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Formal Total Synthesis of Actinoranone: Synthetic Approaches and Cytotoxic Studies

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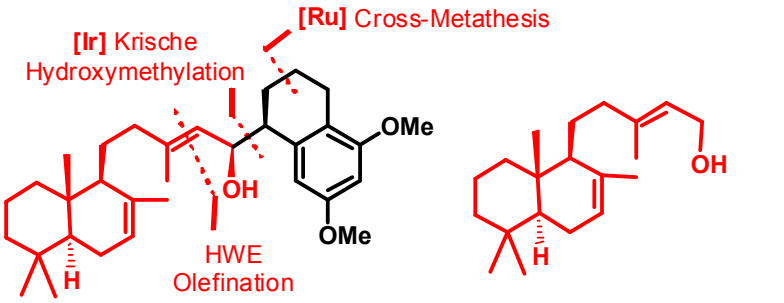


Actinoranone Carbon Backbone
Total of 20 steps
LLS: 11 steps

Labda-7,13-(E)-dien-15-ol
Total of 8 steps
LLS: 8 steps
Enhanced Cytotoxicity *in vitro*

ABSTRACT: This full account describes our efforts towards the total synthesis of actinoranone. Our synthetic strategies rely on a convergent route to connect the terpenoid and polyketide fragments, employing catalysis and powerful classical reactions for the assembly of these key fragments. A new transformation was disclosed during this work, a domino ring-opening and esterification. Initial cytotoxic studies for selected synthetic intermediates are also presented.

■ INTRODUCTION

Synthetic chemistry plays a crucial role in our world. In particular, medicine has benefited from the creation of new drugs or the supply of scarce natural products *via* total synthesis. Even with clear benefits for humankind, the scientific community has struggled with funding constraints, and the current situation urges chemists to develop shorter and more efficient synthetic routes. A few strategies have been employed with these aims, which include redox economy,[1] avoidance of protecting groups[2] and application of catalytic methods.

Compounds isolated from natural sources present a seemingly limitless chemical diversity, and are thus considered privileged scaffolds for drug discovery. In the review of Newman and Cragg,[3] which covers data from 1981 to 2014, natural products and compounds inspired by their architectures comprise more than 50% of all approved small-molecule drugs, showing the importance of their investigation.

In this scenario, we have been working on the development of total syntheses of natural products and analogues, which could be applied in our medicinal chemistry program.[4] We have recently developed a concise formal total synthesis of actinoranone (**1**),[4a] and a full account of our efforts is provided in this manuscript, including failed approaches and preliminary cytotoxic evaluation.

Actinoranone. The meroterpene actinoranone (**1**, **Scheme 1**) was first isolated by Fenical and coworkers in 2013 from the CNQ-027 strain of marine actinomycetes, and presented *in vitro* cytotoxicity against the human colon carcinoma cell line HCT-1116 (IC_{50} = 4.0 μM).[5] Interestingly, the connection between the diterpene labdane and the tetralone fragments has never been observed in other natural products, making this a unique structural feature of this natural product.

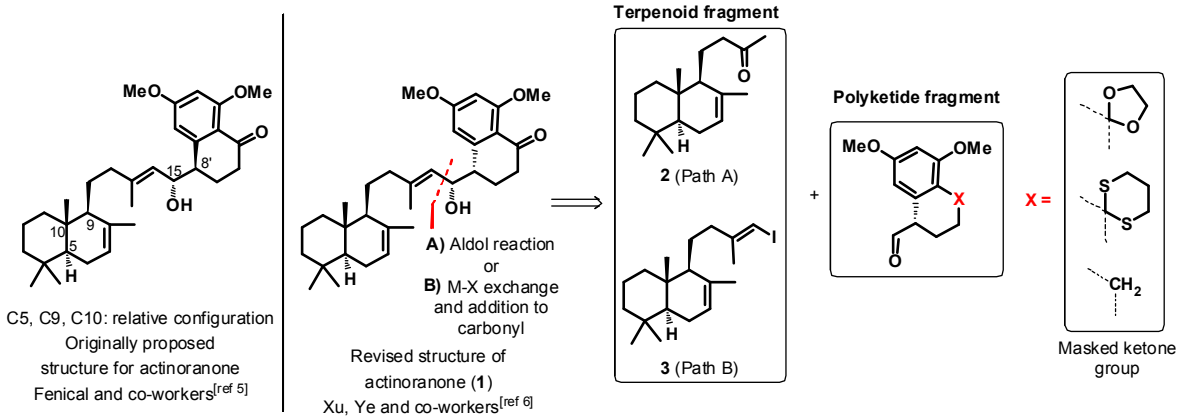
Structural elucidation of actinoranone was performed *via* uni and bidimensional NMR analyses. The relative configuration of the octalin fragment was established as (5*S*,9*S*,10*S*) or (5*R*,9*R*,10*R*). The absolute configuration at C15 was ascribed as (*R*) after analysis of respective Mosher esters, thereafter, C8' was assigned as (*R*) using NOESY experiments.

During our efforts towards actinoranone, its first synthesis was reported independently by Xu, Ye and coworkers.[6] Their work detailed the preparation of four diastereoisomers, varying the stereogenic centers at C15 and C8', and after comparison of spectroscopical data of the natural and synthetic samples, the assignment was revised at C8', and the correct absolute configuration was determined as (5*S*,9*S*,10*S*,15*R*,8'*S*). Spectroscopical methods have evolved astonishingly over the last decades, however unequivocal structural elucidation of natural products remain a challenge nowadays, as observed in the case of actinoranone, for synthetic organic chemistry still plays an important role in this field.[7]

The Xu and Ye synthesis was accomplished in a long sequence, a total of 29 steps, being 19 steps for the longest linear sequence. We therefore sought to establish a shorter synthesis of this natural product, allowing a quicker way to obtain analogues with this new backbone, following cytotoxic studies of selected intermediates.

Our retrosynthetic plan (**Scheme 1**) focused on the disconnection of the C14-C15 bond, which would be constructed with an aldol reaction (path A) or a sequence of metal-halogen exchange followed by the addition to a carbonyl compound (path B). The ketone group from the tetralone bicycle would be masked as a ketal, thioketal or methylene group.

Scheme 1. Originally Proposed (Left) and Revised (Right) Structures for Actinoranone, and Retrosynthetic Disconnection



■ RESULTS AND DISCUSSION

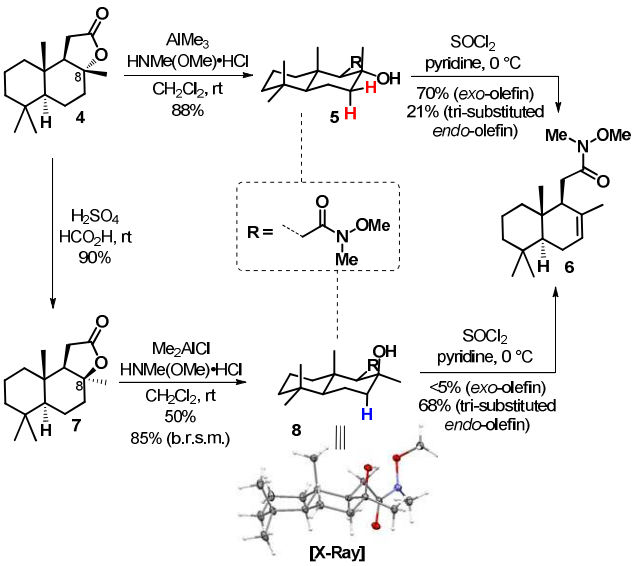
Terpenoid Fragment Synthesis. The terpenoid fragment (compounds **2** or **3**) synthesis required the installment of a trisubstituted *endo*-olefin as an initial challenge. This task was first approached with a sequence developed by de la Torre and co-workers:[8] conversion of (+)-sclareolide (**4**) to its Weinreb amide and tertiary alcohol elimination mediated by $SOCl_2$ in pyridine, as outlined in **Scheme 2**. Unfortunately, the desired *endo*-olefin was obtained in only 21% yield, and multiple chromatographic purifications were necessary to obtain pure **6**. An acid-catalyzed isomerization of the major *exo*-olefin into the desired *endo*-olefin **6** was reported by de la Torre,[8] however, this protocol produced poor results in our hands.

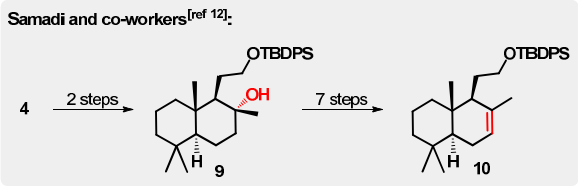
The desired *endo*-olefin **6** can be formed from alcohol **5** only by an E1 mechanism, since the hydrogens marked in red do not have the required alignment with the hydroxyl group to enable an E2 elimination. After this observation, an exchange of the hydroxyl group from an equatorial position in compound **5** to an axial position in compound **8** was hypothesized to be beneficial to the elimination step, as an E2 mechanism could take

place with the hydrogen marked in blue. This strategy began with (+)-sclareolide (**4**) epimerization at C8,[9] followed by the Weinreb amide **8** synthesis with Me_2AlCl,[10] where the axial position of the hydroxyl group was confirmed by X-ray diffraction analysis.[11] Pleasingly, the desired *endo*-olefin **6** was obtained as the major product from the elimination of alcohol **8**, applying the same conditions as before, and a small amount of *exo*-olefin (<5%) was detected.

This challenge was also addressed by Samadi and co-workers during their coscinosulfate synthesis,[12] and a sequence of seven steps, including several redox reactions, were necessary to install the trisubstituted *endo*-olefin from the tertiary alcohol **9** (**Scheme 2**).

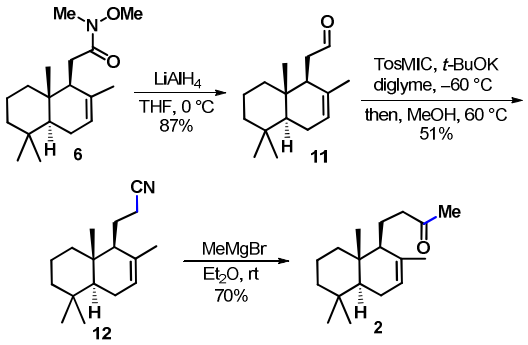
Scheme 2. Amide 6 Synthesis





Thereafter, the methylketone (**2**) synthesis was evaluated. The first approach employed a three-step sequence from Weinreb amide **6**: reduction with $LiAlH_4$, van Leusen reaction,[13] and Grignard addition to nitrile **12** (**Scheme 3**).

Scheme 3. Methylketone 2 Synthesis



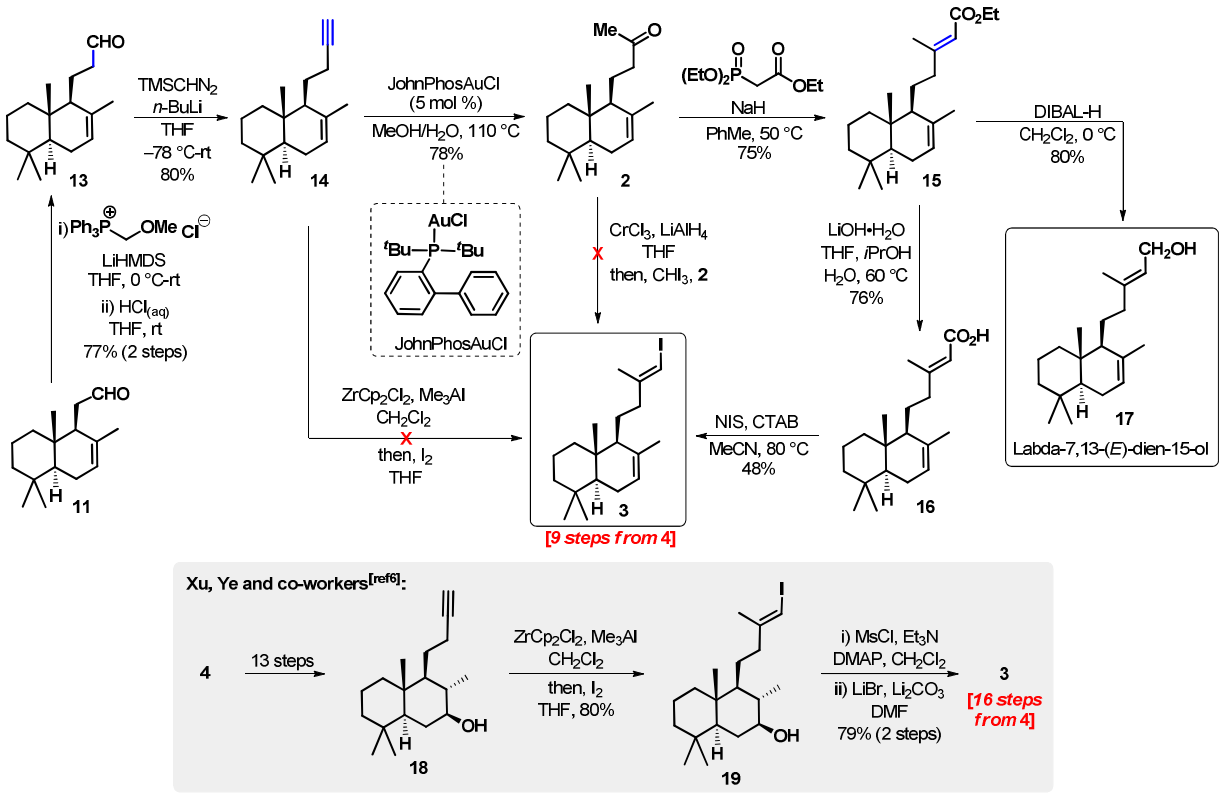
A second approach to methylketone **2** was also developed, applying two one-carbon homologations: a Wittig reaction from aldehyde **11** and a reaction of aldehyde **13** with the anion of $TMSCHN_2$, followed by a gold(I)-catalyzed alkyne hydration[14] (**Scheme 4**).

The vinyl iodide (**3**) synthesis was then studied, as outlined in **Scheme 4**. As first attempt, the use of a carbozirconation reaction of alkyne **14** and consecutive treatment with I_2[15] led to poor results, as only trace formation of **3** was observed by GC/MS analysis. Next, a Takai olefination[16] of ketone **2** was evaluated, generating $CrCl_2$ *in situ*,[17] however, no product was observed and starting material was recovered. The third approach was conducted with a sequential Horner-Wadsworth-Emmons olefination and basic hydrolysis yielding carboxylic acid **16**, which was successfully employed in a decarboxylative iodination with *N*-iodosuccinimide (NIS) in the presence of cetyltrimethylammonium bromide (CTAB).[18]

The vinyl iodide (**3**) synthesis developed by Xu and Ye employed as key step a carbozirconation of alkyne **18**, which contained a free hydroxyl group, followed by treatment with iodine, after which the *endo*-olefin was installed. Their sequence required sixteen steps from (+)-sclareolide (**4**), with use of protecting groups and several redox reactions. Our approach to vinyl iodide **3** was concluded in only nine steps, as no protecting groups were required and the use of redox reactions was minimized.

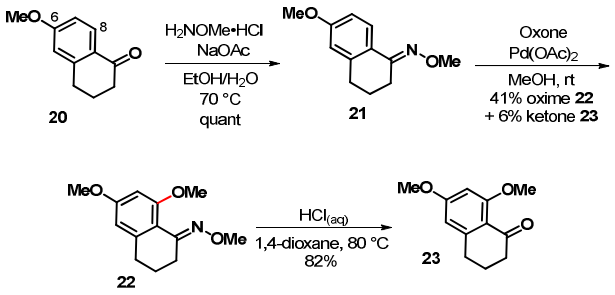
The natural diterpene labda-7,13-(*E*)-dien-15-ol[19] could also be synthesized from ester **15**; this synthesis was accomplished with a DIBAL-H reduction of **15**.

Scheme 4. Synthesis of Vinyl Iodide 3 and Labda-7,13-(*E*)-dien-15-ol



Polyketide Fragment Synthesis. The initial approach to the polyketide fragment started with the regioselective methoxylation of 6-methoxy-1-tetralone (**20**) (**Scheme 5**). This transformation began with the insertion of methyl-oxime as a directing group, followed by a C-H activation using catalytic $Pd(OAc)_2$ and oxone as re-oxidant,[20] which afforded methyl-oxime **22** and a small amount of the desired tetralone **23**. Thus, acidic hydrolysis of the oxime completed the synthesis of **23**, .

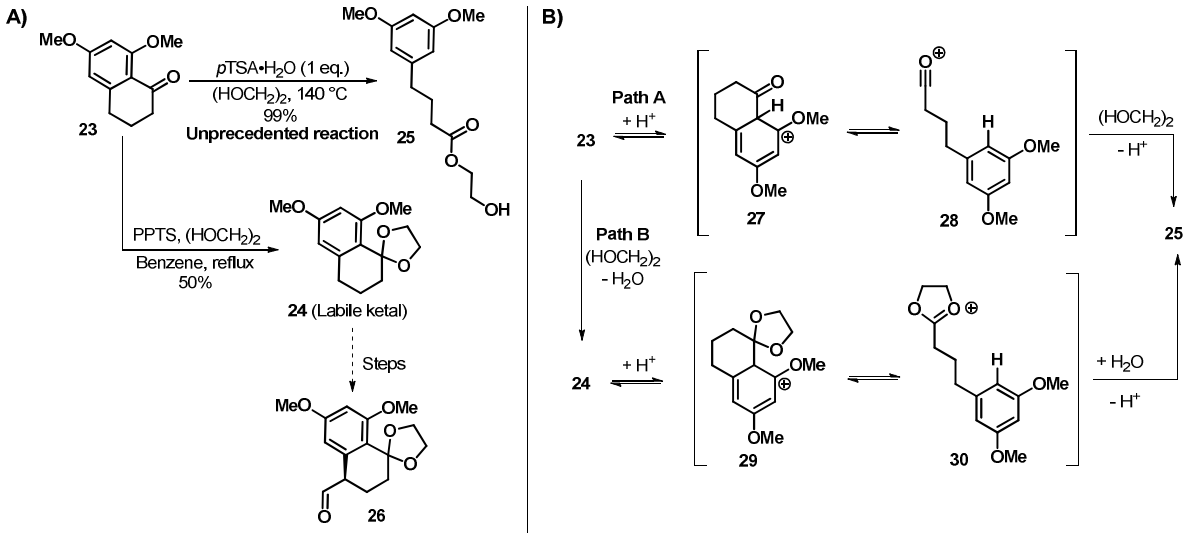
Scheme 5. Tetralone 23 Synthesis



In order to functionalize the benzylic position of **23** towards **26**, the ketone would be protected as a ketal group. Unexpectedly, a common protocol, heating ketone with *p*TSA in ethylene glycol as solvent, led to a ring-opening reaction, which was further investigated. The desired ketal was obtained with a weaker acid (pyridinium *p*-toluenesulfonate) using a Dean-Stark apparatus[21] in 50% yield, however this protecting group presented lability upon storage and during benzylic functionalization attempts (**Scheme 6A**).

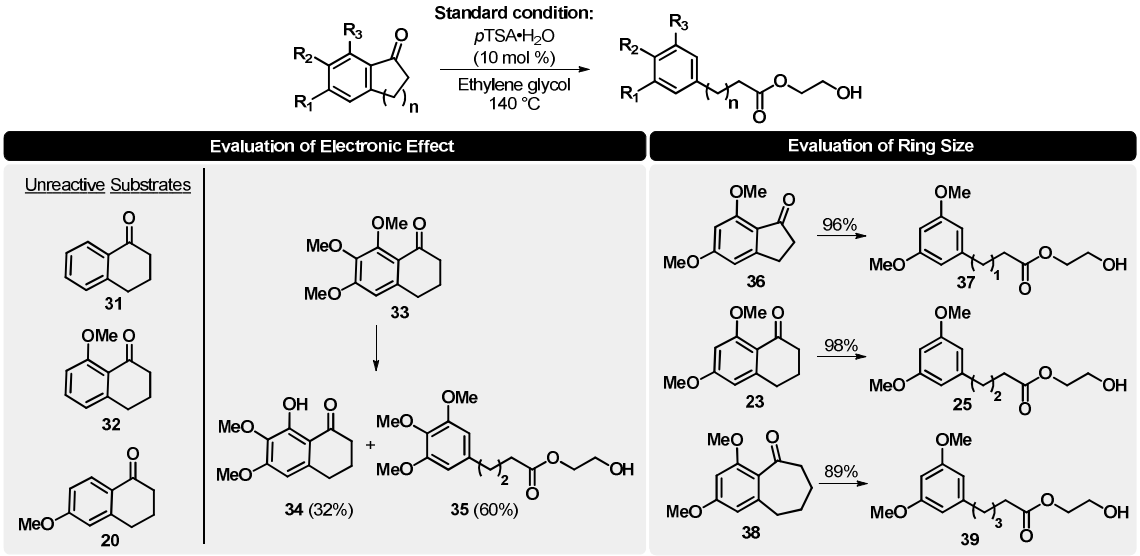
At this point, our attention was turned to the ring-opening reaction. Two mechanisms were proposed, as outlined in **Scheme 6B**. For path A, intermediate **27** would be generated *via* a protonation of the aromatic ring of **23**, followed by a retro Friedel-Crafts acylation and esterification with ethylene glycol. For path B, ketal **24** would be formed initially, following protonation of the aromatic ring, ring-opening and hydrolysis of oxonium **30**.

Scheme 6. A) Unexpected Ring Opening Reaction, B) Proposed Mechanisms



The ring-opening reaction was next evaluated with different substrates. Thus, 1-tetralone (**31**), 6-methoxy-1-tetralone (**32**) and 8-methoxy-1-tetralone (**20**) were subjected to a standard condition, but the starting materials were recovered with no signal of ring-opening nor ketalization reaction (**Scheme 7**). Similar tests with these compounds were performed at 180 °C, but the same results were observed.

Scheme 7. Evaluation of the Ring Opening Reaction



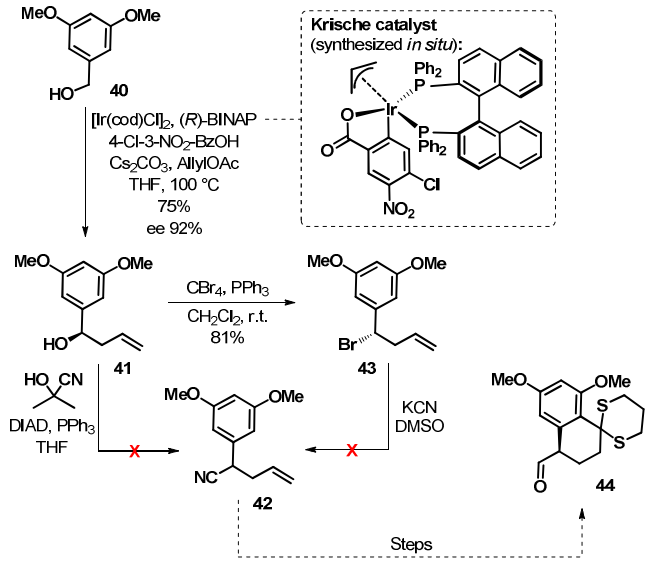
On the other hand, 6,7,8-trimethoxy-1-tetralone (**33**) underwent the domino reaction. Notably, compound **33** also produced the demethylated tetralone **34**, which did not suffer ring-opening nor ketalization, even with longer periods of heating using the standard condition, probably due a high stability provided by an intramolecular hydrogen bonding, evidenced by a downfield shift of the phenolic proton (δ 12.69 ppm).[22] The presence of both methoxy groups at the positions 6 and 8 of the aromatic ring seems to be necessary to the success of the reaction, which agrees with the proposed mechanism shown in **Scheme 6B**.

Next, the size of the ring fused to the aromatic system was evaluated, and the bicycles containing 5, 6 or 7 membered-ring were able to participate in the domino reaction in high yields (**Scheme 7**).

After these experiments, we intended to explore other nucleophiles in order to expand the scope of the reaction, but unfortunately the reaction was not successful when replacing ethylene glycol with other alcohols as solvent. Moreover, these results suggest that path B must be operating under these conditions. In view of the limited application of this reaction, these studies were concluded at this point, and we turned our attention back to the polyketide fragment synthesis.

After this initial approach, a series of asymmetric methods to achieve the second ring with a stereogenic benzylic position was investigated. A route aiming the connection of a nitrile group at the benzylic position began with the Krische allylation[23] of alcohol **40**, obtaining homoallylic alcohol **41** with high enantioselectivity (ee 92%) (**Scheme 8**). Unfortunately, both attempts to synthesize nitrile **42** *via* a Mitsunobu reaction[24] from alcohol **37** or a nucleophilic substitution from bromide **43** were unsuccessfull.

Scheme 8. Attempt to Construct Polyketide Fragment Protected with Dithiane



In face of this difficulty, our strategy was slightly modified, by first generating the stereogenic center with the three carbons attached to it already in place, followed by the formation of the second ring.

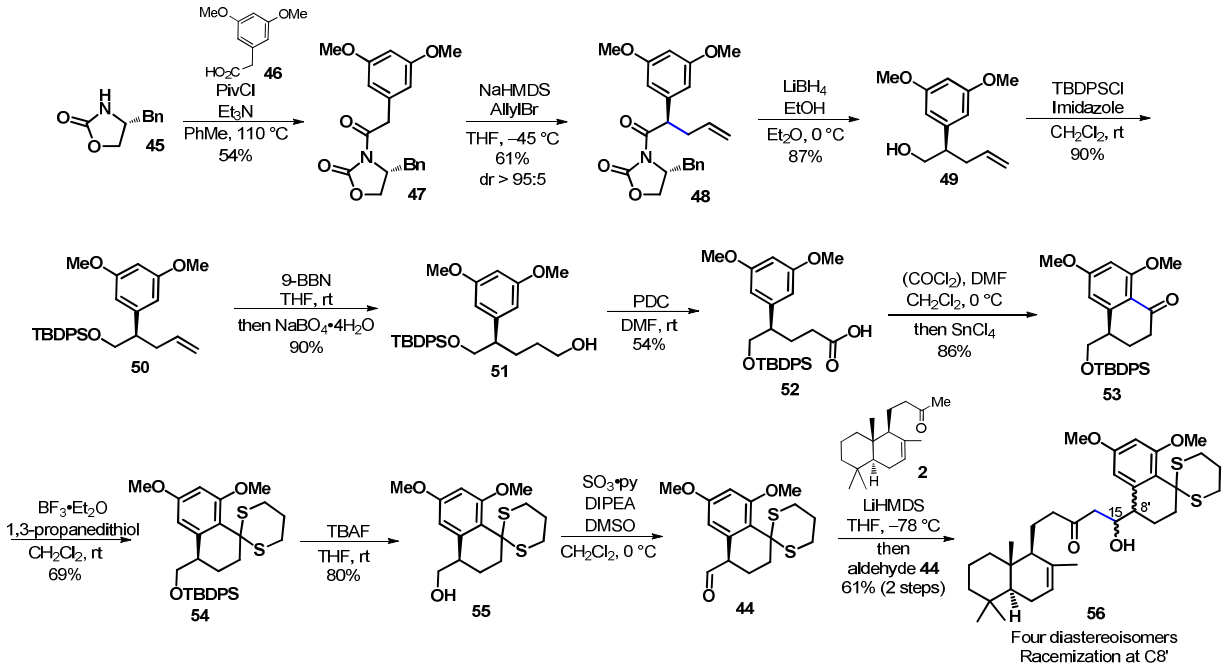
The formation of the tertiary benzylic stereocenter was accomplished by a diastereoselective alkylation of the acyloxazolidinone **47** with allyl bromide (**Scheme 9**).[25] Next, the benzyloxazolidinone was replaced by a protected primary alcohol in two steps, and the terminal alkene was oxidized to a carboxylic acid in two more steps. The second ring was forged by an intramolecular Friedel-Crafts acylation mediated by $SnCl_4$.

The next step would be the protection of the ketone group. As 1,3-dioxolane showed to be a labile protecting group, this time we chose 1,3-dithiane as a protecting group, and its formation under standard conditions (BF_3•Et_2O and 1,3-dithiol) was successfully achieved.

The primary alcohol was then deprotected and oxidized under Parikh-Doering conditions,[26] and the freshly purified aldehyde was employed in an aldol reaction with the lithium enolate derived from ketone **2**, but unfortunately the desired product **56** was obtained as a mixture of four diastereoisomers, probably due to racemization of aldehyde

44 under basic conditions and poor diastereoselectivity during the C-C bond formation step.

Scheme 9. Synthesis of Polyketide Fragment Protected with Dithiane and Attempt of Fragments Coupling

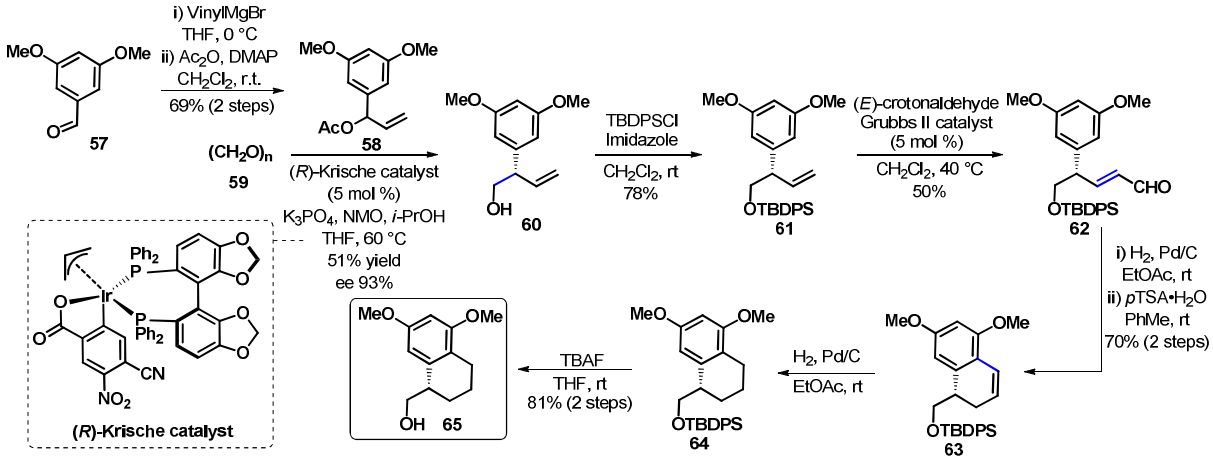


The protecting group for the benzylic ketone became again an issue that needed to be addressed, as the dithiane group was not compatible with other oxidizing conditions to convert the primary alcohol to an aldehyde (Dess-Martin periodinane and $NaHCO_3$, PCC, PDC), in order to avoid racemization. A new approach was disclosed after the first actinoranone total synthesis was reported by Xu, Ye and co-workers,[6] where a benzylic methylene group was employed as a masked ketone.

This route began with the synthesis of allylic acetate **58** from benzaldehyde **57** in two steps. The formation of the tertiary benzylic stereocenter was conducted with a newly developed enantioselective hydroxymethylation catalyzed by an iridium complex, which was developed by the Krische group.[27] Next, alcohol **60** was protected with a silyl group and the alkene of **61** was subjected to a cross-metathesis reaction with (*E*)-

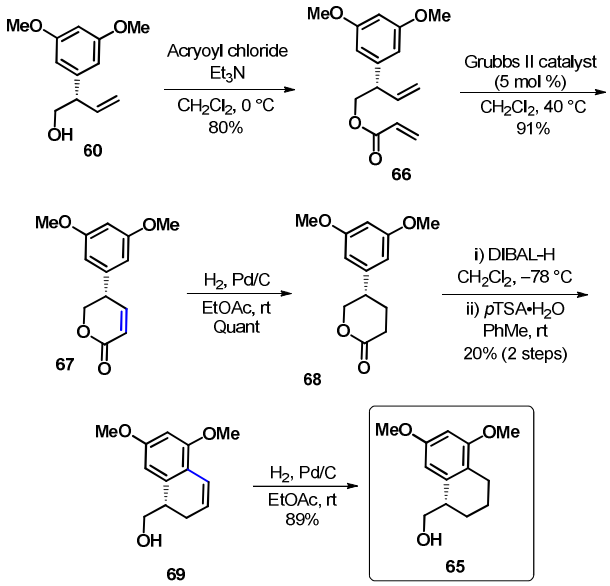
crotonaldehyde.[28] Afterwards, alkene **62** was hydrogenated and the second ring was produced by a domino Friedel-Crafts reaction and dehydration. Polyketide fragment **65** was obtained after a second hydrogenation step and a *O*-deprotection (**Scheme 10**).

Scheme 10. Polyketide Fragment Synthesis



A protecting-group-free synthesis of fragment **65** was explored from alcohol **60** (**Scheme 11**). Initially the alcohol group was converted to an acrylate, following a ring-closing-metathesis reaction and a hydrogenation step. The reduction of lactone **68** with DIBAL-H cleanly afforded the corresponding lactol, which was employed in a domino reaction involving a Friedel-Crafts reaction and a dehydration. This sequence afforded the desired product, but the avoidance of protecting groups caused a low yield to this cyclization step. The fragment synthesis was finished with a hydrogenation of alkene **69**.

Scheme 11. Protecting-Group-Free Synthesis of Polyketide Fragment

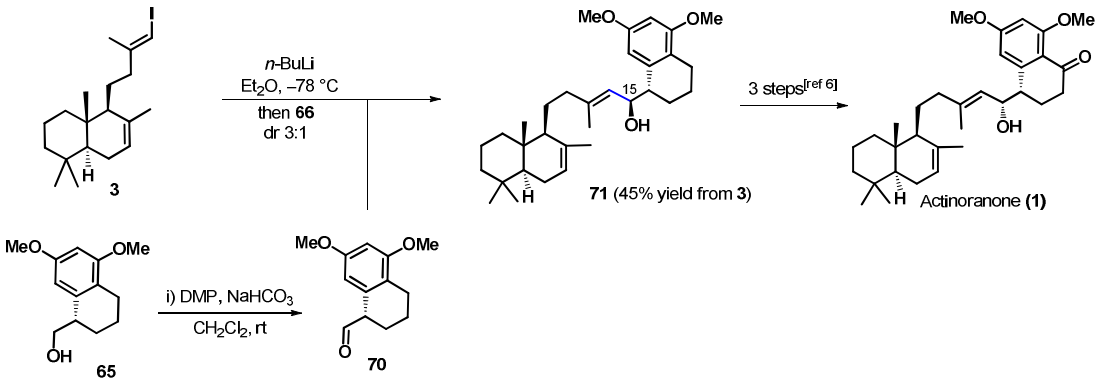


As the protecting-group-free approach would need further development, the route outlined in **Scheme 10** was chosen to finish the synthesis of actinoranone, as it presented a higher overall yield and the same number of steps as the latter route.

Fragments Coupling. The actinoranone carbon backbone was forged by a metal-halogen exchange of vinyl iodide **3** with *n*-BuLi, followed by the addition to the freshly prepared aldehyde **70**, where alcohol **71** was obtained as the major product and could be completely separated by flash column chromatography on silica (**Scheme 12**). Pleasingly, no racemization of aldehyde **70** was observed during the oxidation with Dess-Martin periodinane buffered with $NaHCO_3$ or the addition of the vinyl-lithium reagent.

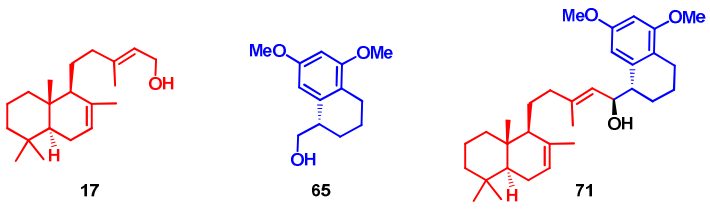
At this point, the formal synthesis of actinoranone was achieved. As Xu and Ye reported,[6] alcohol **71** could be converted to actinoranone in three more steps: a Mitsunobu esterification, a C-H oxidation of the benzylic position and a hydrolysis of the ester introduced during the Mitsunobu step.

Scheme 12. Fragments Coupling and Actinoranone Formal Synthesis



Cell assays. The cytotoxic activity of selected intermediates, compounds **17**, **65** and **71**, was evaluated in four human cell lines, using cell imaging assays. These three compounds were chosen because they present the terpenoid and polyketide fragments, isolated and joined, and the results from these cell assays could contribute to a better understanding of the actinoranone pharmacophoric profile. The concentration of compound responsible for a 50% reduction of the cell population was assigned as the EC_{50} value to each compound, as shown in **Table 1**.

Table 1. Cytotoxicity of componds **17**, **65** and **71** measured in human cell assays. Values are reported as average ± SEM of at least three independent experiments (n).



compound/ cell line	**17**		**65**		**71**		**Tacrine**	
	EC_{50} average ± SEM (μM)	n	EC_{50} average ± SEM (μM)	n	EC_{50} average ± SEM (μM)	n	EC_{50} average ± SEM (μM)	n
HaCat [a]	12.9 ± 2.6	4	> 200	3	39.3 ± 10.8	4	25.0 ± 2.6	3
U2-OS [b]	7.6 ± 1.6	3	> 200	4	25.8 ± 5.8	4	34.6 ± 4.4	3
SCC-9 [c]	13.9 ± 1.7	5	> 200	5	115.3 ± 24.2	3	53.7 ± 3.7	3
HSC-3 [d]	20.5 ± 8.2	5	> 200	5	20.9 ± 2.7	5	38.9 ± 5.8	3

[a] HaCat: immortalized, but not transformed epithelial cell line.
[b] U2-OS: human bone osteosarcoma epithelial cells.
[c] SCC9: squamous cell carcinoma, a tumor cell line originated from a human tongue squamous cell carcinoma.

[d] HSC3: human tongue squamous cell carcinoma cell line.
> 200 μM: concentration-response curves in which 50% cell population reduction was not reached at the highest compound concentration used (200 μM).

Compound **17** was the most cytotoxic, displaying EC_{50} values ranging from 7.6 to 20.5 μM in the 4 cell lines tested. Compound **71** presented moderated cytotoxicity in HaCat, U2-OS and HSC-3 cell lines (EC_{50} values ranging from 20.9 to 39.3 μM), and was barely active in the SCC-9 cell line (EC_{50} of 115. 3 μM). Compound **65** was inactive in all the cell lines evaluated.

Compound **71** carries both the diterpene and polyketide portions of the actinoranone skeleton and was less active than compound **17**, which carries only the diterpenoid portion. Further, polyketide **65** was inactive in the biological assays. These results suggest that the diterpene fragment (compound **17**) is *per se* important for conferring the cytotoxic activity of the actinoranone scaffold. Gademann and co-workers have reviewed similar findings, which include the use of natural product derived fragments achievable in reduced synthetic routes, where the fragments display similar or even improved biological activities, as compared to the parent natural products.[29]

■ CONCLUSIONS

This work demonstrates that the combination of classical and new reactions can afford shortened routes to complex natural products. Here we described the construction of the actinoranone carbon backbone in eleven steps for the longest linear sequence, which was previously accomplished in seventeen steps. This was possible due to the minimization of redox reactions and avoidance of protecting groups, when feasible.

In the present work, we have shown that the bicyclic diterpenoid fragment of actinoranone (compound **17**) displayed higher cell cytotoxicity in comparison to its carbon

backbone (compound **71**), the former being obtained in 8 steps instead of 20, as for the full backbone (**71**).

■ EXPERIMENTAL SECTION

General Information. Starting materials and reagents were obtained from commercial sources and used as received unless otherwise specified. Dichloromethane, triethylamine, diisopropylethylamine (DIPEA) and pyridine were treated with calcium hydride and distilled before use. Tetrahydrofuran (THF) and diethylether were treated with metallic sodium and benzophenone and distilled before use. Anhydrous *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO) and diglyme were obtained from Aldrich. Anhydrous methanol, ethanol, isopropyl alcohol, acetonitrile, toluene and benzene were dried over molecular sieves 3A (10% w/v) for more than one week before use. Anhydrous reactions were carried out with continuous stirring under atmosphere of dry nitrogen or argon. Progress of the reactions was monitored by thin-layer chromatography (TLC) analysis (Merck, silica gel 60 F254 on aluminum plates), unless otherwise stated. Flash chromatography purifications were performed with silica gel 60, 220-440 mesh, Sigma-Aldrich. ^{1}H NMR and ^{13}C NMR were recorded on Bruker 250, the chemical shifts (δ) were reported in parts per million (ppm) relative to deuterated solvent as the internal standard ($CDCl_3$: 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR), coupling constants (*J*) are in hertz (Hz). The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br. = broad signal. NMR spectra were processed using ACD/NMR Processor Academic Edition version 12.01. High resolution mass spectra (HRMS) were recorded on a Waters Xevo Q-Tof apparatus operating in electrospray mode (ES). Infrared spectra with Fourier transform (FTIR) were recorded on a Therm Scientific Nicolet iS5, the principal absorptions are listed in cm^{-1}. Optical rotation were measured at 25 °C in a Perkin–Elmer 341 polarimeter, with sodium lamp, the measure is described as follow $[\alpha]_D^T$ (*c* (g/100 mL), solvent). GC/MS analyses were carried out on an Agilent 9870A gas chromatography with quadrupole mass analyzer (GC-MS) equipped with a split/splitless injector; the column set for all runs consisted of a 30 m × 0.250 mm HP-5MS column; the oven temperature was increased from 60 to 180 °C at the rate of 20 °C/min and was then further increased to 280 °C at 30 °C/min; the injector and MS transfer lines were at 280 and 230 °C, respectively, and the MS ionization source was maintained at 230 °C using 70 eV; the spectrometer was operated with a mass scan range of

30-400 m/z, resulting in an acquisition rate of 25 spectra/s; the data acquisitions were processed via the GC-MS 5975C data analysis. IUPAC names of the compounds were generated using ChemBioDraw Ultra 13.0.

*2-((1R,2R,4aS,8aS)-2-Hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)-N-methoxy-N-methylacetamide (**5**).* Me_3Al (1 M in heptane, 8.0 mL, 8.0 mmol, 2 equiv) was added to a suspension of MeONHMe•HCl (756 mg, 7.7 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL) at 0 °C (*CAUTION! gas evolution*). After addition, the cooling bath was removed and the mixture was kept under magnetic stirring at room temperature for 2 h. Next, a solution of (+)-sclareolide (**4**, 97%, 1.00 g, 3.88 mmol, 1 equiv) in dry CH_2Cl_2 (10 mL) was added to the reaction, and the stirring continued for 18 h at room temperature. After cooling to 0 °C, an aqueous solution of HCl (1 M, 30 mL) was slowly added (*CAUTION! gas evolution*). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 50:50 to 30:70) to furnish amide **5** (908 mg, 2.9 mmol) as a white solid in 75% yield. TLC (SiO_2): R_f = 0.30 (hexanes/EtOAc 50:50); M.p.: 102-106 °C; $[\alpha]_D^{25}$ = +37 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}$ = +39.3 (*c* 0.98, $CHCl_3$);[30] ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.78 (s, 3H), 0.81 (s, 3H), 0.86 (s, 3H), 1.14 (s, 3H), 0.89-1.73 (m, 10H), 1.86-2.03 (m, 2H), 2.37-2.63 (m, 3H), 3.17 (s, 3H), 3.71 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 15.7 (CH_3), 18.4 (CH_2), 20.5 (CH_2), 21.3 (CH_3), 23.2 (CH_3), 26.8 (CH_2), 33.1 (C), 33.2 ($2CH_3$), 38.5 (C), 39.2 (CH_2), 41.7 (CH_2), 44.4 (CH_2), 55.8 (CH), 56.1 (CH), 61.1 (CH_3), 72.7 (C), 176.0 (C).

*(3aS,5aS,9aS,9bR)-3a,6,6,9a-tetramethyldecahydronaphtho[2,1-b]furan-2(3aH)-one (**7**).* Solid (+)-sclareolide (**4**, 97%, 2.58 g, 10.0 mmol, 1 equiv) was added to a solution of sulfuric acid (95%, 1.68 mL, 30.0 mmol, 3 equiv) in formic acid (98%, 42 mL) at room temperature. After 4 h, the mixture was diluted with cold H_2O (100 mL) and extracted with Et_2O (2 x 100 mL). The combined organic phases were washed with saturated aqueous solution of $NaHCO_3$ (30 mL), brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 85:15) to furnish lactone **7** (2.25 g, 9.0 mmol) as a white solid in 90% yield. Note: The high purity of formic acid (>97%) was essential for full conversion. The use of formic acid of 85% purity led to incomplete conversion even with prolonged reaction time. TLC (SiO_2): R_f = 0.70 (hexanes/EtOAc 50:50); M.p.: 87-89 °C; $[\alpha]_D^{25}$ = −27 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}$ = −31.7 (*c* 0.4, $CHCl_3$);[9] ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.78 (s, 3H), 0.82 (s, 6H), 0.75-0.87 (m, 2H), 1.01-1.15 (m, 1H), 1.23 (s, 3H), 1.26-1.61 (m, 7H), 1.69 (d, *J*

= 7.7 Hz, 1H), 2.14-2.26 (m, 1H), 2.27 (d, *J* = 18.0 Hz, 1H), 2.64 (dd, *J* = 17.9, 7.9 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.3 (CH_3), 17.8 (CH_2), 18.0 (CH_2), 21.9 (CH_3), 29.7 (CH_3), 32.1 (CH_2), 32.6 (C), 33.3 (CH_3), 34.8 (CH_2), 35.7 (C), 40.5 (CH_2), 41.4 (CH_2), 51.2 (CH), 54.4 (CH), 85.3 (C), 177.4 (C).

*2-((1R,2S,4aS,8aS)-2-hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)-N-methoxy-N-methylacetamide (**8**).* Me_2AlCl (0.9 M in heptane, 8.0 mL, 7.2 mmol, 3 equiv) was added to a suspension of MeONHMe•HCl (702 mg, 7.2 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL) at 0 °C (*CAUTION! gas evolution*). After addition, the cooling bath was removed and the mixture was kept under magnetic stirring at room temperature for 2 h. Next, a solution of isosclareolide (**7**, 619 mg, 2.4 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL) was added to the reaction, and the stirring continued at room temperature for 18 h. After cooling to 0 °C, an aqueous solution of HCl (1 M, 50 mL) was slowly added (*CAUTION! gas evolution*). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 85:15 to 30:70) to furnish amide **8** (375 mg, 1.2 mmol) as a white solid in 50% yield (85% yield based on the recovery of starting material), along recovered isosclareolide (**7**, 254 mg, 1.0 mmol) as a white solid in 41% yield. Note: Use of Me_3Al led to little conversion (<5%) and the use of Me_2AlCl for prolonged reaction time at rt or use of refluxing conditions did not improve the yield. TLC (SiO_2): R_f = 0.30 (hexanes/EtOAc 50:50); M.p.: 140-144 °C; $[\alpha]_D^{25}$ = +24 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 3450, 2919, 2850, 1644, 1459, 1418, 1387, 1172, 1125, 1001, 915, 899; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.78 (s, 3H), 0.83 (s, 3H), 0.93 (s, 3H), 1.00 (s, 3H), 0.87-1.07 (m, 2H), 1.08-1.76 (m, 10H), 1.81-1.89 (m, 1H), 2.28 (dd, *J* = 18.0, 2.7 Hz, 1H), 2.70 (dd, *J* = 18.0, 5.8 Hz, 1H), 3.13 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 15.6 (CH_3), 18.1 (CH_2), 18.2 (CH_2), 21.5 (CH_3), 26.8 (CH_2), 30.4 (CH_3), 32.7 (CH_3), 33.1 (C), 33.3 (CH_3), 38.0 (C), 38.7 (CH_2), 41.7 (CH_2), 42.3 (CH_2), 52.2 (CH), 55.3 (CH), 61.1 (CH_3), 72.7 (C), 175.3 (C); HRMS (ESI +): *m/z* calculated for $C_{18}H_{33}O_3NNa^+$ $[M+Na]^+$ 334.2353, found 334.2367.

*N-methoxy-N-methyl-2-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetamide (**6**) and N-methoxy-N-methyl-2-((1S,4aS,8aS)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)acetamide.* $SOCl_2$ (1.16 mL, 16 mmol, 10 equiv) was added to dry pyridine (7.5 mL) at 0 °C (*CAUTION! exothermic process*), this solution was stirred for 5 min, then was transferred to a solution of alcohol **5** (498 mg, 1.60 mmol, 1 equiv) in dry pyridine (7.5 mL) at 0 °C. After 30 min, H_2O (30 mL) was slowly added. The mixture was extracted with CH_2Cl_2 (2 x 30 mL), the organic

phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 85:15) to furnish *endo*-olefin **6** (100 mg, 0.34 mmol) as a colorless oil in 21% yield, along *exo*-olefin (330 mg, 1.12 mmol) as a white solid in 70% yield. Note: Attempts to isomerize the *exo*-olefin into the *endo*-olefin **6** as described by de la Torre and coworkers[8] led to poor results, obtaining at the best run 20% of the desired product as an inseparable mixture with isosclareolide (**7**). The experimental procedure was conducted with **8** as reported for its epimer (see above) to furnish the *endo*-olefin **6** (319 mg, 1.09 mmol) as a colorless oil in 68% yield, and trace amounts (less than 5% yield) of the *exo*-olefin. Data for *endo*-olefin **6**: TLC (SiO_2): R_f = 0.26 (hexanes/EtOAc 85:15); $[\alpha]_D^{25}$ = +21 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}$ = +15.2 (*c* 0.25, $CHCl_3$);[8] ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.79 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 1.52 (s, 3H), 1.00-2.06 (m, 9H), 2.28 (dd, *J* = 16.7, 2.5 Hz, 1H), 2.46 (dd, *J* = 16.7, 9.2 Hz, 1H), 2.61-2.72 (m, 1H), 3.17 (s, 3H), 3.68 (s, 3H), 5.40 (br. s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.0 (CH_3), 18.5 (CH_2), 21.1 (CH_3), 21.6 (CH_3), 23.5 (CH_2), 28.9 (CH_2), 32.6 (CH_3), 32.7 (C), 32.9 (CH_3), 35.7 (C), 38.7 (CH_2), 41.9 (CH_2), 48.8 (CH), 49.5 (CH), 60.9 (CH_3), 121.9 (CH), 134.0 (C), 175.2 (C). Data for *exo*-olefin: TLC (SiO_2): R_f = 0.19 (hexanes/EtOAc 85:15); M.p.: 82-85 °C (lit.: 84-86 °C); $[\alpha]_D^{25}$ = −29 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}$ = −30.9 (*c* 0.99, $CHCl_3$);[30] ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.64 (s, 3H), 0.72 (s, 3H), 0.79 (s, 3H), 0.98-1.70 (m, 9H), 1.93-2.11 (m, 1H), 2.21-2.34 (m, 2H), 2.39 (d, *J* = 10.3 Hz, 1H), 2.59 (dd, *J* = 15.5, 9.8 Hz, 1H), 3.05 (s, 3H), 3.62 (s, 3H), 4.34 (s, 1H), 4.62 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.4 (CH_3), 18.9 (CH_2), 21.4 (CH_3), 23.7 (CH_2), 26.8 (CH_2), 32.1 (CH_3), 33.1 (C), 33.2 (CH_3), 37.2 (CH_2), 38.47 (CH_2), 38.53 (C), 41.7 (CH_2), 51.2 (CH), 54.7 (CH), 60.9 (CH_3), 105.5 (CH_2), 149.2 (C), 174.2 (C).

*2-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetaldehyde (**11**).* Solid $LiAlH_4$ (361 mg, 9.5 mmol, 5 equiv) was added to a solution of amide **6** (558 mg, 1.90 mmol, 1 equiv) in dry THF (38 mL) at 0 °C. After 2 h at the same temperature, an aqueous solution of HCl (1 M, 40 mL) was slowly added (*CAUTION! gas evolution*). The mixture was extracted with EtOAc (80 mL), the organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 95:5) to furnish aldehyde **11** (388 mg, 1.65 mmol) as a colorless oil in 87% yield. TLC (SiO_2): R_f = 0.32 (hexanes/EtOAc 95:5); $[\alpha]_D^{25}$ = −15 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}$ = −29.2 (*c* 0.161, $CHCl_3$);[31] ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.77 (s, 3H), 0.87 (s, 3H), 0.88 (s, 3H), 1.51 (s, 3H), 1.00-2.06 (m, 9H), 2.37-2.59 (m, 3H), 5.46 (br. s, 1H), 9.84 (t, *J* = 1.6 Hz, 1H); ^{13}C NMR (62.9 MHz,

$CDCl_3$): δ 14.2 (CH_3), 18.7 (CH_2), 21.8 (CH_3), 22.5 (CH_3), 23.6 (CH_2), 32.9 (C), 33.1 (CH_3), 36.0 (C), 39.5 (CH_2), 42.0 (CH_2), 42.3 (CH_2), 48.5 (CH), 49.8 (CH), 123.4 (CH), 132.9 (C), 203.5 (CH).

*3-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)propanenitrile (**12**)*. TosMIC (83.7 mg, 0.42 mmol, 2 equiv) in dry diglyme (2 mL) was added dropwise to a mixture of *t*-BuOK (74.4 mg, 0.63 mmol, 3 equiv) in diglyme (1 mL) at −60 °C, and the resulting mixture was stirred for 10 min. A solution of aldehyde **11** (49.2 mg, 0.21 mmol, 1 equiv) in diglyme (2 mL) was added dropwise to the reaction at −60 °C, the medium was stirred at this temperature for 1 h, and for 30 min at room temperature. Next, dry MeOH (2.5 mL) was added, and the reaction was stirred at 60 °C for 1 h. After that, the volatiles were removed under reduced pressure, and the residue was diluted with a saturated solution of NH_4Cl and the mixture was extracted with EtOAc (2 x 15 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 95:5 to 90:10) to give the nitrile **12** (26.5 mg, 0.108 mmol) as a colorless oil in 51% yield. TLC (SiO_2): R_f = 0.31 (hexanes/EtOAc 95:5);$[\alpha]_D^{25}$ = − 1 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2923, 2848, 2245, 1457, 1388, 1168, 1051, 805; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.76 (s, 3H), 0.86 (s, 3H), 0.88 (s, 3H), 0.80-1.30 (m, 3H), 1.67 (s, 3H), 1.36-2.08 (m, 9H), 2.25-2.43 (m, 1H), 2.44-2.60 (m, 1H), 5.46 (br. s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.6 (CH_3), 18.6 (CH_2), 18.9 (CH_2), 21.8 (CH_3), 22.0 (CH_3), 23.1 (CH_2), 23.7 (CH_2), 32.9 (C), 33.1 (CH_3), 36.6 (C), 39.0 (CH_2), 42.0 (CH_2), 49.8 (CH), 53.8 (CH), 119.9 (C), 123.9 (CH), 132.9 (C); HRMS (ESI +): *m/z* calculated for $C_{17}H_{27}NNa^+$ $[M+Na]^+$ 268.2036, found 268.2031.

*3-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)propanal (**13**)*. To a suspension of (methoxymethyl)triphenylphosphonium chloride (163 mg, 0.46 mmol, 2 equiv) in dry THF (2 mL) was added a solution of LiHMDS (1 M in THF, 345 µL, 0.345 mmol, 1.5 equiv) at 0 °C and the reaction was stirred at this temperature for 30 min. After this period, the brownish mixture was transferred *via* cannula to a flask containing a solution of aldehyde **11** (53.9 mg, 0.230 mmol, 1 equiv) in dry THF (2 mL) at 0 °C, and the resulting mixture was stirred for 30 min at 0 °C and 4 h at room temperature. Next, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL), and was extracted with EtOAc (10 mL). The organic phase was washed with brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was subjected to flash chromatography (SiO_2, hexanes/EtOAc 95:5) to afford a mixture of (*E*) and (*Z*)-enol ethers, which were immediately used in the next reaction. TLC (SiO_2): R_f = 0.45 (hexanes:EtOAc 95:5). The mixture of (*E*) and (*Z*)-enol ethers obtained

above was diluted in THF (2 mL) and a solution of HCl (6 M in H_2O, 0.4 mL, 2.4 mmol, 10 equiv) was added dropwise at 0 °C. The mixture was stirred at room temperature for 2 h, and was diluted with H_2O (8 mL), followed by an extraction with EtOAc (8 mL). The organic phase was washed with brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 95:5) to give aldehyde **13** (44.0 mg, 0.177 mmol) as a colorless oil in 77% yield. TLC (SiO_2): R_f = 0.30 (hexanes/EtOAc 95:5); $[\alpha]_D^{25}$ = +21 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2923, 2846, 1726, 1457, 1387, 1050, 983; ^1H NMR (250 MHz, $CDCl_3$): δ 0.79 (s, 3H), 0.85 (s, 3H), 0.88 (s, 3H), 0.81-1.04 (m, 1H), 1.15 (dd, *J* = 11.8, 5.0 Hz, 2H), 1.66 (s, 3H), 1.36-1.71 (m, 5H), 1.79-2.03 (m, 4H), 2.43 (dddd, *J* = 17.4, 8.8, 6.5, 1.9 Hz, 1H), 2.65 (dddd, *J* = 17.2, 9.9, 5.5, 1.6 Hz, 1H), 5.42 (br. s, 1H), 9.76 (t, *J* = 1.7 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.6 (CH_3), 18.7 (CH_2), 19.1 (CH_2), 21.8 (CH_3), 22.1 (CH_3), 23.7 (CH_2), 32.9 (C), 33.1 (CH_3), 36.9 (C), 39.4 (CH_2), 42.2 (CH_2), 46.0 (CH_2), 50.0 (CH), 54.3 (CH), 123.2 (CH), 134.1 (C), 202.4 (CH); HRMS (ESI +): *m/z* calculated for $C_{17}H_{28}ONa^+$ $[M+Na]^+$ 271.2032, found 271.2013.

(4aS,5S,8aS)-5-(but-3-yn-1-yl)-1,1,4a,6-tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (***14***). $TMSCHN_2$ solution (2 M in hexanes, 0.76 mL, 1.52 mmol, 4 equiv) was added to THF (5 mL), the resulting mixture was cooled to −78 °C, then a solution of *n*-BuLi (2.5 M in hexanes, 0.46 mL, 1.15 mmol, 3 equiv) was added dropwise and the reaction was stirred at the same temperature for 30 min. Next, a solution of aldehyde **13** (94.4 mg, 0.38 mmol, 1 equiv) in THF (3 mL) was added to the reaction and the resulting mixture was stirred at −78 °C for 1 h, and then at room temperature for 1 h. The reaction was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL), followed by the extraction with Et_2O (2 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes) to afford the alkyne **14** (74.4 mg, 0.30 mmol) as a colorless oil in 80% yield. TLC (SiO_2): R_f = 0.72 (hexanes); $[\alpha]_D^{25}$ = +12 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 3312, 2923, 2847, 2118, 1457, 1387, 1050, 983; ^1H NMR (250 MHz, $CDCl_3$): δ 0.76 (s, 3H), 0.86 (s, 3H), 0.88 (s, 3H), 0.80-1.29 (m, 4H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.35-2.06 (m, 11H), 2.10-2.27 (m, 1H), 2.37 (dddd, *J* = 16.8, 9.0, 5.0, 2.5 Hz, 1H), 5.40 (br. s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.6 (CH_3), 18.7 (CH_2), 20.3 (CH_2), 21.8 (CH_3), 22.1 (CH_3), 23.8 (CH_2), 26.2 (CH_2), 32.9 (C), 33.1 (CH_3), 36.6 (C), 39.1 (CH_2), 42.2 (CH_2), 50.0 (CH), 53.7 (CH), 68.3 (CH), 84.8 (C), 122.8 (CH), 134.5 (C); GC/MS (EI): *m/z* calculated for $C_{17}H_{25}$ $[M-CH_3]^+$ 229, found: 229.

4-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)butan-2-one (***2***).

Procedure A: MeMgBr solution (3 M in Et_2O, 1.6 mL, 4.8 mmol, 3 equiv) was added dropwise to a solution of nitrile **12** (393 mg, 1.6 mmol, 1 equiv) in dry Et_2O (15 mL) at 0 °C, the reaction was warmed to room temperature and was stirred for 16 h. The reaction was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL), followed by extraction with EtOAc (2 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 90:10) to give the ketone **2** (295 mg, 1.1 mmol) as a colorless oil in 70% yield. Note: Nitrile **12** and ketone **2** presented similar R_f using TLC with SiO_2 and different eluents, the progress of reaction was monitored by GC/MS analysis. Procedure B: To a pressure tube, alkyne **14** (16.0 mg, 64 µmol, 1 equiv), methanol (2 mL) and H_2O (1 mL) were added, followed by JohnPhosAuCl (1.7 mg, 3.2 µmol, 5 mol %), the pressure tube was sealed and heated at 110 °C for 90 min. The mixture was cooled to room temperature, then methanol was removed under reduced pressure. The remaining residue was extracted with CH_2Cl_2 (2 x 5 mL), the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 95:5 to 90:10) to give ketone **2** (13.1 mg, 50 µmol) as a colorless oil in 78% yield. TLC (SiO_2): R_f = 0.40 (hexanes/EtOAc 90:10); $[\alpha]_D^{25}$ = +20 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2924, 2851, 1717, 1662, 1463, 1365, 1331, 1162; ^1H NMR (250 MHz, $CDCl_3$): δ 0.77 (s, 3H), 0.85 (s, 3H), 0.88 (s, 3H), 0.81-1.24 (m, 4H), 1.66 (s, 3H), 1.33-1.71 (m, 4H), 1.72-2.05 (m, 4H), 2.14 (s, 3H), 2.41 (ddd, *J* = 16.1, 9.9, 6.0 Hz, 1H), 2.64 (ddd, *J* = 16.7, 10.7, 5.3 Hz, 1H), 5.41 (br. s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.6 (CH_3), 18.7 (CH_2), 20.9 (CH_2), 21.8 (CH_3), 22.1 (CH_3), 23.7 (CH_2), 29.9 (CH_3), 32.9 (C), 33.2 (CH_3), 36.9 (C), 39.3 (CH_2), 42.2 (CH_2), 45.9 (CH_2), 50.1 (CH), 54.3 (CH), 123.0 (CH), 134.4 (C), 208.8 (C); HRMS (ESI +): *m/z* calculated for $C_{18}H_{30}ONa^+$ $[M+Na]^+$ 285.2189, found 285.2200.

*(E)-ethyl 3-methyl-5-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahy-dronaphthalen-1-yl)pent-2-enoate (**15**).* Triethyl phosphonoacetate (583 µL, 2.85 mmol, 3 equiv) was added to a solution of ketone **2** (249 mg, 0.95 mmol, 1 equiv) in dry toluene (9.5 mL) at room temperature. Next, sodium hydride (60% w/w in mineral oil, 110 mg, 2.75 mmol, 2.9 equiv) was added to the mixture, which was then stirred for 10 min at room temperature and for 14 h at 50 °C. After cooling to room temperature, the reaction was quenched by the addition of brine (20 mL) and EtOAc (20 mL) was added to the mixture. The organic phase was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 97:3) to give the ester **15** (236 mg,

0.71 mmol) as a colorless oil in 75% yield. Note: The minor (*Z*)-isomer was detected by GC/MS analysis of the crude (*ca.* 5.5% of the product) and was separated from the (*E*)-isomer during the chromatographic purification. TLC (SiO_2): R_f = 0.48 (hexanes/EtOAc 95:5); $[\alpha]_D^{25}$ = +27 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2923, 1716, 1648, 1457, 1386, 1221, 1143, 1040, 861; ^1H NMR (250 MHz, $CDCl_3$): δ 0.75 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 1.27 (t, *J* = 7.1Hz, 3H), 1.69 (s, 3H), 0.79-1.74 (m, 9H), 2.16 (d, *J* = 1.3 Hz, 3H), 1.74-2.22 (m, 4H), 2.26-2.43 (m, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 5.40 (br. s, 1H), 5.66 (q, *J* = 1.0 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.5 (CH_3), 14.3 (CH_3), 18.7 (CH_2), 18.9 (CH_3), 21.8 (CH_3), 22.1 (CH_3), 23.8 (CH_2), 25.3 (CH_2), 32.9 (C), 33.1 (CH_3), 36.8 (C), 39.1 (CH_2), 42.2 (CH_2), 43.4 (CH_2), 50.1 (CH), 54.4 (CH), 59.4 (CH_2), 115.5 (CH), 122.7 (CH), 134.7 (C), 160.3 (C), 166.8 (C); HRMS (ESI +): *m/z* calculated for $C_{22}H_{36}O_2Na^+$ $[M+Na]^+$ 355.2608, found 355.2613.

*(E)-3-methyl-5-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydrona-phthalen-1-yl)pent-2-enoic acid (**16**).* Solid $LiOH•H_2O$ (298 mg, 12.2 mmol, 20 equiv) was added to a solution of ester **15** (203 mg, 0.610 mmol, 1 equiv) in a mixture of THF, *i*-PrOH and H_2O (21 mL, 1:1:1). The reaction was stirred at 60 °C for 20 h, then the volatiles were removed under reduced pressure. To the remaining residue, EtOAc (30 mL) and HCl solution (1 M, 30 mL) were added. The organic phase was separated, washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 85:15) to give the carboxylic acid **16** (141 mg, 0.463 mmol) as a white solid in 76% yield. TLC (SiO_2): R_f = 0.46 (hexanes/EtOAc 75:25); $[\alpha]_D^{25}$ = +34 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 3441 (broad), 2946 (broad), 2924, 2849, 1693, 1639, 1437, 1257, 1173, 867; ^1H NMR (250 MHz, $CDCl_3$): δ 0.76 (s, 3H), 0.86 (s, 3H), 0.88 (s, 3H), 0.80-1.03 (m, 2H), 1.08-1.73 (m, 7H), 1.70 (s, 3H), 2.19 (d, *J* = 1.1 Hz, 3H), 1.75-2.25 (m, 4H), 2.30-2.46 (m, 1H), 5.41 (br. s, 1H), 5.70 (q, *J* = 0.8 Hz, 1H), 11.46 (br. s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.5 (CH_3), 18.7 (CH_2), 19.3 (CH_3), 21.8 (CH_3), 22.1 (CH_3), 23.8 (CH_2), 25.3 (CH_2), 32.9 (C), 33.1 (CH_3), 36.8 (C), 39.2 (CH_2), 42.2 (CH_2), 43.6 (CH_2), 50.1 (CH), 54.4 (CH), 115.1 (CH), 122.8 (CH), 134.6 (C), 163.6 (C), 172.2 (C); HRMS (ESI +): *m/z* calculated for $C_{20}H_{32}O_2Na^+$ $[M+Na]^+$ 327.2295, found 327.2286.

*(4aS,5S,8aS)-5-((E)-4-iodo-3-methylbut-3-en-1-yl)-1,1,4a,6-tetramethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene (**3**).* A flask was charged with carboxylic acid **16** (93.2 mg, 0.306 mmol, 1 equiv) and CTAB (113 mg, 0.306 mmol, 1 equiv), the flask was purged with nitrogen, and dry acetonitrile (7 mL) was added followed by NIS (138 mg, 0.612 mmol, 2 equiv). The reaction mixture was heated at 80 °C for 1 h and, after cooling to room temperature, solvent was partially removed under reduced pressure to ~1 mL of

crude reaction mixture. This residue was subjected to flash chromatography (SiO_2, hexanes) to give the iodide **3** (56.5 mg, 0.146 mmol) as a colorless oil in 48% yield. TLC (SiO_2): R_f = 0.90 (hexanes); $[\alpha]_D^{25}$ = +5 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}^{20}$ = +3 (*c* 0.8, $CHCl_3$);[6] ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.75 (s, 3H), 0.86 (s, 3H), 0.88 (s, 3H), 0.80-1.02 (m, 2H) 1.07-1.64 (m, 10H), 1.68 (s, 3H), 1.85 (d, *J* = 0.8 Hz, 3H), 1.75-2.06 (m, 3H), 2.16 (ddd, *J* = 14.1, 10.3, 6.3 Hz, 1H), 2.40 (ddd, *J* = 14.4, 11.4, 4.6 Hz, 1H), 5.40 (br. s, 1H), 5.90 (q, *J* = 0.8 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.6 (CH_3), 18.8 (CH_2), 21.8 (CH_3), 22.2 (CH_3), 23.8 (CH_2), 24.0 (CH_3), 25.6 (CH_3), 32.9 (C), 33.1 (CH_3), 36.8 (C), 39.2 (CH_2), 42.0 (CH_2), 42.3 (CH_2), 50.1 (CH), 54.3 (CH), 74.9 (CH), 122.6 (CH), 134.8 (C), 148.5 (C).

*(E)-3-methyl-5-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)pent-2-en-1-ol (**17**)*. A freshly prepared solution of DIBAL-H (1.0 M in CH_2Cl_2, 215 µL, 215 µmol, 5 equiv) was added to a solution of ester **15** (14.3 mg, 43 µmol, 1 equiv) in dry CH_2Cl_2 (2 mL) at 0 °C. After stirring the reaction for 1 h at 0 °C, Et_2O (10 mL) and saturated aqueous solution of Rochelle's salt were added, and the reaction was vigorously stirred for 30 min at 0 °C and 1 h at room temperature. After separation of phases, the aqueous layer was extracted with Et_2O (10 mL). The organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 97:3 to 90:10) to afford the alcohol **17** (10 mg, 34 µmol) as a colorless oil in 80% yield. TLC (SiO_2): R_f = 0.27 (hexanes/EtOAc 90:10); $[\alpha]_D^{25}$ = +5 (*c* 0.5, $CHCl_3$), $[\alpha]_{D,lit}^{25}$ = +12 (*c* 0.690, $CHCl_3$);[19] ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.76 (s, 3H), 0.86 (s, 3H), 0.88 (s, 3H), 0.80-1.04 (m, 2H), 1.56 (s, 3H), 1.69 (s, 3H), 1.05-2.09 (m, 12H), 2.13-2.31 (m, 1H), 4.09-4.20 (m, 2H), 5.33-5.47 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.5 (CH_3), 16.4 (CH_3), 18.8 (CH_2), 21.8 (CH_3), 22.2 (CH_3), 23.8 (CH_2), 25.6 (CH_2), 32.9 (C), 33.1 (CH_3), 36.8 (C), 39.1 (CH_2), 42.0 (CH_2), 42.3 (CH_2), 50.1 (CH), 54.4 (CH), 59.4 (CH_2), 122.3 (CH), 123.3 (CH), 135.2 (C), 140.4 (C).

*(E)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (**21**)*. $MeONH_2$•HCl (690 mg, 8.1 mmol, 2.7 equiv) and NaOAc (1.09 g, 13.2 mmol, 4.4 equiv) were added to a solution of tetralone **20** (534 mg, 3.0 mmol, 1 equiv) in a mixture of ethanol/H_2O (15 mL, 4:1 v/v), then the mixture was stirred for 2 h at 70 °C. Next, the mixture was diluted with brine (25 mL), and was extracted with EtOAc (3 x 25 mL), the organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the methyl oxime **21** (616 mg, 3.0 mmol) as a colorless oil in quantitative yield, which was used in the next step without further purification. TLC (SiO_2): R_f = 0.64 (hexanes/EtOAc 75:25); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.83 (quint., *J* = 6.2 Hz, 2H), 2.71 (t, *J* = 6.5 Hz, 4H), 3.80 (s, 3H), 3.97 (s, 3H), 6.63 (d, *J* = 2.4

Hz, 1H), 6.75 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5 (CH_2), 24.1 (CH_2), 30.0 (CH_2), 55.1 (CH_3), 61.7 (CH_3), 112.7 (CH), 112.8 (CH), 123.4 (C), 125.7 (CH), 141.2 (C), 153.8 (C), 160.1 (C).

*(E)-6,8-dimethoxy-3,4-dihydronaphthalen-1(2H)-one O-methyl oxime (**22**) and 6,8-dimethoxy-3,4-dihydronaphthalen-1(2H)-one (**23**).* First step: Oxone (2.46 g, 4.0 mmol, 2.0 equiv) and $Pd(OAc)_2$ (22.5 mg, 0.1 mmol, 5 mol %) were added to a solution of methyl oxime **21** (411 mg, 2.0 mmol, 1 equiv) in dry MeOH (12 mL) at room temperature, and this mixture was stirred at this temperature for 24 h. Next, the reaction mixture was diluted with EtOAc (50 mL) and washed with H_2O (40 mL), saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 75:25 to 50:50) to furnish methyl oxime **22** (193 mg, 0.82 mmol) as a yellow oil in 41% yield and tetralone **23** (25 mg, 0.12 mmol) as an off-white solid in 6% yield. Second step: A solution of HCl (6 M in H_2O, 1.0 mL, 6.0 mmol, 22 equiv) was added to a solution of oxime **22** (64.0 mg, 0.27 mmol, 1 equiv) in 1,4-dioxane (4.5 mL). After addition, the mixture was heated to 80 °C under magnetic stirring for 2 h. Next, the mixture was diluted with EtOAc (20 mL), washed with brine (2 x 10 mL), the organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 50:50) to furnish tetralone **23** (46.2 mg, 0.22 mmol) as an off-white solid in 82% yield. Data for methyl oxime **22**: TLC (SiO_2): R_f = 0.30 (hexanes/EtOAc 75:25); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.69 (quint., *J* = 6.3 Hz, 2H), 2.58 (t, *J* = 6.0 Hz, 2H), 2.74 (t, *J* = 6.8 Hz, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 3.96 (s, 3H), 6.29 (d, *J* = 2.4 Hz, 2H), 6.36 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.1 (CH_2), 25.4 (CH_2), 31.4 (CH_2), 55.1 (CH_3), 56.0 (CH_3), 61.5 (CH_3), 97.8 (CH), 104.6 (CH), 112.8 (C), 144.4 (C), 153.7 (C), 159.1 (C), 160.2 (C). Data for tetralone **23**: TLC (SiO_2): R_f = 0.36 (hexanes/EtOAc 50:50); M.p.: 62-64 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.98 (quint., *J* = 6.2 Hz, 2H), 2.55 (t, *J* = 6.5 Hz, 2H), 2.85 (t, *J* = 6.1 Hz, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 6.26-6.34 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 22.7 (CH_2), 31.5 (CH_2), 40.7 (CH_2), 55.3 (CH_3), 55.8 (CH_3), 97.1 (CH), 104.5 (CH), 116.3 (C), 149.2 (C), 162.5 (C), 163.7 (C), 196.0 (C).

*2-hydroxyethyl 4-(3,5-dimethoxyphenyl)butanoate (**25**).* *p*TSA•H_2O (1.9 mg, 10 μmol, 10 mol %), tetralone **23** (20.6 mg, 0.1 mmol, 1 equiv) and ethylene glycol (1 mL) were placed in an open flask, which was heated at 140 °C for 24 h. Then, the reaction contents were diluted with EtOAc (20 mL) and saturated solution of $NaHCO_3$ (10 mL), the organic phase was separated, washed with H_2O (10 mL) and brine (10

mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc 60:40) to afford ester **25** (26.3 mg, 98 μmol) in 98% yield as a colorless oil. TLC (SiO_2): R_f = 0.52 (hexanes/EtOAc 50:50); IR (ATR, cm^{-1}): 3432 (broad), 2940, 2841, 1731, 1596, 1461, 1205, 1150, 1070, 832; ^1H NMR (250 MHz, $CDCl_3$): δ 1.95 (quint., *J* = 7.5 Hz, 2H), 2.09 (br. s, 1H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 3.77 (s, 6H), 3.74-3.85 (m, 2H), 4.16-4.23 (m, 2H), 6.27-6.35 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 26.0 (CH_2), 33.2 (CH_2), 35.1 (CH_2), 55.0 ($2CH_3$), 60.7 (CH_2), 65.7 (CH_2), 97.9 (CH), 106.4 (2CH), 143.5 (C), 160.6 (2C), 173.7 (C); HRMS (ESI +): *m/z* calculated for $C_{14}H_{21}O_5^+$ $[M+H]^+$ 269.1383, found 269.1380.

*6',8'-dimethoxy-3',4'-dihydro-2'H-spiro[[1,3]dioxolane-2,1'-naphthalene] (**24**).* PPTS (8.7 mg, 34 μmol, 10 mol %) and ethylene glycol (57 μL, 1 mmol, 3 equiv) were added to a solution of tetralone **23** (70.1 mg, 0.34 mmol, 1 equiv) in dry benzene (8 mL) in a Dean-Stark apparatus, the reaction was stirred under vigorous reflux for 14 h. After cooling to room temperature, solid K_2CO_3 (33 mg) was added and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc/Et_3N 75:25:1) to furnish ketal **24** (42.6 mg, 0.17 mmol) as a colorless oil in 50% yield. Note: Ketal **24** started decomposing back to tetralone **23** in a few hours of storing. TLC (SiO_2): R_f = 0.40 (hexanes/EtOAc 75:25); ^1H NMR (250 MHz, $CDCl_3$): δ 1.75-2.07 (m, 4H), 2.66-2.82 (m, 2H), 3.75 (s, 3H), 3.80 (s, 3H), 4.00-4.30 (m, 4H), 6.20 (d, *J* = 2.0 Hz, 1H), 6.32 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.0 (CH_2), 31.0 (CH_2), 36.7 (CH_2), 55.1 (CH_3), 55.7 (CH_3), 65.3 ($2CH_2$), 97.8 (CH), 104.1 (CH), 108.0 (C), 117.6 (C), 142.2 (C), 159.9 (C), 160.1 (C).

*2-hydroxyethyl 4-(3,4,5-trimethoxyphenyl)butanoate (**35**) and 8-hydroxy-6,7-dimethoxy-3,4-dihydronaphthalen-1(2H)-one (**34**).* *p*TSA•H_2O (1.9 mg, 10 μmol, 10 mol %), tetralone **33** (23.6 mg, 0.1 mmol, 1 equiv) and ethylene glycol (1 mL) were placed in a flask, which was heated at 140 °C for 24 h. Then, the reaction contents were diluted with EtOAc (20 mL) and saturated solution of $NaHCO_3$ (10 mL), the organic phase was separated, washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes:EtOAc 60:40 to 30:70) to afford ester **35** (18.0 mg, 60 μmol) in 60% yield and tetralone **34** (7.1 mg, 32 μmol) in 32% yield. Data for compound **35**: TLC (SiO_2): R_f = 0.36 (hexanes/EtOAc 30:70); IR (ATR, cm^{-1}): 3448 (broad), 2941, 2841, 1730, 1590, 1508, 1458, 1238, 1125, 1006, 826; ^1H NMR (250 MHz, $CDCl_3$): δ 1.90 (br. s, 1H), 1.95 (quint., *J* = 7.4 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 3.84 (s, 6H), 3.79-3.86 (m, 2H), 4.16-4.24 (m, 2H), 6.39 (s, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$):

δ 26.5 (CH_2), 33.4 (CH_2), 35.5 (CH_2), 56.1 ($2CH_3$), 60.8 (CH_3), 61.2 (CH_2), 65.9 (CH_2), 105.4 (2CH), 136.2 (C), 137.0 (C), 153.1 (2C), 173.8 (C); HRMS (ESI +): *m/z* calculated for $C_{15}H_{22}O_6Na^+$ $[M+Na]^+$ 321.1309, found 321.1308. Data for compound **34**: TLC (SiO_2): R_f = 0.44 (hexanes/EtOAc 60:40); IR (ATR, cm^{-1}): 2923, 2844, 1634, 1574, 1422, 1289, 1104, 1012, 789; ^1H NMR (400 MHz, $CDCl_3$): δ 2.07 (quint., *J* = 6.2 Hz, 2H), 2.62 (t, *J* = 6.4 Hz, 2H), 2.86 (t, *J* = 6.1 Hz, 2H), 3.86 (s, 3H), 3.91 (s, 3H), 6.29 (s, 1H), 12.69 (s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 23.0 (CH_2), 30.0 (CH_2), 38.4 (CH_2), 56.0 (CH_3), 60.7 (CH_3), 102.6 (CH), 112.5 (C), 134.4 (C), 141.9 (C), 157.1 (C), 158.3 (C), 203.6 (C); HRMS (ESI +): *m/z* calculated for $C_{12}H_{15}O_4^+$ $[M+H]^+$ 223.0965, found 223.0967.

*2-hydroxyethyl 3-(3,5-dimethoxyphenyl)propanoate (**37**)*. *p*TSA•H_2O (1.9 mg, 10 μmol, 10 mol %), bicycle **36** (19.2 mg, 0.1 mmol, 1 equiv) and ethylene glycol (1 mL) were placed in a flask, which was heated at 140 °C for 24 h. Then, the reaction contents were diluted with EtOAc (20 mL) and saturated solution of $NaHCO_3$ (10 mL), the organic phase was separated, washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes:EtOAc 50:50) furnished ester **37** (24.3 mg, 96 μmol) in 93% yield. TLC (SiO_2): R_f = 0.48 (hexanes/EtOAc 50:50); IR (ATR, cm^{-1}): 3413 (broad), 2965, 2925, 2841, 1732, 1596, 1462, 1205, 1151, 1068, 835; ^1H NMR (250 MHz, $CDCl_3$): δ 1.60-1.74 (m, 4H), 2.01 (br. s, 1H), 2.37 (t, *J* = 7.0 Hz, 2H), 2.57 (t, *J* = 6.8 Hz, 2H), 3.77 (s, 6H), 3.77-3.85 (m, 2H), 4.16-4.23 (m, 2H), 6.30 (t, *J* = 2.0 Hz, 1H), 6.33 (d, *J* = 2.0 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.5 (CH_2), 30.5 (CH_2), 34.0 (CH_2), 35.8 (CH_2), 55.2 ($2CH_3$), 61.2 (CH_2), 65.9 (CH_2), 97.7 (CH), 106.5 (2CH), 144.4 (C), 160.7 (2C), 173.9 (C); HRMS (ESI +): *m/z* calculated for $C_{13}H_{18}O_5Na^+$ $[M+Na]^+$ 277.1046, found 277.1046.

*2-hydroxyethyl 5-(3,5-dimethoxyphenyl)pentanoate (**39**)*. *p*TSA•H_2O (1.9 mg, 10 μmol, 10 mol %), bicycle **38** (22.0 mg, 0.1 mmol, 1 equiv) and ethylene glycol (1 mL) were placed in a flask, which was heated at 140 °C for 24 h. Then, the reaction contents were diluted with EtOAc (20 mL) and saturated solution of $NaHCO_3$ (10 mL), the organic phase was separated, washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (SiO_2, hexanes:EtOAc 50:50) furnished ester **39** (25.2 mg, 89 μmol) in 89% yield. TLC (SiO_2): R_f = 0.50 (hexanes/EtOAc 50:50); IR (ATR, cm^{-1}): 3418 (broad), 2940, 2855, 2833, 1732, 1596, 1461, 1205, 1150, 1056, 831; ^1H NMR (250 MHz, $CDCl_3$): δ 1.88 (br. s, 1H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.91 (t, *J* = 7.6 Hz, 2H), 3.77 (s, 6H), 3.77-3.84 (m, 2H), 4.17-4.25 (m, 2H), 6.32 (t, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 31.2 (CH_2), 35.5 (CH_2), 55.2 ($2CH_3$), 61.1 (CH_2), 66.1 (CH_2), 98.2 (CH), 106.3

(2CH), 142.7 (C), 160.8 (2C), 173.1 (C); HRMS (ESI +): *m/z* calculated for $C_{15}H_{23}O_5^+$ $[M+H]^+$ 283.1540, found 283.1538.

*(R)-1-(3,5-dimethoxyphenyl)but-3-en-1-ol (**41**)*. A pressure tube was charged with $[Ir(cod)Cl_2]$ (31 mg, 45 µmol, 2.5 mol %), Cs_2CO_3 (117 mg, 0.36 mmol, 20 mol %), 4-chloro-3-nitrobenzoic acid (37 mg, 0.18 mmol, 10 mol %), (*R*)-BINAP (57 mg, 90 µmol, 5 mol %) and alcohol **40** (303 mg, 1.8 mmol, 1 equiv). The tube was purged with argon, and dry THF (6 mL) was added followed by allyl acetate (392 µL, 3.6 mmol, 2 equiv), the pressure tube was sealed and heated at 100 °C for 40 h. The solvent was removed under reduced pressure, and the brown residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 75:25) to give the alcohol **41** (280 mg, 1.3 mmol) as a colorless oil in 75% yield. TLC (SiO_2): R_f = 0.40 (hexanes:EtOAc 75:25); ee = 92% (determined by ^{1}H NMR of Mosher ester derivatives); $[\alpha]_D^{25}$ = +39 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.19 (br. s, 1H), 2.44-2.53 (m, 2H), 3.78 (s, 6H), 4.65 (t, *J* = 6.4 Hz, 1H), 5.09-5.21 (m, 2H), 5.80 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 6.37 (t, *J* = 2.3 Hz, 1H), 6.52 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 43.7 (CH_2), 55.3 ($2CH_3$), 73.3 (CH), 99.4 (CH), 103.7 (2CH), 118.3 (CH_2), 134.4 (CH), 146.5 (C), 160.8 (2C); IR (ATR, cm^{-1}): 3404 (broad), 2937, 2840, 1596, 1460, 1430, 1296, 1205, 1151, 1054, 920, 838, 698; HRMS (ESI +): *m/z* calculated for $C_{12}H_{16}O_3Na^+$ $[M+Na]^+$ 231.0992, found 231.0985.

*(S)-1-(1-bromobut-3-en-1-yl)-3,5-dimethoxybenzene (**43**).* CBr_4 (1.61 g, 4.8 mmol, 2 equiv) and PPh_3 (1.26 g, 4.8 mmol, 2 equiv) were added to a solution of alcohol **41** (500 mg, 2.4 mmol, 1 equiv) in CH_2Cl_2 (20 mL) at 0 °C. After stirring the reaction for 1 h at 0 °C, ice-cold H_2O (20 mL) was added. The mixture was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 95:5) to give the bromide **43** (530 mg, 1.95 mmol) as a colorless oil in 81% yield. TLC (SiO_2): R_f = 0.28 (hexanes:EtOAc 95:5); $[\alpha]_D^{25}$ = −78 (*c* 0.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.87-3.05 (m, 2H), 3.80 (s, 6H), 4.87 (t, *J* = 7.4 Hz, 1H), 5.06-5.21 (m, 2H), 5.76 (ddt, *J* = 17.1, 10.3, 6.6 Hz, 1H), 6.39 (t, *J* = 2.3 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 43.9 (CH_2), 54.0 (CH), 55.4 ($2CH_3$), 100.3 (CH), 105.5 (2CH), 118.1 (CH_2), 134.7 (CH), 143.7 (C), 160.8 (2C); IR (ATR, cm^{-1}): 3004, 2939, 2840, 1599, 1462, 1432, 1208, 1158, 1067, 927, 838, 724; HRMS (ESI +): *m/z* calculated for $C_{12}H_{16}O_2Br^+$ $[M+H]^+$ 271.0328, found 271.0329.

*(R)-4-benzyl-3-(2-(3,5-dimethoxyphenyl)acetyl)oxazolidin-2-one (**47**)*. Et_3N (418 µL, 3 mmol, 3 equiv) was added to a mixture of (*R*)-4-benzyl-2-oxazolidinone (**45**, 181 mg, 1 mmol, 1 equiv), carboxylic acid **46**

(226 mg, 1.15 mmol, 1.15 equiv) in dry toluene (1.8 mL) at room temperature. The reaction was stirred at 80 °C to obtain a solution, next pivaloyl chloride (149 µL, 1.2 mmol, 1.2 equiv) was added and the reaction was stirred for 2 h at 110 °C. Finally, a second portion of pivaloyl chloride (75 µL, 0.6 mmol, 1.2 equiv) was added and the reaction was stirred for 3 h at 110 °C. Then, this mixture was cooled to r.t., and was diluted with EtOAc (30 mL) and HCl aqueous solution (1 M, 10 mL), the organic phase was then washed with saturated $NaHCO_3$ solution (10 mL), and brine (10 mL). The organic phase was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 85:15 to 67:33) to furnish imide **47** (191 mg, 0.54 mmol) as a dark oil in 54% yield. TLC (SiO_2): R_f = 0.33 (hexanes:EtOAc 67:33); $[\alpha]_D^{25}$ = −58 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.78 (dt, *J* = 13.4, 9.2 Hz, 1H), 3.23 (dd, *J* = 13.4, 3.0 Hz, 1H), 3.77 (s, 6H), 4.10-4.35 (m, 4H), 4.58-4.73 (m, 1H), 6.41 (t, *J* = 2.0 Hz, 1H), 6.52 (d, *J* = 2.0 Hz, 2H), 7.07-7.17 (m, 2H), 7.20-7.34 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 37.4 (CH_2), 41.4 (CH_2), 54.96 (CH), 55.03 ($2CH_3$), 65.8 (CH_2), 99.1 (CH), 107.6 (2CH), 127.0 (CH), 128.6 (2CH), 129.2 (2CH), 134.9 (C), 135.5 (C), 153.1 (C), 160.6 (2C), 170.6 (C); IR (ATR, cm^{-1}): 2927, 2838, 1778, 1698, 1596, 1456, 1206, 1153, 1065, 734; HRMS (ESI +): *m/z* calculated for $C_{20}H_{21}NO_5Na^+$ $[M+Na]^+$ 378.1312, found 378.1305.

*(R)-4-benzyl-3-((R)-2-(3,5-dimethoxyphenyl)pent-4-enoyl)oxazolidin-2-one (**48**)*. NaHMDS solution (2.0 M in THF, 4.06 mL, 8.12 mmol, 1.4 equiv) was added dropwise to a solution of imide **47** (2.06 g, 5.8 mmol, 1 equiv) in THF (58 mL) at −78 °C, the resulting mixture was stirred for 1 h at the same temperature. Next, allyl bromide (2.0 mL, 22.4 mmol, 3.9 equiv) was added dropwise to the sodium enolate solution, the reaction was stirred for 15 min at −78 °C, and 3 h at −45 °C (cryostat bath). The reaction was quenched by addition of NH_4Cl saturated solution (50 mL), and was extracted with EtOAc (2 x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 75:25) to furnish imide **48** (1.40 g, 3.55 mmol) as a colorless oil in 61% yield. Note: A single diastereoisomer was observed by NMR analysis, and the diatereomeric ratio was considered to be higher than 95:5. TLC (SiO_2): R_f = 0.42 (hexanes:EtOAc 67:33); $[\alpha]_D^{25}$ = −92 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.55 (dt, *J* = 14.2, 6.2 Hz, 1H), 2.78 (dd, *J* = 13.3, 9.6 Hz, 1H), 2.94 (dt, *J* = 14.1, 7.9 Hz, 1H), 3.32 (dd, *J* = 13.3, 3.2 Hz, 1H), 3.78 (s, 6H), 3.98-4.18 (m, 2H), 4.54-4.67 (m, 1H), 5.01-5.20 (m, 3H), 5.81 (ddt, *J* = 16.9, 10.3, 6.9 Hz, 1H), 6.37 (t, *J* = 2.2 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 2H), 7.18-7.38 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 37.9 (CH_2), 38.1 (CH_2), 48.2 (CH), 55.3 ($2CH_3$), 55.7 (CH), 65.7 (CH_2), 99.5 (CH), 106.5 (2CH), 117.2 (CH_2), 127.3 (CH), 128.9

(2CH), 129.4 (2CH), 135.2 (CH), 135.3 (C), 140.4 (C), 152.9 (C), 160.7 (2C), 173.0 (C); IR (ATR, cm^{-1}): 2934, 2838, 1779, 1697, 1595, 1456, 1206, 1157, 1065, 700; HRMS (ESI +): *m/z* calculated for $C_{23}H_{25}NO_5Na$ $[M+Na]^+$ 418.1625, found 418.1619.

*(R)-2-(3,5-dimethoxyphenyl)pent-4-en-1-ol (**49**).* Dry EtOH (996 µL, 17.1 mmol, 5 equiv) was added to a solution of imide **48** (1.35 g, 3.4 mmol, 1 equiv) in Et_2O (34 mL) at 0 °C. Next, solid $LiBH_4$ (391 mg, 17.1 mmol, 5 equiv) was added to the reaction, the resulting mixture was stirred for 4 h at 0 °C. After that, aqueous solution of NaOH (1 M, 30 mL) was carefully added and the resulting mixture was stirred for 1 h, and was extracted with EtOAc (2 x 40 mL). The combined organic phases were washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 67:33) to furnish alcohol **49** (660 mg, 2.97 mmol) as a colorless oil in 87% yield. TLC (SiO_2): R_f = 0.40 (hexanes:EtOAc 60:40); $[\alpha]_D^{25}$ = −14 (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 0.54 (br. s, 1H), 2.28-2.50 (m, 2H), 2.81 (quint., *J* = 6.8 Hz, 1H), 3.65-3.81 (m, 2H), 3.78 (s, 6H), 4.92-5.10 (m, 2H), 5.72 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1H), 6.34 (t, *J* = 2.1 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 36.5 (CH_2), 48.5 (CH), 55.2 ($2CH_3$), 66.8 (CH_2), 98.4 (CH), 106.1 (2CH), 116.4 (CH_2), 136.2 (CH), 144.4 (C), 160.9 (2C); IR (ATR, cm^{-1}): 3380 (broad), 2923, 1595, 1461, 1204, 1151, 1063, 918, 833; HRMS (ESI +): *m/z* calculated for $C_{13}H_{18}O_3Na^+$ $[M+Na]^+$ 245.1148, found 245.1152.

*(R)-tert-butyl((2-(3,5-dimethoxyphenyl)pent-4-en-1-yl)oxy)diphenylsilane (**50**).* Imidazole (366 mg, 5.35 mmol, 1.8 equiv) and TBDPSCl (1.02 mL, 3.86 mmol, 1.3 equiv) were added to a solution of alcohol **49** (660 mg, 2.97 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at room temperature. After stirring the reaction for 12 h, H_2O (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (50 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 90:10) to give the silyl ether **50** (1.23 g, 2.67 mmol) as a colorless oil in 90% yield. TLC (SiO_2): R_f = 0.32 (hexanes:EtOAc 90:10); $[\alpha]_D^{25}$ = −8 (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 1.06 (s, 9H), 2.42 (dt, *J* = 14.1, 7.7 Hz, 1H), 2.68 (dt, *J* = 14.2, 7.1 Hz, 1H), 2.77-2.91 (m, 1H), 3.77 (s, 6H), 3.72-3.82 (m, 2H), 4.90-5.11 (m, 2H), 5.72 (ddt, *J* = 16.9, 9.9, 7.1 Hz, 1H), 6.33-6.39 (m, 3H), 7.31-7.48 (m, 6H), 7.54-7.64 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.2 (C), 26.8 ($3CH_3$), 35.8 (CH_2), 48.5 (CH), 55.2 ($2CH_3$), 67.9 (CH_2), 98.3 (CH), 106.3 (2CH), 116.0 (CH_2), 127.5 (4CH), 129.5 (2CH), 133.6 (C), 133.7 (C), 135.5 (2CH), 135.6 (2CH), 136.8 (CH), 145.0 (C), 160.5 (2C); IR

(ATR, cm^{-1}): 2931, 2857, 1596, 1462, 1428, 1204, 1152, 1111, 824, 700; HRMS (ESI +): *m/z* calculated for $C_{29}H_{36}O_3SiNa^+$ $[M+Na]^+$ 483.2326, found 483.2321.

*(R)-5-((tert-butyldiphenylsilyl)oxy)-4-(3,5-dimethoxyphenyl)pentan-1-ol (**51**)*. 9-BBN solution (0.5 M in THF, 8.0 mL, 4.0 mmol, 1.5 equiv) was added to a solution of alkene **50** (1.22 g, 2.66 mmol, 1 equiv) in THF (50 mL) at 0 °C, after 5 min the ice bath was removed. The reaction was stirred for 2 h at r.t., then, the mixture was cooled to 0 °C and H_2O (50 mL) and solid $NaBO_3$•$4H_2O$ (2.11 g) were added, after 10 min the ice bath was removed, and the mixture was stirred vigorously for 2 h at r.t. Next, the reaction was extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 85:15 to 75:25) to give alcohol **51** (1.15 g, 2.40 mmol) as a colorless oil in 90% yield. TLC (SiO_2): R_f = 0.25 (hexanes:EtOAc 75:25); $[\alpha]_D^{25}$ = −6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.03 (s, 9H), 1.41-1.70 (m, 4H), 1.84-2.01 (m, 1H), 2.64-2.78 (m, 1H), 3.59 (t, *J* = 6.4 Hz, 2H), 3.75 (s, 6H), 3.70-3.80 (m, 2H), 6.27-6.38 (m, 3H), 7.30-7.47 (m, 6H), 7.52-7.63 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.2 (C), 26.8 ($3CH_3$), 27.6 (CH_2), 30.6 (CH_2), 48.6 (CH), 55.2 ($2CH_3$), 62.9 (CH_2), 68.5 (CH_2), 98.2 (CH), 106.2 (2CH), 127.5 (4CH), 129.5 (2CH), 133.6 (C), 133.7 (C), 135.5 (2CH), 135.6 (2CH), 145.3 (C), 160.6 (2C); IR (ATR, cm^{-1}): 3389 (broad), 2932, 2858, 1596, 1462, 1428, 1204, 1152, 1112, 1060, 824, 701; HRMS (ESI +): *m/z* calculated for $C_{29}H_{38}O_4SiNa^+$ $[M+Na]^+$ 501.2432, found 501.2439.

*(R)-5-((tert-butyldiphenylsilyl)oxy)-4-(3,5-dimethoxyphenyl)pentanoic acid (**52**)*. PDC (2.59 g, 6.75 mmol, 3 equiv) was added to a solution of alcohol **51** (1.08 g, 2.25 mmol, 1 equiv) in dry DMF (15 mL), and the mixture was stirred at room temperature for 6 h. After this, H_2O (150 mL) was added to the reaction and the resulting mixture was extracted with EtOAc (2 × 100 mL). Next, the combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 75:25 to 60:40) to give carboxylic acid **52** (602 mg, 1.22 mmol) as a colorless oil in 54% yield. TLC (SiO_2): R_f = 0.15 (hexanes:EtOAc 75:25); $[\alpha]_D^{25}$ = −8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.82-2.02 (m, 1H), 2.19-2.40 (m, 3H), 2.70-2.85 (m, 1H), 3.77 (s, 6H), 3.79 (d, *J* = 7.4 Hz, 2H), 6.33 (d, *J* = 2.1 Hz, 2H), 6.37 (d, *J* = 2.1 Hz, 1H), 7.32-7.47 (m, 6H), 7.57-7.66 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.2 (C), 26.6 (CH_2), 26.8 ($3CH_3$), 32.0 (CH_2), 48.0 (CH), 55.2 ($2CH_3$), 68.3 (CH_2), 98.6 (CH), 106.2 (2CH), 127.6 (4CH), 129.5 (CH), 129.6 (CH), 133.5 (C), 133.6 (C), 135.5 (2CH), 135.6 (2CH), 145.1 (C), 160.7 (2C), 179.8 (C); IR (ATR, cm^{-1}): 2929, 2857, 1709, 1597, 1462,

1429, 1205, 1155, 1112, 702; HRMS (ESI +): *m/z* calculated for $C_{29}H_{36}O_5SiNa^+$ $[M+Na]^+$ 515.2224, found 515.2222.

(R)-4-(((tert-butyldiphenylsilyl)oxy)methyl)-6,8-dimethoxy-3,4-dihydronaphthalen-1(2H)-one (***53***). Oxalyl chloride (110 µL, 1.3 mmol, 2 equiv) and DMF (5.0 µL, 65 µmol, 10 mol %) were added to a solution of carboxylic acid **52** (320 mg, 0.65 mmol, 1 equiv) in anhydrous CH_2Cl_2 (13 mL) at 0 °C, then, the cooling bath was removed and the mixture was stirred for 1.5 h at room temperature. Next, the volatiles were removed under reduced pressure, and the residue was directly diluted in dry CH_2Cl_2 (13 mL). To this solution, $SnCl_4$ (1 M in CH_2Cl_2, 715 µL, 0.71 mmol, 1.1 equiv) was added at 0 °C, and the mixture was stirred for 2 h at the same temperature. Next, water (10 mL) was added to the reaction at 0 °C, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 60:40 to 50:50) to afford tetralone **53** (266 mg, 0.56 mmol) as a colorless oil in 86% overall yield. TLC (SiO_2): R_f = 0.30 (hexanes:EtOAc 60:40); $[\alpha]_D^{25}$ = +50 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.06 (s, 9H), 2.03-2.34 (m, 2H), 2.40-2.69 (m, 2H), 2.97-3.10 (m, 1H), 3.76 (s, 3H), 3.86 (s, 3H), 3.78-3.87 (m, 2H), 6.22 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 7.31-7.47 (m, 6H), 7.59-7.68 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.2 (C), 23.6 (CH_2), 26.8 ($3CH_3$), 36.0 (CH_2), 42.3 (CH), 55.3 (CH_3), 55.9 (CH_3), 66.2 (CH_2), 97.6 (CH), 105.1 (CH), 116.3 (C), 127.7 (4CH), 129.7 (2CH), 133.2 (C), 133.4 (C), 135.5 (4CH), 149.1 (C), 162.3 (C), 163.7 (C), 195.8 (C); IR (ATR, cm^{-1}): 2930, 2857, 1670, 1597, 1455, 1255, 1088, 824, 702; HRMS (ESI +): *m/z* calculated for $C_{29}H_{34}O_4SiNa^+$ $[M+Na]^+$ 497.2119, found 497.2124.

(R)-tert-butyl((6',8'-dimethoxy-3',4'-dihydro-2'H-spiro[[1,3]dithiane-2,1'-naphthalen]-4'-yl)methoxy)diphenylsilane (***54***). 1,3-Propanedithiol (222 µL, 2.19 mmol, 4 equiv) and BF_3•Et_2O (135 µL, 1.1 mmol, 2 equiv) were added to a solution of tetralone **53** (260 mg, 0.55 mmol, 1 equiv) in CH_2Cl_2 (6 mL) at 0 °C. After 10 min, the ice bath was removed and the reaction was stirred for 18 h. Next, the mixture was diluted with $NaHCO_3$ saturated solution (10 mL), and the mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 95:5 to 85:15) to furnish dithiane **54** (213 mg, 0.38 mmol) as a colorless oil in 69% yield. TLC (SiO_2): R_f = 0.35 (hexanes:EtOAc 85:15); $[\alpha]_D^{25}$ = +47 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.11 (s, 9H), 1.93-2.18 (m, 4H), 2.40 (ddd, *J* = 14.5, 10.3, 4.3 Hz, 1H), 2.61-2.88 (m, 3H), 2.88-3.01 (m, 1H), 3.17 (ddd, *J* = 14.5,

10.7, 3.6 Hz, 2H), 3.65 (s, 3H), 3.89 (s, 3H), 3.71-3.92 (m, 2H), 6.11 (d, *J* = 2.5 Hz, 1H), 6.37 (d, *J* = 2.5 Hz, 1H), 7.34-7.48 (m, 6H), 7.63-7.76 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.2 (C), 20.9 (CH_2), 24.6 (CH_2), 26.9 ($3CH_3$), 27.1 (CH_2), 27.6 (CH_2), 33.5 (CH_2), 42.1 (CH), 50.4 (C), 55.1 (CH_3), 56.5 (CH_3), 67.6 (CH_2), 99.9 (CH), 106.4 (CH), 120.2 (C), 127.6 (4CH), 129.6 (2CH), 133.6 (C), 133.8 (C), 135.58 (2CH), 135.62 (2CH), 141.0 (C), 159.5 (C), 161.2 (C); IR (ATR, cm^{-1}): 2930, 2857, 1671, 1597, 1428, 1257, 1155, 1112, 998; HRMS (ESI +): *m/z* calculated for $C_{32}H_{40}O_3S_2SiNa^+$ $[M+Na]^+$ 587.2080, found 587.2061.

*(R)-(6',8'-dimethoxy-3',4'-dihydro-2'H-spiro[[1,3]dithiane-2,1'-naphthalen]-4'-yl)methanol (**55**).* TBAF solution (1 M in THF, 0.80 mL, 0.80 mmol, 2 equiv) was added to a mixture of silyl ether **54** (226 mg, 0.40 mmol, 1 equiv) in dry THF (5 mL) at 0 °C, and after 5 min the ice bath was removed. This mixture was stirred for 2 h, then was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL). The mixture was extracted with EtOAc (2 x 15 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 50:50) to furnish alcohol **55** (105 mg, 0.32 mmol) as a colorless oil in 80% yield. TLC (SiO_2): R_f = 0.33 (hexanes:EtOAc 50:50); $[\alpha]_D^{25}$ = +22 (*c* 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.86-2.18 (m, 5H), 2.45-2.85 (m, 4H), 2.92 (quint, *J* = 6.0 Hz, 1H), 3.07-3.23 (m, 2H), 3.75 (s, 3H), 3.71-3.83 (m, 2H), 3.89 (s, 3H), 6.38 (d, *J* = 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.5 (CH_2), 24.6 (CH_2), 27.2 (CH_2), 27.6 (CH_2), 34.1 (CH_2), 41.9 (CH), 50.4 (C), 55.2 (CH_3), 56.5 (CH_3), 66.8 (CH_2), 99.8 (CH), 106.3 (CH), 120.3 (C), 140.8 (C), 159.9 (C), 161.5 (C); IR (ATR, cm^{-1}): 3427, 2929, 1599, 1455, 1421, 1275, 1212, 1044, 938, 828; HRMS (ESI +): m/z calculated for $C_{16}H_{22}O_3S_2Na^+$ $[M+Na]^+$ 349.0903, found 349.0904.

*1-(6',8'-dimethoxy-3',4'-dihydro-2'H-spiro[[1,3]dithiane-2,1'-naphthalen]-4'-yl)-1-hydroxy-5-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)pentan-3-one (**56**).* SO_3•py (58.6 mg, 0.37 mmol, 4.0 equiv) was added to a solution of alcohol **55** (30.0 mg, 92 µmol, 1.0 equiv), DIPEA (160 µl, 920 µmol, 10 equiv), and DMSO (65 µl, 920 µmol, 10 equiv) in dry CH_2Cl_2 (5 mL) at 0 °C. This mixture was stirred for 1 h, then H_2O (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and were concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 85:15) to furnish aldehyde **44**, which was directly used in the next step. TLC (SiO_2): R_f = 0.61 (hexanes/EtOAc 75:25); LiHMDS solution (1.0 M in THF, 129 µL, 0.13 mmol, 1.4 equiv) was added dropwise to a solution of ketone **2** (31.4 mg, 0.12 mmol, 1.3 equiv) in THF (2.5 mL) at −78 °C, the resulting mixture was stirred for

15 min at the same temperature. Next, a solution of the freshly prepared aldehyde **44** in dry THF (2.5 mL) was added dropwise to lithium enolate solution, the reaction was stirred for 1 h at −78 °C. The reaction was quenched by addition of NH_4Cl saturated solution (15 mL), and was extracted with EtOAc (2 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 85:15 to 75:25) to furnish **56** (33.0 mg, 56 μmol) as a colorless oil in 61% yield (for two steps). Note: The product was obtained as a mixture of 4 diastereoisomers, the ratio of these compounds was not determined. TLC (SiO_2): R_f = 0.24-0.30 (hexanes/EtOAc 75:25); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 and 0.78 (s, 3H), 0.867 and 0.871 (s, 3H), 0.89 and 0.90 (s, 3H), 0.84-1.00 (m, 2H), 1.12-1.21 (m, 2H), 1.34-1.61 (m, 4H), 1.64 and 1.66 (s, 3H), 1.69-2.19 (m, 9H), 2.31-2.98 (m, 9H), 3.11-3.25 (m, 2H), 3.788, 3.792 and 3.81 (s, 3H), 3.940 and 3.943 (s, 3H), 4.38-4.43 and 4.53-4.59 (m, 1H), 5.49 (br. s, 1H), 6.42 and 6.46 (d, *J* = 2.5 Hz, 1H), 6.45 and 6.59 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): *Signals that represent same carbon position from different isomers are marked with same letters* δ 13.59 $(CH_3)^a$, 13.60 $(CH_3)^a$, 18.8 $(CH_2)^b$, 20.19 $(CH_2)^c$, 20.23 $(CH_2)^c$, 20.59 $(CH_2)^{c\ or\ d}$, 20.62 $(CH_2)^{c\ or\ d}$, 20.67 $(CH_2)^{c\ or\ d}$, 21.2 $(CH_2)^d$, 21.9 $(CH_3)^e$, 22.2 $(CH_3)^f$, 23.8 $(CH_2)^g$, 24.60 $(CH_2)^h$, 24.63 $(CH_2)^h$, 27.1 $(CH_2)^i$, 27.2 $(CH_2)^j$, 27.6 $(CH_2)^j$, 27.8 $(CH_2)^j$, 33.0 $(C)^k$, 33.2 $(CH_3)^l$, 35.1 $(CH_2)^m$, 35.5 $(CH_2)^m$, 36.9 $(C)^n$, 39.4 $(CH_2)^o$, 42.2 $(CH_2)^p$, 43.73 $(CH)^q$, 43.75 $(CH)^q$, 44.2 $(CH)^q$, 44.61 $(CH_2)^r$, 44.64 $(CH_2)^r$, 45.77 $(CH_2)^{r\ or\ s}$, 45.81 $(CH_2)^{r\ or\ s}$, 45.9 $(CH_2)^s$, 46.29 $(CH_2)^s$, 46.33 $(CH_2)^s$, 50.1 $(CH)^t$, 50.4 $(C)^u$, 50.6 $(C)^u$, 54.26 $(CH)^v$, 54.30 $(CH)^v$, 54.34 $(CH)^v$, 55.2 $(CH_3)^w$, 55.3 $(CH_3)^w$, 56.4 $(CH_3)^x$, 70.6 $(CH)^y$, 70.7 $(CH)^y$, 70.9 $(CH)^y$, 71.0 $(CH)^y$, 99.5 $(CH)^z$, 99.7 $(CH)^z$, 105.87 $(CH)^{a'}$, 105.88 $(CH)^{a'}$, 106.51 $(CH)^{a'}$, 106.53 $(CH)^{a'}$, 120.6 $(C)^{b'}$, 121.0 $(C)^{b'}$, 123.0 $(CH)^{c'}$, 123.1 $(CH)^{c'}$, 134.4 $(C)^{d'}$, 140.6 $(C)^{e'}$, 140.8 $(C)^{e'}$, 159.8 $(C)^{f'}$, 159.9 $(C)^{f'}$, 161.5 $(C)^{g'}$, 161.6 $(C)^{g'}$, 211.9 $(C)^{h'}$, 212.0 $(C)^{h'}$, 212.25 $(C)^{h'}$, 212.28 $(C)^{h'}$; IR (ATR, cm^{-1}): 3474, 2924, 1706, 1601, 1578, 1308, 1202, 1155, 1051, 754; HRMS (ESI +): *m/z* calculated for $C_{34}H_{50}O_4S_2Na^+$ $[M+Na]^+$ 609.3043, found 609.3015.

*1-(3,5-dimethoxyphenyl)allyl acetate (**58**)*. VinylMgBr (1 M in THF, 7.2 mL, 7.2 mmol, 2 equiv) was added dropwise to a solution of aldehyde **57** (610 mg, 3.6 mmol, 1 equiv) in THF (30 mL) at 0 °C. The reaction was stirred for 30 min at the same temperature and was then quenched by addition of saturated aqueous solution of NH_4Cl (50 mL). The mixture was extracted with EtOAc (2 x 50 mL), the organic phases were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 90:10 to 60:40) to give the allylic alcohol intermediate along with minor impurities (550 mg, 2.83 mmol), this material was used in the next reaction.

The allylic alcohol was diluted in dry CH_2Cl_2 (20 mL) and to this mixture were added Et_3N (0.79 mL, 5.6 mmol, 2 equiv), DMAP (17 mg, 0.14 mmol, 5 mol %) and Ac_2O (0.40 mL, 4.2 mmol, 1.5 equiv) at room temperature, and the reaction mixture was stirred for 1 h. The reaction was quenched by the addition of brine (20 mL) and was extracted with CH_2Cl_2 (2 x 20 mL). The organic phases were combined, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 90:10) to give the acetate **58** (587 mg, 2.48 mmol) as a colorless oil in 69% overall yield (for 2 steps). TLC (SiO_2): R_f = 0.39 (hexanes/EtOAc 90:10); IR (ATR, cm^{-1}): 2955, 2941, 2909, 2840, 1737, 1598, 1460, 1372, 1229, 1206, 1067, 933, 750; ^1H NMR (250 MHz, $CDCl_3$): δ 2.06 (s, 3H), 3.71 (s, 6H), 5.18 (dt, *J* = 10.3, 1.1 Hz, 1H), 5.27 (dt, *J* = 17.2, 1.1 Hz, 1H), 5.95 (ddd, *J* = 17.0, 10.4, 6.0 Hz, 1H), 6.17 (d, *J* = 6.0 Hz, 1H), 6.37 (t, *J* = 2.3 Hz, 1H), 6.50 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.9 (CH_3), 55.1 ($2CH_3$), 76.0 (CH), 99.8 (CH), 105.0 (2CH), 116.7 (CH_2), 136.2 (CH), 141.3 (C), 160.9 (2C), 169.6 (C); HRMS (ESI +): *m/z* calculated for $C_{13}H_{16}O_4Na^+$ $[M+Na]^+$ 259.0941, found 259.0949.

*(S)-2-(3,5-dimethoxyphenyl)but-3-en-1-ol (**60**).* A pressure tube was charged with paraformaldehyde (12.6 mg, 0.42 mmol of CH_2O units, 1 equiv), K_3PO_4 (45.5 mg, 0.21 mmol, 0.5 equiv), (*R*)-Krische catalyst (21.7 mg, 0.021 mmol, 5 mol %),[32] NMO (39.4 mg, 0.34 mmol, 0.8 equiv) and allylic acetate **58** (149 mg, 0.63 mmol, 1.5 equiv). The tube was purged with argon, and dry THF (1.0 mL) was added followed by dry isopropyl alcohol (64.3 µL, 0.84 mmol, 2 equiv), the pressure tube was sealed and heated at 60 °C for 36 h. After this period, the mixture was cooled to room temperature, the volatiles were removed under reduced pressure, and the residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 90:10 to 75:25) to give alcohol **60** (45 mg, 0.216 mmol) as a colorless oil in 51% yield. TLC (SiO_2): R_f = 0.23 (hexanes/EtOAc 75:25); ee = 93% (determined by ^{19}F NMR of Mosher ester derivatives); $[\alpha]_D^{25}$ = +28 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 3393 (broad), 3003, 2395, 2831, 1602, 1466, 1434, 1208, 1153, 1067, 917, 840; ^1H NMR (250 MHz, $CDCl_3$): δ 1.59 (br. s, 1H), 3.46 (q, *J* = 7.1 Hz, 1H), 3.78 (s, 6H), 3.76-3.87 (m, 2H), 5.14-5.27 (m, 2H), 5.89-6.07 (m, 1H), 6.36 (t, *J* = 2.1 Hz, 1H), 6.39 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 52.7 (CH), 55.3 ($2CH_3$), 65.9 (CH_2), 98.6 (CH), 106.1 (2CH), 117.1 (CH_2), 137.9 (CH), 143.0 (C), 161.0 (2C); HRMS (ESI +): *m/z* calculated for $C_{12}H_{16}O_3Na^+$ $[M+Na]^+$ 231.0992, found 231.0994.

*(S)-tert-butyl((2-(3,5-dimethoxyphenyl)but-3-en-1-yl)oxy)diphenylsilane (**61**).* Imidazole (27 mg, 0.40 mmol, 2 equiv) and TBDPSCl (80 µL, 0.30 mmol, 1.5 equiv) were added to a solution of alcohol **60** (41.7 mg, 0.20 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at room temperature. After stirring the reaction for 18 h, H_2O

(15 mL) was added, and the mixture was extracted with CH_2Cl_2 (20 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 90:10) to give the silyl ether **61** (70 mg, 0.16 mmol) as a colorless oil in 78% yield. TLC (SiO_2): R_f = 0.40 (hexanes/EtOAc 90:10); $[\alpha]_D^{25}$ = +10 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 3073, 2955, 2933, 2859, 1598, 1463, 1430, 1206, 1156, 1113, 1070, 1000, 828, 705, 616; ^1H NMR (250 MHz, $CDCl_3$): δ 1.07 (s, 9H), 3.50 (q, *J* = 7.0 Hz, 1H), 3.78 (s, 6H), 3.84-4.00 (m, 2H), 5.13-5.24 (m, 2H), 6.10 (ddd, *J* = 16.4, 11.2, 7.4 Hz, 1H), 6.39 (s, 3H), 7.33-7.50 (m, 6H), 7.58-7.69 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.3 (C), 29.9 ($3CH_3$), 52.5 (CH), 55.2 ($2CH_3$), 67.6 (CH_2), 98.6 (CH), 106.4 (2CH), 116.2 (CH_2), 127.6 (4CH), 129.6 (2CH), 133.7 (C), 133.8 (C), 135.66 (2CH), 135.70 (2CH), 138.6 (CH), 144.2 (C), 160.7 (2C); HRMS (ESI +): *m/z* calculated for $C_{28}H_{34}O_3SiNa^+$ $[M+Na]^+$ 469.2169, found 469.2158.

*(S,E)-5-((tert-butyldiphenylsilyl)oxy)-4-(3,5-dimethoxyphenyl)pent-2-enal (**62**).* Freshly distilled (*E*)-crotonaldehyde (60 µL, 0.65 mmol, 5 equiv) was added to a solution of alkene **61** (58 mg, 0.13 mmol) in CH_2Cl_2 (1.3 mL). Next, 2nd generation Grubbs' catalyst (11 mg, 13 µmol, 10 mol %) was added and the mixture was stirred at 40 °C for 18 h. The reaction contents were directly subjected to flash chromatography (SiO_2, hexanes/EtOAc 90:10) to give enal **62** (31 mg, 65 µmol) as a colorless oil in 50% yield. TLC (SiO_2): R_f = 0.20 (hexanes/EtOAc 90:10); $[\alpha]_D^{25}$ = +10 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2954, 2929, 2857, 1693, 1598, 1460, 1430, 1206, 1156, 1115, 826, 745, 704; ^1H NMR (250 MHz, $CDCl_3$): δ 1.04 (s, 9H), 3.67 (q, *J* = 6.9 Hz, 1H), 3.74 (s, 6H), 3.92-3.99 (m, 2H), 6.17 (ddd, *J* = 15.8, 7.9, 1.3 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 2H), 6.36 (t, *J* = 2.2 Hz, 1H), 6.99 (dd, *J* = 15.8, 6.9 Hz, 1H), 7.32-7.48 (m, 6H), 7.54-7.63 (m, 4H), 9.52 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.2 (C), 26.8 ($3CH_3$), 51.4 (CH), 55.3 ($2CH_3$), 66.6 (CH_2), 99.0 (CH), 106.4 (2CH), 127.7 (4CH), 129.8 (2CH), 133.2 (2C), 133.6 (CH), 135.58 (2CH), 135.61 (2CH), 141.1 (C), 157.6 (CH), 161.0 (2C), 193.9 (CH); HRMS (ESI +): *m/z* calculated for $C_{29}H_{34}O_4SiNa^+$ $[M+Na]^+$ 497.2119, found 497.2117.

*(S)-tert-butyl((5,7-dimethoxy-1,2-dihydronaphthalen-1-yl)methoxy)diphenylsilane (**63**).* Pd/C (5% w/w, 5.6 mg, 2.6 µmol, 5 mol %) was added to a solution of enal **62** (25.2 mg, 53.0 µmol, 1 equiv) in EtOAc (5 mL) at room temperature. This mixture was purged with H_2 and was stirred for 2 h. Next, the reaction contents were directly filtered through a plug of silica using EtOAc as eluent to furnish the saturated aldehyde, which was used in the next step without further purification. TLC (SiO_2): R_f = 0.60 (hexanes/EtOAc 75:25). The saturated aldehyde obtained above was diluted in dry toluene (2.5 mL), and *p*TSA•H_2O (9.2 mg, 53 µmol, 1 equiv) was added to the reaction at room temperature. The mixture was

stirred for 1 h, then saturated aqueous solution of $NaHCO_3$ (5 mL) and EtOAc (15 mL) were added. The organic phase was separated, washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 95: 5 to 90:10) to give the bicycle **63** (17.0 mg, 37.1 μmol) as a colorless oil in 70% yield. TLC (SiO_2): R_f = 0.40 (hexanes/EtOAc 90:10); $[\alpha]_D^{25}$ = +5 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2955, 2926, 2857, 1726, 1605, 1579, 1465, 1428, 1270, 1151, 1087, 830, 704, 616; ^1H NMR (250 MHz, $CDCl_3$): δ 1.10 (s, 9H), 2.35-2.69 (m, 2H), 2.83-2.97 (m, 1H), 3.75 (s, 3H), 3.57-3.77 (m, 2H), 3.80 (s, 3H), 5.64-5.75 (m, 1H), 6.21 (d, *J* = 2.0 Hz, 1H), 6.31 (d, *J* = 2.0 Hz, 1H), 6.68 (dd, *J* = 9.8, 2.7 Hz, 1H), 7.32-7.48 (m, 6H), 7.59-7.70 (4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.3 (C), 24.4 (CH_2), 26.9 ($3CH_3$), 40.8 (CH), 55.3 (CH_3), 55.5 (CH_3), 67.1 (CH_2), 96.9 (CH), 105.5 (CH), 116.1 (C), 120.5 (CH), 122.5 (CH), 127.6 (4CH), 129.5 (2CH), 133.8 (C), 133.9 (C), 135.7 (4CH), 138.1 (C), 155.8 (C), 159.3 (C); HRMS (ESI +): *m/z* calculated for $C_{29}H_{34}O_3SiNa^+$ $[M+Na]^+$ 481.2169, found 481.2153.

*(S)-tert-butyl((5,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methoxy)diphenylsilane (**64**).* Pd/C (5% w/w, 72 mg, 34 μmol, 5 mol %) was added to a solution of alkene **63** (312 mg, 0.68 mmol, 1 equiv) in EtOAc (34 mL) at room temperature. This mixture was purged with H_2 and was stirred for 14 h. Next, the solvent was removed under reduced pressure, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 90:10) to afford the tetraline **64** (290 mg, 0.63 mmol) as a colorless oil in 93% yield. TLC (SiO_2): R_f = 0.44 (hexanes/EtOAc 90:10); $[\alpha]_D^{25}$ = −20 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2933, 2859, 1609, 1594, 1465, 1430, 1203, 1147, 1115, 1087, 826, 705; ^1H NMR (250 MHz, $CDCl_3$): δ 1.11 (s, 9H), 1.62-1.85 (m, 3H), 2.01-2.18 (m, 1H), 2.36-2.53 (m, 1H), 2.62 (dt, *J* = 17.4, 4.9 Hz, 1H), 2.87-3.01 (m, 1H), 3.69 (s, 3H), 3.78 (s, 3H), 3.70-3.89 (m, 2H), 6.16 (d, *J* = 2.2 Hz, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 7.33-7.48 (m, 6H), 7.63-7.76 (4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 18.5 (CH_2), 19.3 (C), 22.6 (CH_2), 24.3 (CH_2), 26.9 ($3CH_3$), 41.0 (CH), 55.2 ($2CH_3$), 67.9 (CH_2), 96.2 (CH), 104.7 (CH), 119.2 (C), 127.6 (4CH), 129.6 (2CH), 133.8 (C), 134.0 (C), 135.65 (2CH), 135.69 (2CH), 138.9 (C), 158.0 (2C); HRMS (ESI +): *m/z* calculated for $C_{29}H_{36}O_3SiNa^+$ $[M+Na]^+$ 483.2326, found 483.2321.

*(S)-(5,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**65**).* TBAF solution (1 M in THF, 1.4 mL, 1.4 mmol, 2 equiv) was added to a mixture of silyl ether **64** (322 mg, 0.70 mmol, 1 equiv) in dry THF (14 mL) at room temperature. This mixture was stirred for 2 h, then was quenched by addition of saturated aqueous solution of NH_4Cl (30 mL). The mixture was extracted with EtOAc (2 x 30 mL). The organic phases were combined, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The

residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 85:15 to 75:25) to furnish alcohol **65** (135 mg, 0.61 mmol) as a colorless oil in 87% yield. TLC (SiO_2): R_f = 0.27 (hexanes/EtOAc 75:25); $[\alpha]_D^{25}$ = − 2 (*c* 1.0, $CHCl_3$), for *ent*-**65** $[\alpha]_{D,lit}^{20}$ = + 3.5 (*c* 1.0, $CHCl_3$);[6] ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.59 (br. s, 1H), 1.68-1.98 (m, 4H), 2.42-2.70 (m, 2H), 2.93 (quint, *J* = 5.3 Hz, 1H), 3.79 (s, 6H), 3.77-3.84 (m, 2H), 6.32 (d, *J* = 2.2 Hz, 1H), 6.39 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.1 (CH_2), 22.6 (CH_2), 24.9 (CH_2), 40.8 (CH), 55.3 ($2CH_3$), 67.0 (CH_2), 96.2 (CH), 104.2 (CH), 119.4 (C), 138.4 (C), 158.3 (2C).

*(S)-2-(3,5-dimethoxyphenyl)but-3-en-1-yl acrylate (**66**).* Triethylamine (42 µL, 0.30 mmol, 3 equiv) and acryloyl chloride (17 µL, 0.20 mmol, 2 equiv) were added to a solution of alcohol **60** (20.8 mg, 0.20 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL) at 0 °C. After stirring the reaction for 1 h at this temperature, brine (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (15 mL). The organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, hexanes/EtOAc 95:5) to give acrylate **66** (21 mg, 80 µmol) as a colorless oil in 80% yield. TLC (SiO_2): R_f = 0.19 (hexanes/EtOAc 95:5); $[\alpha]_D^{25}$ = +25 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2954, 2844, 1726, 1598, 1465, 1409, 1206, 1156, 1065, 990, 812; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.66 (q, *J* = 7.3 Hz, 1H), 3.78 (s, 6H), 4.32-4.46 (m, 2H), 5.10-5.22 (m, 2H), 5.80 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.90-6.16 (m, 2H), 6.32-6.43 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 48.8 (CH), 55.3 ($2CH_3$), 66.8 (CH_2), 98.8 (CH), 106.1 (2CH), 116.8 (CH_2), 128.4 (CH), 130.8 (CH_2), 137.4 (CH), 142.6 (C), 160.9 (2C), 166.0 (C); HRMS (ESI +): *m/z* calculated for $C_{15}H_{18}O_4Na^+$ $[M+Na]^+$ 285.1097, found 285.1088.

*(S)-5-(3,5-dimethoxyphenyl)-5,6-dihydro-2H-pyran-2-one (**67**).* 2nd generation Grubbs catalyst (3.1 mg, 3.6 µmol, 10 mol %) was added to a solution of alkene **66** (19.1 mg, 73 µmol) in dry CH_2Cl_2 (7 mL). Next, reaction was stirred at 40 °C for 3 h. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 75:25 to 67:33) to give lactone **67** (15.7 mg, 67 µmol) as a colorless oil in 91% yield. TLC (SiO_2): R_f = 0.22 (hexanes/EtOAc 75:25); $[\alpha]_D^{25}$ = −66 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2944, 2842, 1732, 1599, 1465, 1208, 1156, 1085, 828; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.75-3.84 (m, 1H), 3.79 (s, 6H), 4.33 (dd, *J* = 11.1, 9.3 Hz, 1H), 4.55 (ddd, *J* = 11.1, 5.5, 0.9 Hz, 1H), 6.14 (dd, *J* = 9.8, 2.2 Hz, 1H), 6.35 (d, *J* = 2.0 Hz, 2H), 6.41 (t, *J* = 2.1 Hz, 1H), 6.96 (ddd, J = 9.9, 3.0, 0.9 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 40.5 (CH), 55.4 ($2CH_3$), 72.1 (CH_2), 99.5 (CH), 106.1 (2CH), 121.4 (CH), 139.5 (C), 148.7 (CH), 161.3 (2C), 163.3 (C); HRMS (ESI +): *m/z* calculated for $C_{13}H_{14}O_4Na^+$ $[M+Na]^+$ 257.0784, found 257.0785.

*(S)-5-(3,5-dimethoxyphenyl)tetrahydro-2H-pyran-2-one (**68**).* Pd/C (5% w/w, 13.8 mg, 6.5 μmol, 5 mol %) was added to a solution of alkene **67** (15.2 mg, 65 μmol, 1 equiv) in EtOAc (10 mL) at room temperature. This mixture was purged with H_2 and was stirred for 16 h. Next, the solvent was removed under reduced pressure, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 67:33) to afford the lactone **68** (15.4 mg, 65 μmol) as a colorless oil in quantitative yield. TLC (SiO_2): R_f = 0.30 (hexanes/EtOAc 67:33); $[\alpha]_D^{25}$ = +18 (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}): 2948, 2842, 1734, 1598, 1463, 1333, 1208, 1154, 1056, 838, 698; ^1H NMR (250 MHz, $CDCl_3$): δ 2.00-2.27 (m, 2H), 2.54-2.84 (m, 2H), 3.12 (tt, *J* = 10.3, 5.1 Hz, 1H), 3.79 (s, 6H), 4.29 (t, *J* = 10.9 Hz, 1H), 4.46 (ddd, *J* = 11.2, 4.7, 1.7 Hz, 1H), 6.38 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 26.5 (CH_2), 29.6 (CH_2), 39.5 (CH), 55.3 ($2CH_3$), 73.7 (CH_2), 98.9 (CH), 105.5 (2CH), 141.9 (C), 161.2 (2C), 170.5 (C); HRMS (ESI +): *m/z* calculated for $C_{13}H_{16}O_4Na^+$ $[M+Na]^+$ 259.0941, found 243.0942.

*(S)-(5,7-dimethoxy-1,2-dihydronaphthalen-1-yl)methanol (**69**).* DIBAL-H solution (1.0 M in CH_2Cl_2, 105 μL, 105 μmol, 1.5 equiv) was added to a solution of lactone **68** (16.5 mg, 70 μmol, 1 equiv) in dry CH_2Cl_2 (3 mL) at −78 °C, and was stirred at this temperature for 1 h. Next, the reaction was quenched by addition of aqueous saturated solution of $NaHCO_3$ (4 mL), Rochelle salt saturated solution (6 mL), and CH_2Cl_2 (10 mL). The resulting mixture was vigorously stirred for 3 h, and the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude lactol was used in the next step without further purification. TLC (SiO_2): R_f = 0.25 (hexanes/EtOAc 67:33). The crude lactol obtained above was diluted in dry toluene (6 mL), and *p*TSA•H_2O (12.2 mg, 70 μmol, 1 equiv) was added to the reaction at room temperature. The mixture was stirred for 3 h, then saturated aqueous solution of $NaHCO_3$ (5 mL) and EtOAc (15 mL) were added. The organic phase was separated, washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 85:15 to 75:25) to furnish the bicycle **69** (3.1 mg, 14 μmol) as a colorless oil in 20% yield. TLC (SiO_2): R_f = 0.27 (hexanes/EtOAc 75:25); $[\alpha]_D^{25}$ = −1 (*c* 0.25, $CHCl_3$); IR (ATR, cm^{-1}): 3383, 2927, 1603, 1577, 1463, 1426, 1203, 1148, 1051, 939, 830; ^1H NMR (250 MHz, $CDCl_3$): δ 1.37 (br.s, 1H), 2.30-2.60 (m, 2H), 2.79-2.92 (m, 1H), 3.65 (d, *J* = 6.3 Hz, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 5.76 (ddd, *J* = 9.9, 5.7, 3.0 Hz, 1H), 6.33-6.39 (m, 2H), 6.72 (dd, *J* = 9.8, 2.8 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 24.9 (CH_2), 40.7 (CH), 55.4 (CH_3), 55.5 (CH_3), 64.7 (CH_2), 96.9 (CH), 105.5 (CH), 115.9 (C),

120.6 (CH), 122.5 (CH), 137.7 (C), 156.1 (C), 159.5 (C); HRMS (ESI +): *m/z* calculated for $C_{13}H_{16}O_3Na^+$ $[M+Na]^+$ 243.0992, found 243.1003.

*(S)-(5,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**65**)*. Pd/C (5% w/w, 2.8 mg, 1.3 μmol, 10 mol %) was added to a solution of alkene **69** (2.9 mg, 13 μmol, 1 equiv) in EtOAc (2 mL) at room temperature. This mixture was purged with H_2 and was stirred for 16 h. Next, the solvent was removed under reduced pressure, and the residue was subjected to flash chromatography (SiO_2, hexanes:EtOAc, 75:25) to afford alcohol **65** (2.5 mg, 11 μmol) as a colorless oil in 89% yield. Spectroscopical and physical data of this compound are described above.

*(S,E)-1-((S)-5,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methyl-5-((1S,4aS,8aS)-2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)pent-2-en-1-ol (**71**).* Solid $NaHCO_3$ (23.0 mg, 0.27 mmol, 2.2 equiv) and Dess-Martin periodinane (79.1 mg, 0.19 mmol, 1.5 equiv) were added to a solution of alcohol **65** (41.4 mg, 0.19 mmol, 1.5 equiv) in dry CH_2Cl_2 (5 mL) at room temperature. This mixture was stirred for 1 h, then the solvent was removed under reduced pressure, and the aldehyde was purified by flash chromatography (SiO_2, hexanes/EtOAc 90:10) to furnish aldehyde **70**, which was immediately used in the next step. TLC (SiO_2): R_f = 0.60 (hexanes/EtOAc 75:25); *n*-BuLi solution (2.14 M in hexanes, 118 μL, 0.25 mmol, 2 equiv) was added dropwisely to a solution of iodide **3** (48.0 mg, 0.12 mmol, 1 equiv) in Et_2O (2 mL) at −78 °C, the resulting mixture was stirred for 1 h at the same temperature. Next, a solution of the freshly prepared aldehyde **70** in dry Et_2O (2 mL) was added dropwisely to the vinyl lithium solution, the reaction was stirred for 1 h at −78 °C, and 16 h at −60 °C (cryostat bath). The reaction was quenched by addition of NH_4Cl saturated solution (10 mL), and was extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography (SiO_2, hexanes/EtOAc 90:10) to furnish alcohol **71** (27.0 mg, 56 μmol) as a colorless oil in 45% yield. Note: Analysis of a crude sample showed dr = 3:1. Substitution of *n*-BuLi by *t*-BuLi led to 25% yield of alcohol **71** and the same dr = 3:1 (crude sample). The analyses were performed with $CHCl_3$ or $CDCl_3$ treated with anhydrous K_2CO_3 to remove residual acidity, in order to prevent decomposition. *n*-BuLi was recently titrated using cyclohexanol (75 mg, 0.75 mmol) diluted in dry THF (5 mL), with 2,2'-bipyridine (bipy) as indicator. Data for isomer **71** (major): TLC (SiO_2): R_f = 0.21 (hexanes/EtOAc 90:10); $[\alpha]_D^{25}$ = +16 (*c* 1.0, $CHCl_3$), $[\alpha]_{D,lit}^{20}$ = +19.2 (*c* 1.6, $CHCl_3$);[6] ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.76 (s, 3H), 0.86 (s, 3H), 0.88 (s, 3H), 0.79-1.04 (m, 1H), 1.58 (d, *J* = 1.1 Hz, 3H), 1.69 (s, 3H), 1.05-1.73 (m, 11H), 1.73-2.07 (m, 6H), 2.21 (td, *J* = 12.8, 4.5 Hz, 1H), 2.43-2.71 (m, 2H), 2.86 (q, *J* = 5.6

Hz, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 4.76 (dd, *J* = 8.2, 4.9 Hz, 1H), 5.30 (dq, *J* = 8.2, 0.9 Hz, 1H), 5.39 (br. s, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.5 (CH_3), 16.8 (CH_3), 18.8 (CH_2), 20.2 (CH_2), 21.8 (CH_3), 22.2 (CH_3), 22.6 (CH_2), 23.4 (CH_2), 23.8 (CH_2), 25.6 (CH_2), 33.0 (C), 33.1 (CH_3), 36.8 (C), 39.2 (CH_2), 42.3 ($2CH_2$), 44.2 (CH), 50.2 (CH), 54.6 (CH), 55.3 ($2CH_3$), 71.6 (CH), 96.0 (CH), 104.6 (CH), 120.3 (C), 122.3 (CH), 125.8 (CH), 135.3 (C), 138.5 (C), 138.9 (C), 158.1 (2C).

Cell culture and Cytotoxicity Assays

Compounds were prepared in DMSO (stock solutions of 50 mM) and transferred (30 µL) to the first and thirteenth columns of a 384 deep well small volume plate (Greiner BioOne) in four replicates, using the Janus Varispan (Perkin Elmer) liquid handler. Serial dilutions were prepared using the Versette (Thermo) liquid handler, in 11 points with a dilution factor of 0.4 (final stock concentrations ranging from 50 to 5.2 mM) in DMSO. The 12th point of the dilution curves contained only DMSO, and was used as the negative control. Tacrine was used as the reference cytotoxic compound, composing the positive control group.

HaCat (immortalized, but not transformed, epithelial cell line) and U2OS (human bone osteosarcoma epithelial cells) were cultivated in high-glucose Dulbecco's modified Eagle's medium (DMEM, Sigma) supplemented with 1% penicillin G-streptomycin (Invitrogen) and 10% heat-inactivated fetal bovine serum (FBS, VitroCell) at 37 °C and 5% CO_2. HSC-3 (human tongue squamous cell carcinoma cell line) and SCC9 (squamous cell carcinoma, a tumor cell line originated from a human tongue squamous cell carcinoma) were cultivated in Dulbecco's modified Eagle's medium HAMF12- medium (CultiLab) containing 1.2 g/L sodium bicarbonate, 2.5 mM L-glutamine, 15 mM HEPES and 0.5 mM sodium pyruvate supplemented with 400 ng/mL hydrocortisone, 10% heat-inactivated fetal bovine serum (VitroCell) and 1% penicillin G-streptomycin (Invitrogen) at 37 °C with 5% CO_2.

Cells were seeded into 384 well plates (µCLEAR Greiner Bio-one) at densities of 2,000 (U2OS and SCC-9), 1,000 (HSC-3), and 1,500 (HaCat) cells per well, using 50 µL of medium and cultivated for 24 h at 37 °C with 5% CO_2. After 24 h, compounds (0.6 µL) were transferred to a dilution plate containing media (60 µL), using the Janus MDT (Perkin Elmer) liquid dispenser. Diluted compounds (30 µL) were then transferred to the plate containing the cells in fresh media (45 µL) and incubated for 48 h at 37 °C and 5% CO_2. Final DMSO concentration in the cell assay was 0.4 %.

MitoTracker Deep Red (#M22426, Invitrogen) was dissolved in DMSO to 1 mM and Hoechst 33342 (Invitrogen) was dissolved in ultra-pure water to 10 mg/mL. A 500 nM MitoTracker, 5 µg/mL Hoechst solution was prepared in pre-warmed media (DMEM, 10% FBS, 1% penicillin/streptomycin or in Dulbecco's modified Eagle's medium HAMF12- medium). Media was removed from plates; residual volume was 10 µL in each well. 20 µL of staining solution was added to the cells and incubated for 45 min at 37 °C and 5% CO_2. Media was removed from plates and 3.7% formaldehyde (in PBS) was added for cell fixation. The plates were then incubated at room temperature for 20 min and wells were washed once with 50 µL 1x PBS.

Cell imaging was performed with the Operetta High-Content Imaging System (PerkinElmer), using a 10X long WD objective. The cell number was quantified using the software Columbus 2.4.0 (Perkin Elmer).

Processed data was transferred to the Prism software (Graph Pad, San Diego, v7). Concentration response curves were constructed using the final compound concentration in the assay, in logarithmic scale, and the average ± SEM of the normalized number of cells (normalized to the negative control group, the later referred as 100% of the cell population), in each compound concentration. Each experiment was carried out in four replicates. Curves were fitted using the normalized concentration-response equation with variable slope implemented in Prism 7. At least three independent experiments with different cell batches were carried out. IC_{50} values reported are the mean ± SEM of these independent experiments.

■ ASSOCIATED CONTENT

Supporting Information

H^1NMR, DEPT135 and C^{13}NMR spectra of all new compounds are provided (PDF).

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Notes

The authors declare no competing financial interest.

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