SUPPORTING INFORMATION

**Authors**: [1]Keri A. Tallman, [2,4]Luke B. Allen, [2]Korinne Klingelsmith, [2]Allison Anderson, [2]Thiago C. Genaro-Mattos, [2,4]Károly Mirnics, [1]Ned A. Porter, [3,4]Zeljka Korade*

# Prescription medications alter neuronal and glial cholesterol synthesis

[1]Department of Chemistry, Vanderbilt Institute of Chemical Biology and Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, TN.

[2]Munroe-Meyer Institute for Genetics and Rehabilitation, University of Nebraska Medical Center, Omaha, NE, USA, 68105.

[3]Department of Pediatrics, [4]Biochemistry and Molecular Biology, College of Medicine, University of Nebraska Medical Center, Omaha, NE, USA, 68198.

*Corresponding Author:

Zeljka Korade, DVM, PhD
Professor of Pediatrics and Biochemistry and Molecular Biology
University of Nebraska Medical Center
982165 Nebraska Medical Center | Omaha, NE 68198
402.559.1312 | zeljka.korade@UNMC.Edu

**CONTENTS**

Additional Figures

Figure S1. Prescribed medications used in the study.

Figure S2. Cholesterol oxysterols included in this LC-MS/MS analysis.

Figure S3. Comparison of PTAD and DMG methods.

Figure S4. Neurons and astrocytes exposed to sertraline.

Figure S5. Profile of cholesterol oxysterols in neurons and astrocytes.

Figure S6. Ratio of 7-DHD/Des and 7-DHC/Chol for neurons and astrocytes.

Figure S7. Representative mass spectrum and fragmentations for DMG-derivatized sterols.

Synthetic procedures

Scheme S1. Synthesis of $d_6$-Lan and $d_7$-dHLan.

Scheme S2. Synthesis of $d_6$-14d-Zym and $d_7$-14d-Zyme.

Scheme S3. Synthesis of $d_6$-Zym and $d_7$-Zyme.

Scheme S4. Synthesis of $d_6$-DHL and $d_7$-Lath.

Scheme S5. Synthesis of $d_6$-7-DHD.

Scheme S6. Synthesis of $d_6$-8-DHD.

Scheme S7. Synthesis of $d_6$-Des and $d_7$-Chol.

Statistics

Table S1. Statistics for Figure 4.

Table S2. Statistics for Figure 5.

Table S3. Statistics for Figure 6A (haloperidol).

Table S4. Statistics for Figure 6B (cariprazine).

Table S5. Statistics for Figure 6C (aripiprazole).

Table S6. Statistics for Figure 6D (trazodone).

Table S7. Statistics for Figure 6E (amiodarone).

Table S8. Statistics for Figure 7.

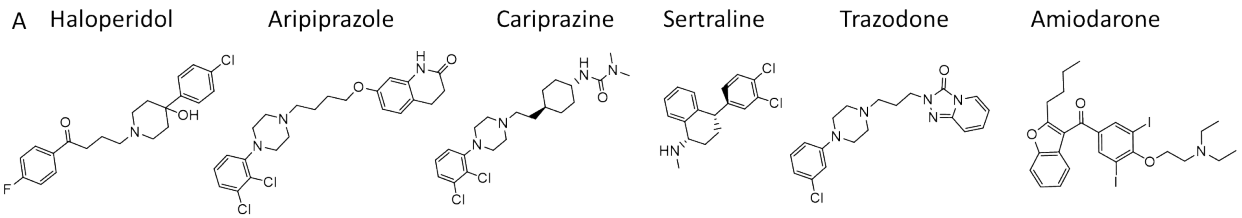
Table S9. Statistics for Figure S3.

Table S10. Statistics for Figure S4.

Table S11. Statistics for Figure S5.

## ADDITIONAL FIGURES

A




B

| Compound | Haloperidol | Aripiprazole | Cariprazine | Sertraline | Trazodone | Amiodarone |
|---|---|---|---|---|---|---|
| Brand name | Desyrel Oleptro | Abilify | Vraylar | Haldol | Zoloft | Cordarone |
| CAS number | 52-86-8 | 129722-12-9 | 839712-12-8 | 79617-96-2 | 19794-93-5 | 1951-25-3 |
| PubChem CID | 3559 | 60795 | 11154555 | 68617 | 5533 | 2157 |
| CompTox Dashboard EPA | DTXSID4034150 | DTXSID3046083 | DTXSID80232867 | DTXSID6023577 | DTXSID5045043 | DTXSID7022592 |
| Yearly prescription (2017) | 1,241,881 | 6,695,764 | unknown | 38,296,630 | 22,311,417 | 2,908,848 |
| Rank (2017) | 30 | 112 | | 296 | 14 | 196 |
| Drug category | antipsychotic | antipsychotic | antipsychotic | antidepressant | antidepressant | antiarrhythmic |
| Primary indication | schizophrenia | schizophrenia, bipolar disorder | schizophrenia, bipolar disorder | major depressive disorder | major depressive disorder | irregular heartbeats |
| Description | SARI | atypical | atypical | typical | SSRI | |
| Pregnancy Category | C | C | not classified yet | C | C | C |
| Pregnancy, breast feeding | excreted in milk | pregnancy registry; excreted in milk | no data | embryotoxic in high doses; excreted in milk | complications in newborn reported, excreted in milk | preterm births, heart, neuro and thyroid problems in baby |
| Elimination half-life | 7-10 hrs | 75 hrs (active metab 94 hrs) | 2-5 days (2-3 weeks for active metab) | 14-26 hrs (IV), 14-37 hrs (oral) | 23-26 hrs (66 less active metabolite) | 58 days (5-142 days) |
| BBB | cross BBB | cross BBB | cross BBB | cross BBB | cross BBB | cross BBB |
| WHO LIST | | | | WHO list of essential medicine | | WHO list of essential medicine |
| Available Forms | 25, 50, 100, 150, 300 mg tablets; 150 and 300 mg extended release | 2, 5, 10, 15, 20, 30 mg; (Aristada long-lasting 2 month injection) | 1.5, 3, 4.5, 6 mg | 0.5, 1, 2, 5, 10, 20 mg | 25, 50, 100 mg | 100, 200, 400 mg |

**Figure S1**. Prescribed medications used in the study. A) Chemical structures. B) Compounds used in the current study showing details about chemical ID, yearly prescription (data from ClinCalc), the use, pregnancy classification, elimination half-life and available prescription tablets.

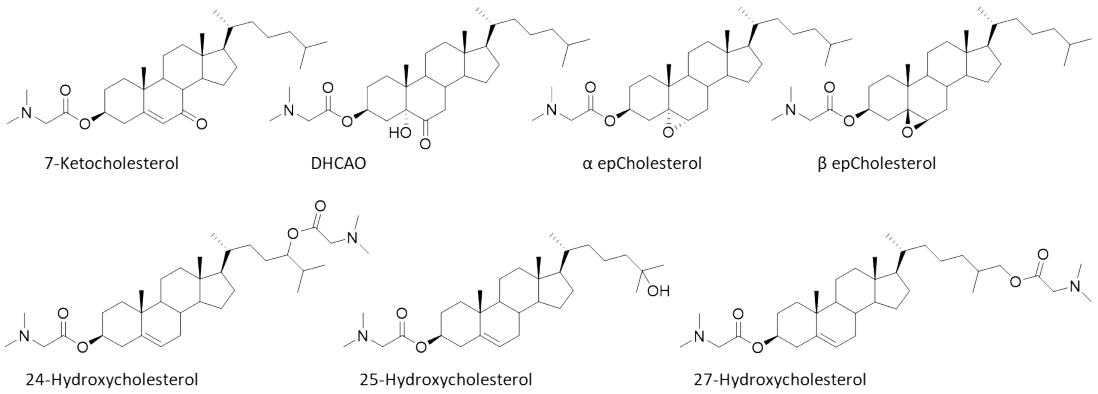



**Figure S2.** Cholesterol oxysterols included in this LC-MS/MS analysis. The structures show the sites of derivatization by dimethyl glycine.

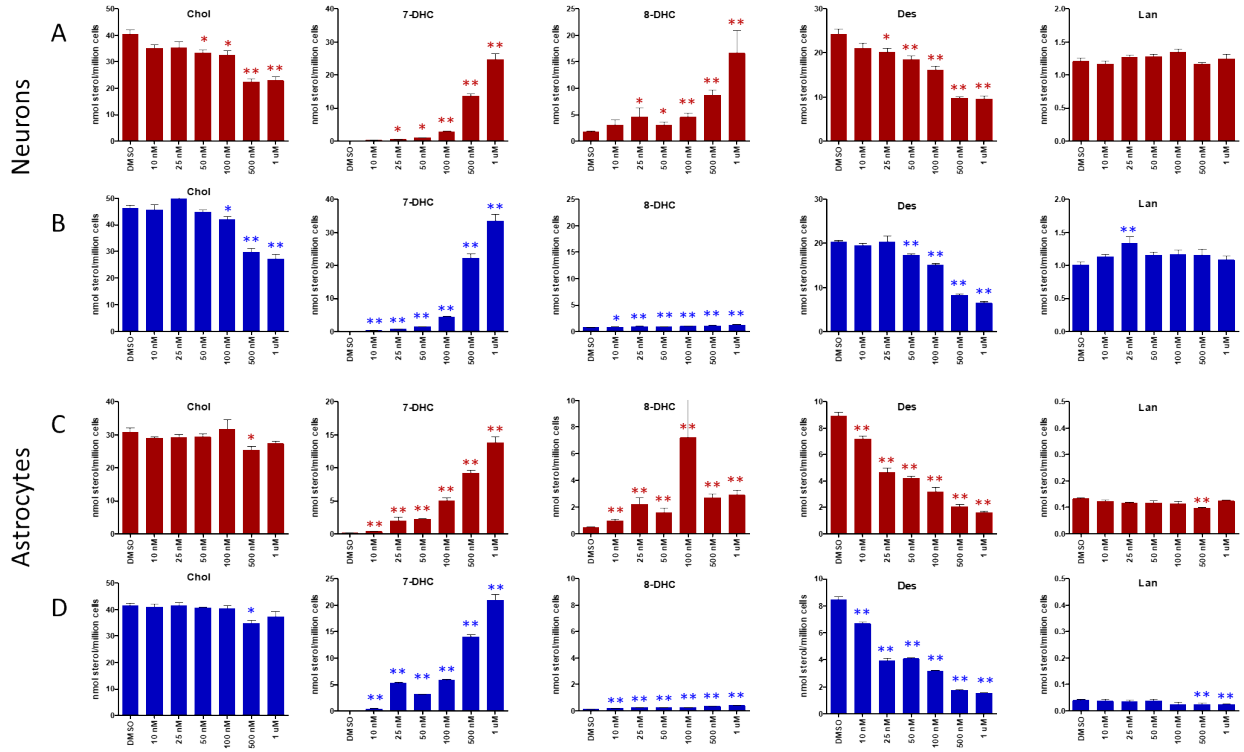



**Figure S3.** Comparison of PTAD and DMG methods in cortical neuronal and astrocytes cultures. (A and C) Sterols analyzed by PTAD method. (B and D) Sterols analyzed by DMG method. (A and B) Cortical neurons and (C and D) astrocytes were grown in 96-well plate in presence and absence of trazodone (10 nM – 1000 nM) for 6 days. Half plate was processed for PTAD method and half plate for DMG method. Statistical significance is marked by * $p<0.01$.

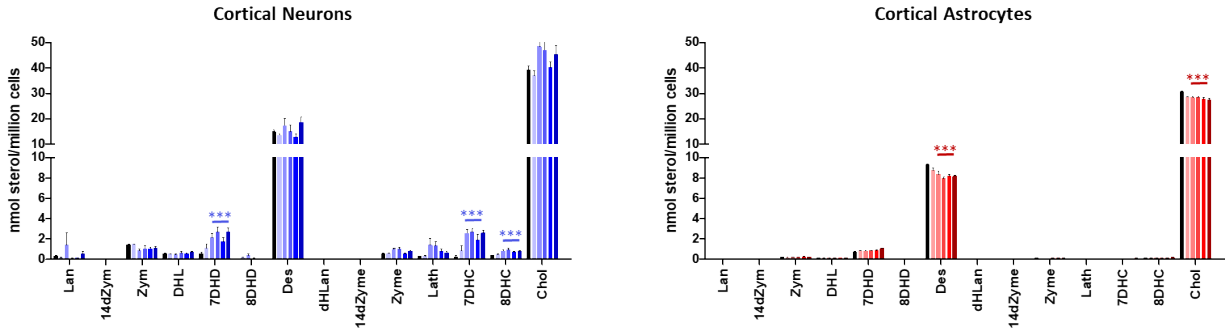



**Figure S4.** Comparison of cholesterol synthesis in neurons and astrocytes exposed to antidepressant sertraline. Neurons and astrocytes were exposed to increasing concentrations of compounds for 6 days and fourteen sterols were analyzed by DMG method. Concentrations for treatments were control (DMSO), 10, 25, 50, 100 and 500 nM. Blue=neurons; red=astrocytes; n=11 for control, n=6 for drug. Statistical significance is marked by * $p<0.01$.

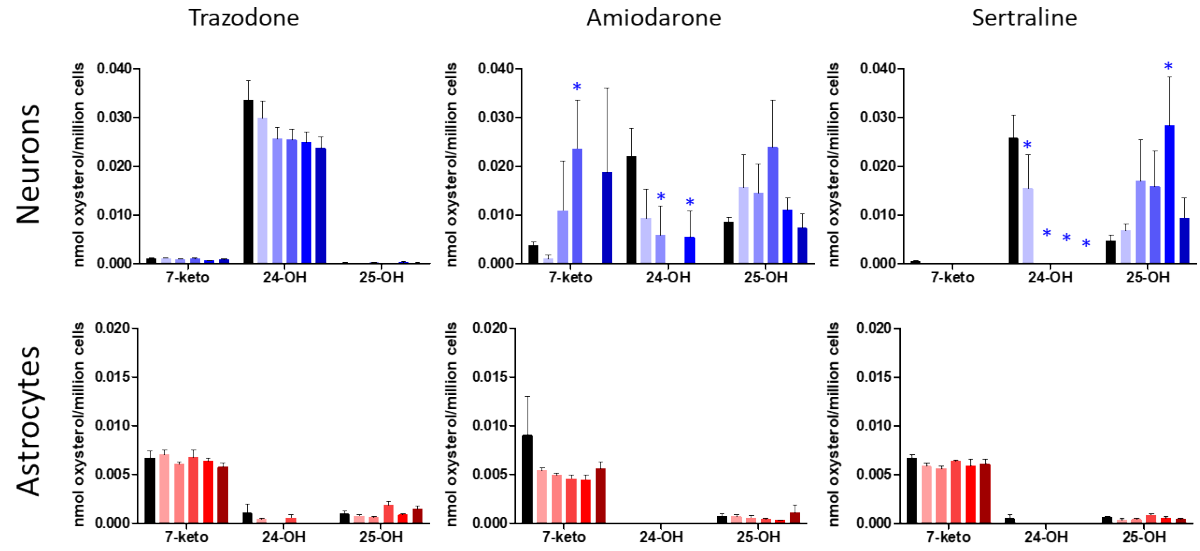



**Figure S5.** Profile of cholesterol oxysterols in neurons and astrocytes exposed to trazodone, amiodarone, and sertraline. Blue = neurons; red = astrocytes. Neurons and astrocytes were exposed to increasing concentrations of compounds for 6 days and seven oxysterols were analyzed by the DMG method. n=11 for control, n=6 for drug. The major oxysterols found are shown here. Concentrations for treatments were control (DMSO), 10, 25, 50, 100 and 500 nM. Statistical significance is marked by *$p<0.05$.

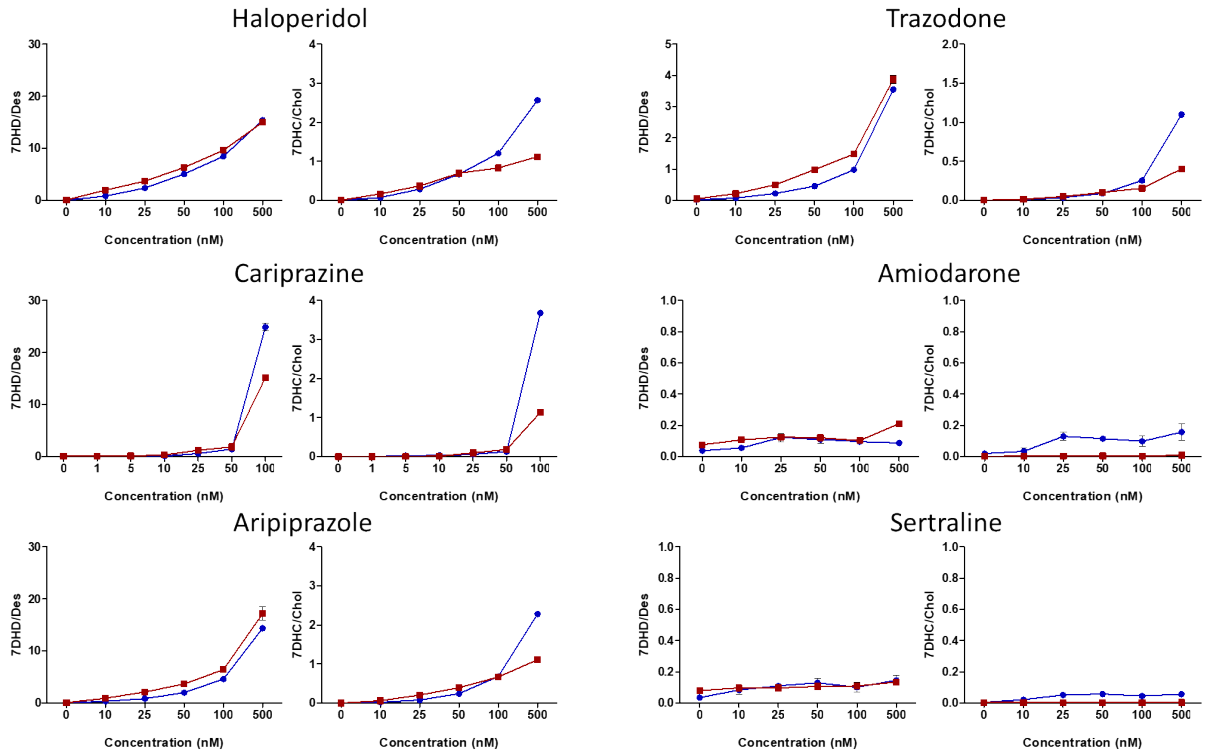
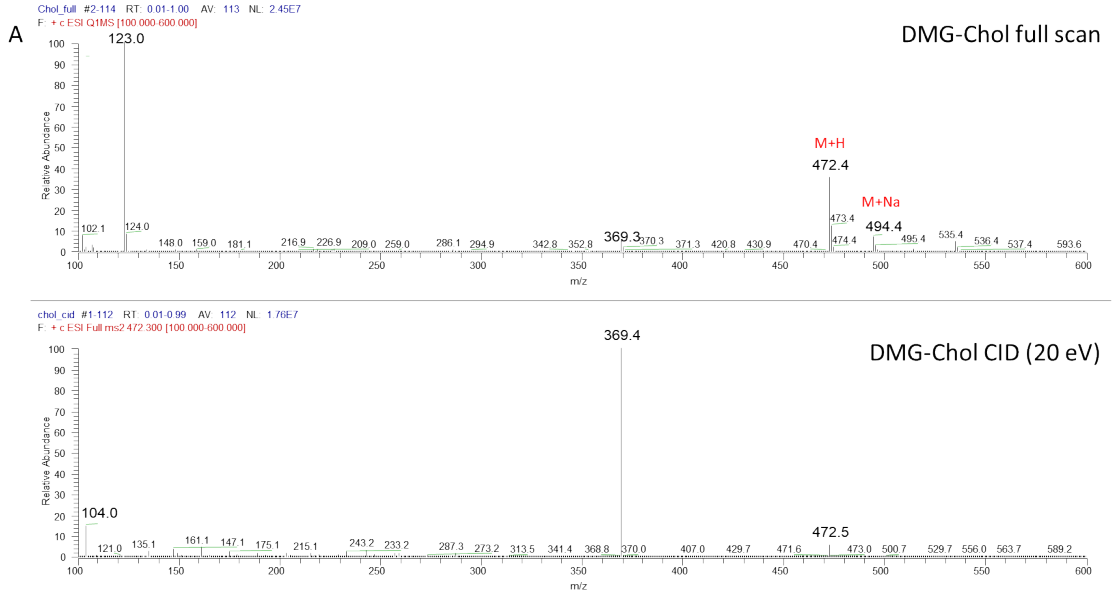



**Figure S6.** Ratio of 7DHD/Des and 7DHC/Chol for neurons and astrocytes. Blue = neurons; red = astrocytes. The data from Figure 6 was used to determine the ratios for neurons and astrocytes upon exposure to haloperidol, cariprazine, aripiprazole, trazodone, amiodarone, and sertraline.



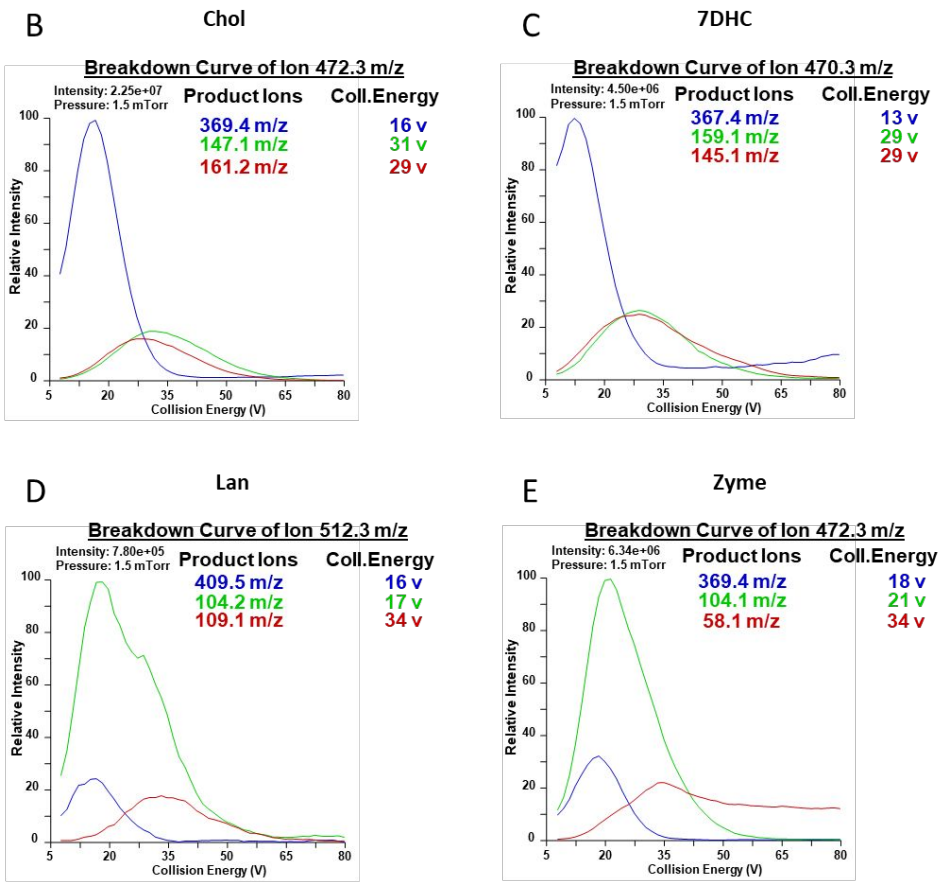
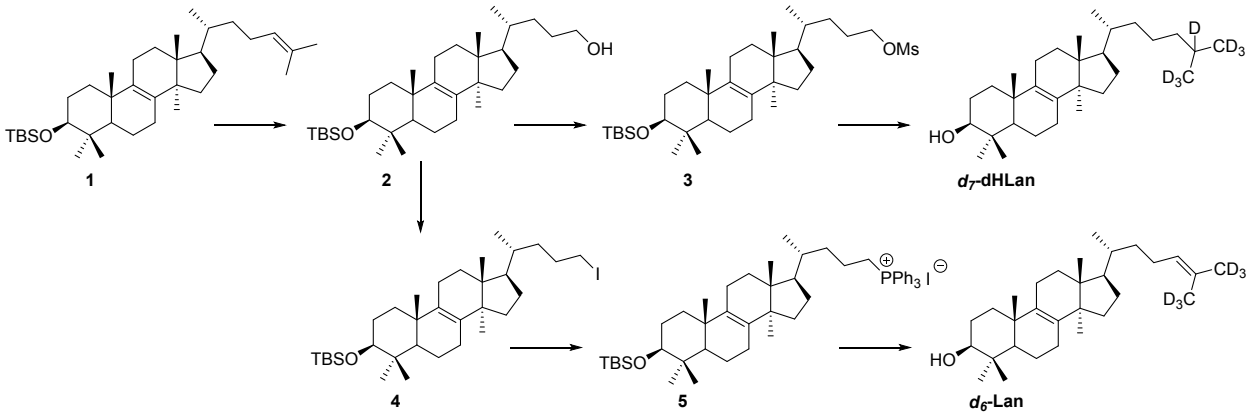



**Figure S7**. Representative mass spectrum and fragmentations for DMG-derivatized sterols. A) Full scan and CID at 20 eV for DMG-Chol and major ions upon CID for B) Chol, C) 7-DHC, D) Lan, and E) Zyme. Sterols containing a 5,6-double bond (Chol and 7-DHC) fragment to give the sterol as the major ion. Sterols lacking a 5,6-double bond (Lan and Zyme) fragment to give the DMG-moiety as the major ion.

## SYNTHETIC PROCEDURES

*Methods and materials*. The synthesis of $d_7$-7-DHC and $d_7$-8-DHC has been reported. All sterol standards are available from Kerafast, Inc. (Boston MA). $^{1}H$ and $^{13}C$ NMR spectra were collected on a 300, 400, or 600 MHz NMR. All reactions were carried out under an atmosphere of argon. THF and $CH_2Cl_2$ were dried using a solvent purification system. Commercial anhydrous solvents were used as received. Purification by column chromatography was carried out on silica gel and TLC plates were visualized by UV and stained with phosphomolybdic acid.

Scheme S1. Synthesis of $d_6$-Lan and $d_7$-dHLan.




*Synthesis of **1***. TBSCl (2.7 g, 0.018 mol) and imidazole (1.6 g, 0.024 mol) were added to a solution of lanosterol (60 % purity, 5.1 g, 0.012 mol) in THF/DMF (60 mL, 1:1). The reaction mixture was heated to 100 °C. After overnight, the reaction mixture was cooled and diluted with hexanes/EtOAc (1:1). The organics were washed with $H_2O$, brine, and dried over $MgSO_4$. The product was purified by column chromatography (hexanes) and isolated as a white powder (3.8 g, 58%). $^1$H NMR ($CDCl_3$) δ 5.09 (t, 1H, J = 7.1 Hz), 3.19 (dd, 1H, J = 4.8, 10.9 Hz), 2.06-1.99 (m, 6H), 1.95-1.87 (m, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.56-1.31 (m, 8H), 1.32-1.03 (m, 6H), 0.97 (s, 3H), 0.90 (s, 3H), 0.89 (d, 3H, J = 3.7 Hz), 0.88 (s, 9H), 0.86 (s, 3H), 0.76 (s, 3H), 0.68 (s, 3H), 0.022 (s, 3H), 0.016 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 134.6, 134.2, 130.8, 125.2, 79.4, 50.4, 49.8, 44.4, 39.4, 36.9, 36.3, 36.2, 35.5, 31.0, 30.8, 28.3, 28.2, 26.5, 25.9, 25.7, 24.9, 24.2, 21.0, 19.2, 18.6, 18.6, 18.1, 17.6, 15.9, 15.7, -3.8, -5.0.

*Synthesis of alcohol **2***. Ozone was bubbled through a solution of **1** (1.2 g, 2.3 mmol) in $CH_2Cl_2$/MeOH (40 mL, 3:1) at 0 °C. After 10 min, the ozone was stopped and $NaBH_4$ (0.30 g, 7.9 mmol) was added. The reaction mixture was stirred for 2 h, allowing it to come to room temperature, and then concentrated. The crude product was dissolved in EtOAc and washed with saturated $NH_4Cl$, brine, and dried over $MgSO_4$. Purification by column chromatography (20% EtOAc/hexanes) yielded the product as a white powder (0.37 g). $^1$H NMR ($CDCl_3$) δ 3.59 (dt, 2H, J = 1.7, 6.5 Hz), 3.17 (dd, 1H, J = 4.9, 10.8 Hz), 2.05-1.83 (m, 5H), 1.68-1.33 (m, 12H), 1.32-0.98 (m, 6H), 0.95 (s, 3H), 0.90 (s, 3H), 0.89 (d, 3H, J = 3.7 Hz), 0.86 (s, 9H), 0.84 (s, 3H), 0.74 (s,

3H), 0.66 (s, 3H), 0.0058 (s, 3H), 0.0001 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 134.6, 134.1, 79.4, 63.6, 50.4, 50.3, 49.7, 44.4, 39.4, 36.9, 36.2, 35.5, 32.1, 31.0, 30.8, 29.5, 28.3, 28.2, 26.5, 25.9, 25.6, 24.2, 20.9, 19.1, 18.6, 18.4, 18.1, 15.9, 15.7, -3.8, -5.0.

*Synthesis of mesylate **3***. MsCl (0.15 mL, 1.9 mmol) was added to a solution of the alcohol **2** (0.60 g, 1.2 mmol) in freshly distilled pyridine (6 mL). After 1 h, the reaction mixture was concentrated under vacuum. The crude product was dissolved in EtOAc and washed with 10% HCl, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. The product (0.54 g, 78%) was isolated as a white powder and used without further purification. $^1$H NMR ($CDCl_3$) δ 4.16 (dt, 2H, J = 2.2, 6.5 Hz), 3.16 (dd, 1H, J = 4.9, 10.9 Hz), 2.96 (s, 3H), 2.10-1.97 (m, 4H), 1.91-1.75 (m, 3H), 1.65-1.39 (m, 10H), 1.38-0.97 (m, 6H), 0.94 (s, 3H), 0.87 (s, 3H), 0.86 (d, 3H, J = 6.9 Hz), 0.85 (s, 9H), 0.83 (s, 3H), 0.73 (s, 3H), 0.65 (s, 3H), -0.0057 (s, 3H), -0.011 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 134.6, 134.1, 79.3, 70.6, 50.3, 50.2, 49.7, 44.4, 39.4, 37.3, 36.8, 35.9, 35.5, 31.7, 31.0, 30.7, 28.3, 28.2, 26.5, 26.0, 25.9, 24.2, 20.9, 19.1, 18.6, 18.5, 18.4, 15.9, 15.7, -3.8, -5.0.

*Synthesis of **$d_7$-dHLan***. A solution of $d_7$-2-bromopropane (0.50 mL, 5.3 mmol) in THF (5 mL) was added in portions to Mg° (0.11 g, 4.5 mmol) in a minimal amount of THF. After 30 min, $Li_2CuCl_4$ (0.1 M/THF, 0.90 mL, 0.090 mmol) was added, followed by a solution of the mesylate **3** (0.54 g, 0.91 mmol) in THF (9 mL). After 1 h, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product was purified by column chromatography (hexanes) and isolated as a white powder (0.39 g, 78%). $^1$H NMR ($CDCl_3$) δ 3.18 (dd, 1H, J = 4.8, 10.9 Hz), 1.98-1.93 (m, 4H), 1.91-1.83 (m, 1H), 1.69-1.61 (m, 4H), 1.58-1.40 (m, 10H), 1.35-1.18 (m, 6H), 0.96 (s, 3H), 0.89 (s, 3H), 0.88 (d, 3H, J = 6.4 Hz), 0.87 (s, 9H), 0.85 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H), 0.015 (s, 3H), 0.0096 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 134.6, 134.2, 79.4, 53.4, 50.5, 50.4, 49.7, 44.4, 39.4, 39.2, 36.9, 36.4, 35.5, 31.0, 30.8, 28.3, 28.2, 26.5, 25.9, 24.2, 24.0, 21.0, 19.1, 18.7, 18.4, 18.1, 15.9, 15.7, -3.8, -5.0.

TBAF (1M/THF, 2.1 mL, 2.1 mmol) was added to a solution of the $d_7$-TBS-dHLan (0.39 g, 0.71 mmol) in THF (4 mL), then the reaction mixture was heated to reflux. After overnight, the reaction mixture was cooled and diluted with EtOAc. The organics were washed with brine and dried over $MgSO_4$. The product (0.29 g, 92%) was isolated as a white powder after purification by column chromatography (20% EtOAc/hexanes). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 3.21 (dd, 1H, J = 4.6, 11.6 Hz), 2.03-1.97 (m, 4H),

1.92-1.84 (m, 1H), 1.72-1.60 (m, 5H), 1.58-1.41 (m, 6H), 1.34-1.30 (m, 4H), 1.29-1.24 (m, 6H), 0.98 (s, 3H), 0.96 (s, 3H), 0.89 (s, 3H), 0.86 (d, 3H, J = 8.1 Hz), 0.79 (s, 3H), 0.67 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 134.4, 134.3, 78.9, 50.4, 50.3, 49.7, 44.4, 39.2, 38.8, 36.9, 36.4, 35.5, 30.9, 30.8, 28.2, 27.9, 27.8, 26.4, 25.6, 24.2, 24.0, 20.9, 19.1, 18.7, 18.2, 15.7, 15.3.

*Synthesis of iodide **4***. Iodine (0.22 g, 0.87 mmol) was added to a solution of the alcohol **2** (0.37 g, 0.72 mmol), imidazole (0.10 g, 1.5 mmol), and $PPh_3$ (0.23 g, 0.88 mmol) in $CH_2Cl_2$ (8 mL). After 1 h, the reaction mixture was diluted with ether and filtered through a pad of silica gel. The product was isolated as a white powder (0.42 g, 93%) and used without further purification. $^1$H NMR ($CDCl_3$) δ 3.22-3.07 (m, 3H), 2.01-1.96 (m, 4H), 1.92-1.84 (m, 1H), 1.71-1.61 (m, 6H), 1.59-1.41 (m, 6H), 1.36-1.13 (m, 6H), 0.95 (s, 3H), 0.89 (s, 3H), 0.87 (apparent s, 12H), 0.85 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H), 0.013 (s, 3H), 0.007 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 134.6, 134.1, 79.4, 50.4, 50.3, 49.8, 44.5, 39.4, 37.1, 36.9, 35.7, 35.5, 31.0, 30.8, 30.6, 28.3, 28.2, 26.5, 25.9, 24.2, 20.9, 19.2, 18.7, 18.4, 18.1, 15.9, 15.7, 7.9, -3.8, -5.0.

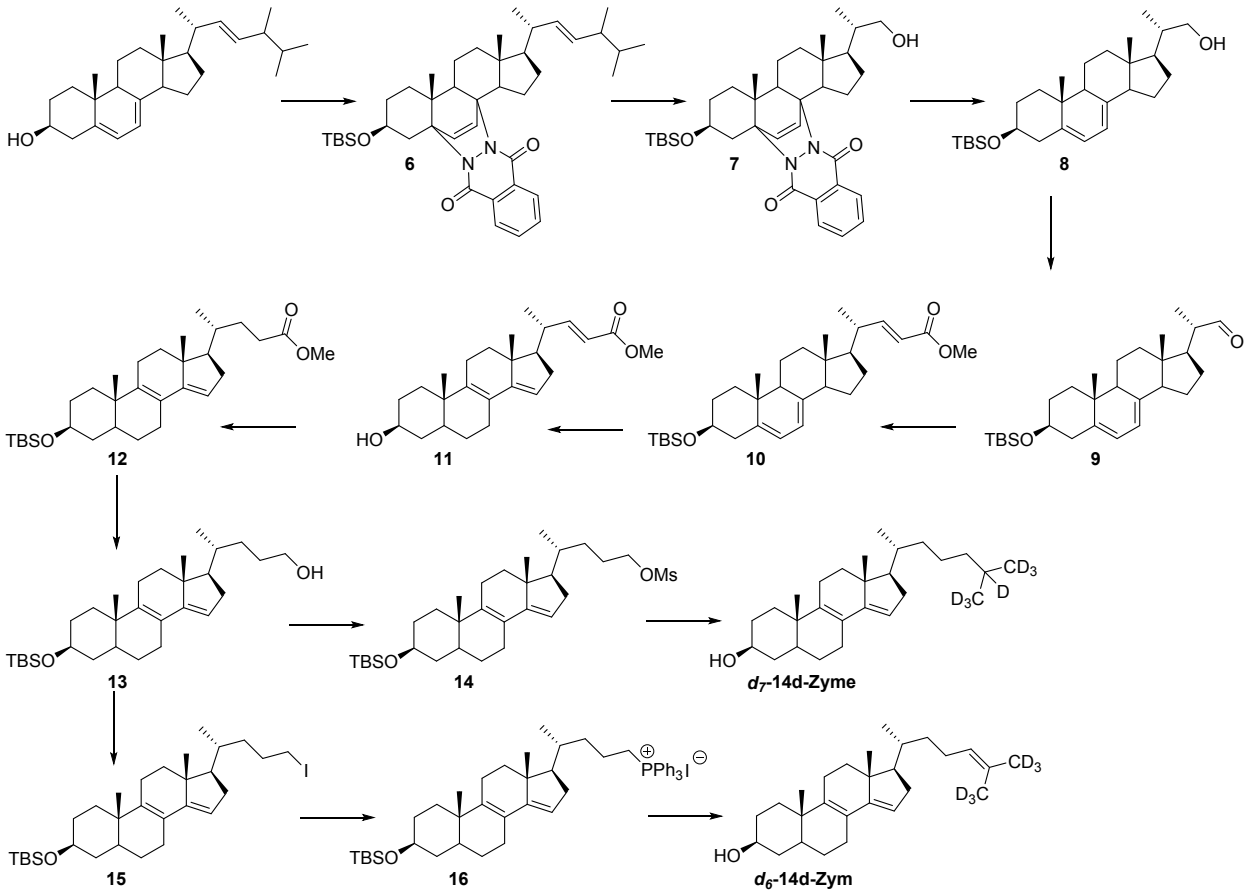
*Synthesis of **5***. $PPh_3$ (0.21 g, 0.80 mmol) was added to a solution of the iodide **4** (0.42 g, 0.67 mmol) and $iPr_2EtN$ (0.35 mL, 2.0 mmol) in anhydrous toluene (3 mL). The reaction mixture was heated to 100 °C. After allowing to react overnight, the reaction mixture was cooled and concentrated. The product (0.36 g) was purified by column chromatography (5% MeOH/$CH_2Cl_2$) and isolated in 60% yield. $^1$H NMR ($CDCl_3$) δ 7.80-7.74 (m 9H), 7.69-7.58 (m, 6H), 3.59-3.52 (m, 2H), 3.17-3.12 (m, 1H), 1.95-1.93 (m, 4H), 1.84-1.68 (m, 4H), 1.64-1.42 (m, 10H), 1.40-1.18 (m, 6H), 1.14-1.03 (m, 2H), 0.90 (s, 3H), 0.86-0.82 (m, 15H), 0.75 (s, 3H), 0.71 (s, 3H), -0.025 (s, 3H), -0.029 (s, 3H).

*Synthesis of **$d_6$-Lan***. BuLi (2.5 M/hexanes, 0.30 mL, 0.75 mmol) was added to a solution of **5** (0.36 g, 0.40 mmol) in THF (4 mL), followed by *$d_6$*-acetone (60 uL, 0.82 mmol) after 15 min. After overnight, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product was isolated as a white powder (49 mg) after purification by column chromatography (hexanes). $^1$H NMR ($CDCl_3$) δ 5.08 (t, 1H, J = 7.1 Hz), 3.18 (dd, 1H, J = 4.8, 11.2 Hz), 2.02-1.97 (m, 4H), 1.92-1.80 (m, 1H), 169-1.63 (m, 4H), 1.60-1.36 (m, 8H), 1.30-1.12 (m, 4H), 1.02-0.98 (m, 2H), 0.96 (s, 3H), 0.89 (s, 3H), 0.89 (d, 3H, J = 6.2 Hz), 0.87 (s, 9H), 0.85 (s, 3H), 0.75 (s, 3H), 0.67 (s, 3H), 0.014 (s, 3H), 0.008 (s, 3H);

$^{13}$C NMR ($CDCl_3$) δ 134.6, 134.2, 125.2, 79.4, 50.4, 49.7, 44.4, 39.4, 36.8, 36.3, 36.2, 35.5, 31.0, 30.8, 28.3, 28.2, 26.5, 25.9, 24.8, 24.2, 20.9, 19.1, 18.6, 18.4, 18.1, 15.8, 15.7, -3.9, -5.0.

TBAF (1 M/THF, 0.30 mL, 0.30 mmol) was added to a solution of the $d_6$-TBS-Lan (49 mg, 0.090 mmol) in THF (1 mL), then the reaction was heated to reflux. After overnight, the reaction mixture was cooled. It was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. Purification by column chromatography (20% EtOAc/hexanes) yielded the product as a white powder (34 mg, 87%). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 5.08 (t, 1H, J = 7.1 Hz), 3.21 (dd, 1H, J = 4.6, 11.6 Hz), 2.03-1.95 (m, 4H), 1.93-1.80 (m, 2H), 1.73-1.63 (m, 4H), 1.61-1.12 (m, 12H), 1.05-1.01 (m, 2H), 0.98 (s, 3H), 0.96 (s, 3H), 0.89 (d, 3H, J = 6.3 Hz), 0.85 (s, 3H), 0.79 (s, 3H), 0.67 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 134.3, 131.0, 125.2, 78.9, 50.3, 49.7, 44.4, 38.8, 37.0, 36.3, 36.2, 35.5, 30.9, 30.8, 28.1, 27.9, 27.8, 26.4, 24.8, 24.2, 20.9, 19.1, 18.6, 18.2, 15.7, 15.3.

Scheme S2. Synthesis of $d_6$-14d-Zym and $d_7$-14d-Zyme.




*Synthesis of* ***6***. TBSCl (6.1 g, 0.040 mol) and imidazole (3.5 g, 0.051 mol) were added to a solution of ergosterol (10 g, 0.026 mol) in DMF/THF (60 mL, 1:1). A precipitate formed immediately. After overnight, the reaction mixture was diluted with hexanes/EtOAc (1:1) and washed with $H_2O$, brine, and dried over $MgSO_4$. The product (11 g, 86%) was isolated as a pale yellow powder after column chromatography (10% EtOAc/hexanes).

$Pb(OAc)_4$ (15 g, 0.033 mol) was added to a solution of the TBS-ergosterol (11 g, 0.022 mol) and phthalhydrazide (5.4 g, 0.033 mol) in $CH_2Cl_2$ (200 mL) and HOAc (20 mL). After 1 h, the reaction mixture was washed with $H_2O$, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. After purification by column chromatography (10% EtOAc/hexanes), the product was isolated as a yellow foam (13 g, 88%). $^1H$ NMR ($CDCl_3$) δ 8.13-8.07 (m, 2H), 7.67-7.65 (m, 2H), 6.62 (d, 1H, J = 8.2 Hz), 6.23

(d, 1H, J = 8.3 Hz), 5.23-5.09 (m, 2H), 3.94-3.84 (m, 2H), 3.60-3.52 (m, 1H), 2.10-1.94 (m, 4H), 1.86-1.79 (m, 2H), 1.73-1.50 (m, 4H), 1.48-1.18 (m, 8H), 0.99 (s, 3H), 0.99 (d, 3H, J = 6.4 Hz), 0.90-0.78 (m, 12H), 0.84 (s, 9H), -0.026 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 161.8, 159.5, 138.4, 135.2, 132.5, 132.4, 132.0, 130.5, 130.2, 128.6, 126.9, 126.4, 68.4, 67.4, 67.0, 56.5, 50.5, 48.9, 44.1, 42.6, 40.3, 39.8, 39.2, 35.5, 34.6, 33.0, 30.5, 28.1, 25.9, 24.4, 21.8, 20.8, 19.8, 19.6, 18.5, 17.9, 17.4, 13.2, -4.4, -5.0.

*Synthesis of **7***. Ozone was bubbled through a solution of **6** (13 g, 0.020 mol) in $CH_2Cl_2$ (200 mL) and MeOH (100 mL) at 0 °C. After 1 h, the ozone was stopped and $NaBH_4$ (2.3g, 0.061 mol) was added. The reaction was warmed to room temperature and stirred for 1 h, then concentrated. The crude product was dissolved in EtOAc and washed with saturated $NH_4Cl$, brine, and dried over $MgSO_4$. The product (12 g, 100 %) was isolated as a yellow foam and used without purification.

*Synthesis of **8***. $LiAlH_4$ (2.3 g, 0.061 mol) was added to a solution of **7** (12 g, 0.020 mol) in THF (100 mL), then heated to reflux. After 1 h, the reaction mixture was cooled and quenched with 10% HCl. The reaction mixture was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. Purification by column chromatography (20% EtOAc/hexanes) yielded the product as a white powder (6.6 g, 72%). $^1$H NMR ($CDCl_3$) δ 5.53 (d, 1H, J = 5.5 Hz), 5.38-5.35 (m, 1H), 3.63 (dd, 1H, J = 3.2, 10.5 Hz), 3.59-3.41 (m, 1H), 3.37 (dd, 1H, J = 6.8, 10.5 Hz), 2.32-2.30 (m, 2H), 2.08-2.03 (m, 1H), 1.97-1.81 (m, 4H), 1.77-1.65 (m, 4H), 1.60-1.31 (m, 8H), 1.06 (d, 3H, J = 6.6 Hz), 0.92 (s, 3H), 0.87 (s, 9H), 0.62 (s, 3H), 0.046 (s, 6H) ; $^{13}$C NMR ($CDCl_3$) δ 140.8, 140.7, 119.1, 116.4, 71.2, 67.8, 54.1, 52.1, 46.2, 43.0, 41.3, 39.0, 38.5, 37.0, 32.3, 27.5, 25.9, 23.0, 21.0, 18.2, 16.8, 16.3, 11.8, -4.7.

*Synthesis of aldehyde **9***. Oxalyl chloride (1.9 mL, 0.022 mol) was added slowly to a solution of DMSO (1.6 mL, 0.023 mol) in $CH_2Cl_2$ (40 mL) at -78 °C. After 30 min, a solution of the alcohol **8** (6.6 g, 0.015 mol) in THF (50 mL) was added. After another 30 min, $Et_3N$ (6.3 mL, 0.045 mol) was added and the reaction mixture was stirred for 1 h, allowing it to come to room temperature. The reaction mixture was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product was purified by column chromatography (10% EtOAc/hexanes) and isolated as a white powder (4.9 g, 74%). $^1$H NMR ($CDCl_3$) δ 9.57 (d, 1H, J = 3.2 Hz), 5.53 (d, 1H, J = 5.5 Hz), 5.39-5.36 (m, 1H), 3.58-3.55 (m, 1H), 2.38-2.30 (m, 1H), 2.30-2.29 (m, 2H), 2.05-1.90 (m, 4H), 1.88-1.83 (apparent dt, 1H, J = 3.5, 13.4

Hz), 1.81-1.70 (m, 3H), 1.67-1.59 (m, 3H), 1.55-1.42 (m, 2H), 1.36-1.25 (m, 2H), 1.13 (d, 3H, J = 6.9 Hz), 0.91 (s, 3H), 0.87 (s, 9H), 0.64 (s, 3H), -0.042 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 204.8, 141.0, 139.9, 119.0, 116.8, 71.1, 53.6, 50.7, 49.7, 46.2, 43.4, 41.3, 38.8, 38.5, 37.0, 32.3, 26.9, 25.8, 23.3, 21.0, 18.2, 16.3, 13.5, 12.1, -4.7.

*Synthesis of **10***. Methyl(triphenylphosphoranylidene)acetate (7.4 g, 0.022 mol) was added to a solution of the aldehyde **9** (4.9 g, 0.011 mol) in $CH_2Cl_2$ (55 mL). The reaction mixture was allowed to stir overnight, then concentrated. After purification by column chromatography (10% EtOAc/hexanes), the product was isolated as a white powder (5.3 g, 96%). $^1$H NMR ($CDCl_3$) δ 6.83 (dd, 1H, J = 9.0, 15.6 Hz), 5.74 (dd, 1H, J = 0.5, 15.6 Hz), 5.52 (d, 1H, J = 5.4 Hz), 5.37-5.34 (m, 1H), 3.70 (s, 3H), 3.61-3.53 (m, 1H), 2.32-2.24 (m, 3H), 2.05-2.02 (m, 1H), 1.97-1.65 (m, 6H), 1.62-1.20 (m, 8H), 1.09 (d, 3H, J = 6.4 Hz), 0.91 (s, 3H), 0.87 (s, 9H), 0.63 (s, 3H), 0.044 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 167.4, 154.7, 140.8, 140.4, 119.1, 118.7, 116.6, 71.1, 54.6, 54.2, 51.3, 46.2, 43.2, 41.3, 39.9, 39.0, 38.4, 37.0, 32.3, 27.8, 25.9, 22.9, 21.0, 19.3, 18.2, 16.3, 12.0, -4.7.

*Synthesis of **11***. HCl (1.6 mL, 0.019 mol) was added to a solution of **10** (6.6 g, 0.013 mol) in $CHCl_3$ (52 mL) and HOAc (13 mL), then the reaction mixture was heated to reflux. After 3 h, the reaction mixture was cooled and diluted with EtOAc. The organic layer was cautiously washed with saturated $NaHCO_3$, brine, and dried over $MgSO_4$. The product (2.6 g, 51%) was isolated as an orange foam after purification by column chromatography (20% EtOAc/hexanes). $^1$H NMR ($CDCl_3$) δ 6.84 (dd, 1H, J = 9.0, 15.6 Hz), 5.77 (d, 1H, J = 15.6 Hz), 5.29 (br s, 1H), 3.70 (s, 3H), 3.65-3.56 (m, 1H(, 2.50-2.40 (m, 1H), 2.32-2.22 (m, 2H), 2.21-2.15 (m, 2H), 2.10-1.95 (m, 2H), 1.87-1.58 (m, 6H), 1.55-1.21 (m, 7H), 1.09 (d, 3H, J = 6.6 Hz), 0.96 (s, 3H), 0.82 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 167.4, 154.7, 150.5, 140.9, 123.0, 118.8, 117.2, 70.9, 55.8, 51.3, 45.2, 40.8, 38.5, 38.2, 36.8, 36.5, 36.1, 35.2, 31.6, 26.5, 25.2, 21.8, 19.4, 18.3, 15.7.

*Synthesis of ester **12***. Raney Nickel (~1 mL) was added to a solution of **11** (2.6 g, 6.7 mmol) in THF (60 mL). The reaction mixture was sparged with $H_2$ for 10 min, then left under an atmosphere of $H_2$. After 1 h, the reaction mixture was filtered through Celite and concentrated. Caution: the catalyst should not be allowed to go dry. The product (2.5 g, 95%) was isolated as a yellow foam and was used without purification.

TBSCl (1.6 g, 11 mmol) and imidazole (0.95 g, 14 mmol) were added to a solution of the alcohol (2.7 g, 7.0 mmol) in DMF (35 mL). After overnight, the reaction mixture was diluted with hexanes/EtOAc (1:1) and washed with $H_2O$, brine, and dried over $MgSO_4$. After purification by column chromatography (10% EtOAc/hexanes), the product was isolated as a yellow oil, which solidified upon standing (3.2 g, 93%). $^1$H NMR ($CDCl_3$) δ 5.31 (br s, 1H), 3.64 (s, 3H), 3.59-3.52 (m, 1H), 2.38-2.30 (m, 2H), 2.26-2.18 (m, 3H), 2.10-1.95 (m, 3H), 1.82-1.57 (m, 5H), 1.54-1.44 (m, 4H), 1.42-1.16 (m, 6H), 0.95 (s, 3H), 0.92 (d, 3H, J = 6.5 Hz), 0.86 (s, 9H), 0.78 (s, 3H), 0.029 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 174.6, 151.0, 141.1, 122.9, 116.9, 71.7, 56.8, 51.4, 45.0, 41.0, 38.7, 36.8, 36.6, 36.5, 35.7, 35.4, 33.9, 32.1, 26.5, 25.9, 25.8, 25.3, 21.8, 18.6, 18.4, 15.6, -4.6.

*Synthesis of alcohol **13***. DIBAL-H (1 M/THF, 20 mL, 20 mmol) was added to a solution of the ester **12** (3.2 g, 6.5 mmol) in THF (30 mL). After 1 h, the reaction mixture was quenched with 10% HCl. The reaction mixture was extracted with EtOAc, then washed with brine and dried over $MgSO_4$. Purification by column chromatography (20% EtOAc/hexanes) yielded the product as a white powder (1.5 g, 50%). $^1$H NMR ($CDCl_3$) δ 5.31 (br s, 1H), 3.62-3.53 (m, 3H), 2.38-2.29 (m, 2H), 2.22-2.15 (m, 2H), 2.10-1.89 (m, 2H), 1.80-1.58 (m, 6H), 1.54-1.08 (m, 12H), 0.96 (s, 3H), 0.93 (d, 3H, J = 8.0 Hz), 0.86 (s, 9H), 0.79 (s, 3H), 0.033 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 151.1, 141.1, 122.9, 117.0, 71.8, 63.5, 57.0, 45.0, 41.0, 38.7, 36.9, 36.5, 35.8, 35.4, 33.8, 32.1, 31.8, 29.3, 26.6, 25.9, 25.3, 21.8, 18.8, 18.4, 18.2, 15.6, -4.6.

*Synthesis of mesylate **14***. MsCl (0.26 mL, 3.4 mmol) was added to a solution of the alcohol **13** (1.0 g, 2.2 mmol) in freshly distilled pyridine (11 mL). After 1 h, the reaction mixture was concentrated under vacuum. The crude product was dissolved in EtOAc and washed with 10% HCl, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. The product (1.1 g, 91%) was isolated as a pale yellow powder and used without further purification. $^1$H NMR ($CDCl_3$) δ 5.31 (br s, 1H), 4.22-4.16 (m, 2H), 3.59-3.52 (m, 1H), 2.98 (s, 3H), 2.35-2.29 (m, 2H), 2.19-1.96 (m, 3H), 1.81-1.57 (m, 6H), 1.53-1.47 (m, 4H), 1.44-1.07 (m, 8H), 0.95 (s, 3H), 0.94 (d, 3H, J = 6.6 Hz), 0.86 (s, 9H), 0.79 (s, 3H), 0.028 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 151.1, 141.2, 122.8, 116.8, 71.7, 70.6, 56.8, 45.0, 41.0, 37.3, 37.2, 36.8, 36.6, 35.8, 35.4, 33.5, 32.1, 31.3, 26.5, 25.9, 25.3, 21.8, 18.7, 18.4, 18.2, 15.6, -4.6.

*Synthesis of* ***d$_7$-14d-Zyme***. A solution of *d$_7$*-2-bromopropane (0.43 mL, 4.6 mmol) in THF (5 mL) was added in portions to Mg° (0.11 g, 4.5 mmol) in a minimal amount of THF. After 30 min, $Li_2CuCl_4$ (0.1 M/THF, 0.90 mL, 0.090 mmol) was added, followed by a solution of the mesylate **14** (0.50 g, 0.91 mmol) in THF (9 mL). After 1 h, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product was purified by column chromatography (10% EtOAc/hexanes) and isolated as a white powder (0.32 g, 70%). $^1$H NMR ($CDCl_3$) δ 5.33 (br s, 1H), 3.60-3.54 (m, 1H), 2.36-2.30 (m, 2H), 2.19-2.16 (m, 2H), 2.11-1.98 (m, 2H), 1.95-1.69 (m, 3H), 1.68-1.49 (m, 6H), 1.43-1.05 (m, 10H), 0.97 (s, 3H), 0.92 (d, 3H, J = 6.6 Hz), 0.88 (s, 9H), 0.80 (s, 3H), 0.044 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 151.1, 141.0, 123.0, 117.1, 71.8, 57.2, 44.9, 41.0, 39.2, 38.8, 36.9, 36.5, 36.1, 35.9, 35.5, 34.0, 32.1, 31.5, 26.6, 25.9, 25.3, 23.7, 22.6, 21.8, 18.8, 18.4, 18.2, 15.6, 14.1, -4.6.

TBAF (1 M/THF, 1.3 mL, 1.3 mmol) was added to a solution of the *d$_7$*-TBS-dHLan (0.32 g, 0.63 mmol) in THF (3 mL). After overnight, the reaction mixture was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. The product (0.18 g, 72%) was isolated as a white powder after purification by column chromatography (20% EtOAc/hexanes). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 5.33 (br s, 1H), 3.64-3.56 (m, 1H), 2.36-2.30 (m, 2H), 2.18-2.10 (m, 2H), 2.09-1.97 (m, 3H), 1.86-1.80 (m, 2H), 1.67-1.30 (m, 11H), 1.30-1.01 (m, 6H), 0.97 (s, 3H), 0.91 (d, 3H, J = 6.4 Hz), 0.79 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 151.0, 140.8, 123.0, 117.4, 70.9, 57.2, 45.0, 40.9, 39.2, 38.3, 36.9, 36.5, 36.1, 35.9, 35.3, 34.0, 31.6, 26.5, 25.2, 23.6, 21.8, 18.8, 18.3, 15.6.

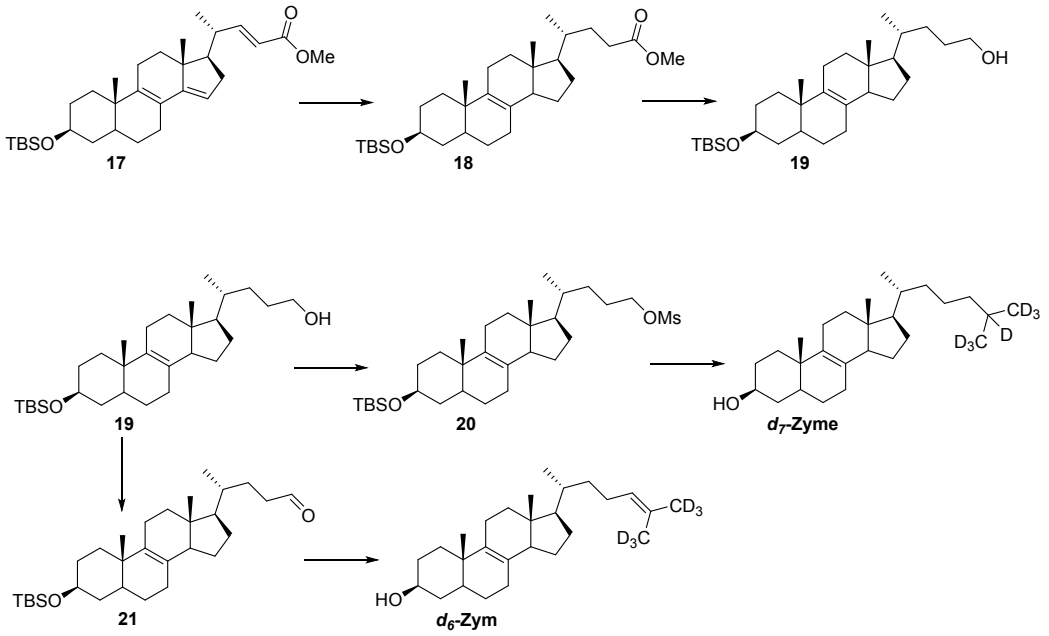
*Synthesis of iodide* ***15***. Iodine (1.3 g, 5.1 mmol) was added to a solution of the alcohol **13** (2.0 g, 4.3 mmol), imidazole (0.6 g, 8.8 mmol), and $PPh_3$ (1.4 g, 5.3 mmol) in $CH_2Cl_2$ (20 mL). After 30 min, the reaction mixture was diluted with ether and filtered through a pad of silica gel. The product was isolated as a white sticky powder (2.4 g, 94%) and used without further purification. $^1$H NMR ($CDCl_3$) δ 5.32 (br s, 1H), 3.57-3.54 (m, 1H), 3.20-3.10 (m, 2H), 2.37-2.31 (m, 2H), 2.22-2.14 (m, 2H), 2.08-2.04 (m, 2H), 1.98 (dd, 1H, J = 4.3, 12.7 Hz), 1.91-1.86 (m, 2H), 1.79-1.70 (m, 2H), 1.67-1.61 (m, 2H), 1.58-1.47 (m, 4H), 1.46-1.34 (m, 4H), 1.22-1.08 (m, 2H), 0.96 (s, 3H), 0.93 (d, 3H, J = 6.5 Hz), 0.87 (s, 9H), 0.79 (s, 3H), 0.035 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 151.1, 141.2, 122.9, 117.0, 71.8, 56.9, 45.1, 41.1, 38.8, 36.9, 36.8, 36.6, 35.9, 35.5, 33.4, 32.2, 30.3, 26.6, 25.9, 25.4, 21.9, 18.9, 18.5, 15.7, 7.9, -4.5.

*Synthesis of **16***. $PPh_3$ (1.0 g, 3.8 mmol) was added to a solution of the iodide **15** (1.7 g, 3.0 mmol) and $iPr_2EtN$ (0.80 mL, 4.6 mmol) in anhydrous toluene (15 mL). The reaction mixture was heated to 100 °C. After allowing to react overnight, the reaction mixture was cooled and concentrated. The product (2.5 g) was purified by column chromatography (10% MeOH/$CH_2Cl_2$) and isolated in 99% yield.

*Synthesis of **$d_6$-14d-Zym***. BuLi (2.5 M/hexanes, 1.0 mL, 2.5 mmol) was added to a solution of **16** (1.4 g, 1.6 mmol) in THF (8 mL) at -78 °C. After 20 min, $d_6$-acetone (0.24 mL, 3.2 mmol) and the reaction was allowed to warm to room temperature. After 3 h, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product was deprotected without purification.

TBAF (1 M/THF, 3.3 mL, 3.3 mmol) was added to a solution of the crude $d_6$-TBS-14d-Zym (1.6 mmol theoretical) in THF (8 mL). After overnight, the reaction was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. Purification by column chromatography (20 to 30% EtOAc/hexanes) yielded the product as a white foam (0.31 g, 49% two steps). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 5.34 (br s, 1H), 5.09 (t, 1H, J = 7.1 Hz), 3.64-3.58 (m, 1H), 2.38-2.31 (m, 2H), 2.19-2.11 (m, 2H), 2.09-1.98 (m, 4H), 1.89-1.81 (m, 2H), 1.68-1.30 (m, 12H), 1.28-1.08 (m, 2H), 0.97 (s, 3H), 0.94 (d, 3H, J = 6.4 Hz), 0.80 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 151.0, 140.8, 125.1, 123.0, 117.4, 71.0, 57.1, 45.0, 40.9, 38.3, 36.9, 36.5, 36.0, 35.8, 35.3, 33.8, 31.7, 26.5, 25.2, 24.6, 21.8, 18.7, 18.3, 15.6.

Scheme S3. Synthesis of $d_6$-Zym and $d_7$-Zyme.




*Synthesis of **17***. TBSCl (1.0 g, 6.6 mmol) and imidazole (0.70 g, 10 mmol) were added to a solution of **11** in DMF (24 mL). After overnight, the reaction mixture was diluted with hexanes/EtOAc (1:1), washed with $H_2O$ and brine, then dried over $MgSO_4$. The product was purified by column chromatography (10% EtOAc/hexanes) and isolated as a yellow powder (2.4 g, 100 %). $^1$H NMR ($CDCl_3$) δ 6.85 (dd, 1H, J = 9.0, 15.6 Hz), 5.77 (d, 1H, J = 15.6 Hz), 5.28 (br s, 1H), 3.70 (s, 3H), 3.59-3.52 (m, 1H), 2.49-2.43 (m, 1H), 2.35-2.24 (m, 1H), 2.21-2.15 (m, 2H), 2.07-1.95 (m, 3H), 1.80-1.71 (m, 2H), 1.66-1.58 (m, 2H), 1.53-1.17 (m, 8H), 1.09 (d, 3H, J = 6.6 Hz), 0.96 (s, 3H), 0.86 (s, 9H), 0.82 (s, 3H), 0.032 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 167.4, 154.7, 150.6, 141.2, 122.8, 118.7, 117.0, 71.7, 55.8, 51.3, 45.2, 41.0, 38.7, 38.5, 36.9, 36.6, 36.1, 35.4, 32.1, 26.5, 25.9, 25.6, 25.2, 21.8, 19.2, 18.4, 18.2, 15.7, -4.6.

*Synthesis of ester **18***. Raney Nickel (~1 mL) was added to a solution of **17** (2.4 g, 4.9 mmol) in THF (50 mL). The reaction mixture was sparged with $H_2$ for 20 min, then left under an atmosphere of $H_2$. After 8 h, the reaction mixture was filtered through Celite and concentrated. Caution: the catalyst should not be allowed to go dry. The product (2.0 g, 80%) was isolated as a white powder and was used without purification. $^1$H NMR ($CDCl_3$) δ 3.64 (s, 3H), 3.58-3.52 (m, 1H), 2.37-2.30 (m, 2H), 2.25-2.15 (m, 2H), 2.08-1.99 (m, 2H), 1.95-1.75 (m, 4H), 1.70-1.57 (m, 4H), 1.55-1.07

(m, 12H), 0.91 (s, 3H), 0.89 (d, 3H, J = 6.6 Hz), 0.86 (s, 9H), 0.58 (s, 3H), 0.029 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 174.7, 135.2, 127.9, 72.0, 54.4, 51.8, 51.4, 42.1, 40.8, 38.8, 36.9, 35.8, 35.7, 35.3, 33.9, 32.0, 31.0, 28.6, 27.2, 25.9, 25.5, 23.7, 22.7, 18.2, 17.8, 11.1, -4.6.

*Synthesis of alcohol **19***. DIBAL-H (1 M/THF, 12 mL, 12 mmol) was added to a solution of **18** (2.0 g, 3.9 mmol) in THF (20 mL). After 30 min, the reaction was quenched with 10% HCl and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product (1.8 g, 96%) was isolated as a white powder and pure enough for the next reaction. $^1$H NMR ($CDCl_3$) δ 3.62-3.52 (m, 3H), 2.36-2.13 (m, 2H), 2.08-2.00 (m, 2H), 1.97-1.74 (m, 3H), 1.70-1.54 (m, 4H), 1.49-1.22 (m, 12H), 1.19-1.03 (m, 4H), 0.92 (s, 3H), 0.92 (d, 3H, J = 6.6 Hz), 0.86 (s, 9H), 0.58 (s, 3H), 0.032 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 135.2, 127.9, 72.0, 63.5, 54.6, 51.8, 42.1, 40.9, 38.8, 36.9, 36.0, 35.7, 35.3, 32.1, 31.7, 29.4, 28.7, 27.2, 25.7, 25.5, 23.7, 22.7, 18.8, 18.4, 17.8, 11.1, -4.6.

*Synthesis of mesylate **20***. MsCl (0.12 mL, 1.6 mmol) was added to a solution of the alcohol **19** (0.47 g, 0.99 mmol) in freshly distilled pyridine (5 mL). After 1 h, the reaction mixture was concentrated under vacuum. The crude product was dissolved in EtOAc and washed with saturated $NH_4Cl$, brine, and dried over $MgSO_4$. The product (0.49 g, 89%) was isolated as a white powder and used without further purification. $^1$H NMR ($CDCl_3$) δ 4.18-4.17 (m, 2H), 3.60-3.46 (m, 1H), 2.97 (s, 3H), 2.34-2.18 (m, 2H), 2.17-2.02 (m, 2H), 2.01-1.88 (m, 2H), 1.84-1.76 (m, 3H), 1.75-1.57 (m, 5H), 1.57-1.07 (m, 12H), 0.91 (s, 3H), 0.91 (d, 3H, J = 6.6 Hz), 0.86 (s, 9H), 0.58 (s, 3H), 0.023 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 135.2, 127.5, 72.0, 70.6, 54.5, 51.8, 42.1, 40.8, 38.7, 37.3, 36.9, 35.7, 35.3, 32.0, 31.4, 28.7, 27.1, 25.9, 25.5, 23.7, 22.7, 18.5, 18.2, 17.8, 11.1, -4.6.

*Synthesis of **$d_7$-Zyme***. A solution of $d_7$-2-bromopropane (0.40 mL, 4.3 mmol) in THF (4 mL) was added in portions to Mg° (0.10 g, 4.1 mmol) in a minimal amount of THF. After 30 min, $Li_2CuCl_4$ (0.1 M/THF, 0.90 mL, 0.090 mmol) was added, followed by a solution of the mesylate **20** (0.49 g, 0.89 mmol) in THF (9 mL). After 30 min, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product was isolated as a yellow oil (0.40 g, 89%).

TBAF (1 M/THF, 1.6 mL, 1.6 mmol) was added to a solution of the $d_7$-TBS-Zyme (0.40 g, 0.79 mmol) in THF (4 mL). After overnight, the reaction mixture was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. The product (0.30 g, 97%) was isolated as a white powder after

purification by column chromatography (20% EtOAc/hexanes). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 3.63-3.55 (m, 1H), 2.09-1.99 (m, 2H), 1.98-1.93 (m, 3H), 1.88-1.80 (m, 2H), 1.76-1.71 (apparent dt, 1H, J = 3.5, 13.0 Hz), 1.64-1.60 (m, 1H), 1.57-1.44 (m, 5H), 1.40-1.05 (m, 15H), 0.93 (s, 3H), 0.90 (d, 3H, J = 6.5 Hz), 0.59 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 134.9, 128.2, 71.2, 54.8, 51.9, 42.0, 40.7, 38.3, 36.9, 36.2, 36.1, 35.7, 35.1, 31.6, 28.7, 27.1, 25.4, 23.8, 23.7, 22.8, 18.7, 17.8, 11.1.

*Synthesis of aldehyde **21***. Dess-Martin periodinane (1.5 g, 3.5 mmol) was added to a solution of the alcohol **19** (1.3 g, 2.8 mmol) in $CH_2Cl_2$ (20 mL). After 1 h, the reaction mixture was diluted with ether and filtered through a pad of silica gel. The product was purified by column chromatography (10% EtOAc/hexanes) and isolated as a white powder (0.84 g, 65%). $^1$H NMR ($CDCl_3$) δ 9.74 (t, 1H, J = 1.9 Hz), 3.58-3.52 (m, 1H), 2.48-2.29 (m, 2H), 2.24-2.00 (m, 3H), 1.95-1.91 (m, 3H), 1.81-1.79 (m, 2H), 1.70-1.65 (m, 2H), 1.61-1.06 (m, 14H), 0.91 (s, 3H), 0.91 (d, 3H, J = 6.6 Hz), 0.86 (s, 9H), 0.58 (s, 3H), 0.025 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 203.1, 135.2, 127.9, 72.0, 54.5, 51.8, 42.1, 40.9, 40.8, 38.8, 36.9, 35.7, 35.6, 35.3, 32.1, 28.6, 27.9, 27.1, 25.8, 25.5, 23.7, 22.7, 18.4, 18.2, 17.8, 11.1, -4.6.

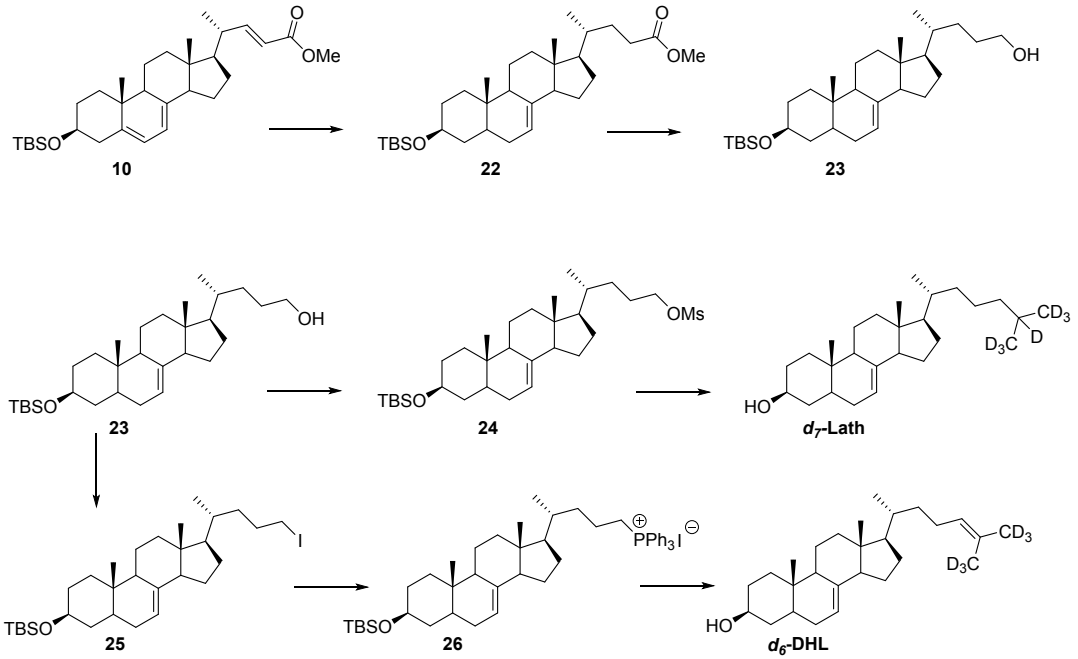
*Synthesis of $d_7$-isopropyltriphenylphosphonium bromide*. $d_7$-2-Bromopropane (0.50 mL, 5.3 mmol) was added to $PPh_3$ (1.4 g, 5.3 mmol) in a pressure tube. The tube was sealed and heated at 150 °C. After overnight, the tube was cooled and the reaction mixture concentrated. The product was dried under vacuum and isolated as white powder (1.8 g, 86%). $^1$H NMR ($CDCl_3$) δ 7.95-7.90 (m, H), 7.74-7.67 (m, 3H), 7.67-7.62 (m, 6H).

*Synthesis of **$d_6$-Zym***. BuLi (2.5 M/hexanes, 1.0 mL, 2.5 mmol) was added to a solution of the $d_7$-isopropyltriphenylphosphonium bromide (1.1 g, 2.8 mmol) in THF (12 mL) at 0 °C. After 30 min, a solution of the aldehyde **21** (0.60 g, 1.3 mmol) in THF (6 mL) was added. After an additional 2 h, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The crude product was immediately deprotected.

TBAF (1 M/THF, 2.5 mL, 2.5 mmol) was added to a solution of the TBS-$d_6$-Zym (1.3 mmol theoretical) in THF (6 mL). After overnight, the reaction mixture was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. The product (0.10 g, 20% two steps) was isolated as a white powder after purification by column chromatography (20% EtOAc/hexanes). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 5.07 (t, 1H, J

= 7.1 Hz), 3.63-3.56 (m, 1H), 2.09-1.93 (m, 7H), 1.90-1.80 (m, 3H), 1.76-1.71 (apparent dt, 1H, J = 3.5, 13.0 Hz), 1.64-1.46 (m, 5H), 1.43-1.31 (m, 7H), 1.28-0.96 (m, 4H), 0.93 (s, 3H), 0.92 (d, 3H, J = 5.3 Hz), 0.59 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 134.9, 128.2, 125.2, 71.2, 54.7, 51.8, 42.1, 40.7, 38.3, 36.9, 36.0, 35.7, 35.1, 31.6, 28.7, 27.1, 25.4, 24.7, 23.7, 22.7, 18.6, 17.8, 11.2.

Scheme S4. Synthesis of $d_6$-DHL and $d_7$-Lath.




*Synthesis of **22***. The selective hydrogenation of **10** only worked on the free alcohol, presumably due to sterics of the TBS-protecting group. TBAF (1 M/THF, 7.0 mL, 7.0 mmol) was added to a solution of **10** (1.8 g, 3.5 mmol) in THF (18 mL). After overnight, the reaction mixture was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. The product (0.97 g, 72%) was isolated as a white foam after purification by column chromatography (30% EtOAc/hexanes).

Raney Nickel (~1 mL) was added to a solution of the previous product (1.7 g, 4.5 mmol) in EtOAc/THF (20 mL, 1:1). The reaction mixture was sparged with $H_2$ for 10 min, then left under an atmosphere of $H_2$. After 3 h, the reaction mixture was filtered through Celite and concentrated. Caution: the catalyst should not be allowed to go dry. The product (1.9 g, 100%) was isolated as a

white powder and was used without purification. $^1$H NMR ($CDCl_3$) δ 5.13 (br s, 1H), 3.63 (s, 3H), 3.61-3.51 (m, 1H), 2.38-2.28 (m, 1H), 2.24-2.14 (m, 1H), 2.00-1.94 (apparent dt, 1H, J = 3.6, 12.5 Hz), 1.91-1.85 (m, 1H), 1.81-1.71 (m, 6H), 1.67-1.48 (m, 6H), 1.45-1.04 (m, 10H), 0.90 (d, 3H, J = 6.3 Hz), 0.76 (s, 3H), 0.50 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 174.7, 139.3, 117.6, 70.9, 55.7, 54.9, 51.5, 49.3, 43.3, 40.2, 39.5, 37.9, 37.1, 35.7, 34.1, 31.4, 31.0, 30.9, 29.6, 27.8, 22.9, 21.5, 18.4, 13.0, 11.8.

TBSCl (0.82 g, 5.4 mmol) and imidazole (0.62 g, 9.1 mmol) were added to a solution of the previous product (1.8 g, 4.5 mmol) in THF/DMF (20 mL, 1:1). After overnight, the reaction mixture was diluted with hexanes/EtOAc (1:1), washed with $H_2O$ and brine, then dried over $MgSO_4$. The product was purified by column chromatography (10% EtOAc/hexanes) and isolated as a white powder (1.8 g, 80%). $^1$H NMR ($CDCl_3$) δ 5.12 (br s, 1H), 3.63 (s, 3H), 3.56-3.48 (m, 1H), 2.38-2.28 (m, 1H), 2.24-2.13 (m, 1H), 2.00-1.94 (apparent dt, 1H, J = 3.5, 12.4 Hz), 1.91-1.84 (m, 1H), 1.78-1.72 (m, 5H), 1.62-1.48 (m, 6H), 1.41-1.00 (m, 10H), 0.90 (d, 3H, J = 6.2 Hz), 0.85 (s, 9H), 0.75 (s, 3H), 0.49 (s, 3H), 0.018 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 174.6, 139.2, 117.7, 71.8, 56.5, 55.7, 54.9, 51.6, 49.4, 43.3, 40.3, 39.5, 38.4, 37.3, 35.7, 34.2, 31.8, 31.0, 30.9, 29.6, 27.8, 25.9, 22.9, 21.4, 18.4, 18.2, 13.0, 11.8, -4.6.

*Synthesis of alcohol **23***. DIBAL-H (1 M/toluene, 11 mL, 11 mmol) was added to a solution of the ester **22** (1.8 g, 3.6 mmol) in THF (18 mL) at 0 °C. After 1 h, the reaction was quenched with 10% HCl and extracted with EtOAc. The organics were washed with brine and dried over $MgSO_4$. After purification by column chromatography (20% EtOAc/hexanes), the product was isolated as a white powder (1.6 g, 92%). $^1$H NMR ($CDCl_3$) δ 5.13 (br s, 1H), 3.59 (dt, 2H, J = 1.8, 6.8 Hz), 3.55-3.49 (m, 1H), 2.02-1.97 (m, 1H), 1.94-1.81 (m, 1H), 1.77-1.50 (m, 9H), 1.48-1.00 (m, 12H), 0.92 (d, 3H, J = 6.4 Hz), 0.86 (s, 9H), 0.76 (s, 3H), 0.51 (s, 3H), 0.027 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 139.4, 117.6, 71.8, 63.5, 55.9, 55.0, 49.5, 43.3, 40.3, 39.5, 38.4, 37.3, 35.9, 34.2, 31.8, 31.7, 29.7, 29.4, 27.9, 25.9, 22.9, 21.5, 18.8, 18.2, 13.0, 11.8, -4.6.

*Synthesis of mesylate **24***. MsCl (0.12 mL, 1.6 mmol) was added to a solution of the alcohol **23** (0.50 g, 1.1 mmol) in freshly distilled pyridine (5 mL). After 30 min, the reaction mixture was concentrated under vacuum. The crude product was dissolved in EtOAc and washed with 10% HCl, saturated $NaHCO_3$, brine, and dried over $MgSO_4$. The product (0.43 g, 74%) was isolated as a white powder and used without further purification. $^1$H NMR ($CDCl_3$) δ 5.11 (br s, 1H), 4.16 (dt,

2H, J = 1.9, 6.5 Hz), 3.55-3.47 (m, 1H), 2.96 (s, 3H), 1.99-1.94 (m, 1H), 1.89-1.63 (m, 6H), 1.61-1.28 (m, 12H), 1.24-0.99 (m, 6H), 0.90 (d, 3H, J = 6.4 Hz), 0.84 (s, 9H), 0.74 (s, 3H), 0.49 (s, 3H), 0.0088 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 139.2, 117.7, 71.8, 70.6, 55.7, 54.9, 49.4, 43.3, 40.3, 39.5, 38.4, 37.3, 35.7, 34.1, 31.8, 31.4, 29.6, 27.9, 25.9, 22.9, 21.4, 18.6, 18.2, 13.0, 11.8, -4.6.

*Synthesis of* ***$d_7$-Lath***. A solution of $d_7$-2-bromopropane (0.40 mL, 4.3 mmol) in THF (4 mL) was added in portions to Mg° (0.10 g, 4.1 mmol) in a minimal amount of THF. After 20 min, $Li_2CuCl_4$ (0.1 M/THF, 0.80 mL, 0.080 mmol) was added, followed by a solution of the mesylate **24** (0.43 g, 0.78 mmol) in THF (8 mL). After 2 h, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product was purified by column chromatography (10% EtOAc/hexanes) and isolated as a white powder (0.27 g, 69%). $^1$H NMR ($CDCl_3$) δ 5.13 (br s, 1H), 3.58-3.48 (m, 1H), 2.03-1.98 (m, 1H), 1.90-1.71 (m, 6H), 1.64-1.27 (m, 12H), 1.27-0.98 (m, 8H), 0.90 (d, 3H, J = 6.5 Hz), 0.87 (s, 9H), 0.77 (s, 3H), 0.51 (s, 3H), 0.035 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 139.5, 117.5, 71.9, 56.1, 55.0, 49.5, 43.3, 40.4, 39.6, 39.2, 38.4, 37.3, 36.2, 36.1, 34.2, 31.8, 29.7, 27.9, 25.9, 23.8, 22.9, 21.5, 18.8, 18.2, 13.0, 11.8, -4.6.

TBAF (1 M/THF, 1.1 mL, 1.1 mmol) was added to a solution of the $d_7$-TBS-Lath (0.27 g, 0.53 mmol) in THF (3 mL). After overnight, the reaction mixture was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. The product (0.18 g, 86%) was isolated as a white powder after purification by column chromatography (20% EtOAc/hexanes). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 5.13 (br s, 1H), 3.62-3.52 (m, 1H), 2.03-1.97 (apparent dt, 1H, J = 3.3, 12.4 Hz), 1.90-1.65 (m, 7H), 1.62-1.44 (m, 6H), 1.40-1.30 (m, 6H), 1.27-0.95 (m, 8H), 0.89 (d, 3H, J = 6.5 Hz), 0.77 (s, 3H), 0.51 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 139.6, 117.4, 71.0, 56.1, 55.0, 49.4, 43.3, 40.2, 39.5, 39.2, 37.9, 37.1, 36.2, 36.1, 34.1, 31.4, 29.6, 27.9, 23.8, 22.9, 21.5, 18.8, 13.0, 11.8.

*Synthesis of iodide* ***25***. Iodine (1.0 g, 3.9 mmol) was added to a solution of the alcohol **23** (1.6 g, 3.3 mmol), imidazole (0.45 g, 6.6 mmol), and $PPh_3$ (1.0 g, 3.8 mmol) in $CH_2Cl_2$ (16 mL). After 1 h, the reaction mixture was diluted with ether and filtered through a pad of silica gel. The product was isolated as a white powder (1.8 g, 94%) after purification by column chromatography (10% EtOAc/hexanes). $^1$H NMR ($CDCl_3$) δ 5.13 (br s, 1H), 3.57-3.47 (m, 1H), 3.20-3.06 (m, 2H), 2.04-1.95 (m, 1H), 1.90-1.84 (m, 2H), 1.81-1.65 (m, 4H), 1.64-1.06 (m, 18H), 0.91 (d, 3H, J = 6.5 Hz),

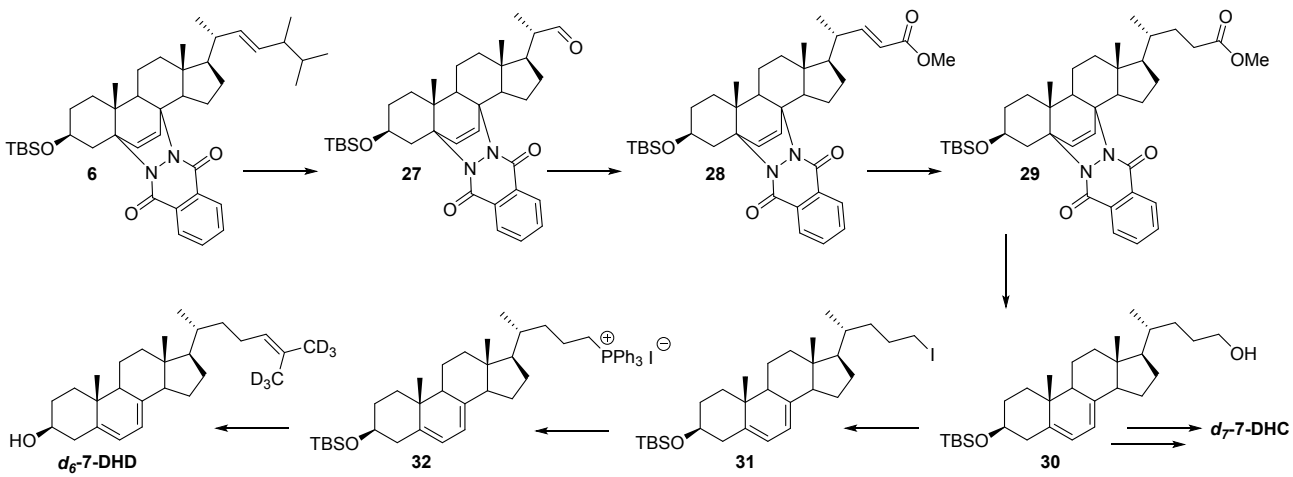
0.86 (s, 9H), 0.76 (s, 3H), 0.50 (s, 3H), 0.027 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 139.3, 117.6, 71.8, 55.8, 55.0, 49.4, 43.4, 40.3, 39.5, 38.4, 37.3, 36.8, 35.4, 34.2, 31.8, 30.3, 29.7, 27.9, 25.9, 22.9, 21.5, 18.9, 18.2, 13.1, 11.8, 7.8, -4.6.

*Synthesis of **26***. $PPh_3$ (1.0 g, 3.8 mmol) was added to a solution of the iodide **25** (1.8 g, 3.1 mmol) and $iPr_2EtN$ (1.6 mL, 9.2 mmol) in anhydrous toluene (15 mL). The reaction mixture was heated to 100 °C. After allowing to react overnight, the reaction mixture was cooled and concentrated. The product (2.2 g) was purified by column chromatography (5% MeOH/$CH_2Cl_2$) and isolated in 84% yield. $^1$H NMR ($CDCl_3$) δ 7.80-7.73 (m, 9H), 7.70-7.64 (m, 6H), 5.06 (br s, 1H), 3.60-3.44 (m, 3H), 1.92-1.85 (m, 1H), 1.80-1.60 (m, 6H), 1.60-0.92 (m, 18H), 0.82 (s, 9H), 0.75 (d, 3H, J = 5.7 Hz), 0.70 (s, 3H), 0.41 (s, 3H), -0.011 (s, 6H).

*Synthesis of **$d_6$-DHL***. BuLi (2.5 M/hexanes, 0.50 mL, 1.3 mmol) was added to a solution of **26** (0.50 g, 0.59 mmol) in THF (3 mL). After 30 min, *$d_6$*-acetone (0.10 mL, 1.4 mmol) was added. After overnight, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product (0.20 g, 66%) was isolated as a white powder after purification by column chromatography (10% EtOAc/hexanes). $^1$H NMR ($CDCl_3$) δ 5.13 (br s, 1H), 5.07 (t, 1H, J = 7.1 Hz), 3.58-3.48 (m, 1H), 2.02-1.98 (m, 2H), 1.89-1.72 (m, 5H), 1.65-1.31 (m, 12H), 1.27-0.97 (m, 6H), 0.92 (d, 3H, J = 6.5 Hz), 0.87 (s, 9H), 0.77 (s, 3H), 0.51 (s, 3H), 0.036 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 139.5, 125.2, 117.5, 71.9, 56.0, 55.0, 49.5, 43.4, 40.3, 39.6, 38.4, 37.3, 36.0, 35.9, 34.2, 31.8, 29.7, 27.9, 25.9, 24.7, 22.9, 21.5, 18.7, 18.2, 13.1, 11.8, -4.6.

TBAF (1 M/THF, 0.80 mL, 0.80 mmol) was added to a solution of *$d_6$*-TBS-DHL (0.20 g, 0.40 mmol) in THF (2 mL). After overnight, the reaction was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. Purification by column chromatography (20% EtOAc/hexanes) yielded the product as a white powder (66 mg, 44%). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 5.13 (br s, 1H), 5.06 (t, 1H, J = 7.0 Hz), 3.60-3.52 (m, 1H), 2.01-1.98 (m, 2H), 1.86-1.67 (m, 9H), 1.65-1.44 (m, 3H), 1.42-1.31 (m, 5H), 1.28-1.15 (m, 5H), 1.08-0.99 (m, 2H), 0.91 (d, 3H, J = 6.4 Hz), 0.76 (s, 3H), 0.50 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 139.5, 130.7, 125.1, 117.4, 70.9, 56.0, 55.0, 49.4, 43.3, 40.2, 39.5, 37.9, 37.1, 36.0, 35.9, 34.1, 31.4, 29.6, 27.8, 24.7, 22.9, 21.5, 18.7, 13.0, 11.8.

Scheme S5. Synthesis of $d_6$-7-DHD.




*Synthesis of aldehyde **27***. Ozone was bubbled through a solution of **6** (11 g, 0.017 mol) in $CH_2Cl_2$ (130 mL) and MeOH (40 mL) at 0 °C. After 1 h, $PPh_3$ (4.9 g, 0.019 mol) was added and the reaction allowed to stir at room temperature for 1 h. The reaction mixture was concentrated and purified by column chromatography (20% EtOAc/hexanes). The product (7.5 g, 75%) was isolated as a yellow foam. $^1$H NMR ($CDCl_3$) δ 9.52 (d, 1H, J = 3.5 Hz), 8.13-8.06 (m, 2H), 7.68-7.65 (m, 2H), 6.44 (d, 1H, J = 8.2 Hz), 6.20 (d, 1H, J = 8.2 Hz), 3.98 (dd, 1H, J = 7.4, 11.5 Hz), 3.85 (dd, 1H, J = 4.6, 14.1 Hz), 3.61-3.50 (m, 1H), 2.35-2.27 (m, 1H), 2.10-2.03 (m, 2H), 1.96-1.90 (m, 3H), 1.78-1.70 (m, 2H), 1.63-1.58 (m, 4H), 1.49-1.34 (m, 4H), 1.10 (d, 3H, J = 3.8 Hz), 0.99 (s, 3H), 0.84 (s, 3H), 0.82 (s, 9H), 0.05 (s, 3H), -0.04 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 204.5, 161.8, 159.6, 138.8, 132.7, 132.5, 130.4, 130.1, 128.1, 127.0, 126.5, 68.0, 67.3, 67.0, 51.7, 50.6, 48.9, 48.4, 44.7, 40.4, 39.1, 35.5, 34.6, 30.4, 26.5, 25.9, 24.3, 22.2, 18.5, 18.0, 13.5, 13.4, -4.4, -5.0.

*Synthesis of ester **28***. Methyl(triphenylphosphoranylidene)acetate (1.1 g, 3.3 mmol) was added to a solution of the aldehyde **9** (1.3 g, 2.2 mmol) in $CH_2Cl_2$ (11 mL). The reaction mixture was allowed to stir overnight, then concentrated. After purification by column chromatography (20% EtOAc/hexanes), the product was isolated as a yellow powder (1.3 g, 90%). $^1$H NMR ($CDCl_3$) δ 8.10-8.02 (m, 2H), 7.64-7.61 (m, 2H), 6.76 (dd, 1H, J = 9.0, 15.6 Hz), 6.59 (d, 1H, J = 8.2 Hz), 6.17 (d, 1H, J = 8.3 Hz), 5.68 (d, 1H, J = 15.6 Hz), 3.91 (dd, 1H, J = 7.1, 11.7 Hz), 3.82 (dd, 1H, J = 4.6, 14.0 Hz), 3.64 (s, 3H), 3.58-3.47 (m, 4H), 1.83-1.73 (m, 1H), 1.61-1.55 (m, 4H), 1.48-1.25 (m, 6H), 1.03 (d, 3H, J = 6.5 Hz), 0.95 (s, 3H), 0.81 (s, 9H), 0.79 (s, 3H), 0.02 (s, 3H), -0.07 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 167.1, 161.7, 159.5, 154.2, 138.6, 132.6, 132.5, 130.4, 130.1, 128.3,

126.9, 126.4, 118.9, 68.0, 67.3, 67.0, 55.5, 51.3, 50.5, 48.6, 44.4, 40.3, 39.2, 35.5, 34.6, 30.4, 27.6, 25.8, 24.3, 21.8, 19.2, 18.5, 18.1, 14.1, 13.3, -4.4, -5.0.

*Synthesis of **29***. Raney Nickel (~1 mL) was added to a solution of **28** (1.3 g, 2.0 mmol) in THF (20 mL). The reaction mixture was sparged with $H_2$ for 20 min, then left under an atmosphere of $H_2$. After 30 min, the reaction mixture was filtered through Celite and concentrated. Caution: the catalyst should not be allowed to go dry. The product (1.2 g, 95%) was isolated as a yellow powder and was used without purification. $^1$H NMR ($CDCl_3$) δ 8.16-8.05 (m, 2H), 7.69-7.62 (m, 2H), 6.61 (d, 1H, J = 8.2 Hz), 6.22 (d, 1H, J = 8.3 Hz), 3.93-3.81 (m, 2H), 3.62 (s, 3H), 3.59-3.51 (m, 1H), 2.38-2.28 (m, 1H), 2.25-2.14 (m, 1H), 2.09-1.93 (m, 4H), 1.82-1.72 (m, 2H), 1.61-1.50 (m, 4H), 1.40-1.33 (m, 8H), 0.98 (s, 3H), 0.90 (d, 3H, J = 6.1 Hz), 0.82 (s, 9H), 0.79 (s, 3H), 0.05 (s, 3H), -0.04 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 174.5, 161.8, 159.5, 138.5, 132.6, 132.5, 130.5, 130.2, 128.5, 126.9, 126.5, 68.3, 67.4, 67.0, 56.2, 5.4, 50.5, 48.8, 44.3, 40.3, 39.3, 35.5, 34.6, 30.7, 30.6, 30.4, 27.4, 25.9, 24.4, 21.8, 18.5, 18.1, 18.0, 13.1, -4.4, -5.0.

*Synthesis of alcohol **30***. $LiAlH_4$ (1 M/THF, 15 mL, 15 mmol) was added to a solution of **29** (1.2 g, 1.9 mmol) in THF (10 mL), then heated to reflux. After 1 h, the reaction was cooled and quenched with 10% HCl. The reaction mixture was extracted with EtOAc, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The product was purified by column chromatography (20% EtOAc/hexanes) and isolated as a white powder (0.53 g, 61%). $^1$H NMR ($CDCl_3$) δ 5.53 (d, 1H, J = 5.5 Hz), 5.37-5.34 (m, 1H), 3.61-3.52 (m, 3H), 2.31 (d, 2H, J = 7.6 Hz), 2.08-2.04 (m, 1H), 1.93-1.80 (m, 4H), 1.72-1.53 (m, 6H), 1.49-1.19 (m, 10H), 0.94 (d, 3H, J = 6.0 Hz), 0.91 (s, 3H), 0.87 (s, 9H), 0.60 (s, 3H), 0.05 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 141.0, 140.7, 119.1, 116.3, 71.2, 63.5, 55.7, 54.4, 46.2, 42.9, 41.3, 39.2, 38.5, 37.0, 35.9, 32.4, 31.7, 29.3, 28.1, 25.9, 23.0, 21.1, 18.8, 18.2, 16.3, 11.8, -4.6.

*Synthesis of iodide **31***. Iodine (0.40 g, 1.6 mmol) was added to a solution of the alcohol **30** (0.53 g, 1.1 mmol), imidazole (0.15 g, 2.2 mmol), and $PPh_3$ (0.40 g, 1.5 mmol) in $CH_2Cl_2$ (10 mL). After 30 min, the reaction mixture was diluted with ether and filtered through a pad of silica gel. The product was isolated as a white powder (0.65 g, 100%) and used without further purification. $^1$H NMR ($CDCl_3$) δ 5.52 (d, 1H, J = 3.3 Hz), 5.37-5.35 (m, 1H), 3.62-3.52 (m, 1H), 3.22-3.07 (m, 2H), 2.31 (d, 2H, J = 7.7 Hz), 2.07-2.03 (apparent dt, 1H, J = 4.1, 10.0 Hz), 1.93-1.81 (m, 5H), 1.75-1.66 (m, 4H), 1.58-1.13 (m, 10H), 0.93 (d, 3H, J = 6.5 Hz), 0.91 (s, 3H), 0.87 (s, 9H), 0.59

(s, 3H), 0.045 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 140.9, 140.7, 119.1, 116.4, 71.2, 55.5, 54.4, 46.2, 42.9, 41.3, 39.1, 38.5, 37.0, 36.8, 35.4, 32.4, 30.3, 28.1, 25.9, 23.0, 21.1, 18.8, 18.2, 16.3, 11.8, 7.8, -4.6.

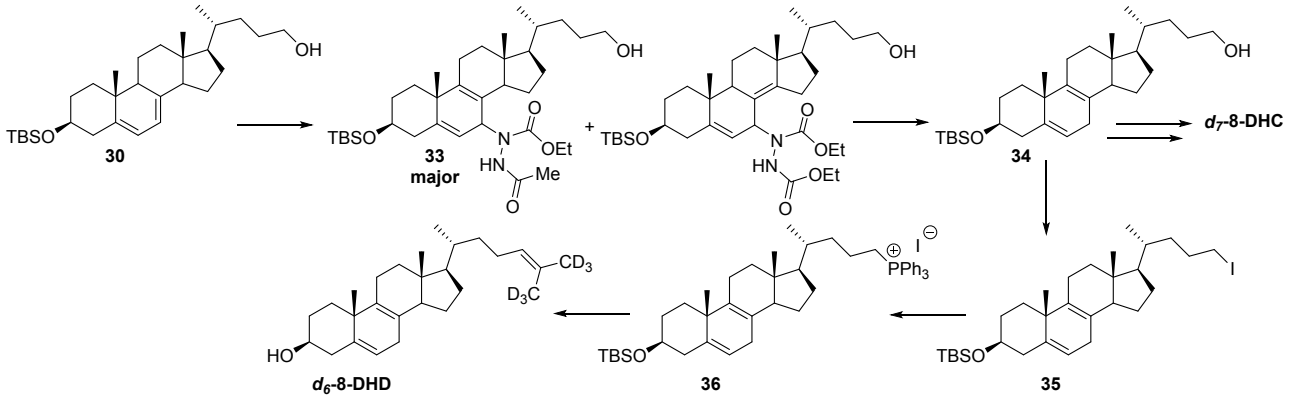
*Synthesis of **32***. $PPh_3$ (0.35 g, 1.3 mmol) was added to a solution of the iodide **31** (0.65 g, 1.1 mmol) and $iPr_2EtN$ (0.60 mL, 3.4 mmol) in anhydrous toluene (6 mL). The reaction mixture was heated to 100 °C. After allowing to react overnight, the reaction mixture was cooled and concentrated. The product (0.94 g) was purified by column chromatography (5% MeOH/$CH_2Cl_2$) and isolated in 100% yield. $^1$H NMR ($CDCl_3$) δ 7.74-7.67 (m, 9H), 7.65-7.58 (m, 6H), 5.42 (d, 1H, J = 5.5 Hz), 5.25-5.23 (m, 1H), 3.52-3.45 (m, 3H), 2.21 (d, 2H, J = 6.8 Hz), 1.90-1.79 (m, 3H), 1.82-1.64 (m, 6H), 1.58-1.38 (m, 5H), 1.26-1.00 (m, 6H), 0.79 (s, 3H), 0.78 (s, 9H), 0.72 (d, 3H, J = 5.7 Hz), 0.45 (s, 3H), -0.048 (s, 6H).

*Synthesis of **$d_6$-7-DHD***. BuLi (2.5 M/hexanes, 1.0 mL, 2.5 mmol) was added to a solution of **32** (1.0 g, 1.2 mmol) in THF (6 mL). After 30 min, $d_6$-acetone (0.20 mL, 2.7 mmol) was added. After overnight, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product (0.25 g, 41%) was isolated as a white powder after purification by column chromatography (10% EtOAc/hexanes). $^1$H NMR ($CDCl_3$) δ 5.53 (d, 1H, J = 5.6 Hz), 5.38-5.35 (m, 1H), 5.08 (t, 1H, J = 7.1 Hz), 3.63-3.53 (m, 1H), 2.31 (d, 2H, J = 7.7 Hz), 2.10-1.81 (m, 6H), 1.73-1.50 (m, 4H), 1.42-1.03 (m, 10H), 0.95 (d, 3H, J = 6.5 Hz), 0.92 (s, 3H), 0.88 (s, 9H), 0.60 (s, 3H), 0.055 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 141.1, 140.6, 125.1, 119.2, 116.3, 71.2, 55.8, 54.4, 46.3, 42.9, 41.3, 39.2, 38.5, 37.0, 36.0, 35.9, 32.4, 28.1, 25.9, 24.7, 23.0, 21.1, 18.7, 18.2, 16.3, 11.8, -4.6.

TBAF (1 M/THF, 2.0 mL, 2.0 mmol) was added to a solution of $d_6$-TBS-DHD (0.25g, 0.50 mmol) in THF (2 mL). After overnight, the reaction was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. Purification by column chromatography (20% EtOAc/hexanes) yielded the product as a white powder (0.17 g, 89%). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 5.54 (dd, 1H, J = 2.2, 5.5 Hz), 5.37-5.35 (m, 1H), 5.07 (t, 1H, J = 7.1 Hz), 3.63-3.57 (m, 1H), 2.44 (ddd, 1H, J = 2.6, 4.8, 14.4 Hz), 2.25 (t, 1H, J = 12.1 Hz), 2.08-2.01 (m, 1H), 2.00-1.89 (m, 2H), 1.88-1.78 (m, 6H), 1.71-1.65 (m, 2H), 1.58-1.08 (m, 10H), 0.94 (d, 3H, J = 6.6 Hz), 0.92 (s, 3H), 0.59 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 141.3, 139.7,

130.7, 125.1, 119.5, 116.2, 70.3, 55.7, 54.4, 46.2, 42.9, 40.7, 39.1, 38.3, 36.9, 36.0, 35.9, 31.9, 28.0, 24.7, 23.0, 21.0, 18.7, 16.2, 11.7.

Scheme S6. Synthesis of $d_6$-8-DHD.




*Synthesis of **33***. Diethyl azodicarboxylate (2.3 M/toluene, 3.5 mL, 8.1 mmol) was added to a solution of the 7-dehydrocholenol **30** (1.2 g, 2.5 mmol) in benzene (13 mL), then heated to reflux. After 3 h, the reaction mixture was cooled and concentrated. The reaction resulted in a 3:1 mixture of isomers in favor of the desired product. The mixture was purified by column chromatography (hexanes:EtOAc, 1:1) to yield the product as a white powder (0.78 g, 48%). The isomers could be partially separated by column chromatography using toluene:EtOAc (1:1).

*Synthesis of **34***. $EtNH_2$ (~6 mL) was condensed into a flask at -78 °C. A cooled solution of **33** (0.78 g, 1.2 mmol) in THF (6 mL) was added, followed by Li° (100 mg, 14 mmol). The reaction mixture turned blue upon completion. After 1 h, the reaction was quenched with saturated $NH_4Cl$ and warmed to room temperature to dissipate the $EtNH_2$. The reaction was diluted with EtOAc and washed with additional saturated $NH_4Cl$, brine, and dried over $MgSO_4$. The product was purified by column chromatography (hexanes:EtOAc, 4:1) and isolated as a white powder (0.20 g, 35%). $^1$H NMR ($CDCl_3$) δ 5.38 (br s, 1H), 3.59 (t, 2H, J = 6.4 Hz), 3.53-3.43 (m, 1H), 2.51 (br s, 2H), 2.32 (t, 1H, J = 13.0 Hz), 2.23-2.16 (m, 1H), 2.12-2.09 (m, 2H), 2.02-1.72 (m, 4H), 1.64-1.55 (m, 4H), 1.46-1.23 (m, 10H), 1.15 (s, 3H), 0.93 (d, 3H, J = 6.5 Hz), 0.86 (s, 9H), 0.63 (s, 3H), 0.03 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 139.7, 132.3, 126.2, 119.0, 72.2, 63.5, 54.5, 51.8, 42.7, 42.0, 37.4, 36.8, 36.0, 35.8, 32.4, 31.7, 29.4, 28.9, 28.8, 25.9, 22.9, 22.8, 22.2, 18.6, 18.2, 11.2, -4.7.

*Synthesis of iodide **35***. Iodine (0.13 g, 0.51 mmol) was added to a solution of the alcohol **34** (0.20 g, 0.42 mmol), imidazole (0.060 g, 0.88 mmol), and $PPh_3$ (0.13 g, 0.50 mmol) in $CH_2Cl_2$ (5 mL). After 30 min, the reaction mixture was diluted with ether and filtered through a pad of silica gel. The product was isolated as a yellow oil (0.20 g, 80%) and used without further purification. $^1$H NMR ($CDCl_3$) δ 5.38 (br s, 1H), 3.55-3.44 (m, 1H), 3.20-3.10 (m, 2H), 2.51 (br s, 2H), 2.35-2.28 (m, 1H), 2.23-2.19 (m, 1H), 2.18-2.06 (m, 2H), 1.98-1.83 (m, 3H), 1.82-1.7 (m, 3H), 1.62-1.55 (m, 3H), 1.53-1.40 ( m, 4H), 1.33-1.22 (m, 4H), 1.15 (s, 3H), 0.93 (d, 3H, J = 6.4 Hz), 0.87 (s, 9H), 0.63 (s, 3H), 0.032 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 139.6, 132.3, 126.2, 119.0, 72.2, 54.4, 51.8, 42.7, 42.0, 37.4, 36.7, 35.7, 35.4, 32.4, 30.3, 28.9, 28.7, 25.9, 22.9, 22.8, 22.2, 18.7, 18.2, 11.2, 7.8, -4.6.

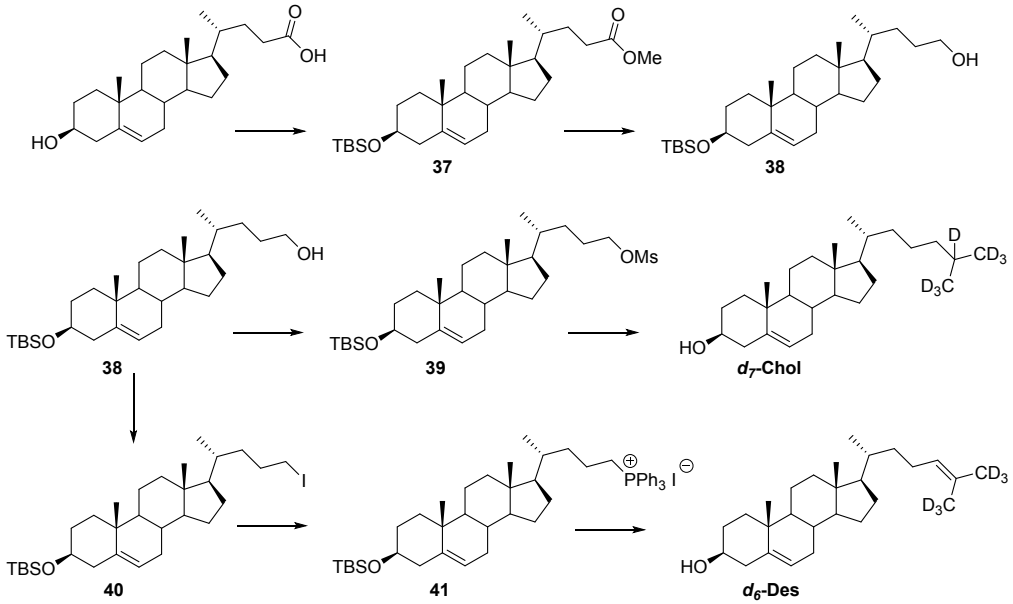
*Synthesis of **36***. $PPh_3$ (0.11 g, 0.42 mmol) was added to a solution of the iodide **35** (0.20 g, 0.34 mmol) and $iPr_2EtN$ (0.20 mL, 1.1 mmol) in anhydrous toluene (2 mL). The reaction mixture was heated to 100 °C. After allowing to react overnight, the reaction mixture was cooled and concentrated. The product (0.0.22 g) was purified by column chromatography (5% MeOH/$CH_2Cl_2$) and isolated in 74% yield. $^1$H NMR ($CDCl_3$) δ 7.83-7.76 (m, 9H), 7.71-7.66 (m, 6H), 5.36 (br s, 1H), 3.69-3.59 (m, 2H), 3.50-3.42 (m, 1H), 2.47 (br s, 2H), 2.29 (app t, 1H, J = 11.0 Hz), 2.20-2.16 (m, 2H), 2.10-1.99 (m, 2H), 1.89-1.65 (m, 6H), 1.58-1.46 (m, 3H), 1.33-1.23 (m, 8H), 1.12 (s, 3H), 0.85 (s, 9H), 0.79 (d, 3H, J = 5.8 Hz), 0.56 (s, 3H), 0.018 (s, 6H).

*Synthesis of **$d_6$-8-DHD***. BuLi (2.5 M/hexanes, 0.20 mL, 0.50 mmol) was added to a solution of **36** (0.22 g, 0.26 mmol) in THF (2 mL). After 30 min, $d_6$-acetone (0.040 mL, 0.54 mmol) was added. After overnight, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product (65 mg, 50%) was isolated as a white powder after purification by column chromatography (10% EtOAc/hexanes). $^1$H NMR ($CDCl_3$) δ 5.38 (br s, 1H), 5.07 (t, 1H, J = 7.1 Hz), 3.53-3.45 (m, 1H), 2.52 (br s, 2H), 2.32 (t, 1H, J = 13.0 Hz), 2.29-2.21 (m, 1H), 2.20-1.89 (m, 6H), 1.83-1.73 (m, 2H), 1.61-1.53 (m, 3H), 1.44-1.27 (m, 8H), 1.16 (s, 3H), 0.94 (d, 3H, J = 6.3 Hz), 0.87 (s, 9H), 0.63 (s, 3H), 0.035 (s, 6H).

TBAF (1M/THF, 0.30 mL, 0.30 mmol) was added to a solution of $d_6$-TBS-DHD (65 mg, 0.13 mmol) in THF (2 mL). After overnight, the reaction was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. Purification by column chromatography (20% EtOAc/hexanes) yielded the

product as a white powder (14 mg, 89%). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^{1}$H NMR ($CDCl_3$) δ 5.41 (br s, 1H), 5.07 (t, 1H, J = 7.1 Hz), 3.57-3.49 (m, 1H), 2.52 (br s, 2H), 2.37-2.25 (m, 2H), 2.20-1.82 (m, 10H), 1.61-1.26 (m, 10H), 1.17 (s, 3H), 0.93 (d, 3H, J = 6.5 Hz), 0.63 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 138.8, 132.0, 130.7, 126.4, 125.1, 119.5, 71.5, 54.7, 51.8, 42.2, 42.0, 37.4, 36.8, 36.1, 35.6, 32.0, 29.3, 29.0, 28.8, 24.8, 23.0, 22.9, 22.3, 18.6, 11.3.

Scheme S7. Synthesis of $d_6$-Des and $d_7$-Chol.




*Synthesis of **37***. TsOH (0.31 g, 1.6 mmol) was added to a milky solution of 5-cholenic acid-3β-ol (3.2 g, 8.4 mmol) in MeOH (40 mL). After stirring overnight, the reaction mixture was concentrated. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$, brine, and dried over $MgSO_4$. The product was isolated as a white powder (3.1 g, 94%). $^{1}$H NMR ($CDCl_3$) δ 5.31 (d, 1H, J = 5.2 Hz), 3.63 (s, 3H), 3.56-3.43 (m, 1H), 2.37-2.13 (m, 4H), 2.01-1.87 (m, 3H), 1.86-1.70 (m, 5H), 1.58-1.13 (m, 10H), 1.11-1.07 (m, 4H), 0.97 (s, 3H), 0.89 (d, 3H, J = 6.4 Hz), 0.64 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 174.8, 140.7, 121.6, 71.7, 56.7, 55.7, 51.5, 50.0, 42.3, 42.2, 39.7, 37.2, 36.4, 35.3, 31.8, 31.5, 31.0, 30.9, 28.0, 24.2, 21.0, 19.3, 18.2, 11.8.

TBSCl (1.4 g, 9.3 mmol) and imidazole (0.80 g, 12 mmol) were added to a solution of the ester (3.1 g, 7.9 mmol) in DMF (16 mL) and THF (8 mL). After overnight, the reaction mixture was diluted with EtOAc, washed with $H_2O$ and brine, then dried over $MgSO_4$. The product was purified by column chromatography (10% EtOAc/hexanes) and isolated as a white powder (3.6 g, 89%). $^1$H NMR ($CDCl_3$) δ 5.26 (d, 1H, J = 5.1 Hz), 3.61 (s, 3H), 3.48-3.36 (m, 1H), 2.36-2.22 (m, 1H), 2.20-2.08 (m, 3H), 1.98-1.65 (m, 7H), 1.53-1.19 (m, 10H), 0.95 (s, 3H), 0.88 (d, 3H, J = 6.3 Hz), 0.84 (s, 9H), 0.63 (s, 3H), 0.0089 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 174.6, 141.4, 121.0, 72.5, 56.7, 55.7, 51.3, 50.1, 42.7, 42.3, 39.7, 37.3, 36.5, 35.3, 32.0, 31.8, 31.5, 30.9, 28.0, 25.8, 24.2, 22.6, 21.0, 19.3, 18.2, 18.1, 14.0, 11.8, -4.7.

*Synthesis of alcohol **38***. DIBAL-H (1 M/toluene, 21 mL, 21 mmol) was added to a solution of the ester **37** (3.6 g, 7.1 mmol) in THF (35 mL) at 0 °C. After 1 h, the reaction was quenched with 10% HCl and extracted with EtOAc. The organics were washed with brine and dried over $MgSO_4$. The product was isolated as a white powder (3.2 g, 94%). $^1$H NMR ($CDCl_3$) δ 5.29 (d, 1H, J = 5.2 Hz), 3.59 (dt, 2H, J = 1.5, 6.8 Hz), 3.51-3.40 (m, 1H), 2.25 (dt, 1H, J = 2.2, 13.1 Hz), 2.14 (ddd, 1H, J = 2.0, 5.1, 13.3 Hz), 2.02-1.91 (m, 2H), 1.84-1.75 (m, 2H), 1.67-1.39 (m, 13H), 1.26-1.02 (7H), 0.97 (s, 3H), 0.91 (d, 3H, J = 6.5 Hz), 0.86 (s, 9H), 0.65 (s, 3H), 0.032 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 141.5, 121.1, 72.6, 63.6, 56.7, 55.9, 50.1, 42.8, 42.3, 39.7, 37.3, 36.5, 35.5, 32.0, 31.9, 31.8, 29.3, 28.2, 25.9, 24.2, 21.0, 19.4, 18.6, 18.2, 11.8, -4.6.

*Synthesis of mesylate **39***. MsCl (0.50 mL, 6.5 mmol) was added to a solution of the alcohol **38** (2.0 g, 4.2 mmol) in freshly distilled pyridine (20 mL) at 0 °C. After 30 min, the reaction mixture was concentrated under vacuum. The crude product was dissolved in EtOAc and washed with $H_2O$, brine, and dried over $MgSO_4$. The product (2.1 g, 88%) was isolated as a white powder and used without further purification. $^1$H NMR ($CDCl_3$) δ 5.29 (d, 1H, J = 5.0 Hz), 4.17 (dt, 2H, J = 2.1, 6.6 Hz), 3.51-3.40 (m, 1H), 2.98 (s, 3H), 2.24 (dt, 1H, J = 1.7, 12.9 Hz), 2.13 (ddd, 1H, J = 1.7, 5.0, 13.5 Hz), 2.02-1.92 (m, 2H), 1.83-1.36 (m, 14H), 1.22-1.01 (m, 7H), 0.97 (s, 3H), 0.92 (d, 3H, J = 6.5 Hz), 0.86 (s, 9H), 0.65 (s, 3H), 0.032 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 141.5, 121.1, 72.6, 70.6, 56.7, 55.7, 50.1, 42.8, 42.3, 39.7, 37.3, 36.5, 35.3, 32.0, 31.8, 31.5, 28.2, 25.9, 25.8, 24.2, 21.0, 19.4, 18.5, 18.2, 11.8, -4.6.

*Synthesis of* ***$d_7$-Chol***. A solution of $d_7$-2-bromopropane (1.8 mL, 19.1 mmol) in THF (20 mL) was added in portions to Mg° (0.50 g, 20 mmol) in a minimal amount of THF. After 30 min, $Li_2CuCl_4$ (0.1 M/THF, 3.7 mL, 0.37 mmol) was added, followed by a solution of the mesylate **39** (2.1 g, 3.7 mmol) in THF (20 mL). After 1 h, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product was purified by column chromatography (5% EtOAc/hexanes) and isolated as a white powder (1.7 g, 88%). $^1$H NMR ($CDCl_3$) δ 5.30 (d, 1H, J = 5.1 Hz), 3.51-3.41 (m, 1H), 2.26 (dt, 1H, 2.0, 13.0 Hz), 2.14 (ddd, 1H, J = 1.9, 5.0, 13.3 Hz), 2.02-1.92 (m, 2H), 1.84-1.68 (m, 3H), 1.57-1.22 (m, 12H), 1.18-1.02 (m, 8H), 0.98 (s, 3H), 0.90 (d, 3H, J = 6.7 Hz), 0.87 (s, 9H), 0.66 (s, 3H), 0.040 (s, 6H); $^{13}$C NMR ($CDCl_3$) δ 141.5, 121.1, 72.6, 56.8, 56.1, 50.2, 42.8, 42.3, 39.8, 39.2, 37.4, 36.5, 36.2, 35.8, 32.1, 31.9, 28.2, 25.9, 24.3, 23.8, 21.0, 19.4, 18.7, 18.2, 11.8, -4.6.

TBAF (1 M/THF, 3.4 mL, 3.4 mmol) was added to a solution of the $d_7$-TBS-Chol (1.2 g, 2.3 mmol) in THF (11 mL). After overnight, the reaction mixture was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. The product (0.44 g, 49%) was isolated as a white powder after purification by column chromatography (20% EtOAc/hexanes). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 5.32 (d, 1H, J = 5.2 Hz), 3.55-3.44 (m, 1H), 2.30-2.16 (m, 2H), 2.02-1.92 (m, 2H), 1.85-1.74 (m, 4H), 1.59-1.20 (m, 12H), 1.14-1.01 (m, 8H), 0.98 (s, 3H), 0.89 (d, 3H, J = 6.5 Hz), 0.65 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 140.7, 121.7, 71.7, 56.7, 56.1, 50.1, 42.3, 39.7, 39.2, 37.2, 36.4, 36.1, 35.7, 31.8, 31.6, 28.2, 24.2, 23.7, 21.0, 19.4, 18.7, 11.8.

*Synthesis of iodide* ***40***. Iodine (1.1 g, 4.2 mmol) was added to a solution of the alcohol **38** (1.7 g, 3.5 mmol), imidazole (0.45 g, 6.6 mmol), and $PPh_3$ (1.1 g, 4.2 mmol) in $CH_2Cl_2$ (18 mL). After 1 h, the reaction mixture was diluted with ether and filtered through a pad of silica gel. The product was isolated as a white powder (2.4 g, 100%). $^1$H NMR ($CDCl_3$) δ 5.29 (d, 1H, J = 7.0 Hz), 3.51-3.40 (m, 1H), 3.21-3.06 (m, 2H), 2.24 (dt, 1H, J = 2.2, 13.2 Hz), 2.14 (ddd, 1H, J = 2.0, 5.1, 13.2 Hz), 1.98-1.67 (m, 7H), 1.58-1.39 (m, 9H), 1.27-1.00 (m, 7H), 0.97 (s, 3H), 0.90 (d, 3H, J = 6.5 Hz), 0.86 (s, 9H), 0.65 (s, 3H), 0.030 (s, 6H).

*Synthesis of* ***41***. $PPh_3$ (1.1 g, 4.2 mmol) was added to a solution of the iodide **40** (2.4 g, 4.2 mmol) in anhydrous $CH_3CN$ (8 mL). The reaction mixture was heated to reflux. After allowing to react overnight, the reaction mixture was cooled and concentrated. The product (3.0 g, 85%) was

purified by column chromatography (5% MeOH/$CH_2Cl_2$) and isolated as a white powder. $^1$H NMR ($CDCl_3$) δ 7.84-7.76 (m, 9H), 7.71-7.65 (m, 6H), 5.26 (br s, 1H), 3.69-3.60 (m, 2H), 3.49-3.38 (m, 1H), 2.26-2.09 (m, 2H), 1.90-1.65 (m, 8H), 1.54-1.30 (m, 10H), 1.23-1.02 (m, 5H), 0.98 (s, 3H), 0.85 (s, 9H), 0.76 (d, 3H, J = 5.8 Hz), 0.58 (s, 3H), 0.019 (s, 6H).

*Synthesis of* ***$d_6$-Des***. BuLi (2.5 M/hexanes, 0.25 mL, 0.63 mmol) was added to a solution of **41** (0.50 g, 0.59 mmol) in THF (3 mL) at 0 °C. After 30 min, *$d_6$*-acetone (0.044 mL, 0.60 mmol) was added. After overnight, the reaction was quenched with saturated $NH_4Cl$ and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The product (0.15 g, 50%) was isolated as a white powder after purification by column chromatography (5% EtOAc/hexanes). $^1$H NMR ($CDCl_3$) δ 5.29 (d, 1H, J = 5.1 Hz), 5.07 (t, 1H, J = 7.1 Hz), 3.50-3.41 (m, 1H), 2.25 (dt, 1H, J = 2.2, 13.2 Hz), 2.14 (ddd, 1H, J = 2.0, 5.2, 13.1 Hz), 2.03-1.92 (m, 3H), 1.86-1.67 (m, 4H), 1.58-1.34 (m, 10H), 1.26-1.02 (m, 6H), 1.00 (s, 3H), 0.91 (d, 3H, J = 6.5 Hz), 0.87 (s, 9H), 0.65 (s, 3H), 0.036 (s, 6H).

TBAF (1 M/THF, 0.75 mL, 0.75 mmol) was added to a solution of *$d_6$*-TBS-Des (0.18 g, 0.36 mmol) in THF (2 mL). After overnight, the reaction was diluted with EtOAc, washed with brine, and dried over $MgSO_4$. Purification by column chromatography (20% EtOAc/hexanes) yielded the product as a white powder (98 mg, 70%). Product of higher purity was obtained after purification by HPLC (C18, MeOH). $^1$H NMR ($CDCl_3$) δ 5.33 (d, 1H, J = 5.2 Hz), 5.06 (t, 1H, J = 7.1 Hz), 3.55-3.45 (m, 1H), 2.30-2.16 (m, 2H), 2.02-1.92 (m, 4H), 1.88-1.75 (m, 4H), 1.58-1.33 (m, 10H), 1.26-1.03 (m, 6H), 0.98 (s, 3H), 0.91 (d, 3H, J = 6.5 Hz), 0.66 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 140.7, 125.2, 121.7, 71.7, 56.7, 56.0, 50.1, 42.3, 42.2, 39.7, 37.2, 36.4, 36.1, 35.6, 31.8, 31.6, 28.2, 24.6, 24.2, 21.0, 19.4, 18.6, 11.8.

STATISTICS

Table S1. Statistics for Figure 4.

| | Neurons | | | Astrocytes | | | |
|---|---|---|---|---|---|---|---|
| | **Mean** | **±SE** | **N** | **Mean** | **±SE** | **N** | P value |
| Lan | 0.351 | 0.015 | 44 | 0.036 | 0.003 | 42 | **<0.001** |
| 14dZym | 0.035 | 0.002 | 44 | 0.007 | 0.000 | 42 | **<0.001** |
| Zym | 1.539 | 0.038 | 44 | 0.249 | 0.010 | 42 | **<0.001** |
| DHL | 0.575 | 0.017 | 44 | 0.148 | 0.005 | 42 | **<0.001** |
| 7DHD | 0.470 | 0.021 | 43 | 0.795 | 0.038 | 42 | **<0.001** |
| 8DHD | 0.067 | 0.003 | 44 | 0.039 | 0.002 | 42 | **<0.001** |
| Des | 14.785 | 0.266 | 44 | 9.429 | 0.249 | 42 | **<0.001** |
| | | | | | | | |
| | **Neurons** | | | **Astrocytes** | | | |
| | **Mean** | **±SE** | **N** | **Mean** | **±SE** | **N** | |
| dHLan | 0.003 | 0.001 | 44 | 0.017 | 0.003 | 42 | **<0.001** |
| 14dZyme | 0.000 | 0.000 | 44 | 0.000 | 0.000 | 42 | |
| Zyme | 0.572 | 0.013 | 44 | 0.139 | 0.010 | 42 | **<0.001** |
| Lath | 0.262 | 0.010 | 44 | 0.069 | 0.003 | 42 | **<0.001** |
| 7DHC | 0.135 | 0.029 | 42 | 0.088 | 0.023 | 42 | **0.221** |
| 8DHC | 0.353 | 0.009 | 44 | 0.160 | 0.006 | 42 | **<0.001** |
| Chol | 35.110 | 0.780 | 44 | 30.629 | 0.779 | 42 | **<0.001** |
| | | | | | | | |
| | | | | | | | P value |
| 7-keto | 0.00169 | 0.000452 | 44 | 0.00694 | 0.00028 | 42 | **<0.001** |
| 24-OH | 0.0233 | 0.001887 | 44 | 0.000116 | 0.000155 | 42 | **<0.001** |
| 25-OH | 0.00804 | 0.000949 | 44 | 0.000473 | 6.5E-05 | 42 | **<0.001** |

Table S2. Statistics for Figure 5.

| | Neurons | | | | |
|---|---|---|---|---|---|
| **HAL** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| Lan | 0.0123 | 0.0132 | 0.0043 | 0.0016 | 0.2393 |
| 14dZym | 0.5996 | 0.0028 | <0.000001 | <0.000001 | <0.000001 |
| Zym | 0.0000 | 0.0000 | <0.000001 | 0.0000 | <0.000001 |
| DHL | 0.0001 | 0.0005 | 0.0004 | 0.0000 | 0.0002 |
| 7DHD | <0.000001 | <0.000001 | <0.000001 | <0.000001 | <0.000001 |
| 8DHD | <0.000001 | <0.000001 | <0.000001 | <0.000001 | <0.000001 |
| Des | <0.000001 | <0.000001 | <0.000001 | <0.000001 | <0.000001 |
| dHLan | 0.0312 | 0.2515 | 0.0955 | 0.4781 | 0.4781 |
| 14dZyme | | | | | |
| Zyme | 0.0197 | 0.9439 | 0.1231 | 0.1087 | 0.0000 |
| Lath | 0.0110 | 0.0455 | 0.4787 | 0.8981 | 0.6568 |
| 7DHC | <0.000001 | <0.000001 | <0.000001 | <0.000001 | <0.000001 |
| 8DHC | <0.000001 | <0.000001 | <0.000001 | <0.000001 | 0.0001 |
| Chol | 0.0060 | 0.0000 | <0.000001 | <0.000001 | <0.000001 |

| | Astrocytes | | | | |
|---|---|---|---|---|---|
| **HAL** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| Lan | 0.5732 | 0.2360 | 0.3738 | 0.1319 | 0.2004 |
| 14dZym | 0.3794 | 0.0091 | 0.0000 | <0.000001 | <0.000001 |
| Zym | 0.0427 | 0.0005 | 0.0000 | 0.0000 | <0.000001 |
| DHL | 0.0189 | 0.0327 | 0.0014 | 0.0004 | 0.0003 |
| 7DHD | <0.000001 | <0.000001 | <0.000001 | <0.000001 | <0.000001 |
| 8DHD | <0.000001 | 0.0000 | 0.0001 | <0.000001 | <0.000001 |
| Des | <0.000001 | <0.000001 | <0.000001 | <0.000001 | <0.000001 |
| dHLan | 0.2412 | 0.5630 | 0.2406 | 0.1745 | 0.7204 |
| 14dZyme | | | | | |
| Zyme | 0.0976 | 0.2667 | 0.0147 | 0.9670 | 0.0042 |
| Lath | 0.0046 | 0.0003 | 0.0004 | 0.0129 | 0.0155 |
| 7DHC | <0.000001 | <0.000001 | <0.000001 | <0.000001 | <0.000001 |
| 8DHC | <0.000001 | <0.000001 | <0.000001 | <0.000001 | <0.000001 |
| Chol | 0.0189 | 0.0004 | 0.0389 | 0.0000 | <0.000001 |

| | Neurons vs Astrocytes | | | | | |
|---|---|---|---|---|---|---|
| | **0** | **10** | **25** | **50** | **100** | **500** |
| Lan | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 14dZym | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Zym | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| DHL | **<0.000001** | **0.000001** | **0.000038** | **0.00019** | **0.000003** | **0.000001** |
| 7DHD | **0.001612** | 0.594617 | **0.000001** | **0.004863** | **0.000176** | **0.000173** |
| 8DHD | **<0.000001** | **0.002234** | **0.001172** | **0.007706** | **0.000538** | **0.000362** |
| Des | **<0.000001** | **<0.000001** | **<0.000001** | **0.000091** | **<0.000001** | **0.000006** |
| dHLan | 0.072611 | 0.052066 | 0.460083 | 0.110254 | | 0.048979 |
| 14dZyme | | | | | | |
| Zyme | **<0.000001** | **<0.000001** | **0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Lath | **<0.000001** | **<0.000001** | **0.000008** | **0.007163** | **0.000214** | **0.002804** |
| 7DHC | 0.108725 | **0.000049** | **0.005082** | 0.029216 | 0.761101 | 0.142016 |
| 8DHC | **<0.000001** | **0.000037** | **0.002593** | 0.557409 | 0.773505 | 0.575636 |
| Chol | 0.488416 | 0.619122 | 0.417791 | 0.043694 | **0.000045** | **<0.000001** |

Table S3. Statistics for Figure 6A (haloperidol).

| | NEURONS | | | | |
|---|---|---|---|---|---|
| **HAL** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| Lan | 0.0123 | 0.0132 | **0.0043** | **0.0016** | 0.2393 |
| 14dZym | 0.5996 | **0.0028** | **<0.00000** | **<0.000001** | **<0.000001** |
| Zym | **0.0000** | **0.0000** | **<0.00000** | **0.0000** | **<0.000001** |
| DHL | **0.0001** | **0.0005** | **0.0004** | **0.0000** | **0.0002** |
| 7DHD | **<0.00000** | **<0.00000** | **<0.00000** | **<0.000001** | **<0.000001** |
| 8DHD | **<0.00000** | **<0.00000** | **<0.00000** | **<0.000001** | **<0.000001** |
| Des | **<0.00000** | **<0.00000** | **<0.00000** | **<0.000001** | **<0.000001** |
| dHLan | 0.0312 | 0.2515 | 0.0955 | 0.4781 | 0.4781 |
| 14dZyme | | | | | |
| Zyme | 0.0197 | 0.9439 | 0.1231 | 0.1087 | **0.0000** |
| Lath | 0.0110 | 0.0455 | 0.4787 | 0.8981 | 0.6568 |
| 7DHC | **<0.00000** | **<0.00000** | **<0.00000** | **<0.000001** | **<0.000001** |
| 8DHC | **<0.00000** | **<0.00000** | **<0.00000** | **<0.000001** | **0.0001** |
| Chol | **0.0060** | **0.0000** | **<0.00000** | **<0.000001** | **<0.000001** |

| | ASTROCYTES | | | | |
|---|---|---|---|---|---|
| **HAL** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| Lan | 0.5732 | 0.2360 | 0.3738 | 0.1319 | 0.2004 |
| 14dZym | 0.3794 | **0.0091** | **0.0000** | **<0.000001** | **<0.000001** |
| Zym | 0.0427 | **0.0005** | **0.0000** | **0.0000** | **<0.000001** |
| DHL | 0.0189 | 0.0327 | 0.0014 | **0.0004** | **0.0003** |
| 7DHD | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHD | **<0.000001** | **0.0000** | **0.0001** | **<0.000001** | **<0.000001** |
| Des | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| dHLan | 0.2412 | 0.5630 | 0.2406 | 0.1745 | 0.7204 |
| 14dZyme | | | | | |
| Zyme | 0.0976 | 0.2667 | 0.0147 | 0.9670 | **0.0042** |
| Lath | **0.0046** | **0.0003** | **0.0004** | 0.0129 | 0.0155 |
| 7DHC | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHC | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Chol | 0.0189 | **0.0004** | 0.0389 | **0.0000** | **<0.000001** |

Table S4. Statistics for Figure 6B (cariprazine).

| | NEURONS | | | | | |
|---|---|---|---|---|---|---|
| CAR | C vs 1 | C vs 5 | C vs 10 | C vs 25 | C vs 50 | C vs 100 |
| Lan | **0.00041** | **0.000347** | **0.000084** | **0.000023** | **0.000022** | **0.000941** |
| 14dZym | **0.000007** | **0.000006** | **0.000083** | **0.000271** | **0.000113** | **<0.000001** |
| Zym | 0.344645 | 0.500499 | 0.063734 | 0.001107 | **0.00068** | **<0.000001** |
| DHL | 0.048546 | 0.040029 | 0.054387 | 0.049778 | 0.031374 | **<0.000001** |
| 7DHD | 0.997484 | 0.015604 | **0.000002** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHD | 0.626923 | 0.06985 | 0.016627 | **0.000019** | **<0.000001** | **<0.000001** |
| Des | 0.023535 | **0.009148** | **0.001945** | **0.000004** | **<0.000001** | **<0.000001** |
| dHLan | 0.158933 | 0.8346 | 0.293177 | 0.471613 | 0.805183 | 0.873327 |
| 14dZyme | | 0.183845 | | | | |
| Zyme | 0.733343 | 0.038278 | 0.029556 | **0.000072** | **<0.000001** | **<0.000001** |
| Lath | **<0.000001** | **0.00311** | 0.261105 | **0.000037** | **0.000097** | 0.08113 |
| 7DHC | 0.634428 | 0.041967 | 0.00375 | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHC | 0.21604 | 0.572956 | 0.042 | **0.000007** | **<0.000001** | **<0.000001** |
| Chol | 0.018182 | 0.081789 | 0.088534 | 0.117876 | **0.002994** | **<0.000001** |

| | ASTROCYTES | | | | | |
|---|---|---|---|---|---|---|
| CAR | C vs 1 | C vs 5 | C vs 10 | C vs 25 | C vs 50 | C vs 100 |
| Lan | **0.001154** | 0.090499 | 0.513583 | 0.287688 | 0.607367 | 0.172336 |
| 14dZym | 0.375826 | 0.502896 | 0.423718 | 0.103223 | 0.51891 | **<0.000001** |
| Zym | 0.391482 | 0.227011 | 0.032695 | **0.000015** | **0.000253** | **0.000001** |
| DHL | 0.03583 | 0.059429 | 0.017932 | **0.000082** | **0.000003** | **<0.000001** |
| 7DHD | 0.15757 | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHD | 0.122889 | **0.003235** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Des | 0.699206 | 0.372854 | **0.004402** | **<0.000001** | **<0.000001** | **<0.000001** |
| dHLan | 0.647902 | 0.335878 | 0.867409 | 0.724227 | 0.537149 | 0.505306 |
| 14dZyme | | | | | | |
| Zyme | 0.042394 | 0.344341 | 0.456012 | 0.621934 | 0.017651 | **0.000013** |
| Lath | **0.004946** | **0.005108** | **0.002758** | **<0.000001** | **<0.000001** | **0.000015** |
| 7DHC | 0.830218 | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHC | 0.673427 | **0.000053** | **0.000028** | **<0.000001** | **<0.000001** | **<0.000001** |
| Chol | 0.188263 | 0.853286 | 0.245154 | 0.288833 | **0.009625** | **<0.000001** |

Table S5. Statistics for Figure 6C (aripiprazole).

| | NEURONS | | | | |
|---|---|---|---|---|---|
| ARI | C vs 10 | C vs 25 | C vs 50 | C vs 100 | C vs 500 |
| Lan | **0.0003** | **0.0000** | **0.0002** | **0.0001** | **0.0091** |
| 14dZym | **0.0002** | **0.0022** | 0.5166 | **<0.000001** | **<0.000001** |
| Zym | **0.0000** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| DHL | **0.0000** | **0.0000** | **0.0000** | **0.0000** | **<0.000001** |
| 7DHD | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHD | **<0.000001** | **<0.000001** | **0.0000** | **<0.000001** | **<0.000001** |
| Des | **0.0000** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| dHLan | 0.1270 | 0.6531 | 0.7698 | 0.0114 | 0.5703 |
| 14dZyme | | | | | |
| Zyme | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Lath | **0.0024** | **0.0002** | **0.0000** | **0.0015** | **0.0095** |
| 7DHC | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHC | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Chol | **0.0086** | **0.0002** | **0.0000** | **<0.000001** | **<0.000001** |

| | ASTROCYTES | | | | |
|---|---|---|---|---|---|
| ARI | C vs 10 | C vs 25 | C vs 50 | C vs 100 | C vs 500 |
| Lan | 0.0385 | 0.0447 | 0.0346 | 0.0100 | 0.0124 |
| 14dZym | 0.1885 | 0.2866 | 0.2146 | 0.1178 | **<0.000001** |
| Zym | 0.6878 | 0.1950 | 0.3259 | 0.0500 | **0.0002** |
| DHL | 0.4132 | 0.0498 | 0.0535 | 0.0404 | **0.0001** |
| 7DHD | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHD | **0.0000** | **0.0000** | **<0.000001** | **<0.000001** | **<0.000001** |
| Des | **0.0001** | **0.0000** | **<0.000001** | **<0.000001** | **<0.000001** |
| dHLan | 0.1042 | 0.3245 | 0.0444 | 0.6640 | 0.5215 |
| 14dZyme | | | | | |
| Zyme | 0.1397 | 0.1912 | 0.3390 | 0.3501 | 0.6467 |
| Lath | 0.3641 | 0.1598 | 0.0309 | 0.0394 | 0.4428 |
| 7DHC | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHC | **0.0001** | **0.0002** | **0.0000** | **0.0000** | **0.0000** |
| Chol | 0.0737 | 0.0154 | **0.0042** | **0.0002** | **0.0000** |

Table S6. Statistics for Figure 6D (trazodone).

| | NEURONS | | | | |
|---|---|---|---|---|---|
| TRZ | C vs 10 | C vs 25 | C vs 50 | C vs 100 | C vs 500 |
| Lan | 0.0814 | 0.1799 | 0.3115 | 0.5463 | 0.6997 |
| 14dZym | 0.1000 | 0.2436 | 0.5695 | 0.0130 | **<0.000001** |
| Zym | 0.3778 | 0.0291 | **0.0047** | **0.0001** | **<0.000001** |
| DHL | 0.0777 | **0.0052** | **0.0015** | **0.0001** | **<0.000001** |
| 7DHD | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHD | **0.0000** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Des | **0.0081** | **0.0003** | **0.0000** | **<0.000001** | **<0.000001** |
| dHLan | 0.2258 | 0.6870 | 0.5992 | 0.7975 | 0.4328 |
| 14dZyme | | | | | |
| Zyme | 0.2492 | 0.1345 | 0.0870 | 0.0333 | 0.0107 |
| Lath | 0.1735 | 0.0535 | 0.1221 | 0.1302 | 0.2466 |
| 7DHC | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHC | 0.2377 | 0.0469 | 0.0171 | **0.0003** | **0.0000** |
| Chol | 0.2863 | 0.1124 | 0.0338 | **0.0037** | **0.0000** |

| | ASTROCYTES | | | | |
|---|---|---|---|---|---|
| TRZ | C vs 10 | C vs 25 | C vs 50 | C vs 100 | C vs 500 |
| Lan | 0.6534 | 0.1442 | **0.0035** | 0.1787 | 0.0051 |
| 14dZym | 0.8828 | 0.8828 | 0.4781 | 0.0844 | **<0.000001** |
| Zym | 0.0526 | 0.0644 | 0.0611 | 0.0463 | **0.0008** |
| DHL | 0.5062 | 0.2096 | 0.0807 | 0.0175 | 0.0116 |
| 7DHD | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHD | **0.0000** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Des | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| dHLan | 0.4781 | 0.4781 | 0.4781 | 0.1091 | 0.4142 |
| 14dZyme | | | | | |
| Zyme | 0.5363 | 0.1170 | 0.3106 | **0.0017** | **0.0005** |
| Lath | 0.6445 | 0.0452 | 0.7820 | 0.0112 | **0.0008** |
| 7DHC | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| 8DHC | 0.0135 | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Chol | **0.0053** | 0.3015 | 0.0418 | 0.9523 | **0.0002** |

Table S7. Statistics for Figure 6E (amiodarone).

| | NEURONS | | | | |
|---|---|---|---|---|---|
| **AMIOD** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| Lan | **0.0001** | **0.0000** | **0.0000** | **0.0001** | **0.0081** |
| 14dZym | **0.0001** | 0.0665 | **<0.000001** | **<0.000001** | **<0.000001** |
| Zym | 0.2235 | 0.4731 | 0.5430 | **0.0003** | **<0.000001** |
| DHL | 0.1357 | 0.2708 | 0.2108 | 0.1367 | **0.0002** |
| 7DHD | 0.0434 | **0.0012** | **0.0024** | **0.0000** | **<0.000001** |
| 8DHD | 0.2847 | 0.3669 | 0.7872 | 0.2771 | **<0.000001** |
| Des | 0.0903 | 0.2671 | 0.0201 | **0.0032** | **0.0005** |
| dHLan | 0.1838 | | 0.1838 | | |
| 14dZyme | | | | | |
| Zyme | 0.1719 | **<0.000001** | **<0.000001** | **<0.000001** | **<0.000001** |
| Lath | **0.0002** | **0.0020** | 0.7881 | 0.7862 | **<0.000001** |
| 7DHC | 0.1440 | **0.0001** | **0.0000** | **0.0052** | **0.0060** |
| 8DHC | 0.9948 | **0.0000** | **<0.000001** | **<0.000001** | **<0.000001** |
| Chol | 0.0872 | 0.5881 | 0.1844 | **0.0019** | **<0.000001** |

| | ASTROCYTES | | | | |
|---|---|---|---|---|---|
| **AMIOD** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| Lan | 0.0511 | 0.3849 | 0.0251 | 0.7033 | 0.2786 |
| 14dZym | 0.8956 | 0.4244 | 0.3417 | 0.3417 | 0.8419 |
| Zym | 0.7653 | 0.1442 | 0.1017 | 0.0350 | **<0.000001** |
| DHL | 0.0710 | 0.0640 | 0.0876 | 0.0604 | 0.0155 |
| 7DHD | **0.0062** | **0.0003** | **0.0001** | **0.0087** | **<0.000001** |
| 8DHD | 0.0646 | 0.0139 | 0.0289 | 0.0162 | **<0.000001** |
| Des | **0.0011** | **0.0015** | **0.0003** | 0.0534 | 0.0112 |
| dHLan | 0.4346 | 0.4346 | 0.4346 | 0.4346 | 0.4346 |
| 14dZyme | | | | | |
| Zyme | 0.6092 | 0.1500 | **0.0001** | **0.0016** | **<0.000001** |
| Lath | 0.9484 | 0.2264 | 0.0542 | 0.8318 | **0.0078** |
| 7DHC | **0.0040** | **0.0007** | **0.0000** | **0.0011** | **<0.000001** |
| 8DHC | 0.7029 | 0.1467 | 0.2580 | 0.1212 | **<0.000001** |
| Chol | 0.0138 | 0.0760 | 0.0123 | **0.0099** | 0.0864 |

Table S8. Statistics for Figure 7.

| | NEURONS | | | | |
|---|---|---|---|---|---|
| **HAL** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| 7-keto | 0.820864 | 0.195313 | 0.180185 | 0.325553 | 0.345252 |
| 24-OH | 0.38498 | **0.009475** | **0.000167** | **0.000002** | **<0.000001** |
| 25-OH | 0.147282 | 0.055791 | **0.00671** | **0.005232** | **0.000707** |
| | | | | | |
| **CAR** | **C vs 5** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** |
| 7-keto | 0.949126 | 0.478059 | 0.478059 | 0.478059 | 0.81706 |
| 24-OH | 0.178196 | 0.013195 | 0.01226 | 0.023346 | **0.002067** |
| 25-OH | 0.099236 | 0.706019 | 0.140157 | 0.886589 | 0.035586 |
| | | | | | |
| **ARI** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| 7-keto | 0.295827 | 0.368838 | 0.37655 | 0.844546 | 0.863488 |
| 24-OH | 0.198314 | 0.085723 | 0.027426 | **0.007143** | **0.000221** |
| 25-OH | 0.035044 | 0.010233 | 0.011699 | **0.007798** | **0.001259** |

| | ASTROCYTES | | | | |
|---|---|---|---|---|---|
| **HAL** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| 7-keto | 0.305303 | 0.426553 | 0.375829 | 0.420775 | **0.006552** |
| 24-OH | | | | | |
| 25-OH | 0.522932 | 0.498951 | **0.003149** | 0.010778 | **0.005167** |
| | | | | | |
| **CAR** | **C vs 5** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** |
| 7-keto | 0.530667 | 0.478241 | 0.703051 | 0.882682 | 0.613628 |
| 24-OH | 0.478059 | 0.478059 | 0.478059 | 0.478059 | 0.478059 |
| 25-OH | 0.817251 | 0.426431 | 0.074524 | 0.048633 | **<0.000001** |
| | | | | | |
| **ARI** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| 7-keto | 0.849479 | 0.81572 | 0.097286 | 0.600533 | 0.05707 |
| 24-OH | | | | | |
| 25-OH | 0.997193 | 0.435064 | 0.77405 | 0.623376 | **0.000993** |

Table S9. Statistics for Figure S3.

| | PTAD | | | | | |
|---|---|---|---|---|---|---|
| **Neurons** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** | **C vs 1000** |
| CHOL | 0.08650 | 0.13720 | **0.02600** | **0.01720** | **0.00010** | **0.00010** |
| 7DHC | 0.08023 | **0.02637** | **0.02377** | **0.00024** | **0.00000** | **0.00010** |
| 8DHC | 0.08023 | **0.02637** | **0.02377** | **0.00024** | **0.00000** | **0.00010** |
| DES | 0.09672 | **0.02899** | **0.00381** | **0.00022** | **0.00000** | **0.00000** |
| LAN | 0.58352 | 0.43194 | 0.33607 | 0.09252 | 0.54066 | 0.64017 |
| | | | | | | |
| | DMG | | | | | |
| **Neurons** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** | **C vs 1000** |
| CHOL | 0.74229 | 0.17269 | 0.33077 | **0.01474** | **0.00000** | **0.00000** |
| 7DHC | **0.00000** | **0.00000** | **0.00000** | **0.00000** | **0.00000** | **0.00000** |
| 8DHC | **0.01298** | **0.00008** | **0.00000** | **0.00000** | **0.00000** | **0.00000** |
| DES | 0.21994 | 0.94557 | **0.00006** | **0.00000** | **0.00000** | **0.00000** |
| LAN | 0.11135 | **0.00403** | 0.06562 | 0.07754 | 0.15836 | 0.37636 |

| | PTAD | | | | | |
|---|---|---|---|---|---|---|
| **Astrocyte** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** | **C vs 1000** |
| CHOL | 0.33515 | 0.41828 | 0.45562 | 0.74476 | **0.01601** | 0.11943 |
| 7DHC | **0.00000** | **0.00008** | **0.00000** | **0.00000** | **0.00000** | **0.00000** |
| 8DHC | **0.00053** | **0.00017** | **0.00019** | **0.00770** | **0.00000** | **0.00000** |
| DES | **0.00066** | **0.00000** | **0.00000** | **0.00000** | **0.00000** | **0.00000** |
| LAN | 0.24357 | 0.04554 | 0.08989 | 0.07279 | **0.00026** | 0.36575 |
| | | | | | | |
| | DMG | | | | | |
| **Astrocyte** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** | **C vs 1000** |
| CHOL | 0.84432 | 0.90176 | 0.64965 | 0.55673 | **0.00118** | 0.06085 |
| 7DHC | **0.00000** | **0.00000** | **0.00000** | **0.00000** | **0.00000** | **0.00000** |
| 8DHC | **0.00057** | **0.00000** | **0.00000** | **0.00000** | **0.00000** | **0.00000** |
| DES | **0.00002** | **0.00000** | **0.00000** | **0.00000** | **0.00000** | **0.00000** |
| LAN | 0.65603 | 0.43294 | 0.84524 | 0.05437 | **0.01592** | **0.00806** |

Table S10. Statistics for Figure S4.

| | NEURONS | | | | | | ASTROCYTES | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **SERT** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** | **SERT** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| Lan | 0.04776 | 0.37711 | **0.00379** | 0.01415 | 0.50508 | Lan | 0.15810 | 0.07456 | 0.15450 | 0.31185 | 0.17252 |
| 14dZym | **0.00369** | **0.00021** | **0.00573** | **0.00003** | **0.00077** | 14dZym | 0.37583 | 0.04773 | 0.01268 | 0.28315 | 0.45398 |
| Zym | 0.54977 | **0.00789** | 0.21986 | 0.01401 | 0.08711 | Zym | 0.00142 | 0.21267 | 0.68316 | 0.32893 | 0.99649 |
| DHL | 0.43255 | 0.12513 | 0.67369 | 0.65497 | 0.13429 | DHL | 0.30722 | 0.42207 | 0.79345 | 0.15636 | 0.24087 |
| 7DHD | 0.20459 | **0.00250** | **0.00128** | 0.01360 | **0.00014** | 7DHD | 0.04486 | 0.25452 | 0.05015 | 0.02578 | <0.000001 |
| 8DHD | 0.11220 | 0.17510 | 0.81725 | 0.25243 | **0.00023** | 8DHD | 0.60650 | 0.55858 | 0.17847 | 0.31082 | 0.00657 |
| Des | 0.16451 | 0.33985 | 0.91869 | 0.13912 | 0.10348 | Des | 0.03078 | **0.00243** | **0.00000** | **0.00003** | **0.00001** |
| dHLan | 0.80566 | 0.49422 | 0.19465 | 0.15238 | 0.37442 | dHLan | 0.82204 | 0.44299 | 0.84542 | 0.72912 | 0.45571 |
| 14dZyme | | 0.34089 | 0.05603 | | 0.21847 | 14dZyme | | | | | |
| Zyme | 0.93552 | 0.00708 | 0.03406 | 0.98377 | **0.00651** | Zyme | 0.07795 | 0.07665 | 0.46154 | 0.94953 | 0.75019 |
| Lath | 0.63629 | 0.12057 | 0.03028 | 0.06857 | **0.00088** | Lath | 0.26881 | 0.96755 | 0.03004 | 0.05415 | 0.80728 |
| 7DHC | 0.28773 | **0.00026** | **0.00003** | **0.01188** | **0.00004** | 7DHC | 0.82264 | 0.58281 | 0.02191 | 0.01053 | **0.00007** |
| 8DHC | 0.28699 | **0.00514** | **0.00368** | 0.04718 | **0.00093** | 8DHC | 0.20797 | 0.12664 | 0.72216 | 0.66573 | 0.13355 |
| Chol | 0.40199 | 0.08593 | 0.18022 | 0.79798 | 0.16187 | Chol | **0.00053** | **0.00159** | **0.00095** | **0.00019** | **0.00031** |

Table S11. Statistics for Figure S5.

| | NEURONS | | | | | | ASTROCYTES | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **TRZ** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** | **TRZ** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| 7-keto | 0.74160 | 0.54242 | 0.92295 | 0.09011 | 0.53120 | 7-keto | 0.76502 | 0.52751 | 0.95841 | 0.74805 | 0.36549 |
| 24-OH | 0.53072 | 0.17419 | 0.16083 | 0.13277 | 0.09496 | 24-OH | 0.64447 | 0.44606 | 0.71945 | 0.44606 | 0.44606 |
| 25-OH | 0.58625 | 0.43266 | 0.23053 | 0.29365 | 0.86720 | 25-OH | 0.67891 | 0.48508 | 0.11620 | 0.86414 | 0.31127 |
| | | | | | | | | | | | |
| **AMIOD** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** | **AMIOD** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| 7-keto | 0.06564 | 0.30185 | **0.01530** | **0.00785** | 0.24809 | 7-keto | 0.52243 | 0.46780 | 0.43122 | 0.42432 | 0.54777 |
| 24-OH | 0.17432 | 0.10722 | **0.01299** | 0.07604 | **0.01299** | 24-OH | | | | | |
| 25-OH | 0.16534 | 0.17314 | 0.04439 | 0.26967 | 0.62471 | 25-OH | 0.91428 | 0.64209 | 0.35663 | 0.20713 | 0.59402 |
| | | | | | | | | | | | |
| **SERT** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** | **SERT** | **C vs 10** | **C vs 25** | **C vs 50** | **C vs 100** | **C vs 500** |
| 7-keto | 0.47806 | 0.47806 | 0.47806 | 0.47806 | 0.47806 | 7-keto | 0.24624 | 0.13587 | 0.65826 | 0.33967 | 0.41644 |
| 24-OH | 0.22213 | **0.00108** | **0.00108** | **0.00108** | **0.00108** | 24-OH | 0.47806 | 0.47806 | 0.47806 | 0.47806 | 0.47806 |
| 25-OH | 0.31839 | 0.07476 | 0.06604 | **0.00593** | 0.18517 | 25-OH | 0.15695 | 0.26838 | 0.24779 | 0.76693 | 0.34863 |