Sulfation made simple: A strategy for synthesising sulfated molecules

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S1. General Methods:

All reactions involving moisture sensitive reagents were carried out in an oven-dried reaction vessel under nitrogen or argon. All anhydrous solvents were either directly obtained from an SPS or treated with 4 Å molecular sieves 24 h prior to use. Solvents used for work up procedures and column chromatography were of technical grade from Honeywell, VWR and Fischer Scientific. Unless stated otherwise, solvents were removed by rotary evaporation under a reduced pressure between 30-50 °C. All chemical reagents were used as received unless stated otherwise.

Reactions were monitored by TLC analysis on Merck silica gel 60 F254 using UV light and/or potassium permanganate.

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance® III (400 MHz) spectrometer at 400 and 101 MHz, respectively. Chemical shift data for protons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane (TMS: δ 0.0) and referenced internally to the residual proton of the solvent. The deuterated solvents used for NMR analysis were: chloroform (CDCl$: \delta_H 7.26, \delta_C 77.16$), dimethyl sulfoxide ((CD$_3$)$_2$SO: $\delta_H 2.50, \delta_C 39.52$), methanol (CD$_3$OD: $\delta_H 3.31, \delta_C 49.00$) and deuterium oxide (D$_2$O: $\delta_H 4.79$). Coupling constants are given in hertz (Hz). All individual assignments were made using 2D NMR ($^1$H-$^1$H COSY, $^1$H-$^{13}$C HSQC, and $^1$H-$^{13}$C HMBC) spectroscopy. The spectroscopic data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiple, br = broad and combinations thereof), coupling constant, integration and structural assignment.

Mass spectra were recorded on a Waters Xevo G2-XS Tof or Synap G2-S mass spectrometer using Zspray, Electro-spray ionisation in positive (ESI+) and negative (ESI-) mode and chemical ionisation (CI).

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR and a Varian 660-IR FTIR spectrometer using Agilent Resolution Pro, with absorption maxima
(ν_{max}) reported in cm^{-1}. Optical rotations were measured using a Bellingham and
Stanley ADP450 Series Peltier® polarimeter at 20 °C using the D line of sodium
(589.3 nm) at the indicated concentration and solvent.
S2. General Procedures

General procedure 1. Synthetic procedure for the preparation of alkyl sulfates using tributyl sulfo ammonium betaine (Bu₃NSO₃, 1).

\[
\begin{align*}
\text{ROH} & \quad \xrightarrow{1) \ 1 \ (2.0 \ \text{eq}) \ \text{MeCN, 90 °C}} \quad \text{ROSO}_3\text{Na} \\
& \quad \xrightarrow{2) \ \text{w/u procedures A-C}} \quad \text{ROSO}_3\text{Na}
\end{align*}
\]

A flame dried 25 mL Schlenk flask was charged with ROH (1.0 mmol) and 1 (2.0 eq. per OH group) under argon. Anhydrous MeCN was added (giving a concentration of 0.50-0.25 Mol dm⁻³ to the limiting reagent) and the reaction mixture heated at 90 °C, monitored by TLC. After the reaction was complete the flask was cooled to room temperature and the solvent removed under reduced pressure. The flask was charged with H₂O (20 mL) and the aqueous mixture extracted with EtOAc (4 × 30 mL). The organic extracts were pooled, dried (MgSO₄), filtered and the filtrate solvent was removed \textit{in vacuo} to afford the desired sulfate ester as its tributylammonium salt.

Work-up procedure A: The flask containing the tributylammonium salt was charged with EtOH (30 mL) and sodium 2-ethylhexanoate (5.0 eq. per sulfate group). The reaction mixture was stirred vigorously for 1 h at room temperature. The solid was collected by filtration, washed with EtOH (3 × 20 mL) and dried to a constant weight to afford the desired sulfate as its sodium salt.

Work-up procedure B: The flask containing the tributylammonium salt was charged with Et₂O (30 mL), EtOH (5 mL) and sodium 2-ethylhexanoate (5.0 eq. per sulfate group). The reaction mixture was stirred vigorously for 1h at room temperature. The solid was removed by filtration, washed with a small amount of cold EtOH and dried to a constant weight to afford the desired sulfate as its sodium salt.
Work-up procedure C: The flask containing the tributylammonium salt was charged with MeCN (20 mL) and sodium iodide (5.0 eq. per sulfate group). The reaction mixture was stirred vigorously for 1h at room temperature. The solid was removed by filtration, washed with MeCN (3 × 30 mL) and dried to a constant weight to afford the desired sulfate as its sodium salt.
S3. Compound characterisation

Preparation of tributyl sulfo ammonium betaine (1) [1]

A three necked round bottom flask was fitted with a temperature probe and a pressure equalising dropping funnel. The flask under an atmosphere of argon was charged with tributylamine (59.4 mL, 0.25 mol) and anhydrous CH₂Cl₂ (200 mL). The solution was stirred vigorously and cooled to -40 °C (MeCN/CO₂). A solution of chlorosulfonic acid (16.75 mL, 0.253 mol) in anhydrous CH₂Cl₂ (200 mL) was added dropwise over 2 h at a rate ensuring the internal temperature did not exceed -30 °C. After full addition of the chlorosulfonic acid solution, and stirring for a further 1 h, ammonia gas was gently bubbled through the reaction mixture until pH 7 was achieved. The white solid was removed by vacuum filtration, washed with CH₂Cl₂ (100 mL) and the filtrate was collected. The solvent was removed in vacuo and the crude product was treated with cold H₂O (500 mL). The precipitate was collected, washed with water (5 × 100 mL) and freeze dried. Recrystallisation from CH₂Cl₂/hexane affording 1 as a white solid (59.8 g, 0.23 mol, 90%).

M.P. 95-96 °C (from CH₂Cl₂/H₂O). Lit. 94 °C[1]

IR. νmax cm⁻¹: 2962w (C-H), 2875w (C-H), 1473m (C-H), 1293m (O-S), 1052m (O-S).

¹H NMR. δH (400 MHz, CDCl₃) 3.32 – 3.22 (m, 6H, N(CH₃)₃), 1.87 – 1.73 (m, 6H, CH₂), 1.37 (dt, J = 7.4 Hz, 6H, CH₃), 0.98 (t, J = 7.4 Hz, 9H, CH₃).

¹³C NMR. δc (101 MHz, CDCl₃) 57.1 (N(CH₃)₃), 25.6 (CH₂), 20.6 (CH₂), 13.7 (CH₃).

LRMS. m/z (ESI-) 264.1 ([M-H]⁻, 100%), 208.1 ([M-C₃H₁₀]⁻, 53).

HRMS. m/z (ESI-) C₁₂H₂₆NO₃S [M-H]⁻ calcd 264.1613, found: 264.1612.
Stability measurement of 1 showed that prolonged exposure to moisture in the air gave ~ 12% degradation of 1 after 15 d by ¹H NMR spectroscopy. Exclusion of moisture from the storage atmosphere (e.g. N₂ or Ar atmosphere) in the vial containing 1 gave longer term stability (minimum 1 month per batch).

Tributylammonium 4-methoxybenzyl sulfate (3c)

Following general procedure 1: 4-methoxybenzyl alcohol (138 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the solvent removed in vacuo. The crude reaction product was purified (SiO₂; CH₂Cl₂/MeOH, 9:1, Rf = 0.6) to yield the title compound as a clear oil (350 mg, 87%).

IR. νmax cm⁻¹: 3467w, 2960m, 2874w, 1613w, 1514s, 1465m, 1247s, 1196s

¹H NMR. δH (400 MHz, CDCl₃): 9.85 (br s, 1H, NH), 7.34 – 7.28 (m, 2H), 6.85 – 6.79 (m, 2H), 5.00 (s, 2H, ArCH₂), 3.77 (s, 3H, OCH₃), 3.03 – 2.90 (m, 6H, N(CH₂)₃), 1.73 – 1.58 (6H, m), 1.33 (h, J = 7.4 Hz, 6H), 0.91 (t, J = 7.4 Hz, 9H)

¹³C NMR. δC (101 MHz, CDCl₃): 159.5, 130.1, 128.9, 113.7, 69.5, 55.3, 52.6, 25.3, 20.1, 13.6

LRMS. m/z (ESI⁺) 186.2 (100%, [M-OMe]²⁻), 589.4 (20%, [M+HNB₃⁺])

HRMS. m/z (ESI⁺) C₃₂H₆₅N₂O₅S requires 589.4614, found 589.4619 [M+HNB₃⁺]⁺
Tributylammonium 2-methoxybenzyl sulfate (3f)

Following general procedure 1: 2-methoxybenzyl alcohol (138 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (1.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the solvent removed in vacuo. The crude reaction product was purified (SiO$_2$; CH$_2$Cl$_2$/MeOH, 9:1, $R_f = 0.6$) to yield the title compound as a clear oil (350 mg, 87%).

**IR.** $\nu_{\text{max}}$ cm$^{-1}$ 3442br, 2960w, 2874w, 1604w, 1590w, 1494m, 1463m, 1243s, 1196s

**$^1$H NMR.** $\delta$ (400 MHz, CDCl$_3$) 9.81 (br s, 1H, NH), 7.46 (d, $J = 5.5$ Hz, 1H), 7.25 – 7.20 (m, 1H), 6.90 (app. t, $J = 7.5$ Hz, 1H), 6.82 (d, $J = 8.2$ Hz, 1H), 5.15 (s, 2H, ArCH$_2$), 3.79 (s 3H, OC$_3$H$_7$), 3.03 – 2.91 (m, 6H, N(CH$_2$)$_3$), 1.67 (m, 6H), 1.33 (h, $J = 6.8$ Hz, 6H), 0.92 (t, $J = 6.8$ Hz, 9H).

**$^{13}$C NMR.** $\delta$ (101 MHz, CDCl$_3$) 157.1, 129.4, 128.9, 125.4, 120.4, 110.2, 64.8, 55.4, 52.6, 25.3, 20.1, 13.6.

**LRMS.** $m/z$ (ESI+) 186.2 (100%, [M-OMe]$^2^+)$, 589.4 (60%, [M+HNBu$_3$]$^+$).

**HRMS.** $m/z$ (ESI+) C$_{32}$H$_{65}$N$_2$O$_5$S requires 589.4614, found 589.4617 [M+HNBu$_3$]$^+$. 

Preparation of sodium benzyl sulfate (4a)$^{[2]}$

Following general procedure 1: benzyl alcohol (108 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and purified by work up procedure A to yield the title sulfate as a bright white solid (200 mg, 95%).

**M.P.** 194-196 °C (lit. 194-196 °C)$^{[2]}$

**IR.** $\nu_{\text{max}}$ cm$^{-1}$ 3064 w, 3032 w, 1455 w, 1204 s.
\[^{1}\text{H NMR}\].  δ\(_{\text{H}}\) (400 MHz, CD\(_{3}\)OD) 7.46 – 7.27 (m, 5H, Ar), 5.03 (s, 2H, ArCH\(_2\)).

\[^{13}\text{C NMR}\].  δ\(_{\text{C}}\) (101 MHz, CD\(_{3}\)OD) 136.4, 128.0, 127.7 (CH and q), 69.4.

\[^{13}\text{C NMR}\].  δ\(_{\text{C}}\) (101 MHz, CD\(_{3}\)OD) 136.4, 128.0, 127.7 (CH and q), 69.4.

\[^{13}\text{C NMR}\].  δ\(_{\text{C}}\) (101 MHz, CD\(_{3}\)OD) 136.4, 128.0, 127.7 (CH and q), 69.4.

\[^{13}\text{C NMR}\].  δ\(_{\text{C}}\) (101 MHz, CD\(_{3}\)OD) 136.4, 128.0, 127.7 (CH and q), 69.4.

**LRMS.**  \(m/z\) (ESI+) 233.0 ([M+Na]\(^+\), 100%).

Data were consistent with the literature.

**Control experiment with sequential PyH to Bu\(_4\)N cation exchange**

Following **general procedure 1**: benzyl alcohol (108 mg, 1.0 mmol) and Py-SO\(_3\) (2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2 h. The reaction was cooled to room temperature and Bu\(_4\)NI (2.0 eq.) was added and stirred for 10 min. Solvents were removed *in vacuo* and the residue dissolved in EtOH (25 mL). Sodium-2-ethylhexanoated (5.0 eq.) was added and the mixture stirred for 1 h at room temperature. The precipitate was collected by filtration, washed with EtOH and dried under vacuum to afford 4a as a white solid (99 mg, 47%).

Sodium 4-chlorobenzyl sulfate (4b)

\[
\begin{array}{c}
\text{Cl} \\
\text{SO}_3\text{Na}
\end{array}
\]

Following **general procedure 1**: 4-chlorobenzyl alcohol (142 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and purified by **work up procedure A** to yield the title sulfate as a bright white solid (229 mg, 94%).

**M.P.** 202-204 °C

**IR.**  \(\nu_{\text{max}}\) cm\(^{-1}\) 2193 w, 1205 w.

\[^{1}\text{H NMR}\].  δ\(_{\text{H}}\) (400 MHz, CD\(_{3}\)OD) 7.46 – 7.28 (m, 4H, Ar), 4.99 (s, 2H, ArCH\(_2\)).

\[^{13}\text{C NMR}\].  δ\(_{\text{C}}\) (101 MHz, CD\(_{3}\)OD) 136.8, 134.8, 130.6, 129.5, 69.8.

**LRMS.**  \(m/z\) (ESI+) 266.9 ([M+Na]\(^+\), 100%).
HRMS. m/z (ESI+) C\textsubscript{7}H\textsubscript{6}ClNa\textsubscript{2}O\textsubscript{4}S requires 266.9470, found 266.9471 [M+Na]\textsuperscript{+}.

Sodium 4-methoxybenzyl sulfate (4c)

\[
\begin{align*}
\text{SO}_3\text{Na} \\
\end{align*}
\]

Tributylammonium 4-methoxybenzyl sulfate (3c) (161 mg, 0.4 mmol) was subjected to work up procedure C to yield the title compound as a lustrous white solid (93 mg, 86%).

M.P. 100 °C (decomposed to a pink solid)

IR. \(\nu_{\text{max}}\) cm\(^{-1}\) 3014w, 2842w, 1612w, 1514m, 1250s

\(^1\)H NMR. \(\delta\) (400 MHz, (CD\textsubscript{3})\textsubscript{2}SO) 7.25 (d, \(J = 8.1\) Hz, 2H, Ar), 6.89 (d, \(J = 8.1\) Hz, 2H, Ar), 4.69 (s, 2H, ArCH\textsubscript{2}), 3.74 (s, 3H, OCH\textsubscript{3}).

\(^{13}\)C NMR. \(\delta\) (101 MHz, (CD\textsubscript{3})\textsubscript{2}SO) 158.7, 129.7, 129.4, 113.6, 67.3, 55.1.

LRMS. m/z (ESI+) 281.1 ([M+Na+H\textsubscript{2}O]\textsuperscript{+}, 100%), 263.0 ([M+Na]\textsuperscript{+}, 10).

HRMS. m/z (ESI+) C\textsubscript{8}H\textsubscript{9}O\textsubscript{5}Na\textsubscript{2}S requires 262.9965, found 262.9966 [M+Na]\textsuperscript{+}.

Sodium 4-nitrobenzyl sulfate (4d)

\[
\begin{align*}
\text{SO}_3\text{Na} \\
\end{align*}
\]

Following general procedure 1: 4-nitrobenzyl alcohol (153 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the contents purified by work up procedure B. Recrystallisation from hot MeOH afforded the title compound as light yellow crystals (216 mg, 85%).

M.P. 162-167 °C (dec.)

IR. \(\nu_{\text{max}}\) cm\(^{-1}\) 2685w, 2593w, 1613w, 1536s, 1351s, 1239s

\(^1\)H NMR. \(\delta\) (400 MHz, D\textsubscript{2}O) 8.26–8.21 (m, 2H), 7.69–7.55 (m, 2H), 5.17 (s, 2H, ArCH\textsubscript{2}).
$^{13}$C NMR. $\delta$C (101 MHz, D$_2$O) 147.4, 143.2, 128.4, 123.8, 69.1.

LRMS. $m/z$ (ESI+) 277.9 ([M+Na]$^+$, 100%).

HRMS. $m/z$ (ESI+) C$_7$H$_6$NO$_6$Na$_2$S requires 277.9711, found 277.9712 [M+Na]$^+$.

Sodium 2-chlorobenzyl sulfate (4e)

Following general procedure 1: 2-chlorobenzyl alcohol (142 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and purified by work up procedure A to yield the title compound as a white solid (242 mg, 99%).

M.P. 219-221 °C

IR. $\nu_{\max}$ cm$^{-1}$ 3580w, 1478w, 1252s, 1203s

$^1$H NMR. $\delta$H (400 MHz, D$_2$O) 7.52–7.43 (m, 2H), 7.39–7.31 (m, 2H), 5.15 (s, 2H, ArCH$_2$).

$^{13}$C NMR. $\delta$C (101 MHz, D$_2$O) 133.5, 132.5, 130.8, 130.4, 129.5, 127.3, 68.1.

LRMS. $m/z$ (ESI+) 266.9 ([M$^{35}$Cl+Na]$^+$, 100%), 268.9 ([M$^{37}$Cl+Na]$^+$, 30%).

HRMS. $m/z$ (ESI+) C$_7$H$_6$O$_4$Na$_2$SCl requires 266.9471, found 266.9475 [M$^{35}$Cl+Na]$^+$.

Sodium 2-nitrobenzyl sulfate (4g)$^{[3]}$

Following general procedure 1: 2-nitrobenzyl alcohol (153 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the contents purified by work up procedure B.
Recrystalisation from hot MeOH yielded the title sulfate as light yellow crystals (180 mg, 71%).

**M.P.** 109-111 °C (dec.)

**IR.** $\nu_{\text{max}}$ cm$^{-1}$ 1610w, 1526s, 1334s, 1225s

$^1$H NMR. $\delta_H$ (400 MHz, D$_2$O) 8.14–8.08 (m, 1H), 7.78–7.69 (m, 2H), 7.59–7.52 (m, 1H), 5.41 (s, 2H, ArCH$_2$).

$^{13}$C NMR. $\delta_C$ (101 MHz, D$_2$O) 144.2, 134.4, 131.2, 129.5, 129.3, 125.0, 67.1.

**LRMS.** $m/z$ (ESI+) 277.9 ([M+Na]$^+$, 100%).

**HRMS.** $m/z$ (ESI+) C$_7$H$_6$NO$_6$Na:S requires 277.9711, found 277.9713 [M+Na]$^+$. Data were in accordance with literature.

Sodium 1-phenylethyl sulfate (4h) [4]

Following **general procedure 1**: 1-phenyl ethanol (122 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 2.5 h. The flask was cooled and purified by **work up procedure B**. The final solid was suspended in EtOAc and filtered to yield the desired sulfate as its sodium salt (200 mg, 89%).

**M.P.** 165-167 °C

**IR.** $\nu_{\text{max}}$ cm$^{-1}$ 1582w, 1388w, 1148s

$^1$H NMR. $\delta_H$ (400 MHz, CD$_3$OD) 7.43–7.38 (m, 2H), 7.34–7.28 (m, 2H), 7.27–7.21 (m, 1H), 5.46 (q, $J = 6.6$ Hz, 1H, ArCH), 1.60 (d, $J = 6.6$ Hz, 3H, CH$_3$).

$^{13}$C NMR. $\delta_C$ (101 MHz, CD$_3$OD) 144.0, 129.2, 128.5, 127.0, 78.0, 23.7.

**LRMS.** $m/z$ (ESI+) 695.2 ([3M+Na]$^+$, 100%), 225.0 ([M+H]$^+$, 40%).

**HRMS.** $m/z$ (ESI+) C$_8$H$_{10}$O$_4$NaS requires 225.0198, found 225.0199 [M+H]$^+$. 
Sodium 4-methoxyphenyl sulfate (4i)

\[
\text{\begin{tikzpicture}
\node[shape=circle,draw,inner sep=1pt] (1) at (0,0) {$\text{OSO}_3\text{Na}$};
\draw[black, thick] (1) -- (1.5,0);\end{tikzpicture}}
\]

Following general procedure 1: 4-methoxy phenol (124 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 5 h. The flask was cooled and purified by work up procedure B to yield the desired sulfate as its sodium salt (176 mg, 78%).

M.P. 265 °C (dec.)

IR. \( \nu_{\max} \text{ cm}^{-1} \) 2955w 2499w, 1504s; 1199s.

\(^1\text{H} \text{ NMR.} \ \delta_{\mathrm{H}} \) (400 MHz, CD$_3$OD) 6.75–6.67 (m, 4H, Ar), 3.69 (s, 3H, OCH$_3$).

\(^{13}\text{C} \text{ NMR.} \ \delta_{\mathrm{C}} \) (101 MHz, CD$_3$OD) 154.4, 152.1, 116.7, 115.7, 56.1.

LRMS. \( m/z \) (ESI+) 331.2 ([3M+2MeCN+Na]$^+$, 100%), 516.3 ([2M+MeCN+Na+H]$^+$, 10%),

HRMS. \( m/z \) (ESI+) \( \text{C}_8\text{H}_{10}\text{O}_4\text{NaS} \) requires 225.0198, found 225.0199, \( \text{C}_9\text{H}_{10}\text{NNa}_2\text{O}_5\text{S} \) requires 290.0075, found 290.0076 [M+MeCN+Na].

Sodium (1R, 2S)-cyclohexane-1,2-diyl bis(sulfate) (5)[5]

\[
\text{\begin{tikzpicture}
\node[shape=circle,draw,inner sep=1pt] (1) at (0,0) {$\text{OSO}_3\text{Na}$};
\node[shape=circle,draw,inner sep=1pt] (2) at (0,-1) {$\text{OSO}_3\text{Na}$};
\draw[black, thick] (1) -- (1.5,-1);\end{tikzpicture}}
\]

Following general procedure 1: cis-cyclohexanediol (116 mg, 1.0 mmol) and 1 (1.06 g, 4.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 5.0 h. The flask was cooled and purified by work up procedure A. Recrystallisation from hot EtOH yielded the title sulfate as a bright white solid (290 mg, 91%).

M.P. 203-205 °C (dec.)

IR. \( \nu_{\max} \text{ cm}^{-1} \) 2946w, 1456w, 1328w, 1258w, 1232w, 1200w.

\(^1\text{H} \text{ NMR.} \ \delta_{\mathrm{H}} \) (400 MHz, D$_2$O) 4.57 – 4.52 (m, 2H)), 1.98-1.95 (m, 2H), 1.76 – 1.55 (m, 4H), 1.49 – 1.33 (m, 2H).

\(^{13}\text{C} \text{ NMR.} \ \delta_{\mathrm{C}} \) (101 MHz, D$_2$O) 77.8, 27.7, 20.8.
LRMS. \( m/z \) (ESI+) 342.9 ([M+Na]\(^+\), 100%), 306.85 (40%), 164.92 (32%).

HRMS. \( m/z \) (ESI+) \( C_6H_{10}O_8Na_3S_2 \) requires 342.9510, found 342.9514 [M+Na]\(^+\).

Data were in accordance with literature.

Sodium propane-1,2,3-triyl tris(sulfate) (6)

![Sodium propane-1,2,3-triyl tris(sulfate) structure](structure_image)

Following **general procedure 1**: Glycerol (92 mg, 1.0 mmol) and 1 (1.59 g, 6.0 mmol) were dissolved in dry MeCN (4.0 mL) and heated under reflux for 8 h. The flask was cooled and purified by **work up procedure A**. Recrystallisation from hot EtOH yielded the title sulfate as a bright white solid (365 mg, 92%).

**M.P.** 210 °C (dec.)

**IR.** \( \nu_{\text{max}} \) cm\(^{-1}\) 1639 w, 1216 s.

**\(^1\)H NMR.** \( \delta_H \) (400 MHz, D\(_2\)O) 4.80 (p, \( J = 4.8 \) Hz, 1H, CHOSO\(_3\)Na), 4.27 (qd, \( J = 11.1, 4.8 \) Hz, 4H, CH\(_2\)OSO\(_3\)Na).

**\(^{13}\)C NMR.** \( \delta_C \) (101 MHz, D\(_2\)O) 74.5, 66.2.

LRMS. \( m/z \) (ESI+) 420.8 (100%, [M+Na]\(^+\)), 306.85 (50%).

HRMS. \( m/z \) (ESI+) \( C_3H_{12}O_{12}Na_4S_3 \) requires 420.8534, found 420.8538 [M+Na]\(^+\)

Tributylammonium (±)-2-isopropyl-5-methylcyclohexyl sulfate (7)

![Tributylammonium (±)-2-isopropyl-5-methylcyclohexyl sulfate structure](structure_image)

Following **general procedure 1**: (±)-menthol (156 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (2.0 mL) and heated under reflux for 3 h. The flask was cooled and the solvent was removed under reduced pressure. The crude
contents were purified (SiO$_2$; CH$_2$Cl$_2$/MeOH, 9:1, $R_f = 0.45$) to yield the title compound as a white crystalline solid (330 mg, 78%).

**M.P.** 92 °C

**IR.** $\nu_{\text{max}}$ cm$^{-1}$ 2957 m, 2870 m, 1458 m, 1248 s

$^1$H NMR. $\delta$H (400 MHz, CDCl$_3$) 9.95 (br s, 1H, NH), 4.16 (td, $J = 10.7$, 4.4 Hz, 1H, CHOSO$_3$), 3.04 – 2.94 (m, 6H, N(CH$_2$)$_3$), 2.49 – 2.43 (m, 1H, CHPr), 2.26 (sd, $J = 7.0$, 2.5 Hz, 1H, CH(CH$_2$)$_3$), 1.74 – 1.63 (m, 6H, N(CH$_2$)$_3$), 1.63 – 1.57 (m, 2H), 1.35 (h, $J = 7.4$ Hz, 6H), 1.24 (tdd, $J = 10.7$, 3.4, 1.7 Hz, 1H), 1.10 – 0.96 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 9H), 0.82 (dd, $J = 6.8$, 4.4 Hz, 6H), 0.77 (d, $J = 6.8$ Hz, 3H, CH$_3$).

$^{13}$C NMR. $\delta$C (101 MHz, CDCl$_3$) 78.9, 52.6, 48.1, 42.0, 34.4, 31.6, 25.4, 25.3, 23.2, 22.2, 21.2, 20.1, 16.0, 13.6.

**LRMS.** $m/z$ (ESI+) 607.62 (100%, [M+NBu$_3$]$^+$).

**HRMS.** $m/z$ (ESI+) C$_{34}$H$_{75}$N$_2$O$_4$S requires 647.5448, found 647.5446 [M+NBu$_3$]$^+$.

Sodium 2-hydroxyphenylethanol sulfate (8)

Following **general procedure 1**: 2-hydroxyphenyl ethanol (138 mg, 1.0 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in dry MeCN (4.0 mL) and heated under reflux for 2.5 h. The flask was cooled and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography CH$_2$Cl$_2$/MeOH (19:1 to 9:1) to afford the title compound as a clear oil (300 mg, 74%)

**IR.** $\nu_{\text{max}}$ cm$^{-1}$ 3259 br, 2962 w, 2874 w, 1596 w, 1456 m, 1245 s, 1200 s

$^1$H NMR. (400 MHz, CDCl$_3$) 7.94 (br s, 2H), 7.08 – 6.97 (m, 2H), 6.89 (dd, $J = 8.0$, 1.3 Hz, 1H), 6.72 (td, $J = 8.0$, 1.3 Hz, 1H), 4.26 (t, $J = 6.7$ Hz, 2H, CH$_2$), 2.98 (t, $J = 6.7$ Hz, 2H, CH$_2$), 2.96 – 2.88 (m, 6H, N(CH$_2$)$_3$), 1.69 – 1.55 (m, 6H), 1.29 (h, $J = 7.4$ Hz, 6H), 0.88 (t, $J = 7.4$ Hz, 9H, CH$_3$)
13C NMR. (101 MHz, CDCl3) δc 155.2, 130.3, 127.5, 124.0, 119.4, 115.8, 68.15, 52.4, 30.5, 25.1, 19.6, 13.2

LRMS. m/z (ESI+) 589.50 (100%, [M+NHBu3]+).


Sodium (17β)-estra-1,3,5(10)-triene-3-ol,17-sulfate (9a)

Following general procedure 1: β-Estradiol (272 mg, 1.0 mmol) and 1 (398 mg, 1.5 mmol) were dissolved in dry MeCN (4.0 mL) and heated under reflux for 3 h. The flask was cooled and the solvent was removed under reduced pressure. The contents were purified (SiO2; CH2Cl2/MeOH, 9:1, Rf = 0.16) to yield an intermediate tributylammonium sulfate as a clear oil (321 mg, 0.6 mmol). The intermediate was purified by work up procedure C to yield the title compound as a bright white solid (225 mg, 60%).

M.P. 170 °C (dec. to a green solid);

IR. νmax cm⁻¹ 3432 br, 2925 w, 2869 w, 1612 w, 1499 w, 1210 s

1H NMR. δH (400 MHz, (CD3)2SO) 9.01 (s, 1H, OH), 7.04 (d, J = 8.5 Hz, 1H, C1H), 6.50 (dd, J = 8.5, 2.6 Hz, 1H, C2H), 6.42 (d, J = 2.6 Hz, 1H, C4H), 4.05 (t, J = 8.5 Hz, 1H), 2.69 (d, J = 6.8 Hz, 2H), 2.29–2.13 (m, 1H), 2.16–1.83 (m, 3H), 1.84–1.70 (m, 1H), 1.66–1.44 (m, 2H), 1.33–1.06 (m, 6H), 0.68 (s, 3H, CH3).

13C NMR. δc (101 MHz, (CD3)2SO) 154.9, 137.1, 130.4, 126.1, 114.9, 112.7, 84.1, 49.2, 43.5, 42.4, 38.5, 36.6, 29.2, 28.2, 26.9, 26.0, 22.7, 11.7.

LRMS. m/z (ESI-) 351.13 (100%, [M-Na]), 725.32 (100%, [2M-Na]+), 703.31 (90%, [2M-2Na+H]+)

HRMS m/z (ESI-) C18H23O5S requires 351.1268, found 351.1268 [M-Na]
Sodium (8R,9S,13S,14S,17S)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diyl bis(sulfate) (9b)

Adapted from **general procedure 1**: β-Estradiol (136 mg, 0.5 mmol) and 1 (663 mg, 2.5 mmol) were dissolved in dry MeCN (1.0 mL) and heated under reflux for 4 h. The flask was cooled and the solvent was removed under reduced pressure. The crude product was purified by **work up procedure C** to produce a white solid containing <4% 12a as an impurity (calculated by ^1^H-NMR). Recrystallization form MeOH/EtOAc afforded the title compound as a bright white solid (200 mg, 84%).

**M.P.** 137-140 °C (dec. to a red solid)

[^][α]D 6.51 (1.0, H$_2$O)

**IR.** $\nu_{\text{max}}$ cm$^{-1}$ 2926 w, 2868 w, 1609 w, 1499 w, 1214 s

**^1^H NMR.** δ$_H$ (400 MHz, (CD$_3$)$_2$SO) δ 7.15 (d, $J = 8.5$ Hz, 1H), 6.93–6.75 (m, 2H), 4.05 (q, $J = 10.9$, 9.7 Hz, 1H, C17-H), 2.85–2.67 (m, 2H), 2.31–2.17 (m, 1H), 2.17–2.09 (m, 1H), 2.09–1.87 (m, 2H), 1.87–1.70 (m, 1H), 1.69–1.48 (m, 2H), 1.44–1.05 (m, 6H), 0.70 (s, 3H).

**^13^C NMR.** δ$_C$ (101 MHz, (CD$_3$)$_2$SO) 151.1, 136.1, 134.8, 125.5, 120.5, 118.0, 84.1, 49.2, 43.6, 42.4, 38.3, 36.6, 29.2, 28.2, 26.8, 25.9, 22.7, 11.7.

**LRMS.** $m/z$ (ESI+) 499.05 (100%, [M+Na]$^+$), 379.01 (50%), 261.01 (50%).

**HRMS.** $m/z$ (ESI+) C$_{18}$H$_{22}$O$_8$Na$_2$S$_2$ requires 499.0449, found 499.0450 [M+Na]$^+$.

Sodium 3-(3-(methoxycarbonyl)-4-(4-(sulfonatooxy)butoxy)phenoxy)propane-1,2-diy1 bis(sulfate) (10)$^7$

Following **general procedure 1**: 13 (314 mg, 1.0 mmol) and 1 (1.59 g, 6.0 mmol) were dissolved in dry MeCN (4.0 mL) and heated under reflux for 12 h. The flask was
cooled and purified by work up procedure C to yield the title compound as a white solid (470 mg, 76%).

M.P. 218 °C (dec.)
IR. $\nu_{\text{max}}$ cm$^{-1}$ 3493, 2951, 1707

$^1$H NMR. $\delta_H$ (400 MHz, D$_2$O) 7.42 (d, $J = 3.2$ Hz, 1H, ArH), 7.25 (dd, $J = 9.1$, 3.2 Hz, 1H, ArH), 7.13 (d, $J = 9.2$ Hz, 1H, ArH), 4.88 (p, $J = 4.8$ Hz, 1H, CHO$_3$SO$_3$Na), 4.46 – 4.30 (m, 3H), 4.27 (dd, $J = 11.0$, 5.1 Hz, 1H), 4.12 (dt, $J = 8.1$, 5.6 Hz, 4H), 3.91 (s, 3H, CH$_3$), 1.94 – 1.81 (m, 4H, (CH$_2$)$_2$).

$^{13}$C NMR. $\delta_C$ (101 MHz, D$_2$O) $\delta_C$ 167.9, 152.1, 151.2, 121.1, 119.6, 116.9, 116.0, 74.5, 69.3, 68.6, 66.9, 65.9, 52.2, 24.8, 24.4.

LRMS. m/z (ESI+) 642.94 (100%, [M+Na]$^+$), 541.00 (80%, [M-SO$_3$]$^-$, 439.06 (50%, [M-Na(SO$_3$)$_2$]$^+$)

HRMS. m/z (ESI+) C$_{15}$H$_{19}$Na$_3$O$_4$S$_3$ requires: 642.9426, Found: 642.9420 [M+Na$^+$]

Data in accordance with literature.

Sodium (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methoxy-3-oxopropyl sulfate (11)

Following general procedure A: Methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-serinate (170 mg, 0.5 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in 2 mL dry MeCN and heated under reflux for 6 h. The tributylammonium salt was purified by cation exchange procedure C to yield the title sulfate as a bright white solid (210 mg, 95%).

Low Temperature method

Methyl (((9H-fluoren-9-yl)methoxy)carbonyl)-L-serinate (170 mg, 0.5 mmol) and 1 (530 mg, 2.0 mmol) were dissolved in 2 mL dry DMF and heated at 38 °C for 52 h.
The flask was charged with H₂O (20 mL) and the aqueous mixture extracted with EtOAc (4 × 30 mL). The organic extracts were pooled and dried over anhydrous MgSO₄. Filtration of the solid and removal of the solvent under reduced pressure yielded the desired sulfate as its tributylammonium salt. The tributylammonium salt was purified by cation exchange procedure C to yield the title sulfate as a bright white solid (200 mg, 90%).

**M.P.** 179-182 °C (decomposed at 189 °C)

[α]D25 4.20 (1.0, H₂O)

**IR.** νmax cm⁻¹ 3602w, 3389m, 3025w, 1740m, 1709s, 1621w, 1522s.

**¹H NMR.** δH (400 MHz, DMSO-d₆) 7.89 (d, J = 7.5 Hz, 2H), 7.83 (d, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.37 - 7.30 (m, 2H), 4.33 (td, J = 7.0, 4.3 Hz, 1H), 4.25 (br q, J = 4.3 Hz, 3H), 4.10 (dd, J = 11.0, 4.3 Hz, 1H), 3.97 (dd, J = 11.0, 6.6 Hz, 1H), 3.65 (s, 3H, C₃H₃).

**¹³C NMR.** δC (101 MHz, DMSO-d₆) 170.6, 155.9, 143.8, 140.7, 127.7, 127.2, 125.4, 120.2, 66.0, 64.8, 54.4, 52.1, 46.6

**LRMS.** m/z (ESI+) 466.06 (100%, [M+2Na]+), 909.10 (50%, [2M+3Na]+).

**HRMS.** m/z (ESI+) C₁₉H₁₈NO₈Na₂S requires 466.0549, found 466.0555 [M+2Na]+.

Chiral HPLC traces are provided for the intermediate Bu₄N salt of 11.
Phenomenex® Cellulose 1 chiral HPLC column traces for the sulfation step on 11

Conditions used: MeCN/H₂O (2:3) 1 ml min⁻¹

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S4. Copies of $^1$H and $^{13}$C NMR spectra
$^1$H NMR spectrum of 1 (400 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of 1 (101 MHz, CDCl$_3$)
$^1$H NMR spectrum of 3c (400 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of 3c (101 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of 3f (101 MHz, CDCl$_3$)
$^1$H NMR of spectrum 4a (400 MHz, CD$_3$OD)
$^{13}$C NMR spectrum of 4a (101 MHz, CD$_3$OD)
$^1$H NMR spectrum of 4b (400 MHz, CD$_3$OD)
$^{13}$C NMR spectrum of 4b (101 MHz, CD$_3$OD)
$^1$H NMR spectrum of 4c (400 MHz, d$_6$-DMSO)
$^{13}$C NMR spectrum of 4c (101 MHz, d$_6$-DMSO)
$^1$H NMR spectrum of 4d (400 MHz, D$_2$O)
$^{13}$C NMR spectrum of 4d (101 MHz, D$_2$O)
$^1$H NMR spectrum of 4e (400 MHz, D$_2$O)
$^{13}$C NMR spectrum of 4e (101 MHz, D$_2$O)
$^1$H NMR spectrum of 4g (400 MHz, D$_2$O)
$^{13}$C NMR spectrum of 4g (101 MHz, D$_2$O)
$^1$H NMR spectrum of 4h (400 MHz, CD$_3$OD)
$^{13}$C NMR spectrum of 4h (101 MHz, CD$_3$OD)
$^1$H NMR spectrum of 4i (400 MHz, CD$_3$OD)
$^{13}$C NMR spectrum of 4i (101 MHz, CD$_3$OD)
$^1$H NMR spectrum of 5 (400 MHz, D$_2$O)
$^{13}$C NMR spectrum of 5 (101 MHz, D$_2$O)
$^1$H NMR spectrum of 6 (400 MHz, D$_2$O)
$^{13}$C NMR spectrum of 6 (101 MHz, D$_2$O)
$^1$H NMR spectrum of 7 (400 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of 7 (101 MHz, CDCl$_3$)
$^1$H NMR spectrum of 8 (400 MHz, CDCl$_3$)
$^{13}$C NMR spectrum of 8 (400 MHz, CDCl$_3$)
$^1$H NMR spectrum of 9a (400 MHz, d$_6$-DMSO)
\textsuperscript{13}C NMR spectrum of 19a (101 MHz, d\textsubscript{6}-DMSO)
$^1$H NMR spectrum of 9b (400 MHz, DMSO-$d_6$)
$^{13}$C NMR spectrum of 9b (100 MHz, DMSO-$d_6$)
$^1H$ NMR spectrum of 10 (400 MHz, D$_2$O)
\(^{13}\)C NMR spectrum of \(10 \) (101 MHz, D\(_2\)O)
$^1$H NMR spectrum of 11 (400 MHz, DMSO-$d_6$)
$^{13}$C NMR spectrum of 11 (100 MHz, DMSO-$d_6$)
S5. Crystallographic data for 1

Crystal Data for C_{12}H_{27}NO_{3}S (M = 265.40 g/mol): trigonal, space group R3c (no. 161),

\[ a = 14.3352(2) \ \text{Å}, \ c = 12.2455(2) \ \text{Å}, \ V = 2179.28(8) \ \text{Å}^3, \ Z = 6, \ T = 100.01(10) \ \text{K}, \ \mu(\text{CuK} \alpha) = 1.969 \ \text{mm}^{-1}, \ D_{\text{calc}} = 1.213 \ \text{g/cm}^3, \]

8776 reflections measured (16.14° ≤ 2Θ ≤ 147.692°), 977 unique (\( R_{\text{int}} = 0.0273, \ R_{\sigma} = 0.0115 \)) which were used in all calculations. The final \( R_1 \) was 0.0209 (I > 2σ(I)) and \( wR_2 \) was 0.0570 (all data).

The dataset was measured on an Agilent SuperNova diffractometer using an Atlas detector. The data collection was driven and processed and an absorption correction was applied using CrysAlisPro. The structure was solved using ShelXT and was refined by a full-matrix least-squares procedure on \( F^2 \) in ShelXL. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (\( U_{eq} \)) of the parent atom. Figures and reports were produced using OLEX2.

The structure occupies a chiral space group and the absolute structure has been determined from the diffraction data, with the Flack parameter being -0.007 (8). The molecule lies on a 3-fold rotation axis running through N(1) and S(1) such that the butyl groups are all symmetrically equivalent.

The CIF for the crystal structures of 1 has been deposited with the CCDC and has been given the deposition number: CCDC 1894165.

Figure S1: Crystal structure of compound 1 with ellipsoids drawn at the 50 % probability level. The molecule lies on a 3-fold rotation axis running through N(1) and S(1) such that the butyl groups are all symmetrically equivalent. Symmetry codes used to generate equivalent atoms: $1, y-x, 1-x, z, $2, 1-y, 1+x-y, z
S6. References


