JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Stereoselective Synthesis of Substituted Tetrahydropyrans and Isochromans by Cyclization of Phenylseleno Alcohols

Andrea Temperini,*[,†] Anna Barattucci,[‡] Paola Maria Bonaccorsi,[‡] Ornelio Rosati,[†] and Lucio Minuti[§]

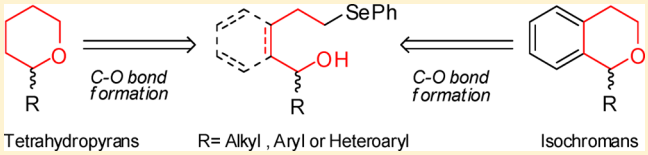
[†]Dipartimento di Scienze Farmaceutiche, Università di Perugia, Via del Liceo 1, 06123 Perugia, Italy

[‡]Dipartimento di Scienze Chimiche, Università di Messina, Viale F. Stagno d'Alcontres 31, 98166 Messina, Italy

[§]Dipartimento di Chimica, Biologia e Biotecnologie, Università di Perugia, Via Elce di Sotto 8, 06123 Perugia, Italy

Supporting Information

ABSTRACT: A selenium-mediated strategy for the stereoselective synthesis of substituted tetrahydropyrans and isochromans has been developed starting from δ-phenylseleno ketones. After enantioselective reduction, the chiral nonracemic phenylseleno alcohols were oxidized to the corresponding selenones, which underwent an effcient 6-*exo*-*tet* ring-closure reaction.



INTRODUCTION

The tetrahydropyran motif is one of the most common scaffolds found in natural products such as antibiotics,[1] marine toxins,[2] and pheromones.[3] In spite of many strategies employed for the synthesis of complex tetrahydropyrans[4] (THPs), few examples of 2-substituted THPs synthesis have been described. Among these, C−O bond formation reactions are probably the most used methodologies, such as alkene seleno- and haloetherification,[5] acid-catalyzed cyclization of vinylsilanes,[6] gold or ytterbium hydroalkoxylation of alkenols[7a] and allenes,[7b] palladium-catalyzed allylic oxidation[8] or oxidative cyclization of alkenols,[9] water[10a] and gold- or iron-catalyzed[10b,c] cyclization of monoallylic diols, gold-catalyzed cyclic ether formation from diols,[11] copper-catalyzed O−H insertion of ω-hydroxy-α-diazoesters,[12] and cycloetherification via intramolecular oxy-Michael addition.[13] Other approaches have focused on the formation of C−C bond as the reaction of cyclic oxonium ion with organometallic reagents,[14] the boron trifluoride-catalyzed rearrangement of 2-aryloxytetrahydropyrans,[15] the C−H arylation/alkylation at the α-position of tetrahydropyran[16a] or dihydropyran,[16b] and finally, the ruthenium-catalyzed ring-closing metathesis.[17] Due to the limitation of the above-mentioned synthetic methods, such as moderate yields and low stereoselectivity, development of efficient and enantioselective methods for the construction of 2-substituted THPs still represents a challenge.

Reports from our laboratory have demonstrated the utility of organochalcogen intermediates in organic synthesis[18] as well as their use in the synthesis of heterocycles.[19] We recently described the easy and stereoselective preparation of 2-substituted tetrahydrofurans[20] via intramolecular displacement of phenylselenone group by hydroxy group.

Based on this process, we envisioned a strategy for the construction of chiral nonracemic 2-substituted THPs **5** (Scheme 1), starting from enantioenriched phenylseleno alcohols **4**. The control of the stereochemistry of the secondary alcohols **4**, by using a catalytic asymmetric transfer hydrogenation (ATH) reaction[21] of δ-phenylseleno ketones **3**, is the cornerstone of our strategy because it allows the expedient generation of THPs **5** in both enantiomeric forms. To the best of our knowledge, use of phenylseleno alcohol **4** as intermediate in the synthesis of 2-substituted THPs has not been previously investigated. Thus, in this study we report (i) our investigation on the stereoselective synthesis of substituted tetrahydropyrans, based on the enantioselective reduction of δ-phenylseleno ketones and oxidation/cyclization of the corresponding alcohols, and (ii) application of this approach to the synthesis of variously substituted isochromans.

RESULTS AND DISCUSSION

Synthesis of 2-Substituted THPs. The required δ-phenylseleno ketones **3a**−**f** (Table 1) have been synthesized for the first time by new procedures. Treatment of 5-(phenylseleno)pentanoic acid **1** with oxalyl chloride afforded the acyl chloride **2** (Scheme 1), that was reacted with the appropriate arylzinc reagent in the presence of Pd(0) catalyst[22] (Negishi coupling). Ketones **3a**−**d** were obtained in 60−80% yields. The reaction of acyl chloride **2** with a suitable (hetero)arylstannane[23] (Stille conditions) gave the ketone **3e** in 65% yield (Scheme 1). Since ketone **3f** was obtained in very low yield by the above-described methodologies, it was prepared, in 69% yield, by reaction of methyl ester of acid **1** with 2-lithiothiazole.[24] Chiral nonracemic δ-phenylseleno alcohols **4** were synthesized from ketones **3** employing the commercially available RuCl[(*S*,*S*)-TsDPEN](mesitylene) as catalyst for the ATH process.[21] We selected the Noyori ATH reaction because of its efficiency and stability and low cost of the catalyst as well as for the simplicity of the experiments.

Received: May 28, 2015
Published: July 28, 2015

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102−8112

Scheme 1. General Strategy for the Stereoselective Synthesis of 2-Substituted Tetrahydropyrans

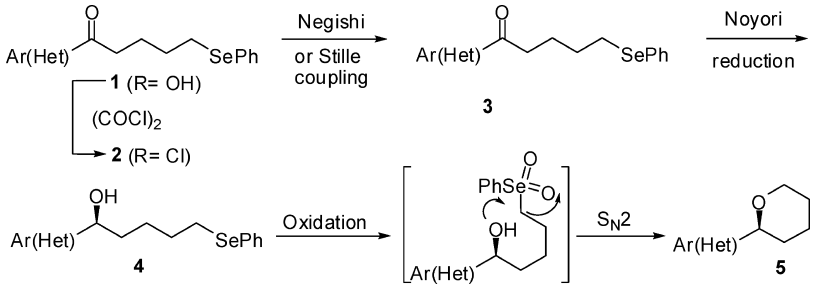
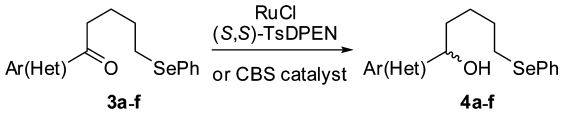
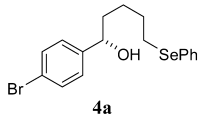
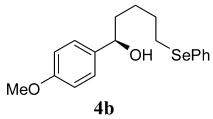
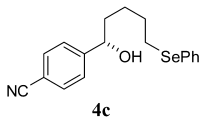
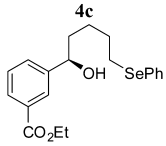
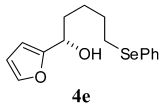
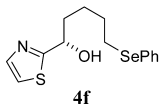


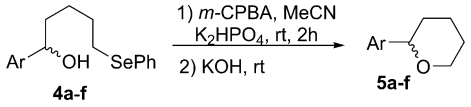
Table 1. Asymmetric Reduction of Ketones 3 into Alcohols 4

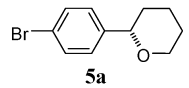
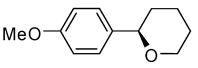
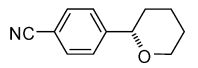
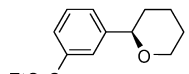
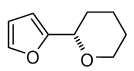
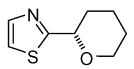


entry	alcohol[a]	time (h)	yield (%)[b]	er[c]
1	 **4a**	2.5	85	---[d]
2	 **4b**	3	89[e]	---[d]
3	 **4c**	3.5	82	89.5:10.5
4	 **4d**	5	92[f]	91.4:8.6
5	 **4e**	4	92	97.2:2.8
6	 **4f**	1.5	89	98.5:1.5

[a]Configuration of the major enantiomers of compounds **4a−f** was tentatively assumed according to the mechanism and their rotation signs.[21,22] [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Not HPLC resolved; see Table 2. [e]RuCl[(R,R)-TsDPEN](mesitylene) was employed. [f](*S*)-Me-CBS was used.

Table 2. Oxidation/Cyclization of Alcohols 4a−f into Tetrahydropyrans 5a−f



entry	tetrahydropyran	time (h)	yield (%)[a]	er[b]
1	 **5a**	8	80	97.6:2.4
2	 **5b**	5	75	88.6:11.4
3	 **5c**	7	72	89.5:10.5
4	 **5d**	2	82	---[c]
5	 **5e**	4	58	---[c]
6	 **5f**	4	67	98.5:1.5

[a]Isolated yield. [b]Determined by chiral HPLC analysis. [c]Not HPLC resolved.

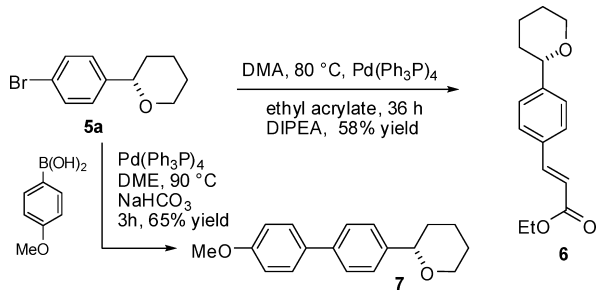
The enantioenriched δ-phenylseleno alcohols **4a−c,e,f** were obtained in excellent yields (Table 1) and in high enantiomeric ratio as shown by chiral HPLC analysis. However, for compounds **4a** and **4b** it was not possible to obtain a good enantiomeric separation with the available chiral stationary phases. Thus, we decided to subject them, as enantioenriched mixtures, to the final cyclization step and separate the corresponding enantioenriched mixtures of tetrahydropyrans **5a** and **5b** (Table 2). Due to the instability of the ester group under the ATH conditions, alcohol **4d** was obtained by the enantioselective reduction of the corresponding ketone with borane in the presence of (*S*)-Me-CBS-oxazaborolidine catalyst[25] (Table 1, entry 4). The configuration of the major enantiomer of compounds **4a−f** was tentatively assigned according to the original mechanisms described by Noyori and Corey.[21,25] Oxidation of δ-phenylseleno alcohols **4a** in THF, with an excess of *m*-chloroperoxybenzoic acid (*m*-CPBA) and dipotassium hydrogen phosphate at rt, gave the phenylselenone intermediate as deduced by thin-layer chromatography (TLC). Unfortunately, the selenone intermediate was unable to turn into the desired THP ring **5a** after addition of powdered potassium hydroxide. Compound **5a** was isolated in 10% yield after 48 h from addition. No significant improvement of the yield was observed with solvent changes (CH_2Cl_2 or EtOAc). The use of magnesium monoperoxyphthalate as oxidant in methanol[19a] gave THP **5a** in moderate yield (35%) alongside the olefin derived from the β-elimination of the selenoxide intermediate.

The yield of **5a** increased up to 66% when we employed *m*-CPBA in methanol. However, when the oxidation/cyclization of **4a** was performed in acetonitrile with an excess of *m*-CPBA and dipotassium hydrogen phosphate, the 2-substituted THP

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102−8112

5a was obtained in excellent yield (80%, Table 2, entry 1) after addition of powdered potassium hydroxide, thus demonstrating that the cyclization step is greatly favorited by polar aprotic solvent. Oxidation/cyclization of alcohols **4b–f** was performed by using the same reaction conditions of **4a**, leading to differently 2-substituted THPs **5b–f** in good to excellent yields (Table 2, entries 2–6) and with good enantiomeric ratios. The enantiomeric composition of THPs **5c** and **5f** reflected that of the corresponding seleno alcohols **4c** and **4f**, thus attesting that no racemization occurred in the oxidation/cyclization step. Although it was not possible to establish the enantiomeric ratios of THPs **5d** and **5e** (Table 2), the composition of the enantioenriched mixtures should be the same as that of the corresponding alcohols **4d** and **4e**, also according to our previous observations.[20] Results reported in Table 2 show that the presence of different functional groups in the aryl moiety does not significantly affect the yields of oxidation and cyclization steps. The high yields, simplicity, and mildness of the experimental conditions of the procedure make our method a general and valuable synthetic process for obtaining chiral nonracemic 2-aryl- and 2-heteroaryl-substituted THPs. Compounds **5b**[11] and **5e**[17] have been previously synthesized by different strategies, and they were obtained in comparable or lower yields as racemic mixture. Interestingly, the presence of bromine substituent in compound **5a** allows an easy conversion into compound **6** (58% yield) by palladium(0)-promoted vinylic substitution reaction[26] or biphenyl **7** (65% yield) by palladium(0)-catalyzed cross-coupling reaction[27] (Scheme 2).

Scheme 2. THP 5a Involved in Palladium(0)-Catalyzed Coupling Reactions



Application to the Stereoselective Synthesis of 2- and 4-Substituted Isochromans. We then turned our attention to the stereoselective synthesis of various substituted isochromans in order to explore the potential of our approach in the construction of six-membered oxygenated heterocycles. Substituted isochromans are present in drugs,[28] natural products,[29] and cosmetics[30] with a wide range of activities such as analgesic, muscle relaxant, antidepressant, antihistaminic, anticoagulant, and antihypertensive (Figure 1). A number of methodologies have been reported for the synthesis of isochromans, such as the oxa-Pictet–Spengler cyclization,[31] radical annulation,[32] intramolecular O–H insertion reaction of diazoesters,[12] palladium-catalyzed allylic oxidation,[8] mercury-activated alkene addition,[33] cyclotrimerization,[34] and the C–H alkylation or arylation at the 1-position of isochromans.[35] Although these are all reliable methods, only a few enantioselective variants of the synthesis of 1- or 4-substituted isochromans have been described in the literature to date.[35d,36]

We envisioned that the phenylselenone-mediated ring-closure reaction, proposed for the construction of THPs, could be used for the building of the six-membered oxygenated heterocycle of isochromans. Thus, the reaction sequence outlined in Scheme 3 started with the preparation of the still-

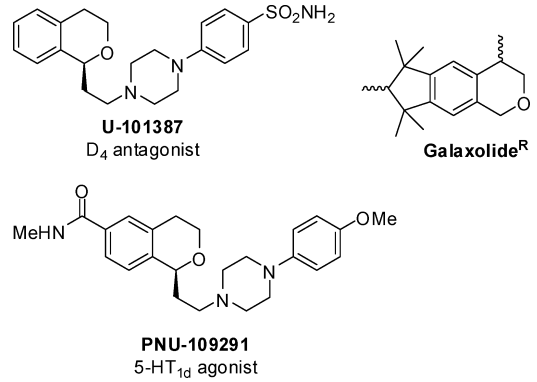
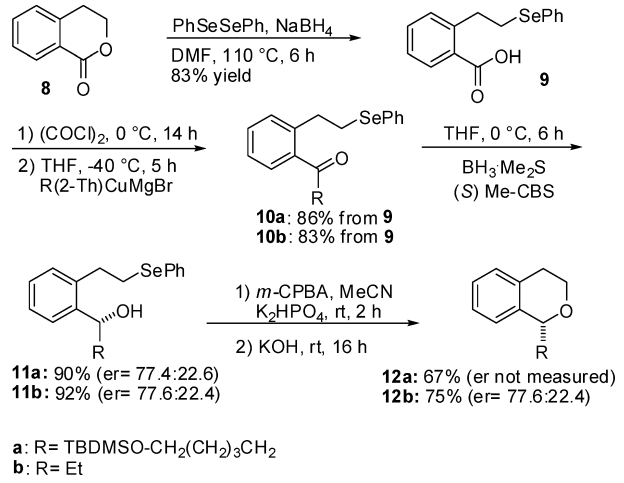


Figure 1. Selected biologically active isochromanes.

Scheme 3. Synthesis of 1-Substituted Isochromans 12a and 12b



unknown phenylseleno acid **9** by cleavage of isochroman-1-one **8** with sodium phenylselenolate. Compound **9** was reacted with oxalyl chloride to give the acyl chloride intermediate, which was coupled with the appropriate mixed magnesium cuprate reagent according to our previous report[20] to furnish the new ketones **10a** and **10b** in excellent yields (Scheme 3). We also explored the direct palladium-catalyzed coupling of acyl chloride of acid **9** with arylzinc reagents, as for the synthesis of **3a–d**, but the expected ketones were obtained in low yields.

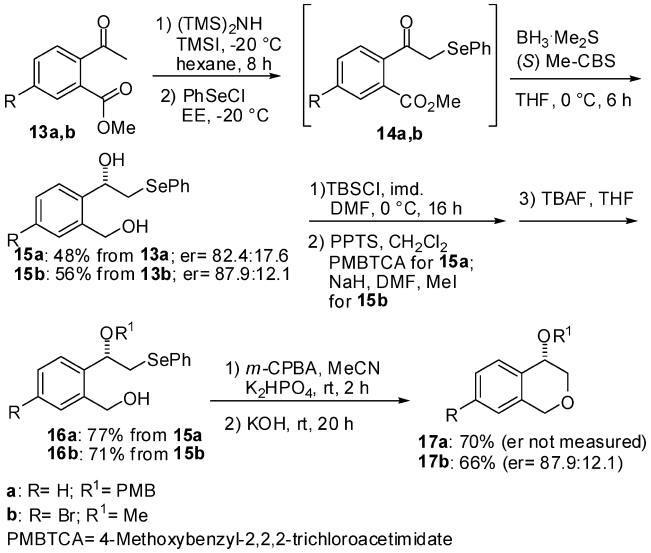
The reduction of ketones **10a** and **10b** under Noyori conditions, as described for **3a-f**, resulted in significant lesser conversion and low level of stereoselectivity. Thus, the enantioenriched phenylseleno alcohols **11a** and **11b** were obtained in excellent yields and good enantiomeric ratio via the chiral oxazaborolidine-catalyzed Corey procedure.[25] The configuration of the major enantiomer of compounds **11a** and **11b** was tentatively assigned according to the original mechanisms described by Corey.[25] The optically active 1-substituted isochromans **12a** and **12b** were finally obtained in good yields by our oxidation/cyclization procedure. Compound **12b** has been previously obtained by a different procedure in comparable yield as a racemic mixture.[35a] On the basis of HPLC analysis on chiral stationary phase, compound **12b**

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102–8112

showed the same enantiomeric composition of its precursor **11b**, thus supporting that no racemization occurred during the cyclization process.[20] Otherwise, for compound **12a** was not possible to obtain a clear separation of the two enantiomers by HPLC.

We next explored the enantioselective synthesis of 4-substituted isochromans **17a** and **17b** from the corresponding phenylseleno alcohols **16a** and **16b** (Scheme 4). Ketoesters **13a**

Scheme 4. Synthesis of 4-Substituted Isochromans 17a and 17b

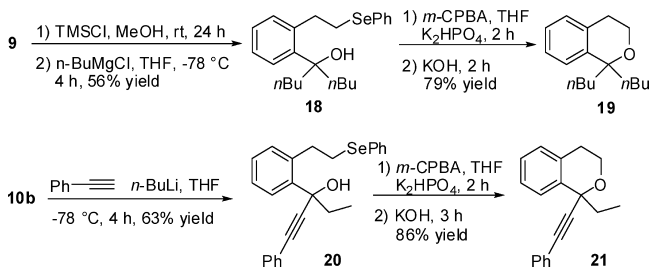


and **13b** were converted, by a two-step procedure, into the intermediate α-phenylseleno ketones **14a** and **14b** which were immediately reduced with borane in the presence of (*S*)-Me-CBS-oxazaborolidine to give the unexpected diols **15a** and **15b** in 48% and 56% total yield, respectively, in good enantiomeric ratio (Scheme 4). It is known that ester group is stable under borane reduction conditions,[37] but in our case, the closer-in-space hydroxy group, formed in the initial reductive step, could affect the reactivity of the carbomethoxy group with borane, most probably through the formation of a lactone intermediate. A high-yielding three-step procedure led to the monoprotected phenylseleno alcohols **16a** and **16b**.

Oxidation of **16a** and **16b** with *m*-CPBA occurred smoothly in MeCN at rt in the presence of dipotassium hydrogen phosphate to give the corresponding phenylselenone intermediates, which cyclized to the enantioenriched 4-substituted isochromans **17a** and **17b** in 70% and 66% yields, respectively, after the addition of potassium hydroxide. HPLC analysis of compound **17b** revealed the same enantiomeric composition of alcohol **16b**, whereas isochroman **17a** did not give appreciable separation with the chiral stationary phases available.

Application to the Synthesis of 1,1-Disubstituted Isochromans. Our selenium-based methodology was extended to the synthesis of 1,1-disubstituted isochromans. Compound **9** was converted into the corresponding methyl ester and then treated with an excess of butylmagnesium bromide to furnish the tertiary alcohol **18** (Scheme 5). The oxidation/cyclization of alcohol **18** gave the 1,1-dialkylisochroman **19** in high yield. Moreover, the lithium phenylacetylide addition to ketone **10b** gave the racemic tertiary alcohol **20** in 63% yield. Oxidation of **20** and cyclization of the phenylselenone intermediate gave the

Scheme 5. Preparation of 1,1-Disubstituted Isochromans 19 and 21



attractive 1-alkyl-1-alkynyl-substituted isochroman **21** in 86% yield, showing clearly that tertiary benzylic and propargylic alcohols are not affected by the reaction conditions employed for pyran ring closure.

CONCLUSIONS

In conclusion, we have applied selenium-based chemistry, via a new 6-*exo*-*tet* ring-closure reaction, to the stereoselective synthesis of substituted THPs and isochromans. Our developed methodology provides a mild, stereoselective, and general approach to the preparation of 2-substituted THPs and 1- or 4-substituted isochromans, from phenylseleno alcohols, that favorably compares with other previously reported methods. Within this work, a new synthetic strategy for the preparation of δ-phenylseleno ketones was developed. Further applications of this new 6-*exo*-*tet* ring-closure reaction, directed to the synthesis of complex tetrahydropyrans as well as natural products, are currently in progress.

EXPERIMENTAL SECTION

General Information. Proton nuclear magnetic resonance (^{1}H NMR) spectra and (^{13}C NMR) spectra were recorded at 200 and 50.3 MHz. Unless otherwise specified, $CDCl_3$ was used as the solvent, and chemical shifts (δ) are reported in parts per million (ppm). The proton signal of residual, nondeuterated solvent (δ 7.27 for $CHCl_3$) was used as an internal reference for ^{1}H spectra. ^{1}H NMR spectral data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broadened), coupling constants, number of protons. Coupling constants (J) are reported in hertz (Hz) to the nearest 0.1 Hz. For ^{13}C spectra, chemical shifts are reported relative to the δ 77.00 resonance of $CDCl_3$ and chemical shifts are expressed in ppm. Infrared (IR) spectra were recorded on a diffuse reflectance sampling cell. Only significant absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). GC–MS analysis were obtained with a gas chromatograph (HP-5MS capillary column 29.0 m, i.d. 0.25, film 0.25 μm) equipped with a mass-selective detector at an ionizing voltage of 70 eV; for the ions containing selenium only the peaks arising from the selenium-80 isotope are given. HPLC enantioseparation were performed on HPLC system equipped with a UV/vis detector with chiral columns and solvents specified. Melting points were determined on a Kofler hotstage apparatus and are uncorrected. Optical rotations were measured in a 50 mm cell using the D line of sodium at the specified temperature. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are quoted in g 100 mL^{-1}. Combustion analyses were carried out on an elemental analyzer. Reactions were monitored by thin-layer chromatography (TLC) carried out on aluminum foil sheets precoated with silica (Merck silica gel 60 F_{254}), which were visualized by the quenching of UV fluorescence (λ_{max}254 nm) and/or by staining with 0.5% w/v potassium permanganate aqueous solution followed by heating. Column chromatography was performed using Kieselgel 60 (70–230 mesh) silica gel.

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102–8112

All reactions of air- and water-sensitive organometallics were carried out in flame-dried glassware under argon using standard techniques. The organozinc and Grignard reagents for the synthesis of compounds **3a–d**, **10b**, and **18** were purchased from Aldrich and used directly from the bottle. The Grignard reagents for the preparation of ketone **10a** were synthesized in large preparation by standard method from commercially available 5-bromo-1-pentanol[38] and analyzed by the method of Knochel[39] prior to use. A freshly opened bottle of cuprous iodide was found to be satisfactory. Commercial-grade tetrahydrofuran, diethyl ether, dichloromethane, acetonitrile, and methanol were dried by using standard procedures. Unless indicated, all chemicals were used without further purification. 3-Chloroperbenzoic acid ≤77% from Aldrich was employed.

The starting phenylseleno acid **1** and the corresponding acyl chloride **2** were prepared as described in the literature.[20] Compounds **8**[40] and **13a**[41] have been previously described in the literature.

General Procedure for the Synthesis of Ketones 3a–d. Acid **1** (3.00 mmol) was reacted with oxalyl chloride (17.71 mmol) at room temperature for 14 h. The solution was evaporated under reduced pressure. The residue was dissolved in dry dichloromethane (5 mL), the solvent was removed, and the acyl chloride **2** obtained was immediately taken in 30 mL of dry THF. The reaction mixture was cooled at 0–5 °C and protected from atmospheric moisture, and powdered tetrakis(triphenylphosphine)palladium(0) (0.15 mmol) was added. Then a 0.5 M solution of organozinc reagent (7.2 mL) was added slowly along the side of the reaction flask by using a syringe pump over 1.5 h with vigorous stirring. The dark solution was allowed to reach room temperature gradually and then stirred at this temperature for 4 h. Saturated aqueous sodium hydrogen carbonate solution (1.5 mL) was added, and the slurry was filtered through a Celite pad, dried over sodium sulfate, filtrated, and evaporated. The residue was purified by column chromatography on silica using a diethyl ether–hexane mixture as eluent afford ketone **3**.

*1-(4-Bromophenyl)-5-(phenylselanyl)pentan-1-one (**3a**).* Following the general procedure, **1** (0.77g, 3.00 mmol) was converted, with 4-bromophenylzinc iodide, in dry THF to **3a** (0.72 g, 61% yield): light yellow solid; mp 85–88 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.81 (d, J = 8.6 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.54–7.44 (m, 2H), 7.35–7.15 (m, 3H), 3.08–2.82 (m, 4H), 1.98–1.70 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.7, 135.6, 132.6 (2C), 131.9 (2C), 130.2, 129.5 (2C), 129.0 (2C), 128.1, 126.8, 37.8, 29.7, 27.5, 24.2; FTIR 2942, 1733, 1682, 1478, 1072, 821, 732 cm^{-1}; EIMS (70 eV) m/z M$^+$ 396 (12), 239 (82), 183 (100), 157 (39), 91 (10), 77 (15). Anal. Calcd for $C_{17}H_{17}BrOSe$: C, 51.54; H, 4.33. Found: C, 51.39; H, 4.57.

*1-(4-Methoxyphenyl)-5-(phenylselanyl)pentan-1-one (**3b**).* Following the general procedure, **1** (0.52 g, 2.00 mmol) was converted, with 4-methoxyphenylzinc iodide, in dry diethyl ether to **3b** (0.50 g, 72% yield): white solid; mp 87–89 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 2H), 7.56–7.48 (m, 2H), 7.32–7.23 (m, 3H), 6.96 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.05–2.86 (m, 4H), 1.98–1.72 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.5, 163.4, 132.5 (2C), 130.3 (2C), 129.9, 129.0, 128.4, 126.7 (2C), 113.7 (2C), 55.4, 37.5, 29.8, 27.5, 24.6; FTIR 2937, 1676, 1599, 1255, 1169, 829, 733 cm^{-1}; EIMS (70 eV) m/z M$^+$ 348 (2), 191 (50), 135 (100), 92 (15), 77(29). Anal. Calcd for $C_{18}H_{20}O_2Se$: C, 62.25; H, 5.80. Found: C, 62.03; H, 6.02.

*4-[5-(Phenylselanyl)pentanoyl]benzonitrile (**3c**).* Following the general procedure, **1** (1.03 g, 4.00 mmol) was converted, with 4-cyanophenylzinc bromide, in dry diethyl ether to **3c** (1.03 g, 73% yield): white solid; mp 80–82 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.57–7.45 (m, 2H), 7.43–7.20 (m, 3H), 3.05–2.92 [t, partly overlapped t (J = 6.5 Hz, 2H), t (J = 6.4 Hz, 2H)], 2.01–1.68 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.3, 139.8, 132.6 (2C), 132.5 (2C), 129.6, 129.0 (2C), 128.4 (2C), 126.8, 117.9, 116.3, 38.2, 29.6, 27.4, 23.9; FTIR 3068, 2936, 2237, 1683, 1477, 1273, 834, 731 cm^{-1}; EIMS (70 eV) m/z M$^+$ 343 (9), 186 (68), 157 (15), 130 (100), 102 (42), 77(14). Anal. Calcd for $C_{18}H_{17}NOSe$: C, 63.16; H, 5.01; N, 4.09. Found: C, 62.97; H, 5.25; N, 4.23.

*Ethyl 3-[5-(Phenylselanyl)pentanoyl]benzoate (**3d**).* Following the general procedure, **1** (1.29 g, 5.00 mmol) was converted, with 3-(ethoxycarbonyl)phenylzinc iodide, in dry THF to **3d** (1.07 g, 55% yield): amorphous solid; mp 38–40 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.58 (dd, J = 1.4, 1.7 Hz, 1H), 8.24 (dt, J = 1.4, 7.7 Hz, 1H), 8.03 (ddd, J = 1.4, 1.7, 7.8 Hz, 1H), 7.61–7.43 (m, 3H), 7.32–7.19 (m, 3H), 4.42 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 6.8 Hz, 2H), 2.96 (t, J = 7.1 Hz, 2H), 1.99–1.70 (m, 4H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.0, 165.8, 137.0, 133.7, 132.5 (2C), 132.0, 131.0, 130.2, 129.1 (2C), 129.0, 128.8, 126.7, 61.4, 38.0, 29.6, 27.5, 24.1, 14.3; FTIR 2934, 1721, 1690, 1205, 1023, 748 cm^{-1}; EIMS (70 eV) m/z M$^+$ 390 (6), 233 (83), 177 (100), 149 (30), 120 (15), 85 (26), 71 (31), 57 (52). Anal. Calcd for $C_{20}H_{22}O_3Se$: C, 61.70; H, 5.70. Found: C, 61.47; H, 5.94.

Preparation of Ketone 3e. Acyl chloride **2** (1.00 mmol) prepared as described above from 0.258 g of acid **1**, and oxalyl chloride (0.5 mL, 5.90 mmol) was dissolved in dry THF (2 mL) at room temperature. Tributyl(2-furyl)stannane (0.346 mL, 1.10 mmol) and powdered tetrakis(triphenylphosphine)palladium(0) (0.02 g, 0.03 mmol) were then added, and the reaction mixture was stirred under argon atmosphere for 20 h.[42] The orange solution was then concentrated, and the residue was subjected to purification by column chromatography on SiO_2 (20% diethyl ether in hexane) affording ketone **3e**.

*1-(2-Furyl)-5-(phenylselanyl)pentan-1-one (**3e**):* 0.20 g, 65% yield; light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58 (dd, J = 0.8, 1.8 Hz, 1H), 7.53–7.46 (m, 2H), 7.30–7.22 (m, 3H), 7.17 (dd, J = 0.8, 3.6 Hz, 1H), 6.54 (dd, J = 1.8, 3.6 Hz, 1H), 2.95 (t, J = 7.1 Hz, 2H), 2.84 (t, J = 7.0 Hz, 2H), 1.95–1.70 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 189.0, 152.6, 132.4 (2C), 130.2, 128.9 (3C), 126.6, 116.8, 112.1, 37.6, 29.6, 27.3 24.2; FTIR 2930, 1676, 1568, 1468, 1022, 762, 736 cm^{-1}; EIMS (70 eV) m/z M$^+$ 308 (30), 157 (29), 151 (96), 123 (13), 95 (100), 77 (25). Anal. Calcd for $C_{15}H_{16}O_2Se$: C, 58.64; H, 5.25. Found: C, 58.51; H, 5.47.

Synthesis of Ketone 3f. Dry methanol (1.0 mL) was added to a mixture of acid chloride **2** (1.36 mmol) in dry THF (10 mL) and triethylamine (0.21 mL, 1.49 mmol) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature. After 3 h, the reaction was quenched with 10 mL of 2 M hydrochloric acid and 50 mL of dichloromethane. The organic phase was separated and washed with 10 mL of saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over sodium sulfate, filtrated, and evaporated to give the crude methyl ester derivative which was dissolved in 3 mL of diethyl ether and then added dropwise at −78 °C to a solution of 2-lithiothiazole (1.50 mmol) in diethyl ether (4.00 mL) prepared as described by Dondoni.[24] After 10 min at −78 °C, the resulting mixture was allowed to warm to 25 °C (1 h) and quenched by addition of 10 mL of saturated aqueous sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over sodium sulfate, filtrated, and evaporated. The resulting oil was purified by chromatography on SiO_2 (30% diethyl ether/petroleum ether) to afford ketone **3f**.

*5-(Phenylselanyl)-1-(1,3-thiazol-2-yl)pentan-1-one (**3f**):* 0.72 g, 69% yield; colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, J = 3.0 Hz, 1H), 7.67 (d, J = 3.0 Hz, 1H), 7.54–7.43 (m, 2H), 7.35–7.18 (m, 3H), 3.18 (t, J = 6.8 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.01–1.70 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.5, 167.0, 144.6, 132.6 (2C), 130.2, 129.0 (2C), 126.7, 126.2, 37.8, 28.8, 27.3 24.0; FTIR 2937, 1684, 1478, 1391, 734 cm^{-1}; EIMS (70 eV) m/z M$^+$ 325 (11), 168 (44), 157 (18), 140 (100), 128 (21), 112 (57), 86 (40), 77 (14). Anal. Calcd for $C_{14}H_{15}NOSSe$: C, 51.85; H, 4.66; N, 4.32. Found: C, 51.63; H, 4.90; N, 4.11.

Typical Procedure for the Asymmetric Reduction of ketones 3a–c,e,f. Powdered RuCl[(*R*,*R*)-TsDPEN](mesitylene) (0.05 mmol) was added to a solution of ketone **3** (1.00 mmol) in 15 mL of degassed 2-propanol at 36 °C followed by 0.06 mmol of potassium hydroxide. The resulting dark brown mixture was stirred vigorously at 36 °C. After the appropriate reaction time (see Table 1), the reaction mixture was quenched with 10 mL of saturated aqueous ammonium chloride solution and then extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with saturated sodium

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102–8112

bicarbonate solution and saturated NaCl solution, dried over sodium sulfate, filtrated, and evaporated. The residue was purified by chromatography on SiO_2 using an ethyl acetate-petroleum ether mixture (2:8) as eluent.

(1S)-1-(4-Bromophenyl)-5-(phenylselanyl)pentan-1-ol ***(4a)***. Following the general procedure ketone **3a** (0.97 g, 2.45 mmol) was reduced to **4a** (0.83 g, 85% yield): amorphous solid; mp 35−37 °C; $[\alpha]^{23}_{D}$ −9.08 (*c* 1.02, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52−7.42 (m, 4H), 7.31−7.14 (m, 5H), 4.59 (dd, *J* = 5.7, 7.1 Hz, 1H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.17 (br s, 1H), 1.89−1.28 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.6, 132.4 (2C), 131.4 (2C), 130.3, 128.9 (2C), 127.5 (2C), 126.6, 121.1, 73.6, 38.3, 29.9, 27.6, 25.7; FTIR 3396, 2932, 1578, 1478, 1009, 826, 736 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 398 (75), 223 (49), 211 (51), 198 (24), 185 (71), 169 (47), 158 (76), 144 (41), 91 (38), 77 (100), 51 (26). Anal. Calcd for $C_{17}H_{19}BrOSe$: C, 51.28; H, 4.81. Found: C, 51.01; H, 5.05.

(1R)-1-(4-Methoxyphenyl)-5-(phenylselanyl)pentan-1-ol ***(4b)***. Following the general procedure, ketone **3b** (0.35 g, 1.00 mmol) was reduced to **4b** (0.31 g, 89% yield): colorless oil; $[\alpha]^{21}_{D}$ +26.04 (*c* 1.64, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52−7.40 (m, 2H), 7.31−7.13 (m, 5H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.58 (t, *J* = 6.3 Hz, 1H), 3.80 (s, 3H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.01 (br s, 1H), 1.88−1.29 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.9, 136.7, 132.3 (2C), 130.4, 128.9 (2C), 127.0 (2C), 126.6, 113.7 (2C), 73.9, 55.2, 38.2, 30.0, 27.6, 26.0; FTIR 3420, 2934, 1612, 1513, 1247, 884, 734 cm^{-1}; EIMS (70 eV) *m*/*z* [M − 18]$^+$ 332 (25), 207 (89), 159 (52), 147 (100), 121 (88), 91 (79), 78 (87). Anal. Calcd for $C_{18}H_{22}O_2Se$: C, 61.89; H, 6.35. Found: C, 61.70; H, 6.65.

4-[(1S)-1-Hydroxy-5-(phenylselanyl)pentyl]benzonitrile ***(4c)***. Following the general procedure, ketone **3c** (0.78 g, 2.30 mmol) was reduced to **4c** (0.64 g, 82% yield): colorless oil; $[\alpha]^{20}_{D}$ −9.52 (*c* 1.49, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2 Hz, 2H), 7.54−7.38 (m, 4H), 7.33−7.20 (m, 3H), 4.72 (t, *J* = 5.5 Hz, 1H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.37 (br s, 1 H), 1.89−1.35 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.1, 132.4 (2C), 132.2 (2C), 130.3, 129.0 (2C), 126.7, 126.5 (2C), 118.8, 111.0, 73.4, 38.5, 29.9, 27.5, 25.6; FTIR 3423, 2934, 2228, 1608, 1478, 1073, 839, 739 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 345 (54), 213 (18), 188 (33), 170 (36), 158 (100), 132 (33), 104 (51), 91 (33), 77(58). Anal. Calcd for $C_{18}H_{19}NOSe$: C, 62.79; H, 5.56; N, 4.07. Found: C, 62.48; H, 5.90; N, 3.88. HPLC analysis on Phenomenex Lux Cellulose-1 column (100 × 4.60 mm i.d.), *n*-hexane/2-propanol = 94:6, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 13.2 min, t_R (*S*-enantiomer, major) = 15.8 min, er = 10.5:89.5.

(1S)-1-(2-Furyl)-5-(phenylselanyl)pentan-1-ol ***(4e)***. Following the general procedure, ketone **3e** (0.57 g, 1.75 mmol) was reduced to **4e** (0.53 g, 92% yield): light yellow oil; $[\alpha]^{24}_{D}$ −5.07 (*c* 2.43, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.57−7.42 (m, 2H), 7.38 (dd, *J* = 0.8, 1.8 Hz, 1H), 7.31−7.21 (m, 3H), 6.34 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.22 (dd, *J* = 0.8, 3.2 Hz, 1H), 4.64 (t, *J* = 6.7 Hz, 1H), 2.91 (t, *J* = 7.1 Hz, 2H), 2.12 (br s, 1 H), 1.95−1.35 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.5, 132.4 (2C), 130.3, 128.9 (2C), 125.6 (2C), 110.0, 105.8, 67.4, 34.8, 29.8, 27.5, 25.6; FTIR 3365, 2933, 1578, 1478, 1007, 736 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 310 (68), 241 (17), 157 (59), 135 (40), 123 (52), 97 (100), 91 (36), 77 (46), 55 (20). Anal. Calcd for $C_{15}H_{18}O_2Se$: C, 58.25; H, 5.87. Found: C, 57.97; H, 6.11. HPLC analysis on Phenomenex Lux Cellulose-1 column (100 × 4.60 mm i.d.), *n*-hexane/2-propanol = 96:4, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 10.5 min, t_R (*S*-enantiomer, major) = 11.4 min, er = 2.8:97.2.

(1S)-5-(Phenylselanyl)-1-(1,3-thiazol-2-yl)pentan-1-ol ***(4f)***. Following the general procedure, ketone **3f** (0.30 g, 0.94 mmol) was reduced to **4f** (0.27 g, 89% yield): yellow oil; $[\alpha]^{27}_{D}$ −10.70 (*c* 1.94, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (d, *J* = 3.1 Hz, 1H), 7.54−7.42 (m, 2H), 7.32−7.20 (m, 4H), 4.99 (dd, *J* = 4.8, 7.4 Hz, 1H), 3.33 (br s, 1 H), 2.92 (t, *J* = 7.1 Hz, 2H), 2.10−1.50 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.8, 141.9, 132.4 (2C), 130.3, 128.9 (2C), 126.6, 118.8, 71.3, 37.5, 29.8, 27.5 25.3; FTIR 3230, 2935, 1578, 1477, 1072, 734 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 327 (14), 281 (10), 207 (36), 168 (42), 140 (100), 128 (51), 112 (75), 86 (92), 77 (30), 55 (26). Anal. Calcd for $C_{14}H_{17}NOSSe$: C, 51.53; H, 5.25; N, 4.29. Found: C, 51.20; H, 5.61; N, 4.02. HPLC analysis on Phenomenex Lux Cellulose-1 column (100 × 4.60 mm i.d.), *n*-hexane/2-propanol = 96:4, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 15.7 min, t_R (*S*-enantiomer, major) = 18.9 min, er = 1.5:98.5

Asymmetric Reduction of Ketone 3d. To a solution of (*S*)-Me-CBS 1.0 M in toluene (0.33 mL, 0.33 mmol) in dry THF (20 mL) at 0 °C was added a 2.0 M borane−dimethyl sulfide complex (0.82 mL, 1.64 mmol).[25] A solution of ketone **3d** (1.64 mmol) in dry THF (13 mL) was added slowly by using a syringe pump over 2 h with vigorous stirring, and the solution was allowed to warm to room temperature. The mixture was stirred at room temperature until the ketone disappeared on TLC monitoring (3 h). The mixture was quenched with methanol and saturated ammonium chloride solution (5 mL). The mixture was extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with brine (5 mL) and dried ($MgSO_4$), filtrated, and concentrated *in vacuo*. The crude product was purified on a silica gel column with a mixture of petroleum ether and ethyl acetate 80:20 as eluent to give the corresponding chiral secondary alcohol **4d**.

Ethyl 3-[(1R)-1-hydroxy-5-(phenylselanyl)pentyl]benzoate ***(4d)***: 0.58 g, 90% yield; colorless oil; $[\alpha]^{25}_{D}$ +10.37 (*c* 1.23, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.04−7.88 (m, 2H), 7.58−7.32 (m, 4H), 7.31−7.17 (m, 3H), 4.70 (dd, *J* = 5.5, 6.9 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.88 (t, *J* = 7.2 Hz, 2H), 2.30 (br s, 1 H), 1.84−1.32 [m, partly overlapped t (*J* = 7.1 Hz, 3H), m (6H)], 1.39; ^{13}C NMR (50 MHz, $CDCl_3$) δ 166.6, 145.0, 132.4 (2C), 130.5, 130.3, 129.6, 128.9 (2C), 128.6, 128.4, 126.9, 126.6, 73.8, 61.0, 38.4, 29.9, 27.5, 25.8, 14.3; FTIR 3504, 2933, 1718, 1478, 1283, 1192, 740 cm^{-1}; EIMS (70 eV) *m*/*z* [M − 158]$^+$ 234 (3), 192 (36), 179 (100), 151 (20), 105 (23), 79 (14). Anal. Calcd for $C_{20}H_{24}O_3Se$: C, 61.38; H, 6.18. Found: C, 61.10; H, 6.47. HPLC analysis on Phenomenex Lux Cellulose-1 column (100 × 4.60 mm i.d.), *n*-hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*S*-enantiomer, minor) = 17.1 min, t_R (*R*-enantiomer, major) = 21.6 min, er = 8.6:91.4.

General Procedure for the Oxidation−Cyclization of Phenylseleno Alcohols 3a−f. To a solution of phenylseleno alcohol **4** (0.50 mmol) in acetonitrile (15 mL) at room temperature were added powdered potassium hydrogen phosphate (2.00 mmol) and *m*-CPBA (1.50 mmol). The reaction mixture was stirred until TLC analysis showed that the starting selenide was completely converted into the corresponding selenone (2 h). Powdered potassium hydroxide (3.75 mmol) was then added at room temperature. The consumption of the selenone was monitored by TLC. After the appropriate time reaction (see Table 2), the mixture was then poured into water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated sodium carbonate solution and saturated NaCl solution, dried over sodium sulfate, filtrated, and evaporated. The reaction product was then purified by column chromatography on silica gel (diethyl ether−petroleum ether mixture) to afford the 2-substituted THP **5**.

(2S)-2-(4-Bromophenyl)tetrahydro-2H-pyran ***(5a)***. Following the general procedure alcohol **4a** (0.20 g, 0.50 mmol) was converted to **5a** (97 mg, 80% yield): light yellow oil; $[\alpha]^{26}_{D}$ −33.90 (*c* 1.89, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 4.30 (dd, *J* = 1.8, 10.6 Hz, 1H), 4.21−4.08 (m, 1H), 3.70−3.52 (m, 1H), 2.02−1.43 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.4, 131.3 (2C), 127.6 (2C), 121.0, 79.3, 69.0, 34.1, 25.8, 23.9; FTIR 2936, 2847, 1489, 1089, 909, 817 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 240 (41), 185 (73), 161 (100), 156 (32), 105 (43), 77 (35), 55 (25). Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.50; H, 5.77. HPLC analysis on Phenomenex Lux Cellulose-2 column (250 × 4.60 mm i.d.), *n*-hexane/2-propanol = 99.6:0.4, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 20.7 min, t_R (*S*-enantiomer, major) = 22.2 min, er = 2.4:97.6.

(2R)-2-(4-Methoxyphenyl)tetrahydro-2H-pyran ***(5b)***.[43] Following the general procedure alcohol **4b** (0.31 g, 0.90 mmol) was converted to **5b** (0.13 g, 75% yield): $[\alpha]^{22}_{D}$ +33.51 (*c* 1.15, $CHCl_3$); HPLC analysis on Chiracel OD-H column (250 × 4.60 mm i.d.), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102−8112

enantiomer, major) = 8.1 min, t_R (*S*-enantiomer, minor) = 15.6 min, er = 88.6:11.4.

*4-[(2S)-Tetrahydro-2H-pyran-2-yl]benzonitrile (**5c**).* Following the general procedure, alcohol **4c** (0.28 g, 0.80 mmol) was converted to **5c** (0.10 g, 67%): colorless oil; $[\alpha]^{19}_D$ −51.47 (*c* 1.65, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 4.39 (dd, *J* = 2.3, 11.0 Hz, 1H), 4.22−4.10 (m, 1H), 3.70−3.53 (m, 1H), 2.10−1.31 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.6, 132.0 (2C), 126.3 (2C), 118.9, 110.7, 78.9, 68.8, 34.0, 25.5, 23.7; FTIR 2941, 2851, 2228, 1610, 1265, 1089, 827 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 187 (52), 158 (21), 130 (100), 116 (43), 102 (49), 84 (37), 55 (57). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.66; H, 7.37; N, 7.20. HPLC analysis on Phenomenex Lux Cellulose-2 column (250 × 4.60 mm i.d.), *n*-hexane/2-propanol = 99:1, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*S*-enantiomer, major) = 16.3 min, t_R (*R*-enantiomer, minor) = 17.9 min, er = 89.5:10.5.

*Ethyl 3-[(2R)-Tetrahydro-2H-pyran-2-yl]benzoate (**5d**).* Following the general procedure, alcohol **4d** (0.21 g, 0.54 mmol) was converted to **5d** (0.10 g, 82% yield): colorless oil; $[\alpha]^{23}_D$ +25.69 (*c* 0.75, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (t, *J* = 1.6 Hz, 1H), 7.95 (dt, *J* = 1.6, 7.7 Hz), 7.56 (dt, *J* = 1.6, 7.7 Hz), 7.41 (t, *J* = 7.7 Hz), 4.45−4.34 [m, partly overlapped q (*J* = 7.1 Hz, 2H), m (1H)], 4.22−4.10 (m, 1H), 3.71−3.55 (m, 1H), 2.01−1.51 (m, 6H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.6, 143.7, 130.4, 130.3, 128.4, 128.3, 126.9, 79.5, 68.9, 60.9, 34.0, 25.7, 23.9, 14.3; FTIR 2937, 2845, 1718, 1280, 1085, 753 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 234 (37), 205 (33), 189 (47), 177 (37), 161 (100), 149 (51), 133 (66), 105 (59), 77 (30). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.50; H, 7.98.

*(2S)-2-(2-Furyl)tetrahydro-2H-pyran (**5e**).*[17] Following the general procedure, alcohol **4e** (0.47 g, 1.50 mmol) was converted to **5e** (0.13 g, 58% yield): colorless oil; $[\alpha]^{27}_D$ −2.42 (*c* 1.72, $CHCl_3$); FTIR 2942, 2850, 1724, 1506, 1085, 902, 734 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 152 (57), 189 (47), 135 (24), 108 (15), 95 (100), 81 (24), 68 (17), 55 (20).

*2-[(2S)-Tetrahydro-2H-pyran-2-yl]-1,3-thiazole (**5f**).* Following the general procedure, alcohol **4f** (0.25 g, 0.77 mmol) was converted to **5f** (85 mg, 67% yield): colorless oil; $[\alpha]^{19}_D$ −39.66 (*c* 1.54, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.71 (d, *J* = 3.3 Hz, 1H), 7.27 (d, *J* = 3.3 Hz, 1H), 4.77−4.70 (m, 1H), 4.22−4.09 (m, 1H), 3.76−3.55 (m, 1H), 2.30−2.10 (m, 1H), 2.07−1.90 (m, 1H), 1.80−1.50 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7, 142.0, 118.5, 77.6, 68.8, 32.5, 25.5, 22.9; FTIR 2940, 2850, 1506, 1090, 1048, 902, 725 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 169 (1), 141 (34), 112 (100), 86 (30), 58 (29). Anal. Calcd for $C_8H_{11}NOS$: C, 56.77; H, 6.55; N, 8.28. Found: C, 56.49; H, 6.85; N, 8.02. HPLC analysis on Phenomenex Lux Cellulose-1 column (100 × 4.60 mm i.d.), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 4.5 min, t_R (*S*-enantiomer, major) = 6.7 min, er = 1.5:98.5.

Synthesis of Compound 6. Powdered tetrakis(triphenylphosphine)palladium(0) (15 mg, 0.005 mmol), tetrabutylammonium chloride (7 mg, 0.025 mmol), compound **5a** (0.06 g, 0.25 mmol), *N*,*N*-diisopropylethylamine (0.09 mL, 0.50 mmol), and ethyl acrylate (0.06 mL, 0.50 mmol) were dissolved in *N*,*N*-dimethylacetamide (2 mL), and the resulting mixture was heated to 80 °C for 36 h.[44] The mixture was then cooled to rt, diluted with diethyl ether (30 mL), washed with brine, dried over sodium sulfate, filtrated, and concentrated to afford the crude product, which was purified by column chromatography on SiO_2 (10% diethyl ether in hexane).

*Ethyl (2E)-3-{4-[(2S)-Tetrahydro-2H-pyran-2-yl]phenyl}acrylate (**6**):* 38 mg, 58% yield; light yellow oil; $[\alpha]^{26}_D$ −60.32 (*c* 1.25, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, *J* = 16.0 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 4.38−4.04 [m, partly overlapped q (*J* = 7.1 Hz, 2H), m (1H), m (1H)], 4.25, 3.69−3.54 (m, 1H), 2.00−1.49 (m, 6H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.0, 145.7, 144.3, 133.4, 128.0 (2C), 126.2 (2C), 117.8, 79.6, 68.9, 60.4, 33.9, 25.7, 23.9, 14.3; FTIR 2937, 2842, 1714, 1636, 1169, 1041, 821 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 260 (53), 214 (51), 203 (40), 187 (100), 175 (57), 159 (51), 131 (67), 103 (47), 77 (24). Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.51; H, 7.99.

Synthesis of Compound 7. A 25 mL round-bottom flask was charged with compound **5a** (0.12 g, 0.50 mmol), powdered tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol), and 4 mL of dimetoxyethane. The red mixture was stirred for 15 min at room temperature under argon atmosphere, and then 4-methoxyphenylboronic acid (91 mg, 0.60 mmol) and 1 mL of 2 M sodium bicarbonate solution were added.[27] The mixture was stirred at 90 °C for 3 h and then allowed to slowly warm to room temperature. The slurry was filtered through a Celite pad, dried over sodium sulfate, filtrated, and evaporated. Purification of the crude product by chromatography on SiO_2 (10% diethyl ether in hexane) afforded 89 mg of compound **7**, 65% yield.

*(2S)-2-(4′-Methoxybiphenyl-4-yl)tetrahydro-2H-pyran (**7**):* white solid; mp 100−102 °C; $[\alpha]^{27}_D$ −34.86 (*c* 0.57, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49−7.56 (m, 4H), 7.40 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.42−4.33 (m, 1H), 4.23−4.11 (m, 1H), 3.86 (s, 3H), 3.73−3.57 (m, 1H), 2.05−1.52 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.0, 141.7, 139.7, 133.5, 128.0 (2C), 126.5 (2C), 126.2 (2C), 114.1(2C), 79.8, 69.0, 55.3, 33.9, 25.9, 24.0; FTIR 2934, 2837, 1607, 1499, 1250, 1039, 821 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 268 (100), 211 (65), 197 (39), 184 (31), 152 (20), 141 (20), 115 (15), 55 (9). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.31; H, 7.87.

Preparation of Acid 9. Commercially available isochroman was oxidized to isochroman-1-one with a mixture of potassium permanganate and copper sulfate pentahydrate as reported in the literature.[40] Isochroman-1-one (1.18 g, 8 mmol) was then cleaved with sodium phenyl selenolate in dry dimethylformamide[20] at reflux to give 1.75 g (83% yield) of acid **9**.

*2-[2-(Phenylselanyl)ethyl]benzoic acid (**9**):* light yellow solid; mp 100−102 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.90 (br s, 1H), 8.10 (dd, J = 1.5, 7.8 Hz, 1H), 7.68−7.52 (m, 3H), 7.50−7.10 (m, 5H), 3.55−3.38 (m, 2H), 3.24−3.17 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 143.8, 133.2, 132.4 (2C), 131.9, 131.7, 130.2, 129.0 (2C), 127.8, 126.7 (2C), 35.7, 28.2; FTIR 3001, 2812, 1699, 1273, 930, 706 cm^{-1}; EIMS (70 eV) *m*/*z* M$^+$ 308 (15), 157 (11), 149 (100), 135 (82), 103(33), 91 (25), 77 (39). Anal. Calcd for $C_{15}H_{14}O_2Se$: C, 59.02; H, 4.62. Found: C, 58.70; H, 4.97.

Synthesis of Ketones 10a and 10b. The ketones **10a** and **10b** were synthesized by acylation of the appropriate mixed magnesium cuprate reagents obtained from 1-bromo-5-[(*tert*-butyldimethylsilyl)oxy]pentane[38] and ethylmagnesium bromide, respectively, with the corresponding acyl chloride of acid **9** as reported in the literature.[20]

*6-[[tert-Butyl(dimethyl)silyl]oxy]-1-[2-[2-(phenylselanyl)ethyl]phenyl]hexan-1-one (**10a**):* 0.42 g, 86% yield; light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66−7.15 (m, 9H), 3.63 (t, *J* = 6.2 Hz, 2H), 3.23−3.12 (m, 4H), 2.89 (t, *J* = 7.2 Hz, 2H), 1.80−1.22 (m, 6H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.5, 140.4, 138.2, 132.3 (2C), 131.5, 131.2, 130.4, 129.0 (2C), 128.5, 126.6, 126.4, 63.0, 41.7, 35.0, 32.7, 28.6, 26.0 (3C), 25.5, 24.1, 18.3, −5.3 (2C); FTIR 2928, 1684, 1478, 1256, 1094, 835, 739 cm^{-1}; EIMS (70 eV) *m*/*z* [M-57]$^+$ 433 (63), 201 (25), 183 (31), 155 (19), 141 (53), 129 (24), 103 (22), 91 (28), 75 (100). Anal. Calcd for $C_{26}H_{38}O_2SeSi$: C, 63.78; H, 7.82. Found: C, 63.44; H, 8.09.

*1-[2-[2-(Phenylselanyl)ethyl]phenyl]propan-1-one (**10b**):* 2.73 g, 83% yield; light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62 (dd, J = 1.5, 7.5 Hz, 1H), 7.55−7.48 (m, 2H), 7.45−7.21 (m, 6H), 3.40−3.05 (m, 4H), 2.90 (q, *J* = 7.3 Hz, 2H), 1.19 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.7, 140.3, 137.9, 132.1 (2C), 131.4, 131.1, 130.3 (2C), 128.9, 128.3, 126.5, 126.3, 34.9, 34.7, 28.5, 8.2; FTIR 2936, 1648, 1478, 1216, 957, 735 cm^{-1}; EIMS (70 eV) *m*/*z* 318 (15), 161 (100), 157 (22), 143 (28), 128 (29), 103 (20), 91 (25), 77 (26). Anal. Calcd for $C_{17}H_{18}OSe$: C, 64.35; H, 5.72. Found: C, 64.04; H, 6.07.

Asymmetric Reduction of Ketones 10a and 10b. The alcohols **11a** and **11b** were obtained by asymmetric reduction of the corresponding ketones with (*S*)-Me-CBS as reported above for ketone **4d**.

*(1R)-6-[(tert-Butyldimethylsilyl)oxy]-1-[2-[2-(phenylselanyl)ethyl]phenyl]hexan-1-ol (**11a**).* As reported above, ketone **10a** (0.20 g, 0.50 mmol) was reduced to **11a** (0.36 g, 90% yield): colorless oil: $[\alpha]^{16}_D$

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102−8112

+10.1 (*c* 1.48, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.60−7.40 (m, 3H), 7.38−7.06 (m, 6H), 4.79 (dd, *J* = 4.9, 7.7 Hz, 1H), 3.60 (t, *J* = 6.5 Hz, 2H), 3.19−2.95 (m, 4H), 1.90 (br s, 1H), 1.85−1.08 (m, 8H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.6, 137.6, 133.0 (2C), 129.8, 129.5, 129.1 (2C), 127.5, 127.1, 127.0, 125.8, 70.1, 63.1, 38.7, 33.1, 32.7, 28.8, 26.0 (3C), 25.8 (2C), 18.3, −5.3 (2C); FTIR 3335, 2929, 1578, 1472, 1255, 1098, 835, 774 cm^{-1}; EIMS (70 eV) *m*/*z* $[M - 57]^+$ 435 (17), 207 (21), 185 (44), 157 (19), 143 (52), 129 (60), 117 (85), 105 (31), 91 (39), 75 (100). Anal. Calcd for $C_{26}H_{40}O_2SeSi$: C, 63.52; H, 8.20. Found: C, 63.15; H, 8.55. HPLC analysis on Phenomenex Lux Amylose-2 column (250 × 4.60 mm i.d.), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, major) = 12.4 min, t_R (*S*-enantiomer, minor) = 13.5 min, er = 77.4:22.6.

*(1R)-1-[2-[2-(Phenylselanyl)ethyl]phenyl]propan-1-ol (**11b**).* As reported above, ketone **10b** was reduced to alcohol **11b** (0.90 g, 92% yield): light yellow oil: $[\alpha]^{16}_D$ +6.00 (*c* 1.56, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.61−7.42 (m, 3H), 7.37−7.11 (m, 6H), 4.72 (dd, *J* = 5.6, 7.4 Hz, 1H), 3.21−2.92 (m, 4H), 2.01 (br s, 1H), 1.88−1.57 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.3, 137.8, 133.0, 129.4, 129.1 (3C), 127.3, 127.0, 126.9 (2C), 125.7, 71.4, 33.1, 31.4, 28.7, 10.5; FTIR 3385, 2963, 1578, 1477, 1437, 972, 734 cm^{-1}; EIMS (70 eV) *m*/*z* 320 (26), 185 (12), 157 (13), 145 (79), 133 (100), 117 (38), 105 (98), 91 (64), 77 (41). Anal. Calcd for $C_{17}H_{20}OSe$: C, 63.95; H, 6.31. Found: C, 63.58; H, 6.59. HPLC analysis on Phenomenex Lux Celulose-2 column (250 × 4.60 mm i.d.), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*S*-enantiomer, minor) = 13.9 min, t_R (*R*-enantiomer, major) = 16.1 min, er = 22.4:77.6.

General Procedure for the Oxidation−Cyclization of Phenylseleno Alcohols 11a and 11b. To a solution of the appropriate phenylseleno alcohol (1.00 mmol) in acetonitrile (15 mL) at room temperature were added powdered potassium hydrogen phosphate (4.00 mmol) and *m*-CPBA (3.00 mmol). The reaction mixture was stirred until TLC analysis showed that the starting selenide was completely converted into the corresponding selenone (2.5 h). Powdered potassium hydroxide (7.50 mmol) was then added at room temperature. The consumption of the selenone was monitored by TLC. After 16 h, the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with saturated sodium carbonate solution and saturated NaCl solution, dried over sodium sulfate, filtrated, and evaporated. The reaction product was purified by column chromatography on SiO_2 (4% diethyl ether in petroleum ether).

*(R)-tert-Butyl[5-(isochroman-1-yl)pentyloxy]dimethylsilane (**12a**).* Following the general procedure, **11a** (0.31 g, 0.63 mmol) was converted to **12a** (0.14 g, 67% yield): colorless oil; $[\alpha]_D^{18}$ +38.5 (*c* 1.14, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−7.04 (m, 4H), 4.77 (dd, *J* = 2.6, 8.0 Hz, 1H), 4.16 (ddd, *J* = 3.7, 5.3, 11.2 Hz, 1H), 3.80 (ddd, *J* = 3.8, 9.6, 11.2 Hz, 1H), 3.64 (t, *J* = 6.5 Hz, 2H), 3.01 (ddd, *J* = 5.3, 9.6, 16.2 Hz, 1H), 2.72 (ddd, *J* = 3.7, 3.8, 16.2 Hz, 1H), 2.00−1.77 (m, 2H), 1.64−1.25 (m, 6H), 0.92 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 133.9, 128.8, 126.1, 126.0, 124.7, 75.8, 63.2, 63.1, 36.0, 32.8, 29.2, 26.0 (3C), 25.9, 25.1, 18.4, −5.3 (2C); FTIR 2933, 1471, 1254, 1104, 836, 742 cm^{-1}; EIMS (70 eV) *m*/*z* $[M - 57]^+$ 277 (11), 185 (23), 143 (36), 133 (100), 129 (35), 117 (45), 105 (21), 75 (35). Anal. Calcd for $C_{20}H_{34}O_2Si$: C, 71.80; H, 10.24. Found: C, 71.54; H, 10.59.

*(1R)-1-Ethylisochroman (**12b**).*[35a] Following the general procedure, **11b** (0.29 g, 0.9 mmol) was converted to **12b** (0.11 g, 75% yield): colorless oil; $[\alpha]^{23}_D$ +80.2 (*c* 1.50, $CHCl_3$); HPLC analysis on Phenomenex Lux cellulose-2 column (250 × 4.60 mm i.d.), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, major) = 4.6 min, t_R (*S*-enantiomer, minor) = 5.4 min, er = 77.6:22.4.

Synthesis of Ketoester 13b. Commercially available 5-bromo-2-hydroxybenzaldehyde was converted into the corresponding 2-acetyl-5-bromobenzaldehyde **22** by the method reported in the literature.[45]

*2-Acetyl-5-bromobenzaldehyde (**22**):*[45] 1.52 g, 70% yield; light yellow solid; mp 73−75 °C (*n*-hexane); FTIR 2893, 2748, 1765, 1676, 1192, 824, 710 cm^{-1}. Oxidation of **22** following the literature procedure[46] gave crude 2-acetyl-5-bromobenzoic acid which was immediately reacted with methanol[41] to give **13b**.

*Methyl 2-acetyl-5-bromobenzoate (**13b**):* 0.70 g, 68% yield; yellow oil; ^1H NMR (200 MHz, $CDCl_3$) δ 7.97 (d, *J* = 2.0 Hz, 1H), 7.69 (dd, *J* = 2.0, 8.2 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 3.90 (s, 3H), 2.54 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.5, 166.2, 140.9, 134.9, 132.6, 130.8, 128.2, 124.4, 52.8, 29.8; FTIR 2952, 1732, 1705, 1262, 967, 830, 750 cm^{-1}; EIMS (70 eV) *m*/*z* 256 (5), 241 (100), 225 (31), 211 (16), 198 (11), 170 (13), 153 (13), 75 (21). Anal. Calcd for $C_{10}H_9BrO_3$: C, 46.72; H, 3.53. Found: C, 46.64; H, 3.58.

Synthesis of Diols 15a and 15b. A solution of methyl 2-acetylbenzoate **13a** (0.10 g, 0.60 mmol) and hexamethyldisilazane (0.16 mL, 0.72 mmol) in hexane (8 mL) was cooled to −20 °C under argon, and trimethylsilyl iodide (0.10 mL, 0.60 mmol) was added.[47] The mixture was stirred first at −20 °C for 10 min then at 25 °C for 8 h. The slurry was filtered through a Celite pad, and the filtrate was washed with 10 mL of cold saturated sodium hydrogen carbonate solution, dried over sodium sulfate, filtrated, and evaporated to give the crude trimethylsilyl enol ether derivative which was dissolved in 2 mL of dry diethyl ether at −20 °C. Phenylselenenyl chloride (0.13 g, 0.66 mmol) dissolved in dry diethyl ether (2.0 mL) was added slowly, and the reaction mixture was allowed to slowly warm to room temperature. After 1 h, the reaction was quenched with saturated aqueous sodium hydrogen carbonate solution (10 mL) and then extracted with diethyl ether (2 × 10 mL). The organic layer was dried over sodium sulfate, filtrated, and evaporated. The residue was passed through a short column of silica gel (20% diethyl ether in petroleum ether) to give the crude α-phenylseleno ketone intermediate **14a** (0.18 g) of sufficient purity for use in subsequent manipulation. The asymmetric reduction of crude **14a** with an equimolecular amount of (*S*)-Me-CBS in the presence of a 2-fold excess of borane dimethylsulfide complex[8] gave 0.09 g of the diol **15a** in 48% global yield from **13a**.

*(1S)-1-[2-(Hydroxymethyl)phenyl]-2-(phenylselanyl)ethanol (**15a**):* colorless oil; $[\alpha]^{19}_D$ +8.9 (*c* 1.68, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.63−7.15 (m, 9H), 5.02 (dd, *J* = 5.6, 8.4 Hz, 1H), 4.58 (s, 2H), 3.48−3.10 (m, 3H), 2.60 (brs, 1H);^{13}C NMR (50 MHz, $CDCl_3$) δ 140.6, 137.8, 133.1, 133.0, 129.8, 129.7, 129.2 (2C), 128.4, 128.1, 127.4, 126.5, 69.9, 63.2, 36.6; FTIR 3325, 2974, 1578, 1340, 762 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_2Se$: C, 58.64; H, 5.25. Found: C, 58.29; H, 5.66. HPLC analysis on Phenomenex Lux amylose-2 column (250 × 4.60 mm i.d.), *n*-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*R*-enantiomer, minor) = 21.4 min, t_R (*S*-enantiomer, major) = 22.8 min, er = 17.6:82.4.

*(1S)-1-[4-Bromo-2-(hydroxymethyl)phenyl]-2-(phenylselanyl)-ethanol (**15b**).* Following the above procedure, **13b** (1.52 g, 6.00 mmol) was converted to **15b** (1.30 g, 56% global yield from **13b**): light yellow oil; $[\alpha]^{23}_D$ −10.70 (*c* 1.14, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.56−7.48 (m, 2H), 7.44−7.37 (m, 2H), 7.33−7.22 (m, 4H), 4.88 (dd, *J* = 4.4, 9.1 Hz, 1H), 4.48 (s, 2H), 3.20−2.90 [m, partly overlapped dd (*J* = 4.4, 12.8 Hz, 1H), dd (*J* = 9.1, 12.8 Hz, 1H), br s (2H)]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.8, 139.3, 133.3 (2C), 132.2, 131.3, 129.3 (2C), 128.7, 128.3, 127.6, 121.9, 69.3, 62.4, 36.6; FTIR 3371, 2932, 1578, 1477, 1022, 828, 736 cm^{-1}; EIMS (70 eV) *m*/*z* $[M-18]^+$ 368 (8), 170 (100), 169 (12), 118 (18), 90 (13), 77 (13). Anal. Calcd for $C_{15}H_{15}BrO_2Se$: C, 46.66; H, 3.92. Found: C, 46.41; H, 4.22. HPLC analysis on Phenomenex Lux cellulose-2 column (250 × 4.60 mm i.d.), *n*-hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*S*-enantiomer, major) = 12.8 min, t_R (*R*-enantiomer, minor) = 22.2 min, er = 87.9:12.1.

Preparation of Alcohol 16a. *tert*-Butyldiphenylsilyl chloride (0.40 mL. 1.57 mmol) was added to a stirred solution of diol **15a** (0.44 g, 1.43 mmol) and imidazole (0.12 g, 1.71 mmol) in dry dimethylformamide (5.0 mL) at 0 °C under an Ar atmosphere. The mixture was stirred for 16 h, quenched with 10 mL of saturated aqueous ammonium chloride solution, and extracted with diethyl ether (2 × 30 mL), and the organic layer was dried over sodium sulfate. The solution was filtrated and evaporated, and the residue was dissolved in dichloromethane (5 mL) at room temperature. To this solution 4-

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102−8112

methoxybenzyl 2,2,2-trichloroacetimidate (0.65 g, 2.28 mmol) and pyridinium *p*-toluensulfonate polymer bound (50 mg) were added.[48] After 24 h, the mixture was filtrate through a short Celite pad and evaporated. The residue was dissolved in THF (15 mL), and TBAF (0.45 g, 1.43 mmol) was added. The reaction mixture was stirred for 6 h, poured into saturated aqueous sodium hydrogen carbonate solution (20 mL), and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over sodium sulfate, filtrated, and evaporated. Pure **16a** (0.48 g) was isolated after column chromatography on SiO_2 (20% diethyl ether/petroleum ether) in a 77% global yield from **15a**.

*[2-[(1S)-1-[(4-Methoxybenzyl)oxy]-2-(phenylselanyl)ethyl]-phenyl]methanol (**16a**):* light yellow oil; $[\alpha]^{21}_{D}$ +29.4 (*c* 1.53, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.58−7.10 (m, 11H), 6.95−6.80 (m, 2H), 4.89 (dd, *J* = 5.2, 8.5 Hz, 1H), 4.66−4.46 (AB system, 2H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.40 (dd, *J* = 8.5, 12.4 Hz, 1H), 3.19 (dd, *J* = 5.2, 12.4 Hz, 1H), 2.39 (br s, 1H);^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2, 139.3, 138.4, 132.8, 130.5, 129.9, 129.5, 129.4, 129.1, 129.0, 128.6, 128.4, 128.1, 127.6, 127.2, 126.9, 113.9, 113.8, 77.1, 70.5, 62.7, 55.3, 35.0; FTIR 3370, 3245, 1696, 1512, 1247, 837, 757 cm^{-1}. Anal. Calcd for $C_{23}H_{24}O_3Se$: C, 64.63; H, 5.66. Found: C, 64.29; H, 6.03.

Preparation of Alcohol 16b. *tert*-Butyldiphenylsilyl chloride (0.56 mL. 2.20 mmol) was added to a stirred solution of diol **15b** (0.77 g, 2.00 mmol) and imidazole (0.16 g, 2.40 mmol) in dry dimethylformamide (6.0 mL) at 0 °C under an Ar atmosphere. The mixture was stirred for 16 h, quenched with 10 mL of saturated aqueous ammonium chloride solution, and extracted with diethyl ether (3 × 30 mL), and the organic layer was dried over sodium sulfate. The solution was filtrated and evaporated, and the residue was dissolved in dimethylformamide (20 mL) at 0 °C. To this solution was added sodium hydride 60% dispersion in mineral oil (0.11 g, 2.8 mmol). After 30 min, methyl iodide was added (0.16 mL, 2.60 mmol). The mixture was stirred for 8 h at rt, quenched with 10 mL of saturated aqueous ammonium chloride solution, and extracted with ethyl ether (3 × 30 mL), and the organic layer was dried over sodium sulfate. The solution was filtrated and evaporated, the residue was dissolved in THF (30 mL), and TBAF (0.63 g, 2.00 mmol) was added. The reaction mixture was stirred for 12 h, poured into saturated aqueous sodium hydrogen carbonate solution (20 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layer was dried over sodium sulfate, filtrated, and evaporated. Pure **16b** (0.48 g) was isolated after column chromatography on SiO_2 (40% diethyl ether/petroleum ether) in a 71% global yield from **15b**.

*[5-Bromo-2-[(1S)-1-methoxy-2-(phenylselanyl)ethyl]phenyl]-methanol (**16b**).* yellow oil; $[\alpha]^{22}_{D}$ +14.95 (*c* 0.64, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53−7.40 (m, 4H), 7.35−7.19 (m, 4H), 4.64 (dd, *J* = 5.6, 8.0 Hz, 1H), 4.58 (AB system, 2H), 3.31 (dd, *J* = 8.0, 12.5 Hz, 1H), 3.23 (s, 3H); 3.11 (dd, *J* = 5.6, 12.5 Hz, 1H), 2.40 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.5, 137.8, 133.0 (2C), 131.6, 131.2, 130.0, 129.1 (2C), 128.7, 127.6, 122.0, 79.4, 62.1, 57.0, 34.4; FTIR 3381, 2931, 1578, 1477, 1091, 883, 739 cm^{-1}; EIMS (70 eV) *m*/*z* 400 (15), 229 (91), 197 (100), 169 (36), 103 (18), 91 (22), 77 (15). Anal. Calcd for $C_{16}H_{17}BrO_2Se$: C, 48.02; H, 4.28. Found: C, 47,77; H, 4.59.

Oxidation−cyclization of Alcohols 16a and 16b. To a solution of phenylseleno alcohol **16a** (0.43 g, 1.00 mmol) in acetonitrile (15 mL) at room temperature were added powdered potassium hydrogen phosphate (0.69 g, 4.00 mmol) and *m*-CPBA (0.52 g, 3.00 mmol). The reaction mixture was stirred until TLC analysis showed that the starting selenide was completely converted into the corresponding selenone (2 h). Powdered potassium hydroxide (0.42 g, 7.50 mmol) was then added at room temperature. The consumption of the selenone was monitored by TLC. After 20 h, the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with saturated sodium carbonate solution and saturated NaCl solution, dried over sodium sulfate, filtrated, and evaporated. The reaction product was purified by column chromatography on SiO_2 (15% ethyl acetate in petroleum ether) to afford **17a**.

*(4S)-4-(4-Methoxybenzyloxy)isochroman (**17a**):* 0.19 g, 70% yield; white gum; $[\alpha]^{20}_{D}$ +11.9 (*c* 1.84, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42−7.16 (m, 5H), 7.10−6.97 (m, 1H), 6.87 (d, *J* = 9.2 Hz, 2H), 4.86 (d, *J* = 15.0 Hz, 1H), 4.68 (d, *J* = 15.0 Hz, 1H), 4.63 (s, 2H), 4.45 (dd, *J* = 3.4, 3.6 Hz, 1H), 4.18 (dd, *J* = 3.6, 12.0 Hz, 1H), 3.90 (dd, *J* = 3.4, 12.0 Hz, 1H), 3.80 (s, 3H);^{13}C NMR (50 MHz, $CDCl_3$) δ 159.2, 135.3, 133.0, 130.4, 129.5 (2C), 129.2, 127.9, 126.7, 124.0, 113.8 (2C), 70.6, 70.3, 68.2, 67.8, 55.3, FTIR 2840, 1730, 1513, 1247, 824, 749 cm^{-1}; EIMS (70 eV) *m*/*z* 270 (5), 137 (29), 121 (100), 105 (19), 91 (21), 77 (21). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.20; H, 7.05.

*(4S)-7-Bromo-4-methoxyisochroman (**17b**).* Following the above procedure, alcohol **16b** (0.16 g, 0.40 mmol) was converted to **17b** (60 mg, 66%): white gum; $[\alpha]^{22}_{D}$ +32.85 (*c* 1.65, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 1.9, 8.1 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 1.9 Hz, 1H), 4.74 (AB system, 2H), 4.20 (dd, *J* = 3.4, 4.1 Hz, 1H), 4.18 (dd, *J* = 3.4, 13.2 Hz, 1H), 3.83 (dd, *J* = 4.1, 13.2 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.5, 131.6, 131.1, 129.9, 127.1, 121.9, 72.5, 67.6, 67.3, 57.5; FTIR 2824, 1772, 1596, 1481, 1193, 1091, 821 cm^{-1}; EIMS (70 eV) *m*/*z* 242 (5), 212 (100), 197 (66), 169 (32), 133 (39), 103 (31), 89 (32). Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found: C, 49.12; H, 4.82. HPLC analysis on Phenomenex Lux Amylose-2 column (250 × 4.60 mm i.d.), *n*-hexane/2-propanol = 98:2, flow rate = 1.0 mL/min, 254 nm UV detector: t_R (*S*-enantiomer, major) = 12.4 min, t_R (*R*-enantiomer, minor) = 13.4 min, er = 87.9:12.1.

Synthesis of Isochroman 19. Acid **9** (0.37 g, 1.2 mmol) was transformed into the corresponding methyl ester derivative by reaction with trimethylsilyl chloride (0.38 mL, 3.00 mmol) in 6 mL of dry methanol for 24 h at 28 °C.[49] The crude methyl ester derivative, with sufficient purity for use in subsequent manipulation, was dissolved in 20 mL of dry THF at −18 °C (ice bath). A 2.0 M butylmagnesium chloride solution in THF (1.8 mL) was added slowly. The resulting mixture was allowed to warm to 25 °C and stirred for an additional 24 h. The reaction was quenched with 10 mL of saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over sodium sulfate, filtrated, and evaporated. The resulting oil was purified by chromatography on SiO_2 (20% diethyl ether/petroleum ether) to afford 0.27 g (56% yield) of compound **18**.

*5-[2-[2-(Phenylselanyl)ethyl]phenyl]nonan-5-ol (**18**):* colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68−7.45 (m, 2H), 7.38−7.09 (m, 7H), 3.38−3.10 (m, 4H), 1.97−1.58 (m, 5H), 1.46−1.02 (m, 8H), 0.85 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.0, 139.2, 133.0 (2C), 131.7, 130.2, 129.0 (2C), 128.0, 126.9, 126.6, 125.9, 78.5, 42.5 (2C), 35.5, 29.8, 25.9 (2C), 23.1 (2C), 14.0 (2C); FTIR 3430, 2954, 1715, 1477, 1023, 734 cm^{-1}; EIMS (70 eV) *m*/*z* 404 (10), 189 (100), 157 (12), 143 (13), 133 (24), 117 (21), 91 (22). Anal. Calcd for $C_{23}H_{32}OSe$: C, 68.47; H, 7.99. Found: C, 68.09; H, 8.30.

Alcohol **18** (0.26 g, 0.62 mmol) was dissolved in MeCN (10 mL) at room temperature, and powdered potassium hydrogen phosphate (0.43 g, 2.49 mmol) and *m*-CPBA (0.32 g, 1.86 mmol) were added. The reaction mixture was stirred for 2 h (TLC analysis showed that the starting selenide was completely converted into the corresponding selenone derivative). Potassium hydroxide (0.26 g, 4.65 mmol) was added, and the consumption of the selenone was monitored by TLC. After 2 h, the mixture was poured into water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with a saturated potassium carbonate solution, dried over sodium sulfate, filtrated, and evaporated. Pure **19** was obtained after column chromatography on SiO_2 (5% diethyl ether/petroleum ether).

*1,1-Dibutylisochroman (**19**):* 0.12 g, 79% yield; colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28−6.92 (m, 4H), 3.93 (t, *J* = 5.5 Hz, 2H), 3.80 (t, *J* = 5.5 Hz, 2H), 1.98−1.70 (m, 4H), 1.54−1.02 (m, 8H), 0.89 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.8, 134.1, 128.5, 126.0, 125.5, 125.3, 78.6, 59.6, 40.3, 29.6 (2C), 25.6 (2C), 23.1 (2C), 14.1 (2C); FTIR 2953, 1724, 1451, 1094, 742 cm^{-1}; EIMS (70 eV) *m*/*z* [M − 57]$^+$ 189 (100), 133 (38), 105 (10), 91 (8). Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.54; H, 10.98.

Synthesis of Isochroman 21. Butyllithium (3.0 mL, 2.40 mmol) was added to a stirred solution of phenylacetylene (0.24 mL, 2.20 mmol) in dry THF (16 mL) at 0 °C. The reaction was allowed to

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102−8112

slowly warm to room temperature. After 2 h, ketone **10b** (0.64 g, 2.40 mmol) was added at 0 °C. The resulting mixture was allowed to warm to 25 °C, stirred for an additional 1 h, and quenched by addition of 5 mL of saturated aqueous ammonium chloride solution, and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$), filtrated, and concentrated. The resulting oil was purified by chromatography on SiO_2 (6% ethyl ether/petroleum ether) to afford alcohol **20**.

*1-Phenyl-3-[2-[2-(phenylselanyl)ethyl]phenyl]pent-1-yn-3-ol (**20**):* 0.53 g, 63% yield; light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82−7.72 (m, 1H), 7.60−7.40 (m, 4H), 7.39−7.12 (m, 9H), 3.49−3.35 (m, 2H), 3.32−3.26 (m, 2H), 2.50 (br s, 1H), 2.05 (q, J = 7.3 Hz, 2H), 1.08 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.2, 138.9, 132.8 (2C), 131.6 (2C), 131.3, 130.2, 128.9 (2C), 128.4, 128.3 (2C), 127.8, 126.8, 126.6, 126.1, 122.4, 91.9, 86.1, 74.0, 36.7, 34.3, 29.3, 9.0; FTIR 3453, 2971, 2225, 1577, 1478, 959, 756 cm^{-1}; EIMS (70 eV) m/z 420 (15), 391 (18), 289 (55), 261 (46), 233 (100), 215 (85), 189 (39), 157 (30), 129 (40), 115 (34), 91 (63), 77 (41). Anal. Calcd for $C_{25}H_{24}OSe$: C, 71.59; H, 5.77. Found: C, 71.30; H, 6.01.

Alcohol **20** (0.13 g, 0.30 mmol) was dissolved in MeCN (10 mL) at room temperature, and powdered potassium hydrogen phosphate (0.21 g, 1.20 mmol) and *m*-CPBA (0.16 g, 0.90 mmol) were added. The reaction mixture was stirred for 1 h (TLC analysis showed that the starting selenide was completely converted into the corresponding selenone derivative). Potassium hydroxide (0.13 g, 2.25 mmol) was added, and the consumption of the selenone was monitored by TLC. After 3 h, the mixture was poured into water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The organic layer was washed with a saturated potassium carbonate solution, dried over sodium sulfate, filtrated, and evaporated. Pure **21** was obtained after column chromatography on SiO_2 (5% ethyl acetate/petroleum ether).

*1-Ethyl-1-(phenylethynyl)isochroman (**21**):* 68 mg, 86% yield; colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49−7.10 (m, 9H), 4.28−4.06 (m, 2H), 3.08 (ddd, J = 6.6, 10.8, 16.2 Hz, 1H), 2.68 (dt, J = 2.6, 16.2 Hz, 1H), 2.29 (dq, J = 7.3, 14.0 Hz, 1H), 2.11 (dq, J = 7.3, 14.0 Hz, 1H), 1.01 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 133.5, 131.7 (2C), 128.8, 128.1 (2C), 126.6, 126.4, 126.0, 125.5, 122.9, 91.7, 84.9, 74.9, 61.3, 36.3, 28.9, 8.2; FTIR 2967, 2221, 1489, 1292, 1094, 754 cm^{-1}; EIMS (70 eV) m/z 262 (1), 233 (100), 215 (30), 202 (23), 189 (15), 129 (10). Anal. Calcd for $C_{19}H_{18}O$: C, 86.90; H, 6.92. Found: C, 86.55; H, 7.28.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01199.

^{1}H NMR and ^{13}C NMR spectra for all new compounds and HPLC charts for the determination of the er values (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: andrea.temperini@unipg.it

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank MIUR (Ministero Istruzione Università e Ricerca) National Project PRIN 20109Z2XRJ_010 and the Fondazione Cassa Risparmio Perugia for financial support.

■ REFERENCES

(1) (a) Mayer, A. M. S.; Gustafson, K. R. *Eur. J. Cancer* **2008**, *44*, 2357−2387. (b) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2474.

(2) (a) Alvarez, E.; Candenas, M. L.; Perez, R.; Ravelo, J. L.; Delgado Martin, J. *Chem. Rev.* **1995**, *95*, 1953−1980. (b) Shimizu, Y. M. *Chem. Rev.* **1993**, *93*, 1685−1698.

(3) (a) Lee, K.-S.; Li, G.; Kim, S. H.; Lee, C.-S.; Woo, M.-H.; Lee, S.-H.; Jhang, Y.-D.; Son, J.-K. *J. Nat. Prod.* **2002**, *65*, 1707−1708. (b) Ali, M. S.; Tezuka, Y.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 491−496. (c) Tezuka, Y.; Ali, A. M. S.; Banskota, A. H.; Kadota, S. *Tetrahedron Lett.* **2000**, *41*, 5903−5907.

(4) (a) Perry, M. A.; Rychnovsky, S. D.; Sizemore, N. In *Synthesis of Saturated Tetrahydropyrans*; Cossy, J., Ed.; Topics in Heterocyclic Chemistry; Springer-Verlag: Berlin, 2014; *35*, pp 43−95. (b) Nunez, M. G.; Garcia, P.; Moro, R. F.; Diez, D. *Tetrahedron* **2010**, *66*, 2089−2109. (c) Larrosa, I.; Romea, P.; Urpi, F. *Tetrahedron* **2008**, *64*, 2683−2723. (d) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, *2006*, 2045−2053.

(5) (a) Nicolaou, K. C.; Magolda, R. L.; Sipio, W. J.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784−3793. (b) Curini, M.; Epifano, F.; Marcotullio, M. C.; Montanari, F. *Synlett* **2004**, 368−370.

(6) Miura, K.; Okajima, S.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Am. Chem. Soc.* **2000**, *122*, 11348−11357.

(7) (a) Dzudza, A.; Marks, T. J. *Org. Lett.* **2009**, *11*, 1523−1526. (b) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066−9073.

(8) Ammann, S. E.; Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 10834−10837.

(9) Yamada, Y. M. A.; Guo, H.; Uozumi, Y. *Org. Lett.* **2007**, *9*, 1501−1504.

(10) (a) Zhang, F.-Z.; Tian, Y.; Li, G.-X.; Qu, J. *J. Org. Chem.* **2015**, *80*, 1107−1115. (b) Aponick, A.; Biannic, B. *Org. Lett.* **2011**, *13*, 1330−1333. (c) Guerinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808−1811.

(11) Jiang, X.; London, E. K.; Morris, D. J.; Clarkson, G. J.; Wills, M. *Tetrahedron* **2010**, *66*, 9828−9834.

(12) Zhu, S.-F.; Song, X.-G.; Li, Y.; Cai, Y.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2010**, *132*, 16374−16376.

(13) Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 16711−16713.

(14) (a) Le Gall, E.; Gosmini, C.; Troupel, M. *Tetrahedron Lett.* **2006**, *47*, 455−458. (b) Kim, S.; Lee, B. S.; Park, J. H. *Bull. Korean Chem. Soc.* **1993**, *14*, 654−655.

(15) Kometani, T.; Kondo, H.; Fujimori, Y. *Synthesis* **1988**, *1988*, 1005−1007.

(16) (a) Singh, P. P.; Gudup, S.; Aruri, H.; Singh, U.; Ambala, S.; Yadav, M.; Sawant, S. D.; Vishwakarma, R. A. *Org. Biomol. Chem.* **2012**, *10*, 1587−1597. (b) Lo, J. C.; Gui, J.; Yabe, Y.; Pan, C.-M.; Baran, P. S. *Nature* **2014**, *516*, 343−348.

(17) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672−7687.

(18) (a) Temperini, A.; Minuti, L. *Tetrahedron Lett.* **2012**, *53*, 2709−2711. (b) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Temperini, A. *Eur. J. Org. Chem.* **2011**, *2011*, 5668−5673. (c) Temperini, A.; Terlizzi, R.; Testaferri, L.; Tiecco, M. *Chem. - Eur. J.* **2009**, *15*, 7883−7895.

(19) (a) Temperini, A.; Curini, M.; Rosati, O.; Minuti, L. *Beilstein J. Org. Chem.* **2014**, *10*, 1267−1271. (b) Tiecco, M.; Testaferri, L.; Temperini, A.; Terlizzi, R.; Bagnoli, L.; Marini, F.; Santi, C. *Org. Biomol. Chem.* **2007**, *5*, 3510−3519. (c) Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Chem. - Eur. J.* **2004**, *10*, 1752−1764.

(20) Minuti, L.; Barattucci, A.; Bonaccorsi, P. M.; Di Gioia, M. L.; Leggio, A.; Siciliano, C.; Temperini, A. *Org. Lett.* **2013**, *15*, 3906−3909.

(21) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562−7563.

(22) Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181−5184.

(23) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634−4642.

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102−8112

(24) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *Tetrahedron* **1989**, *45*, 5141−5150.
(25) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.
(26) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.
(27) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(28) (a) Lakshminarayana, N.; Rajendra, P. Y.; Gharat, L.; Thomas, A.; Ravikumar, P.; Narayanan, S.; Srinivasan, C. V.; Gopalan, B. *Eur. J. Med. Chem.* **2009**, *44*, 3147−3157. (b) Liu, J.; Birzin, E. T.; Chan, W.; Yang, Y. T.; Pai, L.-Y.; Dasilva, C.; Hayes, E. C.; Mosley, R. T.; Dininno, F.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 715−718. (c) TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 2435−2437. (d) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Kokubu, N.; Inoue, Y.; Tsuruo, T.; Tashiro, T. *J. Med. Chem.* **1985**, *28*, 1026−1031.
(29) (a) Lorenz, P.; Zeh, M.; Martens-Lobenhoffer, J.; Schmidt, H.; Wolf, G.; Horn, T. F. W. *Free Radical Res.* **2005**, *39*, 535−545. (b) Isaka, M.; Kongsaeree, P.; Thebtaranonth, Y. J. *J. Antibiot.* **2001**, *54*, 36−43. (c) Malmstrøm, J.; Christophersen, C.; Frisvad, J. C. *Phytochemistry* **2000**, *54*, 301−309.
(30) Fráter, G.; Muller, U.; Kraft, P. *Helv. Chim. Acta* **1999**, *82*, 1656−1665.
(31) Larghi, E. L.; Kaufman, T. S. *Synthesis* **2006**, 187−220.
(32) Gowrisankar, S.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *38*, 2501−2504.
(33) De Koning, C. B.; Green, I. V.; Michael, J. P.; Oliveira, J. R. *Tetrahedron* **2001**, *57*, 9623−9634.
(34) Ramana, C. V.; Suryawanshi, S. B. *Tetrahedron Lett.* **2008**, *49*, 445−448.
(35) (a) Muramatsu, W.; Nakano, K. *Org. Lett.* **2014**, *16*, 2042−2045. (b) Liu, X.; Sun, B.; Xie, Z.; Qin, X.; Liu, L.; Lou, H. *J. Org. Chem.* **2013**, *78*, 3104−3112. (c) Richter, H.; Rohlmann, R.; Mancheno, O. G. *Chem. - Eur. J.* **2011**, *17*, 11622−11627. (d) Tomooka, K.; Wang, L.-F.; Okazaki, F.; Nakai, T. *Tetrahedron Lett.* **2000**, *41*, 6121−6125.
(36) (a) Meng, Z.; Sun, S.; Yuan, H.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 543−547. (b) Rowan, A. S.; Moody, T. S.; Howard, R. M.; Underwood, T. J.; Miskelly, I. R.; He, Y.; Wang, B. *Tetrahedron: Asymmetry* **2013**, *24*, 1369−1381. (c) Ennis, M. D.; Ghazal, N. B.; Hoffman, R. L.; Smith, M. W.; Schlachter, S. K.; Lawson, C. F.; Im, W. B.; Pregenzer, J. F.; Svensson, K. A.; Lewis, R. A.; Hall, E. D.; Sutter, D. M.; Harris, L. T.; McCall, R. B. *J. Med. Chem.* **1998**, *41*, 2180−2183.
(37) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153−3163.
(38) Bohlmann, R.; Bittler, D.; Heindl, J.; Heinrich, N.; Hofmeister, H.; Kunzer, H.; Sauer, G.; Hegele-Hartung, C.; Lichtner, R.; Nishino, Y.; Parczyk, K.; Schneider, M. US Patent 5986115, 1999.
(39) Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, *2006*, 890−891.
(40) Noureldin, N. A.; Zhao, D.; Lee, D. G. *J. Org. Chem.* **1997**, *62*, 8767−8772.
(41) Newman, M. S.; Naiki, K. *J. Org. Chem.* **1962**, *27*, 863−865.
(42) Bailey, T. R. *Synthesis* **1991**, *1991*, 242−243.
(43) Jiang, X.; London, E. K.; Morris, D. J.; Clarkson, G. J.; Wills, M. *Tetrahedron* **2010**, *66*, 9828−9834.
(44) Murray, P. M.; Bower, J. F.; Cox, D. K.; Galbraith, E. K.; Parker, J. S.; Sweeney, J. B. *Org. Process Res. Dev.* **2013**, *17*, 397−405.
(45) Yang, J.; Yoshikai, N. *J. Am. Chem. Soc.* **2014**, *136*, 16748−16751.
(46) Hunsen, M. *Synthesis* **2005**, 2487−2490.
(47) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, *1979*, 730−732.
(48) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto; Jones, H. D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654−8664.
(49) Brook, M. A.; Chan, T. H. *Synthesis* **1983**, *1983*, 201−203.

DOI: 10.1021/acs.joc.5b01199
J. Org. Chem. 2015, 80, 8102−8112