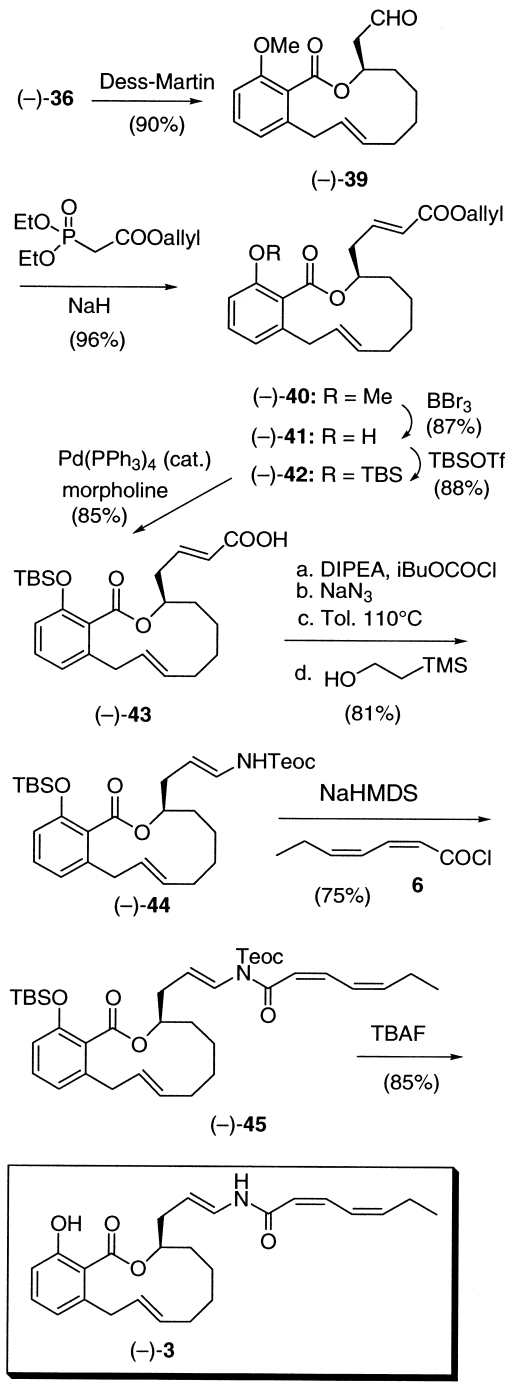
In view of the potential of (−)-salicylihalamide A (**1**) as a lead compound for cancer chemotherapy, we sought to prepare a number of simplified analogs with similar or hopefully improved cytotoxicity. At the outset, we chose to investigate the importance of structural elements present on the (−)-salicylihalamide A macrolactone ring. We therefore selected analogs **3** and **4** (Fig. 1) as initial targets.[40]

Construction of **3** and **4** began with known epoxide (−)-**31**,[41] available in three steps (56% yield) from *S*-aspartic acid (Scheme 7). Secondary alcohol (−)-**33** was prepared by treatment of epoxide (−)-**31** with Grignard **32**, available from 1-bromo-5-hexene and magnesium. Esterification of salicylic acid **8** again exploiting the Mitsunobu protocol,[18] provided diene (−)-**34**. In contrast to the high E-selectivity observed in the total synthesis of **1**, ring closing metathesis[17] afforded an inseparable mixture (2:1/*E*:*Z*) of cyclic congeners. Removal of the PMB group followed by careful column chromatography then afforded the isomeric lactones (−)-**36** (*E*) and (−)-**37** (*Z*). The *Z*-isomer (−)-**37** was hydrogenated to give lactone (+)-**38**.

To access analog **3**, we employed the *E*-isomer (−)-**36** (Scheme 8). Oxidation with Dess–Martin periodinane[35] afforded aldehyde (−)-**39**. In accordance with the De Brabander synthesis of (−)-salicylihalamide A (**1**),[2] Horner–Wadsworth–Emmons homologation employing allyl diethylphosphono-acetate delivered allyl ester (−)-**40** as the *E*-isomer. The anisole methyl group was next removed with BBr_3.[34] Silylation of the resultant phenol to



Scheme 7.



Scheme 8.

afford (−)-**42** was followed by removal of the allyl ester with catalytic $Pd(PPh_3)_4$ in the presence of morpholine to furnish carboxylic acid (−)-**43**,[42] which was readily converted to enecarbamate (−)-**44**, exploiting the stepwise introduction of the enamide side chain as employed to great advantage in our synthesis of the (−)-salicylihalamide A (**1**). Construction of (−)-**3** was then achieved via *N*-acylation with acid chloride **6** to furnish (−)-**45**, followed by exposure to TBAF.

In a similar fashion, the saturated lactone (+)-**38** was converted to analog (−)-**4** (Scheme 9).

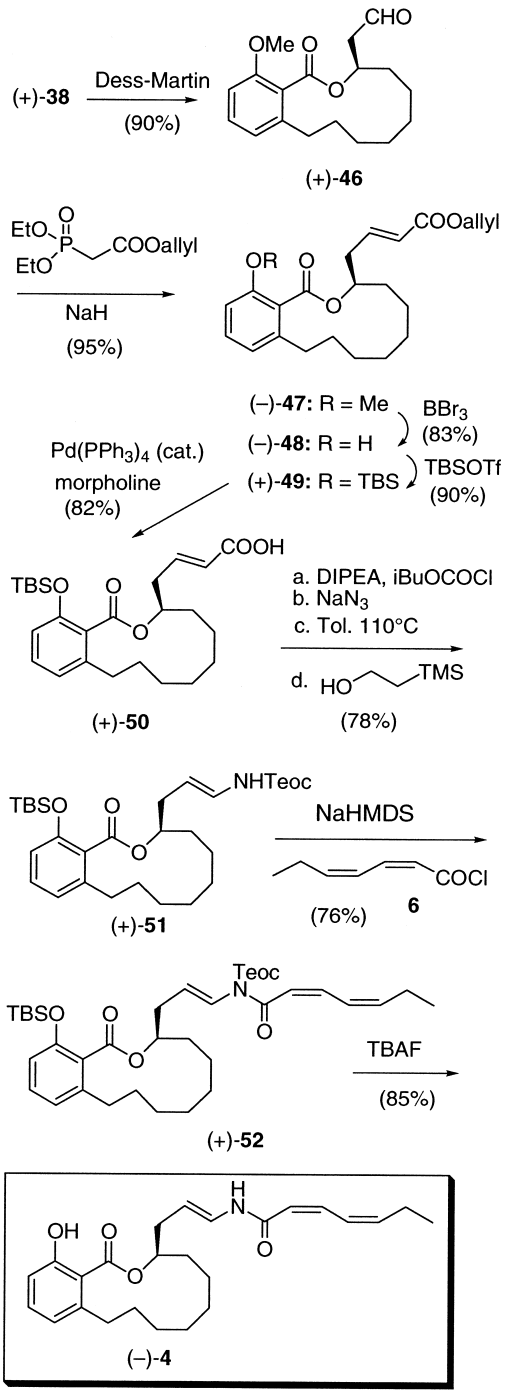
2.3. Biological evaluation

(−)-Salicylihalamide A (**1**) and the structurally simpler analogs (−)-**3** and (−)-**4** were screened in vitro against a series of cell lines for their growth inhibitory activity. Representative cytotoxicity data are presented in Table 1.

As illustrated, analogs (−)-**3** and (−)-**4** retained significant, albeit attenuated activity. Interestingly, removal of the endocyclic olefin reduces the activity (i.e., (−)-**4** vs (−)-**3**). These observations suggest that the structure elements on the lactone ring may be important, but not critical for activity. Presumably their function is to orchestrate the optimal orientation between the side chain and salicylate substituents for receptor binding.

3. Summary

We have achieved an efficient total synthesis of (−)-salicylihalamide A (**1**) in 20 steps from aldehyde (+)-**12**, with an overall yield of 7.4%. The synthesis features both a highly *E*-selective RCM to form the macrolactone ring and an efficient, practical protocol for manipulation of the labile enamide side chain. In addition, we prepared two



Scheme 9.

Table 1. Biological evaluation of salicylihalamide A analogs **3** and **4**

Cell type	Cell line	GI_{50} ($\times 10^{-2}$ μg/mL)		
		1	**3**	**4**
Pancreas-a	BXPC-3	8.0	46	88
Breast adn	MCF-7	7.4	57	48
CNS gliobl	SF268	8.0	11	37
Lung-NSC	NCI-H460	7.3	56	65
Colon	KM20L2	3.8	15	71
Prostate	DU-145	8.1	87	78

structurally simplified analogs ((−)-**3** and (−)-**4**), which retain significant cell growth inhibitory activity.

4. Experimental

4.1. Materials and methods

All reactions were carried out under argon with dry, freshly distilled solvents, vacuum-flamed glassware, and magnetic stirring, unless otherwise stated. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone; benzene and toluene were distilled from sodium, and dichloromethane (CH_2Cl_2) from calcium hydride. Triethylamine, diisopropylethylamine and pyridine were distilled from calcium hydride and stored over KOH. Dimethylsulfoxide (DMSO) was distilled from calcium hydride and stored over 4 Å molecular sieves. All reactions were monitored by thin layer chromatography (TLC) using 0.25 mm E. Merck precoated silica gel plates. Flash chromatography was performed with the indicated solvents and E. Merck silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds, except as otherwise indicated. All melting points were obtained on a Thomas–Hoover apparatus and are corrected. Infrared spectra were recorded on a Perkin–Elmer Model 283B spectrophotometer. Proton NMR spectra were recorded on Bruker AM-500 or Bruker DRX-500 spectrometer; ^{13}C NMR spectra were recorded on a Bruker AM500 instrument. Chemical shifts are reported in δ values relative to tetramethylsilane. Optical rotations were measured with a Perkin–Elmer Model 241 polarimeter in the solvent indicated. High resolution mass spectra were obtained at the University of Pennsylvania Mass Spectrometry Center on either a VG Micromass 70/70H or VG ZAB-E spectrometer.

4.1.1. Alkyl iodide 11. To a solution of **10** (150 mg, 0.607 mmol) in THF (3 mL) and H_2O (1 mL) was added I_2 (770 mg, 3.036 mmol). The solution was stirred at ambient temperature for 24 h, then quenched with saturated $Na_2S_2O_3$ solution until the color of the iodine disappeared, added to brine (20 mL) and extracted with Et_2O (2×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 2:1) provided **11** (126 mg, 65% yield) as a light yellow oil: IR ($CHCl_3$): 2850 (s), 1720 (s), 1580 (s), 1470 (s), 1440 (s), 1275 (s), 1230 (s), 1070 (s), 1050 (s), 920 s), 750 (s), 650 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (t, J=8.4 Hz, 1H), 6.92 (d, J=8.6 Hz, 1H), 6.80 (d, J=8.1 Hz, 1H), 4.45 (m, 1H), 3.93 (s, 3H), 3.45 (dd, J=10.4, 4.8 Hz, 1H), 3.35 (dd, J=10.5, 7.4 Hz, 1H), 3.15 (dd, J=15.9, 3.0 Hz, 1H), 3.04 (dd, J=16.0, 10.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 161.1, 140.5, 134.8, 119.5, 113.1, 111.2, 76.3, 56.2, 34.2, 5.1; high resolution mass spectrum (ESI, Na) m/z 340.9668 [$(M+Na)^+$; calcd for $C_{11}H_{11}IO_3Na$: 340.9651].

4.1.2. Acid 8. To a solution of **11** (114 mg, 0.358 mmol) in acetic acid (2 mL) was added zinc dust (235 mg, 3.584 mmol). The reaction mixture was stirred at 90°C for 24 h and then cooled down to room temperature. The mixture was filtered and then the residue was washed with

hot H_2O (3×10 mL). The filtrate was extracted with ethyl acetate (3×20 mL) and the combined organic phases were washed with brine (10 mL), filtered, and concentrated in vacuo. Flash chromatography (methylene chloride/methanol, 20:1) provided **8** (50 mg, 73% yield) as a white solid: IR ($CHCl_3$): 2500–3600 (s), 1700 (s), 1580 (s), 1470 (s), 1400 (s), 1265 (s), 1220 (s), 970 (s), 910 (s), 750 (s), 650 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, J=8.1 Hz, 1H), 6.87 (d, J=7.7 Hz, 1H), 6.84 (d, J=8.3 Hz, 1H), 5.96 (m, 1H), 5.10 (dd, J=17.3, 1.5 Hz, 1H), 5.07 (d, J=10.4 Hz, 1H), 3.88 (s, 3H), 3.52 (d, J=6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 156.8, 139.6, 136.4, 131.1, 122.2, 122.0, 116.3, 109.3, 56.1, 37.8; high resolution mass spectrum (CI, NH_3) m/z 193.0857 [$(M+H)^+$; calcd for $C_{11}H_{13}O_3$: 193.0865].

4.1.3. Alcohol (+)-14. A solution of (*R*,*R*)-diisopropyl tartrate (*E*)-crotylboronate **13**[22] (46.0 g, 0.152 mol) in dry toluene (1 L) was treated with powdered 4 Å molecular sieve (6 g) at −78°. A solution of (−)-**12** (13.1 g, 0.076 mol) in dry toluene (50 mL) was cooled to −78°C and added dropwise into the suspension via cannula. The resultant reaction mixture was stirred at −78°C for 1 h before an aqueous NaOH (2N, 70 mL) was added. The mixture was warmed up to 0°C, stirred for 30 min and filtered through a pad of celite. The aqueous layer was extracted with Et_2O (3×250 mL) and the combined organic phases were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 7:1) afforded (+)-**14** (15.2 g, 88% yield) as a colorless oil: $[\alpha]_D^{23}$=+9.4° (*c* 3.48, $CHCl_3$); IR (neat): 3150–3600 (br, m), 3074 (s), 2881 (s), 1693 (w), 1463 (m), 1418 (m), 1355 (m), 1173 (m), 1080 (s), 917 (s), 852 (w), 763 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.08 (d, J=5.7, 1.4 Hz, 1H), 4.25 (m, 1H), 4.10 (dd, J=7.9, 5.9 Hz, 1H), 3.68 (m, 1H), 3.50 (t, J=8.0 Hz, 1H), 3.03 (d, J=1.7 Hz, 1H), 2.07 (m, 1H), 1.64 (m, 4H), 1.05 (d, J=6.9 Hz, 3H), 0.89 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 115.4, 113.3, 76.0, 74.1, 70.3, 43.8, 36.8, 29.9, 29.5, 15.5, 8.1, 7.9; high resolution mass spectrum (ESI, Na) m/z 251.1612 [$(M+Na)^+$; calcd for $C_{13}H_{24}O_3Na$: 251.1623].

4.1.4. TBS ether (+)-15. A solution of (+)-**14** (8.5 g, 0.037 mol) in CH_2Cl_2 (500 mL) was treated with 2,6-lutidine (8.67 mL, 0.074 mol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (10.3 mL, 0.045 mmol) at −78°C. After 10 min, the reaction mixture was warmed up to ambient temperature, added to brine-saturated $NaHCO_3$ (1:1, 200 mL), and extracted with CH_2Cl_2 (2×300 mL). The combined organic phases were washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 15:1) afforded (+)-**15** (12.4 g, 97% yield) as a colorless oil: $[\alpha]_D^{23}$=+11.0 (*c* 3.66, $CHCl_3$); IR (neat): 2957 (s), 2858.0 (s), 1643 (m), 1472 (m), 1360 (m), 1254 (s), 1099 (s), 1076 (s), 1040 (s), 915 (s), 836 (s), 774 (s), 668 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.01 (m, 1H), 4.98 (dd, J=11.1, 1.1 Hz, 1H), 4.15 (q, J=6.2 Hz, 1H), 4.03 (t, J=7.8 Hz, 1H), 3.68 (m, 1H), 3.41 (t, J=7.8 Hz, 1H), 2.36 (m, 1H), 1.69 (q, J=6.9 Hz, 1H), 1.61 (m, 4H), 1.02 (d, J=6.8 Hz, 3H), 0.90 (m, 6H), 0.89 (s, 9H), 0.06 (s, 6H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 114.8, 112.3, 73.4, 72.9, 70.4, 42.8, 37.8, 30.0, 29.8, 25.8, 25.6, 18.0, 15.6, 8.2, 7.9, −4.5, −4.6; high resolution mass spectrum (ESI, Na) m/z 343.2665 [$(M+H)^+$; calcd for $C_{19}H_{39}O_3Si$: 343.2669].

4.1.5. Alcohol (+)-16. To a solution of (+)-**15** (690 mg, 2.014 mmol) in THF (40 mL) was added 9-BBN (12.1 mL, 0.5 M in THF, 6.042 mmol). The reaction mixture was heated to reflux for 3 h and then cooled down to 0°C. H_2O (1 mL) was added slowly, followed by NaOH (2N, 8 mL) and 30% H_2O_2 (4 mL). The two phase mixture was warmed up to room temperature and stirred for 1 h. The mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2×50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 6:1) afforded (+)-**16** (611 mg, 89% yield) as a colorless oil: $[\alpha]_D^{23}$=+11.7° (*c* 0.60, $CHCl_3$); IR (neat): 3000–3600 (br, m), 2858 (s), 1463 (s), 1376 (m), 1395 (m), 1173 (s), 1099 (s), 1076 (s), 1057 (s), 919 (m), 836 (s), 774 (s), 671 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.14 (q, J=3.6 Hz, 1H), 4.04 (t, J=7.1 Hz, 1H), 3.72 (m, 2H), 3.58 (m, 1H), 3.44 (t, J=8.7 Hz, 1H), 2.19 (m, 1H), 1.87 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.60 (m, 4H), 1.52 (m, 1H), 0.97 (d, J=6.9 Hz, 3H), 0.98 (s, 9H), 0.88 (m, 6H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 112.5, 73.4, 73.3, 70.4, 60.0, 37.5, 34.2, 30.0, 29.7, 25.8, 18.0, 15.6, 8.1, 7.9, −4.5, −4.6; high resolution mass spectrum (ESI, Na) m/z 361.2771 [$(M+H)^+$; calcd for $C_{19}H_{41}O_4Si$: 361.2775].

4.1.6. Aldehyde (+)-17. A solution of dimethyl sulfoxide (4.5 mL, 0.064 mol) in CH_2Cl_2 (100 mL) at −78°C was treated with oxalyl chloride (2.0 M in CH_2Cl_2, 15.8 mL, 0.032 mol). After 10 min, a solution of (+)-**16** (9.5 g, 0.026 mol) in CH_2Cl_2 (40 mL) was added to the above mixture. The resultant cloudy solution was stirred for an additional 10 min at −78°C before triethylamine (14.7 mL, 0.105 mol) was added. The mixture was then warmed up to ambient temperature and then added to saturated $NaHCO_3$ (150 mL) and extracted with ethyl acetate (2×200 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 10:1) afforded (+)-**17** (9.1 g, 96% yield) as a colorless oil: $[\alpha]_D^{23}$=+4.1° (*c* 0.70, $CHCl_3$); IR (neat): 2955 (s), 2882 (s), 2710 (w), 1727 (s), 1463 (m), 1254 (m), 1173 (m), 1078 (s), 1039 (s), 921 (m), 836 (s), 774 (s), 674 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 4.18 (dt, J=12.1, 4.7 Hz, 1H), 4.04 (dd, J=13.6, 6.2 Hz, 1H), 3.68 (dd, J=10.2, 3.7 Hz, 1H), 3.42 (t, J=7.9 Hz, 1H), 2.52 (dd, J=14.1, 3.2 Hz, 1H), 2.31 (m, 1H), 2.23 (m, 1H), 1.85 (m, 1H), 1.59 (m, 5H), 1.00 (d, J=6.8 Hz, 3H), 0.90 (m, 6H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 112.6, 73.2, 72.8, 70.4, 46.3, 37.8, 32.6, 30.0, 29.7, 25.8, 25.7, 18.0, 16.9, 8.2, 7.9, −4.4, −4.6; high resolution mass spectrum (ESI, Na) m/z 381.2425 [$(M+Na)^+$; calcd for $C_{19}H_{38}O_4SiNa$: 381.2437].

4.1.7. Olefin (+)-18. A suspension of methyltriphenyl phosphonium iodide (631 mg, 1.56 mmol) in THF (15 mL) at 0°C was treated with NaHMDS (1.0 M in THF, 1.61 mL, 1.61 mmol) for 30 min and then cooled down to −78°C. To the resultant yellow solution was added (+)-**17** (373 mg,

1.04 mmol) in THF (5 mL). The reaction mixture was warmed up to room temperature and stirred for 1 h, poured into brine (20 mL) and extracted with ethyl ether (2×30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 40:1) afforded (+)-**18** (298 mg, 81% yield) as a yellow oil: $[\alpha]_D^{23}=+16.5°$ (*c* 4.60, $CHCl_3$); IR (neat): 3076 (s), 2857 (s), 1640 (m), 1463 (s), 1376 (m), 1254 (s), 1173 (m), 1078 (s), 915 (s), 836 (s), 806 (m), 774 (s), 673 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.00 (dd, *J*=9.0, 1.1 Hz, 1H), 4.97 (d, *J*=1.0, 1H), 4.20 (dt, *J*=12.3, 5.7 Hz, 1H), 4.05 (dd, *J*=7.7, 5.4 Hz, 1H), 3.60 (dt, *J*=7.3, 4.4 Hz, 1H), 3.44 (t, *J*=7.9 Hz, 1H), 2.12 (dt, *J*=13.9, 7.0 Hz, 1H), 1.83–1.92 (m, 2H), 1.71 (m, 1H), 1.56 (m, 1H), 1.60 (m, 4H), 0.90 (s, 9H), 0.89 (m, 6H), 0.05 (m, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 115.6, 112.2, 73.6, 72.8, 70.3, 38.1, 37.0, 36.3, 30.0, 29.8, 25.8, 18.0, 14.5, 8.2, 7.9, −4.5, −4.6; high resolution mass spectrum (ES, Na) *m/z* 379.2613 [(M+Na)$^+$; calcd for $C_{20}H_{40}O_3SiNa$: 379.2645].

4.1.8. Diol (+)-19. To a solution of (+)-**18** (185 mg, 0.519 mmol) in CH_2Cl_2 (10 mL) was added 50% aqueous trifluoroacetic acid (0.7 mL). The reaction mixture was stirred vigorously at room temperature for 30 min (reaction monitored by TLC) and then diluted with CH_2Cl_2 (60 mL) and H_2O (20 mL). The organic layer was washed with saturated $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 2:1) afforded (+)-**19** (135 mg, 90% yield) as a white solid: $[\alpha]_D^{23}=+10.8°$ (*c* 4.05, $CHCl_3$); IR (neat): 3100–3600 (br, s), 1640 (m), 1482 (m), 1441 (m), 1413 (m), 1377 (m), 1255 (s), 1066 (s), 1005 (m), 911 (m), 836 (s), 724 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74 (m, 1H), 5.00 (m, 1H), 4.98 (t, *J*=1.2 Hz, 1H), 3.92 (m, 1H), 3.84 (m, 1H), 3.62 (dd, *J*=11.1, 3.6 Hz, 1H), 3.47 (dd, *J*=11.1, 6.0 Hz, 1H), 1.97 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.60 (m, 1H), 1.47 (dt, *J*=14.4, 3.0 Hz, 1H), 0.90 (s, 9H), 0.89 (d, *J*=3.1 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 116.0, 75.7, 71.4, 66.9, 38.7, 37.9, 32.9, 25.8, 17.9, 13.1, −4.1, −4.8; high resolution mass spectrum (ESI, Na) *m/z* 311.2031 [(M+Na)$^+$; calcd for $C_{15}H_{32}O_3SiNa$: 311.2019].

4.1.9. Epoxide (+)-20. To a suspension of NaH (60% dispersion in mineral oil, 59 mg, 1.456 mmol, washed twice with hexanes) in THF (5 mL) at 0°C was added a solution of (+)-**19** (105 mg, 0.346 mmol) in THF (2 mL). The resulting mixture was stirred at 0°C for 30 min and then cooled down to −78°C. A solution of tosylimidazole (89 mg, 0.400 mmol) in THF (2 mL) was added dropwise via cannula. The reaction mixture was warmed up to 0°C and stirred for 1 h before being quenched with saturated NH_4Cl (20 mL). The mixture was poured into Et_2O (30 mL) and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (+)-**20** (75 mg, 81% yield) as a colorless oil: $[\alpha]_D^{23}=+9.7°$ (*c* 1.20, $CHCl_3$); IR (neat): 2856 (s), 1640 (w), 1472 (m), 1407 (m), 1377 (m), 1360 (w), 1254 (s), 1070 (s), 910 (m), 835 (s), 774 (s), 665 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (m, 1H), 5.01 (dd, *J*=3.5, 2.0 Hz, 1H), 4.98 (t, *J*=1.0 Hz, 1H), 3.72 (m, 1H), 3.03 (m, 1H), 2.72 (td, *J*=4.9, 0.7 Hz, 1H), 2.42 (dd, *J*=5.1, 2.7 Hz, 1H), 2.13 (m, 1H), 1.82 (m, 2H), 1.76 (m, 1H), 1.47 (m, 1H), 0.90 (s, 9H), 0.89 (d, *J*=3.0 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 115.6, 73.6, 50.0, 46.8, 38.3, 37.1, 35.7, 25.8, 18.0, 14.6, −4.6; high resolution mass spectrum (CI, NH_3) *m/z* 271.2094 [(M+H)$^+$; calcd for $C_{15}H_{31}O_2Si$: 271.2093].

4.1.10. Alcohol (+)-9. A 1.0 M solution of anhydrous $MgBr_2$ in ether/benzene (3:1) was prepared by addition of 1,2-dibromoethane (0.69 mL, 8 mmol) to a stirred suspension of magnesium turnings (0.2 g, 8.3 mmol) in Et_2O/benzene (3:1, 8 mL) at a rate sufficient to maintain gentle reflux and then stirred for 1 h. Simultaneously, *n*-BuLi (1.6 M in hexanes, 0.333 mL, 0.532 mmol) was added dropwise to **21** (248 mg, 0.532 mmol) in dry THF (3 mL) at −78°C and the resultant mixture was stirred for 1 h at −78°C. To the mixture was added the 1.0 M freshly prepared $MgBr_2$ solution (532 μL, 0.532 mmol) dropwise and the resulting suspension was stirred at −78°C. After 45 min, the mixture was transferred into a suspension of CuI (6 mg, 0.026 mmol) in THF (1 mL) at −78°C via cannula and allowed to stir for 30 min. A solution of (+)-**20** (58 mg, 0.212 mmol) in THF (1.5 mL) was added dropwise at −78°C. The reaction mixture was warmed up slowly to room temperature, stirred for 1 h quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2×30 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 6:1) afforded (+)-**9** (90 mg, 94% yield) as a colorless oil: $[\alpha]_D^{23}=+24.1°$ (*c* 1.6, $CHCl_3$); IR (neat): 3350–3600 (br, m), 2921 (s), 1612 (m), 1513 (s), 1249 (s), 1463 (s), 1068 (s), 1037 (s), 911 (s), 836 (s), 774 (s), 666.6 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J*=8.3 Hz, 2H), 6.86 (d, *J*=8.5 Hz, 2H), 5.62–5.80 (m, 3H), 5.00 (s, 1H), 4.97 (dd, *J*=2.1, 1.0 Hz, 1H), 4.42 (s, 2H), 3.97 (d, *J*=5.8 Hz, 2H), 3.88 (m, 1H), 3.80 (s, 3H), 3.79 (m, 1H), 3.23 (br, s, 1H), 2.23 (t, *J*=6.3 Hz, 2H), 1.93 (m, 1H), 1.88 (m, 1H), 1.76 (m, 1H), 1.60 (m, 2H), 0.89 (s, 9H), 0.8 (d, *J*=7.0 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 137.0, 130.4, 130.3, 129.3, 129.2, 115.9, 113.7, 75.8, 71.5, 70.5, 70.4, 55.2, 40.4, 38.8, 37.9, 35.9, 29.6, 25.8, 17.9, 13.2, −4.1, −4.7; high resolution mass spectrum (ESI, Na) *m/z* 471.2901 [(M+Na)$^+$; calcd for $C_{26}H_{44}O_4SiNa$: 471.2907].

4.1.11. Ester (+)-7. To a solution of (+)-**9** (450 mg, 1.016 mmol), **8** (975 mg, 5.081 mmol), triphenylphosphine (665 mg, 2.541 mmol) in benzene (10 mL) was added diethyl azodicarboxylate (0.409 mL, 2.591 mmol). After 24 h, the resultant mixture was added to brine (25 mL) and extracted with ether (3×25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (+)-**7** (499 mg, 84% yield) as a colorless oil: $[\alpha]_D^{23}=+14.8°$ (*c* 0.29, $CHCl_3$); IR (neat): 2855 (s), 1725 (s), 1584 (m), 1513 (m), 1470 (s), 1264 (s), 1248 (s), 1113 (m), 1066 (s), 835 (m), 807 (m), 774 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (t, *J*=8.1 Hz, 1H), 7.24 (d, *J*=8.2 Hz, 2H), 6.85 (d, *J*=6.7 Hz, 2H), 6.81 (d, *J*=7.8 Hz, 1H), 6.73 (d, *J*=8.2 Hz, 1H), 5.92 (m, 1H), 5.68–5.80 (m,

3H), 5.26 (m, 1H), 5.07 (t, J=1.9 Hz, 1H), 5.02 (dd, J=5.9, 1.7 Hz, 1H), 4.90 (dd, J=9.1, 1 Hz, 1H), 4.62 (s, 1H), 4.03 (s, 1H), 3.69 (m, 1H), 3.85 (m, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.35 (d, J=6.5 Hz, 2H), 2.50 (m, 2H), 2.04 (m, 1H), 1.82 (m, 1H), 1.71 (m, 2H), 1.62 (m, 1H), 0.92 (s, 9H), 0.88 (d, J=6.9 Hz, 3H), 0.13 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 159.1, 156.3, 138.3, 137.3, 136.3, 130.5, 129.8, 129.3, 129.0, 124.1, 121.5, 116.3, 115.6, 113.7, 108.7, 72.7, 72.2, 71.4, 70.2, 55.5, 55.2, 39.2, 37.9, 37.3, 37.2, 36.4, 25.9, 25.8, 18.0, 13.6, −4.3, −4.5; high resolution mass (ESI, Na) m/z 645.3582 [(M+Na)$^+$; calcd for $C_{37}H_{54}O_6SiNa$: 645.3587].

4.1.12. Lactone (−)-23. To a solution of the Grubbs catalyst $(Cy_3P)_2Cl_2Ru$=CHPh (17.2 mg, 0.021 mmol, 10 mol%) in dry CH_2Cl_2 (26 mL) was added a solution of (+)-**7** (130 mg, 0.209 mmol) in CH_2Cl_2 (3 mL). The reaction mxture was stirred for 40 min at ambient temperature and poured into H_2O (20 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 15:1) afforded (−)-**23** (112 mg, 85%) as a colorless oil (contain a small amount of Z-isomer): $[\alpha]_D^{23}$=−41.5° (c 0.55, $CHCl_3$); IR (neat): 2853 (s), 1724 (s), 1584 (m), 1513 (s), 1469 (s), 1275 (s), 1249 (s), 1071 (s), 970 (m), 835 (s), 807 (m), 775 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (dd, J=4.9, 2.9 Hz, 2H), 6.86 (dd, J=4.9, 2.9 Hz, 2H), 7.21 (t, J=8.3 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.74 (d, J=7.6 Hz, 1H), 5.75–5.85 (m, 1H), 5.62–5.71 (m, 1H), 5.41 (ddt, J=13.2, 10.8, 2.1 Hz, 1H), 5.25–5.34 (m, 2H), 4.42 (d, J=3.2 Hz, 2H), 4.25 (dt, J=8.5, 4.9 Hz, 1H), 3.97 (m, 1H), 3.80 (, 3H), 3.74 (s, 3H), 3.71 (dd, J=16.3, 9.4 Hz, 1H), 3.30 (dd, J=16.3, 2.0 Hz, 1H), 2.41–2.52 (m, 1H), 2.28–2.37 (m, 1H), 2.21–2.29 (m, 1H), 1.80 (m, 1H), 1.68 (dd, J=14.9, 8.3 Hz, 2H), 1.43 (dd, J=15.2, 7.8 Hz, 1H), 0.90 (s, 9H), 0.83 (d, J=6.8 Hz, 3H), 0.23 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 159.1, 156.6, 139.0, 131.2, 130.4, 129.9, 129.4, 129.3, 129.2, 128.4, 124.6, 122.6, 113.7, 109.3, 74.6, 72.3, 71.4, 70.3, 55.5, 55.2, 39.0, 37.8, 37.7, 37.3, 36.7, 25.9, 17.9, 13.0, −4.3, −4.5; high resolution mass spectrum (ESI, Na) m/z 617.3265 [(M+Na)$^+$; calcd for $C_{35}H_{50}O_6SiNa$: 617.3275].

4.1.13. Alcohol (−)-24. To a solution of (−)-**23** (83 mg, 0.140 mmol) in CH_2Cl_2 (20 mL) was added DDQ (95 mg, 0.419 mmol) followed by pH 7 buffer (1 mL). The reaction mixture was allowed to stir at room temperature for 45 min before being quenched with saturated $NaHCO_3$ (20 mL). The mixture was diluted with CH_2Cl_2 (100 mL) and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded (−)-**24** (63 mg, 98% yield) as a colorless oil: $[\alpha]_D^{23}$=−53.8° (c 0.45, $CHCl_3$); IR (neat): 3100–3600 (br, m), 2854 (s), 1723 (s), 1583 (m), 1469 (s), 1438 (m), 1275 (s), 1253 (s), 1072 (s), 970 (m), 835 (s), 775 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, J=8.0 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 6.75 (d, J=7.6 Hz, 1H), 5.72–5.83 (m, 2H), 5.40 (ddt, J=13.7, 10.4, 3.0 Hz, 1H), 5.22–5.34 (m, 2H), 4.23 (dd, J=8.6, 3.6 Hz, 1H), 4.11 (d, J=4.8 Hz, 1H), 3.80 (s, 3H), 3.68 (dd, J=16.2, 4.4 Hz, 1H), 3.30 (dt, J=16.2, 2.1 Hz, 1H), 2.45 (m, 1H), 2.21–2.35 (m, 2H), 1.82 (m, 1H), 1.68 (dd, J=15.2, 8.4 Hz, 2H), 1.40 (dd, J=15.2, 8.8 Hz, 1H), 0.91 (s, 9H), 0.85 (d, J=6.8 Hz, 3H), 0.22 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 156.6, 139.0, 131.7, 131.2, 129.9, 128.4, 128.3, 124.7, 122.7, 109.5, 74.5, 72.3, 63.6, 55.7, 38.8, 37.8, 37.7, 37.2, 36.7, 25.9, 18.0, 13.1, −4.3, −4.5; high resolution mass spectrum (ESI, Na) m/z 497.2699 [(M+Na)$^+$; calcd for $C_{27}H_{42}O_5SiNa$: 497.2700].

4.1.14. Enal (−)-25. To a solution of (−)-**24** (53 mg, 0.112 mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (105 mg, 0.246 mmol). The reaction mixture was stirred at room temperature for 30 min before being quenched with aqueous $Na_2S_2O_3$ (15%, 5 mL) and Saturated $NaHCO_3$ (5 mL). The mixture was diluted with EtOAc (100 mL) and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) provided (−)-**25** (51 mg, 98% yield) as a colorless oil: $[\alpha]_D^{23}$=−50.6° (c 0.58, $CHCl_3$); IR (neat): 2854 (s), 1727 (s), 1649 (s), 1584 (m), 1469 (s), 1273 (s), 1251 (s), 1251 (s), 1070 (s), 971 (m), 836 (m), 775 (m), 734 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (d, J=7.8 Hz, 1H), 7.23 (t, J=8.1, 1H), 6.92 (dt, J=15.6, 7.0 Hz, 1H), 6.19 (dd, J=15.7, 7.8 Hz, 1H), 5.35–5.47 (m, 2H), 5.26–5.33 (m, 1H), 4.24 (dd, J=8.8, 3.8 Hz, 1H), 3.77 (s, 1H), 3.70 (dd, J=16.3, 9.5 Hz, 1H), 3.32 (ddt, J=13.9, 4.2, 2.1 Hz, 1H), 2.73 (m, 1H), 2.58 (m, 1H), 2.28 (m, 1H), 1.82 (m, 1H), 1.75 (dd, J=15.1, 8.1 Hz, 1H), 1.67 (dd, J=14.2, 11.5 Hz, 1H), 1.38 (dd, J=15.1, 8.9 Hz, 1H), 0.91 (s, 9H), 0.83 (d, J=6.8 Hz, 2H), 0.23 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 167.8, 156.5, 153.5, 139.1, 134.7, 131.3, 130.1, 128.4, 124.1, 122.8, 109.4, 72.8, 72.3, 55.7, 39.3, 37.8. 37.7, 37.3, 37.1, 25.8, 18.0, 13.0, −4.3, −4.5; high resolution mass spectrum (ES, Na) m/z 495.2551 [(M+Na)$^+$; calcd for $C_{27}H_{40}O_5SiNa$: 495.2543].

4.1.15. Phenol (−)-26. A suspension of (−)-**25** (57 mg, 0.121 mmol) in CH_2Cl_2 (57 mL) at −78°C was treated with BBr_3 (1.0 M in CH_2Cl_2, 362 μL, 0.362 mmol). The mixture was stirred at −78°C for 3 h, and then quenched with saturated NH_4Cl (20 mL). The mixture was allowed to warm up to room temperature and diluted with CH_2Cl_2 (50 mL). The organic layer was washed brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) provided (−)-**26** (45 mg, 82% yield) as a colorless oil: $[\alpha]_D^{23}$=−11.4° (c 0.50, $CHCl_3$); IR (neat): 3000–3500 (br, s), 2852 (s), 1727 (s), 1693 (s), 1606 (m), 1587 (m), 1463 (s), 1379 (m), 1359 (s), 1250 (s), 1062 (s), 970 (m), 836 (s), 806 (m), 775.9 (s), 663 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.92 (br, s, 1H), 9.53 (d, J=7.6 Hz, 1H), 7.31 (t, J=7.6 Hz, 1H), 6.89 (dd, J=8.3, 1.0 Hz, 1H), 6.82 (dt, J=15.7, 7.3 Hz, 1H), 6.71 (dd, J=7.4, 0.9 Hz, 1H), 6.22 (dd, J=15.6, 7.8 Hz, 1H), 5.52 (dt, J=10.7, 4.9 Hz, 1H), 5.45 (dt, J=14.0, 2.0 Hz, 1H), 5.11 (m, 1H), 3.71 (dd, J=16.7, 5.7 Hz, 1H), 3.62 (dd, J=8.2, 3.0 Hz, 1H), 3.40 (d, J=16.5 Hz, 1H), 2.73 (ddd, J=7.3, 6.1, 1.4 Hz, 2H), 2.33 (m, 1H), 2.01 (dd, J=14.7, 10.8 Hz, 1H), 1.74 (m, 2H), 1.39 (ddd, J=10.3, 8.4, 1.8 Hz, 1H), 0.92 (d, J=6.3 Hz, 1H), 0.89 (s, 9H), 0.03 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 170.7, 162.7, 151.8, 142.1, 135.5, 134.2, 132.6, 126.6, 123.6, 116.7, 112.9, 73.3, 71.3, 39.1, 38.6, 38.3, 37.2, 36.4, 29.6, 25.7, 17.9, 3.7, −4.6, −5.0; high resolution mass spectrum (ES,

Na) *m/z* 481.2380 [(M+Na)$^+$; calcd for $C_{26}H_{38}O_5SiNa$: 481.2387].

4.1.16. Acid (−)-27. A solution of (−)-**26** (32 mg, 0.068 mmol) in *t*-butanol (2 mL) and 2-methyl-2-butene (1 mL) was treated with sodium chlorite (156 mg, 1.72 mmol) and $NaH_2PO_4{\cdot}2H_2O$ (402 mg, 2.58 mmol) in water (2 mL). The resultant mixture was stirred vigorously for 1 h, added to brine (20 mL), and extracted with ethyl acetate (4×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 1:2) provided (−)-**27** (31 mg, 97% yield) as a yellow oil: $[\alpha]_D^{23}=-18.9°$ (*c* 0.25, $CHCl_3$); IR (neat): 2500–3510 (br, m), 1698 (s), 1657 (s), 1606 (m), 1463 (s), 1291 (s), 1249 (s), 1063 (s), 970 (m), 939 (m), 836 (s), 805 (m), 775 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.92 (br, s, 1H), 7.30 (t, *J*=7.5 Hz, 1H), 7.07 (dt, *J*=15.1, 72 Hz, 1H), 6.89 (dd, *J*=8.6, 1.0 Hz, 1H), 6.71 (dd, *J*=7.6, 1.0 Hz, 1H), 5.93 (d, *J*=15.7 Hz, 1H), 5.41–5.53 (m, 2H), 5.06 (m, 1H), 3.69 (dd, *J*=16.5, 5.8 Hz, 1H), 3.60 (dd, *J*=8.1, 2.8 Hz, 1H), 3.40 (dd, *J*=16.0, 1.6 Hz, 1H), 2.56–2.68 (m, 2H), 2.26–2.35 (m, 1H), 2.01 (dd, *J*=15.5, 10.9 Hz, 1H), 1.82 (m, 2H), 1.37 (ddd, *J*=14.0, 6.4, 1.0 Hz, 1H), 0.89 (d, *J*=8.1 Hz, 1H), 0.87 (s, 9H), 0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.7, 162.7, 145.8, 142.3, 134.1, 132.7, 126.5, 123.6, 123.5, 116.6, 112.9, 73.4, 71.2, 39.0, 38.3, 38.0, 37.2, 36.2, 25.8, 25.7, 17.9, 13.7, −4.5, −4.6, −4.9, −5.0; high resolution mass spectrum (ESI, Na) *m/z* 497.2358 [(M+Na)$^+$; calcd for $C_{26}H_{38}O_6SiNa$: 497.2336].

4.1.17. Acid (+)-28. To a solution of (−)-**27** (48 mg, 0.098 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (82 μL, 0.590 mmol) followed by TBSOTf (68 μL, 0.294 mmol). The reaction mixture was stirred at ambient temperature for 2 h before being quenched with HCl (1N, 10 mL). The aqueous phase was extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in MeOH (3 mL) and THF (1 mL). A solution of K_2CO_3 (200 mg) in H_2O (1 mL) was added and the mixture was stirred at ambient temperature for 5 min. The reaction was quenched with HCl (1N, 10 mL) and the aqueous phase was extracted with ethyl acetate (2×30 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 2:1) provided (+)-**28** (21 mg, 83% yield) as a colorless oil: $[\alpha]_D^{23}=+6.9°$ (*c* 0.30, $CHCl_3$); IR (neat): 2400–3300 (br, s), 2951 (s), 1727 (s), 1700 (s), 1653 (m), 1581 (m), 1457 (s), 1281 (s), 1253 (s), 1113 (m), 1066 (s), 1036 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (t, *J*=7.8 Hz, 1H), 7.02 (dt, *J*=15.7, 7.2 Hz, 1H), 6.74 (d, *J*=7.5 Hz, 1H), 6.72 (d, *J*=8.2 Hz, 1H), 5.93 (d, *J*=15.7 Hz, 1H), 5.28–5.44 (m, 1H), 3.64 (dd, *J*=16.1, 9.0 Hz, 1H), 3.31 (ddd, *J*=16.6, 3.0, 1.0 Hz, 1H), 2.60 (t, *J*=6.5 Hz, 2H), 2.26 (d, *J*=12.9 Hz, 1H), 1.76–1.85 (m, 1H), 1.69 (dt, *J*=15.0, 10.7 Hz, 2H), 1.41 (dd, *J*=15.1, 8.9 Hz, 1H), 0.96 (s, 9H), 0.91 (s, 9H), 0.83 (d, *J*=6.7 Hz, 3H), 0.22 (s, 3H), 0.19 (s, 3H), 0.16 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 168.1, 152.7, 146.1, 138.7, 131.3, 129.5, 128.3, 127.3, 123.3, 123.1, 117.7, 72.3, 71.9, 38.4, 38.0, 37.9, 37.0, 36.2, 25.9, 25.7, 13.0, −4.2, −4.4, −4.5, −4.6; high resolution mass spectrum (ESI, Na) *m/z* 611.3209 [(M+Na)$^+$; calcd for $C_{32}H_{52}O_6Si_2Na$: 611.3200].

4.1.18. Dienyl acid 29. *tert*-Butyllithium (100 mL, 1.7 M in pentane, 170.0 mmol) was added dropwise to a solution of iodoethane (13.3 g, 85.0 mmol) in Et_2O (100 mL) at −78°C. The solution was stirred at −78°C for 10 min and then at room temperature for 1 h. The resulting solution was added via cannula to a suspesion of $CuBr{\cdot}SMe_2$ (8.7 g, 42.5 mmol) in Et_2O (150 mL) at −40°C. The mixture was stirred at −35°C for 20 min and cooled down to −40°C. Gaseous acetylene (2.86 L, 127.5 mmol) was slowly passed into the solution through a syringe needle. The resulting solution was stirred at −30°C for 15 min and then warmed up to −10°C. The temperature was carefully maintained between −15 and −10°C, while more acetylene gas (4.8 L, 212.5 mmol) was added over 15 min. The resulting mixture was cooled down to −40°C and HMPA (5.9 mL, 34.0 mmol), $(EtO)_3P$ (50 μL) were added dropwise. Gaseous CO_2 was bubbled through while the reaction mixture was warmed up to 10°C. Saturated NH_4Cl (150 mL) and HCl (3N, 50 mL) was added and the organic layer was extracted with Et_2O (2×300 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (methylene chloride/methanol, 30:1) provided a crude brown residue. Vaccum distillation of the crude residue gave **29** (1.07 g, 21% yield) as a light yellow oil: bp 80–85°C/0.5 mm Hg; IR ($CHCl_3$): 2100–3500 (br, s), 1690 (s), 1635 (s), 1595 (s), 1450 (s), 1290 (s), 1245 (s), 1010 (m), 900 (m), 850 (m), 823 (m), 670 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, *J*=11.1 Hz, 1H), 7.05 (t, *J*=11.5 Hz, 1H), 5.96 (dd, *J*=10.8, 7.3 Hz, 1H), 5.67 (d, *J*=11.4 Hz, 1H), 2.30 (dt, *J*=13.6, 6.0 Hz, 2H), 1.03 (t, *J*=7.6 z, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 144.2, 141.0, 123.8, 116.5, 20.8, 13.8; high resolution mass spectrum (CI, NH_3) *m/z* 127.0756 [(M+H)$^+$; calcd for $C_7H_{11}O_2$: 127.0760].

4.1.19. Dienyl acid chloride 6. A solution of **29** (230 mg, 1.825 mmol) in dry benzene (3 mL) was treated with oxalyl chloride (0.321 mL, 3.651 mmol). A trace ammount of DMF was added. The resultant mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was azeotropically dried with benzene (2×1 mL) to afford the corresponding acid chloride **6** as a yellow oil (253 mg, 95%). The acid chloride **6** was used immediately in the following step: IR ($CHCl_3$): 3000 (m), 1735 (s), 1625 (s), 1620 (s), 1575 (s), 1430 (m), 1190 (m), 955 (s), 860 (s), 810 (m), 690 (m), 610 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (m, 2H), 6.25 (m, 1H), 5.97 (m, 1H), 2.32 (dt, *J*=15.5, 6.6 Hz, 2H), 1.07 (t, *J*=7.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 148.9, 142.2, 123.7, 122.0, 21.3, 13.7; high resolution mass spectrum (CI, NH_3) *m/z* 145.0416 [(M+H)$^+$; calcd for $C_7H_{10}ClO$: 145.0420].

4.1.20. Enecarbamate (+)-5. To a solution of (+)-**28** (21 mg, 0.036 mmol) in acetone (2 mL) was sequentially added *N,N*-diisopropylethylamine (10.2 mg, 14 μL, 0.078 mmol) and isobutylchloroformate (9.6 mg, 9 μL, 0.072 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 h, and then a solution of sodium azide (23 mg, 0.347 mmol) in distilled H_2O (1 mL) was

added. The resulting mixture was stirred at room temperature for an additional 30 min. Brine (10 mL) was added and the aqueous phase extracted with ethyl acetate (2×20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was azeotropically dried with benzene (2×1 mL) and then dissolved in toluene (2 ml) and heated at reflux for 15 min. 2-(trimethylsilyl)-ethanol was added in one portion and the mixture was heated at reflux for an additional 10 min. The mixture was then cooled to room temperature and concentrated in vacuo. Flash chromatography (hexane/ethyl acetate, 20:1) afforded (+)-**5** (21.6 mg, 86%) as a colorless oil: $[\alpha]_D^{23}=+17.0°$ (*c* 0.35, CH_2Cl_2); IR (neat): 3200–3400 (br, m), 2856 (s), 1725 (s), 1681 (m), 1581 (m), 1504 (m), 1462 (s), 1259 (s), 1066 (s), 836 (s), 804 (s), 665 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.91 (t, *J*=8.0 Hz, 1H), 6.80–6.89 (m, 1H), 6.70 (d, *J*=8.1, 1H), 6.56 (d, *J*=7.6 Hz, 1H), 5.69 (d, *J*=10.8 Hz, 1H), 5.40–5.47 (m, 1H), 5.31–5.40 (m, 2H), 4.61–4.78 (m, 1H), 4.49 (m, 1H), 4.16 (t, *J*=8.2 Hz, 2H), 3.70 (dd, *J*=16.1, 8.3 Hz, 1H), 3.20 (dd, *J*=16.2, 4.1 Hz, 1H), 2.33–2.47 (m, 2H), 2.11 (m, 1H), 1.68 (m, 1H), 1.59–1.70 (m, 2H), 1.50–1.59 (m, 1H), 1.10 (s, 9H), 1.03 (s, 9H), 0.82–0.90 (m, 5H), 0.28 (s, 6H), 0.16 (s, 3H), 0.11 (s, 3H), −0.11 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.9, 153.2, 153.0, 138.7, 131.2, 129.6, 128.9, 128.8, 126.7, 123.3, 118.1, 104.0, 74.2, 72.1, 63.0, 38.3, 38.1, 37.5, 36.2, 35.9, 26.0, 25.7, 18.3, 18.1, 17.6, 1.1, −1.9, −4.2, −4.3, −4.6, −4.7; high resolution mass spectrum (ES, Na) *m/z* 726.4037 [$(M+Na)^+$; calcd for $C_{37}H_{65}NO_6Si_3Na$: 726.4017].

4.1.21. Enamide (+)-30. A solution of (+)-**5** (8.4 mg, 0.012 mmol) in dry THF (1 mL) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 18 μL, 0.018 mmol) for 5 min at 0°C. A solution of **6** (3 mg, 0.024 mmol) in dry benzene (0.2 mL) was added. The resulting mixture was stirred at 0°C for 10 min before being quenched with saturated NH_4Cl (3 mL) and extracted with ether (2×15 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 10:1) provided (+)-**30** (7.8 mg, 81%) as a colorless oil: $[\alpha]_D^{23}=+19.1°$ (*c* 0.45, CH_2Cl_2); IR (neat): 3587 (m), 2926 (s), 2854 (s), 1728 (s), 1581 (m), 1456 (m), 1382 (m), 1260 (s), 1066 (s), 969 (m), 860 (m), 803 (s) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.54 (t, *J*=11.5 Hz, 1H), 6.90 (t, *J*=7.9 Hz, 1H), 6.65–6.75 (m, 2H), 6.53–6.62 (m, 2H), 6.45 (d, *J*=11.4 Hz, 1H), 5.89 (dt, *J*=14.1, 7.4 Hz, 1H), 5.54–5.65 (m, 2H), 5.33–5.45 (m, 2H), 4.51–4.59 9m, 1H), 4.18 (t, *J*=7.6 Hz, 2H), 3.69 (dd, *J*=16.0, 8.1 Hz, 1H), 3.19 (dd, *J*=16.0, 4.0 Hz, 1H), 2.53–2.69 (m, 2H), 2.10–2.19 (m, 1H), 1.85–1.96 (m, 1H), 1.75–1.85 (m, 2H), 1.65–1.75 (m, 2H), 1.12 (s, 9H), 1.02 (s, 9H), 0.92 (d, *J*=6.6 Hz, 3H), 0.88–0.97 (m, 2H), 0.73 (t, *J*=7.5 Hz, 3H), 0.28 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H), −0.10 (s, 6H); ^{13}C NMR (125 MHz, C6D6) δ 70.0, 166.9, 153.6, 153.0, 142.3, 138.8, 137.0, 131.2, 129.2, 128.6, 127.0, 124.9, 123.3, 121.1, 121.0, 118.0, 73.6, 72.1, 65.0, 38.3, 38.0, 37.5, 37.0, 36.2, 26.0, 25.7, 20.6, 18.3, 18.1, 17.4, 13.7, 1.1, −2.0, −4.2, −4.3, −4.6, −4.7; high resolution mass spectrum (ESI, Na) *m/z* 834.4618 [$(M+Na)^+$; calcd for $C_{44}H_{73}NO_7Si_3Na$: 834.4618].

4.1.22. Salicylihalamide A (−)-1. A solution of (+)-**30** (7.8 mg, 0.010 mmol) in THF (1 mL) was treated with tetrabutylammonium fluoride (1.0 M in THF, 60 μl, 0.060 mmol). The resultant brown solution was stirred for 10 min at 0°C, added to H_2O (5 ml), and extracted with ethyl ether (2×15 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in a solution of HF·py (0.1 g) in pyridine (0.3 mL) and THF (0.9 mL). The reaction mixture was allowed to stir at room temperature. After 48 h, the reaction was carefully quenched with saturated aqueous $NaHCO_3$ (10 mL) extracted with EtOAc (2×20 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 1:1) afforded (−)-**1** (2.6 mg, 56% yield) as a white solid: $[\alpha]_D^{23}=-22.8°$ (*c* 0.11, MeOH); IR (neat): 3280 (br, m), 2964 (s), 1695 (s),1605 (s), 1520 (s), 1460 (s), 1245 (s), 1120 (s), 972 (s), 735 (s) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.30 (t, *J*=12.0 Hz, 1H), 7.12 (t, *J*=7.9 Hz, 1H), 6.87 (t, *J*=11.1 Hz, 1H), 6.80 (d, *J*=14.7 Hz, 1H), 6.73 (d, *J*=8.2 Hz, 1H), 6.64 (d, *J*=7.5 Hz, 1H), 5.81 (dd, *J*=10.8, 7.4 Hz, 1H), 5.68 (d, *J*=11.7 Hz, 1H), 5.22–5.48 (m, 4H), 4.12 (dd, *J*=9.3, 3.4 Hz, 1H), 3.56 (dd, *J*=16.6, 8.3 Hz, 1H), 3.35 (dd, *J*=16.6, 7.7 Hz, 1H), 2.34–2.46 (m, 2H), 2.28 (m, 2H), 1.81–1.91 (m, 1H), 1.70–1.80 (m, 2H), 1.35 (m, 1H), 1.02 (t, *J*=7.4, 3H), 0.85 (d, *J*=6.8 Hz, 3H); ?^{13}C NMR (125 MHz, CD_3OD) δ 171.0, 165.9, 157.1, 142.6, 140.7, 137.7, 131.7, 131.6, 130.7, 126.2, 125.3, 123.0, 122.5, 120.3, 110.4, 76.0, 72.0, 38.9, 38.8, 38.6, 37.6, 36.6, 21.5, 14.4, 13.6; high resolution mass spectrum (ESI, Na) *m/z* 462.2256 [$(M+Na)^+$; calcd for $C_{26}H_{33}NO_5Na$: 462.2256].

4.1.23. Alcohol (−)-33. To a suspension of magnesium turnings (0.61 g, 0.025 mol) in Et_2O (10 mL) was added two drops of 1,2-dibromoethane and the mixture was heated to reflux for 10 min and then cooled down to room temperature. 5-bromo-1-pentene (3.0 g, 0.02 mol) was added dropwise and the resultant mixture was refluxed for 2 h, cooled down to room temperature. This Grignard reagent **32** was transferred into THF (20 mL) and cooled down to −78°C. A solution of Li_2CuCl_4 (0.1 M in THF, 4.49 mL, 0.449 mmol) was added and the mixture was stirred at −78°C for 15 min. A solution of (+)-**31** (1.87 g, 0.009 mol) in THF (10 mL) was added dropwise via cannula. The reaction mixture was stirred at −78°C for 5 min and slowly warmed up to room temperature, quenched with saturated NH_4Cl (20 mL). The aqueous phase was extracted with Et_2O (3×40 mL) and the combined organic phases were washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 6:1) afforded (−)-**33** (2.16 g, 88% yield) as a colorless oil: $[\alpha]_D^{23}=-11.9°$ (*c* 0.82, $CHCl_3$); IR (neat): 3450 (br, m), 3010 (s), 1610 (s), 1505 (s), 1240 (s), 1080 (s), 900 (m), 750 (s), 660 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 5.80 (m, 1H), 4.99 (dd, *J*=17.2, 1.0 Hz, 1H), 4.91 (dd, *J*=10.2, 1.0 Hz, 1H), 4.44 (s, 2H), 3.80 (s, 3H), 3.79 (m, 1H), 3.70 (m, 1H), 3.62 (m, 1H), 2.80 (br, s, 1H), 2.05 (m, 2H), 1.71 (m, 2H), 1.25–1.50 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 138.9, 130.0, 129.2, 114.3, 113.9, 72.9, 71.4, 68.9, 55.2, 37.2, 36.4, 33.7, 28.9, 25.7; high resolution mass spectrum (ESI, Na) *m/z* 278.1877 [$(M+H)^+$; calcd for $C_{17}H_{27}O_3$: 278.1882].

4.1.24. Ester (−)-34. To a solution of (−)-**33** (450 mg, 1.016 mmol), 206 (975 mg, 5.081 mmol), triphenylphosphine (665 mg, 2.541 mmol) in benzene (10 mL) was added diethyl azodicarboxylate (0.409 mL, 2.591 mmol). After 24 h, the resultant mixture was added to brine (25 mL) and extracted with ether (2×25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (−)-**34** (535 mg, 89% yield) as a colorless oil: $[\alpha]_D^{23}=-7.8°$ (*c* 0.50, $CHCl_3$); IR (neat): 3000 (s), 2920 (m), 1720 (s), 1590 (m), 1510 (s), 1470 (s), 1430 (m), 1260 (s), 1200 (s), 1110 (s), 750 (s), 660 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (m, 3H), 6.88 (d, *J*=8.2 Hz, 2H), 6.82 (d, *J*=7.7 Hz, 1H), 6.74 (d, *J*=8.3 Hz, 1H), 5.89–6.00 (m, 1H), 5.77–5.86 (m, 1H), 5.32 (m, 1H), 4.93–5.12 (m, 4H), 4.45 (m, 1H), 3.81 (m, 3H), 3.77 (m, 3H), 3.60 (m, 2H), 3.38 (d, *J*=6.5 Hz, 2H), 2.04 (m, 2H), 1.93 (m, 2H), 1.62–1.75 (m, 2H), 1.33–1.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 159.1, 156.2, 138.7, 138.2, 136.3, 130.5, 130.1, 129.2, 124.2, 121.6, 116.3, 114.4, 113.8, 113.7, 108.9, 72.9, 72.7, 66.5, 55.6, 55.2, 37.2, 34.3, 34.2, 33.6, 28.8, 24.6; high resolution mass spectrum (ESI, Na) *m/z* 475.2448 [(M+Na)$^+$; calcd for $C_{28}H_{36}O_5Na$: 475.2460].

4.1.25. Lactone (−)-36 and (−)-37. To a solution of the Grubbs catalyst $(Cy_3P)_2Cl_2Ru{=}CHPh$ (49 mg, 0.0597 mmol, 10 mol%) in dry CH_2Cl_2 (80 mL) was added a solution of (−)-**34** (270 mg, 0.597 mmol) in CH_2Cl_2 (6 mL). The reaction mxture was stirred for 24 h at ambient temperature and poured into H_2O (20 mL). The organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 9:1) afforded **35** (250 mg, 92%) as a colorless oil which was directly used for the next step. To a solution of **35** (250 mg, 0.589 mmol) in CH_2Cl_2 (20 mL) was added DDQ (267 mg, 1.178 mmol) followed by pH 7 buffer (1 mL). The reaction mixture was allowed to stir at room temperature for 40 min before being quenched with saturated $NaHCO_3$ (20 mL). The mixture was diluted with CH_2Cl_2 (100 mL) and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 2:1) afforded (−)-**36** (110 mg) and (−)-**37** (56 mg) as colorless oil: (−)-**36**: $[\alpha]_D^{23}=-50.0°$ (*c* 1.17, $CHCl_3$); IR (neat): 3530 (br, m), 3000 (m), 2920 (s), 1710 (s), 1580 (s), 1470 (s), 1270 (s), 1120 (s), 1070 (s), 970 (s), 630 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, *J*=8.1 Hz, 1H), 6.80 (m, 2H), 5.35–5.45 (m, 1H), 5.20–5.33 (m, 2H), 3.80 (s, 3H), 3.70–3.90 (m, 2H), 3.14 (d, *J*=11.7 Hz, 1H), 2.82–3.00 (br, s, 1H), 2.12–2.21 (m, 1H), 1.75–1.90 (m, 2H), 1.52–1.77 (m, 4H), 1.44 (m, 1H), 1.25 (m, 1H), 1.06 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 156.7, 140.1, 132.0, 130.5, 128.9, 123.6, 122.8, 109.7, 71.2, 59.0, 55.8, 37.7, 37.2, 33.0, 32.8, 24.6, 19.7; high resolution mass spectrum (ESI, Na) *m/z* 327.1556 [(M+Na)$^+$; calcd for $C_{18}H_{24}O_4Na$: 327.1572]. (−)-**37**: $[\alpha]_D^{23}=-76.0°$ (*c* 0.25, $CHCl_3$); IR (neat): 3495 (br, m), 2923 (s), 2855 (s), 1714 (s), 1587 (s), 1470 (s), 1262 (s), 1072 (s), 1055 (s), 761 (m), 696 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J*=8.0 Hz, 1H), 6.91 (d, *J*=7.7 Hz, 1H), 6.73 (d, *J*=8.4 Hz, 1H), 5.43 (t, *J*=10.7 Hz, 1H), 5.34 (m, 1H), 5.17 (m, 1H), 3.83 (s, 3H), 3.78 (m, 2H), 3.76 (dd, *J*=14.7, 10.9 Hz, 1H), 3.17 (dd, *J*=14.7, 2.7 Hz, 1H), 2.43 (m, 1H), 2.30 (m, 1H), 2.19 (m, 1H), 2.00 (m, 1H), 1.93 (m, 1H), 1.70 (m, 1H), 1.50 (m, 1H), 1.33–1.48 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 155.8, 139.6, 130.4, 130.1, 129.5, 122.2, 108.4, 74.5, 60.5, 55.7, 35.0, 31.4, 30.2, 29.6, 26.5, 24.0, 18.0; high resolution mass spectrum (ESI, Na) *m/z* 327.1580 [(M+Na)$^+$; calcd for $C_{18}H_{24}O_4$: 327.1572].

4.1.26. Alcohol (+)-38. To a suspension of $Pd(OH)_2/C$ (20 mg) in MeOH (2 mL) was added a solution of (−)-**37** (80 mg, 0.2632 mmol) in MeOH (5 mL). The mixture was allowed to stir at ambient temperature under H_2 atmosphere. After 8 h, the mixture was filtered and the concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 2:1) provided (+)-**38** (72 mg, 89% yield) as a colorless oil. $[\alpha]_D^{23}=+1.2°$ (*c* 0.33, $CHCl_3$); IR (neat): 3520 (br, s), 2990 (m), 2920 (s), 1710 (s), 1590 (s), 1460 (s), 1430 (m), 1260 (s), 1110 (s), 1070 (s), 890 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, *J*=8.0 Hz, 1H), 6.81 (d, *J*=7.6 Hz, 1H), 6.73 (d, *J*=8.3 Hz, 1H), 5.38 (m, 1H), 3.80 (s, 3H), 3.71–3.86 (m, 2H), 2.73 (m, 1H), 2.58 (m, 1H), 2.49 (br, s, 1H), 2.10 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.59–1.70 (m, 4H), 1.50 (m, 1H), 1.35–1.47 (m, 3H), 1.20–1.32 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 155.9, 141.9, 130.3, 124.4, 122.4, 108.2, 74.5, 59.8, 55.7, 36.1, 30.3, 26.2, 25.0, 23.7, 20.7; high resolution mass spectrum (ESI, Na) *m/z* 329.1713 [(M+Na)$^+$; calcd for $C_{18}H_{26}O_4Na$: 329.1729].

4.1.27. Aldehyde (−)-39. To a solution of (−)-**36** (82 mg, 0.270 mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (172 mg, 0.405 mmol). The reaction mixture was stirred at room temperature for 30 min before being quenched with aqueous $Na_2S_2O_3$ (15%, 5 mL) and saturated $NaHCO_3$ (5 mL). The mixture was diluted with CH_2Cl_2 (100 mL) and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) provided (−)-**39** (73 mg, 90% yield) as a colorless oil: $[\alpha]_D^{23}=-55.5°$ (*c* 0.47, $CHCl_3$); IR (neat): 2920 (m), 2830 (m), 1720 (s), 1590 (m), 1580 (m), 1460 (s), 1430 (m), 1270 (s), 1250 (m), 1110 (s), 1060 (s), 960 (m), 620 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.89 (t, *J*=2.5 Hz, 1H), 7.27 (t, *J*=9.0 Hz, 1H), 6.80 (d, *J*=8.0 Hz, 2H), 5.50 (m, 1H), 5.38–5.49 (m, 1H), 5.25–5.35 (m, 1H), 3.77 (s, 3H), 3.72 (dd, *J*=14.5, 10.3 Hz, 1H), 3.16 (dd, *J*=14.5, 3.0 Hz, 1H), 2.71 (m, 2H), 2.21 (m, 1H), 1.63–1.79 (m, 4H), 1.50 (m, 1H), 1.24 (m, 1H), 1.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 156.9, 139.6, 132.4, 130.5, 129.0, 123.5, 122.4, 109.4, 67.9, 55.6, 47.7, 37.7, 32.8, 32.6, 24.5, 19.8; high resolution mass spectrum (CI, NH_3); *m/z* 303.1595 [(M+H)$^+$; calcd for $C_{18}H_{23}O_4$: 303.1596].

4.1.28. Allyl ester (−)-40. To a suspension of NaH (60% dispersion in mineral oil, 14 mg, 0.335 mmol) in THF (5 mL) at 0°C was added a solution of allyl diethylphosphonoacetate (75 mg, 0.318 mmol) in THF (2 mL). The resulting mixture was stirred at 0°C for 30 min. A solution of (−)-**39** (92 mg, 0.303 mmol) in THF (3 mL) was added dropwise. The resultant mixture was warmed up to room temperature and stirred for 1 h before being quenched with saturated NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (2×20 mL). The combined organic

phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) provide (−)-**40** (55 mg, 96% yield) as a colorless oil: $[\alpha]_D^{23}=-27.4°$ (*c* 0.39, $CHCl_3$); IR (neat): 2930 (m), 1720 (s), 1583 (m), 1470 (m), 1438 (m), 1275 (s), 1257 (m), 1171 (m), 1117 (m), 1069 (m), 977 (m), 935 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J*=8.2 Hz, 1H), 7.14 (dt, *J*=15.7, 7.3 Hz, 1H), 7.81 (d, *J*=8.4 Hz, 1H), 7.79 (d, *J*=7.5 Hz, 1H), 5.96 (m, 1H), 5.95 (d, *J*=15.7 Hz, 1H), 5.42 (m, 1H), 5.30 (dd, *J*=17.1, 1.5 Hz, 1H), 5.29 (m, 1H), 5.24 (dd, *J*=10.5, 1.5 Hz, 1H), 5.17 (m, 1H), 3.83 (s, 3H), 3.75 (dd, *J*=14.4, 10.5 Hz, 1H), 3.15 (dd, *J*=14.4, 10.5 Hz, 1H), 2.69 (m, 1H), 2.56 (m, 1H), 2.20 (m, 1H), 1.60–1.75 (m, 3H), 1.54 (m, 1H), 1.47 (m, 1H), 1.20–1.34 (m, 2H), 1.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$)??? δ 167.9, 165.8, 156.9, 145.0, 139.6, 132.3, 132.2, 130.0, 129.1, 123.4, 122.4, 118.1, 109.4, 71.0, 64.9, 55.6, 37.7, 36.6, 32.9, 32.1, 24.6, 19.7; high resolution mass spectrum (ESI, Na) *m/z* 407.1843 [(M+H)$^+$; calcd for $C_{23}H_{28}O_5Na$: 407.1834].

4.1.29. Phenol (−)-41. A solution of (−)-**40** (43 mg, 0.112 mmol) in CH_2Cl_2 (40 mL) at −78°C was treated with BBr_3 (1.0 M in CH_2Cl_2, 336 μL, 0.336 mmol). The mixture was stirred at −78°C for 2 h, and then quenched with saturated NH_4Cl (20 mL). The mixture was allowed to warm up to room temperature and diluted with CH_2Cl_2 (50 mL). The organic layer was washed brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) provided (−)-**41** (36 mg, 87% yield) as a colorless oil: $[\alpha]_D^{23}=-21.3°$ (*c* 0.40, $CHCl_3$); IR (neat): 3386 (br, m), 2929 (m), 1722 (s), 1698 (s), 1651 (m), 1588 (m), 1465 (m), 1292 (s), 1257 (s), 1116 (m), 1062 (m), 974 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.75–9.05 (br, s, 1H), 7.29 (t, *J*=7.8 Hz, 1H), 7.03 (dt, *J*=15.7, 7.9 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 1H), 6.77 (d, *J*=7.4 Hz, 1H), 6.00 (dt, *J*=15.6, 1.4 Hz, 1H), 5.95 (m, 1H), 5.25 (d, *J*=17.2 Hz, 1H), 5.29–5.42 (m, 3H), 5.28 (d, *J*=10.5 Hz, 1H), 4.68 (dt, *J*=5.6, 1.4 Hz, 2H), 3.73 (dd, *J*=15.3, 6.5 Hz, 1H), 3.50 (dd, *J*=15.3, 4.4 Hz, 1H), 2.62 (td, *J*=6.1, 1.3 Hz, 2H), 2.10 (m, 1H), 1.96 (m, 1H), 1.60–1.77 (m, 2H), 1.25–1.60 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 165.5, 159.2, 143.5, 142.9, 133.0, 132.2, 130.8, 130.5, 124.3, 123.0, 118.1, 116.1, 73.2, 65.1, 65.0, 38.7, 37.5, 32.8, 32.7, 25.0. 20.6, 20.5; high resolution mass spectrum (ESI, Na) *m/z* 393.1782 [(M+Na)$^+$; calcd for $C_{22}H_{26}O_5Na$: 393.1778].

4.1.30. TBS ether (−)-42. A solution of (−)-**41** (39 mg, 0.105 mmol) in CH_2Cl_2 (8 mL) was treated with triethylamine (45 μL, 0.316 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (29 μL, 0.126 mmol) at −78°C. After 10 min, the solution was warmed up to ambient temperature, added to brine-saturated $NaHCO_3$ (1:1, 20 mL), and extracted with ether (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (−)-**42** (45 mg, 88% yield) as a colorless oil: $[\alpha]_D^{23}=-13.3°$ (*c* 0.85, $CHCl_3$); IR (neat): 2930 (s), 1723 (s), 1580 (m), 1462 (s), 1290 (s), 1258 (s), 1167 (m), 1065 (m), 973 (m), 841 (s), 785 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.12 (t, *J*=7.8 Hz, 1H), 6.94 (dt, *J*=15.6, 7.5 Hz, 1H), 6.76 (d, *J*=7.5 Hz, 1H), 6.74 (d, *J*=8.3 Hz, 1H), 5.95 (m, 1H), 5.93 (m, 1H), 5.35 (dd, *J*=17.6, 1.6 Hz, 1H), 5.30 (m, 1H), 5.27 (d, *J*=10.6 Hz, 1H), 5.00 (m, 1H), 4.63 (d, *J*=5.7 Hz, 1H), 3.70 (dd, *J*=14.4, 10.2 Hz, 1H), 3.14 (dd, *J*=14.4, 2.5 Hz, 1H), 2.78 (m, 1H), 2.50 (m, 1H), 2.19 (m, 1H), 1.62–1.74 (m, 2H), 1.55–1.62 (m, 2H), 1.45 (m, 1H), 1.26 (m, 1H), 1.03 (m, 1H), 0.95 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 165.6, 152.8, 144.1, 140.0, 132.2, 131.6, 129.8, 129.5, 126.5, 123.8, 122.8, 118.1, 117.6, 71.6, 65.0, 37.9, 37.0, 32.8, 31.9, 25.7, 24.7, 19.4, 18.5, −3.9, −4.0; high resolution mass spectrum (ESI, Na) *m/z* 507.2563 [(M+Na)$^+$; calcd for $C_{28}H_{40}O_5SiNa$: 507.2543].

4.1.31. Acid (−)-43. To a solution of (−)-**42** (45 mg, 0.093 mmol) in dry THF (6 mL) was added a solution of $Pd(PPh_3)_4$ (11 mg, 0.0093 mmol) and morpholine (81 μL, 0.93 mmol) at ambient temperature. The reaction mixture was allowed to stir for 12 h. HCl (1N, 10 mL) was added and the aqueous phase was extracted with Et_2O (2×50 mL). The combined organic phases were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded (−)-**43** (35 mg, 85% yield) as a colorless oil: $[\alpha]_D^{23}=-16.0°$ (*c* 0.15, $CHCl_3$); IR (neat): 2930 (s), 1721 (s), 1698 (s), 1655 (m), 1463 (s), 1435 (m), 1288 (s), 1257 (s), 1113 (m), 840 (s), 785 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (t, *J*=7.8 Hz, 1H), 7.05 (m, 1H), 6.78 (d, *J*=7.4 Hz, 1H), 6.74 (d, *J*=8.3 Hz, 1H), 5.91 (d, *J*=15.6 Hz, 1H), 5.40 (m, 1H), 5.31 (m, 1H), 5.01 (m, 1H), 3.72 (dd, *J*=14.4, 10.4 Hz, 1H), 3.16 (dd, *J*=14.4, 2.4 Hz, 1H), 2.80 (m, 1H), 2.54 (m, 1H), 2.20 (m, 1H), 1.68 (m, 2H), 1.59 (m, 2H), 1.46 (m, 1H), 1.30 (m, 1H), 1.05 (m, 1H), 0.97 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 168.3, 152.8, 146.6, 139.8, 131.6, 129.6, 126.5, 123.3, 122.8, 117.6, 71.5, 37.9, 37.1, 32.8, 32.0, 25.8, 24.7, 19.4, 18.5, − 3.9, −4.0; high resolution mass spectrum (ESI, Na) *m/z* 467.2335 [(M+Na)$^+$; calcd for $C_{25}H_{36}O_5Si$: 467.2330].

4.1.32. Enecarbamate (−)-44. To a solution of (−)-**43** (40 mg, 0.090 mmol) in dry acetone (4 mL) was sequentially added *N,N*-diisopropylethylamine (24 mg, 32 μL, 0.094 mmol) and isobutylchloroformate (27 mg, 27 μL, 0.092 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 h, and then a solution of sodium azide (58 mg, 0.902 mmol) in distilled H_2O (2 mL) was added. The resulting mixture was stirred at ambient temperature for an additional 30 min. Brine (10 mL) was added and the aqueous phase extracted with ethyl acetate (2×20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was azeotropically dried with benzene (2×2 mL) and then dissolved in dry toluene (2 ml) and heated at reflux for 15 min. 2-(Trimethylsilyl)-ethanol (130 μL, 0.902 mmol) was added in one portion and the mixture was heated at reflux for an additional 10 min. The mixture was then cooled to ambient temperature and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (−)-**44** (40.6 mg, 81%) as a colorless oil: $[\alpha]_D^{23}=-15.4°$ (*c* 0.80, CH_2Cl_2); IR (neat): 3334 (br, m), 2950 (s), 1715 (s), 1681 (s), 1519 (m), 1463 (s), 1291 (s), 1253 (s), 1230 (s), 839 (s), 785 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.01 (t, *J*=8.1 Hz, 1H), 6.94 (t,

J=12.0 Hz, 1H), 6.77 (d, J=8.3 Hz, 1H), 6.71 (d, J=7.6 Hz, 1H), 6.00 (d, J=9.3 Hz, 1H), 5.51 (m, 1H), 5.40 (m, 1H), 5.12 (m, 1H), 4.84 (m, 1H), 4.32 (t, J=8.1 Hz, 1H), 4.08 (dd, J=14.4, 10.4, Hz, 1H), 3.17 (dd, J=14.4, 2.2 Hz, 1H), 2.80 (m, 1H), 2.43 (m, 1H), 2.15 (m, 1H), 1.60–1.78 (m, 2H), 1.50–1.62 (m, 2H), 1.05 (s, 9H), 0.95–1.00 (m, 3H), 0.24 (s, 3H), 0.20 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.9, 153.2, 153.1, 140.1, 131.6, 129.8, 129.5, 126.3, 122.9, 117.7, 104.9, 73.2, 63.1, 38.1, 34.9, 33.0, 31.6, 25.7, 24.9, 19.5, 18.4, 17.7, −1.89, −4.2, −4.3; high resolution mass spectrum (ESI, Na) m/z 582.3054 [(M+Na)$^+$; calcd for $C_{30}H_{49}NO_5Si_2Na$: 582.3047].

4.1.33. Enamide (−)-45. A solution of (−)-**44** (14 mg, 0.025 mmol) in dry THF (1 mL) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 30 μL, 0.030 mmol) for 5 min at 0°C. A solution of **6** (6.4 mg, 0.050 mmol) in dry benzene (0.1 mL) was added. The resulting mixture was stirred at 0°C for 10 min before being quenched with saturated NH_4Cl (3 mL) and extracted with ether (2×15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 10:1) provided (−)-**45** (12.5 mg, 75%) as a colorless oil: $[\alpha]_D^{23}$=−43.8° (c 0.60, CH_2Cl_2); IR (neat): 2954 (s), 1722 (s), 1594 (m), 1580 (m), 1463 (s), 1290 (s), 1255 (s), 1230 (m), 1117 (m), 1063 (m), 840 (s), 784 (m) cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 7.53 (t, J=11.3 Hz, 1H), 6.92 (t, J=8.0 Hz, 1H), 6.74 (td, J=11.8 Hz, 1.2 Hz, 1H), 6.65 (d, J=8.2 Hz, 1H), 6.61 (d, J=8.5 Hz, 1H), 6.50–6.58 (m, 2H), 5.81 (m, 1H), 5.61 (dd, J=18.2, 9.5 Hz, 1H), 5.35–5.42 (m, 1H), 5.21–5.31 (m, 1H), 5.14 (m, 1H), 4.15–4.21 (m, 2H), 3.98 (dd, J=14.1, 10.4 Hz, 1H), 3.06 (dt, J=14.1, 2.5 Hz, 1H), 2.88 (m, 1H), 2.55 (m, 1H), 2.02 (br, d, J=8.6 Hz, 1H), 1.85–1.94 (m, 2H), 1.60–1.72 (m, 2H), 1.46–1.60 (m, 2H), 1.30–1.46 (m, 3H), 0.95 (s, 9H), 0.86–0.93 (m, 2H), 0.72 (t, J=7.5 Hz, 3H), 0.13 (s, 3H), 0.09 (s, 3H), −0.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 167.2, 154.0, 153.4, 142.8, 140.4, 137.4, 131.8, 130.0, 129.8, 127.8, 126.9, 125.2, 123.2, 122.7, 121.1, 118.0, 72.9, 65.4, 38.3, 35.6, 33.3, 32.0, 26.0, 25.2, 20.9, 19.8, 18.7, 17.6, 13.9, −1.7, −3.8, −4.0; high resolution mass spectrum (ESI, Na) m/z 690.3644 [(M+Na)$^+$; calcd for $C_{37}H_{57}NO_6Si_2Na$: 690.3622].

4.1.34. Analog (−)-3. A solution of (−)-**45** (4.9 mg, 0.0073 mmol) in THF (1 mL) was treated with tetrabutylammonium fluoride (1.0 M in THF, 22 μl, 0.022 mmol) at 0°C. The resultant brown solution was stirred for 10 min at 0°C, added to H_2O (5 ml) and extracted with ethyl ether (2×15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 2:1) afforded (−)-**3** (2.6 mg, 85% yield) as a white solid: $[\alpha]_D^{23}$=−60.0° (c 0.26, MeOH); IR (neat): 3282 (br, s), 2927 (s), 1719 (m), 1649 (s), 1588 (s), 1464 (s), 1294 (s), 1256 (s), 1217 (s), 1060 (m), 972 (m), 955 (m) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.31 (t, J=12.0 Hz, 1H), 7.12 (t, J=7.8 Hz, 1H), 6.86 (td, J=11.6, 1.1 Hz, 1H), 6.81 (d, J=14.3 Hz, 1H), 6.72 (d, J=8.2 Hz, 1H), 6.68 (d, J=7.4 Hz, 1H), 5.81 (apparent q, J=13.8 Hz, 1H), 5.69 (d, J=11.5 Hz, 1H), 5.38 (dt, J=14.5, 7.5 Hz, 1H), 5.30–5.39 (m, 1H), 5.18–5.25 (m, 1H), 4.92–5.04 (m, 1H), 3.67 (dd, J=14.1, 10.5 Hz, 1H), 3.12 (dq, J=14.4, 2.5 Hz, 1H), 2.35–2.49 (m, 2H), 2.28 (apparent, pt, J=7.5, 1.5 Hz, 2H), 2.11–2.19 (m, 1H), 1.58–1.69 (m, 4H), 1.51–1.58 (m, 1H), 1.40–1.49 (m, 1H), 1.25–1.34 (m, 1H), 1.06–1.15 (m, 1H), 1.02 (t, J=7.4 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.4, 165.9, 156.6, 142.5, 141.1, 137.6, 133.5, 131.6, 130.6, 126.1, 125.4, 123.2, 122.2, 120.4, 115.4, 110.5, 73.9, 38.9, 36.3, 33.7, 33.1, 25.9, 21.5, 21.0, 14.4; high resolution mass spectrum (ESI, Na) m/z 432.2149 [(M+Na)$^+$; calcd for $C_{25}H_{31}NO_4Na$: 432.2151].

4.1.35. Aldehyde (+)-46. To a solution of (+)-**38** (85 mg, 0.278 mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (142 mg, 0.333 mmol). The reaction mixture was stirred at ambient temperature for 30 min before being quenched with $Na_2S_2O_3$ (15%, 5 mL) and saturated $NaHCO_3$ (5 mL). The mixture was diluted with CH_2Cl_2 (100 mL) and the organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) provided (+)-**46** (76 mg, 90% yield) as a colorless oil: $[\alpha]_D^{23}$=+8.77° (c 0.46, $CHCl_3$); IR (neat): 2990 (m), 2920 (s), 1720 (s), 1590 (s), 1460 (s), 1430 (m), 1270 (br, s), 1105 (s), 1070 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.27 (t, J=8.1 Hz, 1H), 6.81 (d, J=7.7 Hz, 1H), 5.68 (m, 1H), 3.79 (s, 3H), 2.84 (m, 1H), 2.71 (m, 1H), 2.60 (m, 2H), 2.11 (m, 1H), 1.60–1.78 (m, 4H), 1.55 (m, 1H), 1.40–1.53 (m, 3H), 1.20–1.40 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 168.2, 156.2, 141.6. 130.3, 124.2, 121.9, 121.8, 108.1, 70.7, 55.6, 46.9, 30.3, 30.2, 30.0, 26.4, 25.1, 23.9, 20.8; high resolution mass spectrum (ESI, Na) m/z 327.1679 [(M+Na)$^+$; calcd for $C_{18}H_{24}O_4Na$: 327.1673].

4.1.36. Allyl ester (−)-47. To a suspension of NaH (60% dispersion in mineral oil, 20 mg, 0.489 mmol) in THF (5 mL) at 0°C was added a solution of allyl diethylphosphonoacetate (110 mg, 0.500 mmol) in THF (2 mL). The resulting mixture was stirred at 0°C for 30 min. A solution of (+)-**46** (136 mg, 0.444 mmol) in THF (3 mL) was precooled to 0°C and added dropwise. The resultant mixture was warmed up to ambient temperature and stirred for 1 h before being quenched with saturated NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (2×20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) provided (−)-**47** (81 mg, 95% yield) as a colorless oil: $[\alpha]_D^{23}$=−9.3° (c 0.70, $CHCl_3$); IR (neat): 2936 (s), 2857 (m), 1722 (s), 1656 (m), 1583 (m), 1469 (s), 1273 (s), 1172 (s), 1113 (s), 1073 (m), 957 (m), 928 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J=7.9 Hz, 1H), 7.10 (dt, J=15.7, 7.0 Hz, 1H), 6.80 (d, J=7.7 Hz, 1H), 6.73 (d, J=8.2 Hz, 1H), 5.95 (m, 1H), 5.31 (dd, J=17.2, 1.5 Hz, 1H), 5.26 (m, 1H), 5.24 (dd, J=11.2, 1.5 Hz, 1H), 4.65 (dt, J=5.8, 1.3 Hz, 2H), 3.81 (s, 3H), 2.73 (m, 1H), 2.66 (m, 1H), 2.50–2.63 (m, 2H), 2.01 (m, 1H), 1.60–1.74 (m, 4H), 1.50 (m, 1H), 1.35–1.50 (m, 3H), 1.33 (m, 1H), 1.27 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 165.8, 156.2, 145.1, 141.5, 132.3, 130.1, 123.3, 121.8, 118.1, 108.0, 73.9, 64.9, 55.6, 35.9, 30.3, 30.1, 26.4, 25.3, 23.9, 20.7; high resolution mass spectrum (ESI, Na) m/z 409.1888 [(M+Na)$^+$; calcd for $C_{23}H_{30}O_5Na$: 409.2089].

4.1.37. Phenol (−)-48. A solution of (−)-**47** (74 mg, 0.192 mmol) in CH_2Cl_2 (70 mL) at −78°C was treated with BBr_3 (1.0 M in CH_2Cl_2, 0.576 μL, 0.576 mmol). The mixture was stirred at −78°C for 2 h, and then quenched with saturated NH_4Cl (20 mL). The mixture was allowed to warm up to room temperature and diluted with CH_2Cl_2 (80 mL). The organic layer was washed brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) provided (−)-**48** (55 mg, 83% yield) as a colorless oil: $[\alpha]_D^{23}=-52.5°$ (*c* 0.55, $CHCl_3$); IR (neat): 2932 (s), 1723 (s), 1652 (s), 1605 (s), 1448 (s), 1367 (m), 1290 (s), 1246 (s), 1114 (m), 989 (m), 814 (m), 713 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.88 (s, 1H), 7.28 (t, *J*=7.9 Hz, 1H), 6.94 (dt, *J*=15.6, 7.4 Hz, 1H), 6.81 (d, *J*=8.3 Hz, 1H), 6.72 (d, *J*=7.5 Hz, 1H), 5.95 (m, 1H), 5.92 (d, *J*=15.6 Hz, 1H), 5.37 (dd, *J*=17.2, 1.1 Hz, 1H), 5.23 (d, *J*=10.1 Hz, 1H), 5.25 (m, 1H), 4.61 (d, *J*=5.7 Hz, 2H), 3.40 (td, *J*=12.3, 2.4 Hz, 1H), 2.62 (m, 1H), 2.53 (m, 1H), 2.43 (m, 1H), 1.95 (m, 1H), 1.78 (m, 1H), 1.50–1.70 (m, 4H), 1.29–1.50 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 165.5, 162.4, 146.4, 143.3, 134.1, 132.2, 124.2, 122.5, 118.1, 115.5, 112.2, 76.3, 65.0, 37.2, 33.1, 31.2, 28.8, 27.0, 24.7, 24.2, 21.1; high resolution mass spectrum (ESI, Na) *m/z* 395.1942 $[(M+Na)^+$; calcd for $C_{22}H_{28}O_5Na$: 395.1935].

4.1.38. TBS ether (+)-49. A solution of (−)-**48** (69 mg, 0.185 mmol) in CH_2Cl_2 (8 mL) was treated with triethylamine (78 μL, 0.556 mmol) and butyldimethylsilyl trifluoromethanesulfonate (65 μL, 0.278 mmol) at −78°C. After 10 min, the solution was warmed up to ambient temperature, added to brine-saturated $NaHCO_3$ (1:1, 20 mL), and extracted with Et_2O (2×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (+)-**49** (81 mg, 90% yield) as a colorless oil: $[\alpha]_D^{23}=+15.1°$ (*c* 1.20, $CHCl_3$); IR (neat): 2930 (s), 1726 (s), 1657 (m), 1581 (m), 1464 (s), 1260 (s), 1169 (m), 1106 (m), 839 (s), 784 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, *J*=7.9 Hz, 1H), 6.91 (dt, *J*=15.6, 7.4 Hz, 1H), 6.80 (d, *J*=7.7 Hz, 1H), 6.67 (d, *J*=8.1 Hz, 1H), 5.94 (m, 1H), 5.93 (d, *J*=15.6 Hz, 1H), 5.32 (dd, *J*=17.2, 1.6 Hz, 1H), 5.24 (d, *J*=10.4 Hz, 1H), 5.23 (m, 1H), 4.62 (dt, *J*=5.7, 1.4 Hz, 1H), 2.69 (m, 1H), 2.50–2.65 (m, 3H), 2.00 (m, 1H), 1.60–1.71 (m, 4H), 1.35–1.59 (m, 5H), 1.30 (m, 2H), 0.95 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 165.6, 152.2, 143.9, 141.6, 132.2, 129.7, 127.0, 123.9, 122.2, 118.2, 116.2, 73.6, 65.0, 36.0, 30.8, 30.2, 29.1, 26.1, 25.8, 25.7, 23.3, 21.0, 18.2, −4.0, −4.4; high resolution mass spectrum (ESI, Na) *m/z* 509.2711 $[(M+Na)^+$; calcd for $C_{28}H_{42}O_5SiNa$: 509.2699].

4.1.39. Acid (+)-50. To a solution of (+)-**49** (70 mg, 0.093 mmol) in dry THF (10 mL) was added a solution of $Pd(PPh_3)_4$ (16 mg, 0.015 mmol) and morpholine (126 μL, 1.44 mmol) at room temperature. The reaction mixture was allowed to stir for 3 h. HCl (1N, 10 mL) was added and the aqueous phase was extracted with Et_2O (2×50 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 4:1) afforded (+)-**50** (52 mg, 82% yield) as a colorless oil: $[\alpha]_D^{23}=+13.8°$ (*c* 0.28, $CHCl_3$); IR (neat): 2930 (s), 2858 (s), 1726 (s), 1698 (s), 1464 (s), 1277 (s), 1261 (s), 1107 (m), 1058 (m), 839 (s), 784 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.14 (t, *J*=7.8 Hz, 1H), 7.02 (dt, *J*=15.6, 7.8 Hz, 1H), 6.81 (d, *J*=7.7 Hz, 1H), 6.68 (d, *J*=8.2 Hz, 1H), 5.94 (d, *J*=15.6 Hz, 1H), 5.23 (m, 1H), 2.73 (m, 1H), 2.51–2.68 (m, 3H), 2.02 (m, 1H), 1.59–1.72 (m, 4H), 1.30–1.58 (m, 7H), 0.97 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 168.2, 152.2, 146.4, 141.6, 129.8, 126.9, 123.3, 122.2, 116.3, 73.5, 36.1, 30.8, 30.1, 29.3, 26.1, 25.9, 25.7, 23.2, 21.0, 18.2, −4.1, −4.4; high resolution mass spectrum (ESI, Na) *m/z* 469.2352 $[(M+Na)^+$; calcd for $C_{25}H_{38}O_5SiNa$: 469.2386].

4.1.40. Enecarbamate (+)-51. To a solution of (+)-**50** (25 mg, 0.056 mmol) in acetone (3 mL) was sequentially added *N,N*-diisopropylethylamine (15 mg, 20 μL, 0.117 mmol) and isobutylchloroformate (15 mg, 15 μL, 0.112 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 h and then a solution of sodium azide (36 mg, 0.560 mmol) in distilled H_2O (1.5 mL) was added. The resulting mixture was stirred at room temperature for an additional 30 min. Brine (10 mL) was added and the aqueous phase extracted with ethyl acetate (2×30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was azeotropically dried with benzene (2×1 mL) and dissolved in toluene (2 ml) and heated at reflux for 15 min. 2-(trimethylsilyl)-ethanol (80 μL, 0.560 mmol) was added in one portion and the mixture was heated at reflux for an additional 10 min. The mixture was cooled to room temperature and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 20:1) afforded (+)-**51** (24.6 mg, 78%) as a colorless oil: $[\alpha]_D^{23}=+4.8°$ (*c* 0.95, CH_2Cl_2); IR (neat): 2952 (s), 1722 (s), 1681 (s), 1520 (m), 1464 (s), 1277 s), 1252 (s), 1112 (m), 1057 (m), 838 (s), 783 (m) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.00 (t, *J*=8.0 Hz, 1H), 6.82 (m, 1H), 6.70 (d, *J*=7.7 Hz, 1H), 6.88 (d, *J*=7.2 Hz, 1H), 5.92 (br, d, *J*=9.6 Hz, 1H), 5.25 (m, 1H), 4.64 (m, 1H), 4.23 (t, *J*=8.3 Hz, 2H), 2.76 (m, 1H), 2.50 (m, 2H), 2.28 (m, 1H), 1.95 (m, 1H), 1.71 (m, 1H), 1.44–1.67 (m, 4H), 1.17–1.44 (m, 6H), 1.03 (s, 9H), 0.92 (t, *J*=8.3 Hz, 2H), 0.18 (s, 3H), 0.14 (s, 3H), −0.10 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 167.8, 153.3, 152.6, 141.8, 129.5, 128.3, 126.4, 122.4, 116.6, 104.6, 75.3, 63.1, 33.8, 30.9, 30.2, 28.8, 26.2, 26.1, 25.7, 23.3, 21.4, 18.2, 17.7, −1.9, −4.2, −4.6; high resolution mass spectrum (ESI, Na) *m/z* 584.3292 $[(M+Na)^+$; calcd for $C_{30}H_{51}NO_5SiNa$: 584.3304].

4.1.41. Enamide (+)-52. A solution of (+)-**51** (17 mg, 0.0303 mmol) in dry THF (2 mL) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF, 36 μL, 0.0364 mmol) for 5 min at 0°C. A solution of **6** (7.7 mg, 0.0606 mmol) in dry benzene (0.2 mL) was added. The resulting mixture was stirred at 0°C for 10 min before being quenched with saturated NH_4Cl (5 mL) and extracted with Et_2O (2×20 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 10:1) provided (+)-**52** (15.4 mg, 76%) as a colorless oil: $[\alpha]_D^{23}=+6.0°$ (*c* 0.20, CH_2Cl_2); IR (neat): 2953 (s), 1726 (s), 1692 (m), 1580 (m), 1464 (s), 1278 (s), 1252 (s), 1110 (m), 1053 (m), 839 (s), 783 (m) cm^{-1}; ^1H NMR

(500 MHz, C_6D_6) δ 7.56 (t, J=10.1 Hz, 1H), 6.98 (t, J=7.9 Hz, 1H), 6.74 (t, J=11.7 Hz, 1H), 6.67 (d, J=8.1 Hz, 1H), 6.51 (d, J=11.5 Hz, 1H), 6.49 (d, J=14.2 Hz, 1H), 5.70–5.79 (m, 1H), 5.61 (dd, J=18.2, 9.5 Hz, 1H), 5.33–5.40 (m, 1H), 4.12–4.21 (m, 2H), 2.63–2.79 (m, 2H), 2.43–2.52 (m, 2H), 1.97–2.05 (m, 1H), 1.88–1.95 (m, 2H), 1.62–1.72 (m, 2H), 1.54–1.62 (m, 2H), 1.42–1.50 (m, 1H), 1.26–1.40 (m, 4H), 1.11–1.21 (m, 2H), 1.01 (s, 9H), 0.84–0.90 (m, 2H), 0.62 (t, J=7.6 Hz, 3H), 0.18 (s, 3H), 0.12 (s, 3H), −0.13 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 168.0, 167.2, 154.0, 152.9, 142.8, 142.1, 137.5, 129.8, 128.3, 127.8, 127.0, 125.2, 122.6, 122.4, 121.1, 116.8, 74.9, 65.3, 34.7, 31.2, 30.6, 29.2, 26.2, 26.0, 23.8, 21.4, 21.0, 18.5, 17.6, 13.9, −1.7, −4.0, −4.2; high resolution mass spectrum (ESI, Na) m/z 692.3760 [(M+Na)$^+$; calcd for $C_{37}H_{59}NO_6Si_2Na$: 692.3779].

4.1.42. Analog (−)-4. A solution of (+)-**52** (7.8 mg, 0.0117 mmol) in THF (1 mL) was treated with tetrabutylammonium fluoride (1.0 M in THF, 35 μl, 0.0351 mmol) at 0°C. The resultant brown solution was stirred for 10 min at 0°C, added to H_2O (5 ml), and extracted with ethyl ether (2×15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (hexanes/ethyl acetate, 2:1) afforded (−)-**4** (4.1 mg, 86% yield) as a white solid: $[\alpha]_D^{23}$=−15.9° (c 0.37, CH_2Cl_2); IR (neat): 2953 (s), 1726 (s), 1692 (m), 1580 (m), 1464 (s), 1278 (s), 1252 (s), 1110 (m), 1.53 (m), 839 (s), 783 (m) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.56 (t, J=10.1 Hz, 1H), 6.98 (t, J=7.9 Hz, 1H), 6.74 (t, J=11.7 Hz, 1H), 6.67 (d, J=7.7 Hz, 1H), 6.62 (d, J=8.1 Hz, 1H), 6.51 (d, J=11.5 Hz, 1H), 6.49 (d, J=14.2 Hz, 1H), 5.70–5.79 (m, 1H), 5.61 (dd, J=18.2, 9.5 Hz, 1H), 5.33–5.40 (m, 1H), 4.12–4.21 (m, 2H), 2.63–2.79 (m, 2H), 2.43–2.52 (m, 2H), 1.97–2.05 (m, 1H), 1.88–1.95 (m, 2H), 1.62–1.72 (m, 2H), 1.54–1.62 (m, 2H), 1.42–1.50 (m, 1H), 1.26–1.40 (m, 4H), 1.11–1.21 (m, 2H), 1.01 (s, 9H), 0.84–0.90 (m, 2H), 0.62 (t, J=7.6 Hz, 3H), 0.18 (s, 3H), 0.12 (s, 3H), −0.13 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.0, 167.2, 154.0, 152.9, 142.8, 142.1, 137.5, 129.8, 128.3, 127.8, 127.0, 125.2, 122.6, 122.4, 121.1, 116.8, 74.9, 65.3, 34.7, 31.2, 30.6, 29.2, 26.6, 26.2, 26.0, 23.8, 21.4, 21.0, 18.5, 17.6, 13.9, −1.7, −4.0, −4.2; high resolution mass spectrum (ESI, Na) m/z 434.2307 [(M+Na)$^+$; calcd for $C_{25}H_{33}NO_4Na$: 434.2286].

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References

1. Erickson, K. L.; Beutler, J. A.; Cardellina, II, J. A.; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188–8192. Erickson, K. L.; Beutler, J. A.; Cardellina, II, J. A.; Boyd, M. R. *J. Org. Chem.* **2001**, *66*, 1532.
2. Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 4308–4310. Wu, Y.; Seguil, O. R.; De Brabander, J. K. *Org. Lett.* **2000**, *26*, 4241–4244. Wu, Y.; Liao, X.; Wang, R.; Xie, X.; De Brabander, J. K. *J. Am. Chem. Soc.* **2002**, *124*, 3245–3253.
3. The absolute stereochemistry, initially assigned by Boyd and co-workers based on Mosher ester analysis, was reassigned by De Brabander et al., see: Ref. 2.
4. Paull, K. D.; Hamel, E.; Malspeis, L. Prediction of Biochemical Mechanism of Action from the In vitro Antitumor Screen of the National Cancer Institute. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; American Chemical Society: Washington, DC, 1995.
5. Boyd, M. R.; Farina, C.; Belfiore, P.; Gagliardi, S.; Kim, J. M.; Kayakawa, Y.; Beutler, J. A.; Mckee, T. C.; Bowman, B. J.; Bowman, E. J. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 114–120.
6. Kunze, B.; Jansen, R.; Sasse, F.; Hofle, H.; Reichenbach, H. *J. Antbiot.* **1998**, *51*, 1075–1080. Jansen, R.; Kunze, B.; Sasse, F.; Reichenbach, H.; Hofle, H. *J. Org. Chem.* **2000**, 913–919.
7. McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, II, J. H.; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805–7810. Suzumura, K. I.; Takahashi, I.; Matsumoto, H.; Nagai, K.; Setiawan, B.; Rantiatmodjo, R. M.; Suzuki, K. I.; Nagano, N. *Tetrahedron Lett.* **1997**, *38*, 7573–7576.
8. Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153–155.
9. Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kijima, N. J. *J. Antibiot.* **1998**, *51*, 14–20.
10. Labrecque, D.; Chatton, S.; Sej, R.; Blais, C.; Lamothe, S. *Tetrahedron Lett.* **2001**, *42*, 2645–2648.
11. Snider, B. B.; Song, F. *Org. Lett.* **2001**, *42*, 2645–2648.
12. Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286–5298.
13. Preliminary communication: Smith, A. B.; Zheng, J. *Synlett.* **2001**, 1019–1023, Spec. Issue.
14. For synthetic studies on the salicylihlamides lactone core, see: Furstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731–3734. Feutrill, J. T.; Holloway, G. A.; Hilli, F.; Hugel, H. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2000**, *41*, 8569–8572. Georg, G. I.; Ahn, Y. M.; Blackman, B.; Farokhi, F.; Flaherty, P. T.; Mossman, C. J.; Roy, S.; Yang, K. *Chem. Commun.* **2001**, 255–256.
15. For investigations into syntheses of the salicylihalamide and oximidine side chains, see: Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407–408. Kuramochi, K.; Watanabe, H.; Kitahara, T. *Synlett.* **2000**, 397–399. Shen, R.; Porco, Jr J. A. *Org. Lett.* **2000**, *2*, 1333–1336. Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735–3738. Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955–3957.
16. Shimasaki, H.; Kagechika, H.; Fukasawa, H.; Kawachi, E.; Shudo, K. *Chem. Pharm. Bull.* **1995**, *43*(1), 100–107.
17. For reviews, see: Trnka, T.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. Fürstner, A. *Angew. Chem.* **2000**, *112*, 3140–3172. Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*,

37–72. Fürstner, A.; Seidel, G.; Kiwdler, N. *Tetrahedron* **1999**, *55*, 8215–8230.
18. Mitsunobu, O. *Synthesis* **1981**, 1–28.
19. De Silva, S. O.; Reed, J. N.; Billedeau, R. J.; Wang, X.; Norris, D. J.; Snieckus, V. *Tetrahedron* **1992**, *48*, 4863–4878. Bibi, M. P.; Jalil Miah, M. A.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 737–742.
20. Yoshiharu, T.; Nagata, Y.; Itoh, E.; Hashimoto, M.; Katoh, T.; Terasima, S. *Tetrahedron* **1997**, *53*, 10239–10252.
21. Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J. W.; Ito, Y. *J. Org. Chem.* **1984**, *49*, 2837–2838.
22. Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348. Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348–6359.
23. Brown, H. C.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 5694–5695.
24. Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
25. Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44–57.
26. Shing, T. K. M.; Tam, E. K. W. *Tetrahedron: Asymmetry* **1996**, *7*, 353–356.
27. Hong, C. H.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693–9694.
28. Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *20*, 1503–1505. Linstrumelle, G.; Lorne, R.; Dang, H. P. *Tetrahedron lett.* **1978**, *19*, 4069–4070.
29. Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851–3854.
30. Corey, E. J.; Pan, B. C.; Hua, D. H.; Deardorff, D. R. *J. Am. Chem. Soc.* **1982**, *104*, 6816–6818.
31. Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 3279. Wrobel, J. E.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 3761–3764.
32. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *24*, 5005–5038.
33. For examples of reversible olefin metathesis reactions, see: Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1101–1103. Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302–10316. Hamilton, D. G.; Feeder, N.; Teat, S. J.; Sanders, J. K. M. *J. Chem.* **1998**, *22*, 1019–1021. Smith, III, A. B.; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990–991. Lee, W. C.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145–2147. Fürstner, A.; Thiel, O. R. *Ackermann Org. Lett.* **2001**, *3*, 449–451. Lee, W. C.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155–7158. Wright, D. L.; Usher, L. C.; Estrella-Jimenez, M. *Org. Lett.* **2001**, *3*, 4275–4277.
34. Lampilas, M.; Lett, R. *Tetrahedron Lett.* **1992**, *33*, 777–780.
35. Dess, D. B.; Martin, J. C. *J. Am. Chem.Soc.* **1991**, *113*, 7277–7287.
36. Bogucki, D. E.; Chalton, J. L. *Can. J. Chem.* **1997**, *75*, 1783–1794.
37. Furber, M.; Taylor, R. J. K. *J. Chem. Soc. Perkin Trans. I* **1986**, 1809–1815. Furber, M.; Taylor, R. J. K. J.; Burford, S. C. *Tetrahedron Lett.* **1985**, *26*, 3285–3288.
38. Weinstock, J. *J. Org. Chem.* **1961**, *26*, 3511–3514. Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164–2167.
39. For an example of an enamide-containing natural product and the proposed modification of an *N*-acyliminium ion by an enzyme active site nucleophile, see: Gentle, C. A.; Bugg, T. D. H. *J. Chem. Soc. Perkin Trans. I* **1999**, 1279–1285.
40. For related analogs, see Ref. 2 and Charron, S.; Labrecque, D.; Lamothe, S.; Attardo, G.; Ouellet, F.; Grouix, B.; Leblond, L. *Abstract of papers*, 222nd ACS National Meeting, Chicago, IL, USA, Aug 26–30, 2001.
41. Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. M.; Rapoport, H. *Synthesis* **1992**, 621–623.
42. Kunz, H.; Waldmann, H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 71–72.