Zn/ZnBr$_2$ Catalysed Reaction of Aldehydes with Allylbromide: Synthesis of 2,6-Disubstituted 4-Bromotetrahydropyrans

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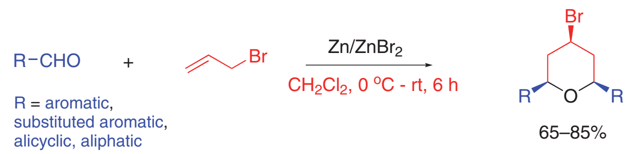

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Abstract An efficient approach for the one-pot synthesis of 4-bromotetrahydropyrans in a highly diastereoselective manner via the alkynylation followed by Prins cyclisation is described. The method employs aldehydes and allyl bromide as reactants, with a Zn/ZnBr$_2$ catalytic system in CH_2Cl_2. A variety of 2,6-disubstituted 4-bromotetrahydropyran derivatives were obtained in good yields.

Key words Prins cyclisation, tetrahydropyrans, aldehydes, allylbromides, one-pot reaction

Tetrahydropyrans (THP) are prominent structural motifs in many natural products showing various biological activities. Examples include diospongin A and B, aza-diospongin A, centolobine, diarylheptanoid, catechola-I and II, the avermectins, aplysiatoxins, oscillatoxins, atrunculins, acutiphycins, kendomycin and phorboxazoles A and B (Figure 1).[1,2] THP rings are also key moieties in molecules demonstrating antiviral, anti-nociceptive, serotonin norepinephrine transporter inhibitory, antimicrobial and antiproliferative activity.[3–5] Due to their wide ranging presence, there are various synthetic tactics to afford THPs.[6] Among those synthetic protocols, the Prins cyclisation has become a pre-eminent tool for the construction of THPs using acidic catalysts for coupling aldehydes and allyl alcohols.[7]

There are relatively few examples in the literature of one-pot formation of THP rings from aldehydes and allyl bromide via Barbier–Prins reactions,[8] and the reported methods suffer from extended reaction times, low yields and poor stereoselectivity.[9]

Zinc bromide ($ZnBr_2$) is known as a mild, non-toxic, moisture-tolerant, catalyst in organic transformations.[10] Herein, we demonstrate that $ZnBr_2$ can act as an efficient promoter for one-pot synthesis of 2,6-disubstituted 4-bromotetrahydropyrans in a highly diastereoselective manner via Babier–Prins cyclisation, using allyl bromide and aldehydes as reactants.

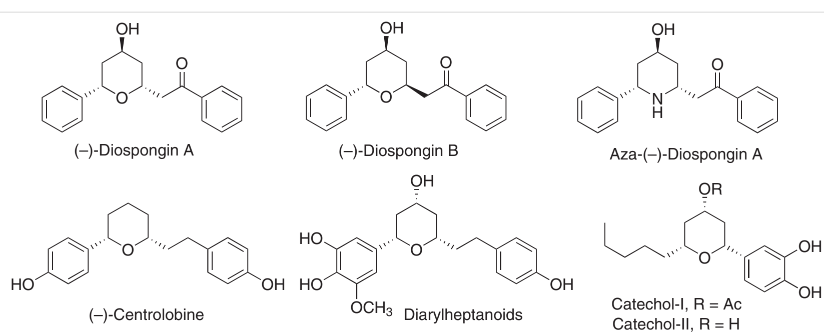
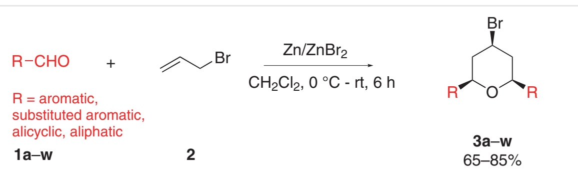


Figure 1 Bioactive compounds featuring a tetrahydropyran moiety

Initial studies were carried out with benzaldehyde (2 mmol) and allyl bromide (1 mmol) in the presence of *p*TSA, at room temperature in CH_2Cl_2. The reaction proceeded smoothly, but gave, 2,6-diphenyl-4-bromotetrahydropyran in low yield. Similarly, we have examined the reaction with CSA and $HClO_4$-SiO_2 catalysts separately and observed that conversions took place but yields were very poor. We then turned our attention to Lewis acid catalyst systems such as Zn/$ZnCl_2$ and Zn/$ZnBr_2$. While, in the case of Zn/$ZnCl_2$ reaction, a mixture of products, 2,6-diphenyl-4-bromotetrahydropyran and 2,6-diphenyl-4-chlorotetrahydropyran were formed, with Zn/$ZnBr_2$, only the desired 2,6-diphenyl-4-bromotetrahydropyran was formed in 85% yield with high diastereoselectivity for the *cis*-product. The predominant formation of this stereoisomer is most likely due to thermodynamic control. Assignment of the stereochemistry was based on the coupling constants of the protons at the C_2 and C_4 positions. The coupling constants of the benzylic proton 2-H_c [δ = 4.5 (J = 11.0 Hz)] and the proton on the carbon bearing the halide group 4-H_c [δ = 4.0 (J = 4.5, 11.0 Hz)] in the ^{1}H NMR spectrum showed a splitting consistent with two phenyl groups and the halide group being in *cis*-equatorial orientations, as shown in Scheme 1.



Scheme 1

To determine the role of solvent, we performed the reaction of benzaldehyde in different solvents such as dichloromethane, toluene, acetonitrile, tetrahydrofuran and found that dichloromethane provided the best results (Table 1).

Table 1 Initial Optimization of Reaction Conditions

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	pTSA	CH_2Cl_2	25	6	60
2	CSA	CH_2Cl_2	25	6	55
3	$HClO_4$-SiO_2	CH_2Cl_2	25	10	50
4	$ZnCl_2$	CH_2Cl_2	25	8	50
5	$ZnBr_2$	CH_2Cl_2	25	6	85
6	$ZnBr_2$	toluene	25	12	44
7	$ZnBr_2$	CH_3CN	25	8	62
8	$ZnBr_2$	THF	25	9	56

Based on the results obtained with benzaldehyde, we next explored the substrate scope of various substituted aromatic as well as aliphatic aldehydes with allyl bromide to probe the generality of the reaction. Aromatic aldehydes having electron-donating or electron-withdrawing groups on the aromatic ring, reacted readily with allyl bromide to afford the corresponding 2,6-disubstituted 4-bromotetrahydropyrans in 65–85% yield (Figure 2). However, aliphatic aldehydes and aromatic aldehydes bearing electron-withdrawing groups reacted more smoothly than those having

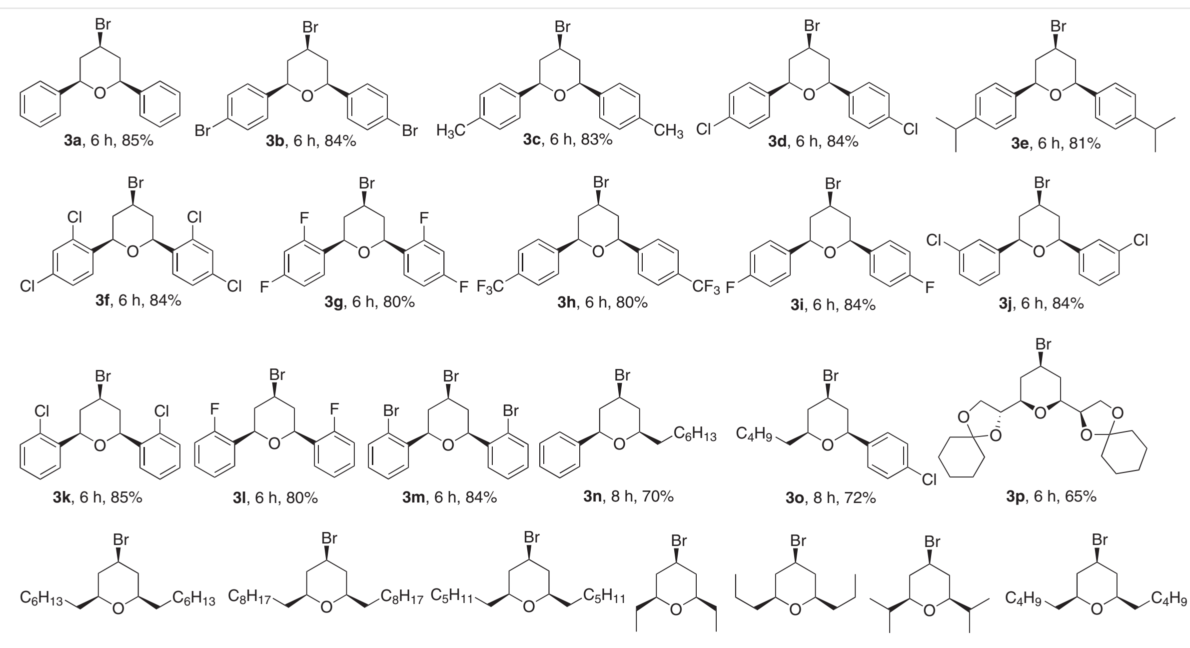
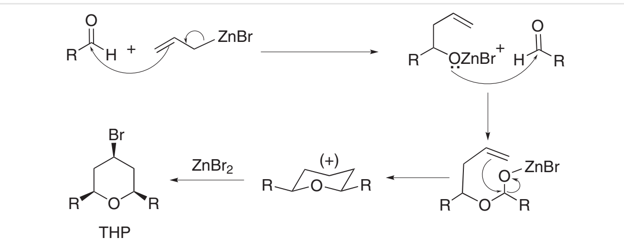


Figure 2 Reaction scope

electron-donating groups. Notably, this protocol was equally applicable to aliphatic, cyclic, and aromatic aldehydes.

On the basis of experimental results and previous reports, a reaction mechanism for the formation of 2,6-disubstituted 4-bromotetrahydropyrans from allyl bromide and aldehydes can be explained by a tandem carbonyl allylation-hemiacetal formation followed by Prins cyclisation and subsequent bromination (Scheme 2). A rationale for the all *cis*-selectivity involves formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has increased stability relative to the open oxo-carbenium ion due to delocalization. The optimal geometry for this delocalization of hydrogen atom at C_4 in a *pseudo*-axial position favours equatorial attack of the activated π-bond nucleophile.[11]



Scheme 2

In conclusion, we have developed a one-pot synthesis of 2,6-disubstituted 4-bromotetrahydropyrans **3a–w** from aldehydes and allyl bromide in a highly diastereoselective manner via alkenylation followed by Prins cyclisation, catalysed by Zn/$ZnBr_2$.

Solvents, aldehydes, allyl bromide and Zn/$ZnBr_2$ were purchased from a commercial source (Spectrochem) and used as received. Progress of reaction was followed by TLC on silica gel-G plates of 0.5-mm thickness, and spots were visualised by iodine vapour and UV light. Flash column chromatography was performed on silica gel (200–300 mesh). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with a Bruker AV 300/400/500 MHz instrument. Chemical shifts are reported in ppm referenced to the residual proton of $CDCl_3$ (7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). ^{1}H NMR data are reported as chemical shift (ppm), multiplicity (standard abbreviations), coupling constants (Hz), and integration. ^{13}C NMR data are reported as ppm. HRMS analyses were performed with a Micromass Q-TOF apparatus.

Synthesis of 2,6-Disubstituted 4-Bromotetrahydropyrans; General Procedure

To a stirred suspension of aldehyde **1a–w** (2 mmol) and Zn dust (4 mmol) in CH_2Cl_2 was added allyl bromide **2** (1 mmol) and the mixture stirred at r.t. for 30 minutes. Then $ZnBr_2$ was added at 0 °C and the mixture was further stirred for 6–8 hours at r.t., with completion of reaction being confirmed by TLC. The reaction mixture was filtered through a bed of Celite®, the filtrate was evaporated, and the residue was triturated with EtOAc (2 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, evaporated under reduced pressure, and purified by column chromatography on silica gel (60–120 mesh), eluting with EtOAc/hexane to afford the corresponding 2,6-disubstituted 4-bromotetrahydropyrans **3a–w**.

4-Bromo-2,6-diphenyltetrahydro-2*H*-pyran (3a)

Yield: 268 mg (85%); colourless solid; mp 86–87 °C.

IR (neat): 2928, 2850, 1665, 1590, 1376, 1288, 1166, 1090, 1051, 1011, 825, 732 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.20 (m, 10 H), 4.54 (dd, *J* = 11.0, 4.5 Hz, 2 H), 4.40 (tt, *J* = 11.0, 4.5 Hz, 1 H), 2.55 (dd, *J* = 12.8, 4.0 Hz, 2 H), 2.08 (q, *J* = 12.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 128.4, 127.7, 125.7, 79.7, 46.1, 45.0, 29.6.

MS (EIMS): *m*/*z* (%) = 237 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{17}O$: 237.45569; found: 237.45570.

4-Bromo-2,6-bis(4-bromophenyl)tetrahydro-2*H*-pyran (3b)

Yield: 399 mg (84%); colourless solid; mp 129–130 °C.

IR (neat): 2958, 2928, 2858, 1901, 1686, 1590, 1486, 1407, 1378, 1290, 1115, 1082, 728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.0 Hz, 4 H), 7.26 (d, *J* = 8.2 Hz, 4 H), 4.51 (d, *J* = 11.2, 4.8 Hz, 2 H), 4.39 (tt, *J* = 11.2, 4.8 Hz, 1 H), 2.52 (d, *J* = 13.0 Hz, 2 H), 2.04 (q, *J* = 12.1 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 131.6, 127.4, 121.7, 78.9, 44.7, 45.2.

MS (EIMS): *m*/*z* (%) = 392 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{15}Br_2O$: 392.94897; found: 392.94767.

4-Bromo-2,6-di-*p*-tolyltetrahydro-2*H*-pyran (3c)

Yield: 285 mg (83%); colourless solid; mp 92–93 °C.

IR (neat): 3040, 2930, 2820, 1610, 1515, 1465, 1340, 1165, 1050, 955, 777 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 7.8 Hz, 4 H), 7.22 (d, *J* = 7.8 Hz, 4 H), 4.34 (dd, *J* = 11.2, 4.0 Hz, 2 H,), 4.28 (tt, *J* = 11.2, 4.0 Hz, 1 H), 2.46 (s, 6 H), 2.20 (dd, *J* = 12.4, 3.6 Hz, 2 H), 1.94 (q, *J* = 11.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.2, 138.6, 134.9, 129.0, 128.2, 126.9, 78.9, 45.6, 44.2, 30.0, 21.4.

MS (EIMS): *m*/*z* (%) = 265 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{19}H_{21}O$: 265.26610; found: 265.26580.

4-Bromo-2,6-bis(4-chlorophenyl)tetrahydro-2*H*-pyran (3d)

Yield: 321 mg (84%); colourless solid; mp 111–112 °C.

IR (neat): 2958, 2928, 2858, 1901, 1686, 1590, 1486, 1407, 1378, 1290, 1115, 1052, 728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.26 (m, 8 H), 4.50 (dd, *J* = 9.7, 1.2 Hz, 2 H), 4.36 (tt, *J* = 12.2, 4.8 Hz, 1 H), 2.54 (dd, *J* = 12.2, 4.8 Hz, 2 H), 2.04 (q, *J* = 12.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.0, 133.5, 130.8, 129.4, 128.6, 127.1, 78.9, 44.7, 45.3, 30.0.

MS (EIMS): *m*/*z* (%) = 305 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{15}Cl_2O$: 305.05000; found: 305.04989.

4-Bromo-2,6-bis(4-isopropylphenyl)tetrahydro-2*H*-pyran (3e)

Yield: 324 mg (81%); colourless solid; mp 101–102 °C.

IR (neat): 2950, 2821, 2850, 1908, 1680, 1590, 1485, 1407, 1290, 1164, 1082, 728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.0 Hz, 4 H), 7.18 (d, *J* = 7.8 Hz, 4 H), 4.50 (dd, *J* = 11.2, 1.2 Hz, 2 H), 4.40 (tt, *J* = 11.2, 1.2 Hz, 1 H), 2.96–2.85 (m, 2 H), 2.54 (dd, *J* = 12.2, 3.2 Hz, 2 H), 2.15 (q, *J* = 12.0, 2 H), 1.24 (d, *J* = 7 Hz, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4, 138.9, 130.8, 128.4, 127.2, 125.8, 45.2, 44.8, 34.4, 30.2, 21.9.

MS (EIMS): *m*/*z* (%) = 321 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{23}H_{29}O$: 321.40719; found: 321.40740.

4-Bromo-2,6-bis(2,4-dichlorophenyl)tetrahydro-2*H*-pyran (3f)

Yield: 378 mg (84%); colourless solid; mp 125–126 °C.

IR (neat): 3092, 2970, 2864, 1897, 1587, 1560, 1469, 1375, 1293, 1203, 1170, 1108, 1083, 1045, 1004, 864, 818, 784 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 2.1 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 4.91 (dd, *J* = 11.2, 1.2 Hz, 2 H), 4.48–4.40 (m, 1 H), 2.72–2.65 (m, 2 H), 1.94–1.84 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 134.0, 131.8, 129.1, 128.0, 127.6, 76.2, 44.4, 43.1.

MS (EIMS): *m*/*z* (%) = 373 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{13}Cl_4O$: 373.20410; found: 373.20412.

4-Bromo-2,6-bis(2,4-difluorophenyl)tetrahydro-2*H*-pyran (3g)

Yield: 310 mg (80%); colourless solid; mp 104–105 °C.

IR (neat): 3050, 2920, 2853, 1610, 1520, 1456, 1410, 1365, 1170, 835, 760 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (td, *J* = 8.4, 6.7 Hz, 2 H), 6.94–6.88 (m, 2 H), 6.84–6.76 (m, 2 H), 4.54 (dd, *J* = 11.1, 1.5 Hz, 2 H), 4.42 (tt, *J* = 12.0, 4.3 Hz, 1 H), 2.57 (dd, *J* = 12.7, 3.9 Hz, 2 H), 2.06 (dd, *J* = 15.8, 11.9 Hz, 2 H).

^{19}F NMR (500 MHz, $CDCl_3$): δ = –110.7780, –110.7930, –115.4618, –115.4768.

^{13}C NMR (125 MHz, $CDCl_3$): δ = (d, $^{1}J_{CF}$ = 248.8 Hz), 159.3 (d, $^{1}J_{CF}$ = 249.0 Hz), 159.2 (d, $^{1}J_{CF}$ = 249.0 Hz), 128.2 (d, $^{3}J_{CF}$ = 9.1 Hz), 128.1 (d, $^{3}J_{CF}$ = 10.0 Hz), 160.2 (d, $^{1}J_{CF}$ = 246 Hz), 136.8 (d, $^{4}J_{CF}$ =2.7 Hz), 124.2 (d, $^{4}J_{CF}$ = 3.6 Hz), 124.1 (d, $^{4}J_{CF}$ = 3.6 Hz), 111.6 (d, $^{2}J_{CF}$ = 20.8 Hz), 111.5 (d, $^{2}J_{CF}$ = 21.7 Hz), 103.7 (d, $^{2}J_{CF}$ = 25.4 Hz), 103.7 (d, $^{2}J_{CF}$ = 26.3 Hz), 73.5, 44.6, 43.7.

MS (EIMS): *m*/*z* (%) = 309 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{13}F_4O$: 309.09025; found: 309.08858.

4-Bromo-2,6-bis(4-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran (3h)

Yield: 361 mg (80%); colourless solid; mp 113–114 °C.

IR (neat): 3050, 2920, 2853, 1610, 1520, 1456, 1365, 1170, 835, 760 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.0 Hz, 4 H), 7.22 (d, *J* = 8.0 Hz, 4 H), 4.61–4.57 (m, 2 H), 4.42 (tt, *J* = 12.0, 4.3 Hz, 1 H), 2.60–2.54 (m, 2 H), 2.14–2.04 (m, 2 H).

^{19}F NMR (500 MHz, $CDCl_3$): δ = –57.9030.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (d, $^{1}J_{CF}$ = 246 Hz), 136.8 (d, $^{4}J_{CF}$ = 2.7 Hz), 127.5 (d, $^{3}J_{CF}$ = 2.7 Hz), 115.3 (d, $^{2}J_{CF}$ = 2.7 Hz), 79.0, 45.5, 44.9.

MS (EIMS):*m*/*zz* (%) = 373 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{19}H_{15}F_6O$: 373.76555; found: 373.76540.

4-Bromo-2,6-bis(4-fluorophenyl)tetrahydro-2*H*-pyran (3i)

Yield: 281 mg (84%); colourless solid; mp 98–99 °C.

IR (neat): 3050, 2920, 2853, 1610, 1520, 1456, 1410, 1365, 1170, 835, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 4 H), 7.08–7.01 (m, 4 H), 4.54 (dd, *J* = 11.2, 1.4 Hz, 2 H), 4.41 (tt, *J* = 11.2, 1.4 Hz, 1 H), 2.55–2.49 (m, 2 H), 2.12–2.03 (m, 2 H).

^{19}F NMR (400 MHz, $CDCl_3$): δ = –118.7734, –119.5223.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 (d, $^{1}J_{CF}$ = 246 Hz), 136.8 (d, $^{4}J_{CF}$ = 2.7 Hz), 127.5 (d, $^{3}J_{CF}$ = 2.7 Hz), 115.3 (d, $^{2}J_{CF}$ =2.7 Hz), 79.0, 45.5, 44.9.

MS (EIMS): *m*/*z* (%) = 273 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{15}F_2O$: 273.10910; found: 273.10974.

4-Bromo-2,6-bis(3-chlorophenyl)tetrahydro-2*H*-pyran (3j)

Yield: 320 mg (84%); colourless solid; mp 104–105 °C.

IR (neat): 2953, 2948, 2858, 1901, 1686, 1486, 1407, 1368, 1368, 1250, 1122, 1052, 728 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 2 H), 7.29–7.22 (m, 6 H), 4.52 (dd, *J* = 10.2, 1.8 Hz, 2 H), 4.42–4.28 (m, 1 H), 2.54 (dd, *J* = 12.6, 4.3 Hz, 2 H), 2.07 (q, *J* = 11.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 134.4, 129.8, 128.0, 125.9, 123.9, 79.0, 45.0, 44.6.

MS (EIMS): *m*/*z* (%) = 305 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{15}Cl_2O$: 305.05000; found: 305.04989.

4-Bromo-2,6-bis(2-chlorophenyl)tetrahydro-2*H*-pyran (3k)

Yield: 306 mg (85%); colourless solid; mp 103–104 °C.

IR (neat): 2924, 2866, 1685, 1536, 1448, 1363, 1325, 1274, 1127, 1047, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (tt, *J* = 7.5, 1.4 Hz, 2 H), 7.28–7.23 (m, 2 H), 7.16 (tt, *J* = 7.4, 1.1 Hz, 2 H), 7.05–7.00 (m, 2 H), 4.90 (dd, *J* = 11.1, 1.2 Hz, 2 H), 4.44 (tt, *J* = 12.1, 4.4 Hz, 1 H), 2.60 (dd, *J* = 12.6, 4.0 Hz, 2 H), 2.07 (q, *J* = 11.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9 (d, $^{1}J_{CF}$ = 245.7 Hz), 128.9 (d, $^{3}J_{CF}$ = 8.1 Hz), 128.2 (d, $^{3}J_{CF}$ = 13.2 Hz), 127.5 (d, $^{4}J_{CF}$ =3.7 Hz), 124.2 (d, $^{4}J_{CF}$ = 2.2 Hz), 115.9 (d, $^{2}J_{CF}$ = 21.0 Hz), 73.4, 45.1, 43.6.

MS (EIMS): *m*/*z* (%) = 273 [M–Br]$^+$.

HRMS (EI): *m*/*z* [M–Br]$^+$ calcd. for $C_{17}H_{15}F_2O$: 273.10910; found: 273.10974.

4-Bromo-2,6-bis(2-fluorophenyl)tetrahydro-2*H*-pyran (3l)

Yield: 298 mg (80%); colourless solid; mp 93–94 °C.

IR (neat): 2922, 2855, 1684, 1534, 1445, 1366, 1322, 1284, 1122, 1044, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 7.6, 1.4 Hz, 2 H), 7.35–7.31 (m, 4 H), 7.25–7.21 (m, 2 H), 4.99 (dd, *J* = 11.2, 1.5 Hz, 2 H), 4.49 (tt, *J* = 12.0, 4.6 Hz, 1 H, 2.72 (dd, *J* = 12.8, 4.4 Hz, 2 H), 1.95 (q, *J* = 11.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 131.1, 129.3, 128.7, 127.2, 127.1, 76.6, 45.2, 43.3.

MS (EIMS): *m*/*z* (%) = 305 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{17}H_{15}Cl_2O$: 305.05000; found: 305.04989.

4-Bromo-2,6-bis(2-bromophenyl)tetrahydro-2*H*-pyran (3m)

Yield: 395 mg (80%); colourless solid; mp 123–124 °C.

IR (neat): 2954, 2920, 2856, 1686, 1590, 1486, 1407, 1377, 1343, 1280, 1115, 1080, 724 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.8 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.38 (t, *J* = 7.6 Hz, 2 H), 4.95 (dd, *J* = 11.2, 1.5 Hz, 2 H), 4.50 (tt, *J* = 12.2, 4.8 Hz, 1 H), 2.76 (dd, *J* = 12.7, 3.2 Hz, 2 H), 1.92 (q, *J* = 12.1 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 132.6, 129.1, 127.8, 127.4, 78.8, 45.1, 43.3.

MS (EIMS): *m*/*z* (%) = 392 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{17}H_{15}Br_2O$: 392.94897; found: 392.94767.

4-Bromo-2-heptyl-6-phenyltetrahydro-2*H*-pyran (3n)

Yield: 182 mg (70%); colourless solid; mp 86–87 °C.

IR (neat): 3028, 2924, 2852, 1648, 1451, 1364, 1140, 1081, 1053, 1010, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.18 (m, 5 H), 4.32 (dd, *J* = 11.3, 2.1 Hz, 1 H), 4.22 (tt, *J* = 11.8., 4.5 Hz, 1 H), 3.50–3.40 (m, 1 H), 2.45 (dd, *J* = 12.8, 4.1 Hz, 1 H), 2.28 (dd, *J* = 12.2, 4.2 Hz, 1 H), 1.94 (q, *J* = 11.9 Hz, 1 H), 1.80 (q, *J* = 12 Hz, 1 H), 1.70–1.57 (m, 1 H), 1.56–1.40 (m, 2 H), 1.38–1.20 (m, 9 H), 0.87 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 128.4, 127.6, 125.7, 77.9, 47.0, 45.2, 43.2, 35.8, 29.5, 29.2, 25.3, 22.6, 14.2.

MS (EIMS): *m*/*z* (%) = 259 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{18}H_{27}O$: 259.20619; found: 259.20580.

4-Bromo-2-(4-chlorophenyl)-6-pentyltetrahydro-2*H*-pyran (3o)

Yield: 247 mg (72%); colourless solid; mp 89–90 °.

IR (neat): 2920, 2820, 1642, 1448, 1362, 1260, 1140, 1082, 1050, 974, 832, 752, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.2 Hz, 2 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 4.34 (dd, *J* = 11.8, 2.2 Hz, 1 H), 4.24 (tt, *J* = 11.8, 4.8 Hz, 1 H), 3.48–3.42 (m, 1 H), 2.40 (dd, *J* = 12.6, 4.1 Hz, 1 H), 2.25 (dd, *J* = 12.2, 3.8 Hz, 1 H), 2.02–1.82 (q, *J* = 11.8 Hz, 1 H), 1.84–1.68 (q, *J* = 11.8 Hz, 1 H), 1.68–1.22 (m, 8 H), 0.86 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.2, 128.6, 128.2, 127.8, 126.5, 79.4, 78.2, 46.8, 45.2, 43.2, 35.1, 31.8, 30.9, 25.3, 22.6, 14.1.

MS (EIMS): *m*/*z* (%) = 266 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{16}H_{22}ClO$: 266.21419; found: 266.21580.

(2*R*,2′*R*)-2,2′-[(2*R*,4*S*,6*S*)-4-Bromotetrahydro-2*H*-pyran-2,6-diyl]bis(1,4-dioxaspiro[4.5]decane) (3p)

Yield: 288 mg (65%); colourless solid; mp 113–114 °C.

IR (neat): 2845, 1260, 1150, 1070, 945, 888, 750 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.37–4.25 (m, 1 H), 4.05 (tt, *J* = 10.8, 2.2 Hz, 2 H), 3.92–3.82 (m, 4 H), 3.41–3.32 (m, 2 H), 2.52 (dd, *J* = 12.4, 3.8 Hz, 2 H), 2.21–1.88 (m, 4 H), 1.78–1.14 (m, 18 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 121.6, 83.4, 79.2, 68.9, 41.4, 34.9, 33.1, 27.2, 24.6.

MS (EIMS): *m*/*z* (%) = 365 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{21}H_{33}O_5$: 365.24064; found: 365.24127.

4-Bromo-2,6-diheptyltetrahydro-2*H*-pyran (3q)

Yield: 282 mg (82%); colourless solid; mp 97–98 °C.

IR (neat): 2925, 2852, 1465, 1325, 1370, 1325, 1258, 1151, 1083, 1024, 961, 781, 566, 1269, 1183, 1014, 718 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.07 (tt, *J* = 11.9, 4.9 Hz, 1 H), 3.22–3.16 (m, 2 H), 2.17 (dd, *J* = 11.9, 4.0 Hz, 2 H), 1.64 (q, *J* = 11.9 Hz, 2 H), 1.56–1.16 (m, 24 H), 0.90 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.4, 47.4, 43.6, 35.6, 31.7, 30.0, 29.9, 29.6, 21.9, 14.1.

MS (EIMS): *m*/*z* (%) = 281 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{19}H_{37}O$: 281.28444; found: 281.28534.

4-Bromo-2,6-dinonyltetrahydro-2*H*-pyran (3r)

Yield: 353 mg (83%); colourless solid; mp 104–105 °C.

IR (neat): 2923, 2851, 1467, 1328, 1330, 1297, 1242, 1151, 1151, 1087, 1034, 991, 718 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.08 (tt, *J* = 11.9, 4.9 Hz, 1 H), 3.26–3.12 (m, 2 H), 2.18 (dd, *J* = 12.0, 4.2 Hz, 2 H), 1.65 (q, *J* = 12.2 Hz, 2 H), 1.56–1.16 (m, 2 H), 1.54–1.22 (m, 30 H), 0.92–0.86 (t, *J* = 6.9 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 77.6, 47.5, 43.5, 35.9, 31.8, 29.5, 29.2, 25.5, 22.6, 14.1.

MS (EIMS): *m*/*z* (%) = 337 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{23}H_{45}O$: 337.34704; found: 337.34677.

4-Bromo-2,6-dihexyltetrahydro-2*H*-pyran (3s)

Yield: 282 mg (82%); colourless solid; mp 91–92 °C.

IR (neat): 2925, 2854, 1466, 1365, 1370, 1269, 1225, 1152, 1183, 1014, 718 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (tt, *J* = 11.8, 4.3 Hz, 1 H), 3.30–3.15 (m, 2 H), 2.18 (dd, *J* = 12.4, 4.3 Hz, 2 H), 1.65 (q, *J* = 12.1 Hz, 2 H), 1.54–1.22 (m, 20 H), 0.88 (t, *J* = 6.9 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.6, 47.4, 43.6, 35.9, 31.8, 29.2, 25.5, 22.6, 14.08.

MS (EIMS): *m*/*z* (%) = 253 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{17}H_{33}O$: 253.25314; found: 253.25214.

4-Bromo-2,6-diethyltetrahydro-2*H*-pyran (3t)

Yield: 183 mg (78%); colourless solid; mp 61–62 °C.

IR (neat): 2952, 2854, 1440, 1330, 1242, 1150, 1082, 1020, 718, 562 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.10 (tt, *J* = 11.7, 1.4 Hz, 1 H), 3.18–3.10 (m, 1 H), 1.24–1.16 (m, 1 H), 1.70–1.40 (m, 6 H), 0.88 (t, *J* = 8.0 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 78.1, 45.2, 43.8, 29.9, 26.6, 9.4.

MS (EIMS): *m*/*z* (%) = 141 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_9H_{17}O$: 141.13584; found: 141.13687.

4-Bromo-2,6-dipropyltetrahydro-2*H*-pyran (3u)

Yield: 210 mg (79%); colourless solid; mp 68–69 °C.

IR (neat): 2950, 2840, 1365, 1278, 1180, 1070, 1025, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08 (tt, *J* = 12.0, 3.8 Hz, 1 H), 3.26–3.18 (m, 2 H), 2.16 (dd, *J* = 12.0, 3.8 Hz, 2 H), 1.64 (q, *J* = 12.0, 3.8 Hz, 2 H), 1.56–1.24 (m, 8 H), 0.88 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 76.8, 45.3, 44.2, 36.2, 29.8, 29.2, 21.8, 14.0.

MS (EIMS): *m*/*z* (%) = 169 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{11}H_{21}O$: 169.65464; found: 169.65460.

4-Bromo-2,6-diisopropyltetrahydro-2*H*-pyran (3v)

Yield: 202 mg (80%); colourless solid; mp 66–67 °C.

IR (neat): 2945, 2853, 2460, 1325, 1242, 1151, 1080, 1025, 716, 562 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08 (tt, *J* = 11.5, 4.4 Hz, 1 H), 2.95–2.90 (m, 2 H), 2.19 (dd, *J* = 12.2, 4.5 Hz, 2 H), 1.72–1.58 (m, 4 H), 0.92 (d, *J* = 6.4 Hz, 6 H), 0.88 (d, *J* = 6.4 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 79.8, 45.4, 44.2, 30.8, 30.1, 19.2.

MS (EIMS): *m*/*z* (%) = 169 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{11}H_{21}O$: 169.64340; found: 169.64321.

4-Bromo-2,6-dipentyltetrahydro-2*H*-pyran (3w)

Yield: 258 mg (81%); colourless solid; mp 82–83 °C.

IR (neat): 2932, 2855, 1465, 1365, 1378, 1280, 1230, 1180, 1160, 1080, 1015, 730 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.08 (tt, *J* = 12.40, 4.3 Hz, 1 H), 3.26–3.17 (m, 2 H), 2.20 (dd, *J* = 12.4, 3.6 Hz, 2 H), 1.65 (q, *J* = 12.4, Hz, 2 H), 1.57–1.23 (m, 16 H), 0.88 (t, *J* = 7.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.6, 47.5, 43.5, 35.8, 30.8, 29.2, 25.5, 22.4, 14.07.

MS (EIMS): *m*/*z* (%) = 225 $[M–Br]^+$.

HRMS (EI): *m*/*z* $[M–Br]^+$ calcd. for $C_{15}H_{29}O$: 225.64632; found: 225.64644.

Conflict of Interest

The authors declare no conflict of interest.

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