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Note

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Scalable Regio- and Stereoselective Synthesis of Functionalized (E)-4-iodobut-3-en-1-ols: Gram-scale Total Synthesis of Fungal Decanolides and Derivatives

Alexander M. Sherwood, Samuel E. Williamson, Stephanie N. Johnson, Anil Yilmaz, Victor W. Day and Thomas E. Prisinzano*

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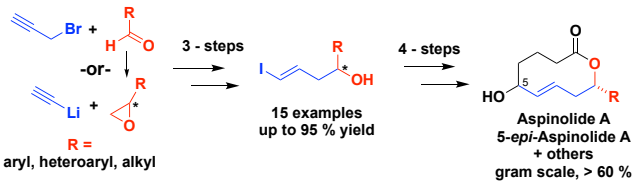
Abstract

A reliable protocol to synthesize both racemic and chiral (*E*)-4-iodobut-3-en-1-ols from aldehydes or epoxides, respectively, containing various aromatic and aliphatic substitutions has been established. The utility of these compounds was then demonstrated by providing access to known fungal decanolides as well as novel aromatic macrocycles. The protocol provided a gram scale route to (–)-aspinolide A and (–)-5-*epi*-aspinolide A utilizing a catalytic Nozaki-Hiyama-Kishi reaction to close the macrolide in the final step in 65-84% yield.



Nature has provided a variety of compounds bearing the structural motif illustrated by **1** (Figure 1), including the anti-tumor compound, rugulactone (**2**) as well as a diverse array of unsaturated macrolide natural products (**3-5**) with an array of biological activities, several of which are illustrated in Figure 1.[1-5] We envisaged that hydroxy vinyl iodides (**6**) could provide viable synthons for producing molecules related to **1**-**5**.

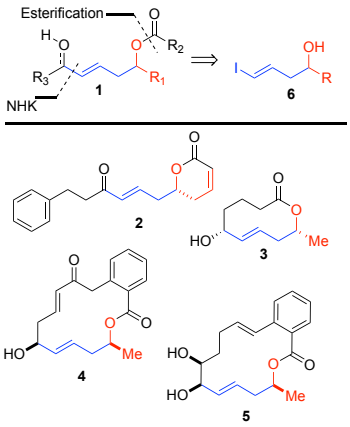


Figure 1. Design rationale for structures of natural products containing hydroxy vinyl core (**1**): rugulactone (**2**), aspinolide A (**3**), pochonin F (**4**), and aigialomycin D (**5**).

One of the key challenges in synthesizing macrocyclic lactones such as **3-5** is the ring-closing step, which must overcome challenging kinetic and thermodynamic barriers to succeed.[6,7] Several methods have been previously reported for synthesizing macrocyclic lactones employing ruthenium catalyzed metathesis (RCM) in the final ring closing step.[8,9] The major drawbacks to macrocycle formation using RCM are the necessary judicious optimization of reaction conditions as well as the challenge in controlling the double bond geometry.[10] In search of a more general method to form macrocyclic lactones containing double bonds, the current literature was surveyed for alternative approaches. Of the available methods for closing strained medium to large rings containing double

bonds to form allylic alcohols or enones with the preservation of double bond geometry, the nickel-chromium mediated Nozaki-Hiyama-Kishi (NHK) coupling reaction has emerged as one of the more viable methods by demonstrating good functional group tolerance, scalability, and its remarkable ability to close strained rings preferentially over forming dimers.[11-13] Furthermore, environmentally favorable catalytic variants of the NHK reaction have been subsequently realized which utilize stoichiometric manganese, allowing the chromium content of the reaction to be reduced to catalytic amounts.[14-16]

Requisite to forming an allylic alcohol-bearing macrocycle (**7**) by NHK conditions is a vinyl iodide tethered aldehyde (**8**, Figure 2). With the goal of taking advantage of the merits of the NHK reaction as a potential route to nature-inspired macrolides via the approach illustrated in Figure 2, a general route to (*E*)-4-iodobut-3-en-1-ols (**6**) was desired.

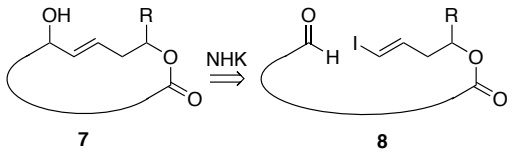


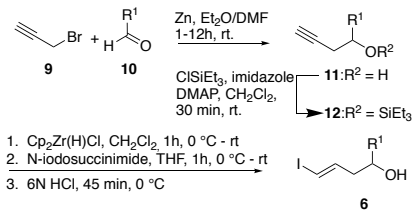
Figure 2. General approach to macrocyclic allylic alcohols.

Hydrozirconated intermediates have proven to be particularly useful for the formation of vinyl iodides. Hydrozirconation of terminal alkynes by Schwartz's reagent ($Cp_2Zr(H)Cl$) has been previously utilized in synthetic organic chemistry for several reasons, including the reagent's acceptance of mild conditions, efficiency, commercial availability, and excellent regiocontrol.[17] Furthermore, despite some reports of the reagent's inherent sensitivity, in our hands, handling Schwartz's reagent in open air had no apparent ill effect on subsequent transformations and the purchased container of Schwartz's reagent was found to retain complete activity after a year, provided the container was blanketed with argon after each use and stored away from light under

refrigeration. In addition to commercial availability, the reagent can also be prepared from inexpensive Cp_2ZrCl_2 and $LiAlH_4$.[18] Despite these advantageous utilities, other methods for vinyl iodide synthesis from alkynes remain popular, including hydrohalogenation,[19] hydrostannation,[20] hydroboration,[21] and hydroalumination.[20] Of these methods, our initial experiments to synthesize **6a** revealed Schwartz's reagent to be a good choice with a broad substrate scope and operationally simple experimental design.

Table 1 illustrates a variety of hydroxy vinyl iodides (**6**) accessed from triethylsilyl protected homopropargyl alcohols (**12**). An array of racemic homopropargyl alcohols (**11**) were synthesized using operationally simple (open air) Barbier conditions with the corresponding aldehydes and propargyl bromide.[22] Though Schwartz's reagent has been reported to tolerate free alcohols,[23] initial efforts to form **6** directly from the homopropargyl alcohols were unfruitful; when the same conditions were applied to the alcohols protected as triethylsilyl ethers, the hydrozirconation reactions proceeded with quantitative yield in most cases. Additionally, it was found that adding a catalytic amount of DMAP to the silylation reactions significantly enhanced reaction rates[24] and afforded the protected alcohols in minutes from homopropargyl alcohols, typically in quantitative yield. Curiously, without catalytic DMAP, the silylations typically had to stir overnight and sometimes did not reach completion. Finally, we were pleased to find that the triethylsilyl ethers were cleanly hydrolyzed by quenching the final reaction with dilute acid affording the hydroxy vinyl iodides (**6**) in one pot.

Table 1. Scope of hydroxy vinyl iodide synthesis via racemic homopropargyl alcohols.



entry	R^1	yield (%)[a]		
		11	12	6
1		11a 94	12a 97	6a 92
2		11b 90	12b 99	6b 83
3		11c 99	12c 99	6c 98
4		11d 70	12d 72	6d 95
5		11e 70	12e 87	6e 90
6		11f 75	12f 77	6f 74
7		11g 79	12g 95	6g 97
8		11h 85	12h 91	6h --[c]
9		11i 65	12i 97	6i 46
10		11j 94	12j 96	6j 93
11		11k 72	12k 99	6k 91
12		11l 70	12l 93	6l 94
13		11m n/a[b]	12m 97	6m 95
14		11n 46	12n 99	6n 99
15		11o 61	12o 95	6o 96

[a] Isolated yield. [b] 11m was commercially available. [c] Hydrozirconation led to competitive reduction of nitrile resulting in an intractable mixture of compounds.

Hydrozirconation of the protected homopropargyl alcohols **12a-o** was accomplished in methylene chloride with Schwartz's reagent in slight excess. The hydrozirconation step was found to be moisture sensitive; in reactions where environmental moisture was not carefully excluded, a major

competing reaction led to reduction of the alkyne to the terminal alkene **13** (Figure 3), which was generally unresolvable by chromatography and can be seen as a trace impurity in the proton NMR spectra of several products. It was found that the terminal olefin formation could be suppressed significantly by azeotroping the protected homopropargyl alcohols from toluene or benzene immediately before use. Iodosuccinimide was implemented instead of elemental iodine for the iodination step, as it is generally easier to handle and may not produce strongly acidic byproducts. Additionally, siloxane byproducts from the final deprotection step were often pervasive in initial NMR spectra. It was found that they could be azeotropically removed from the final products by using toluene.

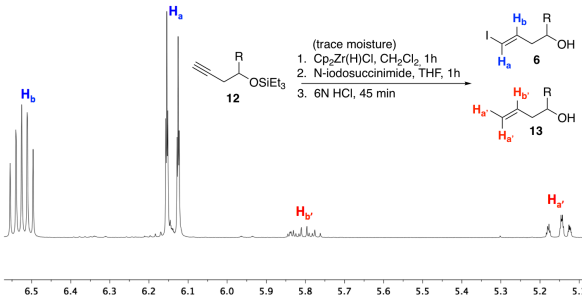


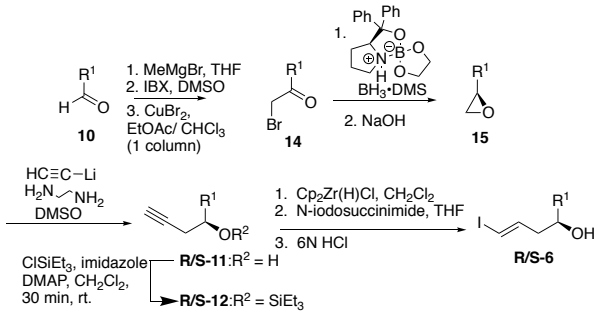
Figure 3. ^{1}H NMR spectra showing vinyl iodide and minor terminal olefin signals resulting from the inclusion of trace moisture in hydrozirconation reaction.

Next, we sought to develop a general asymmetric approach to hydroxy vinyl iodides that could be applied to the synthesis of natural products and derivatives. It is known that homopropargyl alcohols are also readily accessible by the action of lithium acetylide ethylene diamine complex on terminal epoxides.[43] Furthermore, enantiopure terminal epoxides (**15**) are often either commercially available or accessible by straightforward chemistry.

Four representative vinyl iodides from Table 1, **6a**, **6b**, **6j**, and **6m**, incorporating aryl, heteroaryl and alkyl substituents, were selected to demonstrate the general asymmetric approach (Table 2). While styrene oxide (**15a**) and propylene oxide (**15m**) were commercially available in enantiopure

form, the 3-methoxyphenyl and furan-bearing epoxides, **15b** and **15j**, have not been previously described. Likewise, the α-bromoketone **14b** was commercially available and the analogous novel compound **14j** was synthesized in three steps from 3-furancarboxaldehyde (**10j**). Both α-bromoketones **14b** and **14j** were then asymmetrically reduced using Ortiz-Marciales et al.'s recently described[25] air-stable spiroborate catalyst and subsequently cyclized under alkaline conditions to give chiral epoxides **15b** and **15j** in excellent yield and enantiomeric excess (inferred from chiral GC or HPLC analysis of either vinyl iodides **6** or the corresponding homopropargyl alcohols **11**). The crude epoxides were reacted with lithium acetylide ethylenediamine complex and the resulting highly enantioenriched homopropargyl alcohols were reacted as previously described to afford enantioenriched vinyl iodides **6**. This entire sequence was operationally simple, typically requiring only one chromatographic step from the α-bromoketones to protected homopropargyl alcohols **12**.

Table 2. General approach to chiral hydroxyl vinyl iodides



entry	R^1	Yield (%) 14	15	R/S-12	R/S-6	ee (%)
1		--	15a com[a]	(S)12a 95[c]	(S)6a 88	(S)6a 98[e]
2		14b com[a]	15b n/a[b]	(S)12b 89[d]	(S)6b 93	(S)6b 98[e]
3		14j 73	15j n/a[b]	(S)12j 82[d]	(S)6j 80	(S)11j 97[f]
4		--	15m com[a]	(R)12m 67[c]	(R)6m 96	(R)6m 99[f]

[a] intermediate was commercially available. [b] not isolated, used immediately without further purification or characterization. [c] isolated yield over two steps from 15. [d] isolated yield over three steps from 14. [e] enantiomeric excess determined by chiral HPLC AUC analysis. [f] enantiomeric excess determined by chiral GC AUC analysis.

Finally, both **(S)-6a** and **(R)-6m** were used to construct the vinyl iodide tethered aldehyde intermediates **19** and **20** in three steps which subsequently underwent a ligand-supported catalytic variant of the NHK reaction, recently described by Tagami et al.,[16] to afford decanolide natural product (–)-aspinolide A (**3a**) and the corresponding epimer (–)-5-*epi*-aspinolide A (**3b**) as well as the novel macrocycles **21a** and **21b** (Scheme 1). Though the final ring-closing step was not diastereoselective, the epimers were readily separated by chromatography. The absolute stereochemistries of the macrocycles were confirmed by the X-ray structure of **21a and 21b** (Figure 4). The configurations for **3a** were assigned based on spectroscopic agreement with previous reports for aspinolide A.[2]

Scheme 1. Vinyl iodide-mediated macrolide synthesis. Yield ranges reported for reactions over multiple trials.

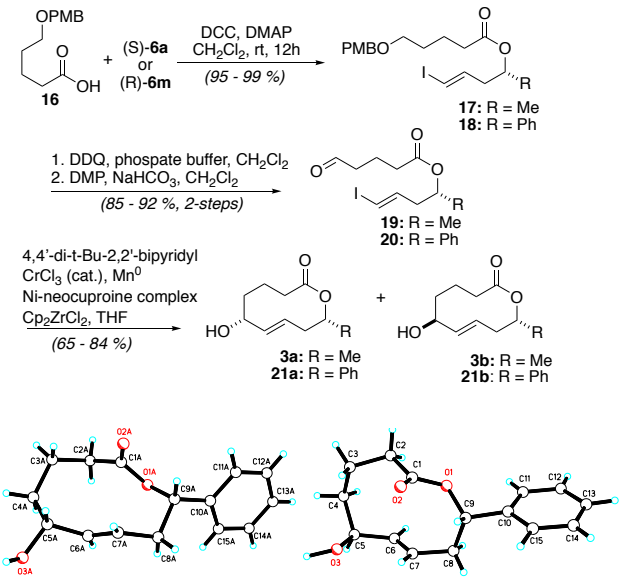


Figure 4. X-ray crystal structures for **21a** (left) and **21b** (right).

Unexpectedly, the NMR data for epimer **3b** did not agree with previously reported data for the matching structure claimed to be the natural product stagonolide F.[1] Even more surprising, three subsequent total synthesis attempts at this natural product that, upon close inspection of the corresponding supporting information files, provided spectra which neither agreed with the isolation report nor our spectra for **3b**[40-42] (**See Supporting Information Fig. S2, Tables S1-S6**) In light of these apparent discrepancies, the following data provided additional support for the structural assignment of **3b** and may suggest the need for structural revision of the compound previously described as stagonolide F: the highly analogous nature of the chemistry and chromatography used to synthesize and isolate **3a/b** compared to **21a/b**, which were unambiguously described by x-ray structure; comparison of the ^{1}H NMR spectra for **3a/b** demonstrated closely related compounds, highly indicative of epimers, with key proton shifts that occurred primarily at the proposed region of epimerization at C5 (**See Supporting Information Fig. S1**); the HRMS data for **3a/b** was identical and corresponded to the expected values, and chromatographically, the two compounds had very close R_f values by TLC, thus ruling out the possibility of **3b** being a dimer. Analysis of the carbon NMR data in the original isolation report for stagonolide F[1] revealed several unexpectedly significant divergences in the spectra when compared against spectra for what should have been its C5 epimer, aspinolide A (and our matching spectra for **3a**). Namely, in the ^{13}C NMR for stagonolide F and aspinolide A, C-8 signals were observed at δ 35.0 and 42.1, respectively. Also, C-3 signals for these two molecules were observed at δ 31.5 and 22.3, respectively. The different alpha/beta configurations of hydroxy and methyl groups would not be expected to change the chemical shifts of carbon atoms that much. Finally, our measured optical rotation of **3b**, $[\alpha]_D^{20}$ –62.0 ° (c 0.1, $CHCl_3$), was not in agreement with the reported rotation of stagonolide F, $[\alpha]_D^{20}$ –27 ° (c 0.1, $CHCl_3$).[1] In light

of the above, compound **3b** has been described as (–)-5-*epi*-aspinolide A instead of stagonolide F in this manuscript.

Conclusion

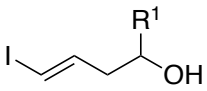
In summary, we have developed a general protocol for the synthesis of (*E*)-4-iodobut-3-en-1-ols and explored their utility towards the synthesis of 10-membered macrocycles, both natural and nature-inspired. We envision that the described protocols will be of utility in future natural product total synthesis efforts as well as for the exploration of derivatives in structure-activity efforts to discover novel medicines.

Experimental Section

General Information. All chemical reagents were purchased from commercial suppliers and used without further purification. Unless mentioned otherwise, all solvents were obtained from a solvent purification system in which solvent was passed through two columns of activated alumina under argon. Reactions performed in standard glassware were performed under an atmosphere of argon using glassware dried overnight in an oven at 120 °C and cooled under a stream of argon unless specified otherwise. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm Analtech GHLF silica gel plates and visualized using a UV Lamp (254 nm) and vanillin solution (7.5 g vanillin dissolved in 125 mL EtOH and 1-2 mL H_2SO_4). Flash column chromatography was performed on silica gel (4-63 mm) from Sorbent Technologies. Optical rotations were measured on a Rudolph Autopol III automatic polarimeter. ^{1}H and ^{13}C NMR were recorded a 500 MHz Bruker AVIII spectrometer equipped with a cryogenically-cooled carbon observe probe using tetramethylsilane as

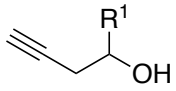
an internal standard. Chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hz. High-resolution mass spectrum (HRMS) was performed on a LCT Premier (Micromass Ltd., Manchester UK) time of flight mass spectrometer with an electrospray ion source in either positive or negative mode. Melting points were measured with a Thomas Capillary Melting Point Apparatus and are uncorrected.

Zinc activation procedure. 50 g of zinc powder was suspended in 350 mL water in a 500 mL Erlenmeyer flask. 5 mL concentrated HCl was added dropwise and the suspension stirred for 30 minutes. The suspension was then decanted and the zinc was sequentially washed with water (3 x 100mL), acetone (3 x 100mL) and ether (2 x 50mL). The activated zinc powder was then dried in vacuo and stored under argon and used within one week.

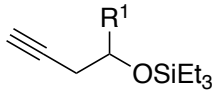


Procedure A: General procedure for the synthesis of (*E*)-4-iodobut-3-en-1-ols (6). A flame-dried RBF was charged with $Cp_2Zr(H)Cl$ (774 mg, 3.0 mmol) then sealed with a rubber septum and purged with argon. The solid was suspended in CH_2Cl_2 (10 mL) and cooled with an external ice bath. Alkyne (2.0 mmol, previously azeotroped from toluene or benzene x 3) in CH_2Cl_2 (10 mL) was added dropwise to the rapidly stirring suspension. The reaction was removed from the ice bath, stirred in the dark and reached room temperature over one hour. The resulting pale yellow-to-orange solution was cooled by an external ice bath and iodosuccinimide (562 mg, 2.5 mmol) in THF (10 mL) was added dropwise. The reaction was removed from the ice bath, stirred in the dark and reached room temperature over one hour. The resulting orange solution was cooled by external ice bath and HCl (6M, 1.5 mL, 9.0 mmol) was added dropwise. The reaction was stirred for 45 minutes at 0°C then poured into a stirring solution of 1:1 saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ (50 mL). Vigorous

stirring continued for 30 minutes resulting in a pale yellow biphasic solution. Et_2O (30 mL) was added and the organic layer was collected. The aqueous layer was further extracted with Et_2O (2 x 30 mL). Combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was azeotroped from toluene (x3) to remove siloxane byproducts. Finally, purification via flash column chromatography (2.5-40% EtOAc/hexanes) afforded vinyl iodides.

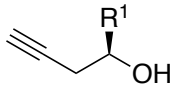


Procedure B: General procedure for the synthesis of homopropargyl alcohols (11) from propargyl bromide and substituted aldehydes. To a 250 mL RBF fitted with a reflux condenser was added aldehyde **10** (10 mmol) in 1:1 ether/DMF (100 mL, tech. grade, not anhydrous) and a solution of 80% propargyl bromide (**9**) in toluene (1.5 mL, 13 mmol). Activated zinc powder (2.0 g, 30 mmol) was then added portion wise over 10 minutes (Caution: very freshly activated zinc can produce very exothermic reactions). The reaction was allowed to stir at room temperature for up to 12 hours with progress monitored by TLC (homopropargyl alcohols typically have *Rf*: 0.3~0.6 in 100 % CH_2Cl_2 and stain deep burgundy with vanillin stain). Upon completion, the reaction was slowly quenched with saturated ammonium chloride and allowed to stir for 30 minutes. The resulting mixture was decanted into a separatory funnel and the organic layer was separated, the aqueous layer extracted with ether (3 x 50mL) and the combined organic layers washed with brine (3 x 75mL), dried with $MgSO_4$, and concentrated in vacuo. The resulting crude product was purified via flash column chromatography to give homopropargyl alcohols (**11**).

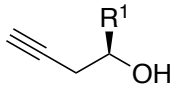


Procedure C: General procedure for the synthesis of triethylsilyl ethers (12) from homopropargyl alcohols. To a stirred solution of homopropargyl alcohol **11** (3.0 mmol) in

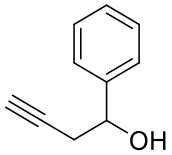
methylene chloride (20 mL) was added imidazole (0.30 g, 4.5 mmol) and DMAP (37 mg, 0.30 mmol). Once all solids were dissolved, chlorotriethylsilane (0.51 mL, 3.0 mmol) was added dropwise, and the reaction was allowed to stir at room temperature for 30 minutes. The reaction was quenched with saturated ammonium chloride and extracted with Et_2O (3 x 25 mL). The organic layers were combined, washed with brine (25mL), dried with $MgSO_4$ and concentrated to give the corresponding homopropargyl triethylsilyl ether that was used in the next step without further purification.



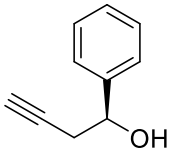
Procedure D: General procedure for the synthesis of asymmetric homopropargyl alcohols (R/S-11) from α-bromoketones via epoxide intermediate. To a stirred solution of (R)-spiroboronate ester catalyst[24] (171 mg, 0.53 mmol) in 15 mL THF was added BH_3•DMS complex (2M in THF, 1.8 mL, 3.7 mmol) at room temperature and stirred for 10 minutes until the cloudy suspension became clear. A solution of α-bromoketone (**14b** or **14j**, 10 mmol) in 10 mL THF was added via syringe pump over one hour and allowed to stir an additional 10 minutes after addition was complete. Reaction was cooled to 0°C and quenched with 10 mL methanol. Volatiles were removed and the residue was taken up in THF (20 mL) and 2M NaOH (10 mL) and stirred at room temperature for 15 minutes. The reaction was extracted with Et_2O (3 x 25 mL) and the combined organic layers washed with brine (1 x 50 mL), dried ($MgSO_4$) and concentrated. The crude epoxide residue was immediately taken up in anhydrous DMSO (5 mL) and the solution added dropwise to a stirred solution of lithium acetylide-ethylene diamine complex (1.47 g, 16.0 mmol) in anhydrous DMSO (15 mL) at room temperature. The reaction was allowed to proceed overnight at room temperature, at which point it was cooled to 0°C and carefully quenched by the addition of saturated aqueous ammonium chloride solution (20 mL). The resulting solution was extracted with ether (5 x 30 mL), washed with brine (3 x 50 mL), dried ($MgSO_4$) and concentrated.



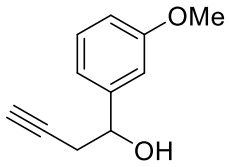
Procedure E: General procedure for the synthesis of asymmetric homopropargyl alcohols (R/S-11) from epoxides. A solution of commercially available epoxide (**15a** or **15m**, 1 eq.) in anhydrous DMSO (2 mmol / mL) was added dropwise to a stirred solution of lithium acetylide-ethylene diamine complex (1.6 eq.) in anhydrous DMSO (1 mmol / mL) at room temperature. The resulting exothermic reaction was allowed to proceed overnight at room temperature, at which point it was cooled to 0°C and carefully quenched by the addition of saturated aqueous ammonium chloride solution. The resulting solution was extracted with ether (20 mL x 3), washed with brine (20 mL x 3), dried ($MgSO_4$) and concentrated. The resulting homopropargyl alcohols were typically used without further purification.



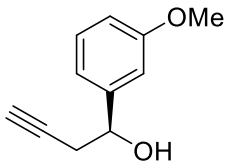
1-phenylbut-3-yn-1-ol (11a) Prepared according to general procedure B from benzaldehyde (1.06 g, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.42 g light yellow, viscous oil, 94%. The spectra were in accordance with the previously reported data.[26]



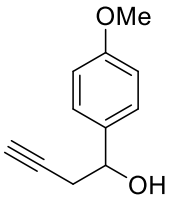
(S)-1-phenylbut-3-yn-1-ol [(S)11a] Prepared according to general procedure D from commercially available (R)-styrene oxide (1.20 g, 10 mmol) to give 1.35 g clear oil, 93%. All spectra were identical to that of racemic **11a**. $[\alpha]_D^{20}$ -25.72° (c. 0.90 , $CHCl_3$){lit[27] $[\alpha]_D^{20}$ -14.5 (c. 4.11, MeOH)}.



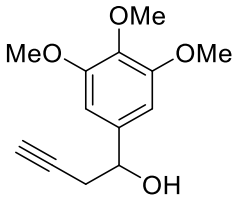
1-(3-methoxyphenyl)but-3-yn-1-ol (11b) Prepared according to general procedure B from *m*-anisaldehyde (1.36 g, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.6 g light yellow, viscous oil, 90%. The spectra were in accordance with the previously reported data.[28]



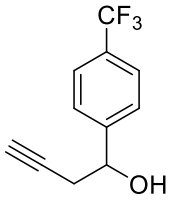
(S)-1-(3-methoxyphenyl)but-3-yn-1-ol [(S)11b] Prepared according to general procedure E from commercially available 2-bromo-1-(3-methoxyphenyl)ethan-1-one **14b** (2.29 g, 10 mmol) to give 1.25 g clear oil, 71% over two steps. All spectra were identical to that of racemic **11b**. $[\alpha]_D^{20}$ -45.49° (c. 1.09, $CHCl_3$).



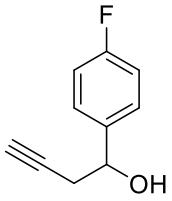
1-(4-methoxyphenyl)but-3-yn-1-ol (11c) Prepared according to general procedure B from *p*-anisaldehyde (1.36 g, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.69 g light yellow, viscous oil, 99%. The spectra were in accordance with the previously reported data.[29]



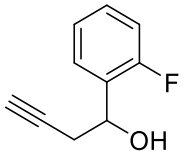
1-(3,4,5-trimethoxyphenyl)but-3-yn-1-ol (11d) Prepared according to general procedure B from 3,4,5-trimethoxybenzaldehyde (2.36 g, 10 mmol); purified by column chromatography (30-40% EtOAc/hexane) to give 1.68 g white solid (m.p. 62-65 °C), 70%. The spectra were in accordance with the previously reported data.[30]



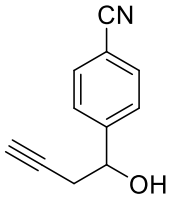
1-(4-(trifluoromethyl)phenyl)but-3-yn-1-ol (11e) Prepared according to general procedure B from 4-(trifluoromethyl)benzaldehyde (1.74 g, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.50 g white crystalline solid (m.p. 34-36 °C), 70%. The spectra were in accordance with the previously reported data.[31]



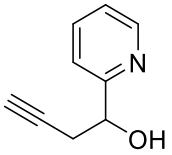
1-(4-fluorophenyl)but-3-yn-1-ol (11f) Prepared according to general procedure B from 4-fluorobenzaldehyde (1.24 g, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.23 g light yellow, viscous oil, 75%. The spectra were in accordance with the previously reported data.[32]



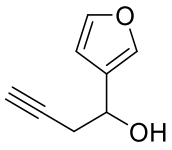
1-(2-fluorophenyl)but-3-yn-1-ol (11g) Prepared according to general procedure B from 2-fluorobenzaldehyde (1.24 g, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.33 g light yellow, viscous oil, 79%. The spectra were in accordance with the previously reported data.[30]



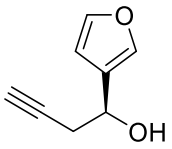
4-(1-hydroxybut-3-yn-1-yl)benzonitrile (11h) Prepared according to general procedure B from 4-cyanobenzaldehyde (1.31 g, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.52 g light yellow crystalline solid (m.p. 106-108 °C), 85%. The spectra were in accordance with the previously reported data.[31]



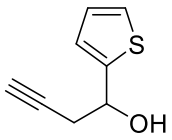
1-(pyridin-2-yl)but-3-yn-1-ol (11i) Prepared according to general procedure B from 2-pyridinecarboxaldehyde (1.07 g, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.04 g purple, viscous oil, 65%. The spectra were in accordance with the previously reported data.[32]



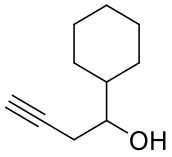
1-(furan-3-yl)but-3-yn-1-ol (11j) Prepared according to general procedure B from 3-furaldehyde (961 mg, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.33 g light yellow, viscous oil, 94%. The spectra were in accordance with the previously reported data.[26,33]



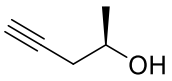
(S)-1-(furan-3-yl)but-3-yn-1-ol [(S)11j] Prepared according to general procedure E from **14j** (1.9 g, 10 mmol). The resulting orange oil was purified by column chromatography (10-15% EtOAc/Pentane) to give 1.2 g light yellow oil, 86% over two steps. Spectra were identical to that of racemic **11j.** $[\alpha]_D^{20}$ -25.6° (c. 1.02, $CHCl_3$) {lit[33] -23.7° (c. 1.25, CH_2Cl_2)}.



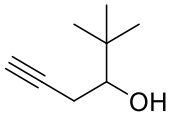
1-(thiophen-2-yl)but-3-yn-1-ol (11k) Prepared according to general procedure B from 2-thiophenecarboxaldehyde (1.12 g, 10 mmol); purified by column chromatography (5-15% EtOAc/hexane) to give 1.13 g colorless, viscous oil, 72%. The spectra were in accordance with the previously reported data.[28]



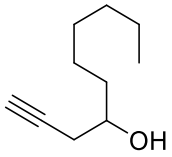
1-cyclohexylbut-3-yn-1-ol (11l) Prepared according to general procedure B from cyclohexanecarboxaldehyde (1.12 g, 10 mmol); purified by column chromatography (20% EtOAc/hexane) to give 1.11 g colorless, viscous oil, 70%. The spectra were in accordance with the previously reported data.[26,29]



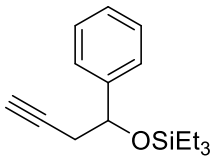
(R)-pent-4-yn-2-ol [(R)11m] Prepared according to general procedure D from commercially available (R)-propylene oxide (10.9 g, 188 mmol) and lithium acetylide-ethylene diamine complex (25 g, 270 mmol) in DMSO (200 mL). Crude product was used in the next step without further purification. Spectra were identical to that of commercially available racemic 4-pentyn-2-ol. $[\alpha]_D^{20}$ -21.3° (c. 1.01 , $CHCl_3$){lit[34] $[\alpha]_D^{20}$ -17.7° (c. 0.13 , $CHCl_3$)}.



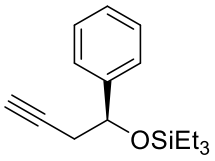
2,2-dimethylhex-5-yn-3-ol (11n) Prepared according to general procedure B from trimethylacetaldehyde (863 mg, 10 mmol); purified by column chromatography (0-10% EtOAc/hexane) to give 583 mg colorless, viscous oil, 46%. The spectra were in accordance with the previously reported data.[35]



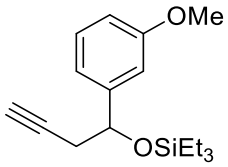
dec-1-yn-4-ol (11o) Prepared according to general procedure B from hexanal (1.0 g, 10 mmol); purified by column chromatography (0-10% EtOAc/hexane) to give 860 mg colorless, viscous oil, 61%. The spectra were in accordance with the previously reported data.[36]



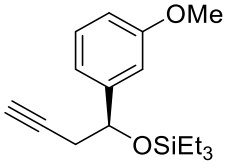
triethyl((1-phenylbut-3-yn-1-yl)oxy)silane (12a) Prepared according to general procedure C from **11a** (438 mg, 3 mmol) to give 760 mg colorless oil, 97%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 2H), 7.29 – 7.15 (m, 3H), 4.74 (t, J = 6.4 Hz, 1H), 2.54 (dddd, J = 16.6, 6.8, 2.7, 0.8 Hz, 1H), 2.48 – 2.39 (m, 1H), 1.88 (t, J = 2.6 Hz, 1H), 0.86 – 0.77 (m, 9H), 0.48 (dtd, J = 16.1, 7.8, 6.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 128.1, 127.5, 125.9, 81.5, 73.5, 70.0, 30.9, 6.8, 4.8. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{24}OSiNa^+$: 283.1489; found: 283.1490.



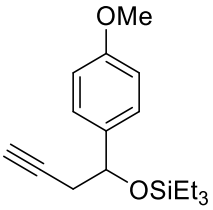
(S)-triethyl((1-phenylbut-3-yn-1-yl)oxy)silane [(S)12a] Prepared according to general procedure C from **(S)11a** (1.30 g, 8.9 mmol) to give 2.27 g clear oil, 98%: All spectra were identical to that of racemic **12a**. $[\alpha]_D^{20}$ -32.29° (c. 1.39 , $CHCl_3$).



triethyl((1-(3-methoxyphenyl)but-3-yn-1-yl)oxy)silane (12b) Prepared according to general procedure C from **11b** (528 mg, 3 mmol) to give 871 mg light yellow oil, 99%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, J = 7.9 Hz, 1H), 6.90 – 6.84 (m, 2H), 6.73 (ddd, J = 8.2, 2.7, 1.1 Hz, 1H), 4.76 – 4.68 (m, 1H), 3.74 (s, 3H), 2.53 (ddd, J = 16.7, 6.9, 2.7 Hz, 1H), 2.43 (ddd, J = 16.6, 6.0, 2.7 Hz, 1H), 1.90 (t, J = 2.7 Hz, 1H), 0.83 (t, J = 7.9 Hz, 9H), 0.56 – 0.42 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 145.7, 129.0, 118.3, 113.0, 111.3, 81.5, 73.4, 70.0, 55.2, 30.9, 6.8, 4.8. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{26}O_2SiNa^+$: 313.1594; found: 313.1575.

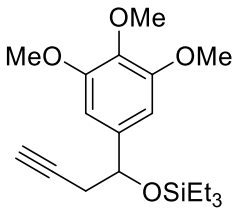


(S)-triethyl((1-(3-methoxyphenyl)but-3-yn-1-yl)oxy)silane [(S)12b] Prepared according to general procedure C from **(S)11b** (1.6 g, 9.1 mmol) to give 2.54 g clear oil, 96%: Spectra were identical to that of racemic **12b**. $[\alpha]_D^{20}$ -37.7° (c. 0.95 , $CHCl_3$).

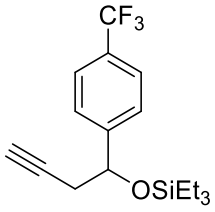


triethyl((1-(4-methoxyphenyl)but-3-yn-1-yl)oxy)silane (12c) Prepared according to general procedure C from **11c** (528 mg, 3 mmol) to give 843 mg colorless oil, 99%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 6.92 – 6.85 (m, 2H), 4.79 (t, J = 6.5 Hz, 1H), 3.83 (s, 3H), 2.62 (ddd, J = 16.6, 6.7, 2.7 Hz, 1H), 2.50 (ddd, J = 16.6, 6.4, 2.7 Hz, 1H), 1.97 (t, J = 2.6 Hz, 1H), 0.91 (t, J = 7.9

Hz, 9H), 0.67 – 0.49 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 136.2, 127.1, 113.4, 81.7, 73.1, 69.9, 55.2, 31.0, 6.8, 4.8. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{26}O_2SiNa^+$: 313.1594; found: 313.1564.

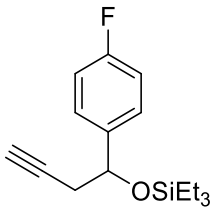


triethyl((1-(3,4,5-trimethoxyphenyl)but-3-yn-1-yl)oxy)silane (12d) Prepared according to general procedure C from **11d** (829 mg, 3 mmol) to give 850 mg colorless oil, 72%: ^{1}H NMR (500 MHz, $CDCl_3$) (major rotamer reported) δ 6.54 (s, 2H), 4.69 (dd, J = 6.8, 6.0 Hz, 1H), 3.78 (s, 9H), 2.55 – 2.37 (m, 2H), 1.92 (t, J = 2.6 Hz, 1H), 0.85 (t, J = 7.9 Hz, 9H), 0.53 (qd, J = 7.9, 2.3 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 139.8, 102.6, 81.6, 73.5, 70.1, 60.9, 56.1, 56.0, 31.1, 6.8, 4.8. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{30}O_4SiNa^+$: 373.1806; found: 373.1802.

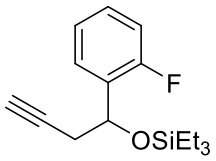


triethyl((1-(4-(trifluoromethyl)phenyl)but-3-yn-1-yl)oxy)silane (12e) Prepared according to general procedure C from **11e** (643 mg, 3 mmol) to give 853 mg colorless oil, 87%: ^{1}H NMR (500 MHz, $CDCl_3$) (**major rotamer**) δ 7.54 – 7.50 (m, 2H), 7.44 – 7.41 (m, 2H), 4.79 (t, J = 6.4 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.43 (ddd, J = 16.6, 6.6, 2.7 Hz, 1H), 1.90 (t, J = 2.7 Hz, 1H), 0.83 (t, J = 7.9 Hz, 9H), 0.53 – 0.47 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 129.6, 126.2, 126.1, 125.1 (q, J = 3.8 Hz),

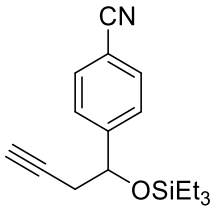
80.7, 71.6, 70.6, 30.8, 6.7, 4.7. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{17}H_{23}F_3OSiNa^+$: 351.1363; found: 351.1361.



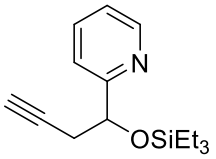
triethyl((1-(4-fluorophenyl)but-3-yn-1-yl)oxy)silane (12f) Prepared according to general procedure C from **11f** (493 mg, 3 mmol) to give 649 mg colorless oil, 77%: ^{1}H NMR (500 MHz, $CDCl_3$) (**major rotamer**) δ 7.34 (ddd, *J* = 8.3, 5.4, 2.3 Hz, 2H), 7.01 (td, *J* = 8.7, 2.3 Hz, 2H), 4.79 (td, *J* = 6.5, 2.3 Hz, 1H), 2.60 (ddt, *J* = 16.6, 6.1, 2.5 Hz, 1H), 2.47 (ddt, *J* = 16.6, 6.6, 2.5 Hz, 1H), 1.95 (q, *J* = 2.5 Hz, 1H), 0.89 (td, *J* = 7.9, 2.3 Hz, 9H), 0.55 (pd, *J* = 7.6, 2.1 Hz, 6H); δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 (d, 245 Hz), 139.7, 127.5 (d, 8.0 Hz), 115.0 (d, 21.4 Hz), 81.2, 72.8, 70.2, 31.0, 6.7, 4.7. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{23}FOSiNa^+$: 301.1394; found: 301.1406.



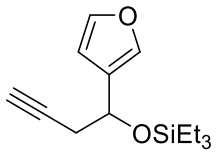
triethyl((1-(2-fluorophenyl)but-3-yn-1-yl)oxy)silane (12g) Prepared according to general procedure C from **11g** (493 mg, 3 mmol) to give 798 mg colorless oil, 95%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (td, J = 7.4, 1.8 Hz, 1H), 7.20 – 7.13 (m, 1H), 7.07 (td, J = 7.6, 1.2 Hz, 1H), 6.92 (ddd, J = 10.4, 8.2, 1.2 Hz, 1H), 5.14 (t, J = 6.1 Hz, 1H), 2.52 (dd, J = 6.1, 2.6 Hz, 2H), 1.86 (t, J = 2.6 Hz, 1H), 0.83 (t, J = 7.9 Hz, 9H), 0.60 – 0.45 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.2 (d, 245 Hz), 130.9 (d, 13.5 Hz), 128.9 (d, 8.2 Hz), 127.8, 124.0, 114.8, 81.0, 69.9, 66.4, 29.6, 6.7, 4.6. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{23}FOSiNa^+$: 301.1394; found: 301.1411.



4-(1-((triethylsilyl)oxy)but-3-yn-1-yl)benzonitrile (12h) Prepared according to general procedure C from **11h** (514 mg, 3 mmol) to give 780 mg colorless oil, 91%: ^{1}H NMR (500 MHz, $CDCl_3$)(**major rotamer**) δ 7.58 – 7.53 (m, 2H), 7.44 – 7.41 (m, 2H), 4.78 (t, J = 6.4 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.42 (ddd, J = 16.6, 6.9, 2.7 Hz, 1H), 1.90 (t, J = 2.7 Hz, 1H), 0.82 (t, J = 7.9 Hz, 9H), 0.54 – 0.47 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 132.0, 126.7, 118.9, 111.4, 80.3, 72.7, 70.9, 30.6, 6.7, 4.7. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{23}NOSiNa^+$: 308.1441; found: 308.1449.

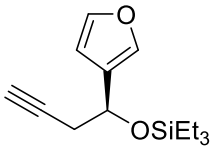


2-(1-((triethylsilyl)oxy)but-3-yn-1-yl)pyridine (12i) Prepared according to general procedure C from **11i** (442 mg, 3 mmol) to give 760 mg colorless oil, 97%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 – 8.43 (m, 1H), 7.82 (s, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 6.1 Hz, 1H), 5.10 (s, 1H), 2.72 (dd, J = 5.5, 2.7 Hz, 2H), 1.85 (d, J = 5.3 Hz, 1H), 0.88 (dt, J = 23.3, 8.0 Hz, 19H), 0.56 (ddt, J = 15.5, 13.0, 7.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.6, 146.2, 138.8, 123.1, 121.7, 80.1, 72.5, 70.7, 29.1, 6.8, 4.7. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{23}NOSiNa^+$: 284.1441; found: 284.1467.

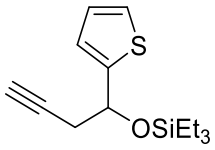


triethyl((1-(furan-3-yl)but-3-yn-1-yl)oxy)silane (12j) Prepared according to general procedure C from **11j** (408 mg, 3 mmol) to give 721 mg colorless oil, 96%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 2H), 6.46 (dd, J = 1.9, 0.9 Hz, 1H), 4.89 – 4.81 (m, 1H), 2.63 (ddd, J = 16.5, 6.1, 2.7 Hz, 1H),

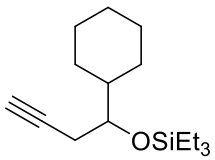
2.54 (ddd, J = 16.5, 6.9, 2.7 Hz, 1H), 2.01 (t, J = 2.7 Hz, 1H), 1.05 – 0.89 (m, 9H), 0.72 – 0.54 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.9, 139.0, 128.6, 108.7, 81.2, 70.2, 66.4, 29.8, 6.8, 4.7. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{22}O_2SiNa^+$: 273.1281; found: 273.1299.



(S)-triethyl((1-(furan-3-yl)but-3-yn-1-yl)oxy)silane [(S)12j] Prepared according to general procedure C from **(S)11j** (528 mg, 3.9 mmol) to give 920 mg colorless oil, 95%: Spectra were identical to that of racemic **12j**. $[\alpha]_D^{20}$ -9.59° (c. 0.99 , $CHCl_3$).

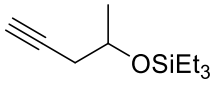


triethyl((1-(thiophen-2-yl)but-3-yn-1-yl)oxy)silane (12k) Prepared according to general procedure C from **11k** (457 mg, 3 mmol) to give 796 mg colorless oil, 99%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (dd, J = 5.0, 1.3 Hz, 1H), 6.96 – 6.84 (m, 2H), 5.02 (td, J = 6.5, 0.8 Hz, 1H), 2.63 (ddd, J = 16.6, 6.4, 2.6 Hz, 1H), 2.54 (ddd, J = 16.6, 6.6, 2.7 Hz, 1H), 0.85 (t, J = 7.9 Hz, 9H), 0.53 (qd, J = 7.9, 3.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 126.3, 124.2, 123.4, 81.0, 70.5, 69.8, 31.4, 6.8, 4.7. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{22}SOSiNa^+$: 289.1053; found: 289.1031.

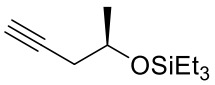


((1-cyclohexylbut-3-yn-1-yl)oxy)triethylsilane (12l) Prepared according to general procedure C from **11l** (457 mg, 3 mmol) to give 750 mg colorless oil, 93%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 –

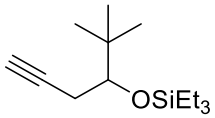
3.48 (m, 1H), 2.35 – 2.20 (m, 2H), 1.90 (t, J = 2.7 Hz, 1H), 1.69 (dddt, J = 14.5, 12.7, 3.3, 1.8 Hz, 2H), 1.59 (dqd, J = 13.5, 3.3, 1.6 Hz, 2H), 1.52 – 1.44 (m, 2H), 1.24 – 1.06 (m, 3H), 1.09 – 0.92 (m, 2H), 0.90 (t, J = 7.9 Hz, 9H), 0.61 – 0.47 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 82.1, 74.9, 69.7, 42.5, 29.4, 27.4, 26.6, 26.4, 26.2, 24.7, 6.9, 5.1. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{30}OSiNa^+$: 289.1958; found: 289.1970.



triethyl(pent-4-yn-2-yloxy)silane (12m) Prepared according to general procedure C from commercially available 4-pentyn-2-ol, (252 mg, 3 mmol) to give 584 mg colorless oil, 97%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.61 (q, *J* = 7.9 Hz, 6H), 0.96 (t, *J* = 7.9 Hz, 9H), 1.26 (d, *J* = 6.1 Hz, 3H), 1.99 (t, *J* = 2.7 Hz, 1H), 2.26 (ddd, *J* = 16.5, 7.4, 2.7 Hz, 1H), 2.37 (ddd, *J* = 16.5, 5.2, 2.7 Hz, 1H), 3.88 – 4.01 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.8, 69.8, 67.3, 29.4, 23.3, 6.8, 4.8. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{22}OSiNa^+$: 221.1332; found: 221.1327.

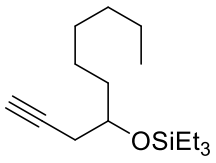


(R)-triethyl(pent-4-yn-2-yloxy)silane [(R)12m] Prepared according to general procedure C from crude **(R)11m** (188 mmol), imidazole (19 g, 282 mmol), DMAP (2.3 g, 18.8 mmol), and chlorotriethylsilane (31.7 mL, 188 mmol) in CH_2Cl_2 to give 25.1 g clear oil, 67% over two steps. Spectra were identical to that of racemic **12m**. $[\alpha]_D^{20}$ +5.15° (c. 0.97 , $CHCl_3$).

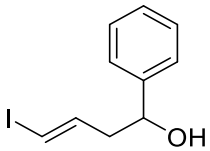


((2,2-dimethylhex-5-yn-3-yl)oxy)triethylsilane (12n) Prepared according to general procedure C from **11n** (378 mg, 3 mmol) to give 713 mg colorless oil, 99%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.52 (dd,

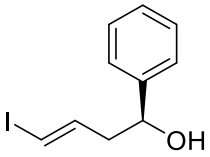
J = 7.0, 4.0 Hz, 1H), 2.44 (ddd, *J* = 17.1, 4.0, 2.7 Hz, 1H), 2.17 (ddd, *J* = 17.0, 7.0, 2.7 Hz, 1H), 1.97 (t, *J* = 2.7 Hz, 1H), 0.98 (t, *J* = 8.0 Hz, 8H), 0.88 (s, 9H), 0.67 (qd, *J* = 7.9, 1.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 83.9, 79.5, 69.6, 36.0, 25.9, 23.5, 7.1, 5.4. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{28}OSiNa^+$: 263.1802; found: 263.1795.



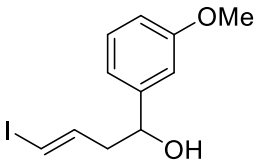
(dec-1-yn-4-yloxy)triethylsilane (12o) Prepared according to general procedure C from **11o** (417 mg, 3.00 mmol) to give 722 mg colorless oil, 95%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 – 3.69 (m, 1H), 2.30 – 2.22 (m, 2H), 1.91 (t, J = 2.7 Hz, 1H), 1.59 – 1.42 (m, 4H), 1.27 – 1.19 (m, 5H), 0.90 (td, J = 8.0, 3.4 Hz, 10H), 0.85 – 0.80 (m, 3H), 0.59 – 0.51 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.8, 70.9, 69.8, 36.7, 31.9, 27.5, 24.9, 22.7, 14.1, 6.9, 4.9. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{32}OSiNa^+$: 291.2115; found: 291.2137.



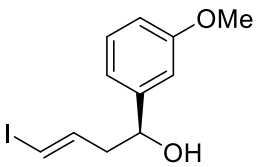
(E)-4-iodo-1-phenylbut-3-en-1-ol (6a) Prepared according to general procedure A from **12a**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 504 mg light yellow, viscous oil, 92%: R_f = 0.49 [silica gel, 20% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$ δ 7.43 – 7.25 (m, 5H), 6.54 (dt, J = 14.7, 7.4 Hz, 1H), 6.16 (dt, J = 14.4, 1.3 Hz, 1H), 4.76 (dd, J = 7.5, 5.3 Hz, 1H), 2.57 – 2.43 (m, 2H), 1.95 (br. s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 142.1, 128.6, 127.9, 125.7, 77.9, 73.0, 45.5. HRMS (ESI): m/z $[M + H - H_2O]^+$ calcd for $C_{10}H_{10}I^+$: 256.9821; found: 256.9824.



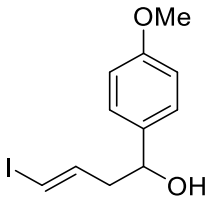
(S,E)-4-iodo-1-phenylbut-3-en-1-ol [(S)6a] Prepared according to general procedure A (reagents scaled linearly) from **(S)12a** (2.60 g, 10 mmol) to give 2.42 g clear oil, 88%: Spectra were identical to that of racemic **6a**. $[\alpha]_D^{20}$ -30.36° (c. 1.43, $CHCl_3$).



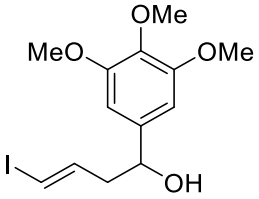
(E)-4-iodo-1-(3-methoxyphenyl)but-3-en-1-ol (6b) Prepared according to general procedure A from **12b**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 509 mg light yellow, viscous oil, 83%: R_f = 0.39 [silica gel, 20% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 1H), 6.95 – 6.86 (m, 2H), 6.87 – 6.80 (m, 1H), 6.54 (dt, J = 14.7, 7.5 Hz, 1H), 6.15 (dt, J = 14.4, 1.3 Hz, 1H), 4.79 – 4.68 (m, 1H), 3.82 (s, 3H), 2.53 – 2.45 (m, 2H), 2.03 – 1.95 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 145.0, 142.1, 129.6, 118.0, 113.3, 111.2, 77.9, 72.9, 55.3, 45.4. HRMS (ESI): m/z $[M + HCOO]^-$ calcd for $C_{12}H_{14}IO_4^-$: 348.9942; found: 348 .9970.



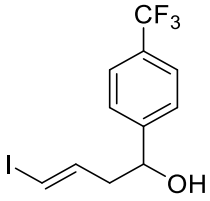
(S,E)-4-iodo-1-(3-methoxyphenyl)but-3-en-1-ol [(S)6b] Prepared according to general procedure A (reagents scaled linearly) from **(S)12b** (1.16 g, 4.0 mmol) to give 1.13 g clear oil, 93%: Spectra were identical to that of racemic **6b**. $[\alpha]_D^{20}$ -20.85° (c. 0.83, $CHCl_3$).



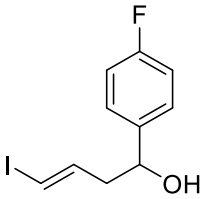
(E)-4-iodo-1-(4-methoxyphenyl)but-3-en-1-ol (6c) Prepared according to general procedure A from **12c**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 596 mg light yellow, viscous oil, 98%: R_f = 0.44 [silica gel, 20% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 2H), 6.95 – 6.86 (m, 2H), 6.53 (dt, J = 14.6, 7.7, 1H), 6.14 (dt, J = 14.4, 1.3 Hz, 1H), 4.70 (ddd, J = 8.1, 5.2, 3.1 Hz, 1H), 3.81 (s, 3H), 2.66 – 2.38 (m, 2H), 1.88 (d, J = 3.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 142.3, 135.4, 127.0, 113.9, 77.8, 72.6, 55.3, 45.45. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{13}INaO_2^+$: 326.9852; found: 326.9831.



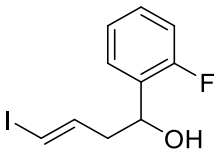
(E)-4-iodo-1-(3,4,5-trimethoxyphenyl)but-3-en-1-ol (6d) Prepared according to general procedure A from **12d**, purified by column chromatography (20% - 40% EtOAc/hexane) to give 692 mg light yellow, viscous oil, 95%: R_f = 0.16 [silica gel, 30% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 – 6.42 (m, 3H), 6.09 (dt, *J* = 14.4, 1.3 Hz, 1H), 4.62 (dd, *J* = 7.3, 5.3 Hz, 1H), 3.80 (s, 6H), 3.77 (s, 3H), 2.50 – 2.28 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 142.1, 139.1, 118.6, 102.5, 78.0, 73.2, 60.9, 56.2, 45.5. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{17}IO_4Na^+$: 387.0064; found: 387.0064.



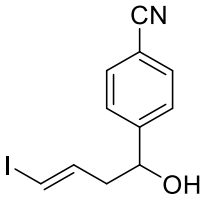
(E)-4-iodo-1-(4-(trifluoromethyl)phenyl)but-3-en-1-ol (6e) Prepared according to general procedure A from **12e**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 616 mg light yellow, viscous oil, 90%: R_f = 0.45 [silica gel, 20% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 6.53 (dt, J = 14.8, 7.4 Hz, 1H), 6.20 (dt, J = 14.5, 1.3 Hz, 1H), 4.83 (td, J = 6.3, 3.3 Hz, 1H), 2.54 – 2.44 (m, 2H), 2.07 (d, J = 3.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2, 141.4, 128.3, 126.1, 125.5 (q, J = 4.1 Hz), 125.1, 123.0, 78.7, 72.3, 45.6. HRMS (ESI): m/z [M + HCOO]$^-$ calcd for $C_{12}H_{11}F_3IO_3^-$: 386.9710; found: 386.9724.



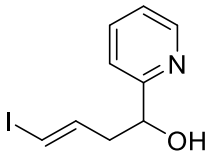
(E)-1-(4-fluorophenyl)-4-iodobut-3-en-1-ol (6f) Prepared according to general procedure A from **12f**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 430 mg light yellow, viscous oil, 74%: R_f = 0.55 [silica gel, 20% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 2H), 7.14 – 6.93 (m, 2H), 6.50 (dt, J = 14.6, 7.4 Hz, 1H), 6.14 (dt, J = 14.4, 1.3 Hz, 1H), 4.72 (ddd, J = 7.8, 5.3, 2.5 Hz, 1H), 2.57 – 2.37 (m, 2H), 2.16 (dd, J = 9.9, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.2 (d, J = 245.9 Hz), 141.8, 139.0 (d, J = 3.1 Hz), 127.4 (d, J = 8.1 Hz), 115.4 (d, J = 21.4 Hz), 78.2, 72.2, 45.6. HRMS (ESI): m/z [M + HCOO$^-$]$^-$ calcd for $C_{11}H_{11}FIO_3^-$: 336.9742; found: 336.9762.



(E)-1-(2-fluorophenyl)-4-iodobut-3-en-1-ol (6g) Prepared according to general procedure A from **12g**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 567 mg light orange crystals, 97%: R_f = 0.59 [silica gel, 20% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.42 (m, 1H), 7.35 – 7.21 (m, 1H), 7.17 (td, J = 7.5, 1.2 Hz, 1H), 7.03 (ddd, J = 10.7, 8.2, 1.2 Hz, 1H), 6.57 (dt, J = 14.7, 7.5 Hz, 1H), 6.17 (dt, J = 14.4, 1.3 Hz, 1H), 5.08 (dt, J = 7.8, 4.5 Hz, 1H), 2.59 – 2.44 (m, 2H), 2.03 (d, J = 4.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.5 (d, J = 245.6 Hz), 141.8, 130.2 (d, J = 13.2 Hz), 129.2 (d, J = 8.3 Hz), 127.1 (d, J = 4.2 Hz), 124.4 (d, J = 3.5 Hz), 115.4 (d, J = 21.7 Hz), 78.2, 66.9 (d, J = 2.1 Hz), 44.3. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{10}H_{10}FINaO^+$: 314.9652; found: 314.9664.

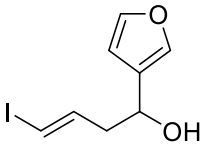


(E)-4-(1-hydroxy-4-iodobut-3-en-1-yl)benzonitrile (6h) Prepared according to general procedure A from **12h**, attempted purification by column chromatography (10% - 20% EtOAc/hexane) yielded an inseparable mixture (~1:1) of desired vinyl iodide and reduced benzaldehyde product.

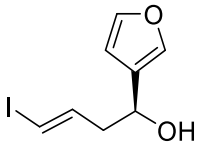


(E)-4-iodo-1-(pyridin-2-yl)but-3-en-1-ol (6i) Prepared according to general procedure A from **12i**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 253 mg tan, viscous oil, 46%: R_f = 0.43 [silica gel, 30% EtOAc in pentanes] yellow with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ

8.51 (ddd, J = 5.0, 1.7, 0.9 Hz, 1H), 7.71 (td, J = 7.7, 1.7 Hz, 1H), 7.27 – 7.20 (m, 2H), 6.48 (dt, J = 14.6, 7.4 Hz, 1H), 6.05 (dt, J = 14.4, 1.4 Hz, 1H), 4.79 (dd, J = 7.2, 4.7 Hz, 1H), 2.56 (dddd, J = 14.5, 7.5, 4.7, 1.4 Hz, 1H), 2.43 (dtd, J = 14.4, 7.2, 1.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3, 147.6, 141.6, 137.7, 122.9, 120.8, 77.9, 71.2, 44.6. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_9H_{11}INO^+$: 275.9880; found: 275.9860.



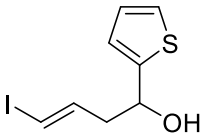
(E)-1-(furan-3-yl)-4-iodobut-3-en-1-ol (6j) Prepared according to general procedure A from **12j**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 491 mg light yellow, viscous oil, 93%: R_f = 0.23 [silica gel, 10% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 2H), 6.47 (dt, J = 14.7, 7.5 Hz, 1H), 6.32 (dd, J = 1.9, 1.0 Hz, 1H), 6.12 (dt, J = 14.4, 1.3 Hz, 1H), 4.67 (t, J = 6.3 Hz, 1H), 2.54 – 2.28 (m, 2H), 1.78 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 141.8, 139.1, 128.0, 108.3, 78.2, 65.6, 44.3. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_8H_{10}IO_2^+$: 264.9720; found: 264.9701.



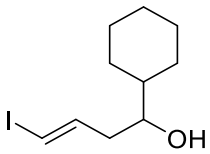
(S,E)-1-(furan-3-yl)-4-iodobut-3-en-1-ol [(S)6j]

Prepared according to general procedure A from **(S)12j** to give 420 mg yellow oil, 80%:

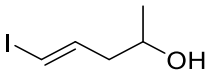
Spectra were identical to that of racemic **6j**. $[\alpha]_D^{20}$ -16.4° (c. 0.61, $CHCl_3$)



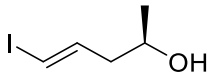
(E)-4-iodo-1-(thiophen-2-yl)but-3-en-1-ol (6k) Prepared according to general procedure A from **12k**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 510 mg light yellow, viscous oil, 91%: R_f = 0.33 [silica gel, 10% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 1H), 7.07 – 6.96 (m, 2H), 6.59 (dt, J = 14.6, 7.4 Hz, 1H), 6.23 (dt, J = 14.4, 1.3 Hz, 1H), 5.04 (t, J = 6.3 Hz, 1H), 2.70 – 2.56 (m, 2H), 2.15 – 2.10 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.1, 141.5, 126.8, 125.0, 124.0, 78.5, 68.9, 45.5. HRMS (ESI): m/z $[M + H - H_2O]^+$ calcd for $C_8H_8IS^+$: 262.9386; found: 262.9377.



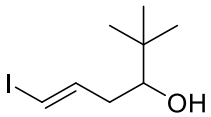
(E)-1-cyclohexyl-4-iodobut-3-en-1-ol (6l) Prepared according to general procedure A from **12l**, purified by column chromatography (2.5% - 12% EtOAc/hexane) to give 527 mg off-white powder, 94%: R_f = 0.57 [silica gel, 10% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (ddd, J = 14.7, 7.9, 7.0 Hz, 1H), 6.12 (dt, J = 14.4, 1.4 Hz, 1H), 3.41 (dtd, J = 8.3, 5.7, 5.1, 2.9 Hz, 1H), 2.29 (dddd, J = 14.4, 7.0, 3.6, 1.5 Hz, 1H), 2.17 (dtd, J = 14.4, 8.2, 1.2 Hz, 1H), 1.83 (dtd, J = 10.7, 3.5, 1.8 Hz, 1H), 1.76 (ddt, J = 10.7, 8.8, 3.3 Hz, 2H), 1.71 – 1.64 (m, 2H), 1.54 (d, J = 4.5 Hz, 1H), 1.34 (tdt, J = 12.0, 5.9, 3.4 Hz, 1H), 1.29 – 1.11 (m, 3H), 1.10 – 0.94 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.3, 77.0, 74.5, 43.0, 40.8, 29.0, 27.9, 26.4, 26.2, 26.0. HRMS (ESI): m/z $[M + HCOO]^-$ calcd for $C_{11}H_{18}IO_3^-$: 325.0306; found: 325.0305.



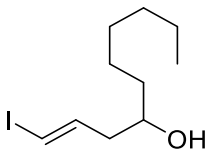
(E)-5-iodopent-4-en-2-ol (6m) Prepared according to general procedure A from **12m**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 402 mg light yellow, viscous oil, 95%: R_f = 0.50 [silica gel, 20% EtOAc in pentanes] dark purple with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (ddd, J = 14.4, 7.9, 7.2 Hz, 1H), 6.15 (dt, J = 14.4, 1.3 Hz, 1H), 3.88 (m, 1H), 2.21 (m, 2H), 1.21 (d, J = 6.2, 3.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.5, 77.5, 66.6, 45.5, 22.9. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_5H_9IONa^+$: 234.9590; found: 234.9599.



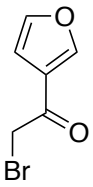
(R,E)-5-iodopent-4-en-2-ol [(R)6m] Prepared according to general procedure A (reagents scaled linearly) from **(R)12m** (4.4 g, 20 mmol) to give 4.5 g clear oil, 96%. Spectra were identical to that of racemic **6m**. $[\alpha]_D^{20}$ -17.43° (c. 0.70 , $CHCl_3$) {lit[25] $[\alpha]_D^{20}$+17.9 (c 1.00, $CHCl_3$), S-enantiomer}



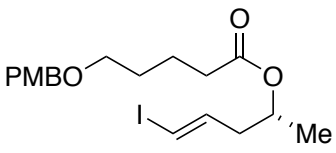
(E)-6-iodo-2,2-dimethylhex-5-en-3-ol (6n) Prepared according to general procedure A from **12n**, purified by column chromatography (10% - 20% EtOAc/hexane) to give 503 mg light yellow, viscous oil, 99%: R_f = 0.70 [silica gel, 10% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (ddd, J = 14.6, 8.1, 6.7 Hz, 1H), 6.13 (dt, J = 14.4, 1.4 Hz, 1H), 3.28 (ddd, J = 10.5, 4.3, 2.2 Hz, 1H), 2.31 (dddd, J = 14.4, 6.8, 2.2, 1.6 Hz, 1H), 2.04 (dddd, J = 14.4, 10.5, 8.1, 1.2 Hz, 1H), 1.54 (d, J = 4.4 Hz, 1H), 0.91 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 78.0, 76.7, 38.6 34.8, 25.6. HRMS (ESI): m/z $[M + HCOO]^-$ calcd for $C_9H_{16}IO_3^-$: 299.0150; found: 299.0163.



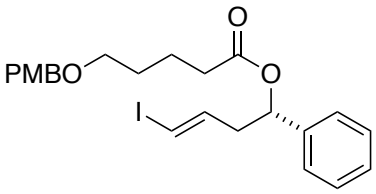
(E)-1-iododec-1-en-4-ol (6o) Prepared according to general procedure A from **12o**, purified by column chromatography (2.5% - 12% EtOAc/hexane)to give 515 mg light yellow, viscous oil, 96%: R_f = 0.50 [silica gel, 10% EtOAc in pentanes] deep blue with vanillin stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 – 6.51 (m, 1H), 6.13 (dt, J = 14.4, 1.3 Hz, 1H), 3.67 (td, J = 7.0, 4.2 Hz, 1H), 2.27 (dddd, J = 14.3, 7.2, 4.3, 1.4 Hz, 1H), 2.17 (dtd, J = 14.3, 7.7, 1.2 Hz, 1H), 1.56 (s, 1H), 1.45 – 1.42 (m, 2H), 1.37 – 1.25 (m, 6H), 0.93 – 0.88 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7, 77.3, 70.4, 43.8, 36.8, 31.8, 25.3, 22.6, 14.0. HRMS (ESI): m/z [M + HCOO]$^-$ calcd for $C_{10}H_{18}IO_3^-$: 313.0306; found: 313.0331.



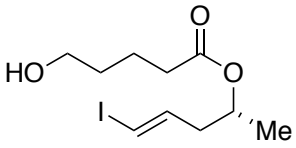
2-bromo-1-(furan-3-yl)ethan-1-one (14j) To a stirred solution of $CuBr_2$ (12.2 g, 54.5 mmol) in EtOAc (100 mL) was added a solution of 3-acetylfuran (synthesized from aldehyde **10j** by known procedure[37]) (3.00 g, 27.2 mmol) in $CHCl_3$ (100 mL). The reaction was brought to reflux for 3 hours then was cooled to room temperature, filtered through a short plug of silica, and concentrated. The crude residue was taken up in hot heptane and placed in the freezer overnight to afford the title compound as light yellow crystals, 3.12 g, 73%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 (s, 2H), 6.81 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.47 – 7.49 (m, 1H), 8.15 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 31.5, 109.0, 124.7, 144.5, 148.3, 186.1. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_6H_5BrO_2Na^+$: 210.9365; found: 210.9364. (**Caution**: this compound is a potent lachrymator!)



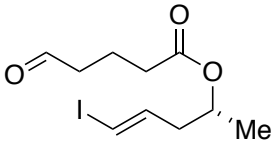
(R,E)-5-iodopent-4-en-2-yl 5-((4-methoxybenzyl)oxy)pentanoate (17) To a solution of (R,E)-5-iodopent-4-en-2-ol **6m** (4.40 g, 20.7 mmol) in CH_2Cl_2 (200 mL) was added 5-((4-methoxybenzyl)oxy)pentanoic acid (**16**)[38] (5.93 g, 24.9 mmol), DCC (5.14 g, 24.9 mmol), and DMAP (253 mg, 2.08 mmol) in one portion and the reaction allowed to stir at room temperature for 16 hours. Reaction was then filtered over Celite, concentrated, and purified by column chromatography (30% EtOAc/Pentane) to give the title compound as a clear oil, 8.21 g, 92%: ^{1}H NMR (500 MHz, CD_3CN) δ1.16 (d, *J* = 6.3 Hz, 3H), 1.52 – 1.66 (m, 4H), 2.21 – 2.33 (m, 4H), 3.44 (t, *J* = 6.1 Hz, 2H), 3.77 (s, 3H), 4.38 (s, 2H), 4.90 (pd, *J* = 6.3, 5.3 Hz, 1H), 6.19 (dt, *J* = 14.5, 1.3 Hz, 1H), 6.51 (dt, *J* = 14.7, 7.5 Hz, 1H), 6.86 – 6.93 (m, 2H), 7.22 – 7.27 (m, 2H). ^{13}C NMR (126 MHz, CD_3CN) δ 18.8, 21.7, 28.8, 33.8, 41.5, 54.9, 68.6, 69.3, 71.9, 77.2, 113.6, 129.2, 131.1, 142.2, 159.1, 172.7. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{18}H_{25}I0_4Na^+$: 455.0690; found: 455.0659. $[\alpha]_D^{20}$ +12.20° (c. 0.97 , $CHCl_3$).



(S,E)-4-iodo-1-phenylbut-3-en-1-yl 5-((4-methoxybenzyl)oxy)pentanoate (18) Prepared according to the procedure for **17** from (S,E)-4-iodo-1-phenylbut-3-en-1-ol (**(S)-6a**) on a 4.8 mmol scale to give a light yellow oil, 2.3 g, 95%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 – 1.66 (m, 2H), 1.71 (dtd, *J* = 8.8, 8.0, 7.2, 6.0 Hz, 2H), 2.36 (td, *J* = 7.5, 4.3 Hz, 2H), 2.53 (dddd, *J* = 14.4, 7.0, 5.6, 1.4 Hz, 1H), 2.61 (dtd, *J* = 14.5, 7.7, 1.2 Hz, 1H), 3.44 (t, *J* = 6.3 Hz, 2H), 3.80 (s, 3H), 4.42 (s, 2H), 5.78 (dd, *J* = 7.7, 5.6 Hz, 1H), 6.10 (dt, *J* = 14.5, 1.3 Hz, 1H), 6.41 (ddd, *J* = 14.6, 7.8, 7.0 Hz, 1H), 6.84 – 6.91 (m, 2H), 7.22 – 7.38 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 29.1, 34.2, 42.8, 55.3, 69.5, 72.6, 73.9, 78.2, 113.8, 126.3, 128.2, 128.6, 129.3, 130.6, 139.5, 140.9, 159.1, 172.6. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{23}H_{27}IO_4Na^+$: 517.0846 ; found: 517.0844. $[\alpha]_D^{20}$ -23.6 ° (c. 1.11, $CHCl_3$)

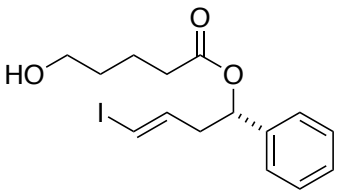


(R,E)-5-iodopent-4-en-2-yl 5-hydroxypentanoate (19.1) To a solution of **17** (6.70 g, 16.2 mmol) in CH_2Cl_2 (150 mL) was added 0.1M pH 7.0 potassium phosphate buffer (8 mL) followed by DDQ (5.51 g, 24.3 mmol) in one portion. Reaction stirred one hour at RT. Reaction was quenched with 1:1 mixture of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ (100 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (3 x 100 mL). The organic layers were combined, washed with brine (2 x 150 mL), dried with $MgSO_4$, concentrated, and purified by column chromatography (10-40% EtOAC/Pentane) to give the title compound as a light yellow oil, 4.86 g, 96%: ^{1}H NMR (500 MHz, CD_3CN) δ 1.17 (d, *J* = 6.4 Hz, 3H), 1.43 – 1.52 (m, 2H), 1.60 (dtd, *J* = 9.0, 7.8, 7.3, 6.2 Hz, 2H), 2.22 – 2.35 (m, 4H), 2.51 (t, *J* = 5.4 Hz, 1H), 3.49 (td, *J* = 6.4, 5.4 Hz, 2H), 4.90 (td, *J* = 6.5, 5.6 Hz, 1H), 6.20 (dt, *J* = 14.4, 1.4 Hz, 1H), 6.51 (dt, *J* = 14.7, 7.5 Hz, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ 142.7, 77.8, 69.1, 61.6, 42.1, 34.4, 32.4, 21.8, 19.3. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{10}H_{17}I0_3Na^+$: 335.0114; found: 335.0138. $[\alpha]_D^{20}$ +9.55° (c 1.02, $CHCl_3$).

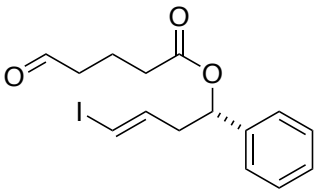


(R,E)-5-iodopent-4-en-2-yl 5-oxopentanoate (19) To a solution of (R,E)-5-iodopent-4-en-2-yl 5-hydroxypentanoate (4.60 g, 14.7 mmol) in water-saturated CH_2Cl_2 at 0° C was added DMP (12.5 g, 29.5 mmol) in one portion followed by solid $NaHCO_3$ (6.19 g, 73.7 mmol). Reaction was brought to RT and stirred one hour. The reaction was then carefully diluted with water (50 mL) and sat. aq. $Na_2S_2O_3$ (50 mL), the organic layer separated, and the aqueous layer extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with brine (2 x 100 mL), dried with $MgSO_4$, concentrated, and purified by column chromatography(25% EtOAc/pentane) to give the title compound as a light yellow oil, 4.17 g, 91%: ^{1}H NMR (500 MHz, CD_3CN) δ 1.17 (d, *J* = 6.3 Hz, 3H),

1.82 (p, *J* = 7.4 Hz, 2H), 2.26 – 2.31 (m, 4H), 2.47 (td, *J* = 7.3, 1.3 Hz, 2H), 4.91 (td, *J* = 6.5, 5.5 Hz, 1H), 6.20 (dt, *J* = 14.5, 1.4 Hz, 1H), 6.51 (dt, *J* = 14.8, 7.5 Hz, 1H), 9.69 (t, *J* = 1.3 Hz, 1H). ^{13}C NMR (126 MHz, CD_3CN) δ 202.9, 142.7, 77.8, 69.4, 43.0, 42.1, 33.6, 19.3, 17.8. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{10}H_{15}I0_3\ Na^+$: 332.9958; found: 332.9970. $[\alpha]_D^{20}$ +27.35° (c. 0.675, $CHCl_3$).

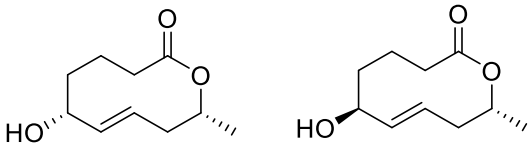


(S,E)-4-iodo-1-phenylbut-3-en-1-yl 5-hydroxypentanoate (20.1) Compound was prepared as described for (R,E)-5-iodopent-4-en-2-yl 5-hydroxypentanoate from **18** on a 4.4 mmol scale to give 1.42 g clear oil, 86%: ^{1}H NMR (500 MHz, CD_3CN) δ 1.41 – 1.51 (m, 2H), 1.56 – 1.67 (m, 2H), 2.35 (td, *J* = 7.4, 3.4 Hz, 2H), 2.49 – 2.65 (m, 3H), 3.48 (td, *J* = 6.4, 5.3 Hz, 2H), 5.75 (dd, *J* = 7.8, 5.4 Hz, 1H), 6.18 (dt, *J* = 14.4, 1.3 Hz, 1H), 6.48 (dt, *J* = 14.6, 7.3 Hz, 1H), 7.27 – 7.35 (m, 3H), 7.32 – 7.41 (m, 2H); ^{13}C NMR (126 MHz, CD_3CN) δ 21.8, 32.4, 34.3, 42.7, 61.6, 74.2, 78.4, 126.7, 128.5, 129.0, 140.8, 142.2, 173.1. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{19}I0_3Na^+$: 397.0271; found: 397.0255. $[\alpha]_D^{20}$ -34.68° (c. 1.710, $CHCl_3$).



(S,E)-4-iodo-1-phenylbut-3-en-1-yl 5-oxopentanoate (20.2) Compound was prepared as described for the preparation of **19** from (S,E)-4-iodo-1-phenylbut-3-en-1-yl 5-hydroxypentanoate (1.2 g, 3.3 mmol), DMP (2.8 g, 6.6 mmol) and $NaHCO_3$ (1.4 g, 16.4 mmol) to give 1.1 g clear oil, 92%: ^{1}H NMR (500 MHz, CD_3CN,) δ 1.84 (p, *J* = 7.3 Hz, 2H), 2.26 – 2.43 (m, 2H), 2.45 (td, *J* = 7.3, 1.3 Hz, 2H), 2.49 – 2.66 (m, 2H), 5.76 (dd, *J* = 7.8, 5.4 Hz, 1H), 6.18 (dt, *J* = 14.5, 1.3 Hz, 1H), 6.48 (dt, *J* = 14.6,

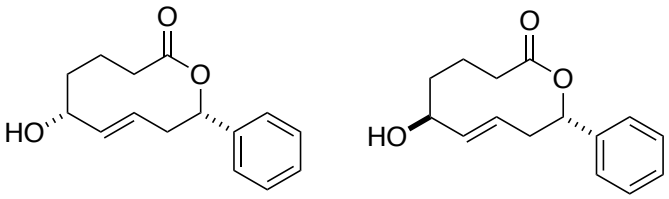
7.3 Hz, 1H), 7.27 – 7.41 (m, 5H), 9.68 (t, *J* = 1.3 Hz, 1H); **13**C NMR (126 MHz, CD_3CN) δ 17.2, 33.0, 42.1, 42.4, 73.9, 77.8, 126.2, 128.0, 128.5, 140.1, 141.6, 202.2. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{17}I0_3Na^+$: 395.0115; found: 395.0101. $[\alpha]_D^{20}$ -45.83° (c. 0.600, $CHCl_3$).



aspinolide A (6R,10R,E)-6-hydroxy-10-methyl-3,4,5,6,9,10-hexahydro-2H-oxecin-2-one (3a) and (–)-5-*epi*-aspinolide A (6S,10R,E)-6-hydroxy-10-methyl-3,4,5,6,9,10-hexahydro-2H-oxecin-2-one (3b)

A 2L round-bottom flask equipped with a magnetic stir bar was charged with <10 micron powdered Mn(0) (2.80 g, 51.6 mmol), flame dried under vacuum, and backfilled with Ar after cooling to room temperature. In a glovebox, a flame dried 100mL RBF was charged with anhydrous $CrCl_3$ (204 mg, 1.29 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (346 mg, 1.29 mmol), and bis(cyclopentadienyl)zirconium(IV) dichloride (5.65 g, 19.3 mmol), and a separate oven dried 20mL vial was charged with Ni-neocuproine**[16]** (213 mg, 0.64 mmol). Both were sealed with a septum and removed from the glovebox, upon which the contents of the 100mL flask were suspended in anhydrous THF (60 mL) and cannulated into the 2L flask, along with an additional 60 mL of THF. The dark suspension was stirred vigorously for 30 minutes, upon which the Ni-neocuproine complex suspended in anhydrous THF (15 mL) was added, and the suspension diluted with anhydrous THF (1.2 L). (R,E)-5-iodopent-4-en-2-yl 5-oxopentanoate (**17**) was taken up in anhydrous THF (100 mL) and added via syringe pump over 10 hours, and the reaction was allowed to stir an additional 4 hours after addition was complete. The reaction was then diluted with pentane (500 mL) and quenched with 10% aqueous citric acid solution (400 mL). The solution was stirred for 30 minutes until a dark yellow biphasic mixture was formed. The organic layer was separated and the aqueous layer was extracted

with diethyl ether (3 x 200 mL), and the combined organic extracts were washed with brine (2 x 250 mL), dried with $MgSO_4$, concentrated, and the diastereomers were separated by column chromatography (20-30% EtOAc/pentane) to give aspinolide A (**3a**) (935 mg, 39%) and stagonolide F (**3b**) (870 mg, 36%) both as clear, viscous oils: **(3a)** ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (ddd, *J* = 15.4, 10.6, 4.8 Hz, 1H), 5.32 (dd, *J* = 15.3, 9.4 Hz, 1H), 5.17 (dqd, *J* = 11.1, 6.4, 3.3 Hz, 1H), 4.01 (td, *J* = 10.2, 3.4 Hz, 1H), 2.43 (ddd, *J* = 15.7, 8.3, 2.6 Hz, 1H), 2.37 (ddd, *J* = 12.4, 4.4, 3.2, Hz, 1H) , 2.06 – 1.86 (m, 5H), 1.55 – 1.44 (m, 2H), 1.32 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 137.3, 131.7, 74.0, 71.7, 42.1, 38.7, 35.7, 22.3, 19.8. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{10}H_{16}O_3Na^+$: 207.0992; found: 207.1020. $[\alpha]_D^{20}$ –44.7 ° (c 0.3, MeOH) {lit[2] $[\alpha]_D^{23}$ –43.8 ° (c 0.3, MeOH)}. **(3b)** ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (dddd, *J* = 15.4, 10.5, 4.8, 2.4 Hz, 1H), 5.45 (dd, *J* = 15.8, 1.8 Hz, 1H), 5.17 (dqd, *J* = 11.1, 6.3, 2.8 Hz, 1H), 4.44 (ddq, *J* = 8.1, 4.0, 2.0 Hz, 1H), 2.53 – 2.40 (m, 2H), 2.16 – 1.92 (m, 5H), 1.70 – 1.63 (m, 1H), 1.57 – 1.50 (m, 1H), 1.32 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 136.7, 126.4, 72.7, 68.4, 42.5, 36.6, 35.8, 19.7, 17.8. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{10}H_{16}O_3Na^+$: 207.0992; found: 207.1022. $[\alpha]_D^{20}$ –62.0 ° (c 0.1, $CHCl_3$) {lit[1] $[\alpha]_D^{23}$ –27 ° (c 0.1, $CHCl_3$)}.



(6R,10S,E)-6-hydroxy-10-phenyl-3,4,5,6,9,10-hexahydro-2H-oxecin-2-one (21a) and (6S,10S,E)-6-hydroxy-10-phenyl-3,4,5,6,9,10-hexahydro-2H-oxecin-2-one (21b)

Prepared according to the procedure for **3a** and **3b** from **20** (1.0 g, 2.7 mmol), Mn(0) (600 mg, 10.8 mmol), $CrCl_3$ (43 mg, 0.27 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridine (73 mg, 0.27 mmol), Cp_2ZrCl_2 (1.20 g, 4.10 mmol), and Ni-neocuproine (44 mg, 0.14 mmol) in THF (375 mL) to give **21a** (279 mg, 42%) and **21b** (260 mg, 39%) as white crystalline solids: **(6R,10S,E)-6-hydroxy-10-phenyl-3,4,5,6,9,10-**

hexahydro-2H-oxecin-2-one (21a) White crystalline solid (m.p. 75-81 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61 (dddd, *J* = 14.4, 12.3, 6.5, 2.4 Hz, 2H), 1.65 – 1.80 (m, 1H), 2.06 – 2.15 (m, 1H), 2.11 – 2.25 (m, 2H), 2.30 – 2.46 (m, 1H), 2.47 – 2.61 (m, 1H), 2.69 (ddt, *J* = 10.1, 5.5, 2.8 Hz, 1H), 4.50 (d, *J* = 5.8 Hz, 1H), 5.60 (dd, *J* = 15.8, 1.8 Hz, 1H), 5.70 (dddd, *J* = 15.1, 10.2, 4.7, 2.3 Hz, 1H), 6.07 (dd, *J* = 11.4, 3.0 Hz, 1H), 7.27 – 7.36 (m, 1H), 7.33 – 7.44 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 139.1, 137.7, 128.6, 128.1, 126.3, 126.1, 68.5, 43.0, 36.7, 35.7, 29.7, 17.9. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{18}O_3Na^+$: 269.1148; found: 269.1169. $[\alpha]_D^{20}$ –153.06 ° (c 1.23, $CHCl_3$). **(6S,10S,E)-6-hydroxy-10-phenyl-3,4,5,6,9,10-hexahydro-2H-oxecin-2-one (21b)** White crystalline solid (m.p. 90-91 °C)**;** ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 – 1.66 (m, 1H), 1.90 – 2.05 (m, 2H), 2.08 (ddt, *J* = 13.8, 5.3, 3.4 Hz, 1H), 2.10 – 2.21 (m, 1H), 2.23 – 2.40 (m, 1H), 2.47 – 2.57 (m, 1H), 2.63 (dddd, *J* = 12.6, 4.5, 3.3, 0.9 Hz, 1H), 4.08 (ddd, *J* = 10.5, 9.4, 3.4 Hz, 1H), 5.47 (dd, *J* = 15.4, 9.5 Hz, 1H), 5.68 (ddd, *J* = 15.3, 10.6, 4.7 Hz, 1H), 6.07 (dd, *J* = 11.5, 3.4 Hz, 1H), 7.28 – 7.37 (m, 1H), 7.34 – 7.44 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 139.2, 138.1, 131.4, 128.6, 128.1, 126.3, 76.4, 74.1, 42.6, 38.7, 35.6, 22.4. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{18}O_3Na^+$: 269.1148; found: 269.1159. $[\alpha]_D^{20}$ –179.23° (c 0.52, $CHCl_3$)**.**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Data includes ^{1}H and ^{13}C NMR spectra of all compounds; chiral GC/HPLC analysis of compounds **(S)-6a**, **(S)-6b**, **(S)-11j** and **(R)-6m;** X-ray crystallographic data for compound **21a**; X-ray crystallographic data for compound **21b.**

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Notes

The authors declare no competing financial interest.

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