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Stannane-Free Chemoselective Hydrodehalogenation of 4-Halotetrahydropyrans: Scope and Application to Natural Product Synthesis

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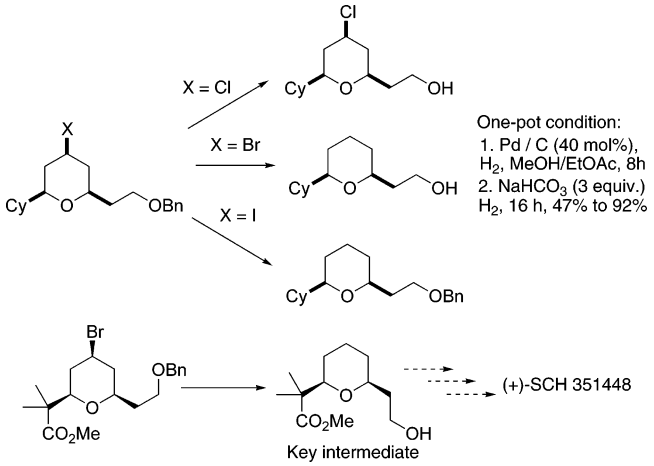

A stannane-free hydrodehalogenation of 4-halotetrahydropyran under very mild conditions has been developed. This methodology allows selective one-pot dehalogenation and/or debenzylation depending on the type of halide−substrate used. The applicability of this methodology is well demonstrated in the synthesis of a key intermediate toward the enantioselective synthesis of (+)-SCH 351448.

Introduction

Natural products[1] containing the 2,6-disubstituted tetrahydropyran exhibit important biological properties[2] which make them attractive targets to organic chemists. Prins cyclization[3] offers a convenient and efficient way to synthesize the tetrahydropyran framework with a halide at the 4-position. Radical dehalogenation is perhaps one of the most important methods to form the desired 2,6-disubstituted THP product from the Prins precursor. This involves radical[4] initiation using AIBN on the organohalide and entrapment with tributyltin hydride[5] to form the corresponding dehalogenated product. This radical reaction is mild and is relatively unaffected by steric or electronic attributes of other functional groups present in the molecule, which makes it an ideal strategy in natural productsynthesis.

(1) (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weiheim, 1996. (b) Nicolaou, K. C.; Synder, S. A. *Classics in Total Synthesis II*: Wiley-VCH: Weinheim, 2003.

(2) For recent references on biological evaluations of selected tetrahydropyran containing natural products, see: (a) Michelet, W.; Genet, J. P. *Curr. Org. Chem.* **2005**, *9*, 405. (b) Nicolaou, K. C.; Kim, D. W.; Baati, R.; O'Brate, A; Giannakakou, P. *Chem.−Eur. J.* **2003**, *9*, 6177. (c) Wender, P. A.; Verma, V. A. *Org. Lett.* **2006**, *8*, 1893.

(3) Selected references on Prins cyclization: (a) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913. (b) Wei, Z. Y.; Li, S. J.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441. (c) Yang, J.; Viswanathan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627. (d) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett.* **2003**, *5*, 3163. (e) Wei, Z. Y.; Li, S. J.; Wang, D.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768. (f) Coppi, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 973. (g) Perron, F.; Albizati, K. F. *J. Org. Chem.* **1987**, *52*, 4128. (h) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271.

(4) (a) Renaud, P.; Sibi, P. M. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001; Vols. 1 and 2. (b) Glese, B.; Gobel, T.; Dickhaut, G.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions*; Paquette, L., Beak, P., Engelbert, C., Curran, D., Czarnik, A., Scott, E., Hegedus, L., Kelly, R., Overman, L., Roush, W. R., Smith, A., White, J., Eds.; Wiley & Sons: New York, 1996; pp 301−856. (c) Glese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, UK, 1986. (d) Curran, D. P. *Synthesis* **1988**, 417. (e) Curran, D. P. *Synlett* **1991**, 63.

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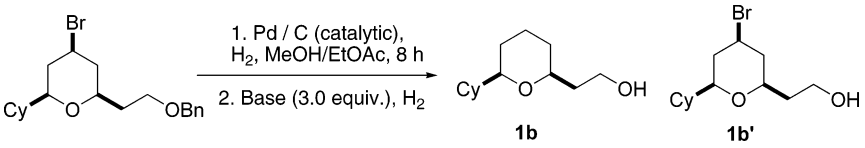
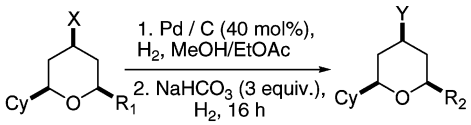
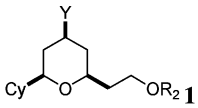
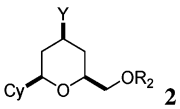
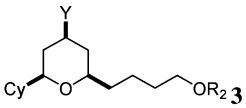
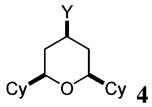
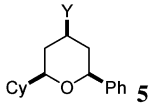
TABLE 1. Optimization of Reaction Conditions for One-Pot Hydrodehalogenation



entry	Pd/C catalyst loading (mol %)	base	time after base addition (h)	yield (%) 1b	yield (%) 1b′
1	5	$NaHCO_3$	72	33	46
2	10	$NaHCO_3$	72	59	23
3	20	$NaHCO_3$	72	73	10
4	40	$NaHCO_3$	16	92	
5	40	KOH	16	81	
6	40	DBU	16	85	

TABLE 2. One-Pot Dehalogenation of Cyclic Halides[a]



entry	X	R_1	product	Y	R_2	yield (%)
1	Cl	CH_2CH_2OBn	 **1**	Cl	H	79 (**1a**)
2	Br			H	H	92 (**1b**)
3	I			H	Bn	74 (**1c**)
4	Cl	CH_2OBn	 **2**	Cl	H	65 (**2a**)
5	Br			H	H	71 (**2b**)
6	I			H	Bn	47 (**2c**)
7	Cl	$(CH_2)_4OBn$	 **3**	Cl	H	60 (**3a**)
8	Br			H	H	71 (**3b**)
9	I			H	Bn	66 (**3c**)
10	Cl	Cy	 **4**	Cl	Cy	N.R
11	Br			H	Cy	79
12	I			H	Cy	76
13	Cl	Ph	 **5**	Cl	Ph	N.R
14	Br			H	Ph	66
15	I			H	Ph	59

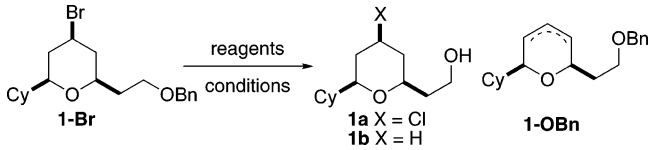
[a] N.R. denotes no observable reaction.

However, its utility at a preparative level is limited because of the toxicity involving stannane reagents. In addition, the quenching of stannane-mediated dehalogenation often involves the use of toxic fluoride[6] reagents. The removal of byproducts using chromatography methods is also a challenge due to very similar retention factor with respect to the dehalogenated product. Hence, the establishment of a more sustainable and convenient route toward dehalogenation will be of high synthetic value in the realm of natural product synthesis. Herein we report a new stannane-free hydrodehalogenation reaction with excellent

(5) Terstiege, I.; Maleczka R. E., Jr. *J. Org, Chem.* **1999**, *64*, 342.

(6) Leibner, J. E.; Jocobus, J. *J. Org. Chem.* **1979**, *44*, 449.

TABLE 3. Investigation on the Elimination Pathway in Hydrodehalogenation



entry	reagents	conditions	yield (%) 1b	yield (%) 1-OBn[a]
control	1. Pd/C (40 mol %), H_2, MeOH/EtOAc 2. $NaHCO_3$, followed by further hydrogenation	25 °C, 18 h	92	N.R.[b]
1	DBU, PhMe	reflux, 24 h	N.R.	N.R.
2	KOH, THF	reflux, 24 h	N.R.	N.R.
3	$NaHCO_3$, activated carbon, MeOH/EtOAc	25 °C, 48 h	N.R.	N.R.
4	Pd/C (40 mol %), $NaHCO_3$, MeOH/EtOAc	25 °C, 96 h	N.R.	N.R.
5	1. Pd/C (40 mol %), H_2, MeOH/EtOAc 2. KOH,[c] followed by further hydrogenation	25 °C, 18 h	91	N.R.

[a] The eliminated product can have the double bond on either side of the THP ring. [b] N.R. denotes no desired product observed. [c] Another experiment was done with 4-chlorobenzyl-THP **1-Cl** using hydrogenation in KOH. It was found that the chloride remained intact, forming **1a**. This shows that the strength of base used has no apparent effect on dehalogenation of chloro-THP.

chemoselectivity and superb efficiency toward non-antiperiplanar cyclic halide systems.

Results and Discussion

Hydrodehalogenation. Inspired by Kovac's[7] work on derivatization of iodosugar molecules, we attempted to carry out base-mediated palladium-catalyzed dehalogenation using readily synthesized 4-bromotetrahydropyran[8] substrates. Various catalyst loading and bases were used in the investigation for a one-pot hydrodehalogenation reaction (Table 1).

Our attempts to follow Kovac's procedure using DMF as a solvent resulted in an unsatisfactory yield of hydrodehalogenated product. However, the ease of reaction was alleviated using a MeOH/EtOAc (9:1) solvent mixture, with sequential addition of $NaHCO_3$ followed by further hydrogenation. It was found that at low palladium catalyst loading, incomplete dehalogenation resulted in a mixture of **1b** and **1b′** (Table 1, entries 1−4). This could be due to significant poisoning effect of the base on low concentration of palladium catalyst. By increasing the amount of palladium, complete hydrodehalogenated product can be obtained over a significantly shorter period of time. Further trials with different bases such as KOH (entry 5) and DBU (entry 6) failed to improve the yield of the dehalo-THP ring or the reaction time. Hence, the optimal condition of 40 mol % palladium with sodium bicarbonate was established, and such encouraging results prompted us to extend the scope to other 4-halo-THP substrates (Table 2).

From the results, it was evident that this methodology was highly chemoselective. The chloro-THP substrates were debenzylated but not dehalogenated (entry 1). On the contrary, the iodobenzyloxy-THP was dehalogenated, but not debenzylated (entry 3). The bromo precursor afforded the highest yield for the dehalogenation and debenzylation product in one pot. Since hydrogenation should affect only the benzyl-protecting group, we envisaged that a greater distance between the halide and the benzyloxy group may affect the regio- and chemoselectivity of the reaction. Therefore, we conducted base-mediated hydrogenation experiments on different benzyloxy substrates (entries 4−9). It was found that the proximity of the benzyloxy group from the halide position exerted no effect on the chemoselectivity of the products. It can be concluded that in the presence of an iodo moiety on the 4-position of the THP, the molecule can be selectively dehalogenated without affecting the benzyl protecting group.

The same phenomenon was observed in the cyclohexyl (entries 10−12) and phenyl (entries 13−15) moieties, with the 4-chloro-THP unaffected by the one-pot base-mediated palladium-catalyzed de-halogenation reaction. Such chemoselective reaction complemented our recent development of the TMSX-mediated Prins cyclization,[9] where versatile incorporation of the halide on 4-position of the THP ring can now be selectively reduced in the presence of other functionality. This interesting finding not only allows one-pot debromination/debenzylation reaction to obtain dehalo-THP products cleanly in a reasonable yield without the use of toxic stannane reagents, but more importantly, establishes groundwork for future endeavors in total synthesis of natural products.

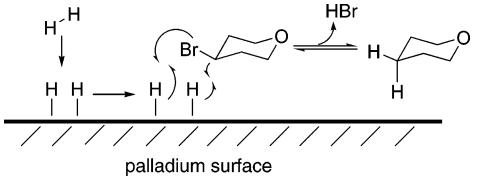
Mechanistic Investigation. In our initial postulation, we assumed that the dehalogenation took place via an elimination of halide followed by hydrogenation of the double bond. This would be an interesting phenomenon because dehalogenation of equatorial halides in a pyran ring would be a violation of the antiperiplanar requirement in the conventional base-mediated formation of *endocyclic* alkene. It was initially proposed that the palladium could have played an active role in distorting the chairlike conformation of the pyran ring, thus placing the halide in a favorable antiperiplanar position for elimination. However,

(7) Lin, T. H.; Kovac, P.; Glaudemans, C. P. *Carbohydr. Res.* **1989**, *188*, 228.

(8) For the synthesis of 4-halo-2,6-disubstituted THP substrates, see: (a) Chan, K. P.; Loh, T. P. *Tetrahedron. Lett.* **2004**, *45*, 1167. (b) Taddei, M.; Coppi, L.; Ricci, A. *Tetrahedron Lett.* **1987**, *28*, 973. (c) Yang, J.; Viswanthan, G. S.; Li, C. J. *Tetrahedron Lett.* **1999**, *40*, 1627. (d) Yang, X.-F.; Mague, J. T.; Li, C. J. *J. Org. Chem.* **2001**, *66*, 739. (e) Ramesh, J.; Vitale, J; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904−9905.

(9) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491.

SCHEME 1. Proposed Mechanism Dehalogenation of 4-Halopyran[a]



[a] The other functional groups have been omitted for clarity. HBr was quenched by excess $NaHCO_3$.

further investigations (Table 3) to justify this postulation revealed that the reaction could have proceeded via a completely different pathway.

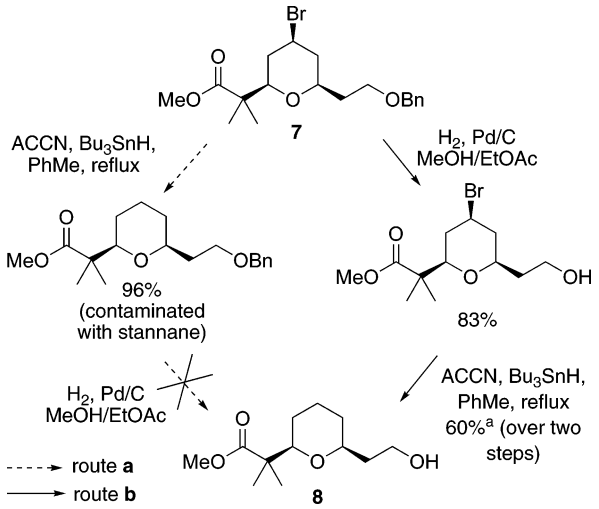
It was observed that both DBU and KOH also failed to afford the elimination product **1-OBn**, which excluded the possible of a direct elimination pathway (entries 1 and 2). The postulation of a palladium-promoted elimination was also excluded since no *endocyclic* alkene was observed in the absence of hydrogen environment (entries 3 and 4). Further attempts to investigate the mechanism of dehalogenation in 4-bromo-THP ring indicated that both palladium and hydrogen are critical in the elimination of the halide, and that hydrogen is critical in initiating the dehalogenation reaction. It was also concluded that the reaction was insensitive to the type of base used (entry 5).

On the basis of this information, a plausible explanation for this unusual phenomenon has been proposed. Upon adsorption of molecular hydrogen on the palladium surface, there could be an atom exchange process via a single electron-transfer mechanism. This resulted in the formation of the dehalogenated THP product upon concurrent removal of HBr in the presence of a base (Scheme 1).

Applications to Enantioselective Synthesis of (+)-SCH 351448. Intrigued by the exemplary result displayed in this methodology, we proposed to demonstrate its applicability on the synthesis of an important fragment of a natural product. (+)-SCH 351448[10] is a novel activator of low-density lipoprotein receptor promoter, which consists of multiple *syn*-2,6-disubstituted-THP rings (Scheme 2). To date, (+)-SCH 351448 is the first small molecule activator of the LDL-R promoter identified; thus, its chemical synthesis[11] posed significant values to many scientists engaging on serum cholesterol research.

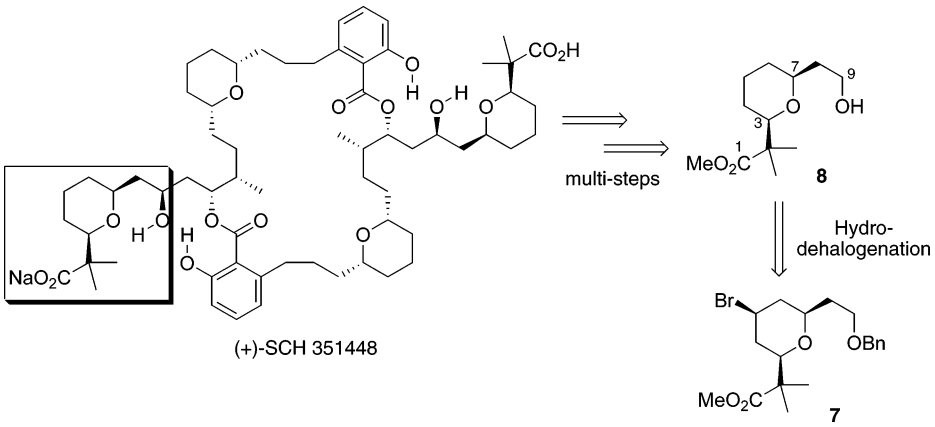
Our focus centered on the C1−C9 THP fragment of (+)-SCH 351448. This is an excellent candidate for the demonstration of hydrodehalogenation, since the 4-bromo precursor **7** can be easily synthesized from catalytic Prins cyclization using TMSBr as additive. The intermediate was subjected to the one-pot base-mediated hydrogenation to yield the desired product **8** in 68% yield (Scheme 3). Since this fragment is in the early stage toward the total synthesis of (+)-SCH 351448, scale-up reaction[12] in multigram quantity is convenient and viable without a significant compromise in yield.

SCHEME 4. Radical Dehalogenation Strategy in the Synthesis of Intermediate 8[a]

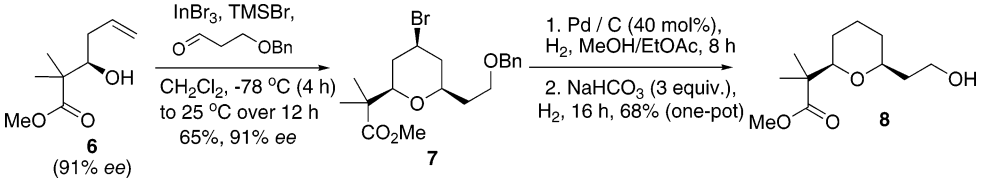


[a] The yield included stannane byproduct, which could not be removed despite several purification processes.

SCHEME 2. Retrosynthesis of (+)-SCH 351448



SCHEME 3. Hydrodehalogenation in the Synthesis of Key Intermediate 8 of (+)-SCH 351448



A comparison was studied between this strategy and the conventional radical dehalogenation pathway using Bu_3SnH (initiated by ACCN[13]). The results (Scheme 4) showed that a two-step dehalogenation followed by debenzylation (route **a**) failed to yield the desired product **8** due to contamination with stannane byproducts even after chromatographic purification. On the other hand, hydrogenation of the 4-bromo-THP **7** yielded 83% of the deprotected bromo alcohol (route **b**). However, the radical debromination which was carried out over 48 h failed to obtain the product cleanly despite several purification processes via flash column chromatography.

Conclusion

In conclusion, a highly chemoselective hydrodehalogenation protocol has been established for 4-halo-THP substrates. Investigation on the mechanism of this reaction revealed that it was unlikely to follow a halide-elimination pathway. Instead, an atom exchange process assisted by palladium might have taken place. The application of this method has been demonstrated in the enantioselective synthesis of the key intermediate toward (+)-SCH 351448.

Experimental

General Procedure for Hydrodehalogenation of 4-Halobenzoxytetrahydro-2*H*-pyran (1a−3c). To a 25 mL round-bottom flask equipped with a magnetic stirring bar was charged 10% Pd in carbon (0.122 g, 0.11 mmol, 0.4 equiv) in methanol (2.57 mL). 4-Halo-6-cyclohexyltetrahydro-2*H*-pyran (0.28 mmol) in ethyl acetate (0.28 mL) was added to the mixture and was allowed to stir under hydrogen atmosphere for 8 h. Sodium bicarbonate (47 mg, 0.56 mmol) was the added to the reaction mixture and was stirred under hydrogen atmosphere for another 16 h. The mixture was filtered through Celite and was then concentrated in vacuo. The residue was diluted with ethyl acetate (5 mL) prior to washing with water (2 × 5 mL) followed by brine solution (2 × 5 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residual crude product was purified via flash column chromatography to afford the dehalotetrahydropyran.

2-(6-Cyclohexyltetrahydro-2*H*-pyran-2-yl)ethanol (1b): colorless oil (55 mg, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (t, J = 4.8 Hz, 2H), 3.58−3.50 (m, 1H), 3.20 (br s, 1H), 3.07 (ddd, J = 11.2, 6.4, 1.9 Hz, 1H), 1.88−1.78 (m, 3H), 1.76−1.66 (m, 5H), 1.65−1.55 (m, 4H), 1.52−1.46 (m, 3H), 1.31−1.23 (m, 2H), 0.97−0.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.6, 79.2, 62.0, 43.0, 37.8, 31.7, 29.0, 29.0, 28.1, 26.5, 26.2, 26.1, 23.6; FTIR (neat) ν_{max} 3370, 2928, 2853, 1449, 1084, 1042, 733 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{24}O_2$ [M$^+$] = 212.1771, found 212.1763.

General Procedure for Hydrodehalogenation of *meso*-4-Halotetrahydro-2*H*-pyran (4 and 5). To a 25 mL round-bottom flask equipped with a magnetic stirring bar was charged 10% Pd in carbon (0.122 g, 0.11 mmol, 0.4 equiv) and sodium bicarbonate (47 mg, 0.56 mmol) in methanol (2.57 mL). *meso*-4-Halotetrahydro-2*H*-pyran (0.28 mmol) in ethyl acetate (0.28 mL) was added to the mixture and was allowed to stir under hydrogen atmosphere for 16 h. The mixture was filtered through Celite and was then concentrated in vacuo. The residue was diluted with ethyl acetate (5 mL) prior to washing with water (2 × 5 mL) followed by brine solution (2 × 5 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated in vacuo. The residual crude product was purified via flash column chromatography to afford the dehalotetrahydropyran.

2,6-Dicyclohexyltetrahydro-2*H*-pyran (4): colorless oil (55 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.89 (ddd, J = 11.0, 7.9, 1.4 Hz, 2H), 2.07−1.96 (m, 2H), 1.88−1.80 (m, 1H), 1.74−1.71 (m, 2H), 1.71−1.66 (m, 3H), 1.66−1.60 (m, 4H), 1.30−1.22 (m, 6H), 1.22−1.12 (m, 6H), 1.01−0.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.4, 43.3, 29.4, 29.0, 28.9, 26.7, 26.3, 26.1, 24.0; FTIR (neat) ν_{max} 2920, 2849, 1449, 1263, 1084, 1072, 1045, 743 cm^{-1}; HRMS (EI) m/z calcd for $C_{17}H_{30}O$ [M$^+$] 250.2297, found 250.2291.

Application to Enantioselective Synthesis of (+)-SCH 351448. Methyl 2-((2*R*,4*S*,6*R*)-6-(2-(Benzyloxy)ethyl)-4-bromotetrahydro-2*H*-pyran-2-yl)-2-methylpropanoate (7). To a solution of homoallylic alcohol **6** (0.88 g, 5 mmol) in dichloromethane (50 mL) was added $InBr_3$ (0.18 g, 0.5 mmol, 0.1 equiv) at 0 °C. The solution was allowed to cool to −78 °C, and trimethylsilyl bromide (0.78 mL, 6 mmol, 1.2 equiv) was added dropwise. The solution was stirred for 1 min and was treated with a solution of 3-(benzyloxy)propanal in dichloromethane (5 mL). The reaction mixture was allowed to stir at −78 °C for 4 h and was allowed to warm gradually to room temperature. The reaction was allowed to proceed for another 12 h prior to quenching with saturated sodium bicarbonate solution (15 mL). The aqueous layer was extracted with diethyl ether (3 × 30 mL), and the combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residual crude product was purified by flash column chromatography (hexane/ether, 25:1) to afford the 4-bromo-THP product as a colorless oil (1.30 g, 65% yield, 91% ee): R_f = 0.59 (4:1 hexane/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.47, (s, 2H), 4.15, (tt, J = 12.0, 4.4 Hz, 1H), 3.64 (s, 3H), 3.55−3.51 (m, 1H) 3.51 (dd, J = 11.7, 4.1 Hz, 1H), 3.50 (t, J = 5.7 Hz, 2H), 2.19 (tdd, J = 12.4, 4.4, 2.1 Hz, 1H), 2.12 (tdd, J = 12.4, 4.4, 2.1 Hz, 1H), 1.77−1.67 (m, 4H), 1.17 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 138.4, 128.4, 127.7, 127.6, 81.5, 74.6, 73.1, 66.5, 51.9, 47.0, 46.5, 43.4, 37.6, 35.9, 20.8, 20.6; FTIR (neat) ν_{max} 2949, 1732, 1275, 1194, 1070, 737, 698 cm^{-1}; HRMS (EI) m/z calcd for $C_{19}H_{27}BrO_4$ [M$^+$] = 398.1087, found 398.1077; $[\alpha]^{23}_D$ +4.2 (*c* 1.65, CH_2Cl_2). The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel ODH column (*n*-hexane/2-propanol 99:1, 1.0 mL/min): t_1 = 8.5 min (minor), t_2 = 14.1 min (major).

Methyl 2-((2*R*,6*S*)-Tetrahydro-6-(2-hydroxyethyl)-2*H*-pyran-2-yl)-2-methylpropanoate (8). To an oven-dried 100 mL round-bottom flask equipped with a magnetic stirring bar was added Pd/C (10% w/w, 2.22 g, 0.3 equiv), and the mixture was flushed with nitrogen before cooling to 0 °C. Methanol (63 mL) was added slowly to the solid with stirring at a minimum speed of 500 rpm. The suspension was allowed to warm to room temperature, and an ethyl acetate (7 mL) solution of 4-bromo-THP methyl ester **7** (2.80 g, 7 mmol) was added. The mixture was allowed to proceed under a H_2 atmosphere introduced through a balloon for 8 h. The reaction mixture was subsequently treated with $NaHCO_3$ (1.76 g, 21 mmol, 3 equiv) and was allowed to stir under H_2 atmosphere for another 16 h. The mixture was filtered through a pad of Celite and flushed with 300 mL of dichloromethane. The solution was concentrated in vacuo and was dissolved in 50 mL of diethyl ether. The organic layer was washed with H_2O (3 × 20 mL) and brine (20 mL) and dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residual crude product was purified by flash column

(10) Hedge, V. R.; Puar, M. S.; Dai, P.; Patel, M.; Gullo, V. P.; Das, P. R.; Bond, R. W.; McPhail, A. T. *Tetrahedron Lett.* **2000**, *41*, 1351.

(11) For other syntheses of (+)-SCH 351448, see: (a) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.* **2004**, *126*, 2680. (b) Soltani, O.; De Brabander, J. K. *Org. Lett.* **2005**, *7*, 2791. (c) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481. (d) Bolshakov, S.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 3809. (e) Backes, J. R.; Koert, U. *Eur. J. Org. Chem.* **2006**, *12*, 2777. (f) Crimmins, M. T.; Grace, S. *Org. Lett.* **2006**, *8*, 2887.

(12) The reaction has been demonstrated to up to 30 mmol scale with the final product (**8**) yield of 66%.

(13) ACCN denotes 1,1′,-azobis(cyclohexane)carbonitrile, a synthetic equivalent to AIBN.

chromatography (hexane/ethyl acetate, 8:1) to afford the THP−alcohol product as colorless oil (1.10 g, 68% yield): $R_f = 0.13$ (4:1 hexane/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73−3.69 (m, 2H), 3.68 (s, 3H), 3.58−3.52 (m, 2H), 2.80 (br s, 1H), 1.90−1.84 (m, 1H), 1.77−1.73 (m, 1H), 1.71−1.67 (m, 2H), 1.53−1.47 (m, 2H), 1.31−1.23 (m, 2H), 1.16 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 177.5, 83.0, 79.3, 61.6, 51.9, 46.6, 38.0, 31.5, 24.8, 23.4, 21.9, 19.7; FTIR (neat) ν_{max} 3446, 2943, 2860, 1732, 1437, 1271, 1088, 1047 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{12}H_{22}O_4$ [M^+] = 230.1513, found 230.1507; $[\alpha]^{23}_D$ +8.8 (*c* 1.55, CH_2Cl_2).

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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