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Synthesis of Scyphostatin Analogues through Hypervalent Iodine-mediated Phenol Dearomatization

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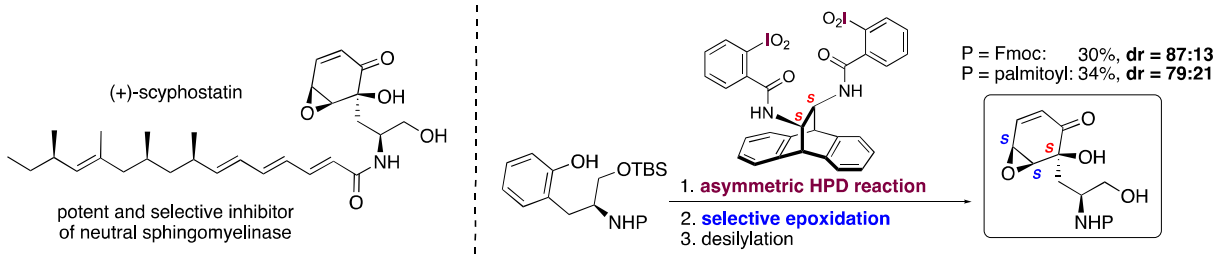
Supporting Information Placeholder



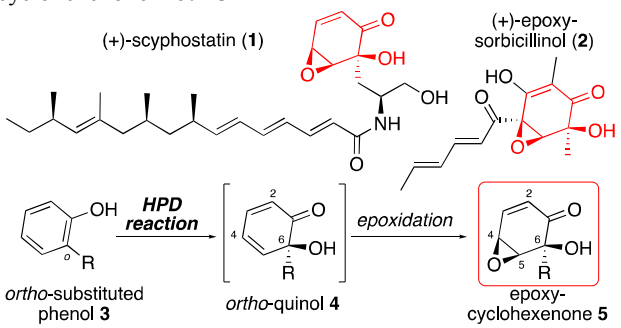
ABSTRACT: A concise synthesis of two scyphostatin analogues is achieved from readily available *ortho*-substituted phenols. Key features include an asymmetric and biomimetic hydroxylative phenol dearomatization (HPD) reaction promoted by a chiral *Salen*-type bis(λ^5-iodane) reagent, followed by an *in situ* regio- and diastereocontrolled epoxidation.

INTRODUCTION

(+)-Scyphostatin (**1**) was isolated in 1997 from a mycelial extract of *Trichopeziza mollissima* (Lasch) Fuckel [syn.: *Dasyscyphus mollisimus* (Lasch) Dennis] that belongs to the Hyaloscyphaceae family.[1] This fungal polyketide exhibits a potent (IC_{50} = 1.0 μM) and selective inhibitory activity against neutral sphingomyelinase (*N*-SMase),[2] a key enzyme of the sphingomyelin metabolism and related ceramide production, which is associated to *inter alia* inflammatory processes, cell apoptosis and neurodegenerative disorders.[3] Hence, (+)-scyphostatin (**1**) has attracted attention as a total synthesis target,[4] and has fuelled numerous methodological developments aiming at the elaboration of its lipophilic side-chain[5] and highly functionalized polar core.[6,7] Such studies gave access to some analogues of **1** as novel *N*-SMase inhibitor candidates.[6a,b,d,8]

The highly oxygenated cyclohexane ring of the scyphostatin polar head, *i.e.*, a 6-alkyl-4,5-epoxy-6-hydroxycyclohex-2-en-1-one moiety, is also found in (+)-epoxysorbicillinol (**2**) (Scheme 1). These polyketides **1** and **2** are the only two natural products we are aware of that display such an epoxy-cyclohexenone motif **5**, which can derive from the hydroxylative phenol dearomatization (HPD) of an *ortho*-substituted phenol **3** into the corresponding *ortho*-quinol **4** (Scheme 1). In fact, such a transformation has recently proven to be operational in the biosynthesis of **2** with the dearomatization of sorbicillin into the *ortho*-quinol sorbicillinol (not shown).[9] Such *ortho*-quinols of type **4** would

Scheme 1. (+)-scyphostatin (**1**), (+)-epoxysorbicillinol (**2**), and proposed biosynthetic elaboration of their epoxy-cyclohexenone motif **5**



then be epoxidized in a regio- and diastereoselective manner to furnish type-**5** epoxy-cyclohexenones (Scheme 1).

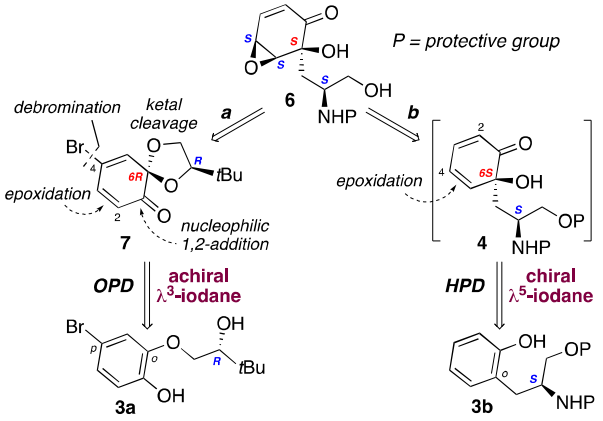
So far, approximately half of the synthesis studies towards the polar head of **1** and analogues thereof[4b,e,6,8b] have relied on oxygenative phenol dearomatization (OPD) processes.[10] Moreover, almost all these OPD reactions were promoted by hypervalent organoiodine reagents (*i.e.*, iodanes), and they were all based on substrate-controlled approaches to reach the desired stereochemistry of the *ortho*-quinol intermediate and final epoxy-cyclohexenone unit.[4b,e,6,8b] However, non-racemic syntheses of *ortho*-quinols[11,12] are also possible through reagent-controlled tactics, notably using chiral iodanes.[13] Herein we describe our own synthesis efforts towards the polar head of scyphos-

tatin (**1**), following two different iodane-mediated OPD approaches, which are based on i) a substrate-stereocontrolled access to chiral *ortho*-quinone monoketals in a non-racemic form using the achiral λ^3-iodane (diacetoxy)iodosylbenzene $PhI(OAc)_2$,[12b] and ii) a reagent-stereocontrolled (and biomimetic) HPD reaction promoted by a home-made chiral λ^5-iodane.[12e]

RESULTS AND DISCUSSION

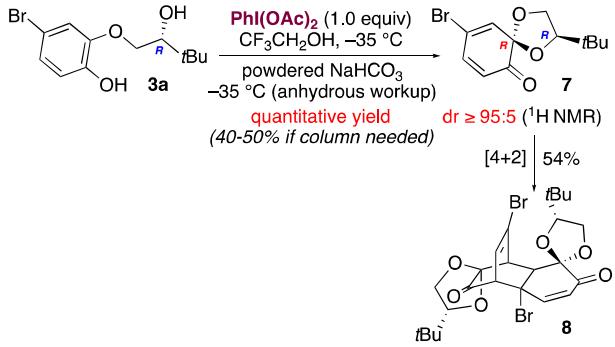
Our retrosynthetic analysis of the polar head of (+)-scyphostatin (**1**), *i.e.*, the (4*S*,5*S*,6*S*)-4,5-epoxy-6-hydroxy-6-[(2*S*)-2-amino-3-hydroxypropyl]cyclohex-2-en-1-one (**6**), is outlined in Scheme 2. We first envisioned a substrate-controlled approach based on the utilization of our *ortho*-quinone spiroketal (*R,R*)-**7**[12b] as the key chiral synthon on which to perform the required functionalization steps (path *a*).[6c,12a,b] The spiroketal **7** can be prepared by a $PhI(OAc)_2$-mediated oxidative dearomatization of phenol (*R*)-**3a**, which bears a chiral pro-spiroketal ethanol unit *O*-tethered to the *ortho* position.[12a,b] The presence of a bromine atom at the *para* position is to prevent or at least retard the self-dimerization of the dearomatized species through [4+2] cycloaddition events.[11] This choice of a bromine atom was inspired by the work of Taylor, who successfully used the *ortho*-quinone monoketal 4-bromo-6,6-dimethoxycyclohexa-2,4-dienone (not shown) for the synthesis of scyphostatin analogues.[6c] Looking for a more straightforward access to **6**, we also considered the preparation of the *ortho*-quinol intermediate (*S,S*)-**4** through an enantioselective (and biomimetic) HPD conversion of phenol (*S*)-**3b** using one of our chiral λ^5-iodane reagents (path *b*).[12e] The added advantage of the *ortho*-quinol (*S,S*)-**4** is that its chiral allylic alcohol moiety would be ideally suited for directing the regio- and stereochemistry of the final epoxidation step.

Scheme 2. Retrosynthetic analysis of the polar head of (+)-scyphostatin (**1**)



Substrate-controlled OPD approach (path *a*). Phenol (*R*)-**3a** was prepared in an overall yield of 88% through 5 steps encompassing a Williamson reaction between 5-bromo-2-benzyloxyphenol and the enantiomerically enriched 2-*tert*-butyloxirane generated by using the Jacobsen's method.[12b] Next, the dearomative spirocyclization of (*R*)-**3a** was achieved upon treatment with $PhI(OAc)_2$ (1.0 equiv) in 2,2,2-trifluoroethanol (*ca.* 0.04 M) at –35 °C, followed by quenching of the released acetic acid with powdered $NaHCO_3$ at the same low temperature, without addition of any water (Scheme 3). A simple filtration–evaporation procedure furnished spiroketal **7** in a nearly quantitative yield with excellent levels of both purity and diastereomeric ratio (dr) ≥ 95:5 (^{1}H NMR analysis) in favor of the (*R,R*)-**7** spiroketal.[12b] Unfortunately, this remarkable diastereocontrol was tarnished by the rapid [4+2] dimerization of **7** into the known cyclodimer **8**[12b,14] (Scheme 3). The bromine atom thus did not fulfill its role of blocking the cyclodimerization event, which was clearly observed during the acquisition of ^{13}C NMR data. No improvement was obtained with the bulkier iodine atom, as dimerization went even faster and was already observed during the ^{1}H NMR analysis. This analysis also indicated a slightly lower diastereocontrol (dr = 90:10).[12a] Therefore, spiroketal (*R,R*)-**7** was systematically freshly prepared and purified by silica gel column chromatography (easily reproducible 40-50% yields) to discard any [4+2] cyclodimer contaminant.

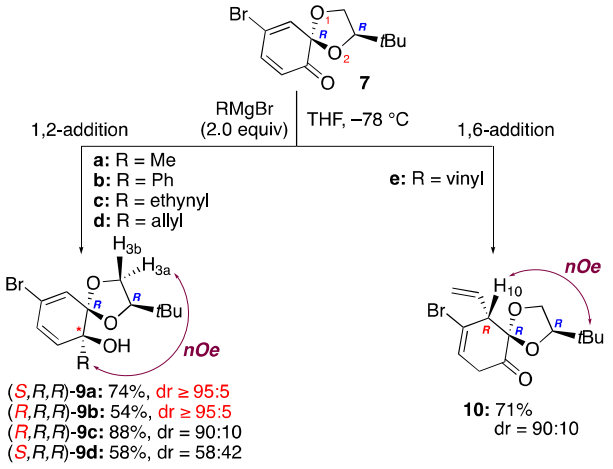
Scheme 3. Synthesis of spiroketal (*R,R*)-**7** and X-ray structure of its [4+2]-cyclodimer **8**



The capacity of this 4-brominated spiroketal (*R,R*)-**7** to induce asymmetry during nucleophilic 1,2-addition was then first evaluated with commercially available Grignard reagents (Scheme 4). Methylmagnesium bromide (MeMgBr, 2 equiv) furnished the expected tertiary alcohol **9a** in 74% yield with an excellent stereoselectivity, as only one diastereomer (dr ≥ 95:5) was observed by ^{1}H NMR analysis. The structure and stereochemistry of the (*S,R,R*)-**9a** was established unambiguously by 2D NMR experiments, including a diagnostic NOESY correlation between the newly introduced methyl group and the H_{3a} signal (see the Supporting Information). A high level of diastereocontrol was also reached using phenylmagnesium bromide (PhMgBr), as the 1,2-adduct (*R,R,R*)-**9b** was also isolated with a dr ≥ 95:5 (^{1}H NMR), albeit in a lower yield of 54%. A better yield (88%) with a slightly lower selectivity (dr = 90:10) was obtained for the major 1,2-adduct (*R,R,R*)-**9c** in the case of the reaction of **7** with ethynylmagnesium bromide. In contrast, a poor selectivity (dr = 58:42) and a moderate yield were noticed when using allylmagnesium bromide to get compound **9d**. Such contrasting results may be due to the facts that i) the allylic carbon nucleophile of the Grignard reagent is not bonded tightly enough to the Mg chelating center, hence weakening any stereodiscriminating interaction with the spiroketalic *tert*-butyl group (*vide infra*), and ii) the formation of **9d** may compete with that of degradation products possibly derived from anionic oxy-Cope rearrangement events. Surprisingly, the addition of vinylmagnesium bromide to spiroketal **7** afforded the remarkably stable 1,6-adduct **10** as the sole product, which was isolated in 71% yield with a dr = 90:10 (^{1}H NMR). The stereochemistry of the major diastereomer (*R,R,R*)-**10** was determined by the

observation of a correlation between the H_{10} signal and that of the spiroketalic *t*Bu group (see the Supporting Information). Addition of $MgBr_2$ (2.0 equiv) to the reaction mixture enabled us to detect by ^1H NMR analysis the formation of the 1,2-adduct, but in an unsatisfactory 1:3 mixture with the 1,6-adduct. The use of vinyl lithium, which was generated through lithium-bromine exchange on vinyl bromide by reaction with *t*BuLi, at a temperature below –100 °C led to the isolation of the 1,2-adduct in a moderate yield (46%) with a disappointing selectivity (dr = 65:35), together with the surprising formation of some **9c** (16%). A competing vinylcarbene rearrangement into an acetylide anion may be invoked to explain the formation of **9c**. In summary, this brief study demonstrated the potential of this two-step sequence in which the chiral tether of phenol **3a** showed its efficacy in inducing asymmetry not only during the $PhI(OAc)_2$-mediated spiroketalization, but also during the 1,2-addition of some Grignard reagents.

Scheme 4. Grignard additions to spiroketal (*R,R*)-**7**



In these reactions, the Grignard reagent would attack the ketone of **7** from its less hindered face, *i.e.*, the face that is not occupied by the *tert*-butyl group on the spiroketal moiety. This facial discrimination might be amplified by chelation of the Mg cation with the spiroketal oxygen farther away from the bulky *tert*-butyl group. This hypothesis was corroborated by DFT calculations (wB97xD/6-31G**,[15] see the Supporting Information), which were performed on the 1,2-addition of MeMgBr onto (*R,R*)-**7**. The study of the potential energy surface (PES) led to the localization of four isomers as local minima. Two pro-*S* (isomers-1 and -3) and two pro-*R* (isomers-2 and -4) intermediates were identified according to the oxygen atoms involved in the Mg-centered chelating system (*i.e.*, O···Mg···O1 *versus* O···Mg···O2) and the resulting orientation of the MeMgBr reagent (Figure 1). These theoretical results showed that isomers involving the spirocyclic O2 atom (*i.e.*, isomers-1 and -2) are slightly higher in energy than those displaying a Mg chelation with the spirocyclic O1 atom (*i.e.*, isomers-3 and -4). Hence, the most favored pro-*S* structure shows that the Mg atom is in interaction with the sp^2 oxygen atom of the carbonyl group ($d_{Mg–O}$ = 2.16 Å) and the spirocyclic oxygen atom O1 ($d_{Mg–O1}$ = 2.28 Å), which is in opposite position to the bulky *tert*-butyl group (Figure 1). These data are in accordance with our experimental observation on (*S,R,R*)-**9a** as the sole isolated product. This bonding situation was also highlighted by natural bond orbital (NBO) analysis (see the Supporting Information). Indeed, the Lewis structure of **isomer-3** shows stabilizing interactions of the oxygen atoms O and O1 with the Grignard moiety. This stabilization involves i) significant donor-acceptor interactions between the oxygen lone pairs and the vacant Mg orbital [*i.e.*, 29.9 (O) and 16.9 (O1) kcal.mol^{-1}], and ii) a negative hyperconjugation of these oxygen lone pairs with the σ*(Mg–Me) and/or σ*(Mg–Br) antibonding orbitals [*i.e.*, 11.3 and 10.4 kcal.mol^{-1}, respectively] (see Figure S8 in the Supporting Information).

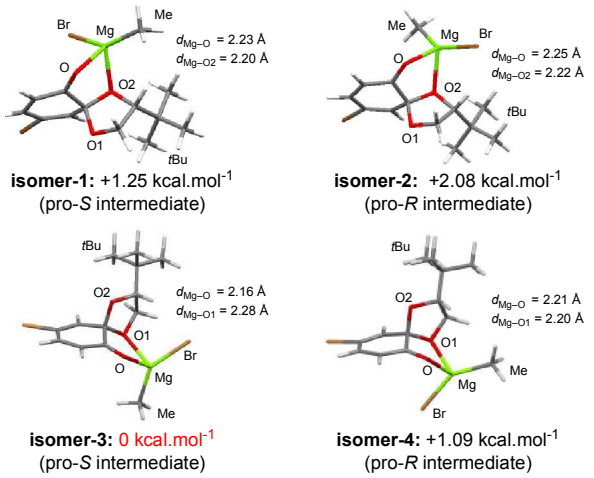
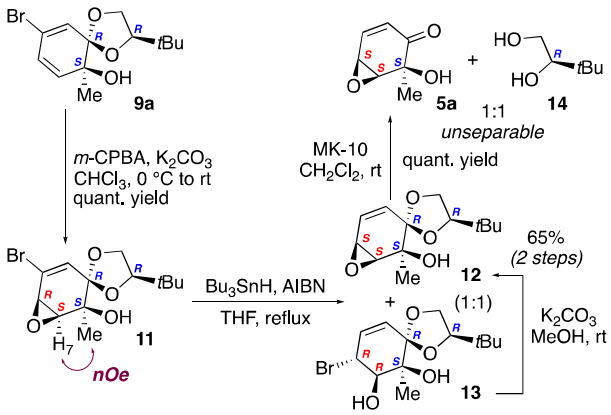


Figure 1. DFT structures and relative stability (Gibbs energies in kcal.mol^{-1}) of the isomers corresponding to the 1,2-addition of MeMgBr onto (*R,R*)-**7**

Scheme 5. Conversion of **9a** into **5a** through an epoxidation/debromination/ketal cleavage sequence



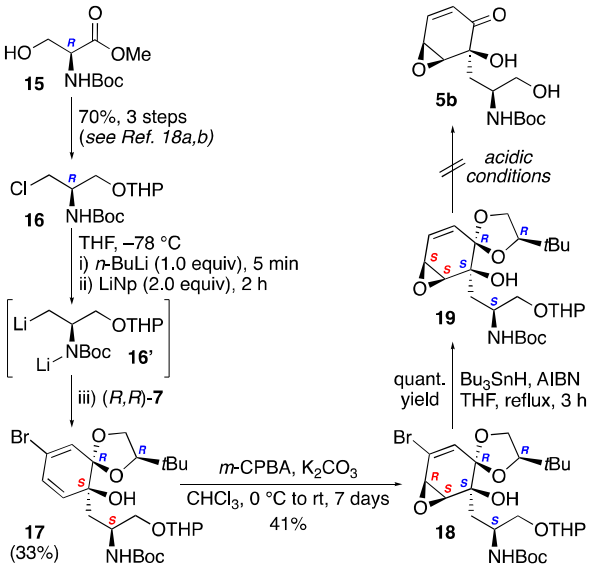
Epoxidation of (*S,R,R*)-**9a** was next considered, and we thus anticipated to draw benefit from its chiral (*S*) allylic alcohol moiety to impose the desired regiochemistry and diastereoselectivity.[16] Indeed, upon treatment with *m*-CPBA in $CHCl_3$ at room temperature, and in the presence of K_2CO_3 to quench the released *m*-chlorobenzoic acid, **9a** was successfully converted into the epoxy-alcohol **11**, which was isolated as the sole diastereomer in a quantitative yield (Scheme 5). The expected *cis* relationship between the hydroxyl group and the oxirane ring of **11** was confirmed through a NOESY correlation between the H_7 signal and that of the methyl group (see the Supporting Information). Of particular note is that direct epoxidation of spiroketal **7** carried out under conditions previously described either for the synthesis of scyphostatin analogues[6c] (*i.e.*, *t*BuOOH/1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-

a]pyrimidine in CH_2Cl_2 at 0 °C) or for the epoxidation of electron-deficient olefins[17] (*i.e.*, $(nBu_4N)_2S_2O_8/H_2O_2$/NaOH in CH_3CN at rt), gave cyclodimer **8** and no epoxidized material.

The next step was the reductive debromination of **11** upon treatment with Bu_3SnH and a catalytic amount of AIBN in refluxing THF. These conditions[6c] furnished the desired compound **12**, but in a 1:1 mixture with the bromohydrin **13**. This undesired concomitant oxirane ring-opening was circumvented by treating the 1:1 mixture with K_2CO_3 in MeOH at room temperature to promote an intramolecular Williamson reaction, which thus enabled the isolation of the advanced intermediate **12** in a 65% overall yield over the two steps (Scheme 5). Finally, removal of the spiroketalic chiral auxiliary was successfully achieved using Montmorillonite K-10 (MK-10)[6c] in CH_2Cl_2 at room temperature to afford the epoxy-cyclohexenone **5a** in a *ca.* 1:1 mixture with diol **14**. Unfortunately, we were unable to separate **5a** and **14** efficiently. Nevertheless, a yield of 54% of **5a** as the sole diastereomer could be estimated by ^1H NMR analysis (see the Supporting Information). Interestingly, as previously observed by Taylor and co-workers using their dimethyl ketal analogue of **11**,[6c] reductive debromination prior to ketal cleavage was crucial. Indeed, the spiroketal moiety of the vinyl bromide **11** survived several acidic conditions, such as MK-10 in CH_2Cl_2, Amberlyst® in THF, *p*-TsOH•H_2O in acetone, and 40% aq. HF in CH_3CN/CH_2Cl_2 (1:3), while the use of stronger acidic media, such as 1M aq. HCl/MeOH/THF (1:1:4) and 2M aq. HCl/THF (1:1) led in nearly quantitative yields (95 and 90%, respectively) to a 1,2-diol that resulted from the oxirane opening, but with the spiroketal moiety still intact (see the Supporting Information).

Therefore, we were pleased to validate this short sequence of stereoselective transformations from our spiroketal (*R,R*)-**7** to access an epoxy-cyclohexenone of type **5**, and we were then eager to try it with a more functionalized and scyphostatin-related 2-amino-3-hydroxypropyl-type nucleophile. This synthon was prepared in gram scale, following a known three-step procedure,[18a,b] starting from commercially available *N*-Boc L-serine methyl ester (**15**). The resulting *N*-Boc chlorotetrahydropyranyl (THP) ether **16** was isolated in an overall yield of 70% (Scheme 6). Its acid sensitive THP protective group was selected to be easily cleaved at a late stage along with the spiroketal moiety of **7**. Next, a combination of *n*-butyllithium (*n*-BuLi, 1.0 equiv) and lithium naphthalenide (LiNp, 2.0 equiv)[18] at –78 °C in THF was used to generate *in situ* the dianion **16'**.[18a,b] The resulting mixture was treated dropwise with freshly prepared spiroketal (*R,R*)-**7** at the same low temperature, and the desired 1,2-adduct **17** was isolated as a sole product in 33% yield (Scheme 6). This moderate yield was unlikely due to technical issues related to the handling of **16'**,[19] but rather to numerous side-reactions and resulting (not isolated) by-products. This somewhat cumbersome reaction could nevertheless be performed using 200-300 mg of **7** to give access to 20-30 mg of the spiroketal **17**. This highly functionalized intermediate was then successfully epoxidized upon treatment with *m*-CPBA in the presence of K_2CO_3 (*vide supra*) in $CHCl_3$ at room temperature for 7 days, and compound **18** was isolated in 41% yield. Reductive debromination of **18** into **19** was cleanly achieved in a quantitative yield, after removing tin salts by trituration with Et_2O. The stereochemistry of compounds **17**, **18** and **19** was here not fully assigned because of the detection in NMR spectra of diastereomeric mixtures due to the THP protective group. In summary, the complete sequence, starting from the dearomative spiroketalization of phenol **3a** into **7**, gave access to the advanced intermediate **19** in an overall yield of about 10% at best. Moreover, our inability to scale-up the preparation of **17** and to improve the epoxidation step efficiency prevented us from generating substantial amounts of **19**. Nevertheless, the final deprotection step could be tested by treating **19** under acidic conditions in the aim of concomitantly cleaving the THP group and the spiroketal unit. Unfortunately, treatment of **19** with the MK-10 clay (*vide supra*) led to a complex and intractable mixture. Complex mixtures were also obtained when **19** was treated with either Amberlite® IR120-H^+ resin in THF/H_2O (20:1), H-Mordenite zeolite in toluene/H_2O (15:1),[20a] or $PdCl_2(CH_3CN)_2$ in acetone.[20b] Although the use of *p*-TsOH•H_2O in acetone[12b] also led to full degradation of **19**, that of *p*-TsOH•H_2O in the presence of pyridinium *p*-toluenesulfonate (PPTS)[20c] in acetone/H_2O (8:1) at room temperature for 2 days enabled the conversion of **19** into a more polar compound. But instead of **5b**, we disappointingly identified a primary alcohol resulting from the cleavage of the THP group, but with the spiroketal moiety still in place. All attempts to subject this compound to either MK-10 clay, Amberlite® IR120-H^+, or formic acid dried over anhydrous copper sulfate[20d] were to no avail. In view of these additional difficulties, we decided to move away from this subtrate-controlled approach and to focus our efforts on the implementation of reagent-controlled asymmetric reactions by taking advantage of our recently developed chiral iodanes.[12e-g]

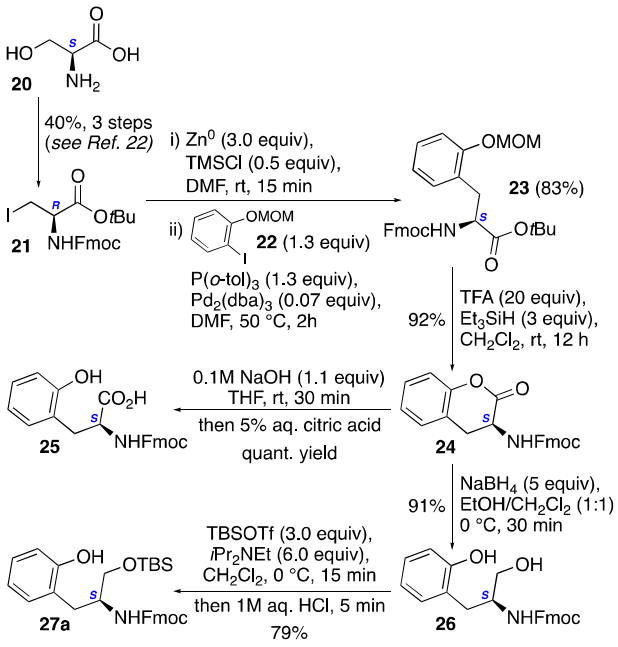
Scheme 6. Substrate-controlled synthesis of the polar head of (+)-scyphostatin (**1**)



Reagent-controlled OPD approach (path *b*). This investigation began with the synthesis of phenols of type **3b** (see Scheme 2) featuring the requisite (2*S*)-2-amino-3-hydroxypropyl side-chain at the *ortho* position. We relied on the known preparation of the *N*-Fmoc protected iodo-derivative of L-serine *tert*-butyl ester **21**,[21] which was readily accessible in 3 steps (40% overall yield) from commercially available L-serine (**20**). A gram-scale Negishi-type coupling

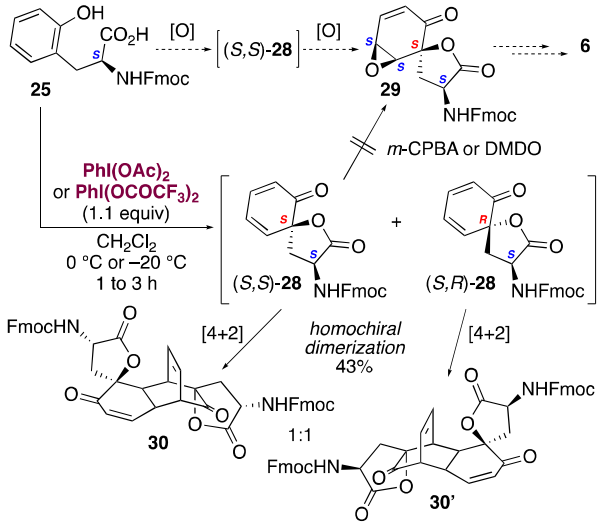
reaction between the *in situ* generated **21**-derived organozinc species and the *O*-MOM protected 2-iodophenol **22** gave access to the *ortho*-substituted adduct **23** in a very good yield of 83% (Scheme 7). Next, both MOM ether and *t*Bu ester functions of **23** were successfully deprotected in one step using acidic conditions (*i.e.*, 20 equiv of trifluoroacetic acid) in the presence of triethylsilane (3 equiv), in CH_2Cl_2 at room temperature, and the lactone **24** was isolated in an excellent 92% yield.[22] Saponification of this lactone **24** using 0.1M aq. NaOH in THF, followed by a mildly acidic treatment (*i.e.*, 5% aq. citric acid, which was crucial to avoid any undesired relactonization back to **24**), gave phenol **25** quantitatively (Scheme 7). Another transformation of lactone **24** consisted in its $NaBH_4$-mediated reduction into the phenolic primary alcohol **26** (91% yield), which was then silylated to obtain phenol **27a** (79% yield).

Scheme 7. Synthesis of phenolic substrates featuring a (*S*)-2-amino-3-hydroxypropyl–type unit at their *ortho* position



With these two phenols in hands, we first envisaged a one-pot dearomative spirolactonization/epoxidation reaction to convert the phenol **25** into the epoxide **29** *via* the spirolactone (*S,S*)-**28** (Scheme 8). In order to verify the reachability of such spirolactone, phenol **25** was first dearomatized using the achiral λ^3-iodane $PhI(OAc)_2$ or its trifluoroacetoxy variant $PhI(OCOCF_3)_2$, in the presence of $NaHCO_3$ in CH_2Cl_2 at low temperature (*i.e.*, 0 °C or –20 °C). Unfortunately, the spirolactone **28** could not be detected, and a 1:1 mixture of the [4+2]-cyclodimers **30** and **30'** could instead be isolated in a combined yield of 43%. Each cyclodimer was separated by preparative thin layer chromatography (*ca.* 15% yield each). Their structure could not be fully determined due to the lack of X-ray quality crystals, but they were unambiguously characterized by NMR analysis, which confirmed that **30** and **30'** were derived from the homochiral [4+2]-cyclodimerization of (*S,S*)-**28** and (*S,R*)-**28**, respectively (Scheme 8).[11a,14] However, all attempts to trap these transient spirolactones with epoxidizing agents, such as *m*-CPBA and 3,3-dimethyldioxirane (DMDO), were to no avail.

Scheme 8. λ^3-Iodane-mediated dearomative spirolactonization/[4+2]-cyclodimerization conversion of phenol **25**



Therefore, we pursued our investigations with phenol **27a**, whose silylated primary alcohol function would prevent any spirocyclization, and which should thus be better adapted to an HPD reaction/epoxidation sequence. Our recent successes in asymmetric HPD reactions promoted by chiral iodanes[12e,f] led us to select our *Salen*-type bis(λ^5-iodanes) **32** and **33**, which are readily accessible in hundreds of milligrams by DMDO-mediated oxygenation of their bis(amidoiodoarene) precursors, themselves easily prepared through coupling of *o*-iodobenzoic acid with C_2-symmetrical chiral diamines (Figure 2).[12e] The simpler amide-containing and achiral λ^5-iodane **31** (Figure 2) was also prepared by DMDO-mediated oxygenation of its *o*-iodobenzamide precursor (see the Supporting Information).

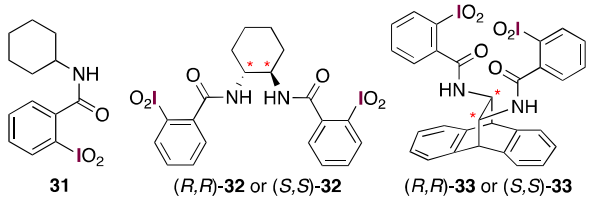
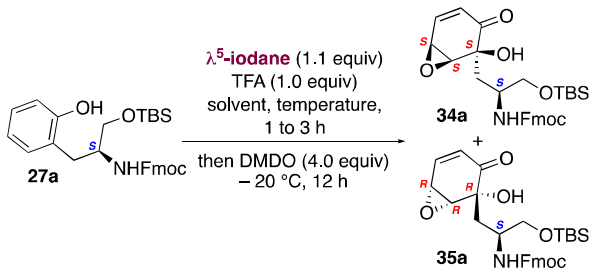


Figure 2. (Chiral) λ^5-iodanes selected for the (asymmetric) hydroxylative phenol dearomatization (HPD) reaction

Table 1 summarizes the main results we gathered using these λ^5-iodanes to initiate the desired HPD reaction/epoxidation transformation of **27a**. When this phenol was treated with 1.1 equivalent of iodane **31** at –20 °C under experimental conditions previously reported [*i.e.*, a 10 mM solution of starting phenol in CH_2Cl_2/CF_3CH_2OH (85:15) in the presence of TFA (1.0 equiv)],[12e] followed by addition of freshly prepared DMDO (*ca.* 0.07 M in acetone; 4 equiv), we were pleased to observe the complete conversion of **27a** into two main products, which were separated by preparative TLC. NMR analysis led to the identification of the expected 4,5-epoxy-6-hydroxy-cyclohex-2-en-1-ones **34a** and **35a**, which were isolated in 49% yield as a 66:34 diastereomeric mixture (Table 1, entry 1). It is worth noting that i) the *ortho*-quinol intermediate(s) of type **4** (see Scheme 2) could not be isolated, and ii) the use of *m*-CPBA as the epoxidizing agent (instead of DMDO) led to degradation of the reaction

material. Furthermore, the isolation of **34a** and **35a** indicates that DMDO was able to epoxidize the *ortho*-quinol intermediate(s) of type **4** in the requested regio- and diastereoselective fashion (*i.e.*, *cis* stereochemistry with respect to the alcohol function). Similar diastereoselectivity was observed when the reaction was run in pure CH_2Cl_2 at –20 °C, but the dr value increased to 74:26 when the temperature was lowered to –50 °C during the HPD step (Table 1, entries 2 and 3). Most importantly, the contribution of our chiral *Salen*-type iodanes **32** and **33** toward our objective to control the asymmetry of the reaction turned out to be significant, since the one-pot HPD/epoxidation conversion of **27a** was achieved at –50 °C with diastereomeric ratios of 82:18 and 87:13 by using (*S,S*)-**32** and (*S,S*)-**33**, respectively (Table 1, entries 5 and 8). In contrast, the conversion of **27a** showed a clear mismatch effect when using the (*R,R*) enantiomers of these bis(λ^5-iodanes), since it led to the **34a**/**35a** mixture with a dr of 47:53 and 35:65 when using (*R,R*)-**32** and (*R,R*)-**33** , respectively (Table 1, entries 6 and 9).

Table 1. λ^5-Iodane-mediated hydroxylative phenol dearomatization/epoxidation conversion of phenol **27a**[a]

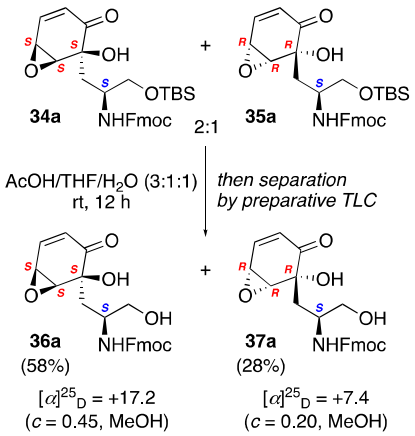


entry	iodane	solvent	temp. (°C)	yield (%)	**34a**:**35a**[b]
1	**31**	CH_2Cl_2/TFE (85:15)	–20	49	66:34
2	**31**	CH_2Cl_2	–20	38	66:34
3	**31**	CH_2Cl_2	–50	47	74:26
4	(*S,S*)-**32**	CH_2Cl_2	–20	44	70:30
5	(*S,S*)-**32**	CH_2Cl_2	–50	30	82:18
6	(*R,R*)-**32**	CH_2Cl_2	–50	33	47:53
7	(*S,S*)-**33**	CH_2Cl_2	–20	42	75:25
8	(*S,S*)-**33**	CH_2Cl_2	–50	30	87:13
9	(*R,R*)-**33**	CH_2Cl_2	–50	33	35:65

[a]Reactions run using [**27a**] = 10 mM, and until consumption of starting material (TLC monitoring). [b]Diastereomeric ratio determined by ^{1}H NMR analysis. TFE = 2,2,2-trifluoroethanol.

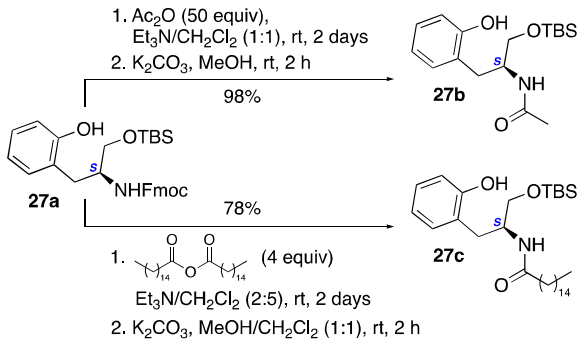
Unfortunately, these reagent-controlled asymmetric transformations of **27a** into **34a**/**35a** suffered from moderate yields of *ca.* 30-40%. These disappointing yields can find explanation in the observation of a concomitant formation of some unstable (and thus not isolated) *ortho*-quinonoid by-product (*ca.* 30% as estimated by ^{1}H NMR) that could result from a competitive iodane-mediated oxygenation at the unsubstituted *ortho* position of the starting phenol. Nevertheless, this straightforward and possibly biomimetic asymmetric HPD/epoxidation sequence gave access to *N*-Fmoc analogues of scyphostatin **36a** and **37a** by simple *O*-desilylation of **34a** and **35a** upon treatment with glacial acetic acid in THF/H_2O (1:1) (Scheme 9). However, unambiguous evidences of the stereochemistry of **34a**/**35a** and thus **36a**/**37a** were still lacking, so we decided to apply our sequence to the synthesis of the known scyphostatin *N*-palmitoyl analogue **36c**,[6f,8b,d] so far one of the most potent irreversible inhibitor of *N*-SMase.[8b]

Scheme 9. Synthesis of the *N*-Fmoc scyphostatin analogues **36a** and **37a**



Phenol **27a** was again selected as starting material, and we first proceeded with its conversion into its *N*-acetyl analogue **27b** (Scheme 10). *N*-Fmoc deprotection of **27a** with triethylamine, followed by *in-situ* amidation with a large excess of acetic anhydride (50 equiv), gave the *N*,*O*-bis(acetylated) derivative, which was smoothly *O*-deacetylated upon treatment with K_2CO_3 in methanol to furnish phenol **27b** in 98% yield. Under similar experimental conditions, this time using commercial palmitic anhydride (4 equiv), phenol **27c** was isolated in 78% yield. These two high-yielding *N*-transprotection reactions were conveniently performed on a 200 mg scale. With this facile access to **27c** from **27a**, we were ready to engage this *N*-palmitoyl phenolic substrate in our iodane-mediated HPD/epoxidation/desilylation sequence.

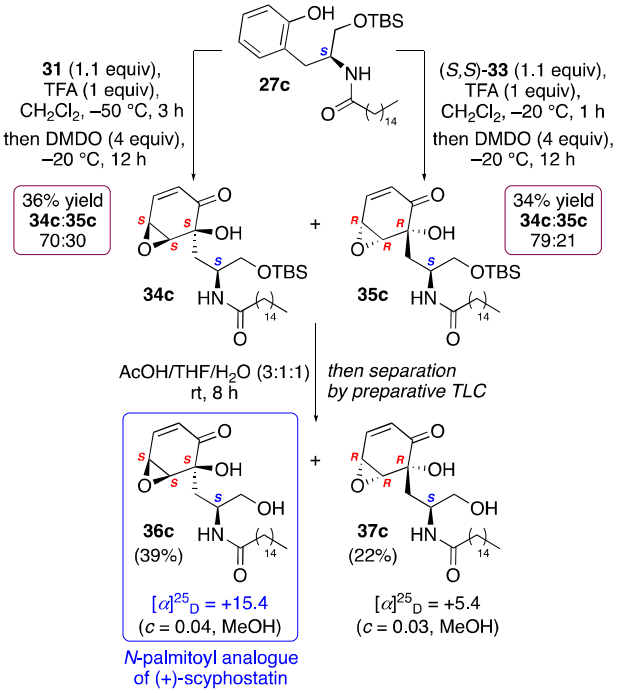
Scheme 10. Conversion of *N*-Fmoc phenol **27a** into its *N*-acetyl and *N*-palmitoyl analogues **27b** and **27c**



Hence, phenol **27c** was dearomatized/epoxidized under the conditions that previously offered the best compromise between yield and diastereoselectivity. Upon treatment with the achiral λ^5-iodane **31** at –50 °C for 3 hours, followed by *in-situ* reaction with DMDO (4 equiv) at –20 °C for 12 hours (see Table 1, entry 3), **27c** was successfully transformed into the expected **34c**/**35c** diastereomeric mixture in 36% yield with a dr of 70:30 (Scheme 11). The added control of asymmetry brought by our chiral λ^5-iodane reagent (*S,S*)-**33** at –20 °C for 1 hour (see Table 1, entry 7) led to a higher value of 79:21 with a similar chemical yield of 34%. The epoxycyclohexenone products **34c** and **35c** could be separated for characterization purpose or directly desilylated with acetic acid in THF/H_2O to furnish the desired *N*-palmitoyl scyphostatin analogues **36c** and **37c**. The (+)-scyphostatin analogue

was unambiguously identified as being the major diastereomer **36c** by comparison with literature data, in particular optical rotation measurements {lit.[8d] $[\alpha]^{27}_D$ = +15.0 (*c* = 0.04, MeOH)}, as well as ^{1}H and ^{13}C NMR spectra[6f] recorded in methanol-d_4 (Scheme 11). Furthermore, the scyphostatin analogues **36c** and **37c** could also be obtained by desilylation of **34c**/**35c** directly generated by *N*-transprotection of the *N*-Fmoc *O*-silylated epoxy-cyclohexenones **34a**/**35a** (see Schemes S3 and S4 in the Supporting Information). NMR data and optical rotation measurement of the resulting epoxy-cyclohexenone **36c** were again consistent with those previously reported.[6f,8d] Thus, this access to **36c** enabled us to confirm the stereochemical assignments of the *N*-Fmoc variants **36a**/**37a**, and hence those of **34a**/**35a** (see Scheme 9).

Scheme 11. Synthesis of the *N*-palmitoyl scyphostatin analogues **36c** and **37c**



CONCLUSION

In summary, we have developed an efficient and concise synthesis of two (+)-scyphostatin analogues (**36a** and **36c**) and their corresponding diastereomers (**37a** and **37c**) from readily available phenols featuring a (2*S*)-2-amino-3-hydroxypropyl side-chain at their *ortho* position. Key features of the synthesis of the highly oxygenated polar head of scyphostatin, and analogues thereof, include an asymmetric and biomimetic hydroxylative phenol dearomatization (HPD) promoted by chiral *Salen*-type bis(λ^5-iodane) reagents, followed by an *in situ* DMDO-mediated regio- and diastereoselective epoxidation. This reagent-controlled oxidative phenol dearomatization (OPD) approach paves the way for a straightforward access to other scyphostatin analogues as *N*-SMase inhibitor candidates.

EXPERIMENTAL SECTION

General Information. All moisture and oxygen sensitive reactions were carried out in flame-dried glassware under N_2. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purified by filtration through alumina under N_2. Synthesis grade 2,2,2-trifluoroethanol (Sigma-Aldrich), acetone, ethyl acetate (EtOAc), and (diacetoxy)iodosylbenzene (Simafex) were used as received. Reactions run at room temperature were performed between 20 and 25 °C. Solvent evaporations were conducted under reduced pressure at temperatures less than 40 °C unless otherwise noted (*e.g.*, volatile compounds). Column chromatography was carried out under positive pressure using 40-63 µm silica gel and the indicated solvents [v/v; used without purification, including petroleum ether (PET, boiling range 40-60 °C)]. Melting points of either recrystallized solids or amorphous powders were measured in open capillary tubes, using a digital Büchi B-540 melting point apparatus, and are uncorrected. Optical rotations were determined on a Krüss P3001 digital polarimeter at λ = 589 nm (*i.e.*, sodium D line), using a 1.0 mL cell (l = 0.5 dm), and are given as $[\alpha]^{25}_D$ (concentration in g/100 mL solvent). IR spectra were recorded between 4000 and 400 cm^{-1} with a Bruker IFS55 (OPUS/IR 3.0.2) FT-IR spectrometer, and samples were dissolved in dichloromethane or acetone before analysis as a thin film on a zinc-selenium pellet after solvent evaporation (neat), unless otherwise noted (NaCl pellets). ^{1}H NMR spectra of samples in the indicated solvent were run at 300 or 400 MHz on Bruker DPX-300 or -400 spectrometers. Chemical shifts are given in ppm (δ) comparatively to the residual solvent signal, which was used as an internal reference (acetone-d_6: δ = 2.05 ppm; $CDCl_3$: δ = 7.26 ppm; DMSO-d_6: δ = 2.50 ppm; methanol-d_4: δ = 3.31 ppm; THF-d_8: δ = 1.72, 3.58 ppm). Coupling constants (*J*) are given in Hertz (Hz), and the following abbreviations are used to describe the signal multiplicity: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). ^{13}C NMR spectra of samples in the indicated solvent were run at 75.5 or 100 MHz on Bruker DPX-300 or -400 spectrometers. Chemical shifts are given in ppm (δ) comparatively to the residual solvent signal, which was used as an internal reference (acetone-d_6: δ = 29.84, 206.26 ppm; $CDCl_3$: δ = 77.16 ppm; DMSO-d_6: δ = 39.52 ppm; methanol-d_4: δ = 49.00 ppm; THF-d_8: δ = 25.31, 67.21 ppm). Carbon multiplicities were determined by either DEPT-135 or *J*-Mod experiments. Stereochemical assignments were achieved by NOESY experiments. Low resolution (LRMS) mass spectra were obtained by electrospray ionization (ESIMS), and were recorded on a Thermo Finnigan LCQ Deca XP spectrometer using an ion trap mass with an electrospray source under atmospheric pressure, at the mass spectrometry laboratory of the Institut Européen de Chimie et Biologie (IECB, CNRS–UMS 3033). High resolution (HRMS) mass spectrometric analyses were obtained from the Centre d'Etude Structurale et d'Analyse des Molécules Organiques (CESAMO, Université de Bordeaux), France.

General procedure for Grignard addition to spiroketal 7. To a stirred solution of freshly purified spiroketal **7**[12b] (1.0 equiv) in dry THF (*ca.* 30 mM) cooled at –78 °C was added dropwise a commercially available solution of RMgBr (2.0 equiv). The resulting mixture was stirred at –78 °C for 1 hour, after which time it was allowed to warm to –50 °C, and stirring was maintained until TLC monitoring, eluting with PET/acetone (4:1), indicated complete consumption of the starting material. Hydrolysis of the reaction mixture was then performed at this temperature by dropwise addition of satu-

rated aqueous NH_4Cl (1 mL). It was then allowed to warm to room temperature, and it was diluted with EtOAc and saturated aqueous NH_4Cl. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give a crude product, which was purified by column chromatography, to give the tertiary alcohol **9**.

(–)-9-Bromo-(2*R*)-*tert*-butyl-(6*S*)-methyl-1,4-dioxaspiro[4.(5*R*)]deca-7,9-dien-6-ol (9a). Reaction was performed using methylmagnesium bromide (3.0 M in THF). Column chromatography, eluting with PET/acetone (95:5), furnished **9a** as a pale yellow oil (45 mg, 74%, dr ≥ 95:5): $[\alpha]^{25}_D$ = –16.9 (*c* = 0.59, $CHCl_3$); IR (neat): ν = 3476, 2957, 2933, 2873, 1145, 1020, 744 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (s, 9H, H-13, *t*Bu), 1.34 (s, 3H, H-11, Me), 2.57 (bs, 1H, OH), 3.73-3.84 (m, 2H, H-2 + H-3b), 4.10 (dd, *J* = 5.4, 7.3 Hz, 1H, H-3a), 5.76 (d, *J* = 10.0 Hz, 1H, H-7), 5.82 (dd, *J* = 1.4, 10.1 Hz, 1H, H-8), 5.97 (d, *J* = 1.0 Hz, 1H, H-10); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 139.7 (C-7), 129.2 (C-10), 125.5 (C-8), 119.4 (C-9), 110.1 (C-5), 85.9 (C-2), 74.2 (C-6), 66.2 (C-3), 32.7 (C-12), 25.5 (C-13), 20.5 (C-11); LRMS (ESIMS): *m/z* (%) = 327 (42) [MNa^+], 325 (42) [MNa^+], 301 (17), 299 (20); HRMS (ESI) calcd for $C_{13}H_{19}{}^{79}BrNaO_3$ 325.0415, found 325.0423.

(–)-9-Bromo-(2*R*)-*tert*-butyl-(6*R*)-phenyl-1,4-dioxaspiro[4.(5*R*)]deca-7,9-dien-6-ol (9b). Reaction was performed using phenylmagnesium bromide (1.0 M in THF). Column chromatography, eluting with PET/acetone (95:5), afforded **9b** as a pale yellow oil (39 mg, 54%, dr ≥ 95:5): $[\alpha]^{25}_D$ = –0.4 (*c* = 0.62, $CHCl_3$); IR (neat): ν = 3534, 2960, 1152, 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (s, 9H, H-13, *t*Bu), 3.63 (t, *J* = 7.4 Hz, 1H, H-3), 3.74 (dd, *J* = 6.1, 7.3 Hz, 1H, H-2), 3.82 (dd, *J* = 6.0, 7.3 Hz, 1H, H-3), 5.86 (d, *J* = 9.8 Hz, 1H, H-7), 6.01 (d, *J* = 1.3 Hz, 1H, H-10), 6.09 (dd, *J* = 1.7, 10.0 Hz, 1H, H-8), 7.29-7.58 (m, 5H, H-14 + H-15 + H-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 138.2 (C-7), 137.7 (C-11), 129.4 (C-10), 127.9 (C-15), 127.8 (C-16), 126.9 (C-8), 126.2 (C-14), 120.2 (C-9), 109.9 (C-5), 86.2 (C-2), 77.2 (C-6), 66.4 (C-3), 32.7 (C-12), 25.4 (C-13); LRMS (ESIMS): *m/z* (%) = 389 (69) [MNa^+], 387 (75) [MNa^+], 365 (100), 363 (81), 349 (9), 347 (12); HRMS (ESI) calcd for $C_{18}H_{21}{}^{79}BrNaO_3$ 387.0572, found 387.0561.

(–)-9-Bromo-(2*R*)-*tert*-butyl-(6*R*)-ethynyl-1,4-dioxaspiro[4.(5*R*)]deca-7,9-dien-6-ol (9c). Reaction was performed using ethynylmagnesium bromide (0.5 M in THF). Column chromatography, eluting with cyclohexane/acetone (4:1), gave **9c** as a white amorphous powder (133 mg, 88%, dr = 90:10), which was crystallized from PET by slow evaporation, to give colorless crystals: mp 92-94 °C; $[\alpha]^{25}_D$ = –1.6 (*c* = 1.23, $CHCl_3$); IR (neat): ν = 3466, 3297, 2964, 2904, 2877, 2115, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (s, 9H, H-14, *t*Bu), 2.49 (s, 1H, H-12), 2.91 (bs, 1H, OH), 3.82 (t, *J* = 8.2 Hz, 1H, H-3), 4.12 (dd, *J* = 6.5, 8.4 Hz, 1H, H-2), 4.25 (dd, *J* = 6.4, 7.9 Hz, 1H, H-3), 5.90 (d, *J* = 9.8 Hz, 1H, H-7), 6.03 (dd, *J* = 1.5, 9.8 Hz, 1H, H-8), 6.08 (d, *J* = 1.1 Hz, 1 H, H-10); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 132.7 (C-7), 129.6 (C-10), 128.1 (C-8), 119.7 (C-9), 108.7 (C-5), 86.6 (C-2), 82.0 (C-12), 73.0 (C-11), 70.2 (C-6), 67.2 (C-3), 32.7 (C-13), 25.4 (C-14); LRMS (ESIMS): *m/z* (%) = 337 (90) [MNa^+], 335 (100) [MNa^+], 256 (19) [$MNa–Br]^+$; HRMS (ESI) calcd for $C_{14}H_{17}{}^{79}BrNaO_3$ 335.0259, found 335.0253.

9-Bromo-(2*R*)-*tert*-butyl-(6*S*)-(prop-2-enyl)-1,4-dioxaspiro[4.(5*R*)]deca-7,9-dien-6-ol (9d). Reaction was performed using allylmagnesium bromide (1.0 M in Et_2O). Column chromatography, eluting with PET/acetone (from 99:1 to 97:3), furnished **9d** as a yellow oil (60 mg, 58%, dr = 58:42): ^1H NMR ($CDCl_3$, 300 MHz): major diastereomer: δ = 0.90 (s, 9H, H-15, *t*Bu), 2.53 (d, *J* = 7.2 Hz, 2H, H-11), 2.55 (bs, 1H, OH), 3.78 (t, *J* = 7.6 Hz, 1H, H-3), 3.83 (t, *J* = 6.7 Hz, 1H, H-2), 4.11 (dd, *J* = 7.3, 7.0 Hz, 1H, H-3), 5.08 (d, *J* = 12.8, 2H, H-13), 5.73 (d, *J* = 10.2 Hz, 1H, H-7), 5.77-5.96 (m, 1H, H-12), 5.88 (dd, *J* = 1.2, 10.2 Hz, 1H, H-8) 5.96 (d, *J* = 0.8 Hz, 1H, H-10), minor diastereomer: δ = 0.95 (s, 9H, H-15, *t*Bu), 2.52 (d, *J* = 7.2 Hz, 2H, H-11), 2.62 (bs, 1H, OH), 3.59-3.70 (m, 1H, H-3), 3.97-4.06 (m, 2H, H-2), 5.08 (d, *J* = 12.3 Hz, 2H, H-13), 5.73 (d, *J* = 10.0 Hz, 1H, H-7), 5.82-5.98 (m, 1H, H-12), 5.87 (dd, *J* = 1.6, 10.2 Hz, 1H, H-8), 6.04 (d, *J* = 1.4 Hz, 1H, H-10).

9-Bromo-(2*R*)-*tert*-butyl-(10*R*)-ethenyl-1,4-dioxaspiro[4.(5*R*)]dec-8-en-6-one (10). Reaction was performed using vinylmagnesium bromide (1.0 M in THF). Column chromatography, eluting with PET/acetone (98:2), afforded **10** as a pale yellow oil (55 mg, 71%, dr = 90:10): IR (neat): ν = 2961, 2908, 2874, 1742, 1638, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): major diastereomer: δ = 0.92 (s, 9H, H-14, *t*Bu), 2.91 (dd, *J* = 3.6, 21.1 Hz, 1H, H-7), 3.16 (dd, *J* = 4.1, 21.1 Hz, 1H, H-7), 3.51 (d, *J* = 7.2 Hz, 1H, H-10), 3.72 (t, *J* = 7.1 Hz 1H, H-2), 3.8 (t, *J* = 7.3 Hz 1H, H-3), 4.05 (t, *J* = 7.2 Hz, 1H, H-3), 5.25 (d, *J* = 18.3 Hz, 1H, H-12a), 5.31 (d, *J* = 10.9 Hz, 1H, H-12b), 5.72 (ddd, *J* = 7.2, 10.2, 17.3 Hz, 1H, H-11), 6.14 (t, *J* = 3.8 Hz, 1H, H-8); ^{13}C NMR ($CDCl_3$, 75.5 MHz): major diastereomer: δ = 201.3 (C-6), 130.9 (C-11), 125.9 (C-8), 119.73 (C-9), 119.69 (C-12), 106.5 (C-5), 84.1 (C-2), 67.2 (C-3), 58.9 (C-10), 39.7 (C-7), 32.7 (C-13), 25.3 (C-14); minor diastereomer: δ = 200.5 (C-6), 130.8 (C-11), 125.7 (C-8), 119.9 (C-9), 119.5 (C-12), 106.8 (C-5), 84.8 (C-2), 67.9 (C-3), 60.2 (C-10), 40.2 (C-7), 31.9 (C-13), 25.6 (C-14); LRMS (ESIMS): *m/z* (%) = 339 (100) [MNa^+], 337 (87) [MNa^+]; HRMS (ESI) calcd for $C_{14}H_{19}{}^{79}BrNaO_3$ 337.0415, found 337.0427.

(–)-9-Bromo-(2*R*)-*tert*-butyl-(7*S*,8*R*)-epoxy-(6*S*)-methyl-1,4-dioxaspiro[4.(5*R*)]dec-9-en-6-ol (11). To a stirred ice-cold solution of cyclohexa-2,4-dienol **9a** (81 mg, 0.27 mmol) in $CHCl_3$ (3 mL, *ca.* 0.1 M) was added K_2CO_3 (48 mg, 0.35 mmol) and *m*-CPBA (70% purity, 72 mg, 0.29 mmol). The reaction mixture was then stirred at room temperature for 3 hours, until total consumption of the starting material [TLC monitoring, PET/Et_2O (3:2)]. The solvent was removed under reduced pressure and the resulting white solid was subjected to column chromatography, eluting with PET/Et_2O (4:1), to give **11** as a yellow oil (84 mg, quantitative yield, dr ≥ 95:5): $[\alpha]^{25}_D$ = –4.7 (*c* = 0.85, $CHCl_3$); IR (neat): ν = 3467, 1640, 1258, 1146, 800 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.91 (s, 9H, H-13, *t*Bu), 1.27 (s, 3H, H-11, Me), 2.90 (bs, 1H, OH), 3.35 (d, *J* = 4.0 Hz, 1H, H-7), 3.60 (dd, *J* = 2.6, 4.1 Hz, 1H, H-8), 3.65 (t, *J* = 8.3 Hz, 1H, H-3b), 3.82 (dd, *J* = 6.1, 8.1 Hz, 1H, H-2), 4.05 (dd, *J* = 6.1, 8.2 Hz, 1H, H-3a), 6.00 (d, *J* = 2.1 Hz, 1H, H-10); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 133.2 (C-10), 121.3 (C-9), 107.1 (C-5), 86.4 (C-2), 73.1 (C-6), 65.7 (C-3), 59.9 (C-7), 55.5 (C-8), 32.6 (C-12), 25.5 (C-13), 19.4 (C-11); LRMS (ESIMS): *m/z* (%) = 343 (100) [MNa^+], 341 (98) [MNa^+]; HRMS (ESI) calcd for $C_{13}H_{19}{}^{79}BrNaO_4$ 341.0364, found 341.0372.

(–)-(2*R*)-*tert*-butyl-(7*S*,8*R*)-epoxy-(6*S*)-methyl-1,4-dioxaspiro[4.(5*R*)]dec-9-en-6-ol (12). To a stirred solution of epoxy-alcohol **11** (66 mg, 0.21 mmol) in dry THF (30 mL) was added Bu_3SnH (90 mg, 0.31 mmol) and AIBN (1.7 mg, 0.01 mmol). The reaction mixture was then heated under reflux for 3 hours, after which time another portion of Bu_3SnH (90 mg, 0.31 mmol) was added. After 2 additional hours under reflux, the reaction mixture was allowed to cool to room temperature, SiO_2 (*ca.* 200 mg) was then added, and stirring at room temperature was maintained for 30 min. The mixture was filtered, and the resulting solid residue was washed with CH_2Cl_2. Evaporation of the combined filtrates afforded a 1:1 mixture (^{1}H NMR analysis) of the expected product **12** and its corresponding bromohydrin **13**. For characterization purpose, compound **13** could be purified by column chromatography, eluting with cyclohexane/acetone (95:5). Otherwise, the **12**/**13** mixture was diluted in dry MeOH (3 mL) and treated with K_2CO_3 (86 mg, 0.62 mmol) at room temperature. The resulting mixture was stirred until disappearance of the bromohydrin [TLC monitoring, PET/acetone (4:1)]. The reaction was made neutral upon washing with saturated aqueous NH_4Cl (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and evaporated. The resulting oily residue was partitioned between hexane (10 mL) and acetonitrile (10 mL). The polar layer was then washed with hexane (2 × 10 mL) to remove all the stannous salts, and evaporated. Purification of the residue by column chromatography, eluting with cyclohexane/acetone (95:5), gave **12** as a colorless oil (46 mg, 65%, dr ≥ 95:5): $[\alpha]^{25}_D$ = –62.3 (*c* = 1.34, $CHCl_3$); IR (neat): ν = 3653, 1248, 1148 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (s, 9H, H-13, *t*Bu), 1.24 (s, 3H, H-11, Me), 2.93 (bs, 1H, OH), 3.33 (d, *J* = 4.0 Hz, 1H, H-7), 3.36 (dt, *J* = 1.9, 4.2 Hz, 1H, H-8), 3.68 (t, *J* = 8.1 Hz, 1H, H-3), 3.83 (dd, *J* = 6.0, 7.9 Hz, 1H, H-2), 4.06 (dd, *J* = 6.1, 8.3 Hz, 1H, H-3), 5.70 (dd, *J* = 1.9, 10.0 Hz, 1H, H-10), 6.09 (dd, *J* = 3.8, 10.0, 1H, H-9); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 134.3 (C-10), 126.5 (C-9), 106.6 (C-5), 86.2 (C-2), 73.6 (C-6), 65.7 (C-3), 59.2 (C-7), 48.7 (C-8), 32.7 (C-12), 25.5 (C-13), 19.5 (C-11); LRMS (ESIMS): *m/z* (%) = 263 (100) [MNa^+]; HRMS (ESI) calcd for $C_{13}H_{20}NaO_4$ 263.1253, found 263.1257.

Bromohydrin 13 was isolated as a colorless oil: $[\alpha]^{25}_D$ = –72.1 (*c* = 0.85, $CHCl_3$); IR (neat): ν = 3467, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (s, 9H, H-13, *t*Bu), 1.40 (s, 3H, H-11, Me), 3.78 (dd, *J* = 8.1, 8.9 Hz, 1H, H-3), 3.94 (dd, *J* = 6.1, 8.9 Hz, 1H, H-2), 3.98 (d, *J* = 6.4 Hz, 1H, H-7), 4.10 (dd, *J* = 6.1, 8.1 Hz, 1H, H-3), 4.75 (ddd, *J* = 1.9, 2.9, 6.4 Hz, 1H, H-8), 5.57 (dd, *J* = 1.7, 10.0 Hz, 1H, H-10), 5.97 (dd, *J* = 2.8, 10.2, 1H, H-9); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 130.0 (C-9), 128.7 (C-10), 107.2 (C-5), 86.7 (C-2), 78.0 (C-7), 76.7 (C-6), 67.2 (C-3), 51.8 (C-8), 32.6 (C-12), 25.5 (C-13), 19.8 (C-11); LRMS (ESIMS): *m/z* (%) = 345 (100) [MNa^+], 343 (92) [MNa^+], 241 (23) [MNa–Br]$^+$; HRMS (ESI) calcd for $C_{13}H_{21}{}^{79}BrNaO_4$ 343.0515, found 343.0507.

9-Bromo-(2*R*)-*tert*-butyl-(6*S*)-[(2*S*)-(*N*-*tert*-butoxycarbonyl)-(*O*-tetrahydropyranyl)-2-amino-3-hydroxypropyl]-1,4-dioxaspiro[4.(5*R*)]deca-7,9-dien-6-ol (17). To a stirred solution of chloride (*R*)-**16** (212 mg, 0.72 mmol) in dry THF (9 mL) at −78 °C, under an atmosphere of argon, was added dropwise *n*-BuLi (1.3 M in hexanes, 0.6 mL, 0.8 mmol). The solution was then stirred at –78 °C for 10 min, after which time freshly prepared LiNp[18c] (0.5 M in THF, 3.3 mL, 1.66 mmol) was added dropwise over 5 min. The resulting dark solution was stirred at −78 °C for 2 hours, after which time freshly prepared *ortho*-quinone spiroketal (*R*,*R*)-**7** (159 mg, 0.55 mmol) was added dropwise. The reaction mixture immediately became colorless. It was kept at low temperature (*i.e.*, between −78 °C and −40 °C) overnight (*ca.* 12 h), and then quenched with saturated aqueous NH_4Cl (1 mL), and allowed to warm to room temperature. The reaction was diluted with EtOAc (20 mL) and saturated aqueous NH_4Cl (20 mL). After separation of the layers, the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Purification of the residue by column chromatography, eluting with cyclohexane/acetone (95:5), afforded the 1,2-adduct **17** as a colorless oil (42 mg, 33%): IR (neat): ν = 3508, 3388, 2956, 2871, 1714, 1505, 1366, 1174, 1034, 987, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): THP-based diastereomeric mixture: δ = 0.88 (s, 9H, H-13, *t*Bu), 1.44 (s, 9H, Boc *t*Bu), 1.48-1.94 (m, 9H), 3.41 (dd, *J* = 4.0, 9.8 Hz, 1H), 3.46-3.51 (m, 1H), 3.65 (dd, *J* = 5.3, 10.0 Hz, 1H), 3.70-3.89 (m, 4H), 4.09 (dd, *J* = 6.2, 7.9 Hz, 1H), 4.55-4.58 (m, 1H), 5.21 (bs, 1H, NH), 5.88 (dd, *J* = 1.7, 10.2 Hz, 1H), 5.95-6.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): THP-based diastereomeric mixture: δ = 155.8, 155.1, 138.0, 129.5, 126.5, 119.7, 110.6, 99.2, 98.7, 85.7, 79.3, 76.2, 70.7, 66.4, 62.4, 62.0, 47.9, 43.4, 32.8, 32.8, 30.5, 30.4, 30.1, 29.7, 28.5, 28.4, 28.3, 26.9, 25.7, 25.4, 25.3, 25.3, 25.2, 25.2, 19.5, 19.1; LRMS (ESIMS): *m/z* (%) = 1117 (60) [2M+Na^+], 1115 (100) [2M+Na^+], 1113 (40) [2M+Na^+], 570 (75) [MNa^+], 568 (70) [MNa^+], 490 (15) [MNa^+–Br+H]; HRMS (ESI) calcd for $C_{25}H_{40}{}^{79}BrNNaO_7$ 568.1886, found 568.1879.

9-Bromo-(2*R*)-*tert*-butyl-(7*S*,8*R*)-epoxy-(6*S*)-[(2*S*)-(*N*-*tert*-butoxycarbonyl)-(*O*-tetrahydropyranyl)-2-amino-3-hydroxypropyl]-1,4-dioxaspiro [4.(5*R*)]dec-9-en-6-ol (18). To a stirred solution of cyclohexa-2,4-dienol **17** (26 mg, 48 µmol) in $CHCl_3$ (1 mL) was added K_2CO_3 (9 mg, 62 µmol) and *m*-CPBA (70% purity, 12 mg, 48 µmol). The reaction mixture was stirred at room temperature overnight (*ca.* 12 h), until total consumption of the starting material [TLC monitoring, PET/acetone (4:1)]. The solvent was removed under reduced pressure and the resulting white solid was subjected to column chromatography, eluting with cyclohexane/acetone (95:5), to afford **18** as a yellow oil (11 mg, 41%): IR (neat): ν = 3520, 3390, 2958, 2926, 2871, 1711, 1502, 1467, 1366, 1251, 1172, 1061, 1033, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.90 (s, 9H, *t*Bu), 1.44 (s, 9H, Boc *t*Bu), 1.44-2.01 (m, 8H), 3.13 (bs, 1H, OH), 3.39 (dd, *J* = 5.1, 9.8 Hz, 1H), 3.49-3.55 (m, 1H), 3.60-3.66 (m, 3H), 3.74 (dd, *J* = 4.1, 8.9 Hz, 1H), 3.79-3.86 (m, 2H), 4.00-4.05 (m, 2H), 4.06 (t, *J* = 3.0 Hz, 1H), 5.04 (bs, 1H, NH), 6.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): major THP-based diastereomer: δ = 155.5, 133.3, 121.9, 107.3, 98.9, 86.7, 86.5, 75.7, 70.6, 65.8, 62.1, 58.2, 55.7, 46.7, 32.6, 31.2, 30.4, 29.7, 28.4, 25.5, 19.3; LRMS (ESIMS): *m/z* (%) = 1149 (49) [2M+Na^+], 1147 (100) [2M+Na^+], 1145 (47) [2M+Na^+], 586 (51) [MNa^+], 584 (48) [MNa^+]; HRMS (ESI) calcd for $C_{25}H_{40}{}^{79}BrNNaO_8$ 584.1835, found 584.1817.

(2*R*)-*tert*-Butyl-(7*S*,8*S*)-epoxy-(6*S*)-[(2*S*)-(*N*-*tert*-butoxycarbonyl)-(*O*-tetrahydropyranyl)-2-amino-3-hydroxy propyl]-1,4-dioxaspiro[4.(5*R*)]dec-9-en-6-ol (19). To a stirred solution of epoxy-alcohol **18** (37 mg, 0.066

mmol) in dry THF (3 mL) was added Bu_3SnH (29 mg, 0.099 mmol) and AIBN (1.1 mg, 0.006 mmol). The reaction mixture was then heated under reflux for 3 hours, after which time it was allowed to cool to room temperature, and then diluted with Et_2O (4 mL). Powdered SiO_2 (80 mg) was added in one portion to the reaction mixture, which was kept under stirring at room temperature for 30 min. The mixture was filtered, and the resulting solid residue was washed with Et_2O. The combined filtrates were evaporated, and the resulting residue was purified by column chromatography, eluting with PET/acetone (9:1), to furnish **19** as a colorless oil (39 mg, quantitative yield): IR (neat): ν = 3515, 3400, 1707, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.91 (s, 9H, *t*Bu), 1.45 (s, 9H, Boc *t*Bu), 1.45-2.02 (m, 8H), 2.52 (m, 1H), 2.97 (bs, 1H, OH), 3.27-3.50 (m, 1H), 3.42-3.56 (m, 2H), 3.69-3.92 (m, 3H), 3.99-4.20 (m, 3H), 4.49-4.66 (m, 2H), 5.70 (d, *J* = 9.3 Hz, 1H), 5.84-5.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): THP-based diastereomeric mixture: δ = 154.7, 154.6, 130.8, 130.7, 127.3 (2C) 107.1, 99.3, 98.6, 86.5, 80.4, 80.3, 73.9, 73.0, 70.6, 69.8, 66.0, 62.3, 62.1, 53.9 (2C), 50.8, 50.6, 34.3, 33.9, 32.6, 30.6, 30.5, 28.3, 25.5, 19.4; LRMS (ESIMS): *m/z* (%) = 990 (57) [2M+Na^+], 988 (15), 986 (100); HRMS (ESI) calcd for $C_{25}H_{41}NNaO_8$ 506.2730, found 506.2746.

(+)-*tert*-Butyl *N*-Fmoc-(2*S*)-2-amino-3-(2-methoxymethoxyphenyl)propanoate (23). To a stirred suspension of Zn (736 mg, powder, 11.25 mmol) in dry DMF (2 mL) was added, at room temperature, TMSCl (237 µL, 1.88 mmol). Stirring at room temperature was maintained for 30 min, after which time a solution of L-serine derivative **21** (1.85 g, 3.75 mmol) in dry DMF (9 mL) was added dropwise. The reaction mixture was stirred for 15 min [*i.e.*, until consumption of **21**, as indicated by TLC monitoring, eluting twice with cyclohexane/EtOAc (85:15)], after which time aryl iodide **22** (1,19 g, 4.88 mmol), P(*o*-tol)$_3$ (1.49 g, 4.88 mmol) and $Pd_2(dba)_3$ (240 mg, 0.263 mmol) were successively added. The resulting mixture was then heated at 50°C for 2 hours, then cooled down to room temperature, diluted with EtOAc (60 mL), and quenched with saturated aqueous $NaHCO_3$ (50 mL). After separation of the two layers, the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated. Purification of the residue by column chromatography, eluting with cyclohexane/EtOAc (85:15), gave **23** (1.57 g, 83%) as an orange amorphous solid: mp 49-50 °C; $[\alpha]^{25}_D$ = +32.5 (*c* = 0.40, $CHCl_3$); IR (neat): ν = 2922, 1726, 1494, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.42 (s, 9H), 3.12 (d, *J* = 7.2 Hz, 2H), 3.50 (s, 3H), 4.19 (t, *J* = 7.0 Hz, 1H), 4.36 (d, *J* = 7.2 Hz, 2H), 4.60 (q, *J* = 7.4 Hz, 1H), 5.15-5.30 (m, 2H), 5.68 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 7.19 (dt, *J* = 7.9, 16.9 Hz, 3H), 7.27-7.36 (m, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.1 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 171.2, 155.7, 155.5, 143.8 (2C), 141.2, 131.2 (2C), 128.4, 127.5 (2C), 126.9 (2C), 125.6, 125.0 (2C), 121.7, 119.8 (2C), 114.0, 94.6, 81.7, 66.7, 56.1, 54.9, 47.0, 33.4, 27.8 (3C); LRMS (ESIMS): *m/z* (%) = 528 (30), 526 (100) [MNa^+], 504 (47) [MH^+]; HRMS (ESI) calcd for $C_{30}H_{34}NO_6$ 504.2381, found 504.2391.

(+)-*N*-Fmoc 3-amino-3,4-dihydrocoumarin (24). To a stirred solution of **23** (100 mg, 0.199 mmol) was added Et_3SiH (95 µL, 0.596 mmol) and TFA (307 µL, 3.98 mmol). The solution was stirred at room temperature overnight (*ca.* 12 h), after which time it was quenched with 1M aqueous HCl (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated. Purification of the residue by column chromatography, eluting with cyclohexane/EtOAc (85:15), furnished lactone **24** (71 mg, 92%) as a white solid: mp 164-165 °C; $[\alpha]^{25}_D$ = +37.8 (*c* = 0.45, $CHCl_3$); IR (neat): ν = 1777, 1721, 1536, 1313, 1226 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.98 (t, *J* = 15.1 Hz, 1H), 3.48 (dd, *J* = 6.7, 15.1 Hz, 1H), 4.25 (t, *J* = 6.7 Hz, 1H), 4.45 (d, *J* = 6.7 Hz, 2H), 4.51-4.69 (m, 1H), 5.81 (d, *J* = 4.0 Hz, 1H), 7.03-7.37 (m, 6H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 168.2, 155.7, 150.8, 143.7, 143.6, 141.3 (2C), 128.9, 128.6, 127.8 (2C), 127.1 (2C), 125.0 (2C), 121.2, 120.0 (2C), 116.7 (2C), 67.3, 49.7, 47.1, 30.8; LRMS (ESIMS): *m/z* (%) = 418 (55), 409 (25), 408 (100) [MNa^+], 504 (47); HRMS (ESI) calcd for $C_{24}H_{19}NNaO_4$ 408.1206, found 408.1218.

(+)-*N*-Fmoc-(2*S*)-2-amino-3-(2-hydroxyphenyl)propanoic acid (25). To a stirred solution of lactone **24** (23 mg, 0.060 mmol) in dry THF (2.6 mL) was added 1M aqueous NaOH (0.7 mL, 0.066 mmol). The solution was stirred at room temperature for 30 min, after which time it was quenched by adding 5% aqueous citric acid (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated to afford **25** as a white solid (24 mg, quantitative yield), which was used without further purification: mp 120-121 °C; $[\alpha]^{25}_D$ = +52.4 (*c* = 0.85, THF); IR (neat): ν = 1720, 1450, 1111 cm^{-1}; ^1H NMR (THF-d_8, 300 MHz): δ = 2.89 (dd, *J* = 9.6, 13.4 Hz, 1H), 3.21 (dd, *J* = 4.7, 13.6 Hz, 1H), 4.03-4.25 (m, 3H), 4.44-4.63 (m, 1H), 6.61-6.67 (m, 3H), 6.96 (t, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 7.14-7.24 (m, 2H), 7.29 (t, *J* = 7.3 Hz, 2H), 7.49-7.62 (m, 2H), 7.71 (d, *J* = 7.4 Hz, 2H), 8.44 (s, 1H); ^{13}C NMR (THF-d_8, 75.5 MHz): δ = 173.8, 156.5, 156.4, 145.1, 142.0, 131.8, 128.2, 128.0 (2C), 127.5 (2C), 126.0 (2C), 125.9, 125.0, 120.3 (2C), 119.9, 115.4 (2C), 67.0, 54.8, 48.0, 33.2; LRMS (ESIMS): *m/z* (%) = 427 (45), 426 (100) [MNa^+]; HRMS (ESI) calcd for $C_{24}H_{21}NNaO_5$ 426.1317, found 426.1328.

(+)-*N*-Fmoc-(2*S*)-2-amino-3-(2-hydroxyphenyl)propanol (26). To a stirred ice-cold suspension of $NaBH_4$ (118 mg, 3.12 mmol) in absolute EtOH (10 mL) was added dropwise a solution of lactone **24** (240 mg, 0.623 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at 0 °C for 30 min, after which time it was diluted with EtOAc (50 mL) and quenched with 1M aqueous HCl (50 mL) at the same temperature. After separation of the two layers, the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with a 1:1 solution of brine and 1M aqueous HCl (20 mL), dried over Na_2SO_4, filtered and evaporated. Purification of the residue by column chromatography, eluting with cyclohexane/EtOAc (40:60), furnished the phenolic alcohol **26** as a white amorphous solid (220 mg, 91%): mp 159-160 °C; $[\alpha]^{25}_D$ = +26.7 (*c* = 0.45, acetone); IR (neat): ν = 3318, 1710, 1703, 1692, 1525 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz): δ = 2.81-2.97 (m, 2H), 3.61 (s, 2H), 3.82-3.98 (m, 1H), 4.07 (m, 1H), 4.13-4.43 (m, 3H), 6.44 (d, *J* = 7.2 Hz, 1H), 6.78 (td, *J*

= 1.1, 7.5 Hz, 1H), 6.87 (dd, *J* = 1.2, 8.1 Hz, 1H), 7.03-7.10 (m, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.31 (tdd, *J* = 1.2 , 3.4, 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.4 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 2H), 8.52 (s, 1H); ^{13}C NMR (acetone-d_6, 75.5 MHz): δ = 157.2, 156.4, 145.1 (2C), 142.1 (2C), 132.2, 128.5 (2C), 128.4, 127.9 (2C), 126.2, 126.1, 125.8, 120.8 (2C), 120.5, 116.2, 67.0, 64.0, 55.0, 48.1, 32.4; LRMS (ESIMS): *m/z* (%) = 412 (100) [MNa^+], 391 (15), 390 (65) [MH^+]; HRMS (ESI) calcd for $C_{24}H_{24}NO_4$ 390.1700, found 390.1710.

(+)-*N*-Fmoc-*O*-(*tert*-butyldimethylsilyl)-(2*S*)-2-amino-3-(2-hydroxyphenyl)propanol (27a). To a stirred ice-cold solution of phenolic alcohol **26** (215 mg, 0.55 mmol) in dry CH_2Cl_2 (25 mL) was added freshly distilled *i*Pr_2NEt (563 µL, 3.31 mmol). The resulting solution was stirred at 0 °C for 20 min, after which time TBSOTf (380 µL, 1.66 mmol) was added dropwise at 0 °C. The reaction mixture was stirred an additional 15 min, after which time it was quenched by adding saturated aqueous $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were then shaken vigorously with 1M aqueous HCl for 5 min. The layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. Purification of the residue by column chromatography, eluting with cyclohexane/EtOAc (90:10), afforded the phenol **27a** as a pale brown solid (220 mg, 79%): mp 38-39 °C; $[\alpha]^{25}_D$ = +40.0 (*c* = 0.30, $CHCl_3$); IR (neat): ν = 2922, 1726, 1494, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.12 (s, 3H, Me), 0.14 (s, 3H, Me), 0.97 (s, 9H, *t*Bu), 2.78 (dd, *J* = 8.9, 13.9 Hz, 1H), 2.97 (d, *J* = 12.6 Hz, 1H), 3.61 (s, 2H), 3.78 (s, 1H), 4.25 (t, *J* = 6.9 Hz, 1H, Fmoc CH), 4.46 (d, *J* = 7.2 Hz, 2H, Fmoc CH_2), 5.19 (bd, *J* = 6.9 Hz, 1H, OH), 6.84 (td, *J* = 1.2, 7.5 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 7.12-7.20 (m, 1H), 7.32 (td, *J* = 1.2, 7.4 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.60 (dd, *J* = 6.0, 12.6 Hz, 3H), 7.78 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 156.7, 155.7, 143.8, 143.7, 141.3 (2C), 131.1, 128.5, 127.7 (2C), 127.0 (2C), 125.03, 124.97, 122.9, 120.2, 120.0 (2C), 116.8, 67.0, 62.3, 52.8, 47.2, 31.8, 25.8 (3C), 18.3, –5.40, –5.43; LRMS (ESIMS): *m/z* (%) = 527 (13), 526 (35) [MNa^+], 505 (40), 504 (100) [MH^+]; HRMS (ESI) calcd for $C_{30}H_{38}NO_4Si$ 504.2565, found 504.2575.

Spirolactone-based [4+2]-Cyclodimers 30 and 30'. To a stirred solution of phenol-carboxylic acid **25** (199 mg, 0.49 mmol) in dry CH_2Cl_2 (20 mL), cooled at 0 °C or –20 °C, was added $NaHCO_3$ (46 mg, 0.54 mmol). After 5 min stirring, $PhI(OAc)_2$ (174 mg, 0.54 mmol) or $PhI(OCOCF_3)_2$ (232 mg, 0.54 mmol) was added in one portion, and the reaction mixture was stirred at the same temperature for 3 hours, after which time the solvent was evaporated. The resulting orange oily residue was purified by column chromatography, eluting with CH_2Cl_2/EtOAc (75:25), to afford a 1:1 mixture of cyclodimer **30** and **30'** (85 mg, 43%). Further purification of 20 mg of this mixture was achieved by preparative TLC, eluting four times with CH_2Cl_2/EtOAc (85:15), to give 7 and 8 mg of each cyclodimer (*i.e.*, 15% yield for each product).

1st cyclodimer (**30** or **30'**), which corresponds to the higher spot on preparative TLC, was isolated as a white amorphous solid: $[\alpha]^{25}_D$ = +52.1 (*c* = 0.35, acetone); IR (neat): ν = 2950, 2927, 1721, 1650, 1548, 1245, 1119 cm^{-1}; ^{1}H NMR (acetone-d_6, 400 MHz): δ = 2.23 (t, *J* = 12.2 Hz, 1H), 2.46-2.66 (m, 2H), 2.72-2.83 (m, 1H), 3.28 (d, *J* = 8.4 Hz, 1H), 3.51 (d, *J* = 5.8 Hz, 1H), 3.58 (d, *J* = 4.5 Hz, 1H), 3.66-3.78 (m, 1H), 4.16-4.28 (m, 2H), 4.29-4.44 (m, 5H), 4.64 (dd, *J* = 9.4, 19.4 Hz, 1H), 6.17 (t, *J* = 8.4 Hz, 2H), 6.46 (t, *J* = 7.4 Hz, 1H), 6.80 (dd, *J* = 3.7, 10.1 Hz, 1H), 7.04 (dd, *J* = 8.4, 17.8 Hz, 2H), 7.26-7.36 (m, 4H), 7.36-7.44 (m, 4H), 7.69 (d, *J* = 7.4 Hz, 4H), 7.86 (d, *J* = 7.4 Hz, 4H); ^{13}C NMR (acetone-d_6, 100 MHz): δ = 207.1, 194.7, 174.2, 173.9, 156.7 (2C), 147.9, 144.9 (4C), 142.1 (4C), 132.4, 131.7, 129.2 (2C), 128.6 (4C), 128.0 (4C), 126.1 (3C), 120.8 (4C), 82.9, 80.9, 67.4, 52.3, 51.4, 51.3, 50.7, 50.6, 47.9, 45.7, 43.8, 42.8, 39.7, 37.4; LRMS (ESIMS): *m/z* (%) = 827 (4), 826 (32), 825 (100) [MNa^+]; HRMS (ESI) calcd for $C_{48}H_{38}N_2NaO_{10}$ 825.2424, found 825.2439.

2nd cyclodimer (**30'** or **30**), which corresponds to the lower spot on preparative TLC, was isolated as a white amorphous solid: $[\alpha]^{25}_D$ = –16.2 (*c* = 0.40, acetone); IR (neat): ν = 2971, 2934, 1717, 1665, 1567, 1164 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz): δ = 2.15 (d, *J* = 12.1 Hz, 1H), 2.28-2.52 (m, 2H), 2.94 (dd, *J* = 9.9, 12.1 Hz, 1H), 3.42 (d, *J* = 8.3 Hz, 1H), 3.49-3.60 m, 1H), 3.66-3.82 (m, 2H), 4.15-4.43 (m, 6H), 4.74-4.98 (m, 2H), 6.06-6.21 (m, 2H), 6.50 (t, *J* = 7.3 Hz, 1H), 6.81 (dd, *J* = 4.3, 10.0 Hz, 1H), 7.03 (dd, *J* = 8.8, 18.0 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 4H), 7.40 (d, *J* = 7.3 Hz, 4H), 7.68 (dd, *J* = 3.9, 10.0 Hz, 4H), 7.85 (d, *J* = 7.4 Hz, 4H); ^{13}C NMR (acetone-d_6, 75.5 MHz): δ = 204.9, 193.3, 174.0, 173.7, 156.7 (2C), 147.5, 144.9 (4C), 142.1 (4C), 135.4, 131.1, 129.8 (2C), 128.6 (4C), 128.0 (4C), 126.1 (3C), 120.8 (4C), 83.1, 80.3, 67.5, 67.4, 52.4, 50.6, 49.8, 47.9, 43.3, 41.4, 40.3, 39.2, 37.6; LRMS (ESIMS): *m/z* (%) = 827 (11), 826 (55), 825 (100) [MNa^+]; HRMS (ESI) calcd for $C_{48}H_{38}N_2NaO_{10}$ 825.2424, found 825.2435.

***N*-Cyclohexyl-2-iodylbenzamide (31).** To a stirred ice-cold solution of commercially available 2-iodobenzoic acid (1.0 g, 4.03 mmol, 1 eq.) in dry CH_2Cl_2 (40 mL) was added dropwise Ghosez's reagent (*i.e.*, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, 0.8 mL, 6.05 mmol). The resulting solution was warmed up to room temperature, and stirred for 30 min, after which time it was cooled again at 0 °C for the addition of cyclohexylamine (0.5 mL, 4.23 mmol) and freshly distilled Et_3N (1.1 mL, 8.06 mmol). After warming to room temperature, the reaction mixture was stirred for 1.5 h, after which time it was successively washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and 1M aqueous HCl (2 × 30 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The resulting solid residue was purified by column chromatography, eluting with cyclohexane/EtOAc (70:30), to afford the *N*-cyclohexyl-2-iodobenzamide as a white powder (1.20 g, 90%): IR (neat): ν = 3230, 1655, 504 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 1.01-2.00 (m, 10H), 3.70 (s, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 6.5 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 8.23 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ = 168.0, 143.5, 138.8, 130.4, 127.9, 127.8, 93.6, 48.1, 32.2 (2C), 25.2, 24.7 (2C); LRMS (ESIMS): *m/z* (%) = 681 (15) [2M+Na^+], 352 (100) [MNa^+]. This material (200 mg, 0.554 mmol) was next oxidized at 0 °C with freshly prepared 3,3-dimethyldioxirane (DMDO, typically 0.07 M in acetone, 4 equiv).[12e] The resulting mixture was stirred at room temperature overnight (*ca.* 12 h), after which time the solvent was evaporated to give

the *N*-cyclohexyl-2-iodylbenzamide (**31**) as a white powder (240 mg, quantitative yield), which was used without further purification: mp 212 °C; IR (neat): ν = 3224, 1650, 725, 550 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ = 1.03-1.50 (m, 5H), 1.55-1.93 (m, 5H), 3.84 (s, 1H), 7.73 (t, J = 7.4 Hz, 1H), 7.93 (t, J = 7.4 Hz, 1H), 8.26 (dd, J = 7.6, 16.1 Hz, 2H), 9.04 (d, J = 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ = 164.9, 149.0, 132.7, 131.3, 128.7, 127.1, 123.1, 49.5, 32.0 (2C), 25.1, 24.8 (2C); LRMS (ESIMS): *m/z* (%) = 745 (38) [2M+Na^+], 384 (100) [MNa^+]; HRMS (ESI) calcd for $C_{13}H_{16}INNaO_3$ 384.0073, found 384.0084.

(4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-6-[(2*S*)-*N*-Fmoc-2-amino-3-(*tert*-butyldimethylsilyloxy)propyl]cyclohex-2-en-1-one (34a) and (4*R*,5*R*,6*R*)-4,5-Epoxy-6-hydroxy-6-[(2*S*)-*N*-Fmoc-2-amino-3-(*tert*-butyldimethylsilyloxy)-propyl]cyclohex-2-en-1-one (35a). A stirred solution of phenol **27a** (52 mg, 0.103 mmol) in dry CH_2Cl_2 (10 mL, *ca.* 10 mM) was cooled at –50 °C (or at –20 °C, see Table 1). The λ^5-iodane reagent (*R,R*)-**32** (72 mg, 0.113 mmol) (or another λ^5-iodane, 1.1 equiv, see Table 1 and the Supporting Information) and TFA (8 μL, 0.103 mmol) were added, and the reaction mixture was stirred at the same low temperature until complete consumption of the starting material as indicated by TLC monitoring (*ca.* 1-3 h). Next, a solution of freshly prepared DMDO (*ca.* 0.07 M in acetone, 4 equiv; *i.e.,* 5.9 mL, 0.412 mmol) was added at –20 °C, and the resulting mixture was stirred overnight (*ca.* 12 h) at this temperature, after which time the solvent was evaporated. The resulting yellow oily residue was subjected to column chromatography, eluting with CH_2Cl_2/cyclohexane/EtOAc (4:4:1) and then with cyclohexane/EtOAc (7:3), to give a 1:1 diastereomeric mixture of **34a**/**35a** as a colorless oil (33% yield). This material was further separated by preparative TLC, eluting three times with cyclohexane/Et_2O (3:7), to furnish pure **34a** and **35a** as colorless oils (10 mg each; *i.e.,*15% each).

Compound 34a: $[\alpha]^{25}_D$ = +14.3 (c = 0.70, $CHCl_3$); IR (neat): ν = 3352, 2937, 1748, 1642, 1226 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.05 (s, 6H), 0.89 (s, 9H), 1.87 (dd, J = 9.6, 14.1 Hz, 1H), 2.01 (dd, J = 3.4, 14.5 Hz, 1H), 3.47-3.74 (m, 4H), 3.76-3.89 (m, 1H), 4.05 (s, 1H), 4.22 (t, J = 6.4 Hz, 1H), 4.32-4.46 (m, 2H), 4.97 (d, J = 8.2 Hz, 1H), 6.12 (dd, J = 1.4, 9.6 Hz, 1H), 7.06 (dd, J = 3.4, 9.6 Hz, 1H), 7.31 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.53-7.63 (m, 2H), 7.76 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 197.8, 155.6, 144.1, 144.0, 143.8, 141.3 (2C), 130.4, 127.7 (2C), 127.0 (2C), 125.0, 124.9, 120.0 (2C), 66.7, 65.5, 56.1, 48.2, 47.9, 47.2, 38.8, 29.7, 25.9 (3C), 18.3, –5.4, –5.5; LRMS (ESIMS): *m/z* (%) = 560 (15), 559 (51), 558 (100) [MNa^+]; HRMS (ESI) calcd for $C_{30}H_{37}NNaO_6Si$ 558.2288, found 558.2289.

Compound 35a: $[\alpha]^{25}_D$ = +10.0 (c = 0.50, $CHCl_3$); IR (neat): ν = 3365, 2912, 1744, 1630, 1255 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.05 (s, 6H), 0.89 (s, 9H), 1.91-1.99 (m, 2H), 3.54-3.63 (m, 3H), 3.73-3.94 (m, 3H), 4.21 (t, J = 6.4 Hz, 1H), 4.41 (d, J = 6.4 Hz, 2H), 5.01 (d, J = 7.4 Hz, 1H), 6.08 (d, J = 6.7 Hz, 1H), 7.32 (t, J = 7.4 Hz, 2H), 7.40 (t, J = 7.4 Hz, 2H), 7.53-7.62 (m, 2H), 7.77 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.1, 155.6, 145.0 (2C), 143.8, 141.3 (2C), 130.0, 127.7 (2C), 127.0 (2C), 125.0 (2C), 120.0 (2C), 66.6, 65.2, 56.3, 48.8, 48.0, 47.2, 39.3, 29.7, 25.8 (3C), 18.2, –5.4, –5.5; LRMS (ESIMS): *m/z* (%) = 560 (6), 559 (44), 558 (100) [MNa^+]; HRMS (ESI) calcd for $C_{30}H_{37}NNaO_6Si$ 558.2288, found 558.2284.

(4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-6-[(2*S*)-*N*-Fmoc-2-amino-3-hydroxy)propyl]cyclohex-2-en-1-one (36a) and (4*R*,5*R*,6*R*)-4,5-Epoxy-6-hydroxy-6-[(2*S*)-*N*-Fmoc-2-amino-3-hydroxypropyl]cyclohex-2-en-1-one (37a). A stirred solution of **34a**/**35a** (66:34 diastereomeric mixture, 20 mg, 0.037 mmol) in a 1:1 mixture of THF/H_2O (2 mL) was treated with glacial AcOH (3 mL) at room temperature, and the resulting mixture was stirred overnight (*ca.* 12 h). Next, the solution was diluted with EtOAc (40 mL), and was poured dropwise onto vigorously stirred saturated aqueous $NaHCO_3$ (150 mL). Stirring was kept for 15 min, after which time the layers were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The resulting oily residue (17 mg) was purified by preparative TLC, eluting three times with EtOAc/acetone (20:1), to afford **36a** as a pale yellow oil (9 mg, 58%) and **37a** as a colorless oil (4 mg, 28%).

Compound 36a: $[\alpha]^{25}_D$ = +17.2 (c = 0.45, MeOH); IR (neat): ν = 3349, 2928, 1745, 1637 cm^{-1}; ^1H NMR (methanol-d_4, 400 MHz): δ = 1.80 (dd, J = 9.9, 14.5 Hz, 1H), 2.00 (dd, J = 2.8, 14.5 Hz, 1H), 3.36 (dd, J = 6.3, 11.0 Hz, 1H), 3.43 (dd, J = 6.3, 11.0 Hz, 1H), 3.47 (td, J = 1.4, 3.8 Hz, 1H), 3.61 (d, J = 3.8 Hz, 1H), 3.62-3.74 (m, 1H), 4.20 (t, J = 6.3 Hz, 1H), 4.34 (dd, J = 6.3, 10.4 Hz, 1H), 4.46 (dd, J = 6.3, 10.4 Hz, 1H), 5.94 (dd, J = 1.4, 9.9 Hz, 1H), 7.05 (dd, J = 3.8, 9.9 Hz, 1H), 7.27-7.35 (m, 2H), 7.35-7.43 (m, 2H), 7.66 (t, J = 6.7 Hz, 2H), 7.79 (d, J = 7.4 Hz, 2H); ^{13}C NMR (methanol-d_4, 100 MHz): δ = 199.8, 158.0, 145.5 (2C), 145.4, 142.69, 142.66, 132.1, 128.8 (2C), 128.2 (2C), 126.2, 126.1, 120.9 (2C), 77.5, 67.5, 65.7, 58.2, 40.2, 30.7, 29.5; LRMS (ESIMS): *m/z* (%) = 445 (45), 444 (100) [MNa^+], 504 (47); HRMS (ESI) calcd for $C_{24}H_{23}NNaO_6$ 444.1418, found 444.1425.

Compound 37a: $[\alpha]^{25}_D$ = +7.4 (c = 0.20, MeOH); IR (neat): ν = 3362, 2911, 1742, 1645 cm^{-1}; ^1H NMR (methanol-d_4, 300 MHz): δ = 1.80-188 (m, 2H), 3.36 (dd, J = 5.5, 10.5 Hz, 1H), 3.44 (dd, J = 5.5, 10.5 Hz, 1H), 3.47-3.52 (m, 1H), 3.64 (d, J = 3.9 Hz, 1H), 3.79-3.89 (m, 1H), 4.19 (t, J = 6.5 Hz, 1H), 4.36 (dd, J = 6.5, 10.5 Hz, 1H), 4.48 (dd, J = 6.5, 10.5 Hz, 1H), 4.57 (s, 1H), 5.89 (dd, J = 1.2, 9.9 Hz, 1H), 7.11 (dd, J = 3.9, 9.9 Hz, 1H), 7.32 (t, J = 7.3 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.66 (d, J = 7.3 Hz, 2H), 7.80 (d, J = 7.3 Hz, 2H); LRMS (ESIMS): *m/z* (%) = 423 (15), 422 (60) [MH^+]; HRMS (ESI) calcd for $C_{24}H_{24}NO_6$ 422.1598, found 422.1606.

(+)-*N*-Acetyl-*O*-(*tert*-butyldimethylsilyl)-(2*S*)-2-amino-3-(2-hydroxyphenyl)propanol (27b). To a stirred solution of *N*-Fmoc phenol **27a** (100 mg, 0.199 mmol) in dry CH_2Cl_2 (2 mL) was added Ac_2O (0.95 mL, 9.95 mmol) and freshly distilled Et_3N (2 mL). The reaction mixture was stirred at room temperature for 2 days, after which time the solvent was evaporated. The resulting residue was taken in MeOH (5 mL), and treated with powdered K_2CO_3 (4.13 g, 29.85 mmol). Stirring at room temperature was kept for 4 h, after which time the reaction mixture was diluted with EtOAc (15 mL), and quenched with 5% aqueous citric acid (30 mL). The layers were then separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4,

filtered and evaporated. The resulting residue was purified by column chromatography, eluting with cyclohexane/EtOAc (9:1), then with CH_2Cl_2, and finally with CH_2Cl_2/EtOAc (4:1), to give *N*-acetyl phenol **27b** as a pale yellow oil (63 mg, 98%): $[\alpha]^{25}_D$ = +28.2 (*c* = 0.50, $CHCl_3$); IR (neat): ν = 3294, 2954, 2927, 1655, 1589, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.11 (s, 3H), 0.13 (s, 3H), 0.95 (s, 9H), 2.05 (s, 3H), 2.72 (dd, *J* = 8.4, 14.1 Hz, 1H), 2.96 (dd, *J* = 2.4, 14.1 Hz, 1H), 3.61 (qd, *J* = 3.7, 10.6 Hz, 2H), 3.75-3.91 (m, 1H), 6.17 (d, *J* = 6.4 Hz, 1H), 6.79 (td, *J* = 1.2, 7.8 Hz, 1H), 6.95 (ddd, *J* = 1.4, 7.8, 16.3 Hz, 2H), 7.09-7.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.3, 156.1 130.7, 128.5, 123.2, 119.7, 116.9, 61.8, 51.9, 32.1, 25.8 (3C), 23.1, 18.3, –5.4, –5.5; LRMS (ESIMS): *m/z* (%) = 326 (11), 325 (39), 324 (100) $[MH^+]$; HRMS (ESI) calcd for $C_{17}H_{30}NO_3Si$ 324.1995, found 324.2010.

(+)-*N*-Palmitoyl-*O*-(*tert*-butyldimethylsilyl)-(2*S*)-2-amino-3-(2-hydroxyphenyl)propanol (27c). To a stirred solution of *N*-Fmoc phenol **27a** (198 mg, 0.393 mmol) in dry CH_2Cl_2 (2 mL) was added commercially available palmitic anhydride (778 mg, 1.57 mmol) and freshly distilled Et_3N (4 mL). The reaction mixture was stirred at room temperature for 2 days, after which time the solvent was evaporated. The resulting residue was taken in a 1:1 mixture of MeOH/CH_2Cl_2 (40 mL), and treated with powdered K_2CO_3 (4.07 g, 29.48 mmol). Stirring at room temperature was kept for 4 hours, after which time the reaction mixture was diluted with EtOAc (30 mL), and quenched with 5% aqueous citric acid (45 mL). The layers were then separated, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated. The resulting residue was purified by column chromatography, eluting with cyclohexane/EtOAc/Et_3N (70:30:3:1), to afford *N*-acetyl phenol **27c** as a colorless oil (146 mg, 72%): $[\alpha]^{20}_D$ = +16.7 (*c* = 0.60, $CHCl_3$); IR (neat): ν = 3294, 2925, 2854, 1650, 1459 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.11(s, 3H), 0.13 (s, 3H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.95 (s, 9H), 1.23-1.27 (m, 24H), 1.61-1.66 (m, 2H), 2.23 (t, *J* = 7.5 Hz, 2H), 2.71 (dd, *J* = 9.3, 14.0 Hz, 1H), 2.96 (dd, *J* = 2.2, 14.0 Hz, 1H), 3.62 (qd, *J* = 3.6, 10.5 Hz, 2H), 3.78-3.94 (m, 1H), 6.21 (d, *J* = 6.7 Hz, 1H), 6.78 (t, *J* = 7.1 Hz, 1H), 6.95 (dd, *J* = 7.1, 18.2 Hz, 2H), 7.08-7.18 (m, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.3, 156.1, 130.6, 128.3, 123.3, 119.5, 116.7, 62.0, 51.7, 36.5, 32.2, 31.9, 29.7, 29.6 (3C), 29.5 (2C), 29.4, 29.3 (2C), 29.1, 25.8 (3C), 25.6, 22.6, 18.2, 14.1, –5.4, –5.5; LRMS (ESIMS): *m/z* (%) = 522 (5), 521 (45), 520 (100) $[MH^+]$; HRMS (ESI) calcd for $C_{31}H_{58}NO_3Si$ 520.4181, found 520.4192.

(4*S*,5*S*,6*S*)-4,5-Epoxy-6-hydroxy-6-[(2*S*)-*N*-palmitoyl-2-amino-3-hydroxy)propyl]cyclohex-2-en-1-one (36c) and (4*R*,5*R*,6*R*)-4,5-Epoxy-6-hydroxy-6-[(2*S*)-*N*-palmitoyl-2-amino-3-hydroxypropyl]cyclohex-2-en-1-one (37c). A stirred solution of phenol **27c** (100 mg, 0.192 mmol) in dry CH_2Cl_2 (20mL, *ca.* 10 mM) was cooled at –20 °C. The λ^5-iodane reagent **31** (76 mg, 0.211 mmol) (or chiral λ^5-iodane (*S,S*)-**33**, 1.1 equiv) and TFA (15 µL, 0.192 mmol) were added, and the reaction mixture was stirred at the same low temperature until complete consumption of the starting material as indicated by TLC monitoring (*ca.* 1-3 h). Next, a solution of DMDO (*ca.* 0.07 M in acetone, 4 equiv; *i.e.,* 11 mL) was added at –20 °C, and the resulting mixture was stirred overnight (*ca.* 12 h), after which time the solvent was evaporated. The resulting yellow oily residue was subjected to column chromatography, eluting with CH_2Cl_2/EtOAc (9:1), to afford a 65:35 diastereomeric mixture **34c**/**35c** as a pale yellow oil (57 mg, 55%). Part of this material (30 mg, 0.056 mmol) was next taken in 10 mL of AcOH/THF/H_2O (3:1:1), at room temperature, and the reaction mixture was stirred overnight (*ca.* 12 h). The solution was then diluted with EtOAc (40 mL) and was poured dropwise onto vigorously stirred saturated aqueous $NaHCO_3$ (150 mL). Stirring was kept for 15 min, after which time layers were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and evaporated to dryness. The resulting oily residue (19 mg) was purified by preparative TLC, eluting twice with EtOAc/acetone (20:1), to furnish **36c** (9 mg, 39%) and **37c** (5 mg, 22%) as white amorphous solids.

Compound 36c: $[\alpha]^{25}_D$ = +15.4 (*c* = 0.04, MeOH) [lit.[8d] $[\alpha]^{27}_D$ = +15.0 (*c* = 0.04, MeOH)]; IR (neat): ν = 3362, 2924, 1743, 1242 cm^{-1}; ^1H NMR (methanol-d_4, 300 MHz): δ = 0.90 (t, *J* = 6.6 Hz, 3H), 1.20-1.36 (m, 24H), 1.49-1.66 (m, 2H), 1.81 (dd, *J* = 9.3, 14.7 Hz, 1H), 2.03 (dd, *J* = 3.0, 14.7 Hz, 1H), 2.08-2.18 (m, 2H), 3.41 (dd, *J* = 5.2, 10.9 Hz, 1H), 3.48 (dd, *J* = 5.2, 10.9 Hz, 1H), 3.61 (td, *J* = 1.4, 3.8 Hz, 1H), 3.66 (d, *J* = 3.8 Hz, 1H), 3.95-4.06 (m, 1H), 6.10 (dd, *J* = 1.4, 9.9 Hz, 1H), 7.17 (dd, *J* = 3.8, 9.9 Hz, 1H); ^{13}C NMR (methanol-d_4, 75 MHz): δ = 199.5, 176.0, 145.8, 132.0, 77.6, 65.6, 58.2, 47.7, 39.5, 37.1, 33.1, 30.8, 30.7, 30.6, 30.5, 30.4, 26.7, 23.7, 14.4; LRMS (ESIMS): *m/z* (%) = 440 (6), 439 (35), 438 (100) $[MH^+]$; HRMS (ESI) calcd for $C_{25}H_{44}NO_5$ 438.3214, found 438.3221.

Compound 37c: $[\alpha]^{25}_D$ = +5.4 (*c* = 0.03, MeOH); IR (neat): ν = 3318, 2923, 2852, 1732, 1466 cm^{-1}; ^1H NMR (methanol-d_4, 300 MHz): δ = 0.90 (t, *J* = 6.6 Hz, 3H), 1.23-1.37 (m, 24H), 1.50-1.65 (m, 2H), 1.86-1.93 (m, 1H), 2.03-2.20 (m, 3H), 3.39 (dd, *J* = 6.0, 10.9 Hz, 1H), 3.47 (dd, *J* = 5.2, 10.9 Hz, 1H), 3.61 (td, *J* = 1.5, 3.9 Hz, 1H), 3.70 (d, *J* = 3.9 Hz, 1H), 4.05-4.16 (m, 1H), 6.05 (dd, *J* = 1.5, 9.9 Hz, 1H), 7.21 (dd, *J* = 1.3, 9.8, 1H); ^{13}C NMR (methanol-d_4, 75 MHz): δ = 200.0, 175.9, 146.5, 131.6, 77.3, 65.4, 58.1, 49.4, 40.4, 37.2, 33.1, 30.8, 30.7, 30.6, 30.5, 30.4, 26.8, 23.7, 14.4; LRMS (ESIMS): *m/z* (%) = 440 (2), 439 (40), 438 (100) $[MH^+]$; HRMS (ESI) calcd for $C_{25}H_{44}NO_5$ 438.3214, found 438.3223.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxx

^1H and ^{13}C NMR spectra for all new compounds; HPLC traces of **27a**; computational results (PDF)

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Notes

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