Asymmetric Synthesis of Bicyclic Dihydropyrans via Organo-catalytic Inverse-Electron-Demand oxo-Diels-Alder Reactions of Enolizable Aliphatic Aldehydes

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Supporting Information

Table of Contents

1. General Information

2. Optimization Study of the Asymmetric oxo-IEDDA Reactions of Aldehyde 1a and the Cyclic Enone 2a

3. General Procedure for the Synthesis of Chiral Bicyclic Dihydropyrans 4 by using Normal Saturated Aldehydes

4. General Procedure for the Synthesis of Chiral Bicyclic Dihydropyrans 6 and 6’ by directly using Aqueous Acetaldehyde

5. Procedure for Synthetic Transformations of 4a

6. Crystal Data and Structure Refinement for the Enantiopure 4b

7. References and Notes

8. NMR and HPLC Spectra of the Chiral Bicyclic Dihydropyranes
1. General Information

**General Procedures.** All reactions were performed in oven-dried or flame-dried reaction vessels, modified Schlenk flasks, or round-bottom flasks. The flasks were fitted with Teflon screw caps and reactions were conducted under an atmosphere of argon if needed. Gas-tight syringes with stainless steel needles were used to transfer air- and moisture-sensitive liquids. All moisture and/or air sensitive solid compounds were manipulated inside normal desiccators. Flash column chromatography was performed using silica gel (40–63 μm, 230–400 mesh).

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F$_{254}$ aluminum plates (Merck) containing a 254 nm fluorescent indicator. TLC plates were visualized by exposure to short wave ultraviolet light (254 nm) and to a solution of KMnO$_4$ (1 g of KMnO$_4$, 6 g of K$_2$CO$_3$ and 0.1 g of KOH in 100 mL of H$_2$O) or vanillin (2 g of vanillin and 4 mL of concentrated H$_2$SO$_4$ in 100 mL of EtOH) followed by heating.

Organic solutions were concentrated at 30-50 °C on rotary evaporators at ~10 torr followed by drying on vacuum pump at ~1 torr. Reaction temperatures are reported as the temperature of the bath surrounding the vessel unless otherwise stated.

**Materials.** Commercial reagents and solvents were obtained from Adamas-beta, Aldrich Chemical Co., Alfa Aesar, Macklin and Energy Chemical and used as received with the following exceptions: THF, Et$_2$O and toluene were purified by refluxing over Na-benzophenone under positive argon pressure followed by distillation. [1] The enone substrates were prepared according to literature procedure. [2]

**Instrumentation.**

- Proton nuclear magnetic resonance (¹H NMR) spectra were recorded with Bruker AV 400 MHz spectrometers. Proton chemical shifts are reported in parts per million (δ scale), and are referenced using residual protium in the NMR solvent (CDCl$_3$: δ 7.26 (CHCl$_3$)). Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant(s) (Hz), integration].
- Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded with Bruker AV 400 MHz spectrometers. Carbon chemical shifts are reported in parts per million (δ scale), and are referenced using the carbon resonances of the solvent (δ 77.0 (CHCl$_3$)). Data are reported as follows: chemical shift [multiplicity (if not singlet), assignment (C$_q$ = fully substituted carbon)].
- High resolution mass spectra (HRMS) were recorded on a Waters SYNAPT G2 using an electrospray (ESI) ionization source.
2. **Optimization Study of the Asymmetric oxo-IEDDA Reactions of Aldehyde 1a and the Cyclic Enone 2a**

![Chemical structure](https://example.com/structure.png)

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*Unless otherwise noted, the title reactions were performed with 0.15 mmol of 1a, 0.1 mmol of 2a, 0.02 mmol of 3a and 0.02 mmol of the acid in 1 mL of the solvent for 16 hours; and the dr value of this reaction was generally >95:5 which was determined by ¹H-NMR analysis of the crude product. BA: Benzoic acid; PNBA: p-Nitrobenzoic acid; ONBA: o-Nitrobenzoic acid; SA: Salicylic acid; AA: Acetic acid. †Isolated yield. ‡ Determined by chiral HPLC analysis. †Reaction was performed in 0.5 ml of the solvent. ††Reaction was performed in 2 ml of the solvent.
We firstly screened the solvent for the secondary amine catalyzed asymmetric oxo-IEDDA reaction of \textit{n}-propanal 1a and the cyclic enone 2a under room temperature. As summarized in the above table (entries 1-9), the co-solvent of THF/H\textsubscript{2}O (10:1) has demonstrated to be the optimal choice. Then, various kinds of acid additives including benzoic acid, \textit{p}-nitrobenzoc acid, \textit{o}-nitrobenzoc acid, salicylic acid and acetic acid, were also investigated (entries 10-14). Regarding the isolated yield, enantioselectivity as well as the cost of the material, we chose benzoic acid as the best additive for this reaction; it is noteworthy that no reaction happened in the absence of acid (entry 10). Finally, we studied the concentration of this reaction; however, lower yield was obtained by either increasing or reducing the amount of the solvent (entries 15-16). Thus, the desired product 4a could be obtained in high yield (90\% yield) and with excellent stereoselectivity (>95:5 dr, >99\% ee) under the optimal condition (entry 7).

3. General Procedure for the Synthesis of Chiral Bicyclic Dihydropyranes 4 by using Normal Saturated Aldehydes

\[ \text{A glass tube was charged with pyrrolidine-2,3-dione 2 (0.2 mmol), amine catalyst 3a (0.04 mmol, 13 mg) and benzoic acid (0.04 mmol, 4.9 mg) in THF/H}_2\text{O (v/v = 10:1, 0.1 M, 2 mL). The saturated aldehydes 1 (0.3 mmol) was added with a syringe, and the reaction was sealed with a Teflon cap and stirred at room temperature for about 16 hours. When the reaction was complete, the mixture was directly purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (6:1 to 2:1) to afford the corresponding bicyclic dihydropyranes 4, which was dried under vacuum and further analyzed by }^{1}\text{H-NMR, }^{13}\text{C-HMR, HRMS, chiral HPLC analysis, etc.}} \]

(2\textit{S},3\textit{R},4\textit{S})-6-benzyl-2-hydroxy-3-methyl-4-phenyl-3,4,5,6-tetrahydropyranol[2,3-\textit{c}]pyrrolo-7(2\textit{H})-one 4a

\[ 4a \]
Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-benzylidene-pyrrolidine-2,3-dione 2a (55.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4a as a white solid with 90% yield. The diastereomeric ratio was determined to be >95:5 by crude 1H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, tmajor = 6.48 min, tminor = 12.19 min; [α]D20 = 86.4 (c = 1.0 in CH2Cl2).

**NMR and HRMS data for the product 4a:**

1H NMR (400 MHz, CDCl3); δ (ppm): 7.32 – 7.26 (m, 4H), 7.25 – 7.22 (m, 2H), 7.19 – 7.16 (m, 2H), 7.14 – 7.12 (m, 2H), 5.66 (d, J = 2.4 Hz, 1H), 4.73 (d, J = 15.2 Hz, 1H), 4.41 (d, J = 15.2 Hz, 1H), 3.53 – 3.36 (m, 3H), 2.16 – 2.07 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H).

13C NMR (100 MHz, CDCl3); δ (ppm): 166.9, 142.4, 140.5, 136.7, 128.7, 128.6, 128.4, 128.0, 127.6, 127.1, 124.3, 96.9, 47.9, 46.5, 41.5, 39.7, 14.2

**HRMS (ESI):** m/z calculated for C21H21NO3Na+: 358.1419, found: 358.1417.

(2S,3R,4S)-6-benzyl-4-(4-bromophenyl)-2-hydroxy-3-methyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 4b

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(4-bromobenzylidene)-pyrrolidine-2,3-dione 2b (71.2 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4b as a white solid with 92% yield. The diastereomeric ratio was determined to be 91:9 by crude 1H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, tmajor = 6.43 min, tminor = 11.10 min; [α]D20 = +46.9 (c = 1.60 in CH2Cl2).

**NMR and HRMS data for the product 4b:**

1H NMR (400 MHz, CDCl3); δ (ppm): 7.43 (d, J = 8.4 Hz, 2H), 7.32 – 7.23 (m, 3H), 7.22 – 7.13 (m, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.24 (br s, 1H), 5.71 (br s, 1H), 4.69 (d, J = 14.8 Hz, 1H), 4.44 (d, J = 14.8 Hz, 1H), 3.50 – 3.44 (m, 2H), 3.35 (d, J = 18.0 Hz, 1H), 2.11 – 2.03 (m, 1H), 0.95 (d, J = 6.8 Hz, 3H).

13C NMR (100 MHz, CDCl3); δ (ppm): 166.7, 142.7, 139.5, 136.6, 131.9, 130.2, 128.7, 128.1, 127.7, 123.3, 121.0, 96.8, 47.8, 46.6, 41.1, 39.8, 14.2

**HRMS (ESI):** m/z calculated for C21H20BrNO3Na+: 436.0524, found: 436.0527.
(2S,3R,4S)-6-benzyl-4-(4-chlorophenyl)-2-hydroxy-3-methyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 4c

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(4-chlorobenzylidene)-pyrrolidine-2,3-dione 2c (62.2 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4c as a white solid with 93% yield. The diastereomeric ratio was determined to be 90:10 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}}$ = 6.36 min, $t_{\text{minor}}$ = 10.88 min; $[\alpha]_{D}^{20} = +68.3$ (c = 1.14 in CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm): 7.24 – 7.18 (m, 5H), 7.12 – 7.09 (m, 2H), 7.02 – 6.98 (m, 2H), 6.11 (br s, 1H), 5.63 (d, $J = 2.4$ Hz, 1H), 4.62 (d, $J = 14.8$ Hz, 1H), 4.37 (d, $J = 14.8$ Hz, 1H), 3.44 – 3.37 (m, 2H), 3.28 (d, $J = 18.4$ Hz, 1H), 2.04 – 1.96 (m, 1H), 0.88 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm): 166.7, 142.6, 139.0, 136.6, 133.0, 129.8, 129.0, 128.7, 128.1, 127.7, 123.5, 96.8, 47.8, 46.6, 41.0, 39.8, 14.1

HRMS (ESI): m/z calculated for C$_{21}$H$_{20}$ClNO$_3$Na$^+$: 392.1029, found: 392.1029.

(2S,3R,4S)-6-benzyl-4-(4-fluorophenyl)-2-hydroxy-3-methyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 4d

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(4-fluorobenzylidene)-pyrrolidine-2,3-dione 2d (59.0 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4d as a white solid with 98% yield. The diastereomeric ratio was determined to be 89:11 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by
chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}} = 6.45 \text{ min}$, $t_{\text{minor}} = 11.48 \text{ min}$; $[\alpha]_D^{20} = +68.9 \text{ (c = 1.51 in CH}_2\text{Cl}_2)$. 

**NMR and HRMS data for the product 4d:**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm): 7.31 – 7.23 (m, 3H), 7.21 – 7.17 (m, 2H), 7.12 – 7.08 (m, 2H), 7.02 – 6.97 (m, 2H), 6.31 (br s, 1H), 5.71 (d, $J = 2.4$ Hz, 1H), 4.69 (d, $J = 14.8$ Hz, 1H), 4.44 (d, $J = 14.8$ Hz, 1H), 3.53 – 3.45 (m, 2H), 3.35 (d, $J = 18.4$ Hz, 1H), 2.11 – 2.03 (m, 1H), 0.95 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 166.8, 163.1, 160.7, 142.5, 136.7, 136.1, 136.0, 129.8, 128.7, 128.1, 127.6, 123.8, 115.8, 115.6, 96.8, 47.8, 46.6, 40.9, 39.9, 14.2

**HRMS (ESI):** $m/z$ calculated for C$_{21}$H$_{20}$FNO$_3$Na$: 376.1325$, found: 376.1325.

(2S,3R,4S)-6-benzyl-2-hydroxy-3-methyl-4-(4-nitrophenyl)-3,4,5,6-tetrahydropyran[2,3-c]pyrrol-7(2H)-one 4e

![Chemical Structure](image)

Prepared according to the general procedure using $n$-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(4-nitrobenzylidene)-pyrrolidine-2,3-dione 2e (64.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4e as a white solid with 98% yield. The diastereomeric ratio was determined to be >95:5 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}} = 9.68 \text{ min}$, $t_{\text{minor}} = 15.75 \text{ min}$; $[\alpha]_D^{20} = +54.8 \text{ (c = 0.99 in CH}_2\text{Cl}_2)$. 

**NMR and HRMS data for the product 4e:**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm): 8.18 (d, $J = 8.8$ Hz, 2H), 7.35 – 7.26 (m, 5H), 7.18 (d, $J = 8.0$ Hz, 2H), 6.74 (br s, 1H), 5.76 (br s, 1H), 4.67 (d, $J = 14.8$ Hz, 1H), 4.48 (d, $J = 14.8$ Hz, 1H), 3.69 (d, $J = 10.8$ Hz, 1H), 3.49 (d, $J = 18.4$ Hz, 1H), 3.34 (d, $J = 18.4$ Hz, 1H), 2.18 – 2.11 (m, 1H), 0.98 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 166.6, 148.4, 147.3, 143.1, 136.4, 129.3, 128.8, 128.1, 127.8, 124.1, 96.6, 47.7, 46.6, 41.7, 39.9, 14.2

**HRMS (ESI):** $m/z$ calculated for C$_{21}$H$_{20}$N$_2$O$_3$Na$: 403.1270$, found: 403.1269.
(2S,3R,4S)-6-benzyl-4-(3-bromophenyl)-2-hydroxy-3-methyl-3,4,5,6-tetrahydropyran-2,3-dione 2f

![Structure of 2f](image)

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(3-bromobenzylidene)-pyrrolidine-2,3-dione 2f (71.2 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4f as a white solid with 94% yield. The diastereomeric ratio was determined to be 90:10 by crude $^1$H-NMR analysis, and the diastereoisomers cannot be separated by simple column chromatography; in order to get clean NMR and HPLC spectrum, 4f was transformed to its analogue $4f'$ [3], thus the enantiomeric excess of $4f'$ was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (10% 2-propanol/hexane, 1 mL/min), UV 220 nm, $t_{\text{major}}$ = 36.58 min, $t_{\text{minor}}$ = 39.84 min; $[\alpha]_D^{20} = +110.5$ ($c = 1.76$ in CH$_2$Cl$_2$, data for 4f).

NMR and HRMS data for the product $4f'$:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm): 7.44 – 7.41 (m, 1H), 7.33 – 7.26 (m, 4H), 7.21 – 7.18 (m, 3H), 7.07 – 7.05 (m, 1H), 6.20 (d, $J = 2.4$ Hz, 1H), 4.75 (d, $J = 14.8$ Hz, 1H), 4.43 (d, $J = 14.8$ Hz, 1H), 3.56 – 3.47 (m, 2H), 3.36 (d, $J = 18.4$ Hz, 1H), 2.44 – 2.36 (m, 1H), 0.95 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 164.1, 141.9, 141.1, 136.5, 131.0, 130.6, 128.7, 127.9, 127.7, 125.1, 123.1, 94.1, 47.2, 46.5, 41.8, 41.7, 14.7

HRMS (ESI): m/z calculated for C$_{21}$H$_{15}$BrClNO$_2$Na$: 454.0185$, found: 454.0186.

(2S,3R,4S)-6-benzyl-4-(3-chlorophenyl)-2-hydroxy-3-methyl-3,4,5,6-tetrahydropyran-2,3-dione 2g

![Structure of 2g](image)

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(3-chlorobenzylidene)-pyrrolidine-2,3-dione 2g (62.2 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4g as a white solid with 95% yield. The diastereomeric ratio was determined to be 91:9 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/hexane, 1 mL/min), UV 220 nm, $t_{\text{major}}$ = 6.16 min, $t_{\text{minor}}$ = 12.18 min; $[\alpha]_D^{20} = +57.1$ ($c = 1.38$ in CH$_2$Cl$_2$).
NMR and HRMS data for the product 4g:

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm): 7.32 – 7.23 (m, 5H), 7.20 – 7.17 (m, 2H), 7.13 – 7.12 (m, 1H), 7.04 – 7.01 (m, 1H), 5.90 (br s, 1H), 5.70 (br s, 1H), 4.74 (d, $J = 14.8$ Hz, 1H), 4.42 (d, $J = 14.8$ Hz, 1H), 3.50 – 3.46 (m, 2H), 3.36 (d, $J = 18.4$ Hz, 1H), 2.14 – 2.06 (m, 1H), 0.97 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm): 166.6, 142.7, 142.6, 136.7, 134.7, 130.1, 128.7, 128.1, 128.0, 127.9, 127.7, 127.5, 123.2, 96.7, 47.7, 46.5, 41.4, 39.7, 14.2

HRMS (ESI): m/z calculated for C$_{21}$H$_{26}$ClNO$_3$Na$: 392.1029$, found: 392.1023.

(2S,3R,4S)-6-benzyl-2-hydroxy-3-methyl-4-(p-tolyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 4h

![Diagram of 4h]

Prepared according to the general procedure using $n$-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(4-methylbenzylidene)-pyrrolidine-2,3-dione 2h (58.2 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4h as a white solid with 96% yield. The diastereomeric ratio was determined to be 90:10 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/$n$-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}} = 5.87$ min, $t_{\text{minor}} = 9.94$ min; [α]$_D^{20}$ = +52.5 (c = 1.71 in CD$_2$Cl$_2$).

NMR and HRMS data for the product 4h:

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm): 7.51 – 7.44 (m, 3H), 7.39 – 7.37 (m, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 5.92 (br s, 1H), 4.90 (d, $J = 14.8$ Hz, 1H), 4.64 (d, $J = 14.8$ Hz, 1H), 3.70 – 3.65 (m, 2H), 3.60 (d, $J = 18.4$ Hz, 1H), 2.53 (s, 3H), 2.33 – 2.28 (m, 1H), 1.16 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm): 166.9, 142.3, 137.4, 136.8, 136.7, 129.4, 128.6, 128.3, 128.0, 127.5, 124.5, 96.9, 48.0, 46.5, 41.1, 39.8, 21.0, 14.2

HRMS (ESI): m/z calculated for C$_{22}$H$_{23}$NO$_3$Na$: 372.1576$, found: 372.1575.
(2S,3R,4S)-6-benzyl-2-hydroxy-4-((4-methoxyphenyl)-3-methyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 4i

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(4-methoxybenzylidene)-pyrrolidine-2,3-dione 2i (61.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4i as a white solid with 99% yield. The diastereomeric ratio was determined to be 92:8 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{major} = 7.14$ min, $t_{minor} = 14.98$ min; $[\alpha]_D^{20} = +58.2$ ($c = 1.66$ in CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm): 7.51 – 7.45 (m, 3H), 7.39 – 7.37 (m, 2H), 7.25 (d, $J = 8.4$ Hz, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 5.91 (br s, 1H), 4.90 (d, $J = 14.8$ Hz, 1H), 4.64 (d, $J = 14.8$ Hz, 1H), 3.99 (s, 3H), 3.71 – 3.57 (m, 3H), 2.30 – 2.25 (m, 1H), 1.16 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm): 166.9, 158.6, 142.3, 136.8, 132.3, 129.3, 128.6, 128.0, 127.5, 124.6, 114.1, 96.9, 55.2, 47.9, 46.5, 40.7, 39.8, 14.2

HRMS (ESI): m/z calculated for C$_{22}$H$_{23}$NO$_4$Na$: 388.1525$, found: 388.1518.

(2S,3R,4S)-6-benzyl-2-hydroxy-3-methyl-4-(m-tolyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 4h

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(3-methylbenzylidene)-pyrrolidine-2,3-dione 2j (58.2 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4j as a white solid with 86% yield. The diastereomeric ratio was determined to be 91:9 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{major} = 5.52$ min, $t_{minor} = 9.56$ min; $[\alpha]_D^{20} = +50.8$ ($c = 1.18$ in CH$_2$Cl$_2$).

NMR and HRMS data for the product 4j:
\[^1\text{H NMR (400 MHz, CDCl}_3\text{): }\delta (\text{ppm}): 7.30 – 7.24 (m, 3H), 7.20 – 7.16 (m, 3H), 7.05 (d, J = 7.6 Hz, 1H), 6.93 – 6.91 (m, 2H), 5.70 (br s, 1H), 4.71 (d, J = 14.8 Hz, 1H), 4.43 (d, J = 14.8 Hz, 1H), 3.50 – 3.36 (m, 3H), 2.31 (s, 3H), 2.15 – 2.08 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H).

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{): }\delta (\text{ppm}): 166.9, 142.3, 137.4, 136.8, 136.7, 129.4, 128.6, 128.3, 128.0, 127.5, 124.5, 96.9, 48.0, 46.5, 41.1, 39.8, 21.0, 14.2

HRMS (ESI): m/z calculated for C\text{_{22}H_{23}NO_3Na}^+: 372.1576, found: 372.1575.

\textbf{(2S,3R,4S)-6-benzyl-2-hydroxy-4-(2-methoxyphenyl)-3-methyl-3,4,5,6-tetrahydropyran[2,3-c]pyrrolo-7(2H)-one 4k}

\begin{center}
\includegraphics[width=0.2\textwidth]{4k.png}
\end{center}

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(2-methoxybenzylidene)-pyrrolidine-2,3-dione 2k (61.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4k as a white solid with 94% yield. The diastereomeric ratio was determined to be 90:10 by crude \[^1\text{H NMR analysis, and the enantiomeric excess of the major product was determined to be 96% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t\text{major} = 8.00 min, t\text{minor} = 17.83 min; [\alpha]_D^{20} = +29.3 (c = 1.66 in CH\text{Cl}_2).}

\textbf{NMR and HRMS data for the product 4k:}

\[^1\text{H NMR (400 MHz, CDCl}_3\text{): }\delta (\text{ppm}): 7.51 – 7.43 (m, 4H), 7.39 – 7.37 (m, 2H), 7.25 (d, J = 7.6 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 5.87 (br s, 1H), 4.78 (q, J = 15.2 Hz, 2H), 4.19 (d, J = 10.4 Hz, 1H), 3.91 (s, 3H), 3.70 (d, J = 18.4 Hz, 1H), 3.56 (d, J = 18.4 Hz, 1H), 2.48 – 2.44 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H).

\[^{13}\text{C NMR (100 MHz, CDCl}_3\text{): }\delta (\text{ppm}): 166.9, 157.8, 141.8, 137.0, 130.0, 128.6, 128.3, 128.1, 127.9, 127.4, 125.0, 120.7, 110.7, 96.9, 60.4, 55.2, 48.0, 46.4, 14.1

HRMS (ESI): m/z calculated for C\text{_{22}H_{23}NO_3Na}^+: 388.1525, found: 388.1528.

\textbf{(2S,3R,4S)-6-benzyl-4-(3,4-dimethoxyphenyl)-2-hydroxy-3-methyl-3,4,5,6-tetrahydropyran[2,3-c]pyrrolo-7(2H)-one 4l}

\begin{center}
\includegraphics[width=0.2\textwidth]{4l.png}
\end{center}
Prepared according to the general procedure using \( n \)-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(3,4-dimethoxybenzylidene)pyrrolidine-2,3-dione 2I (67.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4l as a white solid with 81% yield. The diastereomeric ratio was determined to be 89:11 by crude \( ^{1} \)H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/\( n \)-hexane, 1 mL/min), UV 220 nm, \( t_{\text{major}} = 7.89 \text{ min}, t_{\text{minor}} = 16.68 \text{ min}; [\alpha]_{D}^{20} = 46.3 (c = 1.26 \text{ in CH}_2\text{Cl}_2). \)

\( NMR \) and \( HRMS \) data for the product 4I:

\( ^{1} \)H NMR (400 MHz, CDCl₃): \( \delta \) (ppm): 7.30 – 7.22 (m, 3H), 7.19 – 7.17 (m, 2H), 6.79 (d, \( J = 8.0 \text{ Hz}, 1 \text{H} \)), 6.70 (dd, \( J = 8.4 \text{ Hz}, J = 2.4 \text{ Hz}, 1 \text{H} \)), 6.57 (d, \( J = 2.4 \text{ Hz}, 1 \text{H} \)), 6.41 (br s, 1H), 5.73 (br s, 1H), 4.58 (q, \( J = 15.2 \text{ Hz}, 2 \text{H} \)), 3.86 (s, 3H), 3.79 (s, 3H), 3.52 – 3.38 (m, 3H), 2.12 – 2.04 (m, 1H), 0.98 (d, \( J = 6.8 \text{ Hz}, 3 \text{H} \)).

\( ^{13} \)C NMR (100 MHz, CDCl₃): \( \delta \) (ppm): 166.9, 158.6, 142.3, 136.8, 132.3, 129.3, 128.6, 128.0, 127.5, 124.6, 114.1, 96.9, 55.2, 47.9, 46.5, 40.7, 39.8, 14.2

\( HRMS \) (ESI): \( m/z \) calculated for C₂₂H₂₃NO₄Na⁺: 388.1525, found: 388.1518.

\((2S,3R,4S)-6\text{-}\text{benzyl}-2\text{-}\text{hydroxy}-4\text{-}(3\text{-}\text{hydroxy}-4\text{-}\text{methoxyphenyl})\text{-}3\text{-}\text{methyl}-3,4,5,6\text{-}\text{tetrahydro} \text{pyrano[2,3-c]pyrrole-7(2H)}\text{-}\text{one} \ 4m \)

Prepared according to the general procedure using \( n \)-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(3-hydroxy-4-methoxybenzylidene)pyrrolidine-2,3-dione 2m (64.6 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4m as a white solid with 96% yield. The diastereomeric ratio was determined to be 88:12 by crude \( ^{1} \)H-NMR analysis, and the enantiomeric excess of the major product was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/\( n \)-hexane, 1 mL/min), UV 220 nm, \( t_{\text{major}} = 10.18 \text{ min}, t_{\text{minor}} = 29.14 \text{ min}; [\alpha]_{D}^{20} = +154.6 (c = 0.58 \text{ in CH}_2\text{Cl}_2). \)

\( NMR \) and \( HRMS \) data for the product 4m:

\( ^{1} \)H NMR (400 MHz, CDCl₃): \( \delta \) (ppm): 7.22 – 7.15 (m, 3H), 7.11 – 7.08 (m, 2H), 6.69 (d, \( J = 8.4 \text{ Hz}, 1 \text{H} \)), 6.63 (d, \( J = 2.0 \text{ Hz}, 1 \text{H} \)), 6.54 (dd, \( J = 8.4 \text{ Hz}, J = 2.0 \text{ Hz}, 1 \text{H} \)), 5.63 (br s, 1H), 4.65 (d, \( J = 14.8 \text{ Hz}, 1 \text{H} \)), 4.32 (d, \( J = 14.8 \text{ Hz}, 1 \text{H} \)), 3.78 (s, 3H), 3.42 – 3.30 (m, 3H), 2.02 – 1.99 (m, 9H), 0.88 (d, \( J = 6.8 \text{ Hz}, 3 \text{H} \)).

\( ^{13} \)C NMR (100 MHz, CDCl₃): \( \delta \) (ppm): 166.8, 145.8, 145.6, 142.2, 136.8, 133.5, 128.7, 128.1, 128.0, 127.5, 124.5, 114.3, 110.7, 96.9, 55.9, 47.9, 46.5, 40.9, 39.6, 14.2

\( HRMS \) (ESI): \( m/z \) calculated for C₂₂H₂₃NO₅Na⁺: 404.1474, found: 404.1474.
(2S,3R,4S)-6-benzyl-2-hydroxy-3-methyl-4-(naphthalen-2-yl)-3,4,5,6-tetrahydropyran[2,3-c]pyrro-7(2H)-one 4n

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(naphthalen-2-ylmethylene)-pyrrolidine-2,3-dione 2n (77.0 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4n as a white solid with 95% yield. The diastereomeric ratio was determined to be 92:8 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{major} = 6.92$ min, $t_{minor} = 13.88$ min; $[\alpha]_D^{20} = +65.4$ ($c = 1.72$ in CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm): 8.01 – 7.94 (m, 3H), 7.81 (br s, 1H), 7.69 – 7.62 (m, 2H), 7.47 – 7.40 (m, 4H), 7.35 – 7.33 (m, 2H), 5.98 (br s, 1H), 4.89 (d, $J = 14.8$ Hz, 1H), 4.59 (d, $J = 14.8$ Hz, 1H), 3.89 (d, $J = 10.8$ Hz, 1H), 3.67 (d, $J = 18.4$ Hz, 1H), 3.55 (d, $J = 18.4$ Hz, 1H), 2.47 – 2.42 (m, 1H), 1.19 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ (ppm): 167.0, 142.5, 137.9, 136.6, 133.4, 132.6, 129.9, 128.6, 128.5, 128.1, 127.9, 127.6, 127.5, 127.4, 126.3, 125.8, 124.1, 96.9, 48.0, 46.5, 41.8, 39.6, 14.3

HRMS (ESI): $m/z$ calculated for C$_{25}$H$_{31}$NO$_3$Na$: 408.1576$, found: 408.1574.

(2S,3R,4R)-6-benzyl-2-hydroxy-3-methyl-4-(thiophen-2-yl)-3,4,5,6-tetrahydropyran[2,3-c]pyrro-7(2H)-one 4o

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-(thiophen-2-ylmethylene)-pyrrolidine-2,3-dione 2o (56.6 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4o as a white solid with 87% yield. The diastereomeric ratio was determined to be 85:15 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{major} = 9.22$ min, $t_{minor} = 18.70$ min; $[\alpha]_D^{20} = +55.8$ ($c = 0.53$ in CH$_2$Cl$_2$).
NMR and HRMS data for the product 4o:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm): 7.24 – 7.17 (m, 3H), 7.13 – 7.10 (m, 3H), 6.87 – 6.84 (m, 1H), 6.80 – 6.79 (m, 1H), 6.34 (br s, 1H), 5.64 (br s, 1H), 4.63 (d, $J = 14.8$ Hz, 1H), 4.38 (d, $J = 14.8$ Hz, 1H), 3.81 (d, $J = 10.8$ Hz, 1H), 3.51 – 3.40 (m, 2H), 2.13 – 2.04 (m, 1H), 0.97 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 166.8, 143.6, 141.8, 136.7, 128.7, 128.0, 127.6, 126.7, 126.0, 124.4, 123.6, 96.8, 47.9, 46.5, 40.6, 36.9, 14.3

HRMS (ESI): $m/z$ calculated for C$_{19}$H$_{19}$NO$_3$SNa$: 364.0983$, found: 364.0984.

(2S,3R,4R)-6-benzyl-2-hydroxy-3-methyl-4-((E)-styryl)-3,4,5,6-tetrahydropyran[2,3-c]pyrrol-7(2H)-one 4p

![Chemical structure]

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-((E)-3-phenylallylidene)-pyrrolidine-2,3-dione 2p (60.6 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4p as a white solid with 98% yield. The diastereomeric ratio was determined to be 85:15 by crude $^1$H-NMR analysis, and the diastereoisomers cannot be separated by simple column chromatography; in order to get clean NMR and HPLC spectrum, 4p was transformed to its analogue 4p$^{[3]}$, thus the enantiomeric excess of 4p$^{[3]}$ was determined to be >99% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 254 nm, $t_{\text{major}} = 9.08$ min, $t_{\text{minor}} = 10.79$ min; [$\alpha$]$_{20}^{D} = +216.2$ (c = 0.32 in CH$_2$Cl$_2$, data for 4p$^{[3]}$).

NMR and HRMS data for the product 4p$^{[3]}$:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm): 7.35 – 7.27 (m, 7H), 7.25 – 7.23 (m, 2H), 6.58 (d, $J = 15.4$ Hz, 1H), 6.19 (d, $J = 2.4$ Hz, 1H), 5.85 (dd, $J = 15.4$ Hz, $J = 9.6$ Hz, 1H), 4.61 (q, $J = 14.8$ Hz, 2H), 3.67 – 3.66 (m, 2H), 3.16 (d, $J = 10.4$ Hz, 1H), 2.26 – 2.18 (m, 1H), 1.11 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 164.4, 141.1, 136.8, 136.0, 135.1, 128.8, 128.7, 128.2, 128.1, 127.7, 126.6, 126.3, 125.4, 94.2, 47.7, 46.6, 39.8, 29.7, 15.0

HRMS (ESI): $m/z$ calculated for C$_{23}$H$_{22}$ClNO$_2$Na$: 402.1237$, found: 402.1240.
(2S,3R,4S)-2-hydroxy-6-(4-methoxybenzyl)-3-methyl-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 4q

Prepared according to the general procedure using n-propanal (17.4 mg, 0.3 mmol, 1.5 equiv) and 4-benzylidene-1-(4-methoxybenzyl)-pyrrolidine-2,3-dione 2q (61.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4q as a white solid with 85% yield. The diastereomeric ratio was determined to be 90:10 by crude \(^1\)H-NMR analysis, and the enantiomeric excess of the major product was determined to be 97% by chiral HPLC analysis on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, \(t_{major} = 6.24 \text{ min, } t_{minor} = 11.75 \text{ min; } \left[\alpha\right]_D^{20} = +71.0 \text{ (c = 2.32 in CH}_2\text{Cl}_2\right).\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm): 7.24 – 7.20 (m, 2H), 7.18 – 7.14 (m, 1H), 7.06 – 7.00 (m, 4H), 6.74 – 6.70 (m, 2H), 5.66 (br s, 1H), 4.55 (d, \(J = 14.8\) Hz, 1H), 4.28 (d, \(J = 14.8\) Hz, 1H), 3.68 (s, 3H), 3.44 (d, \(J = 10.8\) Hz, 1H), 3.40 – 3.25 (m, 2H), 2.07 – 1.99 (m, 1H), 0.88 (d, \(J = 6.8\) Hz, 3H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm): 166.9, 159.0, 142.4, 140.5, 129.4, 128.8, 128.6, 128.4, 127.0, 124.0, 114.0, 96.8, 55.2, 47.8, 45.9, 41.5, 39.8, 14.2

HRMS (ESI): \(m/z\) calculated for C\(_{22}\)H\(_{21}\)NO\(_4\)Na\(^+\): 388.1525, found: 388.1528.

(2S,3R,4S)-6-benzyl-3-ethyl-2-hydroxy-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 4r

Prepared according to the general procedure using n-butyraldehyde (21.6 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-benzylidene-pyrrolidine-2,3-dione 2a (55.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4r as a white solid with 88% yield. The diastereomeric ratio was determined to be >95:5 by crude \(^1\)H-NMR analysis, and the enantiomeric excess of the major product was determined to be 98% by chiral HPLC analysis on Chiralpak AD-H column (20% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, \(t_{major} = 5.78 \text{ min, } t_{minor} = 10.08 \text{ min; } \left[\alpha\right]_D^{20} = +79.8 \text{ (c = 0.94 in CH}_2\text{Cl}_2\right).\)

\(^{1}\)H NMR data for the product 4r:
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm): 7.32 – 7.28 (m, 3H), 7.25 – 7.21 (m, 3H), 7.18 – 7.12 (m, 4H), 6.05 (br s, 1H), 5.88 (br s, 1H), 4.72 (d, \(J = 14.8\) Hz, 1H), 4.40 (d, \(J = 14.8\) Hz, 1H), 3.54 (d, \(J = 10.8\) Hz, 1H), 3.49 – 3.31 (m, 2H), 1.97 – 1.90 (m, 1H), 1.57 – 1.47 (m, 2H), 0.87 (t, \(J = 7.2\) Hz, 3H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm): 166.8, 142.3, 140.7, 136.8, 128.7, 128.6, 128.1, 128.0, 127.6, 127.1, 124.4, 94.7, 47.9, 46.5, 46.0, 40.9, 21.6, 11.7

HRMS (ESI): \(m/z\) calculated for C\(_{22}\)H\(_{23}\)NO\(_3\)Na\(^+\): 372.1576, found: 372.1578.

\((2S,3R,4S)-6\)-benzyl-2-hydroxy-4-phenyl-3-propyl-3,4,5,6-tetrahydropyra[2,3-c]pyrrol-7(2H)-one 4s

![Chemical structure of 4s](image)

Prepared according to the general procedure using \(n\)-pentanal (25.8 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-benzylidenepyrrolidine-2,3-dione 2a (55.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4s as a white solid with 92% yield. The diastereomeric ratio was determined to be 94:6 by crude \(^1\)H-NMR analysis, and the enantiomeric excess of the major product was determined to be 96% by chiral HPLC analysis on Chiralpak AD-H column (25\% 2-propanol/\(n\)-hexane, 1 mL/min), UV 220 nm, \(t_{major} = 5.23\) min, \(t_{minor} = 8.47\) min; \([\alpha]\)D\(^{20} = +60.8\) (c = 1.12 in CH\(_2\)Cl\(_2\)).

**NMR and HRMS data for the product 4s:**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm): 7.33 – 7.21 (m, 6H), 7.18 – 7.12 (m, 4H), 6.60 (br s, 1H), 5.88 (br s, 1H), 4.71 (d, \(J = 14.8\) Hz, 1H), 4.40 (d, \(J = 14.8\) Hz, 1H), 3.55 (d, \(J = 10.8\) Hz, 1H), 3.46 (d, \(J = 18.4\) Hz, 1H), 3.32 (d, \(J = 18.4\) Hz, 1H), 2.07 – 2.00 (m, 1H), 1.60 – 1.51 (m, 1H), 1.48 – 1.38 (m, 1H), 1.21 – 1.10 (m, 1H), 0.92 – 0.83 (m, 1H), 0.77 (t, \(J = 7.2\) Hz, 3H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm): 167.0, 142.2, 140.7, 136.7, 128.7, 128.6, 128.0, 127.9, 127.5, 127.1, 124.5, 94.9, 48.0, 46.5, 44.1, 40.9, 30.8, 20.1, 14.1

**HRMS (ESI):** \(m/z\) calculated for C\(_{22}\)H\(_{25}\)NO\(_3\)Na\(^+\): 386.1732, found: 386.1736.

\((2S,3R,4S)-6\)-benzyl-3-butyl-2-hydroxy-4-phenyl-3,4,5,6-tetrahydropyra[2,3-c]pyrrol-7(2H)-one 4t

![Chemical structure of 4t](image)
Prepared according to the general procedure using \( n \)-hexanal (30.0 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-benzylidenepeyrrolidin-2,3-dione \( \textbf{2a} \) (55.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered \textbf{4t} as a white solid with 82\% yield. The diastereomeric ratio was determined to be 93:7 by crude \( ^1\text{H}-\text{NMR} \) analysis, and the enantiomeric excess of the major product was determined to be 97\% by chiral HPLC analysis on Chiralpak AD-H column (25\% 2-propanol/\( n \)-hexane, 1 mL/min), UV 220 nm, \( t_{\text{major}} = 5.08 \) min, \( t_{\text{minor}} = 7.40 \) min; \([\alpha]_D^{20} = +58.2 \) (c = 1.21 in CH\(_2\)Cl\(_2\)).

\textbf{NMR and HRMS data for the product \textbf{4t}:}

\( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) (ppm): 7.32 – 7.27 (m, 4H), 7.24 – 7.21 (m, 2H), 7.18 – 7.16 (m, 2H), 7.14 – 7.12 (m, 2H), 5.83 (br s, 1H), 4.72 (d, \( J = 14.8 \) Hz, 1H), 4.40 (d, \( J = 14.8 \) Hz, 1H), 3.53 (d, \( J = 10.8 \) Hz, 1H), 3.46 (d, \( J = 18.4 \) Hz, 1H), 3.32 (d, \( J = 18.4 \) Hz, 1H), 2.04 – 1.97 (m, 1H), 1.58 – 1.48 (m, 1H), 1.40 – 1.32 (m, 1H), 1.26 – 1.05 (m, 4H), 0.77 (t, \( J = 7.2 \) Hz, 3H).

\( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) (ppm): 166.8, 142.2, 140.6, 136.8, 130.1, 128.7, 128.6, 128.0, 127.6, 127.1, 124.5, 94.9, 47.9, 46.5, 44.2, 40.9, 29.1, 28.3, 22.7, 13.8

\textbf{HRMS (ESI):} \( m/z \) calculated for C\(_{23}\)H\(_{27}\)NO\(_3\)Na\(^+\): 400.1889, found: 400.1892.

(25R,3R,4S)-6-benzyl-2-hydroxy-3-isopropyl-4-phenyl-3,4,5,6-tetrahydropyranol[2,3-c]pyrrol-7(2H)-one \textbf{4u}

![Diagram](attachment:image.png)

Prepared according to the general procedure using 3-methylbutanal (25.8 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-benzylidenepeyrrolidin-2,3-dione \( \textbf{2a} \) (55.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered \textbf{4u} as a white solid with 70\% yield. The diastereomeric ratio was determined to be 85:15 by crude \( ^1\text{H}-\text{NMR} \) analysis, and the diastereoisomers cannot be separated by simple column chromatography; in order to get clean NMR and HPLC spectrum, \textbf{4u} was transformed to its analogue \textbf{4u}\(^3\), thus the enantiomeric excess of \textbf{4u}\(^*\) was determined to be 97\% by chiral HPLC analysis on Chiralpak OD-H column (30\% 2-propanol/\( n \)-hexane, 1 mL/min), UV 220 nm, \( t_{\text{minor}} = 8.74 \) min, \( t_{\text{major}} = 13.03 \) min; \([\alpha]_D^{20} = +175.0 \) (c = 0.26 in CH\(_2\)Cl\(_2\)).

\textbf{NMR and HRMS data for the product \textbf{4u}*:}

\( ^1\text{H} \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) (ppm): 7.33 – 7.24 (m, 6H), 7.17 – 7.14 (m, 4H), 6.36 (d, \( J = 2.4 \) Hz, 1H), 4.75 (d, \( J = 14.8 \) Hz, 1H), 4.35 (d, \( J = 14.8 \) Hz, 1H), 3.81 (d, \( J = 11.2 \) Hz, 1H), 3.50 (d, \( J = 18.4 \) Hz, 1H), 3.19 (d, \( J = 18.4 \) Hz, 1H), 2.42 – 2.37 (m, 1H), 1.75 – 1.67 (m, 1H), 0.95 (d, \( J = 7.2 \) Hz, 3H), 0.79 (d, \( J = 7.2 \) Hz, 3H).

\( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) (ppm): 164.4, 140.9, 139.7, 136.8, 129.1, 128.7, 128.1, 127.9, 127.6, 127.5, 127.4, 91.7, 50.9, 47.4, 46.4, 39.9, 28.1, 21.1, 19.0

\textbf{HRMS (ESI):} \( m/z \) calculated for C\(_{23}\)H\(_{31}\)ClNO\(_2\)Na\(^+\): 404.1393, found: 404.1397.
(2S,3R,4S)-3,6-dibenzyl-2-hydroxy-4-phenyl-3,4,5,6-tetrahydropyran[2,3-c]pyrrol-7(2H)-one 4v

Prepared according to the general procedure using 3-phenylpropanal (40.2 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-benzylideneypyrrroldine-2,3-dione 2a (55.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4v as a white solid with 85% yield. The diastereomeric ratio was determined to be 93:7 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiraltaks AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}}$ = 6.25 min, $t_{\text{minor}}$ = 7.78 min; $[\alpha]_D^{20} = +126.8$ (c = 0.48 in CH$_2$Cl$_2$).

NMR and HRMS data for the product 4v:

$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm): 7.35 – 7.19 (m, 8H), 7.18 – 7.16 (m, 4H), 7.14 – 7.09 (m, 1H), 7.06 – 7.04 (m, 2H), 5.45 (br s, 1H), 4.72 (d, $J = 14.8$ Hz, 1H), 4.40 (d, $J = 14.8$ Hz, 1H), 3.65 (d, $J = 10.8$ Hz, 1H), 3.48 (d, $J = 18.4$ Hz, 1H), 3.33 (d, $J = 18.4$ Hz, 1H), 2.77 – 2.71 (m, 1H), 2.56 (dd, $J = 13.6$ Hz, 7.3 Hz, 1H), 2.29 – 2.22 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$); $\delta$ (ppm): 167.0, 142.2, 140.7, 136.7, 128.7, 128.6, 128.0, 127.9, 127.5, 127.1, 124.5, 94.9, 48.0, 46.5, 44.1, 40.9, 30.8, 20.1, 14.1

HRMS (ESI): m/z calculated for C$_{23}$H$_{25}$NO$_3$Na$^+$: 386.1732, found: 386.1736.

(2S,3R,4S)-6-benzyl-3-(2-(benzyloxy)ethyl)-2-hydroxy-4-phenyl-3,4,5,6-tetrahydropyran[2,3-c]pyrrol-7(2H)-one 4w

Prepared according to the general procedure using 4-(benzyloxy)butanal (40.2 mg, 0.3 mmol, 1.5 equiv) and 1-benzyl-4-benzylideneypyrrroldine-2,3-dione 2a (55.4 mg, 0.2 mmol, 1.0 equiv). Purification of the crude product via column chromatography delivered 4w as a white solid with 80% yield. The diastereomeric ratio was determined to be 94:6 by crude $^1$H-NMR analysis, and the enantiomeric excess of the major product was determined to be 99% by chiral HPLC analysis on Chiraltaks AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}}$ = 7.11 min, $t_{\text{minor}}$ = 10.56 min; $[\alpha]_D^{20} = +69.1$ (c = 1.09 in CH$_2$Cl$_2$).

NMR and HRMS data for the product 4w:

$^1$H NMR (400 MHz, CDCl$_3$); $\delta$ (ppm): 7.33 – 7.24 (m, 8H), 7.23 – 7.21 (m, 3H), 7.18 – 7.12 (m, 4H), 6.37 (br s, 1H), 5.86 (br s, 1H), 4.70 (d, $J = 14.8$ Hz, 1H), 4.41 (d, $J = 14.8$ Hz, 1H),
4.33 (s, 2H), 3.59 (d, J = 10.8 Hz, 1H), 3.50 – 3.42 (m, 2H), 3.37 – 3.31 (m, 2H), 2.29 – 2.23 (m, 1H), 1.91 – 1.81 (m, 1H), 1.66 – 1.58 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 166.8, 142.2, 140.4, 138.2, 136.7, 128.8, 128.6, 128.4, 128.0, 127.6, 127.5, 127.4, 127.2, 124.1, 94.9, 72.6, 68.0, 47.9, 46.5, 41.6, 40.9, 28.7


### 4. General Procedure for the Synthesis of Chiral Bicyclic Dihydropyranes 6 by Directly Using Aqueous Acetaldehyde

A glass tube was charged with pyrrolidine-2,3-dione 2 (0.2 mmol), amine catalyst 3a (0.04 mmol, 13 mg) and benzoic acid (0.04 mmol, 4.9 mg) in 2 mL THF. The 40% aqueous acetaldehyde 5 (0.6 mmol, 66mg) was added with a syringe, and the reaction was sealed with a Teflon cap and stirred at room temperature for about 16 hours. When the reaction was complete, the mixture was directly purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (4:1 to 1:1) to afford the corresponding bicyclic dihydropyranes 6, which was analyzed by crude $^1$H-NMR to determine the diastereoselectivity of the oxo-IEDDA reaction. Since the diastereoisomers of 6 cannot be separated by simple column chromatography in most cases, we transform 6 to its analogue 6' by using the following sequential reactions: a glass tube was charged with 6, Ac$_2$O (5 eq.) and DMAP (0.1 eq.) in 1 mL pyridine, and the reaction was stirred at room temperature for about 2 hours. When the reaction was completed, 2 mL of 20% hydrochloric acid was added to the reaction mixture, and the organic material was extracted with ethyl acetate, washed with brine and dried over anhydrous Na$_2$SO$_4$, then concentrated under reduced pressure to give the corresponding acetylated compound; such compound was dissolved in 2 mL DCM under argon, and TiCl$_4$ (5 eq.) was added into the reaction mixture. The reaction was stirred at room temperature for about 16 hours. When the reaction was completed, 2 mL DCM and 1mL water was added to the reaction mixture. The organic layer was separated, dried over anhydrous Na$_2$SO$_4$ and purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (6:1 to 4:1) to afford the desired pure product 6' (>95:5 d.r.) which was further analyzed by $^1$H-NMR, $^{13}$C-HMR, HRMS, chiral HPLC analysis, etc.
(2S,4S)-6-benzyl-2-hydroxy-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 6a

![Chemical structure of 6a]

According to the general procedure, the crude product was purified via column chromatography delivering 6a as a white solid with 95% yield. The diastereomeric ratio was determined to be 88:12 by crude \(^1\)H-NMR analysis. 6a was transformed to its analogue 6a' (only a single diastereoisomer was obtained) with 86% yield. The enantiomeric excess of 6a' was determined to be 99% by chiral HPLC analysis on Chiralpak OD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t\(_{major}\) = 14.96 min, t\(_{minor}\) = 20.92 min; [\(\alpha\)]\(_D\)^{20} = +124.8 (c = 0.32 in CH\(_2\)Cl\(_2\) data for 6a').

\(\text{NMR and HRMS data for the product 6a'}:\)

\(\text{\(^1\)H NMR (400 MHz, CDCl}_3\): } \delta \text{ (ppm): } 7.35 - 7.27 (m, 6H), 7.21 - 7.15 (m, 4H), 6.44 (t, J = 2.4 Hz, 1H), 4.75 (d, J = 14.8 Hz, 1H), 4.44 (d, J = 14.8 Hz, 1H), 4.07 (dd, J = 11.6 Hz, J = 6.0 Hz, 1H), 3.58 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 3.46 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 2.53 – 2.47 (m, 1H), 2.40 – 2.33 (m, 1H).

\(\text{\(^{13}\)C NMR (100 MHz, CDCl}_3\): } \delta \text{ (ppm): } 164.3, 141.8, 139.6, 136.7, 129.1, 128.8, 128.0, 127.9, 127.7, 127.6, 125.3, 88.4, 47.4, 46.5, 39.6, 34.7

\(\text{HRMS (ESI): } m/z \text{ calculated for C}_{20}H_{18}ClNO_2Na}: 362.0924, \text{ found: } 362.0927.

(2S,4S)-2-hydroxy-6-(4-methoxybenzyl)-4-phenyl-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 6b

![Chemical structure of 6b]

According to the general procedure, the crude product was purified via column chromatography delivering 6b as a white solid with 90% yield. The diastereomeric ratio was determined to be 89:11 by crude \(^1\)H-NMR analysis. 6b was transformed to its analogue 6b' (only a single diastereoisomer was obtained) with 81% yield. The enantiomeric excess of 6b' was determined to be 95% by chiral HPLC analysis on Chiralpak AD-H column (20% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t\(_{major}\) = 22.87 min, t\(_{minor}\) = 26.50 min; [\(\alpha\)]\(_D\)^{20} = +56.6 (c = 0.54 in CH\(_2\)Cl\(_2\) data for 6b').

\(\text{NMR and HRMS data for the product 6b'}:\)

S 20
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm): 7.29 – 7.21 (m, 3H), 7.10 – 7.05 (m, 4H), 6.76 (d, $J = 8.4$ Hz, 2H), 6.36 (t, $J = 2.4$ Hz, 1H), 4.63 (d, $J = 14.8$ Hz, 1H), 4.29 (d, $J = 14.8$ Hz, 1H), 3.98 (dd, $J = 11.6$ Hz, $J = 6.0$ Hz, 1H), 3.71 (s, 3H), 3.48 (dd, $J = 18.4$ Hz, $J = 1.6$ Hz, 1H), 3.36 (dd, $J = 18.4$ Hz, $J = 1.6$ Hz, 1H), 2.45 – 2.39 (m, 1H), 2.32 – 2.25 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 164.2, 159.1, 141.9, 139.7, 129.5, 129.1, 128.8, 127.9, 127.7, 125.2, 114.1, 88.4, 55.3, 47.3, 45.9, 39.6, 34.8

HRMS (ESI): $m/z$ calculated for C$_{21}$H$_{20}$ClNO$_3$Na$: 392.1029$, found: 392.1030.

(2S,4S)-6-benzyl-4-(4-bromophenyl)-2-hydroxy-3,4,5,6-tetrahydropyranol[2,3-c]pyrrol-7(2H)-one 6c

According to the general procedure, the crude product was purified via column chromatography delivering 6c as a white solid with 88% yield. The diastereomeric ratio was determined to be 85:15 by crude $^1$H-NMR analysis. 6c was transformed to its analogue 6c' (only a single diastereoisomer was obtained) with 80% yield. The enantiomeric excess of 6c' was determined to be 97% by chiral HPLC analysis on Chiralpak OD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}} = 16.79$ min, $t_{\text{minor}} = 22.55$ min; $[\alpha]_{D}^{20} = +121.6$ ($c = 0.32$ in CH$_2$Cl$_2$, data for 6c').

NMR and HRMS data for the product 6c':

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm): 7.46 (d, $J = 8.4$ Hz, 2H), 7.34 – 7.27 (m, 3H), 7.21 – 7.19 (m, 2H), 7.05 (d, $J = 8.4$ Hz, 2H), 6.43 (t, $J = 2.4$ Hz, 1H), 4.74 (d, $J = 14.8$ Hz, 1H), 4.45 (d, $J = 14.8$ Hz, 1H), 4.04 (dd, $J = 11.6$ Hz, $J = 6.0$ Hz, 1H), 3.56 (dd, $J = 18.4$ Hz, $J = 1.6$ Hz, 1H), 3.43 (dd, $J = 18.4$ Hz, $J = 1.6$ Hz, 1H), 2.51 – 2.46 (m, 1H), 2.35 – 2.28 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 164.1, 142.1, 138.6, 136.6, 132.3, 129.6, 128.8, 128.1, 127.8, 124.4, 121.7, 88.2, 47.3, 46.5, 39.5, 34.3

HRMS (ESI): $m/z$ calculated for C$_{20}$H$_{17}$BrClNO$_2$Na$: 440.0029$, found: 440.0030.

(2S,4S)-6-benzyl-4-(4-chlorophenyl)-2-hydroxy-3,4,5,6-tetrahydropyranol[2,3-c]pyrrol-7(2H)-one 6d

S 21
According to the general procedure, the crude product was purified via column chromatography delivering 6d as a white solid with 92% yield. The diastereomeric ratio was determined to be 85:15 by crude ¹H-NMR analysis. 6d was transformed to its analogue 6d’ (only a single diastereoisomer was obtained) with 84% yield. The enantiomeric excess of 6c’ was determined to be 95% by chiral HPLC analysis on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_major = 13.38 min, t_minor = 14.79 min; [α]D²⁰ = +56.8 (c = 0.94 in CH₂Cl₂, data for 6d’).

NMR and HRMS data for the product 6d’:

¹H NMR (400 MHz, CDCl₃): δ (ppm): 7.34 – 7.26 (m, 5H), 7.21 – 7.19 (m, 2H), 7.12 – 7.09 (m, 2H), 6.43 (t, J = 2.4 Hz, 1H), 4.74 (d, J = 14.8 Hz, 1H), 4.45 (d, J = 14.8 Hz, 1H), 4.06 (dd, J = 11.6 Hz, J = 6.0 Hz, 1H), 3.57 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 3.43 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 2.51 – 2.46 (m, 1H), 2.35 – 2.28 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ (ppm): 164.1, 142.0, 138.1, 136.6, 133.6, 129.3, 129.2, 128.8, 128.1, 127.7, 124.6, 88.2, 47.3, 46.5, 39.5, 34.2

HRMS (ESI): m/z calculated for C₂₀H₁₇Cl₂NO₂Na⁺: 396.0534, found: 396.0535.

(2S,4S)-6-benzyl-4-(4-fluorophenyl)-2-hydroxy-3,4,5,6-tetrahydroxyflavone[2,3-c]pyrrol-7(2H)-one 6e

According to the general procedure, the crude product was purified via column chromatography delivering 6e as a white solid with 98% yield. The diastereomeric ratio was determined to be 87:13 by crude ¹H-NMR analysis. 6e was transformed to its analogue 6e’ (only a single diastereoisomer was obtained) with 85% yield. The enantiomeric excess of 6e’ was determined to be 96% by chiral HPLC analysis on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_major = 12.89 min, t_minor = 14.60 min; [α]D²⁰ = +58.3 (c = 1.21 in CH₂Cl₂, data for 6e’).

NMR and HRMS data for the product 6e’:

¹H NMR (400 MHz, CDCl₃): δ (ppm): 7.33 – 7.25 (m, 3H), 7.21 – 7.19 (m, 2H), 7.15 – 7.12 (m, 2H), 7.05 – 6.99 (m, 2H), 6.43 (t, J = 2.4 Hz, 1H), 4.74 (d, J = 14.8 Hz, 1H), 4.45 (d, J = 14.8 Hz, 1H), 4.07 (dd, J = 11.6 Hz, J = 6.0 Hz, 1H), 3.57 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 3.43 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 2.52 – 2.46 (m, 1H), 2.36 – 2.29 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ (ppm): 164.2, 163.3, 160.9, 141.9, 136.6, 135.3, 135.2, 129.4, 129.3, 128.8, 128.0, 127.7, 124.9, 116.2, 116.0, 88.3, 47.3, 46.5, 39.7, 34.1

HRMS (ESI): m/z calculated for C₂₀H₁₇ClFNO₂Na⁺: 380.0830, found: 380.0828.
(2S,4S)-6-benzyl-4-(3-bromophenyl)-2-hydroxy-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 6f

According to the general procedure, the crude product was purified via column chromatography delivering 6f as a white solid with 97% yield. The diastereomeric ratio was determined to be 86:14 by crude \(^1\)H-NMR analysis. 6f was transformed to its analogue 6f' (only a single diastereoisomer was obtained) with 82% yield. The enantiomeric excess of 6f' was determined to be 96% by chiral HPLC analysis on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, \(t_{\text{minor}} = 13.32\) min, \(t_{\text{major}} = 15.70\) min; \([\alpha]_D^{20} = +60.8\) (\(c = 0.97\) in \(\text{CH}_2\text{Cl}_2\), data for 6f').

**NMR and HRMS data for the product 6f':**

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm): 7.43 – 7.41 (m, 1H), 7.34 – 7.26 (m, 4H), 7.23 – 7.19 (m, 3H), 7.11 – 7.08 (m, 1H), 6.43 (t, \(J = 2.4\) Hz, 1H), 4.77 (d, \(J = 14.8\) Hz, 1H), 4.45 (d, \(J = 14.8\) Hz, 1H), 4.04 (dd, \(J = 11.6\) Hz, \(J = 6.0\) Hz, 1H), 3.58 (dd, \(J = 18.4\) Hz, \(J = 1.6\) Hz, 1H), 3.45 (dd, \(J = 18.4\) Hz, \(J = 1.6\) Hz, 1H), 2.53 – 2.47 (m, 1H), 2.37 – 2.29 (m, 1H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm): 164.1, 142.1, 142.0, 136.6, 131.0, 130.9, 130.7, 128.8, 128.0, 127.7, 126.5, 124.3, 123.1, 88.1, 47.3, 46.5, 39.4, 34.5

**HRMS (ESI):** m/z calculated for C\(_{20}\)H\(_{17}\)BrClNO\(_2\)Na\(^+\): 440.0029, found: 440.0027.

(2S,4R)-6-benzyl-4-(2-chlorophenyl)-2-hydroxy-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 6g

According to the general procedure, the crude product was purified via column chromatography delivering 6g as a white solid with 95% yield. The diastereomeric ratio was determined to be 84:16 by crude \(^1\)H-NMR analysis. 6g was transformed to its analogue 6g' (only a single diastereoisomer was obtained) with 80% yield. The enantiomeric excess of 6g' was determined to be 95% by chiral HPLC analysis on Chiralpak OD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, \(t_{\text{major}} = 12.99\) min, \(t_{\text{minor}} = 18.38\) min; \([\alpha]_D^{20} = +66.7\) (\(c = 1.06\) in \(\text{CH}_2\text{Cl}_2\), data for 6g').

**NMR and HRMS data for the product 6g':**
\(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm): 7.39 – 7.37 (m, 1H), 7.34 – 7.26 (m, 3H), 7.24 – 7.19 (m, 4H), 7.14 – 7.11 (m, 1H), 6.43 (t, \(J = 2.4\) Hz, 1H), 4.72 (d, \(J = 14.8\) Hz, 1H), 4.63 (br s, 1H), 4.52 (d, \(J = 14.8\) Hz, 1H), 3.64 (dd, \(J = 18.4\) Hz, \(J = 1.6\) Hz, 1H), 3.53 (dd, \(J = 18.4\) Hz, \(J = 1.6\) Hz, 1H), 2.55 – 2.50 (m, 1H), 2.36 (br s, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm): 164.3, 142.5, 137.1, 136.7, 134.1, 130.3, 129.0, 128.8, 128.0, 127.7, 127.6, 124.4, 88.3, 47.5, 46.5, 37.8, 29.7

HRMS (ESI): \(m/z\) calculated for \(C_{20}H_{17}ClNO_2Na^+\): 396.0534, found: 396.0531.

(2S,4R)-6-benzyl-4-(2,4-dichlorophenyl)-2-hydroxy-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 6h

![Chemical Structure]

According to the general procedure, the crude product was purified via column chromatography delivering 6h as a white solid with 86% yield. The diastereomeric ratio was determined to be 82:18 by crude \(^{1}\)H-NMR analysis. 6h was transformed to its analogue 6h* (only a single diastereoisomer was obtained) with 78% yield. The enantiomeric excess of 6h* was determined to be 96% by chiral HPLC analysis on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, \(t_{\text{major}} = 11.91\) min, \(t_{\text{minor}} = 17.52\) min; \([\alpha]_{D}^{20} = +48.7\) (\(c = 1.22\) in \(CH_2Cl_2\), data for 6h*).

NMR and HRMS data for the product 6h*:

\(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) (ppm): 7.40 (d, \(J = 2.4\) Hz, 1H), 7.34 – 7.25 (m, 3H), 7.24 – 7.20 (m, 3H), 7.06 (d, \(J = 8.4\) Hz, 1H), 6.43 (t, \(J = 2.4\) Hz, 1H), 4.70 (d, \(J = 14.8\) Hz, 1H), 4.59 (br s, 1H), 4.53 (d, \(J = 14.8\) Hz, 1H), 3.63 (dd, \(J = 18.4\) Hz, \(J = 1.6\) Hz, 1H), 3.50 (dd, \(J = 18.4\) Hz, \(J = 1.6\) Hz, 1H), 2.53 – 2.48 (m, 1H), 2.32 (br s, 1H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) (ppm): 164.0, 142.7, 136.5, 135.6, 134.7, 134.1, 130.1, 128.8, 128.2, 128.0, 127.9, 127.8, 123.6, 88.0, 47.3, 46.5, 37.8, 29.7

HRMS (ESI): \(m/z\) calculated for \(C_{20}H_{16}ClNO_2Na^+\): 430.0144, found: 430.0142.

(2S,4S)-6-benzyl-2-hydroxy-4-(p-tolyl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 6i

![Chemical Structure]
According to the general procedure, the crude product was purified via column chromatography delivering 6i as a white solid with 91% yield. The diastereomeric ratio was determined to be 86:14 by crude 1H-NMR analysis. 6i was transformed to its analogue 6i’ (only a single diastereoisomer was obtained) with 83% yield. The enantiomeric excess of 6i’ was determined to be 95% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 11.76 min, t_{major} = 12.88 min; [α]D_{20} = +35.4 (c = 1.14 in CH2Cl2; data for 6i’).

NMR and HRMS data for the product 6i’ :

1H NMR (400 MHz, CDCl3): δ (ppm): 7.33 – 7.26 (m, 3H), 7.21 – 7.18 (m, 2H), 7.13 (d, J = 7.8 Hz, 2H), 7.04 (d, J = 7.8 Hz, 2H), 6.43 (t, J = 2.4 Hz, 1H), 4.74 (d, J = 14.8 Hz, 1H), 4.44 (d, J = 14.8 Hz, 1H), 4.03 (dd, J = 11.6 Hz, J = 6.0 Hz, 1H), 3.56 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 3.46 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 2.50 – 2.44 (m, 1H), 2.38 – 2.31 (m, 4H).

13C NMR (100 MHz, CDCl3): δ (ppm): 164.3, 141.7, 137.5, 136.7, 136.5, 129.8, 128.7, 128.0, 127.7, 127.6, 125.6, 88.5, 47.5, 46.5, 39.7, 34.3, 21.0

HRMS (ESI): m/z calculated for C21H20ClNO2Na+: 376.1080, found: 376.1083.

(2S,4S)-6-benzyl-2-hydroxy-4-(4-methoxyphenyl)-3,4,5,6-tetrahydropyran[2,3-c]pyrrol-7(2H)-one 6j

According to the general procedure, the crude product was purified via column chromatography delivering 6j as a white solid with 95% yield. The diastereomeric ratio was determined to be 85:15 by crude 1H-NMR analysis. 6j was transformed to its analogue 6j’ (only a single diastereoisomer was obtained) with 84% yield. The enantiomeric excess of 6j’ was determined to be 95% by chiral HPLC analysis on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{minor} = 15.36 min, t_{major} = 16.89 min; [α]D_{20} = +115.0 (c = 0.23 in CH2Cl2; data for 6j’).

NMR and HRMS data for the product 6j’ :

1H NMR (400 MHz, CDCl3): δ (ppm): 7.26 – 7.19 (m, 3H), 7.14 – 7.11 (m, 2H), 7.02 – 6.99 (m, 2H), 6.80 – 6.76 (m, 2H), 6.36 (t, J = 2.4 Hz, 1H), 4.67 (d, J = 14.8 Hz, 1H), 4.37 (d, J = 14.8 Hz, 1H), 3.95 (dd, J = 11.6 Hz, J = 6.0 Hz, 1H), 3.72 (s, 3H), 3.49 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 3.37 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 2.43 – 2.37 (m, 1H), 2.29 – 2.22 (m, 1H).

13C NMR (100 MHz, CDCl3): δ (ppm): 164.4, 159.1, 141.7, 136.8, 131.5, 128.9, 128.7, 128.1, 127.7, 125.8, 114.5, 88.6, 55.3, 47.5, 46.5, 39.7, 33.9

HRMS (ESI): m/z calculated for C21H26ClNO3Na+: 392.1029, found: 392.1030.
(2S,4S)-6-benzyl-2-hydroxy-4-(2-methoxyphenyl)-3,4,5,6-tetrahydropyran[2,3-c]pyrrolo-7(2H)-one 6k

According to the general procedure, the crude product was purified via column chromatography delivering 6k as a white solid with 90% yield. The diastereomeric ratio was determined to be 86:14 by crude $^1$H-NMR analysis. 6k was transformed to its analogue 6k' (only a single diastereoisomer was obtained) with 81% yield. The enantiomeric excess of 6k' was determined to be 96% by chiral HPLC analysis on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}} = 16.28$ min, $t_{\text{minor}} = 21.60$ min; $[\alpha]_D^{20} = +78.5$ ($c = 0.46$ in CH$_2$Cl$_2$, data for 6k').

NMR and HRMS data for the product 6k':

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm): 7.32 – 7.25 (m, 3H), 7.24 – 7.18 (m, 3H), 7.08 (dd, $J = 7.2$ Hz, $J = 1.6$ Hz, 1H), 6.91 (t, $J = 7.2$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 6.44 (t, $J = 2.4$ Hz, 1H), 4.60 (dd, $J = 17.2$ Hz, $J = 15.2$ Hz, 1H), 4.42 (dd, $J = 11.6$ Hz, $J = 6.0$ Hz, 1H), 3.72 (s, 3H), 3.59 (dd, $J = 18.4$ Hz, $J = 1.6$ Hz, 1H), 3.43 (dd, $J = 18.4$ Hz, $J = 1.6$ Hz, 1H), 2.53 – 2.46 (m, 1H), 2.41 – 2.35 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 164.6, 157.3, 141.1, 137.0, 129.2, 128.8, 128.7, 127.9, 127.6, 127.3, 126.3, 121.0, 110.9, 89.0, 55.2, 47.6, 46.4, 37.1, 29.7

HRMS (ESI): $m/z$ calculated for C$_{21}$H$_{26}$ClNO$_3$Na$: 392.1029$, found: 392.1030.

(2S,4S)-6-benzyl-2-hydroxy-4-((E)-styryl)-3,4,5,6-tetrahydropyran[2,3-c]pyrrolo-7(2H)-one 6l

According to the general procedure, the crude product was purified via column chromatography delivering 6l as a white solid with 89% yield. The diastereomeric ratio was determined to be 82:18 by crude $^1$H-NMR analysis. 6l was transformed to its analogue 6l' (only a single diastereoisomer was obtained) with 70% yield. The enantiomeric excess of 6l' was determined to be 90% by chiral HPLC analysis on Chiralpak AD-H column (20% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}} = 9.83$ min, $t_{\text{minor}} = 18.29$ min; $[\alpha]_D^{20} = +138.5$ ($c = 0.38$ in CH$_2$Cl$_2$, data for 6l').

NMR and HRMS data for the product 6l':
¹H NMR (400 MHz, CDCl₃): δ (ppm): 7.34 – 7.28 (m, 7H), 7.25 – 7.23 (m, 3H), 6.60 (d, J = 15.6 Hz, 1H), 6.42 (t, J = 2.4 Hz, 1H), 5.96 (dd, J = 15.6 Hz, J = 8.8 Hz, 1H), 4.62 (q, J = 14.8 Hz, 2H), 3.71 – 3.70 (m, 3H), 2.43 – 2.37 (m, 1H), 2.23 – 2.16 (m, 1H).

¹³C NMR (100 MHz, CDCl₃): δ (ppm): 164.3, 141.0, 136.7, 136.0, 133.8, 128.8, 128.7, 128.2, 128.1, 127.7, 127.0, 126.3, 124.8, 88.3, 47.7, 46.6, 37.1, 32.4

HRMS (ESI): m/z calculated for C₂₂H₂₀ClNO₂Na⁺: 388.1080, found: 388.1080.

(2S,4S)-6-benzyl-2-hydroxy-4-(naphthalen-2-yl)-3,4,5,6-tetrahydropyrano[2,3-c]pyrrol-7(2H)-one 6m

![Chemical Structure of 6m]

According to the general procedure, the crude product was purified via column chromatography delivering 6m as a white solid with 83% yield. The diastereomeric ratio was determined to be 84:16 by crude ¹H-NMR analysis. 6m was transformed to its analogue 6m’ (only a single diastereoisomer was obtained) with 82% yield. The enantiomeric excess of 6m’ was determined to be 96% by chiral HPLC analysis on Chiralpak AD-H column (25% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_minor = 17.36 min, t_major = 33.53 min; [α]D²⁰ = +45.4 (c = 1.21 in CH₂Cl₂, data for 6m’).

**NMR and HRMS data for the product 6m’**:

¹H NMR (400 MHz, CDCl₃): δ (ppm): 7.83 – 7.76 (m, 3H), 7.66 (br s, 1H), 7.53 – 7.46 (m, 2H), 7.31 – 7.22 (m, 4H), 7.19 – 7.17 (m, 2H), 6.48 (t, J = 2.4 Hz, 1H), 4.75 (d, J = 14.8 Hz, 1H), 4.42 (d, J = 14.8 Hz, 1H), 4.24 (dd, J = 11.6 Hz, J = 6.0 Hz, 1H), 3.59 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 3.45 (dd, J = 18.4 Hz, J = 1.6 Hz, 1H), 2.59 – 2.45 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ (ppm): 164.3, 141.9, 136.9, 136.6, 133.4, 132.7, 129.1, 128.7, 128.1, 127.7, 127.6, 127.5, 127.1, 126.6, 126.3, 125.3, 125.2, 88.4, 47.5, 46.5, 39.4, 34.9

HRMS (ESI): m/z calculated for C₂₄H₂₁ClNO₂Na⁺: 412.1080, found: 412.1081.

5. Procedure for Synthetic Transformations of 4a

![Chemical Reaction]

A dry glass tube was charged with 4a (33.5 mg, 0.1 mmol), Ac₂O (51 mg, 0.5 mmol) and DMAP (1.2 mg, 0.01 mmol) in 1 mL pyridine, and the reaction was stirred at room
temperature for 2 hours. When the reaction was completed, 2 mL of 20% hydrochloric acid was added to the reaction mixture, and the organic material was extracted with ethyl acetate, washed with brine and dried over anhydrous Na$_2$SO$_4$, then concentrated under reduced pressure to give the corresponding acetylated compound; such compound was dissolved in 2 mL of DCM under argon, and TiCl$_4$ (94.5 mg, 0.5 mmol) was added into the reaction mixture. The reaction was stirred at room temperature for 16 hours. When the reaction was completed, 2 mL DCM and 1mL water was added to the reaction mixture. The organic layer was separated, dried over anhydrous Na$_2$SO$_4$ and purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (6:1 to 4:1) to afford the desired pure product 4a as a white solid with 88% yield. The diastereomeric ratio was determined to be >95:5 by crude $^1$H-NMR analysis, and the enantiomeric excess was determined to be 99% by chiral HPLC analysis on Chiralpak AD-H column (30% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, $t_{\text{major}} = 23.32$ min, $t_{\text{minor}} = 25.87$ min; $[\alpha]_D^{20} = +190.2$ (c = 0.67 in CH$_2$Cl$_2$).

**NMR and HRMS data for the product 4a**:  
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm): 7.35 – 7.23 (m, 6H), 7.20 – 7.17 (m, 2H), 7.13 – 7.11 (m, 2H), 6.21 (d, $J = 2.4$ Hz, 1H), 4.74 (d, $J = 14.8$ Hz, 1H), 4.42 (d, $J = 14.8$ Hz, 1H), 3.55 – 3.49 (m, 2H), 3.37 (d, $J = 18.4$ Hz, 1H), 2.47 – 2.38 (m, 1H), 0.94 (d, $J = 6.8$ Hz, 3H).  
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ (ppm): 164.4, 141.7, 138.7, 136.7, 129.0, 128.7, 128.4, 128.0, 127.7, 127.6, 126.1, 94.4, 47.3, 46.5, 42.0, 41.9, 14.8  
HRMS (ESI): m/z calculated for C$_{21}$H$_{20}$ClNO$_2$Na$: 376.1080$, found: 376.1077.

$\square$ In order to rationalize the configuration of newly formed C-Cl bond in the chloro-compound 4a', a proposed reaction mechanism and transition state of the above synthetic transformation was described. As shown in the following scheme, the Ac protected hydroxyl group was firstly eliminated in the presence of Lewis acid. Then, because of anomic effect of the dihydropyran, the nucleophilic chloride preferred to attack the oxonium intermediate from the bottom face, generating a configurationally favored axial bond. Thus, the corresponding product 4a' with excellent stereoselectivity was obtained.
A dry glass tube was charged with 4a (33.5 mg, 0.1 mmol), TsOH (86 mg, 0.5 mmol) in 1 mL toluene, and the reaction was stirred at 90 °C for 2 hours. When the reaction was completed, the reaction mixture was directly purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (6:1 to 4:1) to afford the desired pure product 7 as a white solid with 85% yield. The enantiomeric excess was determined to be 99% by chiral HPLC analysis on Chiralpak AD-H column (20% 2-propanol/n-hexane, 1 mL/min), UV 220 nm, t_{major} = 16.47 min, t_{minor} = 35.97 min; [α]_D^{20} = +10.4 (c = 1.90 in CH_2Cl_2).

_NMR and HRMS data for the product 7:_

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \delta (ppm): 7.33 - 7.22 (m, 6H), 7.19 - 7.16 (m, 4H), 6.51 (s, 1H), 4.82 (d, J = 14.8 Hz, 1H), 4.31 (d, J = 14.8 Hz, 1H), 4.08 (s, 1H), 3.53 (d, J = 18.4 Hz, 1H), 3.34 (d, J = 18.4 Hz, 1H), 1.42 (s, 3H). \]

\[ ^13C \text{ NMR (100 MHz, CDCl}_3) \delta (ppm): 164.1, 141.4, 141.2, 136.7, 135.9, 128.8, 128.7, 128.0, 127.9, 127.6, 127.4, 123.1, 111.7, 47.3, 46.3, 43.2, 16.2 \]

**HRMS (ESI):** \( m/z \) calculated for C_{21}H_{19}NO_2Na^+: 340.1313, found: 340.1316.
6. Crystal Data and Structure Refinement for the Enantiopure 4b

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<th>Value</th>
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<td>Empirical formula</td>
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<tr>
<td>Formula weight</td>
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<td>b/Å</td>
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<td>c/Å</td>
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<td>Reflections collected</td>
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Data/restraints/parameters 6542/1/473
Goodness-of-fit on $F^2$ 1.014
Final R indexes [$I>=2\sigma (I)$] $R_1 = 0.0546$, $wR_2 = 0.1360$
Final R indexes [all data] $R_1 = 0.0616$, $wR_2 = 0.1437$
Largest diff. peak/hole / e Å$^{-3}$ 0.83/-0.52
Flack parameter 0.030(15)

➤ CCDC 1480846 (4b) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

➤ From the crystallographic data, an intermolecular hydrogen bonding interaction was observed. The data of such hydrogen bonding interaction is listed as follows:

Hydrogen bonds with $H..A < r(A) + 2.000$ Angstroms and $<DHA > 110$ deg.

Appropriate HTAB instructions appended to .res file for future use.

\[
\begin{align*}
D-H & \quad d(D-H) \quad d(H..A) \quad <DHA \quad d(D..A) \quad A \\
O006-H006 & \quad 0.840 \quad 2.321 \quad 144.94 \quad 3.047 \quad O005 \\
O006-H006 & \quad 0.840 \quad 2.326 \quad 135.34 \quad 2.983 \quad O007 \\
O008-H008 & \quad 0.840 \quad 2.052 \quad 155.10 \quad 2.836 \quad O004 \\
C00N-H00C & \quad 0.990 \quad 2.597 \quad 116.61 \quad 3.167 \quad O006 \quad [-x+1, y-1/2, -z+1] \\
C00N-H00C & \quad 0.990 \quad 2.472 \quad 170.48 \quad 3.452 \quad O007 \quad [-x+1, y-1/2, -z+1] \\
\end{align*}
\]

7. References and notes


[3] For detail of the procedure for such function group transformation, see in page S27: *Procedure for Synthetic Transformations of 4a*. 
8. NMR and HPLC Spectra of the Chiral Bicyclic Dihydropyranes
### Peak Analysis Report

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![Graph of peak analysis](image1)

### Peak Analysis Report

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![Graph of peak analysis](image2)
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### Peak Analysis Report

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![Graph](image1)

### Peak Analysis Report

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![Graph](image2)
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![Graph 1](image1)

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### Peak Analysis Report

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![Graph 2](image2)
### Peak Analysis Report

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<th>Rel. Area</th>
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<th>Amount</th>
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<td>91.951</td>
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<td>15.75</td>
<td>35.465</td>
<td>50.62</td>
<td>48.646</td>
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</tbody>
</table>

![Graph 1](attachment:image1)

### Peak Analysis Report

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<th>Amount</th>
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<tr>
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<td>99.28</td>
<td>545.506</td>
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![Graph 2](attachment:image2)
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<td>167.913</td>
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<td>49.97</td>
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![Graph 1](image1.png)

### Peak Analysis Report

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<td>39.84</td>
<td>0.002</td>
<td>0.02</td>
<td>0.032</td>
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![Graph 2](image2.png)

### Peak Analysis Report

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<th>Amount</th>
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<tr>
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<td>39.84</td>
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<td>0.02</td>
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![Graph 3](image3.png)
### Peak Analysis Report

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<th>Height</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>6.16</td>
<td>31,491</td>
<td>50.01</td>
<td>711,154</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>12.18</td>
<td>31,477</td>
<td>49.99</td>
<td>46,468</td>
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![Graph of peak analysis](image1.png)

### Peak Analysis Report

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<th>Amount</th>
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<tr>
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<td>6.16</td>
<td>42,247</td>
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<td>177,670</td>
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![Graph of peak analysis](image2.png)
Peak Analysis Report

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<th>Ret Area</th>
<th>Height</th>
<th>Amount</th>
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<tr>
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<td>37206</td>
<td>50.86</td>
<td>67.119</td>
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Peak Analysis Report

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<th>Amount</th>
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<tr>
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### Peak Analysis Report

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<th>%</th>
<th>Height</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>7.15</td>
<td>43,177</td>
<td>50.46</td>
<td>51.14</td>
<td>n.a.</td>
<td>n.a.</td>
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<tr>
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<td>15.03</td>
<td>42,395</td>
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<td>47.39</td>
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### Peak Analysis Report

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<th>Height</th>
<th>Amount</th>
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<td>35,097</td>
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<td>0.14</td>
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<td>n.a.</td>
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### Peak Analysis Report

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<th>Amount</th>
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<tr>
<td>1</td>
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<td>29.332</td>
<td>49.45%</td>
<td>89.465</td>
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<td>2</td>
<td>n.a.</td>
<td>17.93</td>
<td>29.986</td>
<td>50.55%</td>
<td>39.869</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Graph](image1.png)

**Graph 1:**
- Compound: Bn-N-[O-OH-OMe]
- Retention Time: 8.01 min
- Area: 29.332
- Ret. Area: 49.45%
- Height: 89.465 n.a.

**Graph 2:**
- Compound: Bn-N-[O-OH-OMe]
- Retention Time: 17.93 min
- Area: 29.986
- Ret. Area: 50.55%
- Height: 39.869 n.a.

---

**Legend:**
- UV VIS 2
- WVL 220 nm

---

S53
### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
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<th>Area</th>
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<th>Amount</th>
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<td>39.780</td>
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![Graph](image1)

### Peak Analysis Report

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<th>Area</th>
<th>Rel. Area</th>
<th>Height</th>
<th>Amount</th>
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<td>16.66</td>
<td>0.232</td>
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<td>0.411</td>
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![Graph](image2)
### Peak Analysis Report

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<th>Amount</th>
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<tr>
<td>1</td>
<td>n.a.</td>
<td>6.93 min</td>
<td>279.390</td>
<td>50.20</td>
<td>821.440</td>
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<tr>
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<td>13.84 min</td>
<td>227.623</td>
<td>49.80</td>
<td>261.424</td>
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![Graph](image1.png)

### Peak Analysis Report

<table>
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<tr>
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<th>Ret Time (detected)</th>
<th>Area</th>
<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
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<tbody>
<tr>
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<td>6.92 min</td>
<td>266.413</td>
<td>99.50</td>
<td>950.072</td>
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<tr>
<td>2</td>
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<td>13.88 min</td>
<td>1.928</td>
<td>0.50</td>
<td>2.178</td>
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![Graph](image2.png)
Peak Analysis Report

<table>
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<th>Rel. Area</th>
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<th>Amount</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>min</td>
<td>mAU/\min</td>
<td>%</td>
<td>mAU</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>n.a.</td>
<td>9.03</td>
<td>50.292</td>
<td>49.44</td>
<td>162.113</td>
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<td>10.68</td>
<td>51.425</td>
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<td>139.236</td>
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racemate 4p'

Peak Analysis Report

<table>
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<th>Height</th>
<th>Amount</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>min</td>
<td>mAU/\min</td>
<td>%</td>
<td>mAU</td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>553.349</td>
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4p'
### Peak Analysis Report

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<td>40.566</td>
<td>59.98</td>
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![chromatogram with peak at 6.24 min and 11.77 min]

### Peak Analysis Report

<table>
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<th>Ret Time (detected)</th>
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<tr>
<td>1</td>
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<td>8.24</td>
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<td>11.75</td>
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![chromatogram with peak at 8.24 min and 11.75 min]
### Peak Analysis Report

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<th>Ret.Time (detected)</th>
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<th>Amount</th>
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<tr>
<td>1</td>
<td>n.a.</td>
<td>5.75</td>
<td>122.644</td>
<td>50.54%</td>
<td>490.007</td>
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<tr>
<td>2</td>
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<td>10.03</td>
<td>120.991</td>
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<td>205.762</td>
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![Graph 1](image1.png)

### Peak Analysis Report

<table>
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<th>Rel.Area</th>
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<tbody>
<tr>
<td>1</td>
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<td>5.78</td>
<td>408.317</td>
<td>98.69%</td>
<td>1532.134</td>
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</tr>
<tr>
<td>2</td>
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<td>10.08</td>
<td>417.77</td>
<td>101.01%</td>
<td>776.66</td>
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![Graph 2](image2.png)
### Peak Analysis Report

<table>
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<th>Amount</th>
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<tbody>
<tr>
<td>1</td>
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<td>5.37 min</td>
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<tr>
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<td>7.39 min</td>
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<td>210.568 n.a.</td>
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### Peak Analysis Report

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<th>No.</th>
<th>Peak Name</th>
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<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>5.58 min</td>
<td>79.573</td>
<td>98.70</td>
<td>363.694 n.a.</td>
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<tr>
<td>2</td>
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<td>7.40 min</td>
<td>1.047</td>
<td>1.30</td>
<td>2.688  n.a.</td>
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Peak Analysis Report

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<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
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<tr>
<td></td>
<td></td>
<td>min</td>
<td>mAU*min</td>
<td>% mAU</td>
<td>mAU</td>
<td>n.a.</td>
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<tr>
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<td>8.77</td>
<td>21.544</td>
<td>55.37</td>
<td>52.847</td>
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<tr>
<td>2</td>
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<td>13.21</td>
<td>21.529</td>
<td>49.83</td>
<td>33.538</td>
<td>n.a.</td>
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0301E XX OD 30%

UV_VIS_2
WVL:220 nm

racemate 4u'

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Peak Analysis Report

<table>
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<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret. Time (detected)</th>
<th>Area</th>
<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>min</td>
<td>mAU*min</td>
<td>% mAU</td>
<td>mAU</td>
<td>n.a.</td>
</tr>
<tr>
<td>1</td>
<td>n.a.</td>
<td>8.74</td>
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<td>0.96</td>
<td>1.264</td>
<td>n.a.</td>
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<tr>
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<td>13.03</td>
<td>37.169</td>
<td>99.04</td>
<td>58.390</td>
<td>n.a.</td>
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0301E OD 30%

UV_VIS_2
WVL:220 nm

4u'
## Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret Time (detected)</th>
<th>Area</th>
<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>6.24</td>
<td>49.75</td>
<td>181.247</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>7.78</td>
<td>50.25</td>
<td>133.644</td>
<td>n.a.</td>
<td></td>
</tr>
</tbody>
</table>

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**Diagram 1:**

- Compounds: 150621 #59 (modified by Administrator)  
- UV_VIS_2 (WVL 220 nm)

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**Diagram 2:**

- Compounds: 150621 #60 (modified by Administrator)  
- UV_VIS_2 (WVL 220 nm)
### Peak Analysis Report

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<tr>
<th>No.</th>
<th>Peak Name</th>
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<th>Area</th>
<th>Rel. Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>23.26</td>
<td>293 469</td>
<td>69.14</td>
<td>297 773</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>26.65</td>
<td>231 351</td>
<td>49.86</td>
<td>262 973</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Graph 1](image1)

### Peak Analysis Report

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<thead>
<tr>
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<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>22.87</td>
<td>119 965</td>
<td>97.41</td>
<td>146 121</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
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<td>26.50</td>
<td>3.192</td>
<td>2.59</td>
<td>4.375</td>
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</tbody>
</table>

![Graph 2](image2)

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S82
### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret. Time (detected)</th>
<th>Area</th>
<th>Ret. Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>17.03</td>
<td>38916</td>
<td>49.28</td>
<td>45.102</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>22.84</td>
<td>40046</td>
<td>50.72</td>
<td>37.972</td>
<td>n.a.</td>
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### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
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<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>15.79</td>
<td>75333</td>
<td>96.64</td>
<td>90.666</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>22.55</td>
<td>1.195</td>
<td>1.56</td>
<td>1.712</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
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<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>13.38</td>
<td>153.929</td>
<td>49.87</td>
<td>278.999</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>14.77</td>
<td>133.922</td>
<td>50.13</td>
<td>256.485</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

**Diagram 1:**

- Compound: Racemate 6d
- UV_VIS_2
- WVL 220 nm

**Diagram 2:**

- Compound: 6d
- UV_VIS_2
- WVL 220 nm
Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
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<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>12.83</td>
<td>28,779</td>
<td>50.64</td>
<td>63.562</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>14.54</td>
<td>28,048</td>
<td>49.36</td>
<td>56.059</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Peak Analysis Report

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<tr>
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<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>12.89</td>
<td>69,731</td>
<td>98.34</td>
<td>154.677</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>14.60</td>
<td>1,179</td>
<td>1.66</td>
<td>3,162</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
### Peak Analysis Report

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<tr>
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<th>Area</th>
<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>13.00</td>
<td>43,952</td>
<td>0.050</td>
<td>73.551</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>18.12</td>
<td>43,997</td>
<td>0.050</td>
<td>56.322</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

#### Chart 1

![Chart 1](image1)

#### Chart 2

![Chart 2](image2)
### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret Time (detected)</th>
<th>Area</th>
<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>17.70</td>
<td>44,945</td>
<td>48.20</td>
<td>113,276</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>12.83</td>
<td>48,189</td>
<td>51.80</td>
<td>109,593</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret Time (detected)</th>
<th>Area</th>
<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>11.76</td>
<td>616,364</td>
<td>97.37</td>
<td>1407,727</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>12.88</td>
<td>16,675</td>
<td>2.63</td>
<td>41,349</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Rel. Time (detected)</th>
<th>Area</th>
<th>Rel. Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>15.23 min</td>
<td>61,953</td>
<td>50.47 %</td>
<td>116,659</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>16.81 min</td>
<td>60,712</td>
<td>49.53 %</td>
<td>163,457</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Graph 1](image1.png)

**racemate 6′**

### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Rel. Time (detected)</th>
<th>Area</th>
<th>Rel. Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>15.36 min</td>
<td>8,999</td>
<td>2.68 %</td>
<td>14,798</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>16.89 min</td>
<td>293,470</td>
<td>97.32 %</td>
<td>487,195</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Graph 2](image2.png)

**6′**

### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Rel. Time (detected)</th>
<th>Area</th>
<th>Rel. Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>15.36 min</td>
<td>8,999</td>
<td>2.68 %</td>
<td>14,798</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>16.89 min</td>
<td>293,470</td>
<td>97.32 %</td>
<td>487,195</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Graph 3](image3.png)

**6′**

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S98
### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret Time (detected)</th>
<th>Area</th>
<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>15.18 min</td>
<td>67.047 mAU/min</td>
<td>49.70%</td>
<td>118,105 mAU</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>21.47 min</td>
<td>67.667 mAU/min</td>
<td>50.30%</td>
<td>90,616 mAU</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Graph](image1)

---

### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret Time (detected)</th>
<th>Area</th>
<th>Rel Area</th>
<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>16.28 min</td>
<td>501,896 mAU/min</td>
<td>97.82%</td>
<td>921,409 mAU</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>21.60 min</td>
<td>12,319 mAU/min</td>
<td>2.18%</td>
<td>16,557 mAU</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Graph](image2)
### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret Time (detected)</th>
<th>Area (nA·min)</th>
<th>Ret Area %</th>
<th>Height mAU</th>
<th>Amount n.a.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>9.07</td>
<td>83,929</td>
<td>49.24</td>
<td>221,458</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>18.48</td>
<td>86,407</td>
<td>50.76</td>
<td>83,172</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Peak Analysis Graph](image1)

### Peak Analysis Report

<table>
<thead>
<tr>
<th>No.</th>
<th>Peak Name</th>
<th>Ret Time (detected)</th>
<th>Area (nA·min)</th>
<th>Ret Area %</th>
<th>Height mAU</th>
<th>Amount n.a.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>9.63</td>
<td>61,177</td>
<td>94.81</td>
<td>160,809</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>18.29</td>
<td>3,302</td>
<td>6.19</td>
<td>3,424</td>
<td>n.a.</td>
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![Peak Analysis Graph](image2)
### Peak Analysis Report

<table>
<thead>
<tr>
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<th>Height</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>23.33 min</td>
<td>178.42%</td>
<td>50.94%</td>
<td>218.712 mAU</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>25.88 min</td>
<td>164.104 mAU</td>
<td>49.06%</td>
<td>193.696 mAU</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Chromatogram of peak analysis](chart1.png)

---

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<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n.a.</td>
<td>23.72 min</td>
<td>156.02 mAU</td>
<td>99.41%</td>
<td>201.097 mAU</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>n.a.</td>
<td>25.87 min</td>
<td>0.020 mAU</td>
<td>0.59%</td>
<td>1.311   mAU</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

![Chromatogram of peak analysis](chart2.png)