Stereoselective Synthesis of 4-*O*-Tosyltetrahydropyrans via Prins Cyclization Reaction of Enol Ethers

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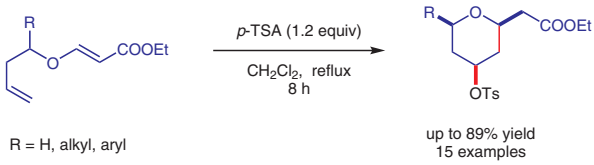

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Abstract Intramolecular cyclization of enol ethers mediated by *para*-toluenesulfonic acid leads to substituted tetrahydropyrans in good to moderate yields. The reaction is diastereoselective.

Key words tosyl tetrahydropyrans, Prins reaction, enol ether, cyclization, heterocycle

Saturated six-membered cyclic ethers, better known as tetrahydropyrans (THPs), are ubiquitous in nature and represent useful precursors for the synthesis of many biologically active molecules.[1] For example, neopeltolide **1** is a marine natural product isolated from *Neopeltidae*, collected from the north Jamaican coast. It inhibits cancer cell lines such as A-549 human lung adenocarcinoma, human ovarian sarcoma, and murine leukaemia, with IC_{50} of 1.2, 5.1, and 0.56 nM, respectively. It also inhibits the growth of the fungal pathogen *Candida albicans* with an inhibitory concentration of 0.62 μg mL^{-1}.[2] 4-Hydroxytetrahydropyran-containing natural products, catechols **2** and **3**, isolated from extracts of *Plectranthus sylvestris* (*labiatae*), a plant found in the woody hills in East Africa, are potent antioxidants and possess anti-inflammatory properties.[3] Similarly, apicularen A **4**, isolated from various strains of the myxobacterial genus *Chondromycesand* shows antiproliferative properties against cancer cell lines such as ovarian, prostate, lung, kidney, cervix, leukaemia, and histiocytic cells with IC_{50} values 0.23–6.79 μM. It is a novel antiangiogenic agent and may suppress growth of tumors in a dose-dependent manner (Figure 1).[4]

Over the years, the 4-substituted tetrahydropyran rings have been constructed via Lewis or Brønsted acid catalyzed/mediated Prins reaction of homoallyl alcohols and aldehydes followed by trapping with various nucleophiles such as hydroxide,[5] halide,[6] aryl,[7] tosyl,[8] and nitrile[9] groups. An earlier report has described the synthesis of 4-hydroxytetrahydropyrans via hydroxyl-Prins cyclization of homoallyl acryloyl ethers mediated by TFA and K_2CO_3.[10]

We have reported the stereoselective synthesis of dihydropyrans, tetrahydrofurans, and tetrahydrothiophenes via Prins reaction of homoallyl, homopropargyl alcohols and thiols.[11] We have also studied the dual role of *p*-TSA as an activator as well as a nucleophile in the aza-Prins cyclization reaction.[12] Based on our experience in Prins cyclization

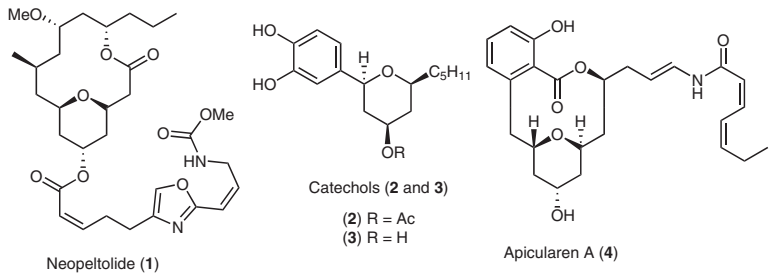


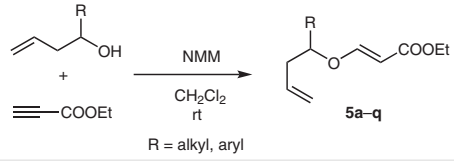
Figure 1 Some biologically active tetrahydropyrans

reactions, we envisaged that *p*-TSA could act as a nucleophile and activator in a Prins cyclization reaction of acryloyl ethers. Herein, we wish to report a mild and efficient approach for the synthesis of 4-*O*-tosyl tetrahydropyrans via Prins reaction of acryloyl enol ethers mediated by *p*-toluenesulfonic acid (*p*-TSA), which acts as an activator as well as a nucleophile.

Initially, we reacted (*E*)-ethyl 3-(but-3-en-1-yloxy)acrylate **5a** with 1.2 equivalents of *p*-TSA acid in dichloromethane at reflux, and the reaction proceeded smoothly to afford ethyl 2-((2*R**,4*S**)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (**6a**) in 68% yield as a mixture of 2,4,6-*cis* and 2,4- and 4,6-*trans* isomers in a ratio of 93:7, with the stereoisomer having the all-*cis* relationship being the major component. Catalytic amounts of *p*-TSA were found to be inefficient, and excess *p*-TSA (more than 1.2 equiv.) produced a mixture of products. It was also found that only CH_2Cl_2 is a suitable solvent; other polar protic solvents such as CH_3OH, EtOH, CH_3COOH and polar aprotic solvents such as CH_3CN, THF, DMF, DMSO did not result in the desired product.

To investigate the substrate scope with these optimal reaction conditions, a variety of homoallyl acryloyl ethers was synthesized according to reported methods by Michael addition of homoallyl alcohols to ethyl propiolate using *N*-methyl morpholine (NMM) as a base in dichloromethane at ambient temperature. (Scheme 1).[11b]

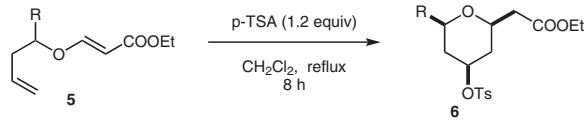
These acryloyl enol ethers were subjected to *p*-TSA-mediated Prins cyclization; the results are shown in Table 1. Both aliphatic and aromatic substituted acryloyl ethers worked well and produced moderate to high yields of cyclized material with high diastereoselectivity. Substrates having aromatic substituents (entries 2–6, 9–12, 16) gave higher yields compared with aliphatic substrates (entries 8, 13–14 and 17). Substrates having aromatic substituents with highly electron-donating (entry 7) or electron-withdrawing groups (entry 15) did not furnish the desired products. This might be due to the interaction of the acid with methoxy[13] and nitro[14] groups of the aromatic aldehydes.



Scheme 1 Synthesis of starting materials

The reaction is highly diastereoselective, with a *cis*-relationship among the substituents on the tetrahydropyran ring. The diastereoselectivity was confirmed by ^1H and ^{13}C NMR spectroscopic analysis of the crude product, and the *cis* stereochemistry was determined based on NOE analysis of compound **6f**. A strong NOE between hydrogen at C-2 and C-4 as well as interaction between C-2 and C-6 clearly suggests all substituents are in a *cis* relationship (Scheme 2).

Table 1 Synthesis of *O*-Tosylated Tetrahydropyrans via Prins Cyclization Reaction



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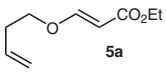
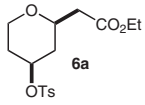
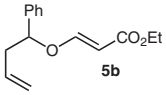
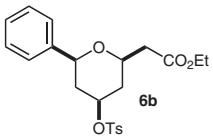
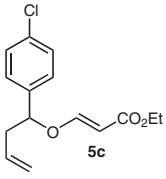
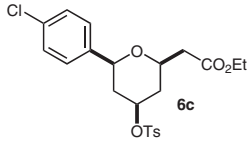
1	 5a	 6a	93:7	68
2	 5b	 6b	93:7	74
3	 5c	 6c	99:1	79

Table 1 (continued)

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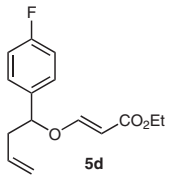
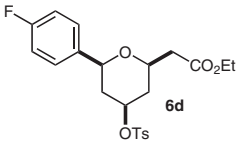
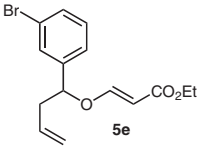
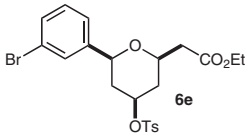
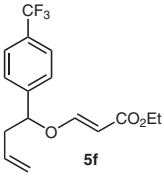
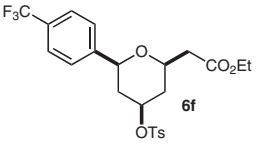
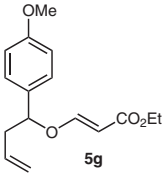
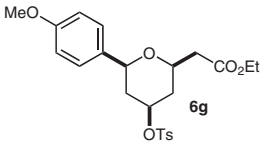
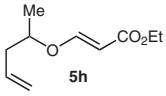
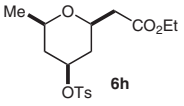
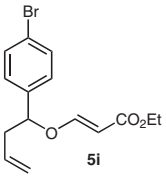
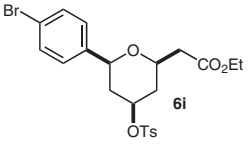
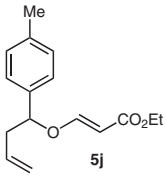
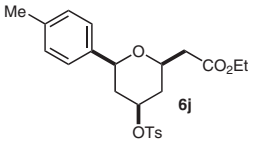
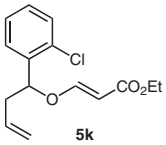
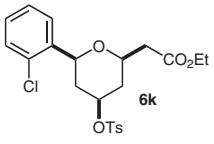
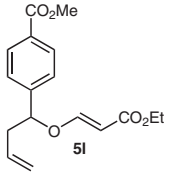
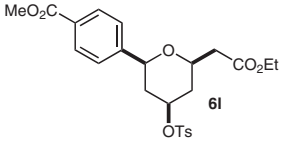
4	 **5d**	 **6d**	95:5	76
5	 **5e**	 **6e**	95:5	84
6	 **5f**	 **6f**	98:2	89
7	 **5g**	 **6g**	–	0
8	 **5h**	 **6h**	86:14	74
9	 **5i**	 **6i**	92:8	75
10	 **5j**	 **6j**	96:4	62
11	 **5k**	 **6k**	92:8	72
12	 **5l**	 **6l**	96:4	64

Table 1 (continued)

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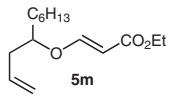
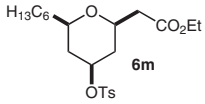
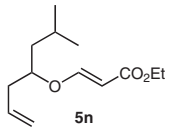
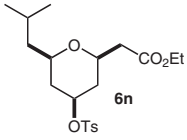
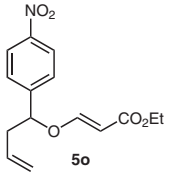
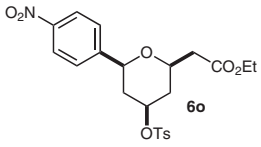
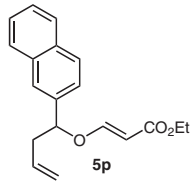
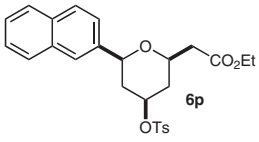
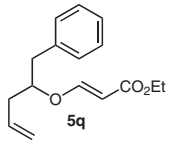
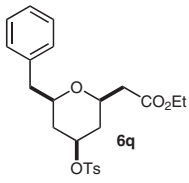
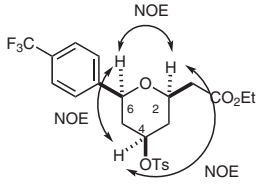
13	 5m	 6m	82:18	54
14	 5n	 6n	93:7	52
15	 5o	 6o	–	0
16	 5p	 6p	90:10	64
17	 5q	 6q	100:0	54

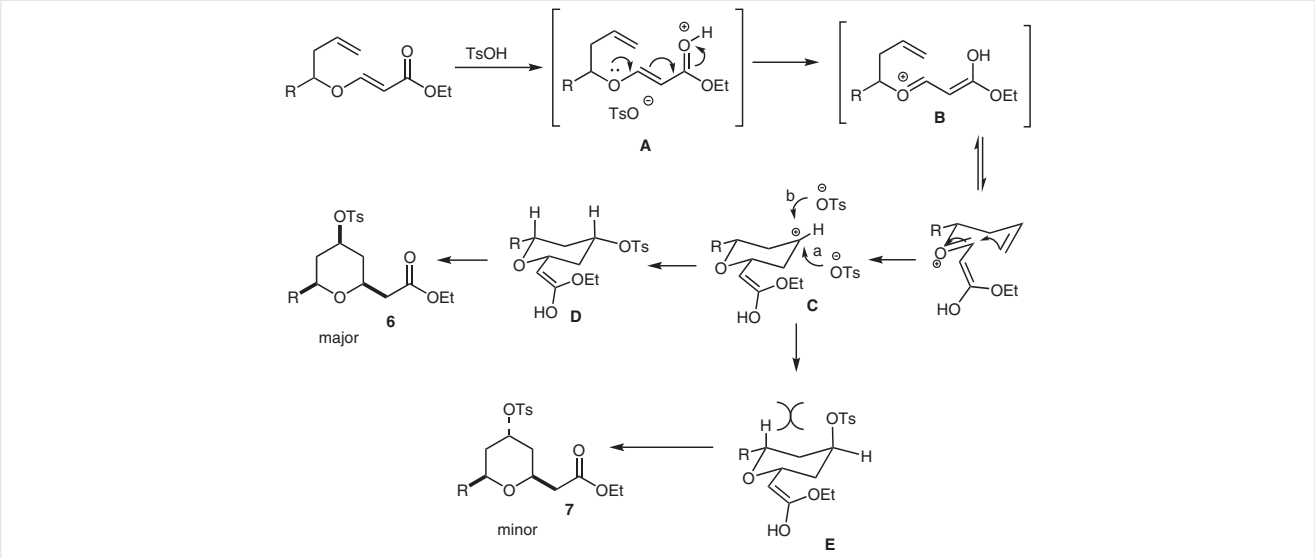
[a] Ratio determined by ^{1}H NMR analysis.
[b] Yield refers to isolated yield.



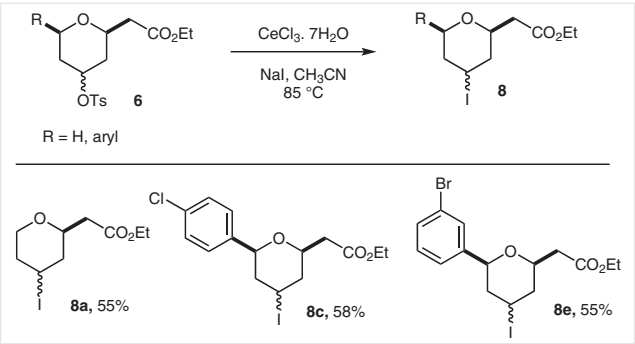
Scheme 2 Key NOE enhancements of (2*R**,4*S**,6*S**)-ethyl 4-(tosyloxy)-6-(4-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran-2-carboxylate (**6f**)

A mechanism proposed for the diastereoselectivity of the reaction involves *p*-TSA protonating the carbonyl group of the ester, leading to formation of oxocarbenium ion **B**, which, after Prins cyclization, forms tetrahydropyranyl cation **C** (Scheme 3). The tosyl nucleophile attacks carbocation **C** equatorially, to give **6** as the major product and **7** as the minor product. This might be due to the lower steric repulsion between the C-2H and C-4H hydrogens compared with intermediate **E**, where there is a strong steric repulsion between the C-2H hydrogen and the C-4 tosyl group.

This methodology was further extended to the synthesis of 4-iodotetrahydropyrans (Scheme 4). Thus, the reaction of 4-tosyl tetrahydropyrans **6a**, **6c**, and **6e** with cerium(III) chloride heptahydrate and sodium iodide in acetonitrile at 85 °C gave the corresponding 4-iodotetrahydropyrans **8a**, **8c**, and **8e** in moderate yields. 2,4-Disubstituted tosyltetrahydropyran **6a** gave a single diastereomer **8a** (55%); whereas 2,4,6-trisubstituted tosyltetrahydropyrans **6c** (58%) and **6e** (55%) gave inseparable mixture of diastereomers **8c** and **8e** with a ratio of 65:35 and 67:33, respectively.

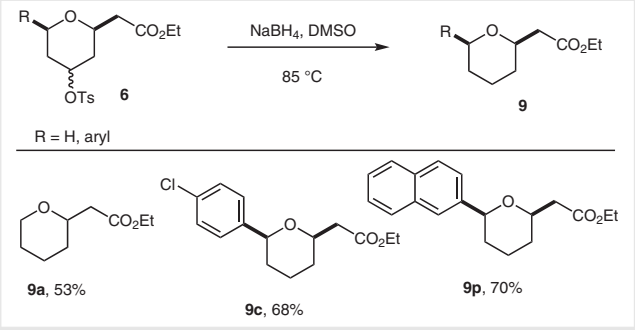


Scheme 3 Plausible reaction mechanism



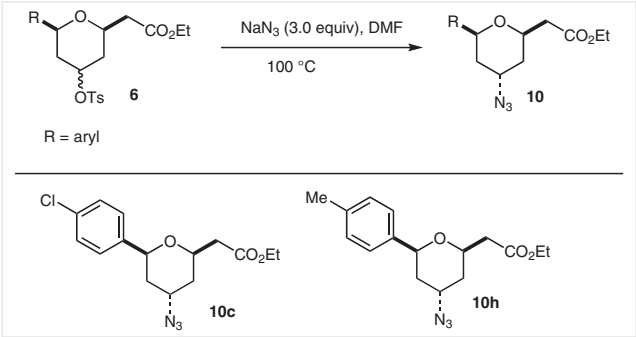
Scheme 4 Synthesis of 4-iodotetrahydropyran

Similarly, the tosyl group of the 4-tosyl tetrahydropyrans **6a**, **6c**, and **6p** can be reduced by sodium borohydride in dimethylsulfoxide at 85 °C to give **9a**, **9c**, and **9p** in 53, 68, and 70% yields, respectively (Scheme 5).



Scheme 5 Detosylation of 4-tosyltetrahydropyran

The tosyl group of the 4-tosyl tetrahydropyran can also be substituted with an azide group (Scheme 6). Compounds **6c** and **6h**, when treated with sodium azide in DMF at 100 °C, provided the corresponding azido compounds **10c** and **10h** in 66 and 60% yields, respectively, with inversion of configuration at C-4. The configuration of the compounds was determined by NOE analysis of compound **10c**. It is noteworthy that the reaction gave only a single diastereomer.



Scheme 6 Synthesis of 4-azidotetrahydropyrans

In conclusion, a methodology for the stereoselective synthesis of tosyl substituted tetrahydropyrans through Prins cyclization reaction of acryloyl enol ethers has been developed. Good yields are achieved with high diastereoselectivity. This methodology will be useful for the synthesis of other substituted pyran rings such as 4-iodotetrahydropyrans and 2,6-disubstituted tetrahydropyrans by substitution or reduction of the tosyl functionality, respectively. The tosyl group can also be replaced by an azido group to prepare 4-azidotetrahydropyrans with inversion of configuration at the 4-position.

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60–120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were determined with a Büchi B-540 melting point apparatus. IR spectra were recorded with a Fourier transform infrared (FTIR) spectrometer either as a neat liquid or as KBr pellets. NMR spectra were obtained with 400 MHz (^{1}H, 400 MHz and ^{13}C, 100 MHz) and 600 MHz (^{1}H, 600 MHz and ^{13}C, 150 MHz) instruments using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were measured with a Q-TOF mass analyzer.

Synthesis of Starting Materials

The homoallyl acryloyl ethers were synthesized by following the reported procedure and the structures and purities of known compounds **5a–q** were confirmed by comparison of their spectroscopic data (^{1}H NMR and ^{13}C NMR) with reported data.[11b]

Synthesis of 4-Tosyloxy Tetrahydropyrans; Typical Procedure

To (*E*)-ethyl 3-(but-3-en-1-yloxy) acrylate (340 mg, 0.5 mmol) in dichloromethane (3 mL) was added *p*-toluenesulfonic acid monohydrate (408 mg, 0.6 mmol). The reaction mixture was heated to reflux for 8 h and the progress of the reaction was monitored by TLC (EtOAc/hexane, 1:4). Upon completion, the reaction was quenched with aq $NaHCO_3$, extracted (EtOAc), washed with brine, dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel, eluting with EtOAc/hexane to give ethyl 2-((2*R**,4*S**)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (**6a**) in 68% yield.

Ethyl 2-((2*R**,4*S**)-4-(Tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6a, Diastereomeric Mixture, 93:7)

Yield: 112 mg (68%); pale-yellow gum.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 1.46–1.52 (m, 1 H), 1.67–1.75 (m, 2 H), 1.84–1.88 (m, 1 H), 1.97–2.00 (m, 1 H), 2.36 (dd, *J* = 15.6, 5.4 Hz, 1 H), 2.45 (s, 3 H), 2.52 (dd, *J* = 15.6, 8.4 Hz, 1 H), 3.36 (dd, *J* = 12.0, 1.2 Hz, 1 H), 3.69–3.75 (m, 1 H), 3.96 (dd, *J* = 12.0, 4.2 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.56–4.62 (m, 1 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 7.79 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.3, 21.8, 32.6, 38.1, 41.1, 60.9, 65.6, 72.6, 77.9, 127.8, 130.1, 134.5, 145.0, 170.7.

IR (KBr, neat): 2968, 2863, 1738, 1598, 1362, 1175, 1083, 899, 670, 576 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{16}H_{23}O_6S$: 343.1210; found: 343.1239.

Ethyl 2-((2*R**,4*R**,6*S**)-6-Phenyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6b, Diastereomeric Mixture, 93:7)

Yield: 150 mg (74%); white solid, mp 87–89 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 1.55–1.60 (m, 1 H), 1.68–1.74 (m, 1 H), 2.06–2.10 (m, 1 H), 2.21–2.24 (m, 1 H), 2.45 (s, 3 H), 2.46 (dd, *J* = 15.6, 6.0 Hz, 1 H), 2.65 (dd, *J* = 15.6, 7.8 Hz, 1 H), 3.92–3.96 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.37 (d, *J* = 10.8 Hz, 1 H), 4.75–4.80 (m, 1 H), 7.26–7.36 (m, 7 H), 7.81 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.3, 21.8, 37.6, 39.6, 40.8, 41.0, 41.1, 60.8, 60.9, 72.3, 78.0, 126.0, 127.8, 127.9, 128.0, 128.5, 128.6, 130.1, 134.4, 140.8, 145.0, 170.7.

IR (KBr, neat): 2873, 1735, 1598, 1413, 1366, 1176, 1097, 956, 758, 669, 579 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{27}O_6S$: 419.1536; found: 419.1536.

Ethyl 2-((2*R**,4*R**,6*S**)-6-(4-Chlorophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6c, Diastereomeric Mixture, 99:1)

Yield: 173 mg (79%); pale-yellow gum.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 1.52–1.59 (m, 1 H), 1.62–1.68 (m, 1 H), 2.06–2.09 (m, 1 H), 2.20–2.23 (m, 1 H), 2.45 (s, 3 H), 2.46 (dd, *J* = 15.6, 5.4 Hz, 1 H), 2.63 (dd, *J* = 15.6, 7.2 Hz, 1 H), 3.92–3.94 (m, 1 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 3.35 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.75–4.79 (m, 1 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.3, 21.9, 37.5, 39.7, 41.0, 60.9, 72.4, 76.5, 77.6, 127.3, 127.8, 128.7, 130.1, 133.7, 134.3, 139.4, 145.1, 170.6.

IR (KBr, neat): 2927, 2854, 1738, 1599, 1494, 1189, 1090, 956, 815, 757, 667, 555 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{26}ClO_5S$: 453.1133; found: 453.1123.

Ethyl 2-((2*R**,4*R**,6*S**)-6-(4-Fluorophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6d, Diastereomeric Mixture, 95:5)

Yield: 160 mg (76%); pale-yellow gum.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 1.53–1.56 (m, 1 H), 1.65–1.71 (m, 1 H), 2.05–2.09 (m, 1 H), 2.21–2.24 (m, 1 H), 2.45 (dd, *J* = 15.6, 5.4 Hz, 1 H), 2.46 (s, 3 H), 2.64 (dd, *J* = 15.6, 7.2 Hz, 1 H), 3.91–3.95 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.35 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.74–4.80 (m, 1 H), 7.00 (t, *J* = 8.4 Hz, 2 H), 7.22–7.25 (m, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 21.9, 37.6, 39.7, 41.0, 60.9, 72.4, 76.6, 77.8, 115.4 (d, *J* = 19.5 Hz), 127.6 (d, *J* = 7.5 Hz), 127.9, 130.1, 134.4, 136.7, 145.1, 162.5 (d, *J* = 246.0 Hz), 170.6.

IR (KBr, neat): 2928, 1733, 1599, 1367, 1176, 1085, 768, 668, 551 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{26}FO_6S$: 437.1429; found: 437.1435.

Ethyl 2-((2*R**,4*R**,6*S**)-6-(3-Bromophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6e, Diastereomeric Mixture, 95:5)

Yield: 202 mg (84%); pale-yellow gum.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 1.41–1.47 (m, 1 H), 1.56–1.62 (m, 1 H), 2.12–2.16 (m, 1 H), 2.24–2.28 (m, 1 H), 2.45 (s, 3 H), 2.49 (dd, *J* = 15.6, 5.4 Hz, 1 H), 2.65 (dd, *J* = 15.6, 7.8 Hz, 1 H), 3.96–4.00 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.60 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.75–4.81 (m, 1 H), 7.09–7.13 (m, 1 H), 7.29 (t, *J* = 7.2 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.44–7.47 (m, 2 H), 7.81 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 21.9, 37.7, 38.2, 41.2, 60.9, 72.5, 76.4, 77.7, 121.6, 127.6, 127.9, 129.3, 130.2, 132.7, 134.4, 140.1, 145.1, 170.5.

IR (KBr, neat): 2980, 2929, 1735, 1598, 1495, 1366, 1177, 1078, 957, 815, 770, 667, 556 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{26}Br^{81}O_6S$: 499.0608; found: 499.0628.

Ethyl 2-((2*R,4*R**,6*S**)-4-(Tosyloxy)-6-(4-(trifluoromethyl)phenyl)-tetrahydro-2*H*-pyran-2-yl)acetate (6f, Diastereomeric Mixture, 98:2)**

Yield: 210 mg (89%); white solid; mp 120–122 °C.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 1.55–1.61 (m, 1 H), 1.62–1.69 (m, 1 H), 2.07–2.10 (m, 1 H), 2.25–2.29 (m, 1 H), 2.46 (s, 3 H), 2.47 (dd, *J* = 15.6, 5.4 Hz, 1 H), 2.65 (dd, *J* = 15.6, 7.8 Hz, 1 H), 3.94–3.68 (m, 1 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 4.44 (dd, *J* = 11.4, 1.8 Hz, 1 H), 4.77–4.82 (m, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 21.9, 37.5, 39.8, 41.0, 60.9, 72.5, 76.5, 77.5, 125.5, 126.2, 126.8 (q, *J* = 270.0 Hz), 127.9, 130.1, 130.2 (q, *J* = 36 Hz), 134.3, 144.8, 145.2, 170.6.

IR (KBr, neat): 2930, 2860, 1735, 1622, 1599, 1370, 1163, 1018, 841, 759, 671, 555 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{23}H_{26}F_3O_6S$: 487.1397; found: 487.1388.

Ethyl 2-((2*R,4*S**,6*R**)-6-Methyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6h, Diastereomeric Mixture; 86:16)**

Yield: 263 mg (74%); yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.2 Hz, 3 H), 1.17 (t, *J* = 7.2, 3 H), 1.25–1.37 (m, 2 H), 1.84–1.90 (m, 2 H), 2.28 (dd, *J* = 15.4, 5.4 Hz, 1 H), 2.36 (s, 3 H), 2.46 (dd, *J* = 15.4, 7.6 Hz, 1 H), 3.34–3.36 (m, 1 H), 3.64–3.75 (m, 1 H), 4.06 (q, *J* = 7.2 Hz, 2 H), 4.48–4.55 (m, 1 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.79 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.2, 21.4, 21.7, 37.3, 39.5, 40.9, 60.2, 71.5, 71.7, 77.9, 127.6, 127.7, 129.9, 134.3, 144.8, 170.6.

IR (KBr, neat): 2961, 2862, 1730, 1594, 1360, 1174, 1081, 894, 671, 572 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{17}H_{25}O_6S$: 357.1366; found: 357.1364.

Ethyl 2-((2*R,4*R**,6*S**)-6-(4-Bromophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6i, diastereomeric mixture; 92:8)**

Yield: (372 mg, 75%); reddish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 1.51–1.69 (m, 2 H), 2.04–2.09 (m, 1 H), 2.18–2.26 (m, 1 H), 2.46 (s, 3 H), 2.47 (dd, *J* = 15.0, 7.2 Hz, 1 H), 2.65 (dd, *J* = 15.0, 7.8 Hz, 1 H), 3.90–3.96 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.35 (d, *J* = 10.5 Hz, 1 H), 4.71–4.80 (m, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.41 (d, *J* = 8.0 Hz, 2 H), 7.80 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 21.9, 37.5, 39.7, 41.0, 60.9, 72.4, 76.4, 77.6, 122.7, 124.5, 127.9, 129.1, 130.2, 134.3, 143.0, 145.1, 176.8.

IR (KBr, neat): 2932, 2862, 1739, 1628, 1600, 1374, 1169, 1012, 842, 758, 679, 559 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{26}BrO_6S$: 497.0628; (Br79); found: 497.0640.

Ethyl 2-((2*R,4*R**,6*S**)-6-(*p*-Tolyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6j, diastereomeric mixture; 96:4)**

Yield: 267 mg (64%); yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 1.51–1.60 (m, 1 H), 1.64–1.75 (m, 1 H), 2.10 (d, *J* = 10.0 Hz, 1 H), 2.22 (d, *J* = 10.0 Hz, 1 H), 2.33 (s, 3 H), 2.47 (s, 3 H), 2.63–2.70 (m, 1 H), 3.91–3.95 (m, 1 H), 4.10–4.16 (m, 2 H), 4.32–4.38 (m, 1 H), 4.75–4.85 (m, 1 H), 7.13–7.18 (m, 4 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.82 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 21.3, 21.9, 37.7, 39.6, 41.1, 60.8, 72.3, 77.0, 78.2, 126.0, 127.8, 129.3, 130.1, 134.4, 137.8, 137.9, 145.0, 170.7.

IR (KBr, neat): 2932, 2865, 1734, 1621, 1594, 1371, 1162, 1012, 842, 754, 672, 5556 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{23}H_{29}O_6S$: 433.1679; found: 433.1693.

Ethyl 2-((2*R,4*R**,6*S**)-6-(2-Chlorophenyl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6k, Diastereomeric Mixture; 92:8)**

Yield: 326 mg (72%); yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.2 Hz, 3 H), 1.43–1.50 (m, 1 H), 1.56–1.62 (m, 1 H), 2.11–2.14 (m, 1 H), 2.23–2.26 (m, 1 H), 2.43 (s, 3 H), 2.48 (dd, *J* = 15.6, 5.4 Hz, 1 H), 2.65 (dd, *J* = 15.6, 7.2 Hz, 1 H), 3.96–4.00 (m, 1 H), 4.10 (q, *J* = 7.2 Hz, 2 H), 4.67 (dd, *J* = 12.0, 1.6 Hz, 1 H), 4.76–4.81 (m, 1 H), 7.16–7.18 (m, 1 H), 7.22–7.27 (m, 2 H), 7.34 (d, *J* = 7.8 Hz, 2 H), 7.46 (d, *J* = 7.8 Hz, 1 H), 7.80 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 14.5, 21.6, 21.9, 35.6, 37.6, 37.7, 39.7, 41.1, 41.3, 60.7, 60.8, 68.3, 68.8, 71.7, 71.9, 76.9, 78.1, 127.8 (4C), 127.9 (4C), 130.2, 134.5, 145.0, 170.9.

IR (KBr, neat): 2926, 2853, 1738, 1, 1598, 1474, 1362, 1189, 1097, 814, 793 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{26}ClO_6S$: 453.1133; found: 453.1117.

Methyl 4-((2*S,4*R**,6*R**)-6-(2-Ethoxy-2-oxoethyl)-4-(tosyloxy)-tetrahydro-2*H*-pyran-2-yl)benzoate (6l, Diastereomeric Mixture; 96:4)**

Yield: 305 mg (64%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 1.50–1.70 (m, 2 H), 1.98–2.10 (m, 1 H), 2.24–2.27 (m, 1 H), 2.33–2.36 (m, 1 H), 2.46 (s, 3 H), 2.63–2.67 (m, 1 H), 3.90 (s, 3 H), 4.07–4.13 (m, 3 H), 4.41 (d, *J* = 10.8 Hz, 2 H), 4.70–4.80 (m, 1 H), 7.34 (t, *J* = 16.2 Hz, 4 H), 7.80 (d, *J* = 9.0 Hz, 2 H), 7.80 (d, *J* = 8.4, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.3, 14.4, 21.9, 37.4, 39.7, 41.0, 61.0, 72.1, 76.7, 77.1, 125.6, 125.8, 127.8, 129.8, 130.1, 134.3, 145.1, 145.2, 167.0, 170.6.

IR (KBr, neat): 2938, 2861, 1734, 1626, 1594, 1372, 1161, 1012, 842, 756, 672, 559 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{24}H_{29}O_8S$: 477.1578; found: 477.1594.

Ethyl 2-((2*R,4*S**,6*R**)-6-Hexyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6m, Diastereomeric Mixture; 82:18)**

Yield: 223 mg (54%); yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 6 H), 1.22–1.42 (m, 12 H), 1.91–1.96 (m, 2 H), 2.35 (dd, *J* = 15.0, 4.8 Hz, 1 H), 2.45 (s, 3 H), 4.52 (dd, *J* = 15.0, 8.4 Hz, 1 H), 3.22–3.27 (m, 1 H), 3.68–3.72 (m, 1 H), 4.13–4.17 (m, 2 H), 4.59–4.64 (m, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.79 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.1, 14.2, 14.3, 21.7, 22.6, 25.4, 31.8, 35.7, 37.7, 38.0, 41.1, 60.5, 60.6, 60.7, 70.7, 71.8, 71.9, 75.5, 78.2, 125.1, 127.7, 128.8, 129.9, 134.4, 144.8, 170.7.

IR (KBr, neat): 2925, 2850, 1735, 1640, 1443, 1379, 1177, 1033, 952, 813, 668, 508 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{22}H_{35}O_6S$: 427.2149; found: 427.2140.

Ethyl 2-((2*R,4*R**,6*S**)-6-Isopropyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6n, Diastereomeric Mixture; 93:7)**

Yield: 207 mg (52%); orange gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 1.10–1.14 (m, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.34–1.44 (m, 2 H), 1.45–1.48 (m, 1 H), 1.68–1.72 (m, 2 H), 1.88–1.96 (m, 2 H), 2.35 (dd, *J* = 15.0, 4.8 Hz, 1 H), 2.46 (s, 3 H), 2.51 (dd, *J* = 15.0, 8.4 Hz, 1 H), 3.31–3.35 (m, 1 H), 3.68–3.73 (m, 1 H), 4.08–4.16 (m, 2 H), 4.57–4.66 (m, 1 H), 7.35 (d, *J* = 7.8 Hz, 2 H), 7.79 (d, *J* = 7.8 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 21.9, 22.1, 23.3, 24.6, 37.8, 38.6, 41.3, 44.8, 60.8, 72.1, 73.8, 78.3, 127.8, 130.1, 134.5, 145.0, 170.9.

IR (KBr, neat): 2955, 2869, 1738, 1598, 1367, 1190, 1097, 935, 844, 793, 669, 579 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{20}H_{32}O_6S$: 399.1836; found: 399.1820.

Ethyl 2-((2*R,4*R**,6*S**)-6-(Naphthalen-1-yl)-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6p, Diastereomeric Mixture; 95:5)**

Yield: 330 mg (64%); pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.0 Hz, 3 H), 1.56–1.66 (m, 1 H), 1.75–1.84 (m, 1 H), 2.09–2.15 (m, 1 H), 2.28–2.33 (m, 1 H), 2.42 (s, 3 H), 2.48 (dd, *J* = 15.6, 5.4 Hz, 1 H), 2.68 (dd, *J* = 15.6, 7.4 Hz, 1 H), 3.96–4.03 (m, 1 H), 4.11 (q, *J* = 7.0 Hz, 2 H), 4.52 (d, *J* = 10.2 Hz, 1 H), 4.79–4.87 (m, 1 H), 7.31–7.33 (m, 2 H), 7.36–7.39 (m, 1 H), 7.43–7.45 (m, 2 H), 7.71 (s, 1 H), 7.77–7.82 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (2C), 21.8, 37.6, 39.6, 41.0, 60.8, 72.4, 78.0, 124.1, 124.7, 126.1, 127.8, 128.1, 128.3, 130.1, 133.1, 133.3, 134.3, 138.2, 145.0, 170.7.

IR (KBr, neat): 2917, 2845, 1732, 1593, 1357, 1188, 1060, 955, 816, 744, 660, 552 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{26}H_{30}O_6S$: 469.1679; found: 469.1691.

Ethyl 2-((2*R,4*S**,6*R**)-6-Benzyl-4-(tosyloxy)tetrahydro-2*H*-pyran-2-yl)acetate (6q, Diastereomeric Mixture; 100:0)**

Yield: 233 mg (54%); pale-yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 3 H), 1.50–1.70 (m, 2 H), 1.98–2.10 (m, 1 H), 2.24–2.27 (m, 1 H), 2.33–2.36 (m, 1 H), 2.46 (s, 3 H), 2.63–2.67 (m, 1 H), 4.07–4.13 (m, 3 H), 4.41 (d, *J* = 10.8 Hz, 2 H), 4.70–4.80 (m, 1 H), 7.34 (t, *J* = 16.2 Hz, 4 H), 7.80 (d, *J* = 9.0 Hz, 2 H), 7.80 (m, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.3, 21.8, 37.5, 37.6, 41.2, 42.2, 60.8, 72.1, 76.3, 78.1, 126.5, 127.8 (2C), 128.4, 129.5, 129.6, 130.1, 134.5, 137.8, 145.0, 170.7.

IR (KBr, neat): 2928, 2853, 1732, 1590, 1363, 1188, 1082, 932, 838, 749, 666, 555 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd. for $C_{23}H_{30}O_6S$: 433.1679; found: 433.1693.

Synthesis of 4-Iodotetrahydropyrans; Typical Procedure

Substrate **6a** (210 mg, 0.61 mmol) and $CeCl_3 \cdot 7H_2O$ (270 mg, 0.73 mmol) in acetonitrile (2–5 mL) were treated with NaI (108 mg, 0.73 mmol) at 85 °C. The progress of the reaction was monitored by TLC until all starting materials were consumed. Upon completion, the reaction was quenched with dil. HCl, washed with brine and extracted (EtOAc, 2 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was further purified by column chromatograph, eluting with EtOAc/hexane; 5:95, to give **8a**.

Ethyl 2-((2*S,4*S**)-4-Iodotetrahydro-2*H*-pyran-2-yl)acetate (8a)**

Yield: 100 mg (55%); yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 2.00 (dd, *J* = 12.4, 12.4 Hz, 1 H), 2.22–2.25 (m, 2 H), 2.35–2.42 (m, 2 H), 2.50–2.55 (dd, *J* = 16.0, 7.7 Hz, 1 H), 3.41–3.48 (m, 1 H), 3.72–3.78 (m, 1 H), 3.81–3.85 (m, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 4.22–4.31 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 21.3, 39.6, 41.0, 45.2, 60.9, 69.5, 75.7, 170.9.

IR (KBr, neat): 28.53, 27.83, 1735, 1400, 1253, 1194, 1083, 1030, 988, 543 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{16}IO_3$: 299.0139; found: 299.0147.

Ethyl 2-((2*S,6*S**)-6-(4-Chlorophenyl)-4-iodotetrahydro-2*H*-pyran-2-yl)acetate (8c, Diastereomeric Mixture; 65:35)**

Yield: 146 mg (58%); yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.27 (m, 3 H), 1.65–1.74 (m, 1 H), 1.97–2.22 (m, 2 H), 2.44–2.55 (m, 2 H), 2.61–2.70 (m, 1 H), 3.95–4.00 (m, 2 H, minor), 4.14 (q, *J* = 7.0 Hz, 2 H), 4.34–4.38 (m, 2 H, major), 4.39–4.47 (m, 1 H, minor), 4.88–4.92 (m, 1 H, major), 7.23 (d, *J* = 8.5 Hz, 2 H), 7.30 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 14.5, 20.4, 28.9, 39.9, 40.8, 40.9, 42.3, 44.3, 46.7, 60.8, 60.9, 71.2, 75.1, 75.6, 80.0, 127.3, 127.4, 128.6, 128.7, 133.4, 133.6, 139.6, 140.3, 170.7, 170.9.

IR (KBr, neat): 3018, 1734, 1400, 1192, 1074, 819, 653, 552 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}ClIO_3$: 409.0062; found: 409.0062.

Ethyl 2-((2*S,4*R**,6*S**)-6-(3-Bromophenyl)-4-iodotetrahydro-2*H*-pyran-2-yl)acetate (8e, Diastereomeric Mixture; 67:33)**

Yield: 152 mg (55%); yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.29 (m, 3 H), 1.66–1.75 (m, 1 H), 1.98–2.23 (m, 2 H), 2.46–2.57 (m, 2 H), 2.62–2.72 (m, 1 H), 3.93–3.98 (m, 2 H, minor), 4.15 (q, *J* = 7.0 Hz, 2 H), 4.34–4.40 (m, 2 H, major), 4.41–4.50 (m, 1 H, minor), 4.88–4.92 (m, 1 H, major), 7.16–7.22 (m, 2 H), 7.37–7.41 (m, 1 H), 7. 48 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 20.2, 28.7, 29.9, 39.8, 40.8, 42.4, 44.3, 46.7, 61.0, 71.2, 75.0, 75.6, 79.8, 122.8, 124.4, 124.6, 129.0, 129.1, 130.1, 130.2, 130.7, 131.0, 143.3, 144.1, 170.8, 170.9.

IR (KBr, neat): 3010, 2859, 1734, 1401, 1194, 1070, 783 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}BrIO_3$: 452.9557; found: 452.9587.

Synthesis of Ethyl 2-(Tetrahydro-2*H*-pyran-2-yl)acetates; Typical Procedure

To a stirred solution of **6a** (200 mg, 0.58 mmol) in DMSO (0.2 M) was slowly added $NaBH_4$ (67 mg, 1.75 mmol). The reaction mixture was stirred at 85 °C for 6 h and progress of the reaction was monitored by TLC. After completion, the reaction was quenched with brine and extracted (EtOAc, 2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with EtOAc/hexane, 5:95 to give **9a**.

Ethyl 2-(Tetrahydro-2*H*-pyran-2-yl)acetate (9a)

Yield: 0.56 (53%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 1.28–1.31 (m, 2 H), 1.47–1.56 (m, 3 H), 1.62–1.66 (m, 1 H), 1.83–1.84 (m, 1 H), 2.38 (dd, *J* = 15.0, 5.0 Hz, 1 H), 2.50 (dd, *J* = 15.0, 8.0 Hz, 1 H), 3.42–3.49 (m, 1 H), 3.71–3.78 (m, 1 H), 3.96 (dd, *J* = 1.0, 2.0 Hz, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 23.5, 31.7, 41.9, 60.6, 68.7, 74.6, 171.6.

IR (KBr, neat): 2928, 2855, 1739, 1401, 1166, 1090, 1045, 831 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{17}O_3$: 273.1172; found: 273.1166.

Ethyl 2-((2*R,6*S**)-6-(4-Chlorophenyl)tetrahydro-2*H*-pyran-2-yl)acetate (9c)**

Yield: 86 mg (68%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3 H), 1.30–1.48 (m, 2 H), 1.68–1.76 (m, 2 H), 1.79–1.87 (m, 1 H), 1.91–1.98 (m, 1 H), 2.47 (dd, *J* = 15.0, 5.8 Hz, 1 H), 2.62 (dd, *J* = 15.0, 7.2 Hz, 1 H), 3.93–4.00 (m, 1 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 4.38 (dd, *J* = 12.0, 2.2 Hz, 1 H), 7.24–7.29 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5, 23.9, 31.0, 33.3, 42.0, 60.6, 75.1, 79.1, 127.3, 128.5, 133.0, 141.8, 171.6.

IR (KBr, neat): 2938, 2859, 1736, 1400, 1249, 1188, 1087, 1045, 831 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}ClO_3$: 283.1095; found: 283.1126.

Ethyl 2-((2*R,6*S**)-6-(Naphthalen-2-yl)tetrahydro-2*H*-pyran-2-yl)acetate (9p)**

Yield: 90 mg (70%); colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.0 Hz, 3 H), 1.40–1.47 (m, 1 H), 1.57–1.64 (m, 2 H), 1.76–1.83 (m, 2 H), 1.97–2.04 (m, 1 H), 2.55 (dd, *J* = 15.0, 6.0 Hz, 1 H), 2.72 (dd, *J* = 15.0, 7.2 Hz, 1 H), 4.05–4.08 (m, 1 H), 4.17 (q, *J* = 7.0 Hz, 2 H), 4.60 (dd, *J* = 11.2, 1.8 Hz, 1 H), 7.46–7.50 (m, 3 H), 7.82–7.85 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.5, 24.1, 31.2, 33.3, 42.1, 60.7, 75.2, 79.9, 124.4, 124.6, 125.8, 126.1, 127.8, 128.0, 128.2, 133.0, 133.5, 140.8, 171.7.

IR (KBr, neat): 2934, 2856, 1735, 1634, 1398, 1285, 1192, 1084, 1042, 817, 745 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{23}O_3$: 299.1642; found: 299.1661.

Synthesis of Ethyl 2-((2*R,4*S**,6*S**)-4-Azido-6-(4-chlorophenyl)tetrahydro-2*H*-pyran-2-yl)acetates; Typical Procedure**

A solution of 4-tosyloxy tetrahydropyran **6c** (190 mg, 0.43 mmol) in anhydrous DMF (3–5 mL) was added to sodium azide (85 mg, 1.3 mmol) and the mixture was stirred continuously at 100 °C for 1 h, monitoring by TLC (EtOAc/hexane, 1:9). After completion of the reaction, ice-cold water was added and the mixture was stirred for a further 10–15 minutes. The organic layer was extracted (EtOAc) and the organic extract washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography, eluting with EtOAc/hexane, 10:90, to give **10c**.

Yield: 92 mg (66%); pale-yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 3 H), 1.69–1.72 (m, 2 H), 1.91–1.97 (m, 2 H), 2.50 (dd, *J* = 15.2, 6.0 Hz, 1 H), 2.64 (dd, *J* = 15.0, 7.2 Hz, 1 H), 4.15–4.20 (m, 3 H), 4.30–4.35 (m, 1 H), 4.74 (d, *J* = 11.2 Hz, 1 H), 7.27 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.4, 34.5, 37.1, 41.3, 55.9, 60.8, 69.6, 73.6, 127.3, 128.7, 133.4, 140.6, 170.9.

IR (KBr, neat): 2928, 2821, 2105, 1736, 1600, 1400, 1270, 1188, 1066, 1029, 836, 722 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}ClN_3O_3$: 324.1109; found: 324.1156.

Ethyl 2-((2*S,4*R**,6*R**)-4-Azido-6-(*p*-Tolyl)tetrahydro-2*H*-pyran-2-yl)acetate (10h)**

Yield: 110 mg (60%); pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.0 Hz, 3 H), 1.62–1.70 (m, 2 H), 1.72–1.79 (m, 1 H), 1.87–1.97 (m, 2 H), 2.32 (s, 3 H), 2.46 (dd, *J* = 15.0, 6.0 Hz, 1 H), 2.63 (dd, *J* = 15.0, 7.0 Hz, 1 H), 4.11–4.18 (m, 3 H), 4.26–4.33 (m, 1 H), 4.71 (d, *J* = 10.0 Hz, 1 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 21.3, 34.6, 36.9, 41.4, 56.1, 60.7, 69.6, 74.1, 125.9, 129.2, 137.4, 139.1, 171.0.

IR (KBr, neat): 2929, 2823, 2103, 1737, 1620, 1400, 12465, 1187, 1065, 1028, 809 cm^{-1}.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{22}N_3O_3$: 304.1656; found: 304.1700.

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Supporting Information

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