Synthesis of Diaryl Hydroxyl Dicarboxylic Acids from Amino Acids

Aleksi E. K. Eronen, Jere K. Mannisto, Karina Moslova, Martin Nieger, Eeva Heliövaara and Timo Repo*

Address: A.I. Virtasen aukio 1, 00014, Helsinki, Finland
Department of Chemistry, University of Helsinki
*email: timo.repo@helsinki.fi

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1 Work safety

Sodium hydroxide (NaOH) at the applied microwave conditions (approximately ~5 bars of pressure) unavoidably dissolve some glass. We did approximately 2000 reactions from which few microwave vials broke during the heating program (Fig. S1). The breaks typically happen during the pressure build-up and will cause small glass shards to fly at a very high speed. We highly recommend to do all these experiments with an appropriate microwave equipment instead of an oil bath due to the pressure build-up and possible glassware failure.

![Broken microwave glassware after eruption. Glass can give in earlier than the caps.](image)

Figure S1

2 Optimization

Method 1 and 2 were optimized to reach the maximum yield and purity of diacid 1. In the graphs, lighter blue refers to pure product and darker blue to product containing impurities. All of the 13 diacids were synthesized with both of the reported methods. When using tert-butanol as a co-solvent, more product 1 was isolated (Method 2).

2.1 Optimization of Method 1

Optimized conditions for Method 1 (M1)

Amino acid (3 mmol) was dissolved into NaOH solution (4.5 mmol, 0.9 ml, 5M) and the solution was placed at microwave vial (10 ml). Next, the corresponding primary alcohol (4.1 ml) was added together with aromatic aldehyde (6 mmol) to the same microwave vial. After stirrer insertion, the vial was capped. The reaction mixture was heated as follows: Heat as fast as possible to 135 °C and maintain heat for 90 minutes. Stirring speed was 600 rpm during the reaction. Pressure typically stays within 3 to 10 bars during the reaction (See Fig. S2). After the reaction, vial is cooled to 50 °C with compressed air. Crystals forms typically within couple of days. If crystals do not form, an addition of EtOH (2 to 3 ml) initiates the crystallization. The colorless crystals were filtered and washed with EtOH and air-dried. If needed, the products were recrystallized with a minimal amount of water and EtOH as an anti-solvent. Impurities, which do not dissolve to water, are filtered out before recrystallization. (Note: Products 3, 7 and 11 require different purification method. For more details, see manuscript experimental section).
Alternative workup: After completion of the reaction, evaporate all solvent in vacuum and wash with EtOH until only crude product is left. Recrystallize from water ethanol mixture.

Figure S2: Microwave heating profile of synthesis of 1 with method 1.

Figure S3: Crystal formation of product 1 on the left. Crystal formation of product 2 on the right.
**Figure S4**: The effect of temperature to the yield of 1. Reaction conditions: NaOH (4.0 mmol, 0.8 ml, 5M), EtOH (4.2 ml), benzaldehyde (6 mmol, 610 µL) and phenylalanine (3 mmol, 495.6 mg), reaction time 2h. 80 and 110 °C runs contained impurities (darker blue).

**Note**: Product 1 does not form at low temperatures. Product 1 is isolated at high purity when reaction is performed around 140 °C.

**Figure S5**: The effect of reaction time to the yield of 1. Reaction conditions: NaOH (4.0 mmol, 0.8 ml, 5M), EtOH (4.2 ml), benzaldehyde (6 mmol, 610 µL) and phenylalanine (3 mmol, 495.6 mg), temperature: 135 °C. 15, 45 and 60 min samples (dark blue) contained impurities.

**Note**: Product 1 forms quickly, but higher purity is achieved with longer reaction time.
Figure S6: The effect of the amount of 5M NaOH to the yield of 1. Reaction conditions: EtOH (5-x ml, x = the amount of NaOH solution as volume), benzaldehyde (6mmol, 610 µL), phenylalanine (3 mmol, 495.6 mg), Temperature: 135 °C, reaction time: 2h. 1 and 1.25 eq. runs contained impurities (darker blue).

Note: High NaOH concentration produced only minor amount of product 1.

Figure S7: Effect of the amount of benzaldehyde to the yield of 1. Reaction conditions: NaOH (4.0 mmol, 0.8 ml, 5M). EtOH (5.0 ml – x, x = volume of benzaldehyde), phenylalanine (3 mmol, 495.6 mg), temperature: 135 °C, reaction time: 2h. 2.6 and 3 eq. samples contained impurities (darker blue).

Note: Optimal amount of benzaldehyde is two equivalents (compared to amino acid).
2.2 Optimization of Method 2

Optimized conditions for Method 2 (M2)
Amino acid (2 mmol), NaOH solution (10 mmol, 1.0 ml, 10M) and tert-butanol/corresponding alcohol mixture (4.0 ml, 75%/25% v/v%) was added into microwave vial (10 ml) equipped with stirrer. Finally, aromatic aldehyde (10 mmol) is added to the same vial. (Note: After all reagents are added, the reaction mixture often becomes solid.) Fast heating during the microwave reaction may cause high pressure spikes when solids are turning into liquids. To avoid the pressure problems slow temperature build up is necessary. After capping the microwave vial it is heated to 135 °C in 5 minutes and maintained for 90 minutes. Stirring speed is 600 rpm during the reaction. Pressure typically stays within 3 to 10 bars during the reaction (See Fig. S8). Afterwards, the vial is cooled to 50 °C with compressed air. Isopropanol (2 ml) is added into the vial to initiate the crystallization. Typically powder like substance is observed after few hours. Next day the solid powder is filtered and washed with EtOH (expect the product 3, 7 and 11, see manuscript experimental section for more details). If needed recrystallize the product from small amount of water using ethanol as antisolvent.

![Figure S8: Microwave heating profile of the synthesis of 1 with method 2.](image-url)
**Figure S9**: Effect of the tert-butanol content vs yield of 1. Yields are calculated as averages from various tests with 3 or 4.5 eq. of NaOH and 3 or 4 eq. of benzaldehyde in each experiments. Reaction conditions: phenylalanine (2 mmol), tert-butanol/EtOH solution (4 ml), temperature program: 135 °C in 5 minutes and maintain for 90 minutes.

**Figure S10**: Benefits of additional benzaldehyde and NaOH for yield of 1 at 75% tert-butanol reaction solution. Optimal amount was 5 eq. for both reagents.
### 3 Yields of the products

**Table S1.** Formation of diacid salts from amino acids and aromatic aldehydes in alkaline alcohol solutions.

![Chemical structure](image)

| Entry / Product number | R\textsuperscript{1} from amino acid | R\textsuperscript{2} from aldehyde | R\textsuperscript{3} from alcohol | Isolated yield (%)\(\textsuperscript{*}\) Method 1\(\textsuperscript{[a]}\) | Isolated yield (%)\(\textsuperscript{*}\) Method 2\(\textsuperscript{[b]}\) |
|------------------------|-------------------------------------|-----------------------------------|---------------------------------|-------------------------------|-------------------------------|
| 1                      | ![Chemical structure](image)         | ![Chemical structure](image)      | -H                              | 22                            | 77                            |
| 2                      | ![Chemical structure](image)         | ![Chemical structure](image)      | -H                              | 18                            | 68                            |
| 3                      | ![Chemical structure](image)         | ![Chemical structure](image)      | -H                              | 13                            | 20                            |
| 4                      | ![Chemical structure](image)         | ![Chemical structure](image)      | -H                              | 20                            | 74                            |
| 5                      | ![Chemical structure](image)         | ![Chemical structure](image)      | -H                              | 6                             | 34                            |
| 6                      | ![Chemical structure](image)         | ![Chemical structure](image)      | -H                              | 8                             | 43                            |
| 7                      | ![Chemical structure](image)         | ![Chemical structure](image)      | -H                              | 3                             | 26                            |
| 8                      | ![Chemical structure](image)         | ![Chemical structure](image)      | -H                              | 20                            | 49                            |
| 9                      | ![Chemical structure](image)         | ![Chemical structure](image)      | -H                              | 10                            | 41                            |
| 10                     | ![Chemical structure](image)         | ![Chemical structure](image)      | -CH\textsubscript{3}            | 15                            | 53                            |
| 11                     | ![Chemical structure](image)         | ![Chemical structure](image)      | -CH\textsubscript{2}CH\textsubscript{3} | <1                            | 22                            |
| 12                     | ![Chemical structure](image)         | ![Chemical structure](image)      | ![Chemical structure](image)    | 21                            | 53                            |
| 13                     | ![Chemical structure](image)         | ![Chemical structure](image)      | ![Chemical structure](image)    | N.R.                          | 18                            |

\(\textsuperscript{*}\)Products were washed with EtOH and weighted after drying at air. N.R. = no reaction. 
\[\textsuperscript{[a]}\] Reaction conditions: amino acid (3 mmol), NaOH (4.5 mmol, 5M at H\textsubscript{2}O solution), aromatic aldehyde (6.0 mmol) and corresponding alcohol (4.1 ml), 135 °C (approx. 5 bars of pressure), 90 min at microwave vial. 
\[\textsuperscript{[b]}\] Reaction conditions: amino acid (2.0 mmol), NaOH (10 mmol, 10M at H\textsubscript{2}O solution), aromatic aldehyde (10 mmol), 75%/25% v/v tert-butanol/corresponding alcohol solution (4 ml), microwave vial was heated to 135 °C over 5 min and kept at 135 °C for 90 min.
4 X-ray diffraction

4.1 Crystal Structure Determination of 1 and 2

The single-crystal X-ray diffraction study were carried out on a Bruker D8 Venture diffractometer with PhotonII CPAD detector at 123(2) K using Cu-Kα radiation (λ = 1.54178 Å). Dual space methods (SHELXT) [G. M. Sheldrick, Acta Crystallogr. 2015, A71, 3-8] were used for structure solution and refinement was carried out using SHELXL-2014 (full-matrix least-squares on F²) [G. M. Sheldrick, Acta Crystallogr. 2015, C71, 3-8]. Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(N, O) free). Semi-empirical absorption corrections were applied.

1: colourless crystals, C₁₈H₂₄Na₂O₉·H₂O, Mᵣ = 448.37, crystal size 0.16 × 0.08 × 0.04 mm, triclinic, space group P-1 (No. 2), a = 6.2002(2) Å, b = 8.7727(3) Å, c = 19.3378(7) Å, α = 101.692(1)°, β = 93.848(1)°, γ = 90.292(1)°, V = 1027.50(6) Å³, Z = 2, ρ = 1.449 Mg/m⁻³, μ(Cu-Kα) = 1.35 mm⁻¹, F(000) = 472, 2Θmax = 144.2°, 16265 reflections, of which 4036 were independent (Rint = 0.023), 304 parameters, 71 restraints, R₁ = 0.029 (for 3895 I > 2σ(I)), wR₂ = 0.075 (all data), S = 1.06, largest diff. peak / hole = 0.33 / -0.40 e Å⁻³.

2: colourless crystals, C₂₀H₂₃Na₂O₈, Mᵣ = 451.37, crystal size 0.18 × 0.08 × 0.04 mm, monoclinic, space group P2₁/n (No. 14), a = 6.2535(2) Å, b = 38.0761(13) Å, c = 9.2033(3) Å, β = 109.594(1)°, V = 2064.49(12) Å³, Z = 4, ρ = 1.452 Mg/m⁻³, μ(Cu-Kα) = 1.30 mm⁻¹, F(000) = 944, 2Θmax = 144.4°, 24450 reflections, of which 4073 were independent (Rint = 0.026), 304 parameters, 11 restraints, R₁ = 0.032 (for 3960 I > 2σ(I)), wR₂ = 0.081 (all data), S = 1.09, largest diff. peak / hole = 0.35 / -0.23 e Å⁻³.

CCDC 1948055 (1), and 1948056 (2) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.2 Single crystal growing

Single crystals were grown by dissolving the products 1 and 2 to water. Ethanol was added as anti-solvent until the point of precipitation was reached. Couple extra drops of water were added and solutions were kept in closed vials at RT. After three months, the single crystals were collected and crystal structure was determined by X-ray diffraction. (Note: the products are easy to crystallize from water-ethanol solution, but growth of single crystals demands a slow growing process).
## 5 ESI-TOF-MS parameters

### Table S2: Reagents and instruments for ESI-TOF-MS measurements

| Name                              | Purity                      | Manufacture/model                          |
|-----------------------------------|-----------------------------|--------------------------------------------|
| Water purification system         |                             | Millipore, Direct-Q 3 UV                   |
| Vortexer                          |                             | Scientific Industries                      |
| Analytical balance                |                             | Sartorius BP 301 S                         |
| Bruker MicroTOF                   |                             | Bruker Daltonics                           |
| Syringe pump                      |                             |                                            |
| Syringe, 1 mL                     |                             | Hamilton                                   |
| Biohit Pipette                    |                             | Biohit proline                             |
| Propan-2-ol                       | HPLC-grade                  | Fisher Scientific, UK                      |
| Methanol                           | 99,9 % Gradient grade       | VWR Chemicals, France                      |
| Acetonitrile                      | >99,9 % Gradient grade      | Honeywell, Riedel-de Haën,                 |
| Sodium hydroxide, 0.1 M           | (0,10013 +/-0,00073) mol L⁻¹ | Oy FF-Chemicals Ab                         |
| Formic acid                       | Suprapur, 98-100%           | Merck, Darmstadt, Germany                  |
| Acetone                            | HPLC, >99.9%                | Sigma Merck, 34850                         |

### Table S3: Example parameters at positive-ion mode:

| Name        | Value                         |
|-------------|-------------------------------|
| End Plate Offset | -1000 V          |
| Capillary Exit | 90 V                          |
| Skimmer 1    | 30,0 V                        |
| Mass Range   | 50-1000 m/z                   |
| Rollin Average | 10 x 1,1 Hz                  |
| Capillary    | -5000 V                       |
| Hexapole 1   | 25,1 V                        |
| Skimmer 2    | 21,2 V                        |
| Dry Gas      | 6,0 L min⁻¹                   |
| Transfer time | 8,0 µs                       |
| Pre Puls Storage | 1,0 µs              |
| Dry Temp     | 250 °C                        |
| Lens 1 Storage | 15,5 V                      |
| Lens 1 Extraction | 33,0 V               |
| Lens 2       | 5,0 V                         |
| Lens 3       | 20,0 V                        |
| Lens 4       | 0,5 V                         |
| Lens 5       | 5,5 V                         |
| Detector     | -1000 V                       |
Table S4: Example parameters at negative-ion mode:

| Parameter          | Value                       |
|--------------------|-----------------------------|
| End Plate Offset   | -1000 V                     |
| Capillary Exit     | -90 V                       |
| Skimmer 1          | -30,0 V                     |
| Positive Ion Polarity | Mass Range 100-1300 m/z    |
| Capillary Exit     | -5000 V                     |
| Hexapole 1         | -25,1 V                     |
| Skimmer 2          | -21,2 V                     |
| Nebulizer          | 0,7 bar                     |
| Hexapole 2         | -19,5 V                     |
| Hexapole RF        | 90,0 Vpp                    |
| Dry Gas            | 6,0 L min⁻¹                 |
| Transfer time      | 3,0 µs                      |
| Pre Puls Storage   | 1,0 µs                      |
| Dry Temp           | 250 °C                      |
| Lens 1 Storage     | -18,4 V                     |
| Lens 1 Extraction  | -21,9 V                     |
| Lens 2             | -5 V                        |
| Lens 3             | 31,0 V                      |
| Lens 4             | 5 V                         |
| Lens 5             | 33,6 V                      |
| Detector           | 0 V                         |

The instrument was calibrated with sodium formate. The stock solution (1000 ppm) was prepared by 0.05% formic acid / MeOH (70/30 v/v%), from which 1 ppm solution was prepared.
6 Spectroscopic data of diacid salts

6.1 Product 1

1D NMR of 1:

Figure S11: $^1$H NMR spectrum of 1 (500 MHz, D$_2$O).
Figure S12: $^{13}$C($^1$H) NMR spectrum of 1 (125 MHz, D$_2$O).
2D NMR of 1:

Figure S13: HSQC spectra of 1 (full area, NMR solvent: D$_2$O)
Figure S14: HSQC of 1 (aliphatic area, NMR solvent: D$_2$O). Blue is negative phase indicating -CH$_2$- group with non-equivalent protons.
Figure S15: HMBC spectra of 1 (full area, NMR solvent: D$_2$O).
Figure S16: HMBC spectra of 1 (aliphatic area, NMR solvent: D$_2$O).
2D NMR Explanation: Protons H1 and H2 are connected to C1 forming CH$_2$ group. The group has connectivity to aliphatic carbons C2 and C3. The group has connectivity to aromatic carbon C6. The group has connectivity to acid carbon C8.

Proton H3 is attached to carbon C3 forming CH group. The group has connectivity to aliphatic carbons C2 and C4. The group has connectivity to aromatic carbon C5 and weaker C6. The group also sees inside the phenyl ring of C5, suggesting a neighboring position.

Proton H4 is attached to carbon C2 forming CH group. This group is connected strongly to carbon C1, C3 and weakly to C4. The group has strong connectivity to aromatic carbon C6 and weaker to C5. This group also see inside the phenyl ring C6, suggesting a neighboring position. The group has weak connectivity to acid carbon C8.

Proton H5 is attached to Carbon C4 forming CH group. The group has connectivity to aliphatic carbons C3 and weaker to C2. The group has connectivity to aromatic carbon C5. The group is only one with connectivity to acid carbon C7.

![Figure S17: 2D NMR explanation for product 1.](image)

UV-vis spectrum of 1:

![UV-vis spectrum of compound 1](image)

*Figure S18: UV-vis spectrum of 1 (MilliQ water): 224 nm (shoulder), 258 nm (max), 265 nm (shoulder).*
Infrared spectrum of 1:

Figure S19: IR spectrum for product 1 (3000 – 3500 (-OH, broad), 1573 (R-COONa, s), 1395 (R-OH, s), 1074 (R-C(OH)-R, m), 698 (Ph, s)).
HRMS spectra of 1:

HRMS (ESI-TOF) m/z: [1+H₂+Na]⁺ Calcd for C_{28}H_{38}O₃Na 337.1046; Found 337.1046; Error: 0.215 ppm

Figure S20: ESI-TOF-MS of [1+H₂+Na]⁺ (peak: 337.1046 m/z, positive-ion mode).

Figure S21: Zoomed ESI-TOF-MS measurement of [1+H₂+Na]⁺ (peak 337.1046 m/z, positive-ion mode).

Figure S22: Measured compound peak of [1+H₂+Na]⁺ (337.1046 m/z, positive-ion mode) at top, simulated peak (C_{28}H_{38}O₃Na) below.
6.2 Product 2

1D NMR of 2:

Figure S23: $^1$H NMR of 2 (500 MHz, D$_2$O).
Figure S24: $^{13}$C(1H) NMR spectrum of 2 (125 MHz, D$_2$O).
Figure S25: $^{13}$C NMR spectrum of 2 from aromatic region (125 MHz, D$_2$O).
2D NMR of 2:

Figure S26: HSCQ spectrum of 2 (full area, NMR solvent: D₂O). Blue color means negative phase. (There is CH₂ group with non-equivalent protons).
Figure S27: HSQC spectrum for 2 (aliphatic area, NMR solvent: D$_2$O).
Figure S28: HMBC spectra of 2 (full area, NMR solvent: D$_2$O).
Figure S29: HMBC spectrum of 2 (aliphatic area, NMR solvent: D$_2$O).
2D NMR Explanations: Protons H1 and H2 are attached to carbon C1 forming CH₂ group. The group has connectivity to aliphatic carbons C2 and C3. The group has connectivity to aromatic carbon C6. The group has strong connectivity to acid carbon C8.

Proton H3 is attached to carbon C2 forming CH group. Due to the carbons C2 and C3 being so close each other it is hard to tell them apart, nevertheless very accurate analysis of HSQC spectrum suggests proton H3 is attach to carbon C2. The group has connectivity at aliphatic region to C3, C1 and weakly to C4. The group has connectivity to aromatic carbon C5 and stronger to C6 carbon. The group sees inside the phenyl of aromatic carbon of C6, suggesting a neighboring position. The group has also connections to acid carbon C8.

Proton H4 is attached to carbon C3 forming CH group. The group has connectivity at aliphatic region to C2 and weak connectivity to C4. Group has strong connectivity to aromatic carbon C5 and has connections to inside of the indole group suggesting it being neighboring group. The CH group has weak connectivity to the aromatic carbon C6.

Proton H5 is attached to carbon C4 forming CH group. The group has connectivity at aliphatic region to C3. The group has connectivity to indole carbon C5 suggesting it to be nearby. The CH group is the only group having connectivity with acid carbon C7 suggesting it being the neighboring group of it.

**Figure S30**: 2D NMR explanation for the product 2.

**UV-vis spectrum of 2**:

![UV-vis spectrum](image)

*Figure S31*: UV-vis spectrum of 2 (MilliQ water): 229 nm (shoulder), 282 nm (max) and 291 nm (shoulder).
Infrared spectrum of 2:

Figure S32: IR spectrum for product 2 (3000 – 3800 (-OH, -N-H, broad), 1670 (N-H, m), 1574 (R-COONa, s), 1384 (R-OH, s), 1274 (C-N, m), 1083 (R-C(OH)-R, s), 704 (Ph, s)).
HRMS spectra of 2:

HRMS (ESI-TOF) m/z: [2+H₂+Na]⁺ Calcd for C₂₀H₁₉NO₃Na 376.1155; Found: 376.1147; Error 2.201 ppm

*Figure S33*: ESI-TOF-MS of [2+H₂+Na]⁺ (peak: 376.1147 m/z, positive-ion mode).

*Figure S34*: Zoomed ESI-TOF-MS measurement of [2+H₂+Na]⁺ (peak 376.1147 m/z, positive-ion mode).

*Figure S35*: Measured compound peak of [2+H₂+Na]⁺ (376.1147 m/z) at top, simulated peak (C₂₀H₁₉NO₃Na) below.
6.3 Product 3

1D NMR of 3:

Figure S36: $^1$H NMR spectrum of 3 (500 MHz, D$_2$O). Very persistent impurity at 1.2 ppm.
Figure S37: $^{13}$C{H} NMR spectrum of 3 (125 MHz, D$_2$O).
2D NMR of 3:

Figure S38: HSQC spectrum of 3 (full area, NMR solvent: D$_2$O).
Figure S39: HMBC spectrum of 3 (full area, NMR solvent: D₂O).
Figure S40: HMBC spectrum of 3 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Protons H1 and H2 are attached to C1 forming CH₂ group. The group has connectivity to aliphatic carbons C2 and C3. The group also has connectivity to aromatic carbon C7. The group has strong connectivity to acid carbon C10. Suggesting the group being next to the acid group.

Proton H3 is attached to carbon C3 forming CH group. The CH group has connectivity to aliphatic carbons C2 and C4. The group has strong connectivity to aromatic carbon C6 of phenol group, suggesting neighboring position of phenol group. The group has no connectivity to acid carbons.

Proton H4 is attached to carbon C2 forming CH group. The group has connectivity to aliphatic carbons C1 and C3 and weak connectivity to C4. The group has strong connectivity to aromatic carbon C7 and sees inside of it, suggesting the group being next to the phenyl group. The group has weak connectivity to acid carbon C10.

Proton H5 is attached to carbon C4 forming CH group. The group has connectivity to aliphatic carbon C3. The group has also connectivity aromatic carbon C6 of the phenol group. The group is only one with connectivity to acid carbon C9, suggesting it being neighboring group.

Aromatic carbon H6 is attached to aromatic carbon C5 forming aromatic CH groups. The group has connectivity at aromatic region to C8 and C6. This group is part of the phenolic aromatic group.

![2D NMR explanation of product 3](image)

**Figure S41**: 2D NMR explanation of product 3.

**UV-vis spectrum of 3**:

![UV-vis spectrum of 3](image)

**Figure S42**: UV-vis spectrum of 3 (MilliQ water): 298 nm (Max) and 331 nm (shoulder).
Infrared spectrum of 3:

Figure S43: IR spectrum for product 3 (2800 – 3500 (-OH, broad), 1556 (-COO, s), 1371 (s), 1248 (s), 700 (s) (Ph-OH), 1078 (R-HCOH-R (m)), 759 (m), 733 (m) (R-Ph 5H adjacent), 522 (w), 465 (s) (R-Ph-R (2H adjacent))).
HRMS spectra of 3:

HRMS (ESI-TOF) m/z: [3+H]⁺ Calcd for C₁₈H₁₇O₆ 329.1020; Found 329.1026; Error 1.967 ppm.

**Figure S44**: ESI-TOF-MS of [3+H]⁺ (peak: 329.1026 m/z, negative-ion mode).

**Figure S45**: Measured compound peak of [3+H]⁺ (329.1026 m/z) at top, simulated peak (C₁₈H₁₇O₆) below.
6.4 Product 4

1D NMR of 4:

*Figure S46: $^1$H NMR spectrum of 4 (500 MHz, D$_2$O).*
Figure S47: $^{13}$C($^1$H) NMR spectrum of 4 (125 MHz, D$_2$O).
Figure S48: HSQC spectrum of 4 (full area, NMR solvent: D$_2$O). H2 and H3 are attached to C2 forming CH$_3$ group.
Figure S49: HMBC spectrum of 4 (full area, NMR solvent: D$_2$O).
Figure S50: HMBC spectrum of 4 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Protons H1 are attached to C1 forming CH$_3$ group. The group has connectivity to aromatic carbon C6, suggesting it being part of toluene group.

Protons H2 and H3 are attached to carbon C2 forming CH$_2$ group. The group has connectivity to aliphatic carbons C3 and C4. The group has also connectivity to aromatic carbon C8. The group has strong connectivity to acid carbon C10 suggesting it to be next to it.

Proton H4 is attached to carbon C4 forming CH group. The group has connectivity to aliphatic carbons C3 and C5. The group has also connectivity to aromatic carbon C7 and inside the phenyl group suggesting it to be next to the phenyl group.

Proton H5 is attached to carbon C3 forming CH group. The group has connectivity to aliphatic carbons C2, C4 and C5. The group has strong connectivity to aromatic carbon C8 and inside to the phenyl group similar to the methyl group (C1/H1), suggesting the group to be next to the methylated phenyl group. The group has also connectivity to acid carbon C10.

Proton H6 is attached to carbon C5 forming CH group. The group has connectivity to aliphatic carbons C3 and C4. The group has also connectivity to aromatic carbon C7. The group is the only one with connectivity to acid carbon C9, suggesting it to be next to it.

![Figure S51: 2D NMR Explanation of product 4.](image)

**UV-vis spectrum of 4:**

![Figure S52: UV-vis spectrum of 4 (MilliQ water): max: 258 nm, 265 nm and 274 nm shoulder: 321 nm and 334 nm.](image)
Infrared spectrum of 4:

Figure S53: IR spectrum of product 4 (2800 – 3200 (-OH, broad), 1612, 1543 (R-COONa, s), 1370 (R-OH, s, R-CH₃, s), 1093 (R-CH(OH)-R, m), 825 (2 adjacent H, Ph, w), 731 (m), 703 (s) (5 adjacent H, Ph)).
HRMS spectra of 4:

HRMS (ESI-TOF) m/z: [4+H₂+Na]⁺ Calcd for C₁₉H₂₀O₅Na 351.1203; Found 351.1203; Error 0.080 ppm.

Figure S54: ESI-TOF-MS of [4+H₂+Na]⁺ (peak: 351.1203 m/z, positive-ion mode).

Figure S55: Zoomed ESI-TOF-MS measurement of [4+H₂+Na]⁺ (peak: 351.1203 m/z, positive-ion mode).

Figure S56: Measured compound peak of [4+H₂+Na]⁺ (351.1203 m/z) at top, simulated peak (C₁₉H₂₀O₅Na) below.
6.5 Product 5

1D NMR of 5:

*Figure S57: $^1$H NMR spectrum of 5 (500 MHz, D$_2$O).*
Figure S58: $^{13}$C($^1$H) NMR spectrum of 5 (125 MHz, D$_2$O) C1 and C2 carbons are heavily overlapping.
Figure S59: HSQC spectrum of 5 (full area, NMR solvent: D$_2$O).
Figure S60: HMBC spectrum of 5 (full area, NMR solvent: D$_2$O).
Figure S61: HMBC spectrum of 5 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Protons H1 and H2 are attached to carbon C1 forming CH₂ group. The group has connectivity to aliphatic carbons C2 and C3. The group have connectivity to aromatic carbon C7. The group has strong connectivity to acid carbon C11, suggesting it to be next to it.

Proton H3 is attached to carbon C3 forming CH group. The group has connectivity to aliphatic carbons C2 or/and C1 (heavy overlapping, hard to tell) and C5. The group has connectivity to aromatic carbon C8 and weakly C7. The group has connectivity to inside of the phenyl, suggesting neighboring position.

Proton H4 is attached to carbon C2 forming CH group. The group has connectivity to aliphatic carbons C1, C3 and C5. The group has connectivity to aromatic carbons C7 and weak connectivity to C8, suggesting group to be next to phenyl group. Group has weak connectivity to acid carbon C11.

Protons H5 are attached to carbon C4 forming CH₃ group. The group has no aliphatic connections. The group is connected to aromatic carbon C9, suggesting it being part of the anisaldehyde methoxy group.

Proton H6 is attached to carbon C5 forming CH group. The group has connectivity to aliphatic carbons C2 and C3. The group has connectivity to aromatic carbon C8. The group is the only one with connectivity to acid carbon C10, suggesting neighboring position of it.

Proton H7 is attached to carbon C6 forming two aromatic CH groups. The groups have connectivity to aromatic carbons C7, C9. Group is part of the methoxy benzaldehyde group.

![Figure S62: 2D NMR explanation for product 5.](image)

**UV-vis spectrum of 5:**

![Figure S63: UV-vis spectrum of 5 (MilliQ water): 275 (max) and 296 nm (shoulder).](image)
Infrared spectrum of 5:

Figure S64: IR spectrum for product 5 (2800 – 3500 (OH, broad) 1612, 1555 (R-COONa, s), 1371 (CH₃, s), 1249 (OH, s) 1027 (R-CH(OH)-R, m), 834 (2 adjacent H (Ph), m), 704 (5 adjacent H (Ph), s)).
HRMS spectra of 5:

HRMS (ESI-TOF) m/z: [5+H₂+Na]⁺ Calcd for C_{29}H_{30}O_{6}Na 367.1152; Found 367.1167; Error -3.976 ppm.

Figure S65: ESI-TOF-MS of [5+H₂+Na]⁺ (peak: 367.1167 m/z, positive-ion mode).

Figure S66: Zoomed ESI-TOF-MS measurement of [5+H₂+Na]⁺ (peak 367.1167 m/z, positive-ion mode).

Figure S67: Measured compound peak of [5+H₂+Na]⁺ (367.1167 m/z) at top, simulated peak (C_{13}H_{20}O_{6}Na) below.
6.6 Product 6

1D NMR of 6:

Figure S68: $^1$H NMR spectrum of 6 (500 MHz, $D_2O$).
Figure S69: $^{13}$C($^1$H) NMR spectrum of 6 (125 MHz, D$_2$O).
2D NMR of 6:

Figure S70: HSQC spectrum of 6 (full area, NMR solvent: D_2O). H1 and H2 are attached to C1 forming CH_2 group.
Figure S71: HMBC spectrum of 6 (full area, NMR solvent: D$_2$O).
Figure S72: HMBC spectrum of 6 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Protons H1 and H2 are attached to carbon C1 forming CH₂ group. The group has connectivity with aliphatic carbons C2 and C3. The group has connectivity with aromatic carbon C6. The group has connectivity with acid carbon C8.

Proton H3 is attached to carbon C3 forming CH group. The group has connectivity at aliphatic region to C2 and C4. The group has connections to aromatic carbon C5 and weaker to C6, also the group has connectivity to inside the non-substituted phenyl group suggesting it being the neighboring group of it.

Proton H4 is attached to carbon C2 forming CH group. It has connectivity at aliphatic region to C1, C3 and weak connectivity to C4. The group has strong connectivity to aromatic carbon C6 and sees inside of the substituted aromatic group, suggesting it being neighbor of it. The group also has also weak connectivity to aromatic carbon C5. The HC group has also weak connectivity to C8 acid carbon.

Proton H5 is attached to carbon C4 forming CH group. The group has connectivity at aliphatic region to C3 and C2. The group has connectivity to non-substituted aromatic carbon C5, suggesting it to be nearby. The group is the only one with connectivity to acid carbon C7, suggesting it being the neighboring group of it.

![Diagram](image)

**Figure S73:** 2D NMR explanation for product 6.

**UV-vis spectrum of 6:**

![Graph](image)

**Figure S74:** UV-vis spectrum for 6 (MilliQ water): 257 nm (max), 260 nm (max) and 278 nm (shoulder).
**Infrared spectrum of 6:**

*Figure S75: IR spectrum for product 6. (2800 – 3500 (-OH, broad), 1614, 1556 (R-COONa, s), 1370 (R-CH(OH)-R, s), 1093 (Ar-Cl / R-CH(OH)-R), s), 829 (2 adjacent H (Ph), m), 702 (5 adjacent H (Ph), s)).*
HRMS spectra of 6:

HRMS (ESI-TOF) m/z: [6+H₂+Na]⁺ Calcd for C₃₈H_{17}ClO₃Na 371.0657; Found 371.0654; Error 0.713 ppm.

**Figure S76**: ESI-TOF-MS of [6+H₂+Na]⁺ (peak: 371.0654 m/z, positive-ion mode).

**Figure S77**: Zoomed ESI-TOF-MS measurement of [6+H₂+Na]⁺ (peak: 371.0654 m/z, positive-ion mode).

**Figure S78**: Measured compound peak of [6+H₂+Na]⁺ (371.0654 m/z) at top, simulated peak (C₂₈H₁₇ClO₃Na) below.
6.7 Product 7

1D NMR of 7:

Figure S79: $^1$H NMR spectrum of 7 (500 MHz, D$_2$O).
Figure S80: $^{13}$C$^{[1]}$H NMR spectrum of 7 (125 MHz, D$_2$O). F atom causes few carbon signals to split at phenyl group, thus some carbon peaks are double such as: C12, C11, C9, C5.
Figure S81: $^{19}$F NMR spectrum of 7 (470 MHz, D$_2$O).
Figure S82: HSQC spectrum of 7 (full area, NMR solvent: D₂O).
Figure S83: HMBC spectrum of 7 (full area, NMR solvent: D₂O).
Figure S84: HMBC spectrum of 7 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Protons H1 and H2 are attached to carbon C1 forming CH₂ group. The group has connectivity to aliphatic carbons C2 and C3. The group has connectivity to aromatic carbon C11. The group has also connectivity to acid carbon C14.

Proton H3 is attached to carbon C3 forming CH group. The group has connectivity at aliphatic region to carbon C2 and very weak C4. The group has connectivity to aromatic carbon C10 and C8, thus suggesting it neighboring the non-substituted phenyl. The group has no connectivity to acid carbons.

Proton H4 is attached to carbon C2 forming CH group. The group has connectivity to aliphatic carbons C1, C3 and weak C4. The group has connectivity to aromatic carbons C11 and C9, suggesting the group being neighbor of the substituted phenyl group. The group has also connectivity to acid carbon C14.

Proton H5 is attached to carbon C4 forming CH group. The group has connectivity to aliphatic carbons C3 and weak C2. The group has connectivity to aromatic carbon C10. The group is only one with connectivity to acid carbon C13.

**Figure S85**: 2D NMR explanation of product 7.

**UV-vis spectrum of 7:**

![UV-vis spectrum of compound 7](image)

**Figure S86**: UV-vis spectrum of 7 (MilliQ water): 289 nm (max) and 298 nm (shoulder). Note: high baseline due high concentration of 7.
Infrared spectrum of 7:

Figure S87: IR spectrum for product 7 (2800 – 3500 (–OH, broad), 1605 (m), 1552 (m), 1390 (m) (-COONa) 1220 (m), 1100 (w) (R-CHOH-R), 839 (w), 791 (w) (R-Ph-R (2H adjacent)), 761 (w), 728 (w), 705 (m) (R-Ph (5H adjacent)), 663 (m), 523 (s) (C-F)).
HRMS spectra of 7:

HRMS (ESI-TOF) m/z: [7+H] Calcd for C_{18}H_{16}FO_5 331.0976; Found 331.0976; Error 0.202 ppm.

Figure S88: ESI-TOF-MS of [7+H] (peak: 331.0976 m/z, negative-ion mode).

Figure S89: Measured compound peak of [7+H] (331.0976 m/z) at top, simulated peak (C_{18}H_{16}FO_5) below.
6.8 Product 8

1D NMR of 8:

Figure S90: $^1$H NMR spectrum of 8 (500 MHz, D$_2$O).
Figure S91: $^{13}$C($^1$H) NMR spectrum of 8 (125 MHz, D$_2$O).
Figure S92: HSQC spectrum of 8 (full area, NMR solvent: D$_2$O).
Figure S93: HMBC Spectrum of 8 (full area, NMR solvent: D$_2$O).
Figure S94: HMBC spectrum of 8 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Protons H1 are attached to carbon C1 forming CH$_3$ group. The group has no connectivity at aliphatic region. The group has connectivity at aromatic region to carbons C7 and has connectivity inside the substituted aromatic phenyl group.

Protons H2 and H3 are attached to carbon C2 forming CH$_2$ group. The group has connectivity at aliphatic region to carbons C3 and C4. The group has also connectivity to aromatic carbon C9. The group has connectivity to acid carbon C11, suggesting it being next to it.

Proton H4 is attached to carbon C4 forming CH group. The group has connectivity to aliphatic carbons C3 and C5. The group has also connectivity to aromatic carbon C8 and weaker to C9, the group has connectivity inside the aromatic ring, suggesting it being next to that group.

Proton H5 is attached to C3 forming CH group. The group has connectivity at aliphatic region to carbons C2, C4 and weak C5. The group has also connectivity to aromatic carbons C9 and weaker C8, the group also has connectivity to inside the aromatic group suggesting it being next to it. The group also has weak connectivity to acid carbon C11.

Proton H6 is attached to carbon C5 forming CH group. The group has connectivity to aliphatic carbons C4 and C3. The group has also connectivity to aromatic carbon C8. The group is only one with connectivity to acid carbon C10, suggesting it being next to it.

![Figure S95: 2D NMR explanation for product 8.](image)

**UV-vis spectrum of 8:**

![UV-vis spectrum of compound 8](image)

*Figure S96: UV-vis spectrum of 8 (MilliQ water): 258 nm (max), 265 nm (max) and 272 nm (shoulder).*
Infrared spectrum of 8:

Figure S97: IR spectrum for product 8 (1610, 1572, 1402 (R-COONa, s), 1376 (CH₃, s), 1102 (R-CH(OH)-R), m), 758 (3 adjacent H (Ph), m), 694 (5 adjacent H (Ph), s)).
Mass spectrometry for product 8:

HRMS (ESI-TOF) m/z: [8+H₂+Na]⁺ Calcd for C₁₉H₂₀O₅Na 351.1203; Found 351.1209; Error -1.694 ppm.

Figure S98: ESI-TOF-MS of [8+H₂+Na]⁺ (peak: 351.1209 m/z, positive-ion mode).

Figure S99: Measured compound peak of [8+H₂+Na]⁺ (351.1209 m/z) at top, simulated peak (C₁₉H₂₀O₅Na) below.
6.9 Product 9

1D NMR of 9:

Figure S100: $^1$H NMR spectrum of 9 (500 MHz, D$_2$O) H2 should be dd, but due the J values it looks like t.
Figure S101: $^{13}$C(H) NMR spectrum of 9 (125 MHz, $D_2$O).
2D NMR of 9:

Figure S102: HSQC spectrum of 9 (full area, NMR solvent: D$_2$O).
Figure S103: HMBC spectrum of 9 (full area, NMR solvent: D$_2$O).
Figure S104: HMBC spectrum of 9 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Protons H1 is attached to carbon C1 forming CH$_3$ group. The group has no connectivity at aliphatic region. The group has connectivity at aromatic region to carbon C8 and inside the aromatic ring, suggesting it being attached to the aromatic ring from ortho position.

Protons H2 and H3 are attached to carbon C3 forming CH$_2$ group. The group has connectivity to aliphatic carbons C2 and C4. The group has also connectivity to aromatic carbon C8. The group has connectivity to acid carbon C10.

Proton H4 is attached to carbon C4 forming CH group. The group has connectivity at aliphatic region to carbon C2. The group has connectivity to aromatic carbon C7 and inside the phenyl group, suggesting it being neighbor of the group.

Proton H5 is attached to carbon C2 forming CH group. The group has connectivity to aliphatic region carbons C3 and C4. The group has connectivity to aromatic carbon C8 and inside the substituted phenyl group, suggesting it being neighbor of it. The group has weak connectivity to acid carbon C10.

Proton H6 is attached to carbon C5 forming CH group. The group has connectivity to aliphatic carbons C4 and weak connectivity to C2. The group has connectivity to aromatic carbon C7. The group is only one with connectivity to acid carbon C9.

![Figure S105: 2D NMR explanation of product 9.](image)

**UV-vis spectrum of 9:**

![UV-vis spectrum for compound 9](image)

*Figure S106: UV-vis spectrum of 9 (MilliQ water): 259 nm (max), 265 nm (max) and 273 nm (shoulder).*
**Infrared spectrum of 9:**

**Figure S107:** IR spectrum for product 9 (3400-2800 (-OH, broad) 1614, 1604, 1401 (R-COONa, s), 1379 (-CH₃, m), 1102 (R-CH(OH)-R), m), 764 (4 adjacent H (Ph), m), 730, 702 (5 adjacent H (Ph), s)).
HRMS spectra of 9:

HRMS (ESI-TOF) m/z: [9+H₂+Na]⁺ Calcd for C_{19}H_{20}O_5Na 351.1203; Found 351.1208; Error -1.520 ppm.

Figure S108: ESI-TOF-MS of [9+H₂+Na]⁺ (peak: 351.1208 m/z, positive-ion mode).

Figure S109: Measured compound peak of [9+H₂+Na]⁺ (351.1208 m/z) at top, simulated peak (C_{19}H_{20}O_5Na) below.
6.10 Product 10

1D NMR of 10:

Figure S110: $^1H$ NMR spectrum of 10 (500 MHz, $D_2O$).
Figure S111: $^{13}$C{[H]} NMR spectrum of 10 (125 MHz, D$_2$O).
2D NMR of 10:

*Figure S112*: HSQC spectrum of 10. (full area, NMR solvent: D$_2$O). Only CH and CH$_3$ groups are observed.
Figure S113: HMBC spectrum of 10 (full area, NMR solvent: D$_2$O).
Figure S114: HMBC spectrum of 10 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Protons H1 are attached to carbon C1 forming CH$_3$ group. The group has connectivity to carbons C2, C3 and weaker C4. The group has connectivity to acid carbon C9.

Proton H2 is attached to carbon C2 forming CH group. The group has connectivity at aliphatic region to C1 and C3. Group has connection to aromatic carbon C7. The group has connectivity to acid carbon C9.

Proton H3 is attached to carbon C4 forming CH group. The group has connectivity at aliphatic region to C2, C3 and weak connectivity to C5. The group has strong connectivity to aromatic carbon C6 and has connections to inside of the substituted aromatic group suggesting it being neighbor of it.

Proton H4 is attached to carbon C3 forming CH group. The group has connectivity at aliphatic region to C1, C2, C4 and C5. The group has connectivity to aromatic carbon C7 suggesting it to be nearby, the group has also weaker connectivity to carbon C6. The CH group has connectivity with acid carbon C9.

Proton H5 is attached to carbon C5 forming CH group. The group has connectivity to carbon C4 at aliphatic region. It has connectivity to C6 at aromatic region. The group is the only one with connectivity to acid carbon C8.

*Figure S115*: 2D NMR explanation of product 10.

**UV-vis spectrum of 10:**

*Figure S116*: UV-vis spectrum of 10 (milliQ water): 259 nm (max) and 264 nm (max).
Infrared spectrum of 10:

Figure S117: IR spectrum for product 10 (2800 – 3500 (-OH, broad), 1593, 1537 (R-COONa, m), 1450 (R-CH₃, m), 1397 (R-CH(OH)-R, m), 1378 (R-CH₃, m), 1281, 1076 (R-CH(OH)-R, m), 699 (5 adjacent H (Ph), s)).
HRMS spectra of 10:

HRMS (ESI-TOF) m/z: [10+H₂+Na]^+ Calcd for C₁₉H₂₇O₅Na 351.1203; Found 351.1207; Error -1.016 ppm.
6.11 Product 11

1D NMR of 11:

Figure S121: $^1$H NMR spectrum of 11 (500 MHz, D$_2$O) H1 should be dd, but due J values it looks like t.
Figure S122: $^{13}$C[H] NMR spectrum of 11 (125 MHz, D$_2$O).
2D NMR of 11:

Figure S123: HSQC spectrum of 11 (full area, NMR solvent: D$_2$O). H2 and H3 are attached to C2 forming CH$_2$ group. H6 is attached to C3 and H5 is attached to C4.
Figure S124: HMBC spectrum of 11 (full area, NMR solvent: D$_2$O).
Figure S125: HMBC spectrum of 11 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Protons H1 are attached to carbon C1 forming CH$_3$ group. This group has connectivity with aliphatic carbons C2 and C5.

Protons H2 and H3 are attached to carbon C2 forming CH$_2$ group. The group has connectivity to aliphatic carbons C1, C5 and weak connectivity to C3. The group has also connectivity to acid carbon C10.

Proton H4 is attached to carbon C5 forming CH group. The group has connectivity to aliphatic carbons C1, C2, and C3 and weak connectivity to C4. The group also has connectivity to aromatic carbon C8. The group has also connectivity to acid carbon C10.

Protons H5 is attached to carbon C4 forming CH group. The group has connectivity to aliphatic carbons C3, C6 and weak one to C5. The group has connectivity to aromatic carbon C7, suggesting neighboring position. Group has no connections to any acid groups.

Proton H6 is attached to carbon C3 forming CH group. The group has connectivity to aliphatic carbons C2, C4 and C5. The group has connectivity to aromatic carbon C8 and weak C7, which suggesting the group to be next to phenyl group of C8. The group has also connectivity to acid carbon C10.

Proton H7 is attached to carbon C6 forming CH group. The group has connectivity to aliphatic carbons C4 and weaker to C3. The group has also connectivity to aromatic carbon C7. The group is only one with connectivity to acid carbon C9.

![Diagram of the molecule](image)

Figure S126: 2D NMR explanation of product 11.

**UV-vis spectrum of 11:**

![UV-vis spectrum graph](image)

Figure S127: UV-vis spectrum of 11 (MilliQ water): 259 nm (max), 264 nm (shoulder) and 293 nm (shoulder).
Infrared spectrum of 11:

Figure S128: IR spectrum for product 11 (2800-3200 (-OH, brood), 1591 (R-COONa, s) 1449 (-CH$_2$ or –CH$_3$, m), 1380 (R-Me, s), 1378 (s), 1448 (s) (R-COONa), 1080 (R-CH(OH)-R, m), 701 (5 adjacent H (Ph))).
HRMS spectra of 11:

HRMS (ESI-TOF) m/z: [11+H2+Na]+ Calcd for C20H22O3Na 365.1359; Found 365.1352; Error 2.029 ppm.

Figure S129: ESI-TOF-MS of [11+H2+Na]+ (peak: 365.1352 m/z, positive-ion mode).

Figure S130: Zoomed ESI-TOF-MS measurement of [11+H2+Na]+ (peak 365.1352 m/z, positive-ion mode).

Figure S131: Measured compound peak of [11+H2+Na]+ (365.1352 m/z) at top, simulated peak (C20H22O3Na) below.
6.12 Product 12

1D NMR of 12:

Figure S132: $^1$H NMR spectrum of 12 (500 MHz, D$_2$O).
Figure S133: $^{13}$C$_{1}$(H) NMR spectrum from 12 (125 MHz, D$_2$O) Only 11 aromatic peaks are observed (should be 12) either 130.7 or 127.9 is double peak, too low resolution to tell.
2D NMR of 12:

Figure S134: HSQC spectrum of 12 (full area, NMR solvent: D$_2$O).
Figure S135: HMBC spectrum of 12 (full area, NMR solvent: D$_2$O).
Figure S136: HMBC spectrum of 12 (aliphatic area, NMR solvent: D$_2$O).
2D NMR explanation: Proton H1 is attached to carbon C2 and forms CH group. This group has connectivity with aliphatic carbons C1 and C4 and weak one to C3. Group has strong connectivity to aromatic carbons C5 and weaker to C7. The group is neighboring phenyl group which C5 belongs to.

Proton H2 is attached to carbon C3 forming CH group. The group has connectivity with aliphatic carbons C1 and C2. The group also has connectivity to aromatic carbon C6, which suggest neighboring position to the mentioned phenyl group. The group has also connectivity to acid carbon C9, suggesting nearby location.

Proton H3 is attached to carbon C1 forming CH group. The group has connectivity with aliphatic carbons C2 and C3. The group has connectivity to aromatic carbon C7 and weak one to C5, suggesting nearby location of phenyl group of C7. The group has very weak connectivity to acid carbon C9.

Proton H4 is attached to carbon C4 forming CH group. The group has connectivity with aliphatic carbons C2 and C1. The group has connectivity with aromatic carbon C5. The group is only with connectivity to acid carbon C8, suggesting nearby location.

Figure S137: 2D NMR explanation of product 12.

UV-vis spectrum of 12:

Figure S138: UV-vis spectrum of 12 (MilliQ water): 299 nm (max).
Infrared spectrum of 12:

Figure S139: IR spectrum for product 12 (3500 – 3200 (-OH, broad), 1623(s), 1599(s), 1549(s) (-COONa), 1374(s), 1096(w), 1071(w) (R-CH(OH)-R), 694 (5 adjacent H (Ph)).
HRMS spectra of 12:

HRMS (ESI-TOF) m/z: [12+H] Calcd for C_{24}H_{21}O_{5} 389.1384; Found 389.1384; Error 0.247 ppm.

Figure S140: ESI-TOF-MS of [12+H] (peak: 389.1384 m/z, negative-ion mode).

Figure S141: Measured compound peak of [12+H] (389.1384 m/z) at top, simulated peak [C_{24}H_{21}O_{5}] below.
6.13 Product 13

1D NMR of 13:

Figure S142: $^1$H NMR spectrum of 13 (500 MHz, D$_2$O) some impurities at aromatic area are detected.
Figure S143: $^{13}$C($^1$H) NMR spectrum of 13 (125 MHz, D$_2$O) (Slight impurities at aromatic region). Peaks pairs C1, C2 and C10, C11 are barely detectable from each other.
Figure S144: HSQC spectrum of 13 (full area, NMR solvent: D$_2$O). H5 and H6 are attached to C4 forming CH$_2$ group.
Figure S145: HMBC spectrum of 13 (full area, NMR solvent: D$_2$O).
Figure S146: HMBC spectrum from 13 (aliphatic area, NMR solvent: D₂O).
2D NMR explanation: Protons H1 and H2 are attached to carbons C1 or C2 (too close to tell) forming two -CH₃ groups. The groups have connectivity to aliphatic carbons C3 and C6 and each other.

Proton H3 is attached to carbon C3 forming CH group. The group has connectivity to aliphatic carbons C1, C2, C6, C7 and C5.

Proton H4 is attached to carbon C6 forming CH group. The group has connectivity to aliphatic carbons C3, C1, C2, C5, C4 and C7. The group has connectivity to aromatic carbon C9. The group has also weak connectivity to acid carbon C11.

Protons H5 and H6 are attached to carbon C4 forming -CH₂- group. The group has connectivity to aliphatic carbons C5 and C6. The group has also connectivity to aromatic carbon C9. The group has connectivity to acid carbon C10, suggesting neighboring location.

Proton H7 is attached to carbon C5 forming CH group. The group has connectivity to aliphatic carbons C4, C6 C7 and weaker C3. The group has connectivity to aromatic carbon C9 and sees inside the phenyl ring, suggesting neighboring location. The group has weak connectivity to acid carbon C10.

Proton H8 is attached to carbon C7 forming CH group. The group has connectivity to aliphatic carbons C6, C5 and C3. The group has strong connectivity to acid carbon C11, suggesting neighboring location.

![Figure S147: 2D NMR explanation of product 13.](image)

**UV-vis spectrum of 13:**

![Figure S148: UV-vis spectrum of 13 (MilliQ water): 288 nm (max) and 293 nm (shoulder).](image)
Infrared spectrum of 13:

Figure S149: IR spectrum for product 13 (3500 – 3200 (-OH, broad), 1602(s), 1556(s), 1362(m) (-COONa), 1403(s), 1319(m), 1288(m) (R-CH(OH)-R), 697(s), 516 (m) (5 adjacent H (Ph))).
HRMS spectra of 13:

HRMS (ESI-TOF) m/z: [13+H] Calcd for C$_{15}$H$_{19}$O$_5$ 279.1227; Found 279.1227; Error 0.053 ppm.

Figure S150: ESI-TOF-MS of [13+H] (peak: 279.1227 m/z, negative-ion mode).

Figure S151: Measured compound peak of [13+H] (279.1227 m/z) at top, simulated peak (C$_{15}$H$_{19}$O$_5$) below.
7 Spectroscopic data of δ-lactone acid

7.1 Product 14 (δ-lactone acid of product 1)

1D NMR of 14:

Figure S152: $^1$H NMR spectrum of 14 (500 MHz, acetone-$d_6$) H3 should be ddd, but it looks like td due the J values.
Figure S153: $^{13}$C($^1$H) NMR spectrum of 14 (125 MHz, acetone-d$_6$). C7 and C8 are barely detectable from each other.
2D NMR of 14

Figure S154: HSQC spectrum of 14 (full area, NMR solvent: acetone-$d_6$).
Figure S155: HMBC spectrum of 14 (full area, NMR solvent: acetone-d₆).
Figure S156: HMBC spectrum of 14 (aliphatic area, NMR solvent: acetone-d$_6$).
2D NMR explanation: Protons H1 and H2 are attached to carbon C1 forming -CH₂- group. The group has connectivity at aliphatic region to carbons C2 and C3. The group has connectivity to aromatic carbon C6. The group has also connectivity to carbonyl carbon C7/C8 (too close to tell apart).

Proton H3 is attached to carbon C2 forming -CH group. The group has connectivity to aliphatic carbons C1, C3 and weak C4. The group has connectivity to aromatic carbons C6 and weaker C5, the group sees inside phenyl group of C6, thus suggesting neighboring position. The group has only weak connectivity to carbonyl carbon(s).

Proton H4 is attached to carbon C3 forming -CH group. The group has connectivity to aliphatic carbons C4, C2 and C1. The group has connectivity to aromatic carbons C5 and weaker C6, the group sees inside the phenyl group of C5, thus it is neighbor. The group has strong connectivity to carbonyl carbons C7/C8.

Proton H5 is attached to carbon C4 forming -CH group. The group has connectivity to aliphatic carbons C3, C2. The group has also connectivity to aromatic carbon C5. The group has strong connectivity to carbonyl carbons C7/C8.

Figure S157: 2D NMR explanation of product 14.

UV-vis spectrum of 14:

Figure S158: UV-vis spectrum of 14 (acetone): 207 nm (max), 210 nm (max), 217 nm (shoulder) and 336 nm (max).
Infrared spectrum of 14:

Figure S159: IR spectrum for product 14 (3000 – 2500 (-COOH, broad), 1730(s), 1204(s), 1160(s), 832(s) (R-O-CO-R), 1681(s), 1416(w), 1087(s), 905 (m) (R-COOH), 1493 (R-CH₂-R, w) 695 (Ph, 5 adjacent H)).

HRMS spectra of 14:

Figure S160: ESI-TOF-MS of 14 (peaks: 319.0938 m/z (monomer) and 615.2006 m/z (dimer), positive-ion mode).
Figure S161: Measured compound peak of [14+Na]+ (319.0938 m/z, monomer) at top, simulated peak (C_{18}H_{16}O_{4}Na) below.

Figure S162: Measured compound peak of [2x14+Na]+ (615.2006 m/z, dimer) at top, simulated peak (C_{36}H_{32}O_{8}Na) below.

HRMS (ESI-TOF) m/z: Monomer [14+Na]+ Calcd for C_{18}H_{16}O_{4}Na 319.0941; Found 319.0938; Error 2.278 ppm; Dimer [2x14+Na]+ Calcd for C_{36}H_{32}O_{8}Na 615.1989; Found 615.2006; Error 1.270 ppm.
7.2 Product 15 (δ-lactone acid of product 2)

1D NMR of 15:

Figure S163: $^1$H NMR spectrum of 15 (500 MHz, acetone-d$_6$).
Figure S164: $^{13}$C{$^1$H} NMR spectrum of 15 (125 MHz, acetone-$d_6$) Significant amount of indole peaks are doublets.
2D NMR of 15

Figure S165: HSQC spectrum of 15 (full area, NMR solvent: acetone-$d_6$).
Figure S166: HMBC spectrum of 15 (full area, NMR solvent: acetone-d$_6$).
Figure S167: HMBC spectrum of 15 (aliphatic area, NMR solvent: acetone-$d_6$).
2D NMR explanation: Protons H1 and H2 are attached to carbon C1 forming CH$_2$ group. The group has connectivity to aliphatic carbons C2 and C3. The group has connectivity to aromatic carbon C7. The group has connectivity to carbonyl carbon C8.

Proton H3 is attached to carbon C3 forming CH group. The group has connectivity to aliphatic carbons C1, C2 and weak C4. The group has connectivity to aromatic carbon C7 and weaker C5. The group sees inside the phenyl group, suggesting neighboring position to it. The group has weak connectivity to carbonyl carbon C8.

Proton H4 is attached to carbon C2 forming CH group. The group has connectivity to aliphatic carbons C3, C1 and C4. The group has connectivity to aromatic carbon C5 and weaker C7. The group sees inside the indole group, thus suggesting neighboring position to it. The group has connectivity to acid carbon C9.

Proton H5 is attached to carbon C4 forming CH group. The group has connectivity to aliphatic carbons C3 and C2. The group has connectivity to aromatic carbon C5. The group has connectivity to both acid and carbonyl carbons C9 and C8, this proofs directly the cyclic nature of the compound.

![Diagram](image)

**Figure S168**: 2D NMR explanation of product 15.

**UV-vis spectrum of 15:**

![UV-vis spectrum](image)

**Figure S169**: UV-vis spectrum of 15 (EtOH): 291 (max), 299 (max).
Infrared spectrum of 15:  

![Infrared spectrum image]

*Figure S170: IR spectrum for product 15 (3400 – 3200 (═NH, broad), 1735 (s), 1405 (m), 939 (m) (R-COOH), 1495 (indole, w), 1458 (R-CH₂-R, m), 1213(s), 1106(s), 1087 (s) (R-O-CO-R), 740(s), 694(s) (Ph, 5 adjacent H)).*

HRMS spectra of 15:  

![HRMS spectra image]

*Figure S171: ESI-TOF-MS of 15 (peaks: 358.1050 m/z (monomer) and 693.2208 m/z (dimer), positive-ion mode).*
HRMS (ESI-TOF) m/z: Monomer [15+Na]+ Calcd for C_{20}H_{17}NO_{4}Na 358.1050; Found 358.1050; Error 0.137 ppm; Dimer [2x15+Na]+ Calcd for C_{40}H_{34}N_{2}O_{8}Na 693.2207; Found 693.2208; Error 0.056 ppm.
7.3 Product 16 (δ-lactone acid of product 4)

1D NMR of 16:

Figure S174: $^1$H NMR spectrum of 16 (500 MHz, acetone-$d_6$).
Figure S175: $^{13}$C($^1$H) NMR spectrum of 16 (125 MHz, acetone-$d_6$). C10 and C9 are barely detectable from each other.
2D NMR of 16

Figure S176: HSQC spectrum of 16 (aliphatic area, NMR solvent: acetone-d$_6$).
Figure S177: HMBC spectrum of 16 (full area, NMR solvent: acetone-d$_6$).
Figure S178: HMBC spectrum of 16 (aliphatic area, NMR solvent: acetone-d$_6$).
2D NMR explanation: Protons H1 are attached to carbon C1 forming -CH₃ group. The group has connectivity to aromatic carbon C6 and inside the phenyl group. The group has no other connectivity.

Protons H2 and H3 are attached to carbon C2 forming -CH₂ group. The group has connectivity to aliphatic carbons C3 and C4. The group has also connectivity to aromatic carbon C8. The group has connectivity to carbonyl carbon C10.

Proton H4 is attached to carbon C3 forming CH group. The group has connectivity to aliphatic carbons C2, C4 and weak C5. The group has strong connectivity to aromatic carbons C8 and weaker C7. The group sees inside the methylated phenyl group, thus suggesting neighboring position. The group has only weak connectivity to carbonyl carbon C10.

Proton H5 is attached to carbon C4 forming CH group. The group has connectivity to aliphatic carbons C3, C2 and C5. The group has connectivity to aromatic carbons C7 and weaker C8. The group sees inside the phenyl group, suggesting neighboring position. The group has connectivity to acid carbon C9.

Proton H6 is attached to carbon C5 forming CH group. The group has connectivity to aliphatic carbons C4 and C3. The group has connectivity to aromatic carbon C7. The group has connectivity to at least acid carbon C9 and maybe carbonyl carbon C10. The resolution isn’t good enough to tell for sure.

![Diagram of molecular structure](Figure S179: 2D NMR explanation for product 16.)

**UV-vis spectrum of 16:**

![Graph of UV-vis spectrum of compound 16 (acetone)](Figure S180: UV-vis spectrum of 16 (acetone): 210 nm (max), 212 nm (shoulder), 216 nm (max) and 332 nm (max).)
Infrared spectrum of 16:

![Infrared spectrum of 16](image)

Figure S181: IR spectrum for product 16 (3200-2800 (-COOH, broad), 1733(s), 1049(s) (R-O-CO-R), 1686(s), 1193(s), 1085(s) (R-COOH), 1415 (w, R-CH₂-R), 1386(m), 822(m) (R-Ph-p-me), 746(s), 695(s) (Ph, 5 adjacent H)).

HRMS spectra of 16:

![HRMS spectra of 16](image)

Figure S182: ESI-TOF-MS of 16 (peaks: 333.1098 m/z (monomer) and 643.2312 m/z (dimer), positive-ion mode).
Figure S183: Measured compound peak of [16+Na]+ (331.1098 m/z, monomer) at top, simulated peak (C_{19}H_{18}O_{4}Na) below.

HRMS (ESI-TOF) m/z: Monomer [16+Na]+ Calcd for C_{19}H_{18}O_{4}Na 333.1097; Found 333.1098; Error 0.130 ppm; Dimer [2x16+Na]+ Calcd for C_{38}H_{36}O_{8}Na 643.2302; Found 643.2312; Error 1.567 ppm.

Figure S184: Measured compound peak of [2x16+Na]+ (643.2312 m/z, dimer) at top, simulated peak (C_{38}H_{36}O_{8}Na) below.
7.4 Product 17 (δ-lactone acid of product 10)

1D NMR of 17:

Figure S185: $^1$H NMR spectrum of 17 (500 MHz, acetone-d$_6$).
Figure S186: $^{13}$C($^1$H) NMR spectrum of 17 (125 MHz, acetone-$d_6$).
2D NMR of 17

Figure S187: HSQC spectrum of 17 (full area, NMR solvent: acetone-$d_6$).
Figure S188: HMBC spectrum of 17 (full area, NMR solvent: acetone-d6).
Figure S189: HMBC spectrum of 17 (aliphatic area, NMR solvent: acetone-\textit{d}_6).
2D NMR explanation: Protons H1 are attached to carbon C1 forming -CH$_3$ group. The group has connectivity to aliphatic carbons C2 and C4. The group has weak connectivity to aromatic carbon C7. The group has connectivity to ester carbon C9.

Proton H2 is attached to carbon C2 forming -CH group. The group has connectivity to aliphatic carbons C1, C4. The group sees aromatic carbon C7. The group has connectivity to ester carbon C9.

Proton H3 is attached to carbon C4 forming -CH group. The group has connectivity to aliphatic carbons C2, C1, C3 and very weak C5. The group has connectivity to aromatic carbons C7 and weaker C6. The group sees inside phenyl group C7, thus being neighboring group. The group has no connectivity on carbonyl carbons.

Proton H4 is attached to carbon C3 forming -CH group. The group has connectivity to aliphatic carbons C5, C4 and C2. The group has connectivity to aromatic carbons C6 and weaker C7. The group sees inside the phenyl group of C6, thus being neighbor of the group. The group sees acid carbon C8.

Proton H5 is attached to carbon C5 forming -CH group. The group has connectivity to aliphatic carbons C3 and maybe C4 (the connectivity is spread between these two carbons). The group has connectivity to aromatic carbon C6. The group has connectivity to both acid carbon C8 and ester carbon C9. This proofs directly the cyclic nature of the compound.

![Diagram of molecular structure](image)

*Figure S190: 2D NMR explanation of product 17.*

UV-vis spectrum of 17:

![UV-vis spectrum graph](image)

*Figure S191: UV-vis spectrum of 17 (acetone): 208 nm (max), 214 nm (max), 217 nm (shoulder) and 338 nm (max).*
Infrared spectrum of 17:

Figure S192: IR spectrum for product 17 (3600 – 3300 (-OH, broad), 3100-2800 (R-COOH, broad), 1731 (s), 1225 (s), 1187 (s), 1088 (s), 775 (m), 761 (m) (R-O-(HCO)-R), 1454 (w, R-CH₃), 1412 (m), 527 (s) (R-COOH), 699 (s), 438 (s) (Ph)).

HRMS spectra of 17:

Figure S193: ESI-TOF-MS of 17 (peaks: 309.1117 m/z (monomer) and 619.2323 m/z (dimer), negative-ion mode).
Figure S194: Measured compound peak of [17-H]- (309.1117 m/z, monomer) at top, simulated peak (C_{19}H_{17}O_4) below.

Figure S195: Measured compound peak of [2x17-H]- (619.2323 m/z, dimer) at top, simulated peak (C_{38}H_{35}O_8) below.

HRMS (ESI-TOF) m/z: Monomer [17-H]^- Calcd for C_{19}H_{17}O_4 309.1121; Found 309.1117; Error 1.551 ppm; Dimer [2x17-H]^- Calcd for C_{38}H_{35}O_8 619.2326; Found 619.2323; Error 0.563 ppm.
8 Spectroscopic data of diacids

8.1 Compound 1H₂

1D NMR of compound 1H₂:

Figure S196: $^1$H NMR spectrum of compound 1H₂ (500 MHz, acetone-d₆).
Figure S197: $^{13}$C($^1$H) NMR spectrum of compound 1H$_2$ (125 MHz, acetone-$d_6$).
2D NMR of 1H₂:

Figure S198: HSQC spectrum of compound 1H₂ (full area, NMR solvent: acetone-d₆).
Figure S199: HMBC spectrum of compound $1H_2$ (full area, NMR solvent: acetone-$d_6$).
Figure S200: HMBC spectrum of compound $\text{1H}_2$ (aliphatic area, NMR solvent: acetone-$d_6$).
2D NMR explanation: Protons H1 and H2 are attached to carbon C1 forming -CH₂ group. This group has connectivity at aliphatic region to carbons C2 and C3. The group has also connectivity to aromatic carbon C6. The group has also connectivity to acid carbon C7.

Proton H3 is attached to carbon C3 forming -CH group. The group has connectivity at aliphatic area to carbons C2, C4 and weak C1. The group has connectivity at aromatic region to carbons C5 and C6. The C5 carbon is stronger, which suggests the group being its neighbor. The group has no connectivity to acid carbons.

Proton H4 is attached to carbon C2 forming -CH group. The group has connectivity at aliphatic region to carbons C1, C3 and C4. The group has connectivity at aromatic region to carbons C6 and C5, C6 being the stronger suggesting it being neighbor of it. The group has also weak connectivity to acid carbon C7.

Proton H5 is attached to carbon C4 forming CH group. The group has connectivity at aliphatic region to carbons C2 and C3. The group has connectivity to aromatic carbon C5. The group is only one with connectivity to acid carbon C8.

Figure S201: 2D NMR explanation of compound 1H₂.

UV-vis spectrum of 1H₂:

Figure S202: UV-vis spectrum of 1H₂ (acetone): 208 nm (max), 211 nm (max), 214 nm (max) and 216 nm (shoulder).
Infrared spectrum of compound 1H₂:

Figure S203: IR spectrum for compound 1H₂. (3400 – 2500 (-OH / -COOH, broad), 1730 (-ROOH, s) 1681 (C=O, s) 1493 (-CH₂, m) 1416 (w), 1160 (s) (-COOH), 1204 (m), 1087 (s) R-(HCOH)-R, m), 695 (5 adjacent H (Ph), s)).
8.2 Compound 2H₂

1D NMR of compound 2H₂:

Figure S204: $^1$H NMR spectrum of compound 2H₂ (500 MHz, acetone-d₆).
Figure S205: $^{13}$C($^1$H) NMR spectrum of compound $2H_2$ (125 MHz, acetone-$d_6$).
Figure S206: $^{13}$C($^1$H) NMR spectrum of compound 2H$_2$ from aromatic region for clarity (125 MHz, acetone-d$_6$).
2D NMR of 2H₂:

Figure S207: HSQC spectrum of compound 2H₂ (full area, NMR solvent: acetone-d₆).
Figure S208: HMBC spectrum of compound 2H₂ from full region (NMR solvent: acetone-d₆).
Figure S209: HMBC spectrum of compound \( \text{2H}_2 \) (aliphatic area, NMR solvent: acetone-\( \text{d}_6 \)).
2D NMR explanation: Protons H1 and H2 are attached to carbon C1 forming -CH₂ group. The group has connectivity to aliphatic carbons C3 and C2. The group has connectivity to aromatic carbon C7. The group has connectivity to acid carbon C8.

Proton H3 is attached to carbon C3 forming -CH group. The group has connectivity to aliphatic carbons C1, C2 and C4. The group has also connectivity to aromatic carbons C7 and C5. The group sees inside phenyl group thus, it is at neighboring position. The group has connectivity to acid carbon C8.

Proton H4 is attached to carbon C2 forming -CH group. The group has connectivity to aliphatic carbons C3, C4 and C1. The groups has connectivity to aromatic carbons C5 and C7, the group sees inside the indole group suggesting a neighboring position. The group has no connectivity to acid carbons.

Protons H5 is attached to carbon C4 forming –CH group. The group has connectivity to aliphatic carbon C2. The group has connectivity to aromatic carbon C5. The group is only one with connectivity to acid carbon C9.

![Figure S210: 2D NMR explanation for compound 2H₂.](image)

**UV-vis spectrum of compound 2H₂:**

![UV-vis spectrum of compound 2H₂ (acetone)](image)

*Figure S211: UV-vis spectrum of 2H₂ (acetone): 207 nm (max), 212 nm (max), 215 nm (max) and 220 nm (shoulder).*
Infrared spectrum of compound 2H₂:

Figure S212: IR spectrum for compound 2H₂. Due heavy similarities of –COOH and -OH groups it is very difficult to be exactly sure which peaks belong to which part of the molecule. (3391 (N-H, s), 1722 (-ROOH, s), 1455, 1425 (-CH₂-, m), 1275, 1214 (-COOH, m) 1106 (R-HCOH-R, s), 739, 697 (5 adjacent H (Ph), s)).
8.3 Compound 4H₂

1D NMR of compound 4H₂:

*Figure S213:* $^1$H NMR spectrum of compound 4H₂ (500 MHz, acetone-d$_6$).
Figure S214: $^{13}$C\textsuperscript{1}H NMR spectrum of compound 4H$_2$ (125 MHz, acetone-d$_6$).
2D NMR of compound 4H₂:

Figure S215: HSQC spectrum of compound 4H₂ (full area, NMR solvent: acetone-d₆).
Figure S216: HMBC spectrum of compound 4H₃ (full area, NMR solvent: acetone-d₆).
Figure S217: HMBC spectrum of compound 4H₂ (aliphatic area, NMR solvent: acetone-d₆).
2D NMR explanation: Protons H1 are attached to carbon C1 forming CH₃ group. The group has connectivity to aromatic carbons C6 and weak C8. Methyl group is clearly attached to the phenyl ring. The group has also connectivity inside the phenyl ring. The group has no other connectivity.

Protons H2 and H3 are attached to carbon C2 forming CH₂ group. The group has connectivity to aliphatic carbons C3 and C4. The group has connectivity to aromatic carbon C8. The group has connectivity to acid carbon C9.

Proton H4 is attached to carbon C4 forming CH group. The group has connectivity to aliphatic carbons C3, C5 and C2. The group has connectivity to aromatic carbon C7 and sees inside the phenyl group, suggesting neighboring position. The group has no connectivity to acid carbons.

Proton H5 is attached to carbon C3 forming CH group. The group has connectivity to aliphatic carbons C2, C4 and weak C5. The group has connectivity to aromatic carbon C8 and sees inside of the group similarly to the methyl group H1, C1, suggesting that the group is next to the methylated phenyl ring. The group has connectivity to acid carbon C9.

Proton H6 is attached to Carbon C5 forming CH group. The group has connectivity to aliphatic carbons C4 and C3. The group has connectivity to aromatic carbon C7. The group is the only one with connectivity to acid carbon C10, suggesting neighboring position.

![Diagram](image)

**Figure S218**: 2D NMR explanation of compound 4H₂.

**UV-vis spectrum of compound 4H₂:**

![UV-vis spectrum](image)

**Figure S219**: UV-vis spectrum of 4H₂ (acetone): 208 nm (max), 212 nm (max), 214 nm (max), 217 nm (max) and 222 nm (shoulder).
Infrared spectrum of compound 4H$_2$:

Figure S220: IR spectrum for compound 4H$_2$. Note that lactone and acid functionality have very similar peaks thus they are hard to tell apart. (1729 (-ROOH, s), 1671 (C=O, s) 1493 (-CH$_2$, m), 1453 (-CH$_3$, w), 1216 (m), 1158 (w) 1086 (s) (R-HCOH-R), 837, 805 (2 adjacent H (Ph), m) 741, 695 (5 adjacent H (Ph), s)).
8.4 Reference spectra for 7H₂

1D NMR of compound 7H₂:

Figure S221: $^1$H NMR spectrum of compound 7H₂ (500 MHz, acetone-d₆).
Figure S222: $^{13}$C($^1$H) NMR spectrum of compound $7H_2$ (125 MHz, acetone-$d_6$) F atom causes the phenyl group peaks to split, such as: C12, C10, C9 and C5).
Figure S223: $^{19}$F NMR spectrum of compound $7H_2$ (470 MHz, acetone-$d_6$).
2D NMR of compound $\text{7H}_2$:

Figure S224: HSQC spectrum of compound $\text{7H}_2$ (full area, NMR solvent: acetone-$d_6$).
Figure S225: HMBC spectrum of compound 7H₂ (full area, NMR solvent: acetone-d₆).
Figure S226: HMBC spectrum of compound 7H₂ (aliphatic area, NMR solvent: acetone-d₆).
2D NMR explanation: Protons H1 and H2 are attached to carbon C1 forming \(-\text{CH}_2\)- group. The group has connectivity to aliphatic carbons C2 and C3. The group have connectivity to aromatic carbon C10. The group has also connectivity to acid carbon C13.

Proton H3 is attached to carbon C3 forming \(-\text{CH}\) group. The group has connectivity to aliphatic carbons C2, C4 and C1. The group has also connectivity to aromatic carbon C11 and C8, suggesting neighboring location to the non-substituted phenyl group. The group has no connectivity to acid carbons.

Proton H4 is attached to carbon C2 forming \(-\text{CH}\) group. The group has connectivity to aliphatic carbons C1, C3 and C4. The group has also connectivity to aromatic carbons C10 and C9, suggesting neighboring position to the substituted phenyl ring. The group has also connectivity to acid carbon C13.

Proton H5 is attached to carbon C4 forming \(-\text{CH}\) group. The group has connectivity to aliphatic carbons C3 and C2. The group has connectivity to aromatic carbon C11. The group is only one with connectivity to acid carbon C14.

**Figure S227:** 2D NMR explanation for compound \(7\text{H}_2\).

**UV-vis spectrum of compound \(7\text{H}_2\):**

**Figure S228:** UV-vis spectrum of \(7\text{H}_2\) (acetone) 209 nm (max) and 214 nm (shoulder). Note: high baseline due high concentration of \(7\text{H}_2\).
Infrared spectrum of compound 7H$_2$:

Figure S229: IR spectrum for compound 7H$_2$ (3437 (-OH, br), 3200-2800 (-COOH, br) 1730 (m), 1680(m) 1158 (s) (-COOH), 1218 (s), 1090 (s) (R-HCOH-R), 847 (s), 811 (m), 699 (s), 671 (w), 568 (s) 420 (m) (R-Ph-F, either 2H adjacent vibrations or C-F movements), 746 (s), 718 (w), 628 (m) (Ph-R, 5H adjacent)).
8.5 Compound 10H₂

1D NMR of compound 10H₂:

Figure S230: $^1$H NMR spectrum of compound 10H₂ (500 MHz, acetone-d₆).
Figure S231: $^{13}$C($^1$H) NMR spectrum of compound 10H$_2$ (125 MHz, acetone-$d_6$).
2D NMR of compound 10H₂:

Figure S232: HSQC spectrum of compound 10H₂ (full area, NMR solvent: acetone-d₆).
Figure S233: HMBC spectrum of compound 10H$_2$ (full area, NMR solvent: acetone-$_d_6$).
Figure S234: HMBC spectrum of compound 1OH₂ (aliphatic area, NMR solvent: acetone-d₆).
2D NMR explanation: Protons H1 are attached to carbon C1 forming -CH3 group. The group has connectivity to aliphatic carbons C2 and C3. The group has no connectivity to aromatic carbons. The group has also connectivity to acid carbon C9.

Proton H2 is attached to carbon C2 forming CH group. The group has connectivity to aliphatic carbons C1, C3 and C4. The group has connectivity to aromatic carbon C7. The group has connectivity to acid carbon C9.

Proton H3 is attached to carbon C4 forming CH group. The group has connectivity to aliphatic carbons C5, C3 and C2. The group has connectivity to aromatic carbon C6 and sees inside the phenyl group, suggesting nearby location. The group has no connectivity to acid carbons.

Protons H4 is attached to carbon C3 forming CH group. The group has connectivity to aliphatic carbons C2, C1, C4 and C5. The group has connectivity to aromatic carbon C7 and sees inside the phenyl group, suggesting neighboring location. The group has connectivity to acid carbon C9.

Proton H5 is attached to carbon C5 forming CH group. The group has connectivity to aliphatic carbons C4 and C3. The group has connectivity to aromatic carbon C6. The group is only one with connectivity to acid carbon C8.

Figure S235: 2D NMR explanation for compound 10H₂.

UV-vis spectrum of compound 10H₂:

Figure S236: UV-vis spectrum of 10H₂ (acetone): 209 nm (max), 214 nm (shoulder) and 216 nm (shoulder).
Infrared spectrum of compound 10H₂:

Figure S237: IR spectrum for compound 10H₂ (1704 (-ROOH, s), 1453, 1392 (-CH₃, m), 1233 (-COOH, s) 1093 (R-HCOH-R, s), 697 (5 adjacent H (Ph), s)).
9 Mechanistic studies

Diacid salts are formed in a three component reaction between amino acid ($R_1$), aromatic aldehyde ($R_2$) and primary alcohol ($R_3$) in alkaline conditions (Fig. S238). Amino acid and aromatic aldehyde react into phenylpyruvic acid $I$ (Fig. S239) and aromatic aldehyde reacts with primary alcohol into cinnamaldehyde $IV$ (Fig. S241). These two in situ formed species react further to the final diacid salt product (Fig. S243). According to the solid-state structures of 1 and 2, the compounds are generated as stereoisomer (RRR) or its enantiomer (SSS). The formation of these stereocenters is described in detail in section 9.1.

![Overall synthesis of diacid salts](image)

*Figure S238: Overall synthesis of diacid salts.*

The reaction begins with a condensation reaction between amino acid and aromatic aldehyde (Fig. S239). The formed imine compound undergoes isomerization reaction, which is most likely catalyzed by either base or alcohols in the solution and is mediated by forming a six-membered ring. Oxygen atom of the catalyst extracts a proton from the α-carbon and donates another proton to the double bond of imine functionality (see details in Fig. S240). After isomerization, the compound undergoes hydrolysis to phenylpyruvic acid salt $I$ and benzyl amine $II$. The benzyl amine further reacts with benzaldehyde or with itself to generate observed side-product benzylidenebenzylamine $III$. Mass spectrum and $^1$H NMR spectrum were recorded from the reaction solution and benzylidenebenzylamine $III$ and its chloro derivative were confirmed (Fig. S259–S264).

![Phenylpyruvic acid salt $I$ formation. The side product $II$ reacts further with benzaldehyde to generate observed compound $III$.](image)

*Figure S239: Phenylpyruvic acid salt $I$ formation. The side product $II$ reacts further with benzaldehyde to generate observed compound $III$.*

In method 1, the isomerization is either catalyzed by a base or ethanol. In method 2 also tert-butanol can act as the catalyst. As method 2 results in higher yields of 1, tert-butanol is proposed to affect the
rate of isomerization. It is also possible that tert-butoxide, which is a highly powerful base for extracting the α-proton, forms in the applied reaction conditions.

In the reaction, aromatic aldehyde undergoes Meerwein-Pondorf-Verley (MPV) reaction with primary alcohol. As a result, primary alcohol turns into aldehyde and aromatic aldehyde turns into aromatic alcohol (Fig. S241). The formed aldehyde undergoes keto-enol tautomerization. Then the enol reacts with another aromatic aldehyde molecule by the Aldol condensation reaction and generates cinnamaldehyde IV.

Based on GC-MS measured from the reaction, a high reactivity of IV is suggested, as IV is not observed experimentally (Figs. S259–S267). However, IV formation was tested in a reaction between ethanol and benzaldehyde at the applied microwave conditions, and the generation of an alcohol analogue of IV was observed. With IV derivatives either alcohol or aldehyde analogues were observed (Fig. S242). The composition of alcohol/aldehyde is dependent on the length of the side chain; shorter side chain produces alcohol and longer chains produces aldehyde (Fig. S242). The phenomena is probably related
to Cannizzaro or MPV reaction as sterically hindered aldehydes seem to be less likely to undergo the transformation to alcohol.

Figure S242: Partial composition of cinnamaldehyde and its derivatives analyzed from the reaction solution.

Phenylpyruvic acid I undergoes keto-enol tautomerization and the enol form reacts with cinnamaldehyde IV forming a hemiacetal adduct i. The intermediate undergoes [3,3]-sigmatropic rearrangement reaction forming intermediate product ii. Hydroxide attacks the carbonyl group in ii and the intermediate undergoes Na\(^+\)-ion assisted hydride transfer generating the final product.

Figure S243: The formation of diacid from phenylpyruvic acid I and cinnamaldehyde IV.
9.1 Origin of the stereocenters

The diacid salts possess 3-4 stereocenters. Phenylpyruvic acid salt I undergoes keto-enol tautomerization into two different enolate forms (E or Z). Similarly, prochiral cinnamaldehyde IV (and its derivatives) has two different isomers (trans or cis). The hemiacetal intermediate i can form by different combinations of E or Z enolate of I with cis or trans form of IV from si or re face and trans/cis isomers of IV can be at different angle (m1 or m2) (see Fig. S244).

The chiral hemiacetal i is formed by enolate of I (E or Z) attacking the cinnamaldehyde IV from either re or si face (See Fig. S245). Additionally, IV has cis or trans isomers which both can appear at different angle (m1 or m2) at hemiacetal i structure. Thus, the amount of possible reaction combinations are limited to 16, but only 8 of those can proceed to ii (see Fig. S248) as the [3,3]-sigmatropic rearrangement only occurs when the phenyl groups of I and IV are not overlapping. The repulsion of phenyl groups is illustrated in Figs. S246 and S247.
**Figure S245:** Enolate of I attacks cinnamaldehyde IV either from re or si face. (Enolate structures omitted for clarity).

**Figure S246:** The rearrangement occurs only when the phenyl groups are pointing in different directions.
As the chiral hemiacetal i is formed either by re or si face attack of enolate form of I (E or Z) to the prochiral cinnamaldehyde IV. Hemiacetal i with R configuration gives ii as a SS diastereomer with E enolate or RR diastereomer with Z enolate. Similarly, hemiacetal i with S configuration gives ii as a RR diastereomer with E enolate or SS diastereomer with Z enolate (See Fig. S248). RS or SR combinations are impossible, as these would require phenyl groups to be at unfavorable position. The [3,3]-sigmatropic rearrangement is the underlying reason why this reaction produces only enantiomer pair SSS(S) / RRR(R) as a final product. Interestingly, IV configuration has no effect on formed stereocenters at ii.

Figure S247: Hemiacetal formations: On the left hand side, the phenyl group repulsion prevents further reactions taking place. On the right hand side, the phenyl groups are pointing to different direction, which enable sigmatropic rearrangement to proceed.
After [3,3]-sigmatropic rearrangement reaction, the intermediate ii gains a proton from the solution (from water or alcohols) and undergoes keto-enol tautomerization. If the final product has four stereocenters, the third stereocenter forms during this keto-enol tautomerization. The third stereocenter folds to a position where \( R_3 \) group is at equatorial position during the final \( Na^+ \)-ion assisted hydride transfer, as it is most favored in energy (see Figs. S249 and S250).
**Compound with three stereocenters**

\[
\begin{align*}
\text{Keto-enol tautomerization} \quad &+ \text{H}^+ \\
\end{align*}
\]

**Compound with four stereocenters**

\[
\begin{align*}
\text{Keto-enol tautomerization} \quad &+ \text{H}^+ \\
\end{align*}
\]

*Figure S249: Keto-enol tautomerization of \textit{ii} before hydride transfer. (Note: the number of stereocenters refers to the final product)*

Hydroxide attacks to the carbonyl group in the aldehyde, followed by Na\(^+\)-ion assisted hydride transfer reaction. Reaction only happens in chair conformation, where the phenyl groups are in equatorial position. The hydride transfer from \(\varepsilon\)-carbon to \(\alpha\)-carbon was confirmed with ethanol-d\(_6\) labeling studies (Section 9.2).
Figure S250: Na⁺-ion assisted hydride transfer. Reaction only happens at chair conformation where the phenyl groups are at equatorial position. The unfavorable cases where phenyl groups would be at axial positions are marked by red color.

The Na⁺-ion forms together with the newly formed carboxylic acid and ketone another chair conformation, which assists the intramolecular hydride transfer.

Figure S251: The equatorial position of R³ is energetically favored for the hydride transfer; therefore the stereocenters are RRRR or mirror image SSSS.
9.2 Labeling studies

Product 1 was synthesized from ethanol in NaOD/D₂O solution. The areas of signals belonging to protons at β and δ carbons dropped in the ¹H NMR spectrum indicating the replacement of protons by deuterium. As was suggested in Section 9, these positions undergo keto-enol tautomerization.

Figure S253: Synthesis of 1 from D₂O (0.9 ml), NaDO (4.5 mmol), EtOH (4.1 ml) and benzaldehyde (610 µL) at 135 °C, 90 min (microwave).
When product 1 synthesized in deuterated ethanol (DO-CD$_2$-CD$_3$), similarly, proton integral values dropped at β and δ position as ethanol-d$_6$ exchanges deuterium to protons from water. The proton of α carbon disappeared from the $^1$H NMR spectrum (Fig. S256). This is explained by hydride transfer from ε carbon to α carbon.
Figure S255: Synthesis of 1 from deuterated ethanol. Deuterium is replacing protons at β and δ carbons but also at α carbon. This is a direct proof of hydride transfer from ε to α carbon.

Figure S256: $^1$H NMR spectrum of 1 when synthesized from ethanol-d$_6$ in NaOH/H$_2$O solution. Proton H5 has turned into deuterium 100%.
9.3 Synthesis of 1 from commercial I and IV

Phenylpyruvic acid I (3 mmol) was placed into a microwave vial together with cinnamaldehyde IV (3 mmol). NaOH (4.5 mmol, 5M, 0.9 ml) and EtOH (4.1 ml) were added. Reaction was conducted in microwave at 135 °C for 90 min. Similar to synthesis of 1, white crystals were formed. Yield: 56% (602 mg). Product was same as 1 (see Fig. S258 for NMR comparison). This experiment proofs that I and IV are related intermediate species for the synthesis of 1.
Figure S258: $^1$H NMR spectra of 1 prepared with different approaches.
9.4 GC-MS data

Reaction solutions were studied by GC-MS after filtering the product out. Few drops of the remaining reaction solution was diluted with ethyl acetate and the sample was filtered prior to the measurement. The chromatogram contained small peaks belonging to unreacted benzaldehyde and a side-product benzyl alcohol. The most intensive signal belonged to benzylidenebenzylamine III (Fig. S259). Signals related to III were also found in $^1$H NMR spectrum measured from the reaction solution (Fig. S261). When benzaldehyde was replaced by 4-chlorobenzaldehyde, the mass peak of III-Cl$_2$ was observed in GC-MS (Figs. S262-S264).

![GC-MS chromatogram from the reaction solution of 1. Mesitylene was used as an internal standard (300 µL). Compound III was observed as a major side product.](image)
Figure S260: Mass spectrum of benzylidenebenzylamine III from the reaction solution of 1.

Figure S261: $^1$H NMR spectrum from the reaction solution of 1 (chloroform-d) confirming the presence of benzylidenebenzylamine III.
Figure S262: GC-MS chromatogram from the reaction solution of 6. Mesitylene was used as an internal standard (300 µL). Dichlorobenzylidenebenzylamine III-Cl₂ was observed as the major side-product.

Figure S263: Mass spectrum of dichlorobenzylidenebenzylamine III-Cl₂.
Cinnamaldehyde IV formation was tested with ethanol and benzaldehyde at applied reaction conditions (method 1). A sample for GC-MS was taken from the reaction solution and diluted with ethyl acetate.

**Cinnamaldehyde test**

Figure S265: GC-MS chromatogram of cinnamaldehyde IV synthesis from ethanol and benzaldehyde. The reaction conditions: 135 °C, 90 min, NaOH (4.5 mmol, 0.9 ml of 5M solution), benzaldehyde (6 mmol, 610 µL) and EtOH (4.1ml). Cinnamaldehyde was observed as alcohol derivative.
When 1-propanol and benzaldehyde were reacted similarly, the reaction produces alcohol and aldehyde analogues (Fig. S268).
Figure S268: GC-MS chromatogram of a test reaction of 1-propanol and benzaldehyde. Reaction conditions: 135 °C, 90 min, NaOH (4.5 mmol, 0.9 ml of 5M solution), benzaldehyde (6 mmol, 610 µL) and 1-propanol (4.1 ml). Both aldehyde and alcohol forms were observed.

Figure S269: Mass spectrum of 2-methyl-3-phenylpropanal.
A test reaction between 1-octanol and benzaldehyde produced the aldehyde product (Figs. S271 and S272).

**Figure S270**: Mass spectrum of 2-methyl-3-phenylpropanol.

**Figure S271**: GC-MS chromatogram of test reaction between 1-octanol and benzaldehyde. Reaction conditions: 135 °C, 90 min, NaOH (4.5 mmol, 0.9 ml of 5M solution), benzaldehyde (6 mmol, 610 µL) and 1-octanol (4.1 ml).
Figure S272: Mass spectrum of 2-(phenylmethylene)octanal.
10 Crystal structure data

10.1 Crystal structure of 1

*Figure S273: Content of the unit cell of 1 (displacement parameters are drawn at 50 % probability level)*
Figure S274: Structure of the dianion of 1 (displacement parameters are drawn at 50 % probability level)
Figure S275: Crystal packing of 1 (projection down the a-axis)

Table S5: Crystal data for product 1

| Property                                      | Value                                      |
|-----------------------------------------------|--------------------------------------------|
| Chemical Formula                              | $\text{C}_{18}\text{H}_{24}\text{Na}_2\text{O}_7\cdot\text{H}_2\text{O}$ |
| $M_r$                                         | 448.37                                     |
| $F(000)$                                      | 472                                        |
| Space Group                                   | Triclinic, $P-1$ (no.2)                    |
| $D_x$                                         | 1.449 Mg m$^{-3}$                          |
| $a$                                           | 6.2002 (2) Å                              |
| $b$                                           | 8.7727 (3) Å                              |
| $c$                                           | 19.3378 (7) Å                             |
| $\alpha$                                      | 101.692 (1)$^\circ$                       |
| $\beta$                                       | 93.848 (1)$^\circ$                        |
| $\gamma$                                      | 90.292 (1)$^\circ$                        |
| $V$                                           | 1027.50 (6) Å                             |
| $\theta$                                      | 4.6–72.0$^\circ$                          |
| $\mu$                                         | 1.35 mm$^{-1}$                            |
| $T$                                           | 123 K                                     |
| Crystal Habit                                 | Blocks, colourless                        |
| Dimension                                    | 0.16 × 0.08 × 0.04 mm                     |
**Table S6: Data collection**

| Description                                                                 | Details                                                                 |
|----------------------------------------------------------------------------|------------------------------------------------------------------------|
| Bruker D8 VENTURE diffractometer with PhotonII CPAD detector               | 3895 reflections with $I > 2\sigma(I)$                                 |
| Radiation source: INCOATEC microfocus sealed tube                          | $R_{int} = 0.023$                                                      |
| rotation in $\phi$ and $\omega$, 1°, shutterless scans                    | $\theta_{\text{max}} = 72.1^\circ$, $\theta_{\text{min}} = 2.3^\circ$ |
| Absorption correction: multi-scan SADABS (Sheldrick, 2014)                | $h = -7 \rightarrow 7$                                                |
| $T_{\text{min}} = 0.826$, $T_{\text{max}} = 0.942$                       | $k = -10 \rightarrow 10$                                              |
| 16265 measured reflections                                                 | $l = -23 \rightarrow 23$                                              |
| 4036 independent reflections                                              |                                                                        |

**Table S7: Refinement**

| Description                                           | Details                                                                 |
|-------------------------------------------------------|------------------------------------------------------------------------|
| Refinement on $F^2$                                   | Primary atom site location: dual                                       |
| Least-squares matrix: full                            | Secondary atom site location: difference Fourier map                   |
| $R[F^2 > 2\sigma(F^2)] = 0.029$                       | Hydrogen site location: difference Fourier map                         |
| $wR(F^2) = 0.075$                                     | H atoms treated by a mixture of independent and constrained refinement |
| $S = 1.06$                                            | $w = 1/[\sigma^2(F_o^2) + (0.0321P)^2 + 0.4936P]$ where $P = (F_o^2 + 2F_c^2)/3$ |
| 4036 reflections                                      | $(\Delta/\sigma)_{\text{max}} = 0.001$                                |
| 304 parameters                                        | $\Delta\rho_{\text{max}} = 0.33$ e Å$^{-3}$                           |
| 71 restraints                                         | $\Delta\rho_{\text{min}} = -0.40$ e Å$^{-3}$                          |
10.2 Crystal structure of 2

*Figure S276*: Content of the unit cell of 2 (displacement parameters are drawn at 50 % probability level).
Figure S277: Structure of the dianion of 2 (displacement parameters are drawn at 50 % probability level).
**Table S8: Crystal data for product 2**

| Property                  | Value                          |
|---------------------------|--------------------------------|
| Chemical formula          | C$_{20}$H$_{23}$NNa$_2$O$_8$    |
| $F(000)$                  | 944                            |
| $M_r$                     | 451.37                         |
| $D_x$                     | 1.452 Mg m$^{-3}$              |
| Crystal system            | Monoclinic, $P2_1/n$ (no.14)   |
| Cu K$\alpha$ radiation, $\lambda$ | 1.54178 Å                     |
| $a$ (Å)                   | 6.2535 (2)                     |
| $b$ (Å)                   | 38.0761 (13)                   |
| $c$ (Å)                   | 9.2033 (3)                     |
| $\beta$ (°)              | 109.594 (1)                    |
| $V$ (Å$^3$)               | 2064.49 (12)                   |
| $Z$                       | 4                              |
| Dimensions (mm)           | 0.18 × 0.08 × 0.04             |

*Figure S278: Crystal packing of 2 (projection down the a-axis).*
### Table S9: Data collection

| Description                                                                 | Details |
|-----------------------------------------------------------------------------|---------|
| Bruker D8 VENTURE diffractometer with PhotonII CPAD detector                | 3960 reflections with $I > 2\sigma(I)$ |
| Radiation source: INCOATEC microfocus sealed tube                           | $R_{int} = 0.026$ |
| rotation in $\phi$ and $\omega$, 1°, shutterless scans                     | $\theta_{\max} = 72.2^\circ$, $\theta_{\min} = 4.6^\circ$ |
| Absorption correction: multi-scan SADABS (Sheldrick, 2014)                 | $h = -7 \rightarrow 7$ |
| $T_{\min} = 0.820$, $T_{\max} = 0.942$                                   | $k = -47 \rightarrow 47$ |
| 24450 measured reflections                                                 | $l = -11 \rightarrow 11$ |
| 4073 independent reflections                                               |         |

### Table S10: Refinement

| Description                                                                 | Details |
|-----------------------------------------------------------------------------|---------|
| Refinement on $F^2$                                                         | Primary atom site location: dual |
| Least-squares matrix: full                                                  | Secondary atom site location: difference Fourier map |
| $R[F^2 > 2\sigma(F^2)] = 0.032$                                             | Hydrogen site location: difference Fourier map |
| $wR(F^2) = 0.081$                                                           | H atoms treated by a mixture of independent and constrained refinement |
| $S = 1.09$                                                                  | $w = 1/\left[\sigma^2(F_o^2) + (0.033P)^2 + 1.2144P\right]$ where $P = (F_o^2 + 2F_c^2)/3$ |
| 4073 reflections                                                            | $(\Delta/\sigma)_{\max} < 0.001$ |
| 304 parameters                                                              | $\Delta\rho_{\max} = 0.35 \text{ e Å}^{-3}$ |
| 11 restraints                                                               | $\Delta\rho_{\min} = -0.23 \text{ e Å}^{-3}$ |