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Stereoselective Synthesis of Isochromanones by an Asymmetric Ortho-Lithiation Strategy: Synthetic Access to the Isochromanone Core of the Ajudazols

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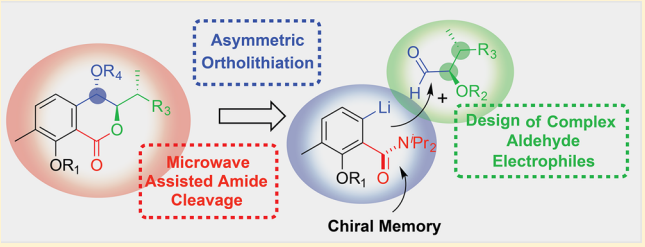
Supporting Information

ABSTRACT: Full details on the design, development, and application of a highly stereoselective strategy for the synthesis of isochromanones are reported. The method is based on an asymmetric ortho lithiation with aldehyde electrophiles and utilizes the chiral memory of a preoriented atropisomeric amide axis for stereocontrol. For direct transformation of sterically hindered amides to isochromanones, efficient and mild one-pot protocols involving either *O*-alkylation or acidic microwave activation were developed. The procedures may be applied also to highly functionalized as well as stereochemically complex and sensitive substrates and demonstrate a high protective group tolerance. Furthermore, asymmetric crotylborations of axially chiral amides were studied in detail. These methodologies enable a general access to all possible stereoisomers of hydroxyl-isochromanones with up to three contiguous stereocenters. The true applicability of our approach was finally demonstrated by synthesis of the authentic *anti,anti*-configured isochromanone core of the ajudazols, highly potent inhibitors of the mitochondrial respiratory chain from myxobacteria.



INTRODUCTION

Isochromanones are key structural features in a variety of natural products and bioactive agents.[1] A remarkable variety of potent biological activities have been reported for these compounds, which include cytostatic potencies,[2] ACE inhibitory effects,[3] plant growth regulation,[4] effects on the central nervous system,[5] and immunomodulatory,[6] antinoceptive, antiplasmodic,[1d] and antidiabetic activities.[7] Two isochromanone-based structures (AC-7954 and FL 68)[8] are presently in clinical phase II studies for cardiovascular diseases and diabetes.[9]

Within the context of a natural product total synthesis of the ajudazols A (**1**) and B (**2**) (Figure 1),[10] we became interested in the development of an efficient route to hydroxyl-substituted isochromanones. These are also present in a number of bioactive natural products, including benaphtamycin (**3**),[11] thailandolid B (**4**),[12] hydroxyochratoxin (**5**),[13] and bergenin (**6**).[14]

The ajudazols are distinguished by a hydroxyl-isochromanone with three consecutive *anti,anti*-configured stereocenters (C_8−C_{10}) together with an extended side chain that contains an oxazole, a *Z*,*Z*-diene, and a 3-methoxybutenoic acid amide as structural features. So far, two ajudazols have been reported.[10] The main metabolite, ajudazol A (**1**), bears an *exo*-methylene group next to the oxazole (C_{15}), while ajudazol B (**2**) has a methyl group at this position. The first biological characterization revealed that the ajudazols are potent antifungal agents but have only weak antibacterial and antiproliferative activities.[15] On a molecular level they are described as highly effective inhibitors of the mitochondrial respiratory chain by selective binding to complex I (NADH-dehydrogenase). The NADH oxidation level in beef heart submitochondrial particles was inhibited at an IC_{50} value of 13.0 ng/mL (22.0 nM) for ajudazol A (**1**) and 10.9 ng/mL (18.4 nM) for ajudazol B (**2**).

However, despite the high relevance of isochomanones as bioactive substructures in a variety of natural products, a general synthetic access to these structural elements is largely missing. Especially, the generation of hydroxyl-isochromanones has proved to be particularly challenging, which has also prevented a total synthesis of the ajudazols for a long time.[16] In the past, different approaches for synthesis of isochromanones have been described in the literature on the basis of intramolecular Diels−Alder reactions (IMDA),[16a,b,17] rearrangement reactions,[16c−e] gold catalysis,[18] and asymmetric iodolactonization reactions.[19] These approaches have been limited, however, by apparent difficulties to either install substituents into the isochromanone core structure or to flexibly control the stereochemistry of such substituents. Additionally, C_8-hydroxyl-substituted isochromanones such as the ajudazols (**1**, **2**) are known to be labile under basic conditions and can undergo translactonization reactions to form thermodynamically more stable five-membered-ring analogues.[10,19c]

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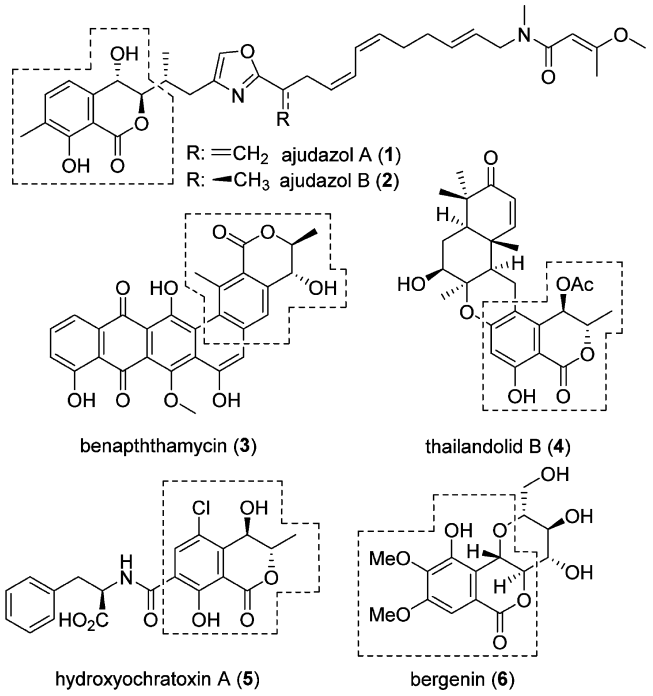


Figure 1. Natural products with hydroxyl-isochromanone motives.

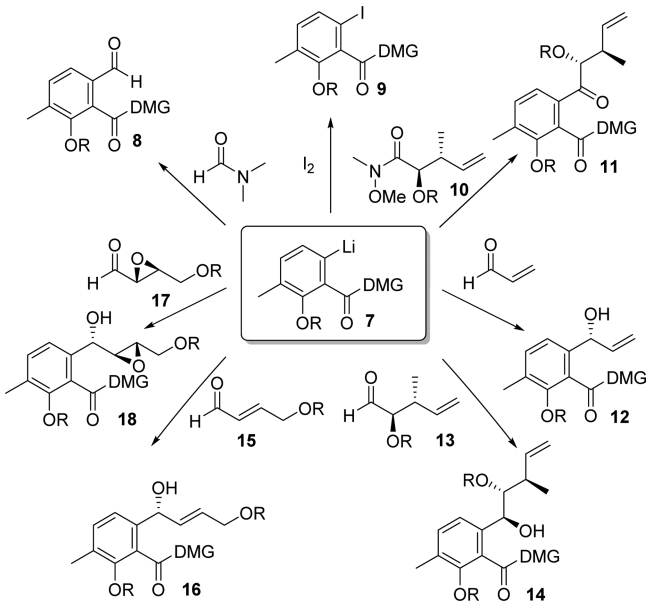
For these reasons we designed a conceptually novel approach for the construction of isochromanones on the basis of asymmetric ortho lithiation as a key step. Herein, we discuss the design of our strategies and approaches that we initially developed for the isochromanone fragment of the ajudazols but that are also generally useful for other compounds with stereochemically complex isochromanone motifs.[20]

RESULTS AND DISCUSSION

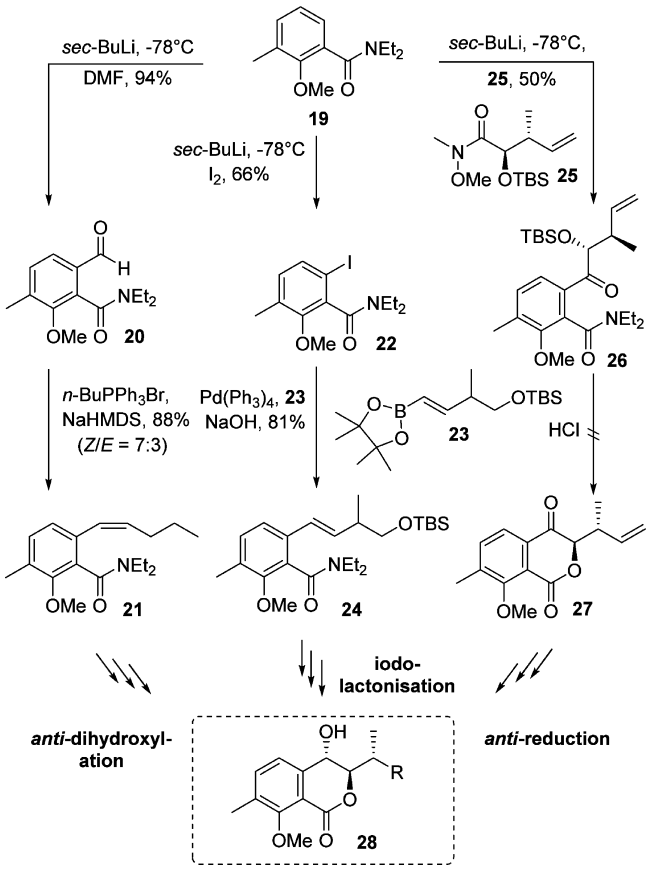
Exploratory Study of Ortholithiation-Based Strategies for the Synthesis of Isochromanones. Ortho-lithiation reactions have been demonstrated as a reliable and efficient tool for the effective substitution of aromatic compounds with various electrophiles, and multiple applications have been reported.[21] Direct metalation groups (DMGs), typically tertiary amides, carbamates, and ethers, control the regioselectivity of the metalation reaction and direct the subsequent electrophilic ipso substitution to the ortho position of the DMG.[22] Inspired by the ajudazols, we were attracted to study the potential utilization of this reaction type for synthesis of hydroxyl-isochromanones by a modular functionalization of 3-methyl-salicylic acid in a short and regioselective sequence (Scheme 1). The flexible exchange of the electrophile thereby opens up several possibilities to generate the correct stereochemistry of the three consecutive stereocenters. As outlined in Scheme 1, we explored both conventional and asymmetric ortho-lithiation approaches. This would generate different precursors for further transformations such as iodolactonizations (**8**, **9**), reductions (**11**), aldol reactions (**12**), crotylation (**12**), epoxidation (**16**, **18**), and direct lactonization reactions (**14**).

In a first model study a precursor (**21**) for a *Z*-configured double bond was built up by the ortho lithiation of **19** and reaction of the resulting lithiated intermediate with DMF. A subsequent Wittig reaction of **20** to alkene **21** should then allow introduction of the C_8/C_9 stereochemistry by an asymmetric dihydroxylation[23] (Scheme 2, left part). Although moderate selectivities (*Z*:*E* = 7:3) of the Wittig reaction could

Scheme 1. Various Conventional (Upper Half) and Asymmetric (Lower Half) Ortho-Lithiation Approaches Explored for Synthesis of the Ajudazol Isochromanone Fragment



Scheme 2. Conventional Ortho-Lithiation Approaches for the Construction of Suitable Precursors for Further Stereoselective Transformation to Isochromanone 28



be compensated by HPLC separation of the two isomers, the further functionalization of *Z*-**21** by asymmetric dihydroxylation was limited by moderate yields (51%) and selectivities (d.r. =

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3.5:1) and a lack of regioselective protection strategies for the generated C_8-alcohol. In contrast to the highly reliable asymmetric dihydroxylation of *E*-configured alkenes, the selectivities of *Z*-configured substrates are known to be highly substrate dependent.[24]

Alkene precursors such as **21** can potentially also be directly transformed into isochromanone **28** by an iodolactonization approach (Scheme 2, middle part).[25] To test this hypothesis, we also synthesized different analogues of **21** by ortho iodination of **19** and modular Suzuki cross-coupling of **22** and **23**.[26] We then explored different conditions for the iodolactonization.[26] Although the desired 6-*endo*-trig cyclization product **28** could be obtained in a regioselective and diastereoselective way, the outcome of the reaction was highly sensitive to the nature of the side-chain substituents and also a stereoselective control of the reaction by substrate induction, chiral catalysts,[27] or auxiliaries[19a,28] appeared to be difficult.[26]

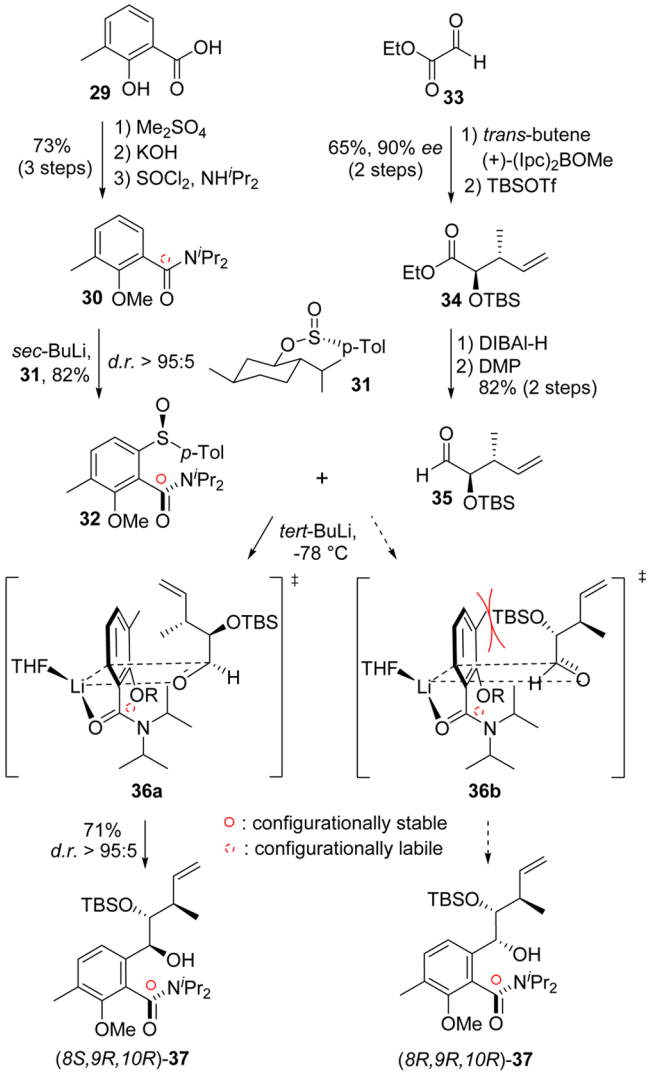
In order to increase the selectivity of the cyclization process, we additionally envisioned a precursor for a C_8-*anti*-reduction strategy and introduced two of the three stereocenters of the isochromanone into Weinreb amide **25**[29] by an asymmetric crotylboration (see Scheme 3 and the Supporting Information). Ortho lithiation of **19** and substitution with **25** led to product **26** in moderate yields (Scheme 2, right part).

However, cyclization of **26** to **27** could not be realized under several acidic conditions and only decomposition of the starting material was observed. In addition, *anti*-reduction of **26** with $Zn(BH_4)_2$ failed.[30]

Finally we tested whether these problems could be solved by using aldehyde **13** as an electrophile. This strategy would generate the C_8-stereocenter directly to form the corresponding alcohol (Scheme 1). In general, ortho lithiations with aldehydes have been less well investigated in comparison to other electrophiles and ortho lithiations with complex aldehydes such as **13** are nearly unknown.[31] However, in our initial attempts with aldehyde **13** we could detect significant amounts of the desired product **14** (67%). Unfortunately, the observed substrate-induced stereoselectivity in the sense of a moderate Felkin−Anh control was not sufficient (d.r. = 2.1/1). Therefore, a continuation of this study by establishing a suitable orthogonal protection group strategy to enable a regioselective cyclization was not pursued.

Isochromanone Strategy of the First Generation: Strength and Weakness of an Asymmetric Ortho-Lithiation Approach. The difficulties of the conventional ortho-lithiation approaches described above made us think about options for an asymmetric control of this reaction type (Scheme 1, lower half). The development of stereoselective ortho-lithiation reactions has been a considerable methodological challenge for many years, and several approaches based on chiral DMGs,[32] chiral chelating reagents such as sparteine,[33] and chiral bases[34] are limited by either low stereoselectivity or narrow substrate scope. In 2002 a pioneering study[35] of the Clayden group demonstrated that a combination of a tertiary amide as DMG and a chiral sulfoxide[36] acting as an easily removable temporary stereogenic center[37] can potentially solve these problems. According to their approach, a chiral sulfoxide leads by chirality transfer to a preorientation of the nonplanar amide axis of the DMG,[38] as shown for example for the conversion of **30** to **32** (Scheme 3). This orientation is retained after cleavage of the sulfoxide by *tert*-BuLi during the ortho-lithiation reaction at low temperatures (chiral memory). Electrophilic attack of the resulting atropochiral aryllithium

Scheme 3. First Asymmetric Ortho-Lithiation Approach of Sulfoxide 32 with Complex Aldehyde 35 Leading to (8*S*,9*R*,10*R*)-37



species with an aldehyde then allows the generation of chiral benzylic alcohols (viz. **32**−**37**) with high asymmetric induction in the sense of a "self-regeneration of the stereocenter" (SRS principle).[39] Nevertheless, the true applicability of this method has been restricted by apparent difficulties resulting from cleavage of the tertiary amide DMG, the control of the ring size in the case of alternative cyclization reactions, and the lability of the newly generated benzylic alcohol with regard to epimerization.[40] In contrast, the use of such a type of asymmetric ortho lithiation as key step in the isochromanone synthesis of the ajudazols seemed to be particularly rewarding in terms of modularity and elegance and we therefore tried to find solutions for these challenges.

In order to build up the aromatic reaction partner, the phenol group of 3-methylsalicylic acid (**29**) was first protected by methylation, as shown in Scheme 3. A methyl group was chosen due to the high stability toward alkyllithium species and a reported positive influence on the selectivity of the asymmetric ortho lithiation.[35,40a] After conversion to the acid chloride by treatment with thionyl chloride and amide coupling with diisoproylamine, the sterically hindered but configurationally labile amide axis of **30** was subsequently fixed by ortho

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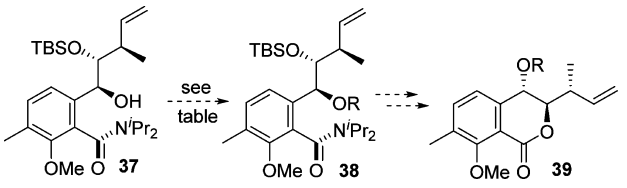
lithiation with Andersen reagent **31**[41] to yield *S*-sulfoxide **32**. A diisopropyl group was chosen in order to obtain a higher configurational stability of the amide axis in comparison to a diethyl group. The required aldehyde reaction partner **35** for this sulfoxide was then built up from ethyl glyoxalate **33** by asymmetric crotylboration (70%, d.r. = 98:2, 90% ee).[20,42] The correct absolute configuration of the resulting alcohol **33a** was subsequently confirmed by Mosher ester analysis.[43] Use of the Roush reagent (compound **50**; Table 4)[44] instead of the shown Brown reagent **51** for asymmetric crotylboration resulted in higher yields (81%) but lower enantioselectivity (71% ee). For protection of the newly generated alcohol, a *tert*-butyldimethylsilyl (TBS) group was chosen, which should allow different options for an orthogonal protection of the subsequently generated hydroxyl-bearing stereocenter at C_8. TBS-ester **34** could then be further transformed to aldehyde **35** using a sequential reduction oxidation procedure (82%, two steps). The pivotal asymmetric substitution of lithiated **32** with aldehyde **35** then generated the desired *anti,anti* product **37** in high selectivity (d.r. > 95:5).[45] In accordance with the literature,[38a] the preferred formation of **37** can be rationalized by transition states **36a,b**. In contrast to **36a**, which leads to the observed *anti,anti* product **37**, formation of intermediate **36b** to give *syn,anti* product **37** is significantly disfavored by steric interaction of the TBS group of the attacking aldehyde **35** with the aromatic ring of the aryllithium species. It is surprising to note that in both postulated transition states the attack of the electrophile occurs from the diisopropylamide-containing site due to a space-demanding Li-THF cluster shielding the opposite side.[38a,d]

As anticipated, the subsequent conversion of **37** into the desired isochromanone **39** proved challenging (Table 1). Several strategies to introduce a *p*-methoxybenzyl (PMB) protecting group at the C_8-alcohol (**38**) which is orthogonal to the C_9-TBS-protected alcohol failed (entries 1−7, Table 1).

Table 1. Study of Different Orthogonal Protecting Groups for the C_8-Alcohol of 37



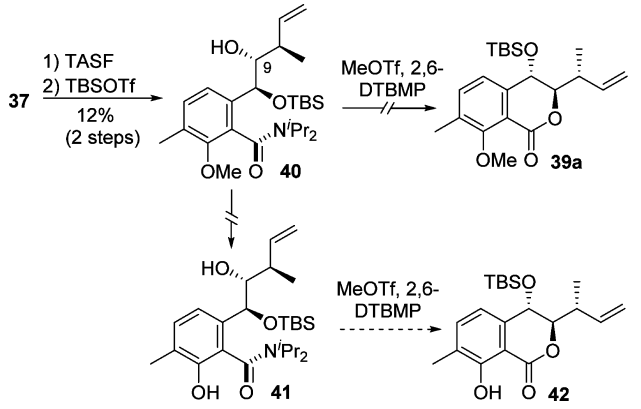
entry	R	protection conditions	yield
1	PMB	NaH, PMBCl, DMF	
2		NaH, PMBCl, THF	
3		NaH, PMBBr, THF	
4		NaH, PMBBr, TBAI, DMF	
5		PMB-OC(CCl_3)=NH, CSA, THF	
6		PMB-OC(CCl_3)=NH, TfOH, Et_2O	*a*
7		PMB-OC(CCl_3)=NH, Sc($OTf)_3$, toluene[47]	*a*
8	MEM	MEMCl, DIPEA, CH_2Cl_2	*a*
9		NaH, MEMCl, THF	
10	Ac	$(Ac)_2O$, DMAP, Pyr	
11		$(Ac)_2O$, DMAP, NEt_3, CH_2Cl_2	*a*
12		$(Ac)_2O$, I_2[48]	*a*
13	Me	MeOTf, 2,6-DTBMP, CH_2Cl_2[49]	*b*
14		Me_3OBF_4, Proton Sponge, CH_2Cl_2[50]	*b*

[a]No conversion, recovery of the starting material. [b]*O*-Alkylation and cleavage of the diisopropylamide was observed.

However, the protection of this hydroxyl group is necessary in order to control the subsequent cyclization toward the desired 6-ring product.[46] We initially assumed that the spatial demand of the nearby TBS and diisoproylamide groups of **37** diminished the chemical accessibility of the C_8-alcohol. Therefore, we tried to reduce the size of this protecting group. However, also smaller protecting groups such as MEM (entries 8 and 9, Table 1) and acetyl (entries 10 and 12, Table 1) could not be successfully installed. Even protection with a methyl group (entries 13 and 14, Table 1)—the smallest possible protection strategy we could think of—failed, and no C_8-protected product could be detected. However, during these protection studies cleavage of the tertiary amide and formation of a five-membered lactone was unexpectedly observed. This finding opened up an efficient and mild protocol for the cleavage of the tertiary amide.

Therefore, we then tried to combine this protocol with a TBS de- and reprotection strategy (Scheme 4). Initial attempts

Scheme 4. Attempts To Generate Isochromanones by TBS De- and Reprotection and *O*-Alkylation



to regioselectively introduce a TBS group at the benzylic hydroxyl after deprotection of the hydroxyl group at C_9 with TASF[51] using TBSOTf or TBSCl gave nearly no conversion or were inefficient. Additionally, amide cleavage of **40** with MeOTf to generate **39a** under the same conditions as used before in order to form the six-membered lactone did not result in any conversion.

Evidence from the literature suggested that methyl-protected phenol groups in positions ortho to the amide can prevent amide cleavage.[52] We therefore tried to deprotect the phenol group of **40** by several strategies, including BCl_3,[53] MgI_2·OEt_2,[54] LiCl,[55] PhSH,[56] and PPh_2Li,[57] to yield compound **41**. However, none of these efforts were successful. In summary, these results suggested that an inappropriate phenolic protecting group was chosen.

The Correct Order Makes a Difference: Isochromanone Strategy of the Second Generation. Our first experiences with an asymmetric ortho-lithiation approach with a complex aldehyde electrophile had clearly shown that, although the key step worked efficiently and selectively, a successful transformation into an isochromanone highly depends on a suitable protecting group strategy. For this reason we changed our previous approach in two ways: (1) we evaluated the stability and orthogonality of different protecting groups for the phenolic hydroxyl group, and (2) we reduced the functional complexity of the ortho-lithiation system to allow

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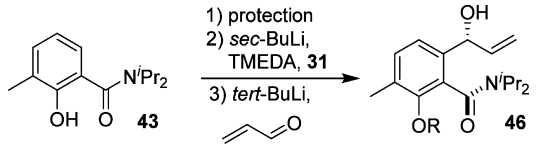
an easy introduction of a C_8-protecting group by changing the order of ortho lithiation and crotylboration.

As shown in Table 2, several protecting groups, which are known to be orthogonal to a secondary TBS-protected alcohol,

Table 2. Study of Different Protecting Group Strategies for the Asymmetric Ortho-Lithation with Acrolein



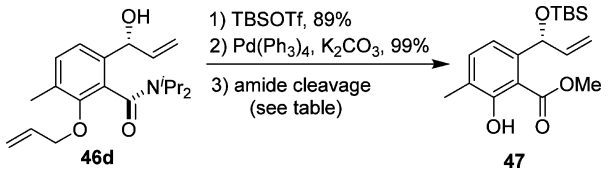
		yield (%)[a,b]		
entry	R	step 1	step 2	step 3
1	PMB	90 (**44a**)	78 (**45a**)	71 (**46a**)
2	TBS	98 (**44b**)	85 (**45b**)	39 (**46b**)
3	Ac	88 (**44c**)	– (**45c**)	– (**46c**)
4	allyl	97 (**44d**)	88 (**45d**)	92 (**46d**)
5	Bn	68 (**44e**)	82 (**45e**)	68 (**46e**)
6	Me	– (**30**)	82 (**32**)	73 (**46f**)

[a]**43** was obtained from deprotection of **30** with $MgI_2{\cdot}OEt_2$. [b]For detailed protection conditions see the Experimental Section.

could be installed efficiently at the phenolic alcohol of **43**, which was efficiently (95%) generated by methyl deprotection of **30** with $MgI_2{\cdot}OEt_2$.[54] After introduction of various protecting groups, the chiral sulfoxide could subsequently be obtained in high yields by ortho lithation with Andersen reagent **31**.[41] Only the acetyl-containing compound **44c** (entry 3, Table 2) was deprotected under these conditions. In the final asymmetric ortho lithiation with acrolein as a simplified electrophile, significant differences in the observed yield became apparent between the different protecting groups. Surprisingly, the highest yields were obtained with an allyl-protected aromatic system (**44d**–**46d**, entry 4, Table 2).

In this case quenching the reaction mixture has to be strictly done at −78 °C to avoid deprotection which may be caused by *tert*-BuLi-induced Wittig rearrangement of the allyl group.[58] To test the orthogonality of this protecting group strategy, we introduced a TBS protecting group at the C_8-stereocenter of **46d** (Table 3). The phenolic allyl group could then efficiently be removed under basic conditions by $Pd(PPh_3)_4$-catalyzed isomerization[59] without affecting the TBS group. In addition,

Table 3. Cleavage of Tertiary Amide 46d by *O*-Alkylation



entry	conditions	solvent	yield (%)
1	Me_3OBF_4 (5 equiv), Na_2HPO_4 (2.5 equiv)	MeCN	54
2	Me_3OBF_4 (3 equiv). Na_2HPO_4 (1.5 equiv)	MeCN	55
3	Me_3OBF_4 (2 equiv)	CH_2Cl_2	15
4	Me_3OBF_4 (3 equiv), Na_2HPO_4 (1.5 equiv)	MeCN	51
5	Me_3OBF_4 (3 equiv), Na_2HPO_4 (1.5 equiv)	MeCN	49
6	MeOTf (2 equiv), 2,6-DTBMP (4 equiv)	CH_2Cl_2	53
7	MeOTf (2 equiv), 2,6-DTBMP (4 equiv)	CH_2Cl_2	59
8	MeOTf (2 equiv), 2,6-DTBMP (4 equiv)	CH_2Cl_2	62

installation of an orthogonal PMB protecting group at the newly generated stereocenter with PMB-trichloroacetimidate and $Sc(OTf)_3$[47] was possible. However, this approach was not further pursued due to expected deprotection problems at a later stage of the synthesis. In order to cleave the tertiary amide, we tested next an *O*-alkylation strategy for a direct transformation of amides to esters which was inspired by our findings during the aforementioned methyl protection attempts. We initially used a known protocol based on alkylation with Meerwein's salt (entries 1–5, Table 3).[52b] However, the yields of this reaction were only moderate, although we detected full conversion of the starting material. These could not be further improved by modifications of the methylation conditions, use of an alternative solvent, or modified workup conditions ($NaHCO_3$, Na_2CO_3, K_3PO_4, NaOH).

Small improvements were only obtained by using the MeOTf protocol discovered above (entries 6–8, Table 3). For conversion to ester **47** with either protocol an unprotected phenol seemed to be crucial, in agreement with a precedent from the literature.[52b]

The free phenol group of **47** was subsequently protected by PMB to avoid side reactions in the subsequent ozonolysis of the double bond (Table 4). The ozonolysis has to be carefully monitored and worked up to avoid deprotection of the PMB group and racemization of the stereocenter. The resulting aldehyde (+)-**48** (83%, two steps) served as the starting material for an asymmetric crotylboration, allowing the introduction of the remaining two stereocenters. In our initial attempts we could efficiently perform this reaction with the Roush reagent (*E*,*S*,*S*)-**50** in 95% yield (entry 1, Table 4). This reagent was chosen due to its convenient storage, high stability, and easy removability.[44] Under consideration of the postulated mechanism for crotylboration reactions,[42b,60] saponification of the ester was expected to give the desired *anti*,*anti*-configured isochromanone (Scheme 6). In contrast, the observed ^3J coupling constant between H_8 and H_9 in the ^{1}H NMR spectra of the generated lactone **54** (Scheme 5) was only 2.1 Hz, which was significantly too low for an *anti*,*anti* system and the chemical shifts of these protons completely differed from those of the isochromanone part of the ajudazols.

After various efforts to determine the structure of **54** by derivatization and NMR analysis, we could finally crystallize **54** (Scheme 5). An X-ray structure analysis showed unexpectedly that **54** is a *syn*,*anti*-configured five-membered lactone. In combination with additional analysis of ^{1}H,^{29}Si-HMBC data of precursor **49**, this finding revealed a migration of the TBS protecting group during the crotylboration and also indicated the existence of an alternative transition state[60a,b,61] (see the discussion below) which leads to the *syn*,*anti* configuration of **49**. Although migration of silyl groups has been described for aldol reactions,[62] we could not find a literature precedence for allyl- and crotylboration reactions. In addition, crotylboration of a very similar ortho-unsubstituted aldehyde has been reported to clearly give the desired product.[63]

We then tried to influence the outcome of the crotylboration by (a) changing the stereochemistry of the aldehyde substrate **48** (entry 2, Table 4) or by (b) exchange of the crotylboration reagent (entries 3–5, Table 4). However, both strategies showed no effect.[65] The substrate overcontrolled the influence of the crotylboration reagent, leading in all cases to a *syn*,*anti*-configured product with d.r. > 99:1. In addition, replacement of the crotylboration by an iridium-catalyzed[66] crotylation reaction known for its different transition state (entry 6, Table 4)[67]

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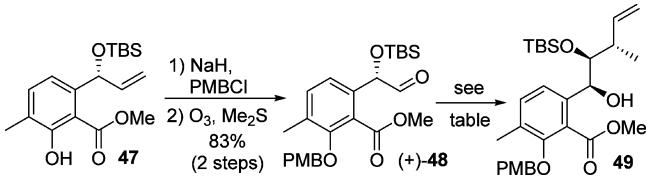
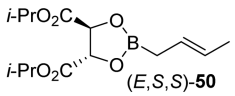
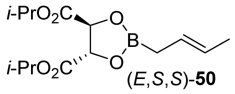
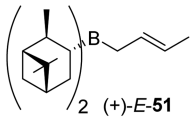
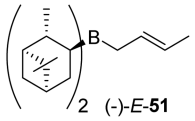
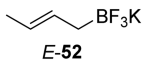
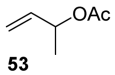
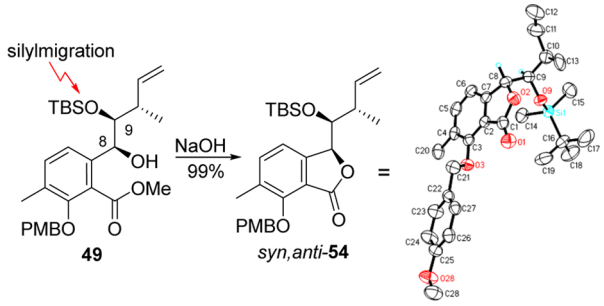
Table 4. Generation and Crotylboration of Aromatic Aldehyde 48



entry	conditions	yield[a] (%)
1	(+)-**48**,  (*E*,*S*,*S*)-**50**	95 (+)-*syn*,*anti*-**49**
2	(-)-**48**,[64]  (*E*,*S*,*S*)-**50**	93 (-)-*syn*,*anti*-**49**
3	(+)-**48**, $BF_3{\cdot}OEt_2$,  2 (+)-*E*-**51**	57 (+)-*syn*,*anti*-**49**
4	(+)-**48**, $BF_3{\cdot}OEt_2$,  2 (-)-*E*-**51**	59 (+)-*syn*,*anti*-**49**
5	(+)-**48**, TBAI,  *E*-**52**	93 (+)-*syn*,*anti*-**49**
6	(+)-**48**, $Ir(COD)Cl_2$, (*S*)-Segphos, 4-CN-3-NO_2BzOH, $Cs(CO_3)_2$, ^{i}PrOH,  **53**	- [b]

[a] d.r. > 99:1 for all reactions. [b] Decomposition.

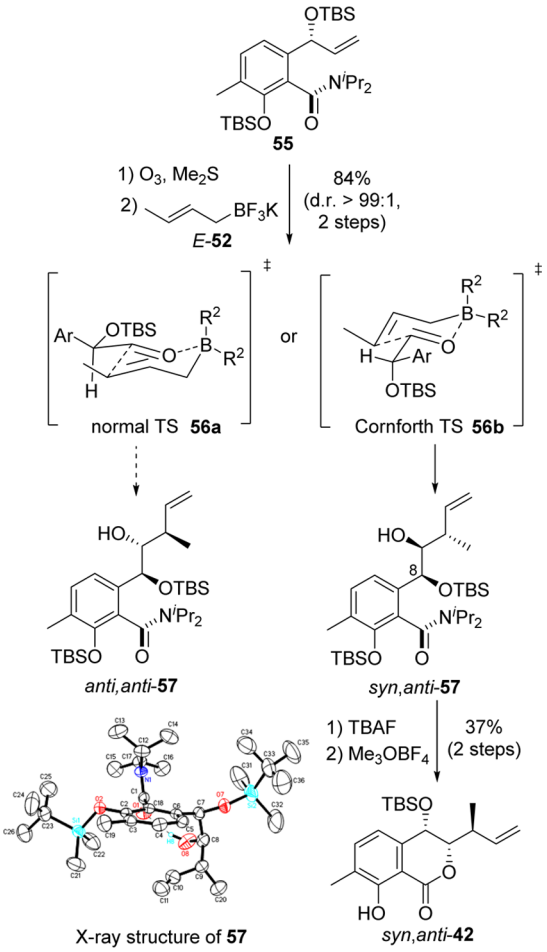
Scheme 5. Cyclization of Crotylboration Product 49 Leading to *syn*,*anti*-Configured Five-Membered Lactone 54



failed due to the decomposition of the starting material. Oxidation of the generated C_8-alcohol with DMP and reduction with $NaBH_4$ also generated again the same configuration (69% over two steps).

We then evaluated whether a modification of the reaction sequence could make a difference in the outcome of the crotylboration. Therefore, we changed the order of amide cleavage and crotylboration, as an atropochiral tertiary amide instead of an ester should potentially act as an additional element for stereoinduction. Due to the obvious instability of allyl protecting groups against the ozonolysis conditions the bis-TBS-protected compound **55** was used as the starting material for this sequence (Scheme 6). After crotylboration of

Scheme 6. Crotylboration of an Amide-Containing Aromatic Aldehyde Leading to *syn*,*anti*-57 via an Unconventional Cornforth Transition State



the intermediate aldehyde with either Roush reagent (*E*,*S*,*S*)-**50** or trifluoroborate (*E*)-**52**[68] only the product **57** could be obtained in high yield and diastereoselectivity (d.r. > 99:1). However, X-ray structure analysis of this product revealed **57** to be again *syn*,*anti*-configured. In contrast to the crotylboration of the ester-containing substrate **48**, no migration of the silyl protecting group could be detected during the crotylboration with the modified amide aldehyde derived from **55**. We speculate that the repeated occurrence of the *syn*,*anti*-configured product during the crotylboration can be rationalized by the preference of the uncommon Cornforth transition state **56b**[61] to the normal transition state **56a**.[42b,60] Substituents of the aromatic ring in this Cornforth transition state **56b** are closer to the borane and can potentially stabilize this transition state, leading exclusively to the *syn*,*anti* product.

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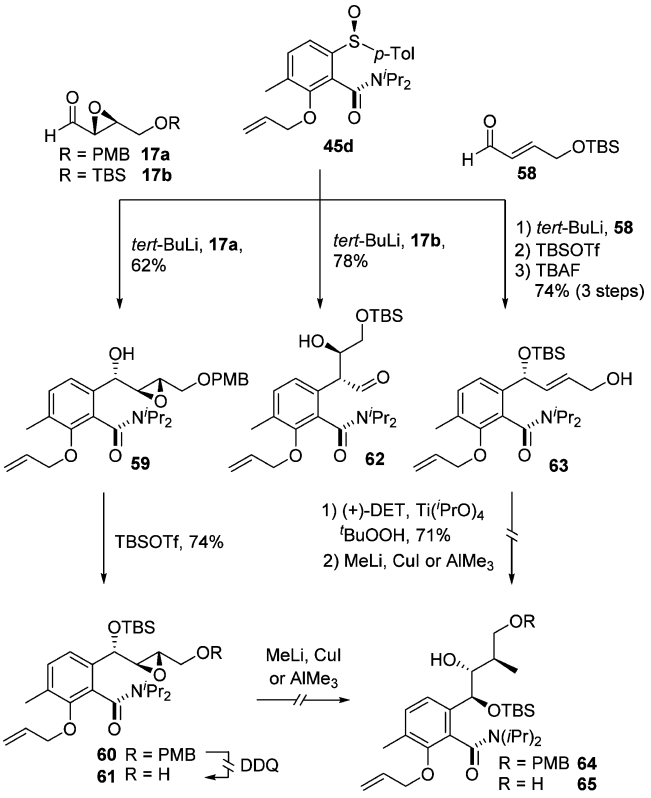
Furthermore, the steric repulsion of the diisopropylamide-containing aryl substituent and the methyl group of the crotylborane is reduced in transition state **56b** in comparison to the case for **56a**.

A strong hydrogen bond between the newly generated alcohol at C_9 and the carbonyl function of the amide appearing in the X-ray structure of **57** may additionally contribute to this explanation. Although the configuration at C_8 in **57** was wrong, this product could still be transformed into the corresponding Isochromanone *syn,anti*-**42** by selective TBS deprotection of the phenolic TBS group and cyclization via amide cleavage with Meerwein salt in moderate yields (37%, two steps).[52b]

As we were unable to influence the stereochemistry of the crotylboration, we tried to investigate whether this step could be replaced by an asymmetric epoxidation,[69] as one of the most reliable transformations in asymmetric synthesis.[70] We therefore first focused on an efficient synthesis of the aldehyde electrophile **17** with an appended chiral epoxide.[71] Asymmetric ortho lithiation of **45d** with a PMB-protected version of epoxyaldehyde **17a** then gave alcohol **59** without affecting the epoxide (Scheme 7, left part). After TBS protection we explored several approaches for a regioselective opening of the epoxide group of **60** with methyllithium cuprates[71a,72] or $AlMe_3$.[73] In all cases we could not observe any conversion to **64**. For this reason we modified **60** by deprotection of the primary PMB group with DDQ or other reagents in order to increase the reactivity of **61**, as reported[71a,72,73] for other substrates. However, this led to complete decomposition of **60**, which may possibly be caused by the sensitivity of the allyl groups to radical conditions.[74] We tried next to solve this problem by variation of the protecting group and synthesized a TBS-protected analogue of **17**. Unexpectedly, after asymmetric ortho lithiation between **45d** and **17b** we observed the exclusive formation of alcohol **62**, bearing an aldehyde function (Scheme 7, middle part). These findings suggested that the protecting group has a significant influence on the position where the electrophile is attacked by the aryllithium species. A TBS protecting group directs an opening of the epoxide, while in contrast a PMB group allows the attack of the aldehyde function.

Scheme 7. Asymmetric Ortho-Lithation of 45d with Complex Epoxide-Containing Aldehydes for a Stereoselective Epoxide-Opening Strategy



Therefore, we modified the route again and planned to introduce the epoxide at a later stage of the synthesis (Scheme 7, right part). Accordingly, we evaluated allylic alcohol **63**, which was obtained by coupling of **45d** with **58**, protection of the newly generated secondary alcohol with TBS, and careful TBS deprotection of the primary alcohol with TBAF. Subsequent asymmetric epoxidation of **63** with L-(+)-DET[71] then gave the desired epoxide with a free primary alcohol function. Unfortunately, opening of the epoxide of this substrate with methyllithium cuprates,[71a,72] methylmagnesium cuprates,[75] or $AlMe_3$[73] to obtain compound **65** was also not successful.

Isochromanone Strategy of the Third Generation: Orthogonal Silyl Protection and Efficient Amide Cleavage Leading to Success. While all attempts to reduce the complexity of the aldehyde electrophile by introducing some of the three consecutive stereocenters of the ajudazol core structure at a later stage failed, the newly acquired knowledge should finally help us to overcome the limitations of the initial asymmetric ortho-lithiation approach with complex aldehyde **35**. Our first strategy (Scheme 3) that clearly generated the desired *anti,anti* configuration among C_8, C_9, and C_{10} could now be combined with the newly developed protecting group strategy for the phenol and the protocol for the amide cleavage by *O*-alkylation. The last remaining challenge was finally the identification of a suitable orthogonal protecting group strategy for the C_8 and C_9 alcohols. We therefore focused on selectivity improvements of the previously applied de- and reprotection strategy (Table 2) and synthesized the required allyl-group- and TBS-group-containing precursor **66** by asymmetric ortho lithiation of **45d** (Scheme 8). Subsequently, the free diol **67** could be efficiently obtained by deprotection of **66** with TASF as a mild fluoride source.[51]

This compound could also be crystallized, and an X-ray structure analysis confirmed the correct *anti,anti* configuration. However, the reprotection of diol **67** under various conditions with different silyl sources (TBSCl, TBSOTf, TESCl, TESOTf), amounts (0.2−2.0 equiv), and temperatures (−78 to 0 °C) generated the desired C_8 monoprotected compound **68** as only a minor product, preventing us from performing a cyclization of **68** at this stage. In contrast, when the reaction was executed with greater amounts of TBSOTf (>0.5 equiv) the double-TBS-protected diol **69** could always be identified as the main product. Notably, a C_9 monoprotected byproduct has never been detected. Selective monodeprotection of **69**, which was reported in the literature for various substrates with TBAF,[76] CSA,[77] and HF·pyridine[78] to obtain **68**, did not solve this problem and either led to complete deprotection or gave no conversion.

The observation that the double-TBS-protected compound **69** may be obtained clearly demonstrated that installing two protecting groups at C_8 and C_9 is in general possible and inspired us to think about an orthogonal silyl protecting group

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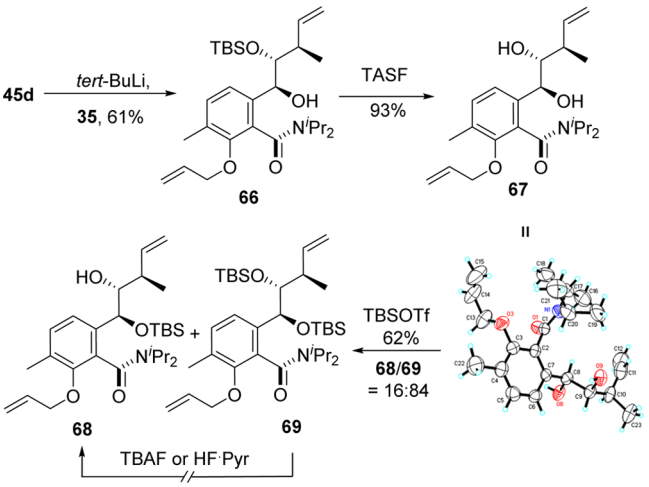
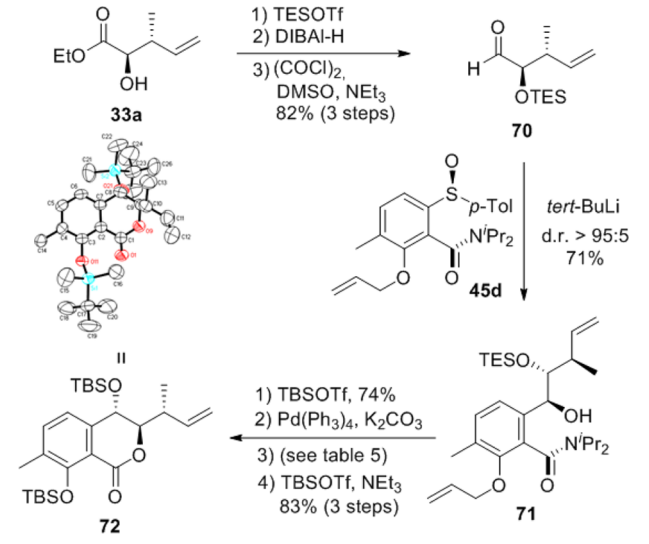
Scheme 8. Optimization Attempts of a TBS De- and Reprotection Strategy with Asymmetric Ortho-Lithiation Product 66



strategy. Consequently, we replaced the TBS group by a triethylsilyl (TES) group and synthesized TES-protected aldehyde **70** by transformation of crotylboration product **33a** (Scheme 9). In contrast to the synthesis of TBS-protected **34**

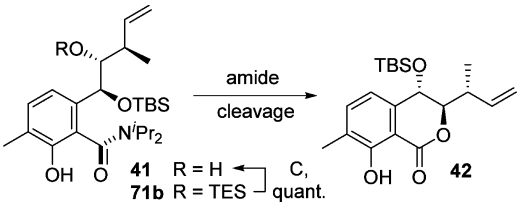
Scheme 9. Successful Asymmetric Ortho-Lithiation Approach Leading to *anti,anti*-Configured Isochromanone 72 by an Orthogonal Silyl Protecting Group Strategy



the conditions for the reduction of TES-protected **34a** have to be carefully optimized by using exactly 2.1 equiv of DIBAl-H in order to avoid deprotection of the TES group. Asymmetric ortho lithiation with sulfoxide **45d** then led to alcohol **71** without affecting the TES protecting group by *tert*-BuLi (d.r. > 95:5).

In the next sequence the C_8-alcohol was TBS protected with TBSOTf followed by selective removal of the phenolic allyl group under basic conditions by $Pd(PPh_3)_4$ catalysis.[59] In order to generate the required precursor **41** (Table 5) for amide cleavage and cyclization, we developed next a protocol for selective cleavage of the TES group in the presence of the TBS group. While initial attempts with HF·pyridine, TFA, TBAF,

Table 5. Study of Different Protocols for Amide Cleavage of 41 To Form Isochromanone 42[a]



entry	conditions	solvent	T	t	yield (%)
1	$(MeO)_3BF_4$ (3.0 equiv), Na_2HPO_4 (1.5 equiv), then $NaHCO_3$	MeCN	room temp	4 h/ 24 h	
2	MeOTf (2 equiv), 2,6-DTBMP (4 equiv), then $NaHCO_3$	CH_2Cl_2	room temp	6 h/ 14 h	
3	6 N NaOH (60 equiv)	EtOH	ΔT	14 h	*b*
4	KO^{t}Bu (6 equiv), H_2O (2.0 equiv)	THF	ΔT	6 h	
5	KOAc (20 equiv)	xylene	ΔT	24 h	
6	$LiBH_3$·pyrolidine (1.2 equiv)	THF	ΔT	24 h	*c*
7	$MeSO_3H$ (5 equiv)	THF	ΔT	20 h	*b*
8	AcOH (250 equiv)		room temp	24 h	*c*
9	AcOH (250 equiv)		ΔT	24 h	traces
10	AcOH (25 equiv)	toluene	ΔT	7 days	39
11	HCOOH (25 equiv)	toluene	ΔT	24 h	*b*
12	AcOH (25 equiv), H_2O (50 equiv)	toluene	ΔT	24 h	*b*
13	AcOH (25 equiv)	THF	ΔT	24 h	
14	AcOH (25 equiv), MW	toluene	130 °C	3 h	81
15	AcOH (30 equiv), MW, 71b	toluene	150 °C	3.5 h	86[d]

[a]Compound **41** was generated by the mild acidic deprotection of **71b** with charcoal: for experimental details, see the Experimental Section. [b]Deprotection of the TBS group. [c]No conversion, recovery of the starting material. [d]TES-protected starting material **71b** was used.

and TASF failed, we could finally generate **41** by using slightly acidic activated charcoal.[79]

However, when we tried to cleave the tertiary amide of compound **41** (Table 5) with the previously applied *O*-alkylation protocols (entries 1 and 2, Table 5) we could not detect the desired product, although the starting material was fully converted. In addition, variation of the reaction conditions did not lead to any improvements. Due to the high stability of tertiary amide, the cleavage of this substrate class is known to be difficult to achieve.[40b,80]

We therefore screened several basic (entries 3–5, Table 5)[40a,81] and reductive (entry 6, Table 5)[80c] cleavage conditions which were previously reported for the cleavage of amides, but all of these attempts were not successful. We next focused on the exploration of acidic cleavage conditions (entries 7–15, Table 5), which obviously require a fine balance between sufficient acidity to cleave the amide of substrate **41** and not too strong acidity in order to prevent acidic deprotection of the TBS group. In this context methanesulfonic acid (entry 7, Table 5)[35] or formic acid (entry 12, Table 5) were too acidic (pK_a = −1.92 and 3.77, respectively) and caused TBS deprotection. First traces of isochromanone **42** could be observed after refluxing **41** in anhydrous acetic acid (pK_a = 4.76, entry 9, Table 5). The choice of a suitable cosolvent seems to be crucial for the success of this protocol. With

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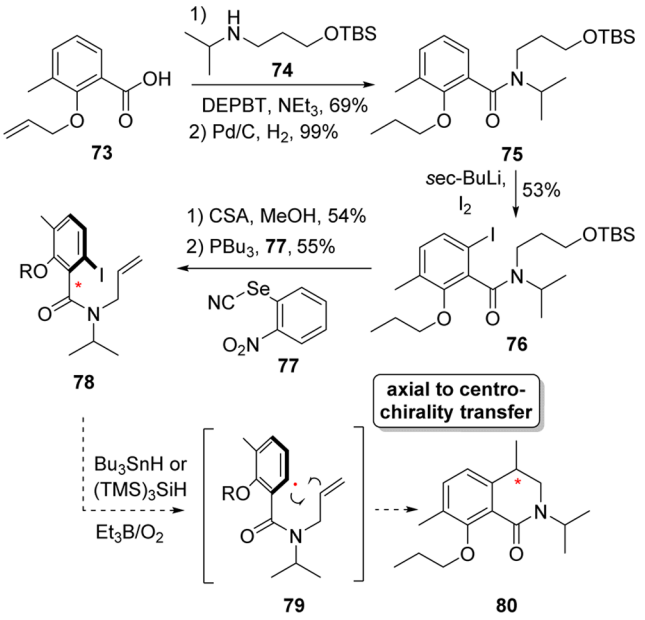
toluene, detectable yields of 39% (entry 10, Table 5) could be obtained, whereas the use of other cosolvents such as water (entry 12, Table 5) and THF (entry 13, Table 5) either deprotected the TBS group or gave no conversion. Significant improvements of the yield of up to 81% and minimization of the reaction time (7 days to 3 h) could be achieved by the assistance of microwave irradiation (entry 14, Table 5).[82] Notably, simultaneous cleavage of the TES group of **71b** in a one-pot process could also be achieved (entry 15, Table 5) and further increases the effectiveness of the protocol. The free phenol group of **41** and **71b** proved to be essential for the cleavage, as allyl-protected **71a** could not be cyclized under these conditions. The determination of the absolute and relative configurations of **72** by NMR methods proved challenging. The ^3J coupling constant between H_8 and H_9 was still very low (3.4 Hz). Although we could crystallize the direct cyclization precursor **41** (see the Supporting Information), the configuration of the C_9-stereocenter could be inverted during amide cleavage and cyclization by a carbocation to form *syn,syn*-**42**. We therefore synthesized *syn,syn*-**42** in the same way as *anti,anti*-**42** starting from crotylboration of **33** with (*Z,R,R*)-**50** (for details see the Experimental Section). However, the H_8/H_9 coupling constant of *syn,syn*-**42** was very similar to the that of *anti,anti*-**42** (2.9 Hz). Absolute certainty could finally only be obtained by crystallization and an absolute X-ray structure analysis of **72**, indicating the formation of the desired six-membered lactone with complete configurational retention during the cyclization.[83] In total, the final stereoselective route allowed the efficient synthesis of the *anti,anti*-configured isochromanone **72** in nine steps with an overall yield of 29%. As an alternative way to avoid the complex protective group strategies, we also considered a replacement of the lactone by a lactam moiety instead. Such 6-ring lactams are much more stable in comparison to the corresponding lactones, and unfavorable translactonization processes would also be avoided. Eventually, this will be of importance for the development of more stable analogues, which would require a general approach to lactams of general type **80**. As shown in Scheme 10, such lactams may be accessible by a radical transfer process involving the generation of an aromatic radical (**79**) and subsequent cyclization in a 6-*exo*-type fashion. These studies were carried out by Florian Wolf in our group. Additionally, a relay of the axial chirality to the centrochirality may even be possible to set the newly generated center with asymmetric induction. Radical reactions are in general fast and are therefore prime candidates for this kind of chirality transfer. However, examples are rare. In the past ring strain[84] and conformational effects[85] have been elegantly used to transfer chirality from a radical or biradical precursor to the corresponding product starting with centrosymmetric C radicals. In contrast, the relay of axial chirality to centrochiral compounds is much less advanced and reported examples mainly involve the cyclization of an axially chiral *o*-iodoaniline such as **78**.[86] Accordingly, the axially chiral benzamide **78**, which was in this first model study used as a racemate, was generated from the protected 3-methylsalicylic acid derivative **73** and amine **74**, involving amide formation to **75**, iodination, TBS deprotection of derived **76**, and Grieco elimination of **76** with **77**.[87] An axially chiral version of **78** should be accessible by iodination of a chiral sulfoxide bearing precursor similar to **45d**. With achiral **78** in hand, first studies involving the transformation to **80** were initiated, using tributyltin hydride[88] or tris(trimethylsilyl)silane[89] in the presence of triethylborane and oxygen. However, no traces of the desired lactam **80** could be detected, suggesting that a modified substrate and more extensive studies would be required to enable this promising transformation.

Scheme 10. Preparation of Aryl Iodide 78 for a Projected Synthesis of Aza-Isochromanone Analogues Such as 80 by a Radical Axial to Central Chirality Transfer



CONCLUSIONS

In summary, we have reported an efficient novel method for the synthesis of hydroxyl-isochromanones, which present key structural features of the ajudazols and a range of bioactive natural products and simplified structures. The procedure relies on application of an asymmetric ortho-lithiation strategy and subsequent one-pot cleavage and direct transformation of the chiral amide axis to the targeted six-membered lactones. The applicability and protecting group tolerance of this synthetically easily feasible procedure have been demonstrated. In addition, asymmetric crotylborations of axially chiral amides were studied in detail, revealing excellent degrees of asymmetric induction of these highly useful C−C coupling reactions that are purely based on substrate control. The developed strategies are generally applicable, allowing an access to all possible stereoisomers of hydroxyl-isochromanones with up to three contiguous stereocenters. Furthermore, we have developed efficient protocols for the cleavage of sterically highly hindered amides, which involve either *O*-alkylation of the amide with MeOTf or the utilization of acetic acid under microwave activation. These mild procedures were effectively applied even to sensitive substrates, including labile stereogenic centers and protective groups or esters that are prone to translactonizations. The true applicability of this novel isochromanone synthesis was demonstrated in a highly concise synthesis of the authentic isochromanone core of the ajudazols, whose total synthesis served as an inspiration for this study, including an effective generation of three *anti,anti*-configured contiguous stereogenic centers. Importantly, this scalable process presents the first and so far only synthetic route to this labile fragment, which further underlines the high significance of these results.

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EXPERIMENTAL SECTION

Materials and Methods. Starting materials and reagents were obtained from commercial sources and used as received unless otherwise specified. The following reagents and building blocks were prepared according to literature procedures: Andersen reagent **31**,[90] Roush reagent **50**,[44b] potassium (2-butenyl)trifluoroborate **52**,[91] IBX,[92] and Dess–Martin periodinane.[93] Unless stated otherwise, all nonaqueous reactions were performed in flame-dried glassware under an atmosphere of argon. The progress of the reactions was monitored by thin-layer chromatography (TLC) analysis (Polygram Sil G/UV254 on plastic). Flash column chromatography was performed by using silica gel S (pore size 60 Å, 0.040–0.063 mm, Sigma-Aldrich). Preparative high performance liquid chromatography (PHPLC) was carried out on a Eurospher II 100 RP C-18, 5 μm, 250 × 16.0 mm column (Knauer) with precolumn (30 × 16.0 mmg). Optical rotations were measured in a 1 dm cuvette, using a sodium lamp. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature with ^{1}H operating frequencies of 300, 400, 500, and 600 MHz and with ^{13}C operating frequencies of 75, 100, 125, and 150 MHz. The chemical shifts are reported in parts per million (ppm) and are given in δ units relative to deuterated solvents as internal standard ($CDCl_3$ 7.27 ppm, 77.0 ppm).[94] Coupling constants are given in hertz (Hz). Chemical shifts associated with the major rotamers are marked with an asterisk (*), the minor rotamers are marked with a hash (#), the major diastereomers are marked with a superscript a (^{a}), the minor diastereomer are marked with a superscript b (^{b}), both diastereomers are marked with a superscript c (^{c}). IUPAC names and atom numbering were generated using the program ChemBioDraw Ultra 13.0.

Methyl 2-Methoxy-3-methylbenzoate (29a). 3-Methylsalicylic acid (**29**; 15.0 g, 98.6 mmol) was stirred at room temperature with benzyltributylammonium chloride (6.2 g, 19.7 mmol, 0.20 equiv) mol), NaOH (12.0 g, 300 mmol, 3.0 equiv), and dimethyl sulfate (37.5 mL, 394 mmol, 4.0 equiv) in a mixture of H_2O (400 mL) and CH_2Cl_2 (400 mL) for 24 h. The organic layer was separated, and the aqueous phase was extracted with 3 × 150 mL of CH_2Cl_2. The combined organic phases were stirred with a 15% aqueous NH_4OH solution (150 mL) for 2 h. After the separation of the organic layer, the solvent was evaporated and the residue was taken up in Et_2O (200 mL) and stirred with 50 mL of a 15% aqueous NH_4OH solution for 2 h. The ethereal phase was separated, the aqueous layer was extracted with 3 × 50 mL of Et_2O, and the combined ether solutions were dried over $MgSO_4$, filtered, and evaporated to give a yellow liquid which was distilled (bp 112–114 °C, 6.4 mbar) to afford **29a** in 96% yield as a colorless liquid (17.1 g, 95.0 mmol). TLC: R_f = 0.70 (petroleum ether/ethyl acetate 3/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.32 (3 H, s), 3.83 (3 H, s), 3.91 (3 H, s), 7.05 (1 H, dd, J = 7.7 Hz), 7.31–7.36 (1 H, m), 7.63 (1 H, dd, J = 7.9 Hz, J = 1.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.9, 52.0, 61.4, 123.4, 124.5, 129.0, 132.7, 135.1, 158.3, 166.8. HRMS (EI-TOF): calculated for $[M]^+ = C_{10}H_{12}O_3$, 180.0886; found, 180.0893 (Δ = +0.7 mmu).

2-Methoxy-3-methylbenzoic Acid (29b). Methyl 2-methoxy-3-methylbenzoate (**29a**; 8.0 g. 44.4 mmol, 1.0 equiv) was dissolved in dry methanol (25 mL), and the mixture was heated to 35 °C. After the mixture was stirred for 10 min, a solution of anhydrous KOH (5.0 g, 88.8 mmol, 2.0 equiv) in dry MeOH (10 mL) was added and the contents were stirred for 45 min The reaction was quenched by the addition of 50 mL of water, unreactive ester was removed by extraction with 2 × 15 mL of Et_2O, and the remaining aqueous mixture was acidified to pH 2 with 6 N HCl. After the extraction with 3 × 50 mL of Et_2O the recent combined ether extracts were dried with $MgSO_4$ and the solvent was removed in vacuo to yield acid **29b** (7.1 g, 42.5 mmol) in 94% as a white solid. TLC: R_f = 0.19 (petroleum ether/ethyl acetate 3/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.37 (3 H, s), 3.92 (3 H, s), 7.17 (1 H, t, J = 7.7 Hz), 7.43 (1 H, dd, J = 7.5 Hz, J = 0.9 Hz), 7.94 (1 H, dd, J = 7.9 Hz, J = 1.3 Hz), 9.76 (1 H, br s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.9, 62.0, 122.1, 124.8, 130.6, 131.8, 136.8, 158.0, 167.3. HRMS (EI-TOF): calculated for $[M]^+ = C_9H_{10}O_3$, 166.0694; found, 166.0721 (Δ = +2.7 mmu). Mp: 48–49 °C.

***N,N*-Diethyl-2-methoxy-3-methylbenzamide (19).** A solution of acid **29b** (1.0 g, 6.02 mmol, 1.0 equiv) in dry CH_2Cl_2 (30 mL) was treated with fresh distilled $SOCl_2$ (2.2 mL, 30.09 mmol, 5.0 equiv), and the mixture was refluxed for 5 h. After evaporation of unreacted $SOCl_2$ on a rotary evaporator, the residual solution was resolved in dry CH_2Cl_2 (50 mL) and cooled to 0 °C. A solution of diethylamine (3.1 mL, 30.09 mmol, 5.0 equiv) in dry CH_2Cl_2 (15 mL) was added dropwise, and the mixture was stirred for 14 h overnight. Then water (30 mL) was added, the organic layer was separated, and the aqueous layer was extracted with 3 × 50 mL of Et_2O. The combined organic layers were washed with an aqueous HCl solution (2 M, 10 mL), an aqueous NaOH solution (2 M, 10 mL), and water (10 mL) and were dried over $MgSO_4$. After removal of the solvent the resulting yellow oil was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 3/1) to give the title compound **19** (1.18 g, 5.31 mmol) in 88% yield as a clear oil. TLC: R_f = 0.23 (petroleum ether/ethyl acetate 3/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.01 (t, J = 7.14 Hz, 3 H), 1.25 (t, J = 7.14 Hz, 3 H), 2.28 (s, 3 H), 3.14 (quin, J = 7.14 Hz, 2 H), 3.24–3.46 (m, 1 H), 3.68–3.89 (m, 1 H), 3.78 (s, 3 H), 6.97–7.08 (m, 2 H), 7.17 (dd, J = 6.59 Hz, 2.20 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.7, 13.8, 15.9, 38.8, 42.9, 61.3, 124.0, 125.1, 131.2, 131.4, 131.6, 154.0, 169.1. HRMS (EI-TOF): calculated for $[M]^+ = C_{13}H_{19}O_2N$, 221.1416; found, 221.1425 (Δ = +0.9 mmu).

***N,N*-Diethyl-6-formyl-2-methoxy-3-methylbenzamide (20).** To a stirred solution of *N,N*-diethylbenzamide (**19**; 120 mg, 0.54 mmol, 1.0 equiv) and TMEDA (98 μL, 0.651 mmol, 1.2 equiv) in dry THF (10 mL) at −78 °C (acetone/dry ice) was added dropwise a solution of *sec*-BuLi in hexane (1.4 M, 0.46 mL, 0.65 mmol, 1.2 equiv). The mixture was stirred at −78 °C for 1 h, and then a solution of DMF (84 μL, 1.08 mmol, 2.0 equiv) in dry THF (2 mL) was injected into the lithiated solution at −78 °C. After 1 h the cooling bath was removed and the solution was stirred at room temperature for 3 h. The mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with 3 × 20 mL of Et_2O, and the combined organic layers were dried over $MgSO_4$ and evaporated to give a residue which was purified by flash column chromatography on silica gel (*n*-hexane/ethyl acetate 2/1) to afford the yellowish oil **20** (127 mg, 0.51 mmol) in 94% yield. TLC: R_f = 0.22 (*n*-hexane/ethyl acetate 2/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.99 (t, J = 7.18 Hz, 3 H), 1.30 (t, J = 7.18 Hz, 3 H), 2.36 (s, 3 H), 3.08 (qd, J = 7.19 Hz, J = 1.72 Hz, 2 H), 3.54 (dq, J = 13.81 Hz, J = 6.99 Hz, 1 H), 3.71 (dq, J = 13.75 Hz, J = 7.12 Hz, 1 H), 3.81 (s, 3 H), 7.32 (d, J = 7.80 Hz, 1 H), 7.60 (d, J = 7.80 Hz, 1 H), 9.92 (s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.5, 13.6, 16.5, 39.0, 43.0, 61.7, 125.2, 131.7, 132.0, 133.7, 139.2, 147.2, 154.5, 166.1, 190.0. HRMS (EI-TOF): calculated for $[M]^+ = C_{14}H_{19}O_3N$, 249.1365; found, 249.1366 (Δ = +0.1 mmu).

***(Z)*-*N,N*-Diethyl-2-methoxy-3-methyl-6-(pent-1-enyl)-benzamide (21).** To a white slurry of *n*-Bu_4PBr (841 mg, 2.11 mmol, 1.5 equiv) in dry THF (8 mL) was added a solution of NaHMDS in THF (1 M, 2.0 mL, 1.97 mmol, 1.4 equiv). The resulting red mixture was cooled to −78 °C (acetone/dry ice) and treated with the aldehyde **20** (350 mg, 1.40 mmol, 1.0 equiv) in dry THF (2 mL) in a dropwise manner. After it was stirred for 2 h at −78 °C, the mixture was warmed to room temperature and stirred for 14 h overnight. Then the mixture was partitioned between H_2O (5 mL) and Et_2O (5 mL), followed by an extraction with 3 × 10 mL of Et_2O. The combined organic layers were washed with brine (7 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduce pressure and purification by column chromatography on silica gel (*n*-hexane/ethyl acetate 3/1) gave a 7/3 mixture of the *E*/*Z*-alkene **21** (358 mg, 1.24 mmol, 88%). The *E*/*Z* isomers could be separated by preparative HPLC on silica gel (*n*-hexane/ethyl acetate 9/1; Nucleosil 100-7; flow 25 mL; retention time (*E*-**21**) 22 min; retention time (*Z*-**21**) 24 min). TLC: R_f = 0.50 (*n*-hexane/ethyl acetate 3/1). ^{1}H NMR *Z*-**21** ($CDCl_3$, 300 MHz): δ 0.92 (t, J = 7.33 Hz, 3 H), 0.99 (t, J = 7.18 Hz, 3 H), 1.25 (t, J = 7.10 Hz, 3 H), 1.35–1.55 (m, 2 H), 2.14–2.30 (m, 2 H), 2.29 (s, 3 H), 3.05 (m_C, 2 H), 3.44–3.70 (m, 2 H), 3.78 (s, 3 H), 5.66 (dt, J = 11.70 Hz, J = 7.25 Hz, 1 H), 6.32 (d, J = 11.55 Hz, 1 H), 7.01 (d, J = 7.96 Hz, 1 H), 7.12 (d, J = 7.80 Hz, 1 H). ^{13}C NMR *Z*-**21** ($CDCl_3$, 75 MHz): δ 12.6, 13.7, 13.9, 15.8, 23.0, 30.8, 38.6, 42.7, 61.5, 124.9, 125.5, 129.6, 130.5,

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131.1, 133.3, 133.9, 154.1, 168.1. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{18}H_{27}O_2N$, 290.2115; found, 290.2115 (Δ = 0 mmu).

***N,N*-Diethyl-6-iodo-2-methoxy-3-methylbenzamide (22).** *N,N*-Diethyl-2-methoxy-3-methylbenzamide (**19**; 2 g, 9.0 mmol, 1 equiv) was mixed with TMEDA (1.25 g, 11 mmol, 1.2 equiv) in 200 mL of dry THF and cooled to −78 °C. *sec*-BuLi (7.2 mL, 11 mmol, 1.2 equiv) was added dropwise, and the resulting mixture was stirred at −78 °C for 30 min. Iodine (1.4 g, 11 mmol, 1.2 equiv) was dissolved in dry THF (10 mL) and added dropwise until the iodine color was persistent. After a further 1 h of stirring at −78 °C, the mixture was quenched by addition of saturated sodium thiosulfate solution (20 mL) and extracted with diethyl ether (3 × 50 mL). The organic extracts were washed with water and dried over $MgSO_4$, and the solvent was removed in vacuo, yielding 2.12 g of *N,N*-diethyl-6-iodo-2-methoxy-3-methylbenzamide (**22**) as a pale yellow oil in 66% yield. TLC: R_f = 0.53 (petroleum ether/ethyl acetate 1/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (3 H, t, *J* = 7.3 Hz), 1.14 (3 H, t, *J* = 7.1 Hz), 2.09 (3 H, s), 2.95 (2 H, m), 3.27−3.44 (1 H, m), 3.44−3.58 (1 H, m), 3.61 (3 H, s), 6.74 (1 H, d, *J* = 8.2 Hz), 7.28 (1 H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.0, 13.3, 15.3, 38.4, 42.5, 61.2, 89.3, 131.3, 132.1, 134.0, 136.8, 154.5, 167.4. HRMS (ESI-TOF): calculated for $[M + H]^+ = C_{13}H_{19}INO_2$, 348.0460; found, 348.0457 (Δ = −0.3 mmu).

3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropan-1-ol (23a). 2-Methylpropane-1,3-diol (9.0 g, 0.1 mol, 1.0 equiv) was dissolved in 150 mL of dry THF, and NaH (4.0 g, 60%, 0.1 mol, 1.0 equiv) was added in portions over 15 min. The resulting mixture was stirred for 45 min, and TBSCl (15.4 g, 0.1 mol, 1.0 equiv) was added in one portion. After it was stirred at room temperature for 3 days, the reaction mixture was quenched with water, extracted with diethyl ether (3 × 100 mL), and washed with water, and the organic layers were dried over $MgSO_4$. The solvents were removed in vacuo, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 4/1) to yield 3-butyldimethylsilyloxy-2-methylpropan-1-ol (**23a**; 11.4 g, 56%) as a colorless liquid. TLC: R_f = 0.68 (petroleum ether/ethyl acetate 1/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.00 (6 H, s), 0.78 (3 H, d, *J* = 6.9 Hz), 0.83 (9 H, s), 1.83 (1 H, m), 3.32 (1 H, br s), 3.43−3.50 (1 H, m), 3.52 (2 H, d, *J* = 5.8 Hz), 3.62 (1 H, dd, *J* = 9.9, 4.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.7, −3.7, 13.0, 18.1, 25.7 (3 C), 37.1, 67.4, 68.0. HRMS (ESI-TOF): calculated for $[M + H]^+ = C_{10}H_{25}O_2Si$, 205.1624; found, 205.1617 (Δ = −0.7 mmu).

(*E*)-4-(Butyldimethylsilyloxy)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-methylbut-1-ene (23). Alcohol **23a** (5.0 g, 24.4 mmol, 1 equiv) was dissolved in dry CH_2Cl_2, and Dess−Martin periodinane (25 g, 59 mmol, 2.4 equiv) was added. The resulting mixture was stirred for 2.5 h at room temperature and quenched with satured sodium thiosulfate solution (20 mL) and saturated $NaHCO_3$ solution (20 mL). The organic phase was separated and the water phase extracted with DCM (2 × 50 mL); the combined organic extracts were washed with water, dried over $MgSO_4$, and filtered through a pad of silica gel. After removal of the solvent in vacuo, the crude aldehyde **23b** (~3.0 g, 15 mmol, 1 equiv) and dichloromethylboronic acid pinacol ester (6.3 g, 30 mmol, 2.0 equiv) were dissolved in dry THF (50 mL) and added slowly to a suspension of $CrCl_2$ (15 g, 120 mmol, 8.0 equiv) in THF (100 mL) with cooling in an ice bath. LiI (7.5 g, 60 mmol, 4.0 equiv) was dissolved in 80 mL of THF and added to the mixture. The resulting suspension was stirred at room temperature for 16 h. The crude reaction mixture was filtered through a pad of Celite, water was added, the phases were separated, and the water phase was extracted with diethyl ether (2 × 50 mL). The combined organic phases were washed with water and dried over $MgSO_4$, and the solvent was removed in vacuo. After purification by flash column chromatography (silica gel, petroleum ether/ethyl acetate 10/1), 3.13 g of (*E*)-4-(butyldimethylsilyloxy-3-methylbut-1-enyl)-boronic acid pinacol ester **23** could be obtained as a colorless liquid in 39% yield over two steps. TLC: R_f = 0.75 (petroleum ether/ethyl acetate 4/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.55 (dd, *J* = 18.1, 6.9 Hz, 1 H), 5.46 (d, *J* = 19.5 Hz, 1H), 3.57 (dd, *J* = 9.9, 6.0 Hz, 1 H), 3.34−3.47 (m, 1 H), 2.40 (dt, *J* = 13.7, 7.1 Hz, 1 H), 1.26 (s, 12 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.3, −5.3, 15.6, 18.3, 24.7, 24.8 (2 C), (2 C), 25.9 (3 C), 42.0, 67.4, 83.0 (2 C), 118.0 (br s), 156.4. HRMS (ESI-TOF): calculated for $[M + H]^+ = C_{17}H_{36}BO_3Si$, 327.2527; found, 327.2522 (Δ = −0.5 mmu).

(*E*)-6-(4-*tert*-Butyldimethylsilyloxy-3-methyl-but-1-enyl)-*N,N*-diethyl-2-methoxy-3-methylbenzamide (24). Borane **23** (1.41 g, 4.32 mmol, 1.0 equiv), iodide **22** (1.50 g, 4.32 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (250 mg, 22 μmmol, 5 mol %), and NaOH (2 N, 4.3 mL, 8.64 mmol, 2.0 equiv) were dissolved in 20 mL of dioxane and refluxed for 3 h. The reaction mixture was quenched with water and extracted with Et_2O (3 × 50 mL), and the combined extracts were dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 2/1) to afford 1.45 g of the title compound **24** (81%) as a faintly yellow oil. TLC: R_f = 0.68 (petroleum ether/ethyl acetate 1/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.18−7.23 (m, 1 H), 7.08−7.12 (m, 1 H), 6.28−6.35 (m, 1 H), 6.09−6.17 (m, 1 H), 3.77 (s, 3 H), 3.40−3.65 (m, 4 H), 3.06 (ddd, *J* = 7.1, 4.1, 1.9 Hz, 2 H), 2.45 (dt, *J* = 13.4, 6.6 Hz, 1 H), 2.27 (s, 3 H), 1.28 (t, *J* = 7.0 Hz, 4 H), 1.05 (dd, *J* = 6.7, 3.4 Hz, 3 H), 1.00 (t, *J* = 7.1 Hz, 3 H), 0.89 (s, 9 H), 0.04 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.4, −5.4, 12.8, 13.8, 15.7, 16.5, 18.3, 25.9 (3 C), 38.8, 40.0, 42.9, 61.5, 68.1, 120.7, 125.7, 129.7, 130.2, 131.1, 133.6, 134.9, 154.2, 168.1. HRMS (ESI-TOF): calculated for $[M + H]^+ = C_{24}H_{42}NO_3Si$, 420.2934; found, 420.2930 (Δ = −0.4 mmu).

Ethyl (2*R*,3*R*)-2-Hydroxy-3-methylpent-4-enoate (33a). To a stirred mixture of KO*t*Bu (7.76 g, 16.0 mmol, 1.03 equiv, dried at 1.0 mbar/80 °C/12 h) in dry THF (35 mL) was added liquid *trans*-2-butene (10.5 g, 188 mmol, 2.8 equiv) via transfer by cannula at −78 °C (acetone/dry ice). Then a solution of *n*-BuLi (2.5 M in hexane, 26.8 mL, 67.0 mmol, 1.0 equiv) was added dropwise within 30 min via syringe driver. Thirty minutes after complete addition of *n*-BuLi the mixture was stirred at −45 °C (acetone/dry ice) for 10 min. The resulting orange solution was recooled to −78 °C, and to it was added dropwise a solution of (+)-$(Ipc)_2$BOMe (25.1 g, 79.2 mmol, 1.18 equiv) in dry Et_2O (80 mL). After the reaction mixture was stirred at −78 °C for 30 min, $BF_3{\cdot}OEt_2$ (12.1 mL, 96.0 mmol, 1.4 equiv) was added dropwise within 20 min via syringe, followed by a technical solution of ethyl glyoxalate **33** in toluene (ca. 4.9 M, 34.2 mL, 168 mmol, 2.5 equiv) within 30 min. The mixture was now stirred at −78 °C for 4 h and after the removal of the cooling bath treated with an aqueous NaOH solution (1 N, 150 mL, 2.25 equiv) and carefully with H_2O_2 (30%, 21.0 mL). Then the contents were stirred for 2 h at room temperature. The organic layer was separated, the aqueous layer was extracted with 3 × 100 mL of Et_2O, and the combined organic layers were washed with water (30 mL) and brine (30 mL) and dried over $MgSO_4$. After removal of the solvents the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 10/1) to yield 70% of *anti*-**33a** (7.43 g, 47.0 mmol, d.r. = 98:2, ee = 90% determined by Mosher ester analysis) as a colorless liquid with a fruity odor. TLC: R_f = 0.33 (petroleum ether/ethyl acetate 10/1). $[\alpha]_D^{23}$ = −4.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.16 (3 H, d, *J* = 7.0 Hz)[a], 1.30 (3 H, t, *J* = 7.1 Hz)[a], 1.37 (1 H, d, *J* = 7.0 Hz)[b], 1.51 (1 H, t, *J* = 7.1 Hz)[b], 2.17−2.28 (1 H, m)[b], 2.49 (1 H, br s)[b], 2.59−2.72 (1 H, m)[a], 2.74 (1 H, br s)[a], 4.11 (1 H, d, *J* = 3.3 Hz)[a], 4.16 (1 H, d, *J* = 2.6 Hz)[b], 4.14−4.33 (2 H, m)[a], 4.34−4.50 (1 H, m)[b], 5.01−5.07 (1 H, m)[a], 5.07−5.11 (1 H, m)[a], 5.11−5.13 (1 H, m)[b], 5.14−5.18 (1 H, m)[b], 5.68−5.82 (1 H, m)[a], 5.79−5.92 (1 H, m)[b]. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.5[b], 14.2[a], 15.1[b], 16.3[a], 41.6[b], 41.9[a], 61.6[a], 64.1[b], 73.8[b], 74.3[a], 115.5[b], 116.4[a], 137.6[a], 139.4[b], 174.2[a]. HRMS (EI-TOF): calculated for $[M]^+ = C_8H_{14}O_3$, 158.0943; found, 158.0951 (Δ = +0.8 mmu).

Ethyl (2*R*,3*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-3-methylpent-4-enoate (34). To an ice-cooled solution of the ester **33a** (2.43 g, 15.4 mmol, 1.0 equiv) in dry CH_2Cl_2 (120 mL) were added 2,6-lutidine (7.13 mL, 61.4 mmol, 4.0 equiv) and TBSOTf (10.6 mL, 46.1 mmol, 3.0 equiv). The resulting mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with

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saturated aqueous $NaHCO_3$ solution (40 mL) and extracted with 3 × 40 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 60/1) afforded 93% of silyl ether **34** (3.9 g, 14.4 mmol) as a pale yellow liquid. TLC: R_f = 0.17 (petroleum ether/ethyl acetate 60/1). $[\alpha]_D^{23}$ = +20.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.04 (3H, s), 0.08 (3H, s), 0.92 (s, 9 H), 1.07 (3 H, d, *J* = 7.0 Hz), 1.27 (3 H, t, *J* = 7.1 Hz), 2.55−2.70 (1 H, m), 4.07 (1 H, d, *J* = 4.8 Hz), 4.17 (2 H, m_c), 4.99 (1 H, s), 5.01−5.06 (1 H, m), 5.82 (1 H, ddd, *J* = 17.2, 10.4, 8.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ −5.3, −4.9, 14.3, 16.8, 18.3, 25.7 (3 C), 42.8, 60.5, 76.3, 115.3, 139.0, 172.9. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{14}H_{29}O_3Si$, 273.1880; found, 273.1881 (Δ = −0.1 mmu).

(2*R*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,3-dimethylpent-4-enamide (25). Weinreb's amine hydrochloride MeNH(OMe)·HCl (161 mg, 1.65 mmol, 3.0 equiv) was dissolved in dry THF (2 mL), and TBS-protected ester **34** (150 mg, 0.55 mmol) in dry THF (0.5 mL) was added. The mixture was cooled to −20 °C (acetone/dry ice), and a solution of *i*-PrMgCl in THF (2.0 M in THF, 1.65 mL, 3.30 mmol, 6.0 equiv) was injected dropwise over 30 min. The mixture was stirred for an additional 1 h at −20 °C, the bath was then removed, and the mixture was stirred for 1 h at room temperature. The reaction was quenched with the dropwise addition of a half-saturated aqueous NH_4Cl solution (2.5 mL). After extraction of the aqueous layer with 3 × 15 mL of Et_2O, the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1) to afford Weinreb's amide **25** (146 mg, 0.51 mmol) in 92% yield as a colorless oil. $[\alpha]_D^{23}$ = +25.5 (*c* 1.0, $CHCl_3$). TLC: R_f = 0.30 (petroleum ether/ethyl acetate 9/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.06 (d, *J* = 3.74 Hz, 6 H), 0.91 (s, 9 H), 1.04 (d, *J* = 6.86 Hz, 3 H), 2.62 (sxt, *J* = 6.74 Hz, 1 H), 3.22 (s, 3 H), 3.71 (s, 3 H), 4.30−4.45 (m, 1 H), 4.97−5.03 (m, 1 H), 5.05 (s, 1 H), 5.78−5.95 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75.48 MHz): δ −5.1, −4.7, 16.6, 18.3, 25.8 (3 C), 32.8, 41.8, 61.1, 74.0, 115.1, 139.9, 147.2. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{14}H_{30}O_3NSi$, 288.1989; found, 288.1988 (Δ = +0.1 mmu).

6-((2*R*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methylpent-4-enoyl)-*N*,*N*-diethyl-2-methoxy-3-methylbenzamide (26). To a stirred solution of *N*,*N*-diethylbenzamide (**19**; 219 mg, 0.99 mmol, 2.3 equiv) and TMEDA (103 μL, 0.68 mmol, 1.6 equiv) in Et_2O (5 mL) at −78 °C (acetone/dry ice) was added dropwise a solution of *sec*-BuLi in hexane (1.4 M, 0.5 mL, 0.69 mmol, 1.6 equiv) within 30 min, The mixture was stirred at −78 °C for 3 h, and then a solution of Weinreb's amide **25** (123 mg, 0.43 mmol, 1.0 equiv) in dry Et_2O (1.5 mL) was injected into the lithiated solution at −78 °C within 20 min. After 3 h the cooling bath was removed and the solution was stirred at room temperature overnight (14 h). The mixture was quenched with saturated aqueous NH_4Cl solution (3 mL) and extracted with 3 × 20 mL of Et_2O, and the combined organic layers were dried over $MgSO_4$ and evaporated to give a residue which was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1) to afford the white solid **26** (107 mg, 0.24 mmol) in 56% yield. TLC: R_f = 0.25 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +30.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.14 (s, 3 H)$^{\#}$, −0.03 (s, 3 H)$^{\#}$, 0.06 (d, *J* = 1.56 Hz, 3 H)*, 0.11 (d, *J* = 2.18 Hz, 2 H)*, 0.85−1.00 (m, 9 H), 0.97−1.05 (m, 3 H), 1.08 (dd, *J* = 6.80 Hz, *J* = 2.50 Hz, 3 H), 1.16 (d, *J* = 6.86 Hz, 3 H)$^{\#}$, 1.23−1.36 (m, 3 H)*, 2.33 (s, 3 H)*, 2.36 (s, 3 H)$^{\#}$, 2.59−2.72 (m, 1 H), 2.83 (dd, *J* = 11.16 Hz, *J* = 5.07 Hz, 2 H), 2.94−3.26 (m, 1 H), 3.36−3.49 (m, 1 H), 3.77 (s, 3 H)*, 3.79 (s, 3H)$^{\#}$, 4.03 (dd, *J* = 12.48 Hz, *J* = 3.28 Hz, 1 H), 4.27 (d, *J* = 7.33 Hz, 1 H)$^{\#}$,4.50 (d, *J* = 4.68 Hz, 1 H)$^{\#}$, 4.94−5.22 (m, 2 H), 5.65−5.99 (m, 1 H), 7.21 (dd, *J* = 10.69 Hz, 8.04 Hz, 1 H), 7.57 (d, *J* = 7.96 Hz, 1 H)*, 8.00 (d, *J* = 8.11 Hz, 1 H)$^{\#}$. ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.3$^{\#}$, −5.2*, −5.0*, −4.8$^{\#}$, 12.5, 13.2*, 13.3$^{\#}$, 15.3, 16.3$^{\#}$, 16.4*, 16.9, 25.3*, 25.4$^{\#}$, 25.6*, 25.7$^{\#}$, 25.8*, 25.9$^{\#}$, 41.1, 42.6*, 42.6$^{\#}$, 42.9, 43.1, 61.5*, 61.7$^{\#}$, 75.2, 77.6, 81.6, 83.8, 115.4*, 115.6$^{\#}$, 117.2, 125.8*, 126.4$^{\#}$, 130.0*, 130.7$^{\#}$, 137.8$^{\#}$, 138.4*, 139.2*, 139.8$^{\#}$. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{25}H_{42}NO_4Si$, 448.2878; found, 448.2878 (Δ = 0 mmu).

***N*,*N*-Diisopropyl-2-methoxy-3-methylbenzamide (30).** The procedure described above for **19** was performed with acid **29b** (1.0 g, 6.02 mmol, 1.0 equiv), $SOCl_2$ (2.2 mL, 30.1 mmol, 5.0 equiv), and diisopropylamine (4.25 mL, 30.1 mmol, 5.0 equiv) to give compound **30** (1.22 g, 4.89 mmol) in 81% yield as a white solid after purification by flash column chromatography on silica gel (petroleum ether/ethyl acetate 7/1). TLC: R_f = 0.35 (petroleum ether/ethyl acetate 5/1). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.05 (3 H, d, *J* = 6.7 Hz), 1.18 (3 H, d, *J* = 6.7 Hz), 1.56 (3 H, d, *J* = 2.8 Hz), 1.59 (3 H, d, *J* = 2.8 Hz), 2.30 (3 H, s), 3.52 (1 H, spt, *J* = 6.9 Hz), 3.69 (1 H, spt, *J* = 6.7 Hz), 3.81 (3 H, s,), 7.01 (2 H, d, *J* = 5.0 Hz), 7.12−7.21 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.0, 20.2, 20.4, 20.7, 20.7, 45.7, 51.1, 61.3, 124.0, 124.7, 131.2, 131.4, 132.6, 154.1, 168.9. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{15}H_{24}O_2N$, 250.1800; found, 250.1802 (Δ = +0.2 mmu). Mp: 89−91 °C.

(*S*)-*N*,*N*-Diisopropyl-2-methoxy-3-methyl-6-(*p*-tolylsulfinyl)benzamide (32). A representative procedure for the construction of the chiral sulfoxides is as follows. In a stirred solution of the amide **32** (5.50 g, 22.1 mmol, 1.0 equiv) and TMEDA (3.66 mL, 24.3 mmol, 1.1 equiv) in dry THF (110 mL, 0.2 M) at −78 °C (acetone/dry ice) was injected dropwise *sec*-BuLi (1.4 M in hexane, 17.3 mL, 24.3 mmol, 1.1 equiv) within 15 min. The lithiated solution was stirred at −78 °C for 20 min, and then it was cannulated to a solution of (1*R*,2*S*,5*R*,*SS*)-(−)-menthyl *p*-toluenesulfinate (**31**; 13.0 g, 44.1 mmol, 2.0 equiv) in dry THF (110 mL, 0.2 M). After 1.5 h the mixture was quenched with saturated aqueous NH_4Cl solution (200 mL) at −78 °C, br ught up to room temperature, and extracted with 3 × 200 mL of Et_2O. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure to give a residue which was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 1/1) to afford the white crystalline sulfoxide **32** (7.03 g, 18.1 mmol) in 82% yield. TLC: R_f = 0.25 (petroleum ether/ethyl acetate 3/1). $[\alpha]_D^{23}$ = −117.3 (*c* 1.0, $CHCl_3$): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (3 H, d, *J* = 6.7 Hz), 1.26 (3 H, d, *J* = 6.7 Hz), 1.63 (6 H, t, *J* = 6.9 Hz), 2.29 (3 H, s), 2.35 (3 H, s), 3.60 (1 H, sxt, *J* = 6.7 Hz), 3.74 (1 H, sxt, *J* = 6.8 Hz,), 3.81 (3 H, s), 7.25 (3 H, dd, *J* = 8.3 Hz, 2.2 Hz,), 7.43 (1 H, d, *J* = 8.0 Hz,), 7.73 (2 H, d, *J* = 8.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.2, 20.3, 20.3, 20.6, 21.0, 21.3, 46.2, 51.8, 61.5, 120.6, 124.5 (2 C), 129.7 (2 C), 132.2, 132.3, 135.1, 140.7, 142.0, 142.1, 153.4, 165.2. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{22}H_{30}O_3NS$, 388.1941; found, 388.1941 (Δ = 0 mmu). Mp: 95−96 °C.

(2*R*,3*R*)-2-(*tert*-Butyldimethylsilyloxy)-3-methylpent-4-en-1-al (35). A stirred solution of the TBS-protected ester **34** (850 mg, 3.12 mmol, 1.0 equiv) in dry CH_2Cl_2 (15 mL) was cooled to −78 °C (acetone/dry ice). Then a solution of DIBAl-H (1.0 M in CH_2Cl_2, 14.3 mL, 9.36 mmol, 3.0 equiv) was injected dropwise over a period of 30 min. The reaction mixture was warmed to room temperature overnight (12 h) and poured into a saturated solution of potassium sodium tartrate (50 mL). Et_2O (30 mL) was added, and the mixture was stirred vigorously until two phases appeared. Extraction with 3 × 50 mL of CH_2Cl_2, drying over $MgSO_4$, and evaporation of the solvent yielded 91% of liquid alcohol **34a** (657 mg, 2.85 mmol), which was used in the following reaction without further purification. TLC: R_f = 0.28 (petroleum ether/ethyl acetate 30/1).

Oxalyl chloride (273 μL, 3.19 mmol, 1.35 equiv) was dissolved in dry CH_2Cl_2 (10 mL). The mixture was cooled to −78 °C, and a solution of DMSO (435 μL, 6.14 mmol, 2.6 equiv) in dry CH_2Cl_2 (3 mL) was added within 5 min. The mixture was stirred at this temperature for 25 min before a solution of TBS-protected alcohol **34a** (544 mg, 2.36 mmol, 1.0 equiv) in dry CH_2Cl_2 (3 mL) was added dropwise. After it was stirred for 1 h, the mixture was treated with dry NEt_3 (1.31 mL, 9.44 mmol, 4.0 equiv) and stirring was continued at −78 °C for 30 min before the mixture was slowly warmed to room temperature over 1.5 h. Then water was added, the phases were separated, and the aqueous phase was extracted with 3 × 20 mL of CH_2Cl_2. The combined organic layers were washed with brine (2 × 20 mL), and the solvent was evaporated under reduced pressure. Flash

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column chromatography on silica gel (petroleum ether/ethyl acetate 70/1) yielded 85% of the TBS-protected aldehyde **35** (461 mg, 2.02 mmol) as a colorless liquid. TLC: R_f = 0.30 (petroleum ether/ethyl acetate 70/1). $[\alpha]_D^{23}$ = +15.7 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.06 (3 H, s), 0.08 (3 H, s), 0.94 (s, 9 H), 1.10 (3 H, d, *J* = 7.0 Hz), 2.54−2.67 (1 H, m), 3.85 (1 H, dd, *J* = 4.4, 1.8 Hz), 5.02−5.09 (m, 2 H), 5.70−5.90 (m, 1 H), 9.56 (1 H, d, *J* = 2.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.1, −4.6, 16.3, 18.2, 25.7 (3 C), 41.6, 81.0, 116.0, 138.2, 204.5. HRMS (ESI-TOF, arginine): calculated for $[M + Na]^+ = C_{12}H_{24}O_2SiNa$, 251.1340; found, 251.1338 (Δ = −0.2 mmu).

6-((1*S*,2*R*,3*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-3-methylpent-4-en-1-yl)-*N*,*N*-diisopropyl-2-methoxy-3-methylbenzamide (37). A solution of *tert*-BuLi (1.7 M, 0.39 mL, 656 μmol, 3.0 equiv) was added dropwise to a stirred solution of sulfoxide **31** (212 mg, 547 μmol, 2.5 equiv) in dry THF (8 mL) at −90 °C. After 5 min the TBS-protected aldehyde **35** (50.0 mg, 218 μmol, 1.0 equiv) in THF (1.0 mL) was added dropwise at −90 °C within 2 min. After it was stirred for 45 min at −90 °C, the mixture was quenched with water (10 mL) and the solution was stirred for 20 min at room temperature. The organic layer was separated, the aqueous layer was extracted with 3 × 20 mL of Et_2O, and the combined organic layers were dried over $MgSO_4$ and evaporated to give a residue which was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 1/1) to afford the alcohol **37** (74 mg, 154 μmol) as a colorless oil in 71% yield. TLC: R_f = 0.31 (petroleum ether/ethyl acetate 5/1). $[\alpha]_D^{23}$ = +76.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ −0.48 (s, 3 H), 0.09 (s, 3 H), 0.76 (s, 9 H), 1.06 (d, *J* = 6.71 Hz, 3 H), 1.19 (dd, *J* = 13.26 Hz, *J* = 6.86 Hz, 6 H), 1.57 (dd, *J* = 6.79 Hz, *J* = 3.67 Hz, 6 H), 2.27 (s, 3 H), 2.78 (quin, *J* = 7.22 Hz, 1 H), 3.07 (br s, 1 H), 3.53 (dt, *J* = 13.53 Hz, *J* = 6.73 Hz, 1 H), 3.73 (s, 3 H), 4.19 (dd, *J* = 8.82 Hz, *J* = 2.11 Hz, 1 H), 4.43 (d, *J* = 8.89 Hz, 1 H), 4.99−5.15 (m, 2 H), 6.01 (ddd, *J* = 17.44 Hz, *J* = 10.26, *J* = 8.04 Hz, 1 H), 7.14 (s, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ −4.3, −4.2, 15.9, 16.4, 20.3, 20.5, 20.5, 21.1, 26.5 (3 C), 41.7, 46.0, 51.8, 61.1, 72.8, 77.7, 114.9, 123.9, 131.1, 132.2, 133.2, 138.7, 140.0, 141.0, 154.0, 169.1. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{27}H_{48}NO_4Si$, 478.3347; found, 478.3346 (Δ = −0.1 mmu).

6-((1*S*,2*R*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-3-methylpent-4-en-1-yl)-*N*,*N*-diisopropyl-2-methoxy-3-methylbenzamide (40). To a solution of C_9-TBS-protected **37** (35.5 mg, 72.2 μmol, 1.0 equiv) in DMF (1.5 mL) was added tris(dimethylamino)sulfoniumdifluorotrimethyl silicate (TASF; 260 mg, 721 μmol, 10.0 equiv). The reaction was monitored by TLC until the starting material was consumed (14 h). The reaction mixture was then diluted with EtOAc (10 mL) and washed with water (3 × 5 mL). The aqueous layer was extracted with 3 × 10 mL of EtOAc, and the combined organic layers were washed again with water (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (petroleum ether/ethyl acetate 1/1 to pure ethyl acetate) afforded diol **37a** (24.6 mg, 65.1 μmol) in 90% yield as a yellow oil. To a solution of diol **37a** (23.5 mg, 62.3 μmol, 1.0 equiv) in CH_2Cl_2 (3 mL) at −78 °C were added 2,6-lutidine (22 μL, 187 μmol, 3.0 equiv) and TBSOTf (16 μL, 68.5 μmol, 1.1 equiv). The resulting mixture was stirred at −78 °C for 3 h; it was then warmed to −40 °C within 1.5 h and finally to 0 °C while stirring was continued for an additional 3 h. Subsequently, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with 3 × 5 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 3/1) afforded 13% of C_8-TBS-protected alcohol **40** (4.0 mg, 8.13 μmol) as a pale yellow liquid. TLC: R_f = 0.21 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +46.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 600 MHz): δ −0.21 (3 H, s), 0.10 (3 H, s), 0.75 (3 H, d, *J* = 7.0 Hz), 0.95 (9 H, s), 1.10−1.14 (6 H, m), 1.55−1.64 (6 H, m), 1.59−1.62 (1 H, m), 2.27 (3 H, s), 3.46−3.54 (2 H, m), 3.72 (3 H, s), 4.10−4.13 (1 H, m), 4.76 (1 H, d, *J* = 2.9 Hz), 4.86−4.97 (2 H, m), 5.72−5.89 (1 H, m), 7.14 (1 H, d, *J* = 8.1 Hz), 7.35 (1 H, d, *J* = 8.1 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz) δ −4.9, −4.5, 18.5, 18.8, 19.9 (2 C), 21.0, 22.3, 22.3, 25.8 (3 C), 33.5, 45.8, 50.9, 61.3, 77.6, 78.5, 114.1, 123.6, 129.8, 130.2, 132.1, 138.0, 139.7, 154.1, 167.8. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{27}H_{48}NO_4Si$, 478.3347; found, 478.3342 (Δ = −0.5 mmu).

2-Hydroxy-*N*,*N*-diisopropyl-3-methylbenzamide (43). A solution of MgI_2, prepared from a refluxing mixture of magnesium turnings (124 mg, 10.0 mmol, 1.25 equiv) and iodine (2.34 g, 9.22 mmol, 1.15 equiv) in Et_2O (15 mL) and toluene (30 mL), was added dropwise to a stirred mixture of **30** (2.0 g, 8.02 mmol, 1.0 equiv) in toluene (35 mL). The mixture was then refluxed for 12 h and cooled, and water (20 mL) was added. The resulting mixture was acidified to pH 3 with 1 M HCl and extracted with 3 × 50 mL of Et_2O, and the combined organic layers were dried over $MgSO_4$. After removal of the solvent the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 5/1) to give the title compound **43** (1.80 g, 7.65 mmol) in 95% yield as a yellow solid. TLC: R_f = 0.51 (petroleum ether/ethyl acetate 5/1). ^1H NMR ($CDCl_3$, 300 MHz): 1.38 (6 H, s), 1.41 (6 H, s), 2.27 (3 H, s), 3.80−4.09 (2 H, m), 6.74 (1 H, dd, *J* = 7.6 Hz), 7.03 (1 H, dd, *J* = 7.9, 1.6 Hz), 7.10−7.22 (1 H, m), 9.20 (1 H, br s.). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.9, 21.0 (4 C), 48.9 (2 C), 117.9, 119.5, 124.2, 127.0, 132.5, 156.2, 171.5. HRMS (EI-TOF): calculated for $[M]^+ = C_{14}H_{21}O_2N$, 235.1572; found, 235.1581 (Δ = +0.9 mmu). Mp: 110−112 °C.

***N*,*N*-Diisopropyl-2-((4-methoxybenzyl)oxy)-3-methylbenzamide (44a).** To an ice-cooled suspension of NaH (60% dispersion in mineral oil, 81.6 mg, 2.04 mmol, 1.60 equiv) in DMF (5 mL) was added dropwise a solution of phenol **43** (300 mg, 1.27 mmol, 1.0 equiv) in DMF (4 mL), and the resultant mixture was stirred for 0.5 h. PMBCl (309 μL, 2.29 mmol, 1.80 equiv) was added, and the mixture was heated at 60 °C for 15 h before it was cooled to room temperature. Then EtOAc (10 mL) and H_2O (10 mL) were added, the mixture was extracted with 3 × 10 mL of EtOAc, and the organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 9/1) furnished PMB ether **44a** (407 mg, 1.14 mmol, 90%) as a white solid. TLC: R_f = 0.29 (petroleum ether/ethyl acetate 9/1). ^1H NMR ($CDCl_3$, 300 MHz): 1.03 (3 H, d, *J* = 6.6 Hz), 1.12 (3 H, d, *J* = 6.6 Hz), 1.56 (3 H, d, *J* = 6.6 Hz), 1.57 (3 H, d, *J* = 6.7 Hz), 2.27 (3 H, s), 3.49 (1 H, spt, *J* = 6.7 Hz), 3.69 (1 H, spt, *J* = 6.6 Hz), 3.82 (3 H, s), 4.81 (1 H, d, *J* = 10.5 Hz), 5.04 (1 H, d, *J* = 10.6 Hz), 6.89 (2 H, m, *J* = 8.5 Hz), 7.04 (2 H, d, *J* = 4.7 Hz), 7.09−7.21 (1 H, m), 7.38 (2 H, m, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.4, 20.5, 20.6 (3 C), 45.6, 51.0, 55.2, 75.4, 113.7 (2 C), 124.1, 124.7, 129.8 (2 C), 129.9, 131.0, 131.9, 133.5, 152.8, 159.3, 169.0. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{22}H_{30}O_3N$, 356.2226; found, 356.2236 (Δ = +1.0 mmu). Mp: 81−82 °C.

2-((*tert*-Butyldimethylsilyl)oxy)-*N*,*N*-diisopropyl-3-methylbenzamide (44b). To an ice-cooled solution of phenol **43** (600 mg, 3.79 mmol, 1.0 equiv) in dry CH_2Cl_2 (15 mL) were added 2,6-lutidine (370 μL, 3.19 mmol, 2.5 equiv) and TBSOTf (529 μL, 2.29 mmol, 1.8 equiv). The resulting mixture was stirred at room temperature overnight (14 h), and then water (10 mL) was added followed by extraction with 3 × 10 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 15/1) afforded 98% of silyl ether **44b** (438 mg, 1.25 mmol) as a colorless liquid. TLC: R_f = 0.25 (petroleum ether/ethyl acetate 15/1). ^1H NMR ($CDCl_3$, 300 MHz): 0.13 (3 H, s), 0.27 (3 H, s), 0.95 (3 H, d, *J* = 6.6 Hz), 1.03 (9 H, s), 1.18 (3 H, d, *J* = 6.8 Hz), 1.51 (3 H, d, *J* = 6.8 Hz), 1.55 (3 H, d, *J* = 6.9 Hz), 2.26 (3 H, s), 3.48 (1 H, spt, *J* = 6.9 Hz), 3.56 (1 H, spt, *J* = 6.7 Hz), 6.83−6.97 (2 H, m), 7.07−7.13 (1 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.9, −2.8, 18.2, 18.8, 20.3, 20.4, 20.9, 21.4, 26.4 (3 C), 45.6, 50.4, 121.7, 125.2, 129.4, 131.1, 131.7, 149.0, 169.4. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{20}H_{36}O_2NSi$, 350.2510; found, 350.2513 (Δ = +0.3 mmu).

2-(Diisopropylcarbamoyl)-6-methylphenyl Acetate (44c). To a stirred mixture of phenol **43** (275 mg, 1.17 mmol, 1.0 equiv) and iodine (29 mg, 0.12 mmol, 0.1 equiv) was added Ac_2O (132 μL, 1.40 mmol, 1.2 equiv), and the mixture was stirred in an ultrasonic bath at

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room temperature for 15 min. After completion of the reaction, the iodine was destroyed by adding a saturated solution of NaS_2O_3 (15 mL). Et_2O (10 mL) was added, and the phases were separated. The organic phase was washed with saturated $NaHCO_3$ solution (2 × 15 mL) and brine (2 × 15 mL), dried over $MgSO_4$, filtered, and concentrated to give the product **44c** in 88% yield as a white solid (285 mg, 1.03 mmol). TLC: R_f = 0.16 (petroleum ether/ethyl acetate 5/1). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.11 (6 H, d, J = 6.6 Hz), 1.53 (3 H, d, J = 6.0 Hz), 1.55 (3 H, d, J = 6.0 Hz), 2.19 (3 H, s), 2.28 (3 H, s), 3.48 (1 H, spt, J = 6.8 Hz), 3.78 (1 H, spt, J = 6.7 Hz), 7.02−7.09 (1 H, m), 7.15 (1 H, dd, J = 7.4 Hz), 7.19−7.25 (1 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 20.4, 20.5 (3 C), 20.9, 45.8, 50.9, 123.7, 125.9, 131.0, 131.7, 132.1, 145.5, 167.1, 168.5. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{16}H_{24}O_3N$, 278.1751; found, 278.1752 (Δ = +0.1 mmu). Mp: 71−73 °C.

2-(Allyloxy)-*N*,*N*-diisopropyl-3-methylbenzamide (44d). To an ice-cooled suspension of NaH (60% dispersion in mineral oil, 74.0 mg, 1.85 mmol, 1.40 equiv) in DMF (4 mL) was added dropwise a solution of phenol **43** (311 mg, 1.32 mmol, 1.0 equiv) in DMF (2 mL), and the resultant mixture was stirred for 1 h. Then allyl iodide (241 μL, 2.64 mmol, 2.00 equiv) was added and the mixture was stirred at room temperature for 3 h before EtOAc (10 mL) and H_2O (10 mL) were added. The mixture was extracted with 3 × 15 mL of EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 9/1 to 5/1) furnished allyl ether **44d** (352 mg, 1.28 mmol) in 97% yield as a white solid. TLC: R_f = 0.30 (petroleum ether/ethyl acetate 9/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.03 (3 H, d, J = 6.7 Hz), 1.18 (3 H, d, J = 6.6 Hz), 1.55 (3 H, d, J = 6.7 Hz), 1.56 (3 H, d, J = 6.6 Hz), 2.29 (3 H, s), 3.49 (1 H, spt, J = 6.8 Hz), 3.68 (1 H, spt, J = 6.7 Hz), 4.34 (1 H, ddt, J = 12.2 Hz, 5.5 Hz, 1.4 Hz), 4.57 (1 H, ddt, J = 12.2 Hz, 5.4 Hz, 1.4 Hz), 5.20 (1 H, dq, J = 10.5 Hz, 1.4 Hz), 5.38 (1 H, dq, J = 17.2 Hz, 1.7 Hz), 6.05 (1 H, ddt, J = 17.2 Hz, 10.6 Hz, 5.4 Hz), 6.91−7.08 (2 H, m), 7.10−7.22 (1 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.2, 20.2, 20.5, 20.7, 20.8, 45.6, 51.0, 74.6, 116.9, 124.2, 124.6, 131.0, 131.7, 133.4, 134.1, 152.9, 168.9. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{17}H_{26}O_2N$, 276.1958; found, 276.1957 (Δ = −0.1 mmu). Mp: 95−96 °C.

2-(Benzyloxy)-*N*,*N*-diisopropyl-3-methylbenzamide (44e). To an ice-cooled suspension of NaH (60% dispersion in mineral oil, 81.6 mg, 2.04 mmol, 1.60 equiv) in DMF (5 mL) was added dropwise a solution of phenol **43** (300 mg, 1.27 mmol, 1.0 equiv) in DMF (4 mL), and the resultant mixture was stirred for 0.5 h. BnBr (273 μL, 2.29 mmol, 1.80 equiv) was added, and the mixture was stirred at room temperature for 18 h before EtOAc (10 mL) and H_2O (10 mL) were added. The mixture was extracted with 3 × 10 mL of EtOAc, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 9/1) furnished benzyl ether **44e** (283 mg, 1.27 mmol, 68%) as a white solid. TLC: R_f = 0.30 (petroleum ether/ethyl acetate 5/1). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.03 (3 H, d, J = 6.9 Hz), 1.13 (3 H, d, J = 6.6 Hz), 1.57 (3 H, d, J = 6.9 Hz), 1.52 (3 H, d, J = 6.6 Hz), 2.29 (3 H, s), 3.49 (1 H, spt, J = 6.8 Hz), 3.71 (1 H, spt, J = 6.7 Hz), 4.87 (1 H, d, J = 11.0 Hz), 5.13 (1 H, d, J = 11.0 Hz), 7.04 (1 H, s), 7.06 (1 H, m), 7.15−7.20 (1 H, m), 7.26−7.39 (3 H, m), 7.43−7.46 (1 H, m), 7.47 (1 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 20.4, 20.6, 20.6, 20.7, 45.6, 51.0, 75.6, 124.2, 124.7, 127.7, 127.9 (2 C), 128.2 (2 C), 131.1, 131.8, 133.4, 137.7, 152.8, 169.0. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{21}H_{28}O_2N$, 326.2120; found, 326.2115 (Δ = −0.5 mmu). Mp: 84−86 °C.

(*S*)-*N*,*N*-Diisopropyl-2-((4-methoxybenzyl)oxy)-3-methyl-6-(*p*-tolylsulfinyl)benzamide (45a). The representative procedure given for **32** was carried out with amide **44a** (467 mg, 1.31 mmol, 1.0 equiv) to afford the white crystalline sulfoxide **45a** after flash column chromatography on silica gel (petroleum ether/ethyl acetate 5/1 to 1/1) in 78% yield (508 mg, 1.03 mmol). TLC: R_f = 0.43 (petroleum ether/ethyl acetate 3/1). $[\alpha]_D^{23}$ = −72.3 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): 0.98 (3 H, d, J = 6.7 Hz), 1.11 (3 H, d, J = 6.5 Hz), 1.55 (3 H, d, J = 6.5 Hz), 1.55 (3 H, d, J = 6.7 Hz), 2.22 (3 H, s), 3.48 (1 H, spt, J = 6.7 Hz), 3.68 (1 H, spt, J = 6.5 Hz), 3.80 (3 H, s), 3.82 (3 H, s), 4.77 (1 H, d, J = 10.6 Hz), 5.01 (1 H, d, J = 10.5 Hz), 6.83−6.97 (6 H, m), 7.11 (2 H, d, J = 8.0 Hz), 7.37 (2 H, d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 16.4, 20.4, 20.5, 20.6, 20.6, 40.2, 45.6, 50.9, 55.2, 75.4, 113.6 (2 C), 113.8 (2 C), 124.8, 129.8 (4 C), 129.9, 131.4, 131.8, 133.1, 133.2, 137.3, 151.0, 157.9, 159.2, 169.1. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{29}H_{36}O_4NS$, 494.2365; found, 494.2361 (Δ = −0.4 mmu). Mp: 112−113 °C.

(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-*N*,*N*-diisopropyl-3-methyl-6-(*p*-tolylsulfinyl)benzamide (45b). The representative procedure given for **32** was carried out with amide **44b** (471 mg, 1.35 mmol, 1.0 equiv) to afford the white crystalline sulfoxide **45b** after flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 3/1) in 85% yield (557 mg, 1.14 mmol). TLC: R_f = 0.34 (petroleum ether/ethyl acetate 3/1). $[\alpha]_D^{23}$ = −88.3 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): 0.11 (3 H, s), 0.30 (3 H, s), 1.02 (9 H, s), 1.18 (3 H, d, J = 6.6 Hz), 1.22 (3 H, d, J = 6.6 Hz), 1.60 (3 H, d, J = 6.6 Hz), 1.62 (3 H, d, J = 6.7 Hz), 2.25 (3 H, s), 2.34 (3 H, s), 3.61 (2 H, spt, J = 6.7 Hz), 7.20 (1 H, d, J = 8.0 Hz), 7.24 (2 H, m, J = 8.0 Hz), 7.31 (1 H, d, J = 8.0 Hz), 7.76 (2 H, m, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.7, −2.5, 18.3, 18.8, 20.0, 20.8, 21.0, 21.3, 21.6, 26.4 (3 C), 46.5, 51.2, 118.3, 124.4 (2 C), 129.6 (2 C), 130.3, 132.5, 132.6, 140.3, 142.4, 142.9, 148.8, 165.6. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{27}H_{42}O_3NSSi$, 488.2656; found, 488.2654 (Δ = −0.2 mmu). Mp: 88−89 °C.

(*S*)-2-(Allyloxy)-*N*,*N*-diisopropyl-3-methyl-6-(*p*-tolylsulfinyl)-benzamide (45d). The representative procedure given for **32** was carried out with amide **44d** (7.00 g, 21.8 mmol, 1.0 equiv) to afford the white crystalline sulfoxide **45d** after flash column chromatography on silica gel (petroleum ether/ethyl acetate 5/1 to 1/1) in 88% yield (7.90 g, 19.1 mmol). TLC: R_f = 0.15 (petroleum ether/ethyl acetate 3/1). $[\alpha]_D^{23}$ = −94.6 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (3 H, d, J = 7.3 Hz), 1.25 (3 H, d, J = 7.4 Hz), 1.61 (3 H, d, J = 6.9 Hz), 1.64 (3 H, d, J = 6.9 Hz), 2.29 (3 H, s), 2.35 (3 H, s), 3.60 (1 H, spt, J = 6.9 Hz), 3.76 (1 H, spt, J = 6.7 Hz), 4.32 (1 H, ddt, J = 12.1 Hz, 5.5 Hz, 1.4 Hz), 4.57 (1 H, ddt, J = 12.1 Hz, 5.5 Hz, 1.4 Hz), 5.22 (1 H, dq, J = 10.4 Hz, 1.4 Hz), 5.38 (1 H, dq, J = 17.3 Hz, 1.6 Hz), 6.03 (1 H, ddt, J = 17.1 Hz, 10.6 Hz, 5.5 Hz), 7.16−7.29 (3 H, m), 7.45 (1 H, d, J = 8.0 Hz), 7.73 (2 H, d, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.4, 20.2, 20.4, 20.6, 21.0, 21.3, 46.2, 51.7, 74.9, 117.3, 120.7, 124.5 (2 C), 129.7 (2 C), 132.3, 132.4, 133.5, 135.4, 140.7, 142.1, 142.2, 152.2, 165.3. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{24}H_{32}O_3NS$, 414.2097; found, 414.2099 (Δ = +0.2 mmu). Mp: 99−102 °C.

(*S*)-2-(Benzyloxy)-*N*,*N*-diisopropyl-3-methyl-6-(*p*-tolylsulfinyl)benzamide (45e). The representative procedure given for **32** was carried out with amide **44e** (200 mg, 614 μmol, 1.0 equiv) to afford the white crystalline sulfoxide **45e** after flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 5/1) in 82% yield (233 mg, 504 μmol). TLC: R_f = 0.16 (petroleum ether/ethyl acetate 5/1). $[\alpha]_D^{23}$ = −56.6° (c 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 300 MHz): 1.09 (3 H, d, J = 6.6 Hz), 1.17 (3 H, d, J = 6.6 Hz), 1.45 (3 H, d, J = 6.9 Hz), 1.56 (3 H, d, J = 6.9 Hz), 2.21 (3 H, s), 2.30 (3 H, s), 3.51 (1 H, spt, J = 6.8 Hz), 3.70 (1 H, spt, J = 6.7 Hz), 4.78 (1 H, d, J = 10.7 Hz), 5.05 (1 H, d, J = 10.7 Hz), 7.17−7.23 (3 H, m), 7.24−7.32 (3 H, m), 7.33−7.38 (2 H, m), 7.40 (1 H, d, J = 8.0 Hz), 7.68 (2 H, d, J = 8.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.6, 20.2, 20.5, 20.7, 20.9, 21.4, 46.3, 51.8, 75.9, 120.8, 124.5 (2 C), 127.9 (2 C), 128.0, 128.3 (2 C), 129.8 (2 C), 132.4, 132.5, 135.5, 137.1, 140.7, 142.2, 142.2, 152.1, 165.4. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{28}H_{34}O_3NS$, 464.2254; found, 464.2256 (Δ = +0.2 mmu). Mp: 101−103 °C.

(*R*)-6-(1-Hydroxyallyl)-*N*,*N*-diisopropyl-2-methoxy-3-methylbenzamide (46f). A representative procedure for the asymmetric ortho lithiation with acrolein is as follows. A solution of *tert*-BuLi (1.7 M in pentane, 1.59 mL, 2.71 mmol, 3.0 equiv) was added dropwise to a stirred solution of sulfoxide **32** (350 mg, 0.90 mmol, 1.0 equiv) in dry THF (13 mL, 0.07 M) at −90 °C (acetone/liquid nitrogen). After 5 min dry acrolein (362 μL, 5.42 mmol, 6.0 equiv) was added dropwise within 5 min. The mixture was warmed to −78 °C and stirred for 0.5 h at this temperature. Then an aqueous solution of

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NH_4Cl (40 mL) was added at −78 °C and the mixture was warmed to room temperature. Extraction with 3 × 50 mL of Et_2O, drying over $MgSO_4$, filtration, and evaporation of the solvent gave a residue which was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 5/1 to 2/1) to afford the ortho-lithiation product **46f** (202 mg, 0.66 mmol) in 73% yield as a colorless oil. TLC: R_f = 0.41 (petroleum ether/ethyl acetate 2/1). $[\alpha]_D^{23}$ = +116.6 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): 1.03 (3 H, d, *J* = 6.6 Hz), 1.22 (3 H, d, *J* = 6.6 Hz), 1.61 (3 H, d, *J* = 6.7 Hz), 1.60 (3 H, d, *J* = 6.8 Hz), 2.27 (3 H, s), 3.55 (1 H, spt, *J* = 6.8 Hz), 3.70 (1 H, spt, *J* = 6.7 Hz), 3.75 (3 H, s), 5.15 (1 H, dt, *J* = 4.7, 1.6 Hz), 5.31 (1 H, dt, *J* = 10.4, 1.6 Hz), 5.47 (1 H, dt, *J* = 17.1, 1.7 Hz), 6.08 (1 H, ddd, *J* = 17.2, 10.6, 4.8 Hz), 7.10 (1 H, d, *J* = 7.8 Hz), 7.16 (1 H, d, *J* = 7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.7, 20.1, 20.3, 20.6, 20.9, 46.0, 51.6, 61.0, 70.9, 115.6, 122.9, 130.8, 131.3, 132.0, 137.5, 139.2, 153.7, 168.8. HRMS (ESI-TOF, arginine): calculated for $[M + Na]^+$ = $C_{18}H_{27}O_3NNa$, 328.1883; found, 328.1886 (Δ = +0.3 mmu).

(*R*)-6-(1-Hydroxyallyl)-*N*,*N*-diisopropyl-2-((4-methoxybenzyl)oxy)-3-methylbenzamide (46a). The representative procedure given for **46f** was carried out with sulfoxide **45a** (200 mg, 409 μmol, 1.0 equiv) to afford the colorless oil **46a** after flash column chromatography on silica gel (petroleum ether/ethyl acetate 5/1 to 3/1) in 71% yield (119 mg, 289 μmol). TLC: R_f = 0.29 (petroleum ether/ethyl acetate 3/1). $[\alpha]_D^{23}$ = +96.6 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): 1.19 (3 H, d, *J* = 6.0 Hz), 1.21 (3 H, d, *J* = 5.8 Hz), 1.61 (3 H, d, *J* = 6.9 Hz), 1.68 (3 H, d, *J* = 6.9 Hz), 2.36 (3 H, s), 3.60 (1 H, spt, *J* = 6.8 Hz), 3.79 (1 H, spt, *J* = 6.7 Hz), 3.92 (3 H, s), 4.84 (1 H, d, *J* = 10.7 Hz), 5.07 (1 H, d, *J* = 10.7 Hz), 5.21−5.31 (2 H, m), 5.47−5.56 (1 H, m), 6.13−6.30 (1 H, m), 6.95−7.02 (2 H, m), 7.22−7.31 (2 H, m), 7.43−7.50 (2 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.0, 19.9, 20.2, 20.3, 20.4, 45.6, 51.1, 55.0, 72.6, 75.2, 113.4 (2 C), 113.5, 123.0, 129.3 (2 C), 129.5, 130.6, 131.0, 131.3, 138.7, 140.2, 152.6, 159.0, 168.0. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{25}H_{34}O_4N$, 412.2488; found, 412.2484 (Δ = −0.4 mmu).

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-(1-hydroxyallyl)-*N*,*N*-diisopropyl-3-methylbenzamide (46b). The representative procedure given for **46f** was carried out with sulfoxide **45b** (200 mg, 409 μmol, 1.0 equiv) to afford the colorless oil **46b** after flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 3/1) in 39% yield (64 mg, 157 μmol). TLC: R_f = 0.32 (petroleum ether/ethyl acetate 3/1). $[\alpha]_D^{23}$ = +123.6 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): 0.08 (3 H, s), 0.26 (3 H, s), 0.94 (3 H, d, *J* = 6.6 Hz), 1.03 (9 H, s), 1.24 (3 H, d, *J* = 6.9 Hz), 1.59 (6 H, d, *J* = 6.9 Hz), 2.24 (3 H, s), 3.54 (1 H, spt, *J* = 6.7 Hz), 3.62 (1 H, spt, *J* = 6.6 Hz), 5.06−5.15 (1 H, m), 5.34 (1 H, dt, *J* = 10.7, 1.6 Hz), 5.50 (1 H, dt, *J* = 17.1, 1.7 Hz), 6.10 (1 H, ddd, *J* = 17.2, 10.6, 4.8 Hz), 6.99 (1 H, d, *J* = 7.7 Hz), 7.12 (1 H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.1, −2.5, 17.9, 18.8, 20.3, 20.5, 20.7, 21.4, 26.5 (3 C), 46.3, 51.0, 70.6, 115.6, 120.7, 128.9, 130.4, 131.3, 137.2, 139.2, 149.1, 169.7. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{23}H_{40}O_3NSi$, 406.2772; found, 406.2773 (Δ = +0.1 mmu).

(*R*)-2-(Allyloxy)-6-(1-hydroxyallyl)-*N*,*N*-diisopropyl-3-methylbenzamide (46d). The representative procedure given for **46f** was carried out with sulfoxide **45d** (5.01 g, 12.1 mmol, 1.0 equiv) to afford the colorless oil **46d** after flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 3/1) in 92% yield (3.71 g, 11.1 mmol). TLC: R_f = 0.33 (petroleum ether/ethyl acetate 3/1). $[\alpha]_D^{23}$ = +144.4 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.02 (3 H, d, *J* = 6.9 Hz), 1.23 (2 H, d, *J* = 6.9 Hz), 1.57 (3 H, d, *J* = 6.9 Hz), 1.60 (3 H, d, *J* = 6.9 Hz), 2.27 (3 H, s), 3.54 (1 H, spt, *J* = 6.9 Hz), 3.72 (1 H, spt, *J* = 6.8 Hz), 3.84 (1 H, br s), 4.29 (1 H, ddt, *J* = 12.3, 5.5, 1.4 Hz), 4.47 (1 H, ddt, *J* = 12.3, 5.7, 1.4 Hz), 5.15 (1 H, d, *J* = 4.1 Hz), 5.21 (1 H, dd, *J* = 10.4, 1.4 Hz), 5.32 (1 H, dt, *J* = 10.7, 1.6 Hz), 5.34−5.39 (1 H, m), 5.48 (1 H, dt, *J* = 17.3, 1.6 Hz), 5.89−6.06 (1 H, m), 6.06−6.13 (1 H, m), 7.11 (1 H, d, *J* = 8.0 Hz), 7.17 (1 H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.0, 20.1, 20.3, 20.5, 20.8, 46.0, 51.5, 70.8, 74.6, 115.7, 117.2, 123.0, 131.0, 131.3, 132.2, 133.8, 137.4, 139.1, 152.5, 168.9. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{20}H_{30}O_3N$, 332.2220; found, 332.2222 (Δ = +0.2 mmu).

(*R*)-2-(Benzyloxy)-6-(1-hydroxyallyl)-*N*,*N*-diisopropyl-3-methylbenzamide (46e). The representative procedure given for **46f** was carried out with sulfoxide **45e** (77 mg, 166 μmol, 1.0 equiv) to afford the colorless oil **46e** after flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 3/1) in 68% yield (43 mg, 112 μmol). TLC: R_f = 0.27 (petroleum ether/ethyl acetate 3/1). $[\alpha]_D^{23}$ = +124.4 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): 1.01 (3 H, d, *J* = 6.8 Hz), 1.14 (3 H, d, *J* = 6.6 Hz), 1.47 (3 H, d, *J* = 6.8 Hz), 1.59 (3 H, d, *J* = 7.0 Hz), 1.72 (1 H, br s), 2.26 (3 H, s), 3.50 (1 H, spt, *J* = 6.8 Hz), 3.72 (1 H, spt, *J* = 6.8 Hz), 4.83 (1 H, d, *J* = 11.2 Hz), 4.99 (1 H, d, *J* = 11.2 Hz), 5.14−5.19 (1 H, m), 5.32 (1 H, dt, *J* = 10.6, 1.7 Hz), 5.48 (1 H, dt, *J* = 17.2, 1.7 Hz), 6.09 (1 H, ddd, *J* = 17.1, 10.6, 4.8 Hz), 7.15−7.21 (2 H, m), 7.28−7.39 (3 H, m), 7.40−7.45 (2 H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 16.0, 20.0, 20.2, 20.3, 20.4, 45.6, 51.1, 70.5, 75.2, 113.3, 123.0, 129.3 (2 C), 129.5, 130.6 (2 C), 131.0, 131.3, 131.9, 138.7, 138.9, 140.2, 152.6, 168.0. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{24}H_{32}O_3N$, 382.2382; found, 382.2387 (Δ = +0.5 mmu).

(*R*)-2-(Allyloxy)-6-(1-((*tert*-butyldimethylsilyl)oxy)allyl)-*N*,*N*-diisopropyl-3-methylbenzamide (47a). To an ice-cooled solution of alcohol **46d** (2.80 g, 8.45 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL) were added 2,6-lutidine (3.92 mL, 33.8 mmol, 4.0 equiv) and TBSOTf (3.88 mL, 16.9 mmol, 2.0 equiv). The resulting mixture was warmed to room temperature and stirred overnight (14 h), and then water (50 mL) was added followed by extraction with 3 × 50 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 30/1) afforded 89% of silyl-protected alcohol **47a** (3.35 g, 7.51 mmol) as a colorless liquid. TLC: R_f = 0.32 (petroleum ether/ethyl acetate 30/1). $[\alpha]_D^{23}$ = +109.6 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ −0.08 (3 H, s), 0.09 (3 H, s), 0.89 (9 H, s), 1.04 (3 H, d, *J* = 6.6 Hz), 1.18 (3 H, d, *J* = 6.6 Hz), 1.57 (3 H, d, *J* = 6.4 Hz), 1.59 (3 H, d, *J* = 6.4 Hz), 2.26 (3 H, s), 3.48 (1 H, spt, *J* = 6.5 Hz), 3.57 (1 H, spt, *J* = 6.6 Hz), 4.25 (1 H, dd, *J* = 12.2, 5.4 Hz), 4.54 (1 H, dd, *J* = 12.3, 5.4 Hz), 5.05 (1 H, d, *J* = 10.2 Hz), 5.18 (1 H, d, *J* = 10.5 Hz), 5.23−5.40 (3 H, m), 5.79−5.95 (1 H, m), 5.95−6.11 (1 H, m), 7.15 (1 H, d, *J* = 8.0 Hz), 7.21 (1 H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.2, −4.9, 15.9, 18.1, 20.3, 20.5, 20.8, 21.1, 25.9 (3 C), 45.8, 50.9, 70.8, 74.7, 113.6, 116.8, 123.3, 129.9, 130.8, 131.0, 134.1, 139.5, 141.1, 152.4, 167.5. HRMS (ESI-TOF, arginine): calculated for $[M + Na]^+$ = $C_{26}H_{43}O_3NSiNa$, 468.2910; found, 468.2913 (Δ = +0.3 mmu).

(*R*)-6-(1-((*tert*-Butyldimethylsilyl)oxy)allyl)-2-hydroxy-*N*,*N*-diisopropyl-3-methylbenzamide (47b). Allyl ether **47a** (3.0 g, 6.73 mmol, 1.0 equiv) was dissolved in dry MeOH (70 mL), followed by the addition of $[Pd(Ph_3)_4]$ (77.1 mg, 67.3 μmol, 1 mol %). After the mixture was stirred for 10 min at room temperature, K_2CO_3 (2.79 g, 20.2 mmol, 3.0 equiv) was added to the resulting yellow solution and stirring was continued for 3 h until TLC control indicated complete consumption of the starting material. Then the solvent was evaporated under reduced pressure and the resulting slurry was resolved in water (50 mL), acidified with a solution of HCl (1 N) to pH 5, and extracted with 3 × 50 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford phenol **47b** (2.73 g, 6.73 mmol) in quantitative yield as a pale yellow solid. TLC: R_f = 0.26 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +40.1 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ −0.02 (3 H, s), 0.09 (3 H, s), 0.91 (9 H, s), 1.21−1.51 (12 H, m), 2.13 (3 H, s), 3.63 (2 H, spt, *J* = 6.6 Hz), 5.03 (1 H, d, *J* = 10.2 Hz), 5.16 (1 H, d, *J* = 5.1 Hz), 5.28 (1 H, d, *J* = 16.9 Hz), 5.64 (1 H, br s), 5.94 (1 H, ddd, *J* = 16.9, 10.2, 5.3 Hz), 6.91−7.10 (2 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.8 (2 C), 15.7, 18.2, 20.8 (4 C), 25.8 (3 C), 48.6 (2 C), 72.1, 113.6, 118.7, 124.0, 128.4, 130.6, 138.7, 141.2, 149.5, 168.3. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{23}H_{40}O_3NSi$, 406.2778; found, 406.2779 (Δ = +0.1 mmu).

Methyl (*R*)-6-(1-((*tert*-Butyldimethylsilyl)oxy)allyl)-2-hydroxy-3-methylbenzoate (47). To a solution of *N*,*N*-diisopropylamide **47b** (500 mg, 1.23 mmol, 1.0 equiv) and 2,6-DTBMP (1.01 g, 4.03 mmol, 3.25 equiv) in CH_2Cl_2 (15 mL) was added MeOTf (305 μL, 2.47 mmol, 2.0 equiv) dropwise. The mixture was then refluxed for

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6 h, cooled to room temperature, and treated with a saturated solution of $NaHCO_3$ (20 mL). The resulting mixture was stirred for 14 h and then extracted with 3 × 30 mL of EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. After purification by flash column chromatography on silica gel (petroleum ether/ethyl acetate 30/1) ester **47** (261 mg, 776 μmol) was obtained in 62% yield as a colorless liquid. TLC: R_f = 0.48 (petroleum ether/ethyl acetate 30/1). $[\alpha]_D^{23}$ = +74.2 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ −0.01 (3 H, s), 0.06 (3 H, s), 0.92 (9 H, s), 2.25 (3 H, s), 3.97 (3 H, s), 4.92−5.06 (1 H, m), 5.17−5.28 (1 H, m), 5.83−5.98 (1 H, m), 5.99−6.03 (1 H, m), 7.20 (1 H, d, *J* = 8.0 Hz), 7.30 (1 H, d, *J* = 8.0 Hz), 11.10 (1 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.9 (2 C), 16.0, 18.4, 25.9 (3 C), 52.1, 71.8, 109.5, 112.5, 117.8, 125.2, 135.5, 141.4, 144.1, 159.8, 171.6. HRMS (ESI-TOF, arginine): calculated for $[M + Na]^+ = C_{18}H_{28}O_4SiNa$, 359.1654; found, 359.1653 (Δ = −0.1 mmu).

Methyl (*R*)-6-(1-((*tert*-Butyldimethylsilyl)oxy)allyl)-2-((4-methoxybenzyl)oxy)-3-methylbenzoate (47c). To an ice-cooled suspension of NaH (60% dispersion in mineral oil, 70.0 mg, 482 μmol, 1.40 equiv) in DMF (12 mL) was added dropwise a solution of phenol **47** (421 mg, 1.25 mmol, 1.0 equiv) in DMF (4 mL), and the resultant mixture was stirred for 30 min. PMBCl (270 μL, 2.0 mmol, 1.60 equiv) was added, and the mixture was heated to 60 °C for 18 h, before it was cooled to room temperature. Then CH_2Cl_2 (10 mL) and H_2O (10 mL) were added, and the mixture was extracted with 3 × 25 mL of CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 50/1 to 15/1) furnished PMB ether **47c** (533 mg, 1.17 mmol, 93%) as a colorless liquid. TLC: R_f = 0.24 (petroleum ether/ethyl acetate 30/1). $[\alpha]_D^{23}$ = +40.1 (*c* 1.0, $CHCl_3$): ^1H NMR ($CDCl_3$, 300 MHz): δ −0.01 (3 H, s), 0.07 (3 H, s), 0.91 (9 H, s), 2.31 (3 H, s), 3.83 (3 H, s), 3.83 (3 H, s), 4.85 (2 H, s), 5.03 (1 H, dt, *J* = 10.3, 1.3 Hz), 5.16−5.36 (2 H, m), 5.95 (1 H, ddd, *J* = 17.3, 10.3, 5.0 Hz), 6.92 (2 H, d, *J* = 8.8 Hz), 7.24 (2 H, s), 7.36 (2 H, d, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.1, −5.0, 16.1, 18.3, 25.8 (3 C), 52.0, 55.3, 72.9, 75.7, 113.1, 113.8 (2 C), 122.2, 126.6, 129.5, 129.6 (2 C), 130.3, 132.6, 140.4, 141.0, 153.6, 159.5, 168.5. HRMS (ESI-TOF, arginine): calculated for $[M + Na]^+ = C_{26}H_{36}O_5SiNa$, 479.2229; found, 479.2227 (Δ = −0.2 mmu).

Methyl (*S*)-6-(1-((*tert*-Butyldimethylsilyl)oxy)-2-oxoethyl)-2-((4-methoxybenzyl)oxy)-3-methylbenzoate (48). To a solution of alkene **47c** (105 mg, 229 μmol, 1.0 equiv) in CH_2Cl_2 (10 mL) were added 3 drops of a solution of Sudan III in CH_2Cl_2 (0.05 M), and the mixture was cooled to −78 °C. Then a stream of O_3 was blown through the reaction flask until the mixture changed from red to colorless (1.5 min), followed by the addition of Me_2S (337 μL, 4.6 mmol, 20 equiv). The mixture was warmed to room temperature within 1 h, stirred for an additional 3 h, and filtered through a small pad of Celite to give crude aldehyde **48** (95.0 mg, 207 μmol, 89%) as a colorless liquid which was used in the next reaction without further purification. TLC: R_f = 0.18 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +30.4 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.01 (3 H, s), 0.11 (3 H, s), 0.92 (9 H, s), 2.31 (3 H, s), 3.83 (3 H, s), 3.83 (3 H, s), 4.80 (1 H, d, *J* = 10.5 Hz), 4.92 (1 H, d, *J* = 10.6 Hz), 5.06 (1 H, s), 6.91 (2 H, m, *J* = 8.7 Hz), 7.13 (1 H, d, *J* = 8.0 Hz), 7.28 (1 H, d, *J* = 8.0 Hz), 7.35 (2 H, m, *J* = 8.7 Hz), 9.60 (1 H, d, *J* = 1.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.1, −5.0, 16.3, 18.3, 25.7 (3 C), 52.2, 55.3, 75.9, 78.7, 113.8 (2 C), 123.7, 127.0, 129.2, 129.6 (2 C), 132.6, 132.8, 134.7, 154.9, 159.6, 167.8, 199.4. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{25}H_{35}O_6Si$, 459.2202; found, 459.2203 (Δ = +0.1 mmu).

(1*S*,2*S*,3*S*)-2-((*tert*-Butyldimethylsilyl)oxy)-1-(3-((4-methoxybenzyl)oxy)-4-methyl-2-((methylperoxy)-λ$_2$-methyl)-phenyl)-3-methylpent-4-en-1-ol (49). A solution of (*E*,*S*,*S*)-crotylboronate **50** in dry toluene (1.0 M, 455 μL, 2.2 equiv) was treated with powdered 4 Å molecular sieves (25 mg) and was then cooled to −78 °C. A solution of aldehyde **48** in toluene (95 mg, 207 μmol, 1.0 equiv, dried by coevaporation of dry toluene) was then added dropwise within 15 min. The reaction mixture was stirred at −78 °C for 3 h and then was treated with a saturated solution of $NaHCO_3$ (5 mL) to hydrolyze the borane. The two-phase mixture was warmed to room temperature and stirred for 1 h before being filtered through a glass filter. The aqueous layer was extracted with 3 × 15 mL of Et_2O, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 15/1 to 9/1) to yield 95% of **49** (101 mg, 196 μmol) as a colorless liquid. TLC: R_f = 0.30 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +32.1 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ −0.18 (3 H, s), 0.07 (3 H, s), 0.90 (9 H, s), 1.05 (3 H, d, *J* = 6.9 Hz), 2.26 (1 H, sxt, *J* = 7.0 Hz), 2.32 (3 H, s), 2.58 (1 H, d, *J* = 5.8 Hz), 3.42−3.54 (1 H, m), 3.82 (3 H, s), 3.83 (3 H, s), 4.73 (1 H, d, *J* = 4.7 Hz), 4.80 (1 H, d, *J* = 10.3 Hz), 4.86 (1 H, d, *J* = 10.3 Hz), 5.00−5.13 (2 H, m), 5.92 (1 H, ddd, *J* = 17.2, 10.6, 7.7 Hz), 6.91 (2 H, m, *J* = 8.8 Hz), 7.18−7.25 (2 H, m), 7.34 (2 H, m, *J* = 8.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.3, −4.6, 16.2, 17.6, 18.1, 25.9 (3 C), 39.9, 52.2, 55.3, 75.8, 77.2, 78.7, 113.8 (2 C), 115.1, 123.7, 127.3, 129.3, 129.6 (2 C), 130.9, 132.2, 138.7, 140.2, 153.7, 159.5, 168.4. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{29}H_{43}O_6Si$, 515.2828; found, 515.2833 (Δ = +0.5 mmu).

(*S*)-3-((1*S*,2*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylbut-3-en-1-yl)-7-((4-methoxybenzyl)oxy)-6-methylisobenzofuran-1(3*H*)-one (54). Ester **49** (60 mg, 116 μmol, 1.0 equiv) was dissolved in THF (2 mL) and treated with a solution of NaOH (2.0 M, 2.91 mL, 50 equiv) at room temperature. After 0.5 h water was added (2 mL) and the reaction mixture was extracted with 3 × 5 mL of Et_2O. The combined organic layers were dried over $MgSO_4$, filtered off, and concentrated under reduced pressure to give **54** (55 mg, 114 μmol) in 99% yield as a clourless liquid without further purification. TLC: R_f = 0.43 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = −11.8 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ −0.17 (3 H, s), 0.06 (3 H, s), 0.82 (9 H, s), 1.14 (3 H, d, *J* = 7.0 Hz), 2.24 (3 H, s), 2.48−2.59 (1 H, m), 3.83 (3 H, s), 3.97 (1 H, dd, *J* = 4.3, 3.2 Hz), 4.92−5.05 (2 H, m), 5.10 (1 H, d, *J* = 10.5 Hz), 5.30 (1 H, d, *J* = 10.5 Hz), 5.37 (1 H, d, *J* = 3.2 Hz), 5.85 (1 H, ddd, *J* = 17.4, 10.2, 7.7 Hz), 6.91 (2 H, m, *J* = 8.7 Hz), 7.10 (1 H, d, *J* = 7.6 Hz), 7.41 (1 H, d, *J* = 7.7 Hz), 7.46 (2 H, m, *J* = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.8, −4.6, 16.0, 16.5, 18.1, 25.7 (3 C), 41.4, 55.3, 76.5, 76.5, 80.4, 113.8 (2 C), 115.2, 117.4, 118.6, 129.5, 130.4 (2 C), 132.2, 136.8, 139.8, 148.3, 156.1, 159.6, 168.4. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{28}H_{39}O_5Si$, 483.2561; found, 483.2570 (Δ = +0.9 mmu).

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-(1-((*tert*-butyldimethylsilyl)oxy)allyl)-*N*,*N*-diisopropyl-3-methylbenzamide (55). The procedure described above for TBS protection of **46d** was carried out with alcohol **46b** (500 mg, 1.23 mmol, 1.0 equiv) to yield the bis-TBS-protected alcohol **55** (594 mg, 1.23 mmol, 93%) as a colorless oil after flash column chromatography on silica gel (petroleum ether/ethyl acetate 15/1). TLC: R_f = 0.33 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +58.3 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ −0.10 (3 H, s), 0.05 (3 H, s), 0.09 (3 H, s), 0.29 (3 H, s), 0.85 (9 H, s), 0.97 (3 H, d, *J* = 6.6 Hz), 1.02 (9 H, s), 1.17 (3 H, d, *J* = 6.6 Hz), 1.53 (3 H, d, *J* = 6.9 Hz), 1.61 (3 H, d, *J* = 6.9 Hz), 2.23 (3 H, s), 3.29−3.47 (1 H, m), 3.47−3.59 (1 H, m), 4.96−5.10 (1 H, m), 5.25−5.39 (2 H, m), 5.81−5.99 (1 H, m), 7.09 (2 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.1, −5.0, −4.2, −2.2, 18.1, 18.2, 18.9, 20.4, 20.9, 21.4, 21.7, 25.9 (3 C), 26.6 (3 C), 45.9, 50.4, 70.5, 113.2, 121.4, 127.4, 128.7, 130.8, 139.8, 141.3, 148.9, 167.5. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{29}H_{54}O_3NSi_2$, 520.3642; found, 520.3638 (Δ = −0.4 mmu).

2-((*tert*-Butyldimethylsilyl)oxy)-6-((1*S*,2*S*,3*S*)-1-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-3-methylpent-4-en-1-yl)-*N*,*N*-diisopropyl-3-methylbenzamide (57). The procedure described above for ozonolysis of **47c** was carried out with alkene **55** (500 mg, 0.96 mmol, 1.0 equiv) to yield the corresponding aldehyde **55a** as a colorless liquid, which was immediately used in the following crotylboration without further purification.

For crotylboration of **55a**, the aldehyde was dissolved in CH_2Cl_2 (5 mL) and water (5 mL) and treated with potassium (2-butenyl)-trifluoroborate **52** (311 mg, 1.92 mmol, 2.0 equiv) and TBAI (35.4 mg, 96 μmol, 0.1 equiv). The reaction mixture was then stirred

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vigorously at room temperature for 1 h and finally diluted with CH_2Cl_2 (15 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 5/1) to yield 84% of **57** (465 mg, 0.80 mmol) over two steps as a colorless oil. TLC: R_f = 0.33 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +39.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.27 (3 H, s), 0.01 (3 H, s), 0.13 (3 H, s), 0.28 (3 H, s), 0.87 (9 H, s), 0.98 (3 H, d, *J* = 6.6 Hz), 1.02 (9 H, s), 1.08 (3 H, d, *J* = 6.9 Hz), 1.19 (3 H, d, *J* = 6.8 Hz), 1.56 (3 H, d, *J* = 6.9 Hz), 1.61 (3 H, d, *J* = 6.9 Hz), 2.23 (3 H, s), 2.41 (1 H, q, *J* = 7.0 Hz), 2.48 (1 H, d, *J* = 9.3 Hz), 3.24 (1 H, dd, *J* = 9.1, 6.3 Hz), 3.44 (1 H, spt, *J* = 6.7 Hz), 3.52 (1 H, spt, *J* = 6.9 Hz), 5.01 (1 H, s), 5.02−5.13 (2 H, m), 5.84−6.03 (1 H, m), 7.10 (1 H, d, *J* = 8.0 Hz), 7.27 (1 H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.0, −4.9, −4.3, −2.2, 17.2, 18.0, 18.1, 18.9, 20.9, 21.0, 21.0, 21.6, 26.0 (3 C), 26.6 (3 C), 43.1, 46.0, 50.5, 69.7, 77.6, 114.9, 122.3, 128.0, 128.3, 130.6, 138.9, 140.4, 148.9, 167.6. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{32}H_{60}O_4NSi_2$, 578.4061; found, 578.4046 (Δ = +1.5 mmu).

(3*S*,4*S*)-3-((*S*)-But-3-en-2-yl)-4-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-7-methylisochroman-1-one (*syn,anti*-42). To a solution of the bis-TBS-protected alcohol **78** (90 mg, 155 μmol, 1.0 equiv) in THF (5 mL) was added TBAF (1 M in THF, 171 μL, 171 μmol, 1.1 equiv) at 0 °C. The mixture was then stirred at this temperature for 3 h before water (10 mL) was added. The phases were separated, and the aqueous phase was extracted with 3 × 15 mL of EtOAc, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography on silica gel (petroleum ether/ethyl acetate 12/1 to 5/1) afforded the corresponding phenol **41** (68 mg, 147 μmol) in 94% yield as a colorless oil.

To a solution of this phenol **41** and solid Na_2HPO_4 (30.3 mg, 213 μmol, 1.5 equiv) in MeCN (2 mL) was added Me_3OBF_4 (63.2 mg, 356 μmol, 3.0 equiv). The mixture was then stirred for 5 h at room temperature until complete consumption of the starting material and treated with a saturated solution of $NaHCO_3$ (2 mL). The resulting mixture was stirred for 14 h at room temperature and then extracted with 3 × 10 mL of EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. After purification by flash column chromatography on silica gel (petroleum ether/ethyl acetate 30/1 to 15/1) isochromanone *syn,anti*-**42** (19.6 mg, 54.1 μmol) was obtained in 39% yield as a colorless oil. TLC: R_f = 0.33 (petroleum ether/ethyl acetate 15/1). $[\alpha]_D^{23}$ = +14.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.21 (3 H, s), 0.03 (3 H, s), 0.80 (9 H, s), 1.14 (3 H, d, *J* = 7.2 Hz), 2.29 (3 H, s), 2.47−2.64 (1 H, m), 3.90 (1 H, t, *J* = 3.9 Hz), 5.00−5.12 (2 H, m), 5.42 (1 H, d, *J* = 3.6 Hz), 5.80−5.93 (1 H, m), 6.87 (1 H, d, *J* = 7.7 Hz), 7.36 (1 H, d, *J* = 8.0 Hz), 7.90 (1 H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.9, −4.7, 14.5, 15.7, 25.7 (3 C), 30.4, 41.5, 76.6, 82.6, 113.7, 115.6, 125.1, 127.6, 136.3, 139.5, 145.7, 160.3, 169.4. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{20}H_{31}O_4Si$, 363.1991; found, 363.1992 (Δ = +0.1 mmu).

(2*R*,3*S*)-3-(((4-Methoxybenzyl)oxy)methyl)oxirane-2-carbaldehyde (17a). To an ice-cooled suspension of NaH (60% dispersion in mineral oil, 1.40 g, 35 mmol, 0.55 equiv) in DMF (25 mL) was added dropwise a solution of (*E*)-but-2-en-1,4-diole **81** (5.60 g, 63.6 mmol, 1.0 equiv) in DMF (5 mL), and the resultant mixture was stirred for 40 min. PMBCl (5.78 mL, 41.3 mmol, 0.65 equiv) was added, and the mixture was stirred at 0 °C for 20 min before it was warmed to room temperature. After the mixture was stirred at this temperature for 14 h, EtOAc (100 mL) and H_2O (100 mL) were added, the mixture was extracted with 3 × 50 mL of EtOAc, and the organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate 15/1 to 9/1) furnished mono-PMB-protected **81a** (8.66 g, 41.6 mmol, 65%) as a colorless liquid.

To a flask containing freshly activated MS (4 Å) and CH_2Cl_2 (80 mL) was added L-(+)-diisopropyl tartrate (0.71 mL, 4.16 mmol, 0.1 equiv), and the mixture was cooled to −20 °C before Ti(O-*i*-Pr)$_4$ (0.86 mL, 2.91 mmol, 0.07 equiv) and *t*-BuOOH (~5.5 M in decane, 15.1 mL, 83.2 mmol, 2.0 equiv) were added successively. The mixture was stirred vigorously for 30 min before a solution of allylic alcohol **81a** (8.66 g, 41.6 mmol, 1.0 equiv) in CH_2Cl_2 (80 mL) was added dropwise. The reaction mixture was then stirred at −20 °C for 32 h before it was quenched by addition of an aqueous solution of $FeSO_4$ and citric acid. After the mixture was stirred for 15 min, an aqueous solution of NaOH (1 M, 15 mL) was added and stirring was continued at 0 °C for 1 h before the phases were separated and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, the solvent was removed in vacuo, and the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1) to afford epoxy alcohol **81b** as a colorless oil (7.56 g, 33.7 mmol, 81%).

The obtained epoxide **81c** was resolved (2.0 g, 8.92 mmol, 1.0 equiv) in CH_2Cl_2 (100 mL) and cooled to 0 °C, and Dess−Martin periodinane (7.57 g, 17.8 mmol, 2.0 equiv) was added in three portions over a period of 10 min. The white slurry was stirred at this temperature for 4 h. Silica gel was added, and the solvent was evaporated. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 15/1 to 9/1) afforded 71% of aldehyde **17a** (1.41 g, 6.34 mmol) as a colorless liquid. $[\alpha]_D^{23}$ = +22.3 (*c* 1.0, $CHCl_3$). TLC: R_f = 0.23 (petroleum ether/ethyl acetate 15/1). ^{1}H NMR ($CDCl_3$, 300 MHz): 3.33 (1 H, dd, *J* = 6.3, 1.9 Hz), 3.43−3.48 (1 H, m), 3.50−3.60 (1 H, m), 3.76−3.85 (1 H, m), 3.82 (3 H, s), 4.47−4.58 (2 H, m), 6.80−6.95 (2 H, m), 7.21−7.36 (2 H, m), 9.05 (1 H, d, *J* = 6.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.2, 55.3, 56.3, 68.0, 73.2, 113.9 (2 C), 129.4, 129.5, 141.5, 159.4, 197.5. HRMS (EI-TOF): calculated for $[M]^+$ = $C_{12}H_{14}O_4$, 222.0892; found, 222.0903 (Δ = +1.1 mmu).

(2*R*,3*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)oxirane-2-carbaldehyde (17b). (*E*)-But-2-en-1,4-diole (3.50 g, 39.7 mmol, 1.0 equiv) was dissolved in DMF (15 mL), and imidazole (2.65 g, 38.9 mmol, 0.98 equiv) was added at 0 °C, followed by the addition of TBSCl (6.00 g, 39.7 mmol, 1.0 equiv). The resulting mixture was stirred at this temperature for 4 h before it was warmed to room temperature, and stirring was continued for an additional 14 h. The reaction mixture was then treated with water (30 mL) and extracted with 3 × 30 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 30/1) afforded 74% of mono-TBS-protected **81d** (5.96 g, 29.45 mmol) as a colorless oil.

The procedure described above for asymmetric epoxidation of **81a** was carried out with allyl alcohol **81d** (5.00 g, 24.7 mmol, 1.0 equiv) to yield the corresponding epoxide **81e** (3.98 g, 18.23 mmol, 74%) after flash column chromatography on silica gel (petroleum ether/ethyl acetate 15/1).

Epoxy alcohol **81e** (1.50 g, 6.87 mmol, 1.0 equiv) was then oxidized with Dess−Martin periodinane in the same way described above for compound **81c** to yield aldehyde **17b** (1.12 g, 5.18 mmol, 75%) after flash column chromatography on silica gel (petroleum ether/ethyl acetate 30/1) as a colorless liquid. TLC: R_f = 0.28 (petroleum ether/ethyl acetate 30/1). $[\alpha]_D^{23}$ = +28.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.06 (3 H, s), 0.08 (3 H, s), 0.89 (9 H, s), 3.32−3.42 (2 H, m), 3.78 (1 H, dd, *J* = 12.2, 3.8 Hz), 3.99 (1 H, dd, *J* = 12.4, 2.2 Hz), 9.07 (1 H, d, *J* = 6.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.5, −5.5, 18.2, 25.7 (3 C), 56.1, 56.6, 61.3, 198.0. HRMS (EI-TOF): calculated for $[M]^+$ = $C_{10}H_{20}O_3Si$, 216.1181; found, 216.1199 (Δ = +1.8 mmu).

(*E*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-enal (58). A solution of SO_3·Py (3.15 g, 19.7 mmol, 2.0 equiv) in DMSO (10 mL) was added to a solution of alcohol **81d** (2.00 g, 9.88 mmol, 1.0 equiv) and Et_3N (4.1 mL, 29.6 mmol, 3.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C. After it was stirred at 0 °C for 4 h, the reaction mixture was added to a mixture of brine (50 mL) at 0 °C and the aqueous layer was extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (petroleum ether/ethyl acetate 60/1) gave **58** (1.65 g, 8.24 mmol) in 83% yield. TLC: R_f = 0.29 (petroleum ether/ethyl acetate 60/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.10 (6 H, s), 0.93 (9 H, s), 4.46 (2 H, dd, *J* = 3.3, 2.2 Hz), 6.41 (1 H, ddt, *J* = 15.4, 8.0, 2.2, 2.2 Hz), 6.89 (1

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H, dt, J = 15.4, 3.3 Hz), 9.61 (1 H, d, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.5 (2 C), 18.3, 25.8 (2 C), 62.2, 130.6, 156.5, 193.4. HRMS (EI-TOF): calculated for $[M]^+$ = $C_{10}H_{20}O_2Si$, 200.1232; found, 200.1254 (Δ = +2.2 mmu).

2-(Allyloxy)-6-((*S*)-((*tert*-butyldimethylsilyl)oxy)((2*R*,3*S*)-3-(((4-methoxybenzyl)oxy)methyl)oxiran-2-yl)methyl)-*N*,*N*-diisopropyl-3-methylbenzamide (60). The procedure for asymmetric ortholithiation of **37** was carried out with epoxy aldehyd **17a** (322 mg, 1.45 mmol, 3.0 equiv), sulfoxide **45d** (200 mg, 0.48 mmol, 1.0 equiv), and *tert*-BuLi (1.7 M in pentane, 0.57 mL, 0.97 mmol, 2.0 equiv). After flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 5/1) the corresponding epoxy alcohol **59** (149 mg, 0.30 mmol) was obtained in 62% as a colorless oil.

To an ice-cooled solution of **59** (111 mg, 0.23 mmol, 1.0 equiv) in DMF (1 mL) were added 2,6-lutidine (103 μL, 0.89 mmol, 4.0 equiv) and TBSOTf (102 μL, 0.45 mmol, 2.0 equiv). The resulting mixture was stirred at 0 °C for 1 h and warmed to room temperature, and stirring was continued for an additional 3 h. Subsequently, the reaction was worked up with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with 3 × 15 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1) afforded 74% of silyl ether **60** (101 mg, 0.17 mmol) as a colorless oil. TLC: R_f = 0.31 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +89.3 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.11 (3 H, s), 0.09 (3 H, s), 0.85 (9 H, s), 1.06 (3 H, d, J = 6.6 Hz), 1.19 (3 H, d, J = 6.3 Hz), 1.57 (3 H, d, J = 6.7 Hz), 1.58 (3 H, d, J = 6.7 Hz), 2.28 (3 H, s), 2.85 (1 H, dd, J = 2.9, 1.8 Hz), 3.42−3.46 (2 H, m), 3.46−3.52 (1 H, m), 3.57−3.66 (1 H, m), 3.67−3.76 (1 H, m), 3.80 (3 H, s), 4.25 (1 H, ddt, J = 12.3, 5.5, 1.4, 1.4 Hz), 4.41−4.49 (2 H, m), 4.50−4.56 (1 H, m), 4.83 (1 H, d, J = 2.8 Hz), 5.18 (1 H, dq, J = 10.5, 1.4 Hz), 5.35 (1 H, dq, J = 17.3, 1.7 Hz), 6.03 (1 H, ddt, J = 17.2, 10.6, 5.5, 5.5 Hz), 6.81−6.88 (2 H, m), 7.15−7.19 (2 H, m), 7.19−7.23 (2 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.4, −4.5, 16.0, 18.0, 20.3, 20.6, 20.9, 21.0, 25.8 (3 C), 45.9, 51.0, 53.8, 55.2, 59.1, 67.9, 69.6, 72.8, 74.7, 113.7 (2 C), 116.9, 123.3, 129.3 (2 C), 130.1, 130.8, 131.0, 131.8, 133.9, 137.3, 152.5, 159.2, 167.3. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{35}H_{54}NO_6Si$, 612.3720; found, 612.3706 (Δ = −1.4 mmu).

2-(Allyloxy)-6-((2*R*,3*R*)-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-1-oxobutan-2-yl)-*N*,*N*-diisopropyl-3-methylbenzamide (62). The procedure for asymmetric ortho lithiation of **37** was carried out with epoxy aldehyde **17b** (1.04 g, 4.81 mmol, 2.75 equiv), sulfoxide **45d** (723 mg, 1.75 mmol, 1.0 equiv), and *tert*-BuLi (1.7 M in pentane, 2.57 mL, 4.38 mmol, 2.5 equiv). After flash column chromatography on silica gel (petroleum ether/ethyl acetate 12/1 to 5/1) aldehyde **62** (662 mg, 1.35 mmol) was obtained in 78% as a colorless oil. TLC: R_f = 0.44 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +56.2 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.03 (3 H, s), 0.04 (3 H, s), 0.87 (9 H, s), 1.07 (3 H, d, J = 6.6 Hz), 1.17 (3 H, d, J = 6.6 Hz), 1.55 (3 H, d, J = 6.9 Hz), 1.55 (3 H, d, J = 6.8 Hz), 2.29 (3 H, s), 2.43 (1 H, d, J = 5.8 Hz), 3.20−3.25 (1 H, m), 3.50 (1 H, spt, J = 6.8 Hz), 3.57−3.70 (2 H, m), 3.93 (1 H, dd, J = 12.2, 2.3 Hz), 4.29 (1 H, ddt, J = 12.2, 5.5, 1.4, 1.4 Hz), 4.48 (1 H, d, J = 5.2 Hz), 4.53 (1 H, ddt, J = 12.3, 5.5, 1.4, 1.4 Hz), 5.20 (1 H, dq, J = 10.5, 1.5 Hz), 5.37 (1 H, dq, J = 17.1, 1.7 Hz), 6.04 (1 H, ddt, J = 17.1, 10.6, 5.4, 5.4 Hz), 7.18−7.23 (1 H, m), 7.28 (1 H, d, J = 8.0 Hz), 9.09 (1 H, d, J = 6.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.4 (2 C), 16.0, 18.3, 20.3, 20.5, 20.6, 25.8 (3 C), 32.3, 45.7, 51.3, 58.8, 62.5, 70.2, 74.6, 116.8, 122.3, 131.2, 131.4, 132.2, 133.9, 135.8, 152.6, 167.4, 198.1. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{27}H_{46}NO_5Si$, 492.3145; found, 492.3129 (Δ = −1.6 mmu).

(*R*,*E*)-2-(Allyloxy)-6-(1-((*tert*-butyldimethylsilyl)oxy)-4-hydroxybut-2-en-1-yl)-*N*,*N*-diisopropyl-3-methylbenzamide (63). The procedure for asymmetric ortho lithiation of **37** was carried out with aldehyde **58** (350 mg, 1.75 mmol, 2.5 equiv), sulfoxide **45d** (289 mg, 0.70 mmol, 1.0 equiv), and *tert*-BuLi (1.7 M in pentane, 0.82 mL, 1.40 mmol, 2.0 equiv). After flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 5/1) alcohol **58a** (317 mg, 0.66 mmol) was obtained in 95% as a colorless oil.

TBS protection of the generated alcohol **58a** (170 mg, 0.35 mmol, 1.0 equiv) was then performed as described above for compound **59** to yield bis-TBS-protected **58b** (197 mg, 0.33 mmol) in 93% yield as a colorless oil.

To an ice-cooled solution of bis-TBS-protected **58b** (89 mg, 0.15 mmol, 1.0 equiv) in THF (5 mL) was added TBAF (1 M in THF, 165 μL, 0.16 mmol, 1.1 equiv). The mixture was stirred at this temperature for 4 h before water (10 mL) was added, and the aqueous phase was extracted with 3 × 15 mL of EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1 to 5/1) afforded compound **63** (60.3 mg, 0.13 mmol) in 84% yield as a colorless oil. TLC: R_f = 0.49 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +38.6 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.10 (3 H, s), 0.09 (3 H, s), 0.89 (9 H, s), 1.05 (3 H, d, J = 6.6 Hz), 1.19 (3 H, d, J = 6.6 Hz), 1.57 (3 H, d, J = 6.8 Hz), 1.59 (3 H, d, J = 6.7 Hz), 2.26 (3 H, s), 3.48 (1 H, spt, J = 6.9 Hz), 3.59 (1 H, spt, J = 6.6 Hz), 4.06−4.19 (2 H, m), 4.19−4.29 (1 H, m), 4.53 (1 H, ddt, J = 12.3, 5.6, 1.4, 1.4 Hz), 5.18 (1 H, dd, J = 10.6, 1.5 Hz), 5.28 (1 H, s), 5.35 (1 H, dq, J = 17.1, 1.7 Hz), 5.72−5.94 (2 H, m), 6.03 (1 H, ddt, J = 17.2, 10.7, 5.5, 5.5 Hz), 7.15 (1 H, d, J = 7.8 Hz), 7.19 (1 H, d, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.2, −4.8, 16.0, 18.2, 20.3, 20.6, 20.8, 21.1, 25.9 (3 C), 45.8, 50.8, 63.1, 69.9, 74.7, 116.8, 123.5, 128.1, 130.0, 130.9, 130.9, 134.0, 134.6, 139.5, 152.4, 167.4. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{27}H_{46}NO_4Si$, 476.3196; found, 476.3194 (Δ = −0.2 mmu).

2-(Allyloxy)-6-((1*S*,2*R*,3*R*)-2-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-3-methylpent-4-en-1-yl)-*N*,*N*-diisopropyl-3-methylbenzamide (66). The procedure described for the asymmetric ortholithiation of **37** was carried out with aldehyde **35** (440 mg, 1.93 mmol, 1.0 equiv), sulfoxide **45d** (1.57 g, 3.85 mmol, 2.0 equiv), and *tert*-BuLi (1.7 M in pentane, 2.83 mL, 1.93 mmol, 2.5 equiv), yielding after flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1) 61% of the alcohol **66** (591 mg, 1.17 mmol) as a colorless liquid. TLC: R_f = 0.26 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +63.2 (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.46 (3 H, s), 0.10 (3 H, s), 0.77 (9 H, s), 1.06 (3 H, d, J = 6.6 Hz), 1.17 (3 H, d, J = 7.2 Hz), 1.22 (3 H, d, J = 6.6 Hz), 1.55 (3 H, d, J = 6.8 Hz), 1.56 (3 H, d, J = 6.9 Hz), 2.27 (3 H, s), 2.51 (1 H, br s), 2.72−2.85 (1 H, m), 3.51 (1 H, spt, J = 6.8 Hz), 3.75 (1 H, spt, J = 6.7 Hz), 4.21 (1 H, dd, J = 8.9, 2.1 Hz), 4.27 (1 H, dt, J = 5.4, 1.5 Hz), 4.43 (1 H, d, J = 9.1 Hz), 4.40−4.51 (1 H, m), 4.99−5.07 (1 H, m), 5.07−5.16 (1 H, m), 5.20 (1 H, dq, J = 10.5, 1.4 Hz), 5.37 (1 H, dq, J = 17.2, 1.7 Hz), 5.95−6.12 (2 H, m), 7.14 (2 H, br s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.5, −4.4, 15.9, 16.1, 18.5, 20.2, 20.3, 20.4, 20.8, 26.2 (3 C), 41.5, 45.8, 51.5, 72.7, 74.4, 76.6, 114.7, 116.9, 123.7, 130.5, 130.7, 133.4, 134.0, 138.4, 140.8, 152.6, 168.9. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{29}H_{50}O_4SiN$, 504.3509; found, 504.3501 (Δ = −0.8 mmu).

2-(Allyloxy)-6-((1*S*,2*R*,3*R*)-1,2-dihydroxy-3-methylpent-4-en-1-yl)-*N*,*N*-diisopropyl-3-methylbenzamide (67). To a solution of TBS-protected alcohol **66** (250.0 mg, 496 μmol, 1.0 equiv) in DMF (3 mL) and H_2O (89 μL, 4.96 mmol, 10 equiv) was added tris(dimethylamino)sulfoniumdifluorotrimethyl silicate (TAS-F, 1.5 M in DMF, 1.65 mL, 2.48 mmol, 5.0 equiv). After it was stirred overnight (14 h), the reaction mixture was then diluted with Et_2O (5 mL) and washed with pH 7 buffer (3 × 5 mL). The aqueous layer was extracted with 3 × 15 mL of Et_2O, and the combined organic layers were washed again with pH 7 buffer (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 93% of **67** (179 mg, 459 μmol). TLC: R_f = 0.17 (petroleum ether/ethyl acetate 3/1). $[\alpha]_D^{23}$ = +16.7 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.04 (3 H, d, J = 6.6 Hz), 1.14 (3 H, d, J = 7.2 Hz), 1.21 (3 H, d, J = 6.6 Hz), 1.55 (6 H, d, J = 6.9 Hz), 2.03 (1 H, br s), 2.28 (3 H, s), 2.73−2.92 (1 H, m), 3.43 (1 H, br s), 3.52 (1 H, spt, J = 6.9 Hz), 3.71 (1 H, spt, J = 6.6 Hz), 3.84−4.01 (1 H, m), 4.23−4.33 (1 H, m), 4.41 (1 H, d, J = 8.8 Hz), 4.44−4.55 (1 H, m), 5.06−5.18 (2 H, m), 5.18−5.25 (1 H, m), 5.32−5.41 (1 H, m), 5.81−5.94 (1 H, m), 6.04 (1 H, ddt, J = 17.3, 10.6, 5.4 Hz), 7.21 (2 H, s). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.0, 17.4, 20.1, 20.3, 20.4, 20.5, 39.0, 45.9, 51.7, 71.8, 74.5, 75.3, 116.3, 117.1, 122.5,

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131.1, 131.5, 133.8, 133.8, 137.6, 138.8, 152.8, 168.9. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{23}H_{36}O_4N$, 390.2644; found, 390.2661 (Δ = +1.5 mmu).

2-(Allyloxy)-6-((5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-*N*,*N*-diisopropyl-3-methylbenzamide (69). To a solution of alcohol **67** (170 mg, 463 μmol, 1.0 equiv) in dry CH_2Cl_2 (10 mL) were added 2,6-lutidine (136 μL, 1.18 mmol, 2.7 equiv) and, after cooling to −78 °C, TBSOTf (130 μL, 567 μmol, 1.3 equiv). The resulting mixture was stirred for 1.5 h at −78 °C, for 1 h at −20 °C, and for 1 h at 0 °C before water (10 mL) was added followed by extraction with 3 × 20 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 15/1 to 9/1) afforded 53% of bis-silyl-protected alcohol **69** (143 mg, 231 μmol) and 10% of the mono-silyl-protected alcohol **68** (21.4 mg, 42.5 μmol) as a byproduct. TLC: R_f = 0.61 (petroleum ether/ethyl acetate 15/1). $[\alpha]_D^{23}$ = +16.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.37 (3 H, s), 0.03 (3 H, s), 0.10 (3 H, s), 0.11 (3 H, s), 0.81 (9 H, s), 0.84 (9 H, s), 1.09−1.19 (9 H, m), 1.56 (6 H, d, *J* = 6.7 Hz), 2.27 (3 H, s), 2.81 (1 H, quin, *J* = 7.5 Hz), 3.43−3.56 (1 H, m), 3.74−3.85 (2 H, m), 4.13−4.23 (1 H, m), 4.49−4.58 (2 H, m), 4.97−5.07 (2 H, m), 5.17 (1 H, dd, *J* = 10.5, 1.7 Hz), 5.35 (1 H, dq, *J* = 17.2, 1.7 Hz), 5.89−6.13 (2 H, m), 7.06−7.25 (2 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.4, −5.1, −2.9, −2.2, 16.0, 18.0, 19.2, 20.3, 20.6, 20.6, 21.0, 21.6, 25.7 (3 C), 26.0 (3 C), 27.1, 45.7, 50.6, 74.5, 74.6, 77.2, 116.3, 116.6, 130.1, 130.4, 130.6, 134.2 (2 C), 138.7, 143.1, 152.9, 167.3. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{35}H_{64}O_4NSi_2$, 618.4373; found, 618.4363 (Δ = −1.0 mmu).

(2*R*,3*R*)-Ethyl 3-Methyl-2-((triethylsilyl)oxy)pent-4-enoate (*anti*-33b). To an ice-cooled solution of the ester **33a** (4.6 g, 29.1 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL) were added 2,6-lutidine (8.45 mL, 72.9 mmol, 2.5 equiv) and TESOTf (8.22 mL, 36.4 mmol, 1.25 equiv). The resulting mixture was stirred at room temperature for 3 h until TLC control indicated complete consumption of the starting material. The reaction mixture was quenched with water (80 mL) and extracted with 3 × 50 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 50/1 to 30/1) afforded 99% of silyl ether *anti*-**33b** (7.85 g, 28.8 mmol) as a colorless liquid. TLC: R_f = 0.60 (petroleum ether/ethyl acetate 30/1). $[\alpha]_D^{23}$ = +10.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.63 (6 H, m), 0.96 (9 H, t, *J* = 7.8 Hz), 1.06 (3 H, d, *J* = 7.0 Hz), 1.27 (3 H, t, *J* = 7.2 Hz), 2.52−2.68 (1 H, m), 4.08 (1 H, d, *J* = 4.9 Hz), 4.17 (2 H, qd, *J* = 7.0 Hz, 2.4 Hz), 4.95−5.08 (2 H, m), 5.73−5.93 (1 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 4.6 (3 C), 6.7 (3 C), 14.3, 16.4, 42.7, 60.5, 76.1, 115.3, 139.0, 172.8. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{14}H_{29}O_3Si$, 273.1881; found, 273.1880 (Δ = −0.1 mmu).

(2*R*,3*R*)-3-Methyl-2-((triethylsilyl)oxy)pent-4-enal (70). The procedure described below for DIBAl-H reduction of **34a** was carried out with **33b** (1.70 g, 5.93 mmol, 1.0 equiv) and gave alcohol **33c** (1.43 g, 5.91 mmol) in nearly quantitative yield as a colorless liquid. TLC: R_f = 0.41 (petroleum ether/ethyl acetate 9/1).

The procedure described above for the Swern oxidation of **35** was carried out with alcohol **33c** (1.17 g, 5.08 mmol, 1.0 equiv) and yielded after flash column chromatography on silica gel (petroleum ether/ethyl acetate 40/1 to 9/1) 82% of the TES-protected aldehyde **70** (948 mg, 4.15 mmol) as a colorless liquid. TLC: R_f = 0.46 (petroleum ether/ethyl acetate 30/1). $[\alpha]_D^{23}$ = +27.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.63 (6 H, q, *J* = 7.9 Hz), 0.97 (9 H, t, *J* = 7.9 Hz), 1.10 (3 H, d, *J* = 6.9 Hz), 2.50−2.72 (1 H, m), 3.86 (1 H, dd, *J* = 4.5, 2.2 Hz), 4.91−5.27 (2 H, m), 5.65−6.00 (1 H, m), 9.57 (1 H, d, *J* = 2.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 4.8 (3 C), 6.7 (3 C), 16.0, 41.7, 80.9, 115.9, 138.3, 204.4. HRMS (ESI-TOF, arginine): calculated for $[M + Na]^+ = C_{12}H_{24}O_2SiNa$, 251.1443; found, 251.1440 (Δ = −0.3 mmu).

2-(Allyloxy)-6-((1*S*,2*R*,3*R*)-1-hydroxy-3-methyl-2-((triethylsilyl)oxy)pent-4-en-1-yl)-*N*,*N*-diisopropyl-3-methylbenzamide (71). A solution of ^{t}BuLi (1.7 M in pentane, 3.90 mL, 6.63 mmol, 1.4 equiv) was added dropwise to a stirred solution of sulfoxide **45d** (1.96 g, 4.73 mmol, 1.0 equiv) in dry THF (40 mL) at −90 °C (acetone/liquid nitrogen). After 5 min the TES-protected aldehyde **70** (2.0 g, 5.76 mmol, 1.85 equiv) in THF (5 mL) was added dropwise within 4 min. The mixture was warmed to −78 °C and stirred for 20 min at this temperature. Then an aqueous solution of NH_4Cl (40 mL) was added at −78 °C, and the mixture was warmed to room temperature. Extraction with 3 × 30 mL of Et_2O, drying over $MgSO_4$, and evaporation of the solvent gave a residue which was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 15/1 to 9/1 to 5/1) to afford the ortho-lithiation product **71** (1.69, 3.35 mmol) in 71% yield as a colorless oil. TLC: R_f = 0.25 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +61.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.38−0.52 (6 H, m), 0.70−0.86 (9 H, m), 1.06 (3 H, d, *J* = 6.6 Hz), 1.16 (3 H, d, *J* = 7.2 Hz), 1.22 (3 H, d, *J* = 6.6 Hz), 1.55 (3 H, d, *J* = 6.8 Hz), 1.56 (3 H, d, *J* = 6.3 Hz), 2.27 (3 H, s), 2.74−2.86 (1 H, m), 3.51 (1 H, spt, *J* = 6.8 Hz), 3.77 (1 H, spt, *J* = 6.6 Hz), 4.18 (1 H, dd, *J* = 9.2, 1.9 Hz), 4.22−4.31 (1 H, m), 4.40 (1 H, d, *J* = 9.2 Hz), 4.43−4.51 (1 H, m), 5.02 (1 H, dd, *J* = 10.2, 2.1 Hz), 5.12 (1 H, dd, *J* = 17.4, 1.3 Hz), 5.20 (1 H, dd, *J* = 10.5, 1.5 Hz), 5.37 (1 H, dd, *J* = 17.2, 1.7 Hz), 5.86−6.00 (1 H, m), 6.00−6.12 (1 H, m), 7.09−7.22 (2 H, m). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 6.4 (3 C), 6.8 (3 C), 16.0, 17.4, 20.1, 20.3, 20.4, 20.5, 38.9, 46.0, 51.8, 71.7, 74.5, 75.2, 116.5, 117.1, 121.8, 122.4, 131.2, 131.6, 133.8, 137.5, 138.7, 152.8, 168.9. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{29}H_{50}O_4NSi$, 504.3509; found, 504.3498 (Δ = −1.1 mmu).

2-(Allyloxy)-6-((5*S*,6*R*)-6-((*R*)-but-3-en-2-yl)-8,8-diethyl-2,2,3,3-tetramethyl-4,7-dioxa-3,8-disiladecan-5-yl)-*N*,*N*-diisopropyl-3-methylbenzamide (71a). The procedure described above for the TBS protection of **69** was carried out with alcohol **71** (950 mg, 1.89 mmol, 1.0 equiv) and yielded after flash column chromatography on silica gel (petroleum ether/ethyl acetate 50/1 to 15/1) 74% of the TBS-protected aldehyde **71a** (863 mg, 1.39 mmol) as a colorless oil. TLC: R_f = 0.27 (petroleum ether/ethyl acetate 30/1). $[\alpha]_D^{23}$ = +13.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.36 (3 H, s), 0.11 (3 H, s), 0.22−0.48 (6 H, m), 0.75 (9 H, t, *J* = 7.9 Hz), 0.83 (9 H, s), 1.12 (3 H, d, *J* = 6.8 Hz), 1.14 (3 H, d, *J* = 7.1 Hz), 1.15 (3 H, d, *J* = 7.3 Hz), 1.55 (3 H, d, *J* = 6.8 Hz), 1.56 (3 H, d, *J* = 7.0 Hz), 2.26 (3 H, s), 2.80 (1 H, quin, *J* = 7.6 Hz), 3.49 (1 H, spt, *J* = 6.8 Hz), 3.79 (1 H, dd, *J* = 8.9, 1.3 Hz), 3.80 (1 H, spt, *J* = 6.6 Hz), 4.18 (1 H, ddt, *J* = 12.4, 5.5, 1.5 Hz), 4.40 (1 H, d, *J* = 8.8 Hz), 4.55 (1 H, ddt, *J* = 12.4, 5.4, 1.4 Hz), 4.98−5.09 (2 H, m), 5.17 (1 H, dd, *J* = 10.5, 1.7 Hz), 5.36 (1 H, dq, *J* = 17.2, 1.6 Hz), 5.87 (1 H, ddd, *J* = 17.3, 10.1, 9.1 Hz), 6.03 (1 H, ddt, *J* = 17.2, 10.6, 5.4 Hz), 7.09 (1 H, d, *J* = 8.0 Hz), 7.14 (1 H, d, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.4, −5.1, 5.4, 6.8, 16.0, 18.0, 19.1, 19.9, 20.3, 20.5, 20.9, 25.9, 41.0, 45.7, 50.7, 71.3, 74.6, 81.0, 115.3, 116.5, 123.6, 129.9, 130.3, 133.7, 134.2, 138.8, 140.3, 152.7, 169.2. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+ = C_{35}H_{64}O_4NSi_2$, 618.4368; found, 618.4374 (Δ = +0.6 mmu).

6-((1*S*,2*R*,3*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-hydroxy-3-methylpent-4-en-1-yl)-2-hydroxy-*N*,*N*-diisopropyl-3-methylbenzamide (41). Allyl ether **71a** (450 mg, 0.72 mmol, 1.0 equiv) was dissolved in dry MeOH (30 mL), followed by the addition of $[Pd(Ph_3)_4]$ (8.40 mg, 7.28 μmol, 1 mol %). After the mixture was stirred for 10 min at room temperature, K_2CO_3 (302 mg, 2.18 mmol, 3.0 equiv) was added to the resulting yellow solution and stirring was continued for 4 h until TLC control indicated complete consumption of the starting material. Then the solvent was evaporated under reduced pressure and the resulting slurry was resolved in water (50 mL), acidified with a solution of HCl (1 N) to pH 6, and extracted with 3 × 20 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to afford phenol **71b** (420 mg, 0.72 mmol) in quantitative yield as a pale yellow solid.

TBS-TES-protected diol **71b** (335 mg, 579 μmol, 1.0 equiv) was dissolved in dry MeOH (20 mL) and treated with Pd on activated charcoal (10% Pd, 123 mg, 115 μmol, 0.2 equiv). After 4 h TLC indicated the cleavage of the TES group and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in Et_2O and filtered over a plug of Celite to afford in 99% yield the TBS-protected alcohol **41** (266 mg, 573 μmol) as a colorless

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liquid, which was used in the microwave assisted amide cleavage without further purification. TLC: R_f = 0.12 (petroleum ether/ethyl acetate 9/1). $[\alpha]_D^{23}$ = +17.0 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ −0.34 (3 H, s), 0.02 (3 H, s), 0.92 (9 H, s), 1.07 (3 H, d, *J* = 6.0 Hz), 1.13 (3 H, d, *J* = 6.9 Hz), 1.28 (3 H, d, *J* = 6.3 Hz), 1.54 (3 H, d, *J* = 6.9 Hz), 1.56 (1 H, br s), 1.57 (3 H, d, *J* = 6.9 Hz), 2.08 (3 H, s), 2.65 (1 H, quin, *J* = 7.3 Hz), 3.21 (1 H, d, *J* = 7.7 Hz), 3.52 (1 H, spt, *J* = 6.5 Hz), 3.76 (1 H, spt, *J* = 6.5 Hz), 4.41 (1 H, d, *J* = 8.5 Hz), 5.00−5.09 (2 H, m), 5.88−6.07 (1 H, m), 6.44 (1 H, br s), 7.03 (d, *J* = 8.00 Hz, 1 H), 7.06 (d, *J* = 7.90 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.9, −3.7, 16.0, 17.9, 19.0, 20.4, 20.7, 21.1, 21.9, 25.7 (3 C), 40.7, 46.7, 51.0, 72.2, 80.8, 115.2, 118.7, 123.9, 131.2, 131.9, 139.9, 140.3, 149.3, 168.7. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{26}H_{46}O_4NSi$, 464.3191; found, 464.3188 (Δ = −0.3 mmu).

(3*R*,4*S*)-3-((*R*)-but-3-en-2-yl)-4-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-7-methylisochroman-1-one (*anti,anti*-42). Compound **71b** (439 mg, 759 μmol, 1.0 equiv) was dissolved in dry toluene (6 mL) and placed in a septum-sealed microwave vessel, and acetic acid (99.9%, 0.97 mL, 30 equiv) was added. The resulting mixture was heated to 150 °C in a microwave reactor (ca. 60 W continuous power) for 3.5 h. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 30/1) to yield 86% of the TBS-protected hydroxyisochromanone *anti,anti*-**42** (237 mg, 654 μmol) as a colorless oil. TLC: R_f = 0.33 (petroleum ether/ethyl acetate 30/1). $[\alpha]_D^{23}$ = +69.1 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 600 MHz): δ 0.00 (3 H, s), 0.14 (3 H, s), 0.87 (9 H, s), 1.08 (3 H, d, *J* = 6.9 Hz), 2.28 (3 H, s), 2.41 (1 H, sxt, *J* = 6.8 Hz), 4.40 (1 H, dd, *J* = 7.2, 3.6 Hz), 4.73 (1 H, d, *J* = 3.6 Hz), 5.03 (1 H, d, *J* = 17.2 Hz), 5.08 (1 H, d, *J* = 10.4 Hz), 5.83 (1 H, ddd, *J* = 17.4, 10.2, 7.5 Hz), 6.73 (1 H, d, *J* = 7.5 Hz), 7.35 (1 H, d, *J* = 7.5 Hz), 11.28 (1 H, s). ^{13}C NMR ($CDCl_3$, 151 MHz): δ −4.3, −4.2, 15.7, 17.0, 18.1, 25.7 (3 C), 39.1, 66.7, 88.0, 106.8, 116.5, 117.2, 127.0, 136.8, 137.4, 137.9, 160.0, 168.5 HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{20}H_{31}O_4Si$, 363.1986; found, 363.2000 (Δ = +1.4 mmu).

(3*R*,4*S*)-3-((*R*)-But-3-en-2-yl)-4,8-bis((*tert*-butyldimethylsilyl)-oxy)-7-methylisochroman-1-one (72). To an ice-cooled solution of isochromanone *anti,anti*-**42** (150 mg, 398 μmol, 1.0 equiv) in dry CH_2Cl_2 (3 mL) were added NEt_3 (131 μL, 1.63 mmol, 4.0 equiv) and TBSOTf (186 μL, 0.82 mmol, 2.0 equiv). The resulting mixture was stirred at room temperature overnight (15 h, and then water (10 mL) was added followed by extraction with 3 × 5 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography on silica gel (petroleum ether/ethyl acetate 60/1 to 30/1) afforded 97% of bis-silyl ether **72** (185 mg, 385 μmol) as a colorless liquid. TLC: R_f = 0.29 (petroleum ether/ethyl acetate 30/1). $[\alpha]_D^{23}$ = +55.2 (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.02 (3 H, s), 0.14 (3 H, s), 0.15 (3 H, s), 0.17 (3 H, s), 0.88 (9 H, s), 1.04 (9 H, s), 1.08 (3 H, d, *J* = 7.0 Hz), 2.27 (3 H, s), 2.34−2.48 (1 H, m), 4.20 (1 H, dd, *J* = 7.1, 4.7 Hz), 4.70 (1 H, d, *J* = 4.8 Hz), 5.01−5.13 (2 H, m), 5.97 (1 H, ddd, *J* = 17.3, 10.5, 7.1 Hz), 6.87 (1 H, d, *J* = 7.7 Hz), 7.34 (1 H, d, *J* = 7.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.2, −4.1, −3.5, −3.4, 17.1, 17.6, 18.1, 18.6, 25.7 (3 C), 26.0 (3 C), 38.2, 67.6, 86.2, 115.9, 116.1, 119.1, 131.6, 135.6, 138.5, 139.4, 154.7, 161.8. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{26}H_{45}O_4Si_2$, 477.2851; found, 477.2855 (Δ = +0.4 mmu).

Allyl 2-(Allyloxy)-3-methylbenzoate (29c). 3-Methylsalicylic acid (**29**; 12.0 g, 78.8 mmol) was dissolved in DMF (160 mL) and cooled to 0 °C, and NaH (60% in mineral oil, 7.57 g, 189 mmol, 2.4 equiv) was added in three portions over a period of 20 min. The reaction mixture was stirred at this temperature for 1.5 h before allyl bromide (18.8 mL, 236 mmol, 3.0 equiv) was added dropwise. After complete conversion of the starting material (1.5 h), water (200 mL) and Et_2O (100 mL) were added. The organic layer was separated, and the aqueous layer was extracted with 3 × 150 mL of Et_2O. The combined organic phases were washed with brine (2 × 100 mL) and were dried over $MgSO_4$, filtered, and evaporated to give a yellow liquid of crude **29c** in quantitative yield (18.3 g, 78.9 mmol). TLC: R_f = 0.62 (petroleum ether/ethyl acetate 15/1). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.32 (3 H, s), 4.45 (2 H, dt, *J* = 5.6 Hz, 1.4 Hz), 4.81 (2 H, dt, *J* = 5.8 Hz, 1.4 Hz), 5.22−5.32 (2 H, m), 5.35−5.46 (2 H, m), 5.91−6.24 (2 H, m), 7.06 (1 H, dd, *J* = 7.6 Hz), 7.35 (1 H, d, *J* = 7.0 Hz), 7.67 (1 H, d, *J* = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 16.3, 65.7, 75.0, 117.5, 118.5, 123.6, 125.0, 129.1, 132.2, 133.0, 133.9, 135.1, 157.1, 166.1. HRMS (EI-TOF): calculated for $[M]^+$ = $C_{14}H_{16}O_3$, 232.1099; found, 232.1122 (Δ = +2.3 mmu).

2-(Allyloxy)-3-methylbenzoic Acid (73). To ester **29c** (18.0 g, 77.5 mmol, 1.0 equiv) was added methanol (300 mL) followed by aqueous sodium hydroxide (6 M, 78 mL, 465 mmol, 6.0 equiv), and the mixture was heated under reflux for 4 h. The solvent was then removed under reduced pressure to leave a dense white residue. This was dissolved in water (150 mL), and the solution was acidified to pH 3 with aqueous sulfuric acid (2 N) and extracted with 3 × 100 mL of Et_2O. The combined organic extracts were washed with water (100 mL), dried with $MgSO_4$, and concentrated under reduced pressure to provide the product **73** as a white solid in quantitative yield (14.9 g, 77.5 mmol). TLC: R_f = 0.42 (petroleum ether/ethyl acetate 9/1). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.39 (3 H, s), 4.53 (2 H, dt, *J* = 5.9 Hz, 1.2 Hz), 5.39 (1 H, dd, *J* = 10.6 Hz, 1.1 Hz), 5.48 (1 H, dq, *J* = 17.2, 1.3 Hz), 6.15 (1 H, ddt, *J* = 16.9 Hz, 10.6 Hz, 6.0 Hz), 7.19 (1 H, dd, *J* = 7.7 Hz), 7.46 (1 H, m), 7.96 (1 H, d, *J* = 7.8 Hz), 10.71 (1 H, br s). 13C NMR ($CDCl_3$, 75 MHz): δ 16.1, 75.8, 120.0, 122.7, 124.8, 130.5, 131.9, 131.9, 136.8, 156.4, 167.1. HRMS (EI-TOF): calculated for $[M]^+$ = $C_{11}H_{12}O_3$, 192.0786; found, 192.0795 (Δ = +0.8 mmu). Mp: 52−54 °C.

Isopropylpropan-3-olamine (74a). To a solution of 3-amino-1-propanol (9.90 mL, 133 mmol, 1.0 equiv) in ethanol (250 mL) was added acetone (14.9 mL, 200 mmol, 1.5 equiv). The reaction mixture was stirred overnight at room temperature and cooled to 0 °C. Sodium borohydride (7.60 g, 200 mmol, 1.5 equiv) was added slowly under a gentle flow of argon, with the temperature of the mixture kept at 4 °C. The reaction mixture was stirred at 5 °C for an additional 2 h before the mixture was quenched with cold H_2O (50 mL), diluted with DCM (25 mL), and filtered. The solvents were removed in vacuo, and the aqueous residue was extracted with EtO_2 (3 × 60 mL). The combined organic layers were dried over $MgSO_4$ and filtered. After evaporation of the solvents the product was obtained as a colorless liquid (9.80 g, 83.8 mmol, 63%). The crude product **74a** was used without further purification. TLC: R_f = 0.14 (cyclohexane/2% $H_2N(i\text{-Pr})$). ^1H NMR ($CDCl_3$, 400 MHz): δ 1.07 (dd, *J* = 6.3 Hz, 6H), 1.69 (pent, *J* = 5.8 Hz, 2H), 2.80 (sept, *J* = 6.3 Hz, 1H), 2.87 (t, *J* = 5.8 Hz, 2H), 3.12 (br s, 2H), 3.80 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.9, 31.3, 47.3, 49.1, 64.4. HRMS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_6H_{16}NO$, 118.1232; found, 118.1226 (Δ = −0.6 mmu).

3-(*t*-Butyldimethylsilyloxy)propaneisopropylamine (74). To a stirred solution of **74a** (1.00 g, 8.50 mmol, 1.0 equiv) and TBSCl (1.80 mL, 9.40 mmol, 1.1 equiv) in DCM (15 mL) was added NEt_3 (3.10 mL, 22.1 mmol, 2.6 equiv). The reaction mixture was stirred for 12 h at room temperature. The resulting solution was quenched with H_2O (15 mL), and the organic phase was washed with a saturated aqueous NaCl solution (15 mL), dried over $MgSO_4$, and filtered. The solvent was removed in vacuo, and the resulting oil was purified by flash column chromatography (silica gel, cyclohexane/2% $H_2N(i\text{-Pr})$) yielding **74** as a colorless oil (1.30 g, 5.80 mmol, 68%). TLC: R_f = 0.62 (cyclohexane/2% $H_2N(i\text{-Pr})$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.09 (d, *J* = 6.3 Hz, 6H), 1.74 (tt, *J* = 7.0, 6.0 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.85 (sept, *J* = 6.3 Hz, 1H), 3.69 (t, *J* = 6.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.2, −3.4, 11.5, 18.4, 22.6, 25.8, 26.1, 32.7, 44.8, 46.4, 49.1, 62.0. HR/MS (ESI-TOF, arginine): calculated for $[M + H]^+$ = $C_{12}H_{30}NOSi$, 232.2097; found, 232.2091 (Δ = −0.6 mmu).

***N,N*-3-(*t*-Butyldimethylsilyloxy)propaneisopropyl-3-methyl-2-propanoxybenzamide (75).** To a stirred solution of acid **73** (1.25 g, 6.50 mmol, 1.0 equiv), amine **74** (1.50 g, 6.50 mmol, 1.0 equiv), and Na_2CO_3 (3.40 g, 32.4 mmol, 5.0 equiv) in THF (60 mL) were added NEt_3 (4.50 mL, 32.4 mmol, 5.0 equiv) and DEPBT (2.50 g, 8.36 mmol, 1.3 equiv). The reaction mixture was stirred for 12 h at room temperature before a saturated aqueous Na_2CO_3 solution (50 mL) and Et_2O (50 mL) were added, forming a white suspension. The white precipitate was solved by addition of H_2O, and the organic layer was

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separated. The aqueous layer was extracted with EA (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$. After filtration and concentration in vacuo the product was purified by flash column chromatography (silica gel, cyclohexane/2% $H_2N(i\text{-Pr})$) to afford **73a** as a pale yellow oil (1.80 g, 4.44 mmol, 68%). TLC: R_f = 0.31 (cyclohexane/ethyl acetate 5/1)

To a slurry of 10% Pd/C (76.0 mg, 0.07 mmol, 0.15 equiv) in DCM (20 mL) was carefully added a solution of **73a** (200 mg, 0.49 mol, 1.0 equiv) in MeOH (25 mL) in a fashion such that the Pd/C was constantly covered with solvent. The reaction vessel was evacuated and filled with H_2 (1 atm) five times before it was stirred under H_2 for 30 min. Then the reaction mixture was filtered over a plug of silica gel topped with Celite and washed with DCM in a fashion such that the Pd/C would not go dry, before all of the MeOH was removed. After removal of the solvents in vacuo the product was obtained as a pale yellow oil (198 mg, 0.49 mmol, 99%). The product **75** was obtained as a mixture of rotamers (1.5/1) and used without further purification. TLC: R_f = 0.31 (cyclohexane/ethyl acetate 5/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ −0.08 (s, 6H)#, 0.08 (s, 6H), 0.80 (s, 9H)#, 0.92 (s, 9H), 0.99 (t, J = 7.4 Hz, 3H), 1.02 (d, J = 6.5 Hz, 3H), 1.20 (d, J = 6.7 Hz, 3H), 1.25 (d, J = 6.7 Hz, 3H)#, 1.28 (d, J = 6.9 Hz, 3H)#, 1.73 (sxt, J = 7.1 Hz, 2H), 1.84−1.95 (m, 1H), 1.98−2.10 (m, 1H)*, 2.68 (s, 3H)#, 2.28 (s, 3H), 3.29−3.38 (m, 1H), 3.43−3.54 (m, 1H), 3.65−3.80 (m, 3H), 3.88−3.94 (m, 1H), 6.97−7.05 (m, 2H), 7.13−7.17 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.4#, −5.2#, −5.2, −5.2, 10.7, 16.1#, 16.4, 18.3#, 18.4, 20.5#, 20.7#, 21.1, 21.3, 23.7#, 23.8, 26.0#, 26.1, 32.3, 34.2#, 38.2, 42.1#, 46.0#, 50.5, 53.6#, 60.9, 61.0#, 61.5, 75.6, 75.7#, 77.4#, 118.1#, 124.0#, 124.0, 125.0#, 125.2, 125.6, 131.5, 131.6#, 131.7, 132.1, 132.5#, 133.2#, 153.1#, 153.6, 169.6, 170.2#. HR/MS (ESI-TOF, arginine): calculated for $[M + Na]^+$ = $C_{23}H_{41}NO_3SiNa$, 430.2753; found, 430.2748 (Δ = −0.5 mmu).

***N,N*-3-(*t*-Butyldimethylsilyloxy)propaneisopropyl-6-iodo-3-methyl-2-propanoxybenzamide (76).** To a stirred solution of **75** (204 mg, 0.50 mmol, 1.0 equiv) and TMEDA (90.0 μL, 0.60 mmol, 1.2 equiv) in THF (5 mL) at −78 °C was added *sec*-BuLi (1.4 M in *n*-hexane, 430 μL, 0.60 mmol, 1.2 equiv) dropwise, and the reaction mixture was stirred for 30 min at that temperature. Then a solution of iodine (152 mg, 0.60 mmol, 1.2 equiv) in THF (5 mL) was added dropwise, with the temperature kept below 70 °C. The reaction mixture was stirred for an additional 1 h before it was quenched with a saturated aqueous $Na_2S_2O_3$ solution (10 mL) at that temperature. The organic layer was separated, and the aqueous layer was washed with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O (25 mL) and a saturated aqueous NaCl solution (25 mL) before it was dried over $MgSO_4$. After filtration and removal of the solvents in vacuo the resulting oil was purified by flash column chromatography (silica gel, cyclohexane/ethyl acetate 10/1) to afford a pale yellow oil (144 mg, 0.27 mmol, 54%). The iodide **76** was obtained as a mixture of rotamers (2.5/1). TLC: R_f = 0.18 (cyclohexane/ethyl acetate 10/1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ −0.06 (s, 3H)#, 0.08 (s, 3H), 0.80 (s, 9H)#, 0.92 (s, 9H), 0.97−1.01 (m, 3H), 1.15 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.7 Hz, 3H), 1.31 (d, J = 6.7 Hz, 3H)#, 1.33 (d, 6.7 Hz, 3H)#, 1.68−1.73 (m, 2H), 1.94−2.04 (m, 1H), 2.06−2.16 (m, 1H), 2.21 (s, 3H)#, 2.23 (s, 3H), 2.99−3.07 (m, 2H)#, 3.11−3.19 (m, 2H)#, 3.34−3.43 (m, 1H), 3.44−3.51 (m, 1H), 3.59 (sept, J = 6.7 Hz), 3.71−3.80 (m, 2H), 3.89−3.97 (m, 1H). 4.73 (sept, J = 6.7 Hz, 1H)#, 6.85 (d, J = 8.1 Hz, 1H)#, 6.86 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H)#, 7.44 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ −5.4#, −5.3#, −5.2, −5.2, 10.6, 15.4#, 16.1, 16.1#, 18.3#, 18.4, 20.2#, 20.5#, 21.3, 21.5, 23.6#, 23.6, 25.5#, 26.0#, 26.1, 26.1, 31.9, 33.4#, 38.3, 42.7#, 46.4#, 51.0, 61.1#, 61.5, 66.0, 75.9, 76.0#, 77.4, 89.8, 90.4#, 132.1, 132.1#, 132.5, 132.5#, 134.5#, 134.6, 138.1, 138.1#, 154.3#, 154.5, 168.6, 168.9#. HR/MS (ESI-TOF, arginine): calculated for $[M + Na]^+$ = $C_{23}H_{40}INO_3SiNa$, 556.1720; found, 556.1714 (Δ = −0.6 mmu).

***N*-Allyl-6-iodo-*N*-isopropyl-3-methyl-2-propoxybenzamide (78).** To a stirred solution of **76** (115 mg, 0.22 mmol, 1.0 equiv) in MeOH (3.5 mL) was added CSA (14.0 mg, 60 μmol, 0.3 equiv), and the mixture was stirred for 30 min. Then the mixture was diluted with EA (35 mL) and washed with a saturated aqueous $NaHCO_3$ solution (2 × 35 mL) and a saturated aqueous NaCl solution (35 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$. After removal of the solvents in vacuo the alcohol **77** was obtained as a pale yellow oil in quantitative yield (91.3 mg, 0.22 mmol, 99%). The product was obtained as a mixture of rotamers (11/1). The product was used without further purifications. TLC: R_f = (cyclohexane/ethyl acetate 3/1).

To a stirred solution of alcohol **77** (75.0 mg, 0.19 mmol, 1.0 equiv) in THF (1 mL) was added 2-nitrophenylselenium cyanate (43.1 mg, 0.19 mmol, 1.0 equiv), and the dark red solution was cooled to 0 °C. Then PBu_3 (46.9 μL, 0.19 mmol, 1.0 equiv) was added and the reaction mixture was stirred at 0 °C for 3 h until the color of the solution lightened. The reaction was quenched with a saturated aqueous NH_4Cl solution (1 mL), and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were removed in vacuo. The crude mixture was resolved in THF (1 mL) and cooled to 0 °C. Then 35% aqueous hydrogen peroxide (23.0 μL, 0.29 mmol, 1.5 equiv) was added, and the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with a saturated aqueous $NaHSO_4$ solution (1 mL), and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with H_2O (5 mL) and saturated aqueous NaCl solution (5 mL), dried over $MgSO_4$, and filtered. The solvents were removed in vacuo, and the product was purified by flash column chromatography (*n*-pentane/Et_2O 10/1) to yield a pale yellow oil of **78** (41.9 mg, 0.10 mmol, 55%). The product was obtained as a mixture of rotamers (1.7/1). TLC: R_f = 0.13 (*n*-pentane/Et_2O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.98 (t, J = 7.4 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H)#, 1.15 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.7 Hz, 3H), 1.29 (d, J = 7.0 Hz, 3H)#, 1.32 (d, J = 6.9 Hz, 3H)#, 1.72 (m, 2H), 2.21 (s, 3H)#, 2.23 (s, 3H), 3.61−3.69 (m, 2H + 1H#), 3.72−3.80 (m, 2H + 1H#), 3.89−3.95 (m, 1H), 4.00 (ddt, J = 15.5, 6.5, 1.6 Hz, 1H), 4.11 (ddt, J = 15.3, 5.7, 1.6 Hz, 1H), 4.72 (sept, J = 6.9 Hz, 1H)#, 4.87 (ddt, J = 17.1, 1.5 Hz, 1.5 Hz, 1H)#, 4.95 (ddt, J = 10.1, 1.5 Hz, 1.5 Hz, 1H)#, 5.15 (ddt, J = 10.3, 1.5 Hz, 1.5 Hz, 1H), 5.32 (ddt, J = 17.3, 1.5 Hz, 1.5 Hz, 1H), 5.79−5.89 (m, 1H)#, 6.05−6.15 (m, 1H), 6.85 (d, J = 8.1 Hz, 1H)#, 6.87 (d, J = 8.1 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H)#, 7.44 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 10.6, 15.4#, 16.0, 20.2#, 20.4#, 21.5, 21.7, 23.6, 29.8#, 30.5#, 43.3, 46.4#, 48.5#, 51.1, 66.0#, 75.9, 89.7, 90.2#, 116.5, 116.8#, 132.1, 132.2#, 132.6, 134.5, 134.6#, 135.6, 136.1, 137.8#, 154.3#, 154.5, 168.5, 168.8#. HR/MS (ESI-TOF, arginine): calculated for $[M + Na]^+$ = $C_{17}H_{24}INO_2Na$, 424.0750; found, 424.0744 (Δ = −0.6 mmu).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02781.

^{1}H and ^{13}C NMR spectra and crystallographic data and thermal ellipsoid plots for **41**, **54**, **57**, **67**, and **72** (PDF)

X-ray crystallographic data for **41**, **54**, **57**, **67**, and **72** (CIF)

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Notes

The authors declare no competing financial interest.

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