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ORIGINAL PAPER

Synthesis of enantiopure 2-iodomandelic acid and determination of its absolute configuration by VCD spectroscopy

Anikó Nemes[1] · **Elemér Vass**[1] · **István Jalsovszky**[1] · **Dénes Szabó**[1]

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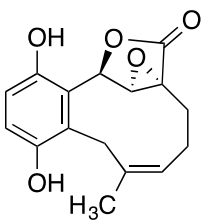
Abstract
Racemic 2-iodomandelic acid **1** was synthesized from commercially available 2-iodobenzoic acid **2**. Acyl chloride **3** was reacted with diethyl malonate, then the formed diester was hydrolysed and decarboxylated in a one-pot reaction. The obtained 2-iodoacetophenone **4** was reacted with bromine and the dibromoacetophenone derivative **5** was hydrolysed to give the racemic 2-iodomandelic acid (±)-**1**. Optical resolution of (±)-**1** via diastereomeric crystallization with strychnine afforded enantiopure (*R*)-(−)-**1**. Absolute configuration of (−)-**1** and of its methyl ester (−)-**6** was determined by VCD spectroscopy.

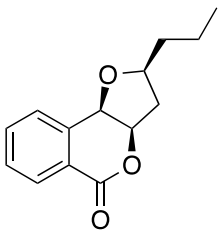
Keywords Mandelic acid derivatives · Building block · Optical resolution · Determination of absolute configuration

Introduction

Optically active mandelic acid derivatives are important chiral building blocks for natural products and active pharmaceutical ingredients (APIs). For example (+)-clavilactone A is a tyrosine kinase inhibitor, and a lead compound for new antitumor molecules (Takao et al. 2013). (+)-Monocerin has antifungal, insectidal and plant pathogenic properties (Kwon et al. 2008).



(+)-clavilactone A



(+)-monocerin

To date, numerous stereoselective synthetic routes were developed for optically active mandelic acid derivatives, such as C–H activation (Dastbaravardeh et al. 2015; Xiao et al. 2016), hydrogenation of α-ketoesters (Carpentier and Mortreux 1997; Meng et al. 2008; Yin et al. 2009), arylation of carbonyl compounds (Bolm et al. 2001), biocatalytic processes (Patterson et al. 1981) and asymmetric Friedel–Crafts reactions (Yuan et al. 2004; Li et al. 2006; Gathergood et al. 2000). These methods were used mostly for substituting H or halogen atoms in the *ortho*-position with functional groups attached through C-, O-, or N atoms to the aromatic ring.

The direct synthesis of pure 1,2-disubstituted aromatic compounds is usually difficult due to the formed regioisomers. Thus, in these cases, starting from commercially available *ortho*-disubstituted materials and use functional group conversions is more advantageous, because the purification is easier. Since aromatic iodides show enhanced reactivity in transition metal catalyzed coupling reactions (Nicolaou et al. 2005; Jana et al. 2011; Daugulis et al. 2009; Kunz et al. 2003), enantiopure 2-iodomandelic acid **1** offers new synthetic pathway for natural product syntheses.

Racemic **1** was synthesized by the decomposition of 2-iodosophenylacetic acid in low yield (Leffler et al. 1963). In this paper, we present the laboratory (multigram) scale synthesis of (±)-**1** from cheap, commercially available 2-iodobenzoic acid, and an optimized optical resolution process, extended with the determination of the absolute configuration by vibrational circular dichroism (VCD) spectroscopy (Freedman et al. 2003; Stephens et al. 2008),

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✉ Anikó Nemes
neagaft@elte.hu

✉ Dénes Szabó
szabod@elte.hu

[1] Institute of Chemistry, Eötvös Loránd University, Pázmány Péter sétány 1/A, Budapest 1117, Hungary

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combined with quantum chemical calculations at DFT level. Optically pure methyl (*R*)-(−)-2-iodomandelate (*R*)-(−)-**6** was also synthesized for VCD measurements to verify the absolute configuration.

Experimental

Materials and instruments

All starting materials and solvents were purchased from Molar Chemicals Kft (Hungary).

Optical rotations were measured on a Polamat A, Zeiss, Jena polarimeter (concentration *c* is given as g/100 ml). Melting points were determined using a Boetius apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 250 spectrometer (250 MHz for ^{1}H) in $CDCl_3$ with the signals of the solvent as the internal standard.

Synthesis of racemic 2-iodomandelic acid

2-Iodobenzoyl chloride (3)

To 2-iodobenzoic acid **2** (496 g, 2 mol) $SOCl_2$ (292 mL, 4 mol) was added. The reaction mixture was heated under reflux for 1 h then the unreacted $SOCl_2$ was removed by distillation. The crude product was purified by distillation in vacuo. Yield: 448 g (84%) colorless liquid, bp 136–140 °C/15 mmHg.

^{1}H NMR ($CDCl_3$) δ: 7.25 (1H, ddd, $^{3}J_{HH} = 7.9$ Hz, $^{3}J_{HH} = 7.5$ Hz, $^{4}J_{HH} = 1.7$ Hz, Ar-5), 7.51 (1H, ddd, $^{3}J_{HH} = 7.9$ Hz, $^{3}J_{HH} = 7.5$ Hz, $^{4}J_{HH} = 1.2$ Hz, Ar-4), 8.05 (1H, dd, $^{3}J_{HH} = 7.7$ Hz, $^{4}J_{HH} = 0.9$ Hz, Ar-3), 8.08 (1H, dd, $^{3}J_{HH} = 7.3$ Hz, $^{4}J_{HH} = 1.3$ Hz, Ar-6). ^{13}C NMR ($CDCl_3$) δ: 94.2 (Ar-2), 128.7 (Ar-5), 133.8 (Ar-6), 134.7 (Ar-4), 138.3 (Ar-3), 142.3 (Ar-1), 167.3 (CO).

2-Iodoacetophenone (4)

To the suspension of Mg (27 g, 1.1 mol) in absolute EtOH (25 mL) CCl_4 (2.5 mL) was added. At the beginning of the gas evolution Et_2O (1500 mL) and then the solution of diethyl malonate (176 g, 1.1 mol) in abs. EtOH (100 mL) and Et_2O (125 mL) was added at a rate that maintains reflux (0.5 h). The reaction mixture was heated under reflux for 3 h then the solution of 2-iodobenzoyl chloride **3** (266.5 g, 1 mol) in Et_2O (250 mL) was added and the mixture was boiled for an additional 2 h. After cooling to rt 65 m/m % H_2SO_4 (200 g) was added. The phases were separated and the aqueous phase was extracted with Et_2O (400 mL). The combined organic phases were washed with sat. NaCl (400 mL) and evaporated in vacuo. The remaining oil was dissolved in the mixture of AcOH (300 mL), H_2O (200 mL) and 98 m/m % H_2SO_4 (40 mL) and heated for 10 h. The reaction mixture was cooled to rt, alkalized to pH 12 with 20 m/m % NaOH and extracted with Et_2O (3 × 400 mL). The combined Et_2O phases were washed with sat. NaCl (3 × 200 mL) and dried over Na_2SO_4. The solvent was distilled off, and the crude product was purified by distillation in vacuo. Yield: 208 g (85%), colorless liquid, bp 143–144 °C/15 mmHg.

^{1}H NMR ($CDCl_3$) δ: 2.60 (3H, s, CH_3), 7.11 (1H, td, $^{3}J_{HH} = 7.6$ Hz, $^{4}J_{HH} = 2.2$ Hz, Ar-5), 7.38 (1H, dd, $^{3}J_{HH} = 7.7$ Hz, $^{4}J_{HH} = 1.0$ Hz, Ar-4), 7.44 (1H, dd, $^{3}J_{HH} = 7.6$ Hz, $^{4}J_{HH} = 2.0$ Hz, Ar-3), 7.92 (1H, dd, $^{3}J_{HH} = 7.9$ Hz, $^{4}J_{HH} = 1.0$ Hz, Ar-6). ^{13}C NMR ($CDCl_3$) δ: 29.9 (CH_3), 91.4 (Ar-2), 128.5 (Ar-5), 128.7 (Ar-6), 132.2 (Ar-4), 141.3 (Ar-3), 144.4 (Ar-1), 202.2 (CO).

2,2-Dibromo-1-(2′-iodophenyl)ethan-1-one (5)

To the solution of 2-iodoacetophenone **4** (24.6 g, 0.1 mol) in AcOH (40 mL) Br_2 (10 mL, 32 g, 0.2 mol) was added in one portion (heat evolution). After stirring for 10 min, the reaction mixture was poured into water (400 mL) and the unreacted Br_2 was neutralized by adding sat $Na_2S_2O_3$ and extracted with $CHCl_3$ (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed by evaporation in vacuo. To the crude product Et_2O (30 mL) and EtOH (30 mL) was added, and the product was crystallized at − 20 °C. Yield: 81 g (66%) mp 60–62 °C.

^{1}H NMR ($CDCl_3$) δ: 6.67 (1H, s, CH_3), 7.21 (1H, td, $^{3}J_{HH} = 7.6$ Hz, $^{4}J_{HH} = 1.6$ Hz, Ar-5), 7.43 (1H, d, $^{3}J_{HH} = 7.7$ Hz, Ar-4), 7.51 (1H, d, $^{3}J_{HH} = 7.7$ Hz, $^{4}J_{HH} = 1.7$ Hz, Ar-3), 7.92 (1H, d, $^{3}J_{HH} = 8.0$ Hz, Ar-6). ^{13}C NMR ($CDCl_3$) δ: 41.5 (CH), 92.3 (Ar-2), 128.6 (Ar-5), 130.3 (Ar-6), 133.1 (Ar-4), 140.4 (Ar-3), 140.7 (Ar-1), 190.0 (CO).

Racemic 2-iodomandelic acid [(±)-1]

The suspension of finely powdered 2,2-dibromo-1-(2-iodophenyl)ethan-1-one **5** (80 g, 0.2 mol) in 0.5 M KOH (1.6 L) was stirred at rt for 2 days then at 90 °C for 1 h. Then, the reaction mixture was cooled to rt and washed with Et_2O (3 × 200 mL). The aqueous phase was cooled to 0 °C and acidified with azeotropic HCl (140 mL) and was extracted with Et_2O (6 × 200 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was removed by evaporation in vacuo. The crude product was purified by crystallization from toluene (200 mL) at rt. Yield: 35.5 g (64%), mp 108–110 °C.

^{1}H NMR ($CDCl_3$) δ: 5.21 (1H, s, CH), 5.70 (2H, br s, OH, COOH), 6.80 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.7 Hz, Ar-5), 7.15 (1H, td, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 0.8 Hz, Ar-4), 7.25 (1H, dd, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.6 Hz, Ar-3), 7.92 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.7 Hz, Ar-6). ^{13}C NMR ($CDCl_3$) δ: 76.7 (CH), 99.6 (Ar-2), 128.4 (Ar-5), 128.8 (Ar-6), 130.1 (Ar-4), 139.8 (Ar-3), 142.4 (Ar-1), 174.7 (CO).

Optical resolution of racemic 2-iodomandelic acid

To a solution of racemic 2-iodomandelic acid (±)-**1** (10.00 g, 36 mmol) in 0.1 M NaOH (360 mL) was added strychnine nitrate (7.15 g, 18 mmol) at 90 °C. The mixture was heated on a steam bath for 5.5 h and allowed to stand at rt overnight. The precipitate was filtered and dried to give the diastereomeric salt with (−) rotation {10.32 g, mp 149–155 °C, $[\alpha]_{578} = -116$ (c = 0.5 DMF)}. To liberate acid (−)-**1**, (10.00 g), the latter salt was suspended in 1 M HCl (50 mL) and extracted with DCM (3 × 70 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was evaporated to afford (−)-**1** {2.03 g, 40%, mp 97–104 °C, $[\alpha]_{578} = -130$ (c = 0.5 DMF)}.

The aqueous filtrate of the (+) salt was evaporated to ~ 100 ml, acidified with 37 m/m % HCl (10 mL) to pH ~ 2 and extracted with DCM (100 mL). The organic solution was dried over Na_2SO_4, and the solvent was evaporated. The crude product was crystallized from toluene (30 ml) at rt to give (+)-**1** {1.08 g, 20%, mp 93–100 °C, $[\alpha]_{578} = +108$ (c = 0.5 DMF)}.

Methyl (R)-(−)-2-iodomandelate [(R)-(−)-6]

To the solution of (*R*)-(−)-2-iodomandelic acid in Et_2O (20 mL) 2.8 M etheral diazomethane solution (1.8 mL) was added. The solution was stirred for 20 min, then the solvent was removed in vacuo to afford (*R*)-(−)-**6**. Yield: 1.07 g (96%), mp 92–95 °C, $[\alpha]_{578} = -77$ (c = 0.5 DMF).

^{1}H NMR ($CDCl_3$) δ: 3,64 (1H, br s, OH), 3.77 (3H, s, CH_3), 5.50 (1H, s, CH), 7.03 (1H, ddd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.7 Hz, Ar-5), 7.22–7.43 (2H, m, Ar-3, Ar-4), 7.92 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.7 Hz, Ar-6). ^{13}C NMR ($CDCl_3$) δ: 53.55 (CH_3), 77.0 (CH), 99.4 (Ar-2), 128.5 (Ar-5), 129.1 (Ar-6), 130.6 (Ar-4), 140.3 (Ar-3), 144.2 (Ar-1), 174.1 (CO).

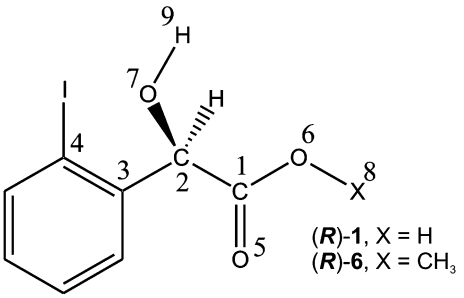
VCD measurements

The VCD spectra of (−)-**1** and (−)-**6** at a resolution of 4 cm^{-1} were recorded in $CDCl_3$ solution using a Bruker PMA 37 VCD/PM-IRRAS module connected to an Equinox 55 FT-IR spectrometer (Bruker Optics, Germany). The ZnSe photoelastic modulator of the instrument was set to 1400 cm^{-1} and an optical filter with a transmission range of 1800–800 cm^{-1} was used to optimize the instrument for the fingerprint region. The instrument was calibrated for VCD intensity with a CdS multiple-wave plate. A CaF_2 cell of 0.207 mm pathlength and sample concentrations of ~ 20 (saturated solution) and 40 mg/mL were used for (−)-**1** and (−)-**6**, respectively. The spectra were averaged for 10 h (corresponding to ~ 36 000 accumulated scans). Baseline correction was achieved by subtracting the spectrum of the solvent obtained under the same conditions. The IR spectra were calculated from the single-channel absorption (DC) spectra of the sample and solvent, respectively.

Quantum chemical calculations

Preliminary conformational search for (*R*)-**1** and (*R*)-**6** was performed with the Hyper Chem 8.0.3 software package by systematic variation (increments of ± 60°–± 180°) of dihedral angles θ_1–θ_4 (for definition, see Fig. 1), using MM+ force field, with no cut-offs and keeping conformers within a 20 kcal/mol relative energy limit. Starting from the results of MM calculations, final geometry optimizations and the computation of vibrational frequencies and VCD rotatory strengths were carried out with the Gaussian 09 software package (Frisch et al. 2013) at DFT level using the B3PW91 functional combined with the 6-31G(d) basis set for C, H, O and the LanL2DZ basis set for the iodine atoms with predefined effective core potential (ECP). The calculated vibrational frequencies were scaled by a factor of 0.963, proved to be suitable for vibrational spectra calculated at similar B3LYP/6-31G(d)/LanL2DZ level for chiral Rh complexes of amino acids (Szilvágyi et al. 2011).

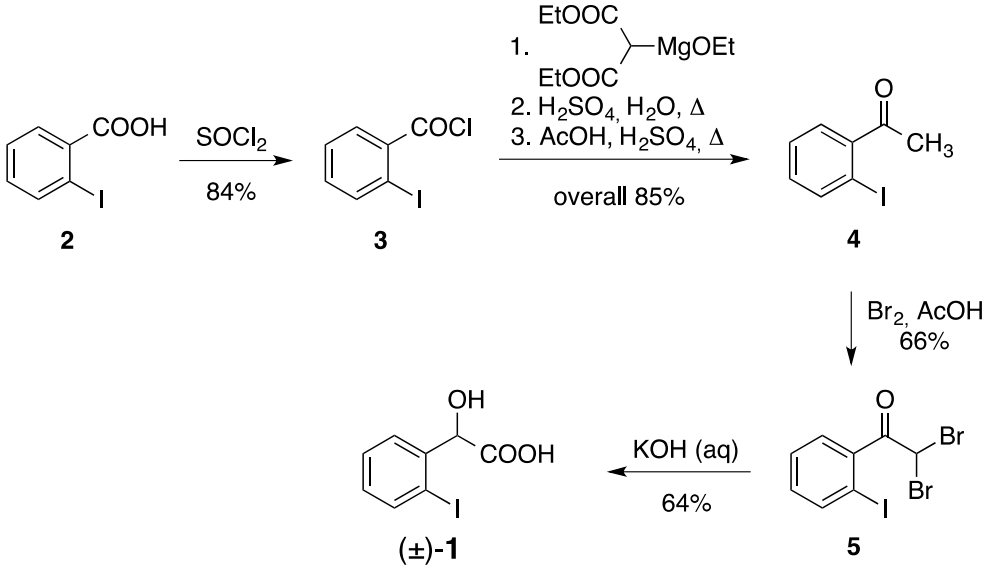
VCD curves were simulated from the calculated wavenumber and rotatory strength data using Lorentzian band shape and a half-width at half-height value of 10 cm^{-1}.

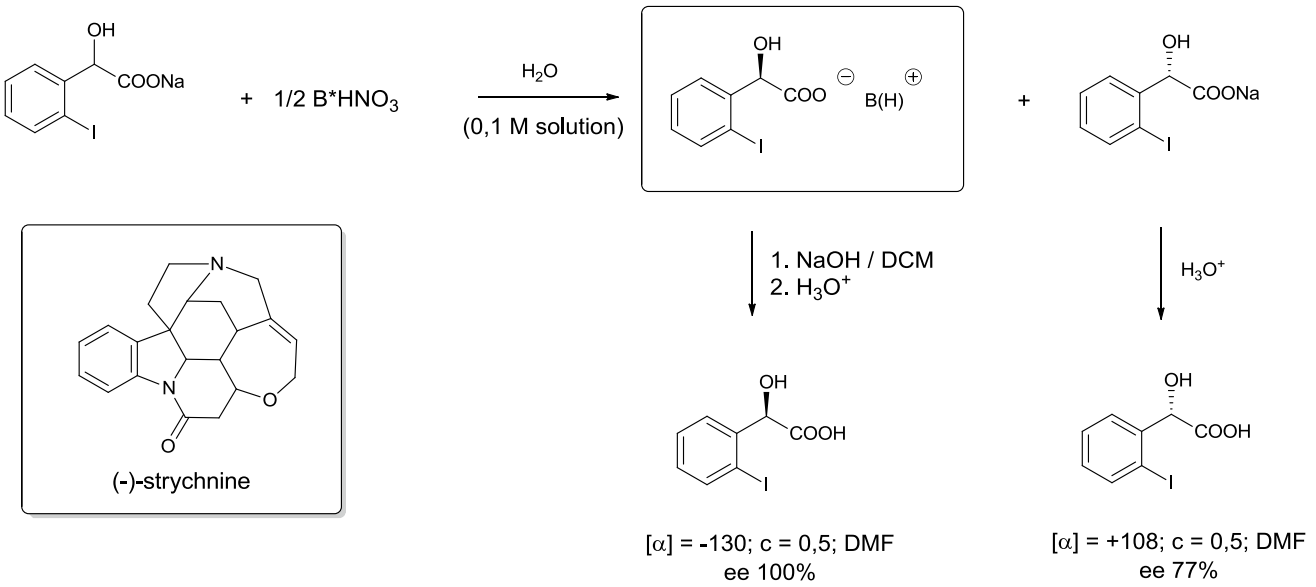


θ_1 = C1-C2-C3-C4
θ_2 = C1-C2-O7-H9
θ_3 = C3-C2-C1-O5
θ_4 = O5-C1-O6-X8

Fig. 1 Definition of dihedral angles θ_1–θ_4 describing the conformational flexibility of (*R*)-**1** and (*R*)-**6**

Scheme 1 Synthesis of (±)-**1**





Scheme 2 Optical resolution of (±)-**1** with strychnine

The theoretical VCD curves of the (*R*)-**1** monomer and its ester derivative (*R*)-**6** were obtained as population-weighted sums of the calculated spectra of individual conformers, considering a Boltzmann distribution. Theoretical VCD spectrum was also calculated for the H-bonded cyclic dimer of the most stable conformer of (*R*)-**1**, using the same level of theory.

Results and discussion

2-Iodoacetophenone **4** and 2-iodomandelic acid **1** were prepared by a slightly modified method given for the synthesis of 2-nitroacetophenone (Reynolds and Hauser 1963) and 4-bromomandelic acid, respectively, (Klingenberg, 1963). Starting material 2-iodobenzoic acid **2** was converted into acyl chloride **3** using thionyl chloride, and then it was reacted with ethoxymagnesiummalonic ester (Price and Tarbell 1963). The formed diester was hydrolyzed and decarboxylated yielding crude 2-iodoacetophenone **4** which was purified by vacuum distillation. Bromination of

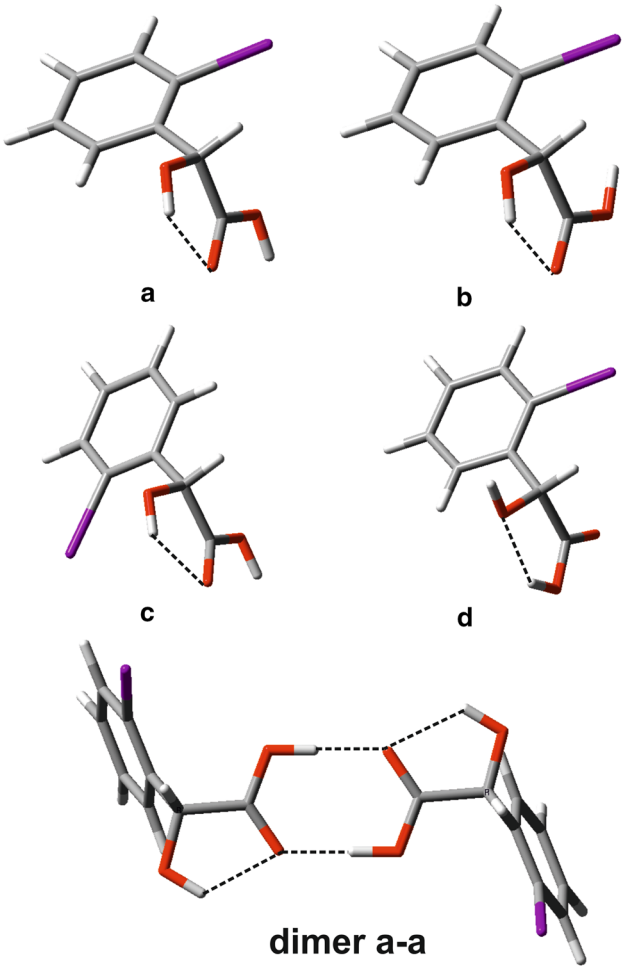


Fig. 2 Relevant conformers (**a**–**d**) of (*R*)-**1** with predicted populations of more than 1% and the structure of H-bonded dimer **a**–**a** at the B3PW91/6-31G(d)/LanL2DZ level of theory (for details see Tables S1–S2 in the Supporting Information)

the pure **4** afforded the dibromoacetophenone **5** in moderate yield. The hydrolysis of **5** and the consecutive Cannizzaro reaction of the intermediate α-keto-aldehyde (Engler and Wöhrle 1887) resulted in the target (±)-**1** (Scheme 1).

Optical resolution of racemic **1** was carried out by diastereomeric crystallization (Faigl et al. 2008). To find the optimal conditions for the optical resolution of (±)-**1** we tested several methods (Nemes et al. 2017), using strychnine, brucine, optochin, quinine, quinidine cinchonine, cinchonidine, (*S*)-1-methylbenzylamine and ephedrine as resolving agents. It is worthy to note, that although ephedrine was successful resolving agent for other mandelic acid derivatives (Collet and Jacques 1973; Valnte et al. 1995), in the case of (±)-**1**, the crystallization trials did not give filterable precipitate. We obtained the enantiopure (−)-**1** using 0.5 equiv of the organic base strychnine as a resolving agent in warm aqueous media (Scheme 2).

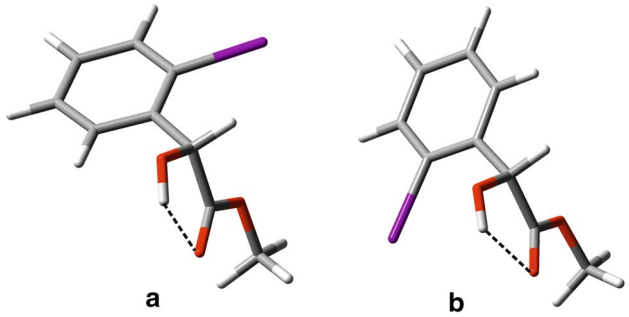


Fig. 3 Relevant conformers of (*R*)-**6** with predicted populations of more than 1% at the B3PW91/6-31G(d)/LanL2DZ level of theory (for details see Table S3 in the Supporting Information)

To one equiv of (±)-**1** were added 1 equiv of NaOH and 0.5 equiv of strychnine nitrate ($B \times HNO_3$). One of the diastereomeric salts [(−)-**1** × B] separated in crystalline form, from which (−)-**1** was regenerated with aqueous NaOH solution. This method provided the enantiopure (−)-**1** {ee > 99%, $[\alpha]_{578} = -130$ ($c = 0.5$, DMF)}. (+)-**1** was isolated from the mother liquor after partial evaporation and acidification in 77% ee {$[\alpha]_{578} = +108$ ($c = 0.5$, DMF)} (Scheme 2.). After crystallization from toluene, the ee of **1** was 94% {$[\alpha]_{578} = +115$ ($c = 0.5$, DMF)}. Enantiomeric excess (ee) of the products was determined by ^{1}H NMR spectroscopy using (*S*)-1-methylbenzylamine as chiral solvating agent (see Supporting Information). The calculated ee values of the products based on the measured optical rotation are slightly different from that obtained by ^{1}H NMR method, due to the presence of impurities in the crude products.

The conformational analysis on (*R*)-**1** resulted in 20 conformers at the B3PW91/6-31G(d)/LanL2DZ level of theory, out of which only four, denoted **a**–**d** (Fig. 2), have an estimated population of more than 1% (92.9, 1.5, 1.3 and 1%, respectively). These structures feature an intramolecular H-bond. The low number of favourable conformers is a result of steric hindrance caused by the bulky iodine atom in *ortho*-position, as well as of the stabilizing effect of intramolecular H-bonds involving the α-OH group. The main conformer (**a**), as well as its H-bonded dimer **a**–**a** of C_2 symmetry (Fig. 2) were supposed to essentially contribute to the IR and VCD spectrum. H-bonded dimers of higher energy conformers (such as **a**–**c**, **c**–**c**, **b**–**b**, the latter formed via the carbonyl oxygen and α-OH groups) were also considered but could be ruled out based on their very high calculated Gibbs-free energies relative to dimer **a**–**a**.

The methyl ester (*R*)-**6** has even less low-energy conformers (two out of a total number of 18 calculated conformers at the B3PW91/6-31G(d)/LanL2DZ level of theory), structures **a** and **b** shown in Fig. 3, having populations of 98.1

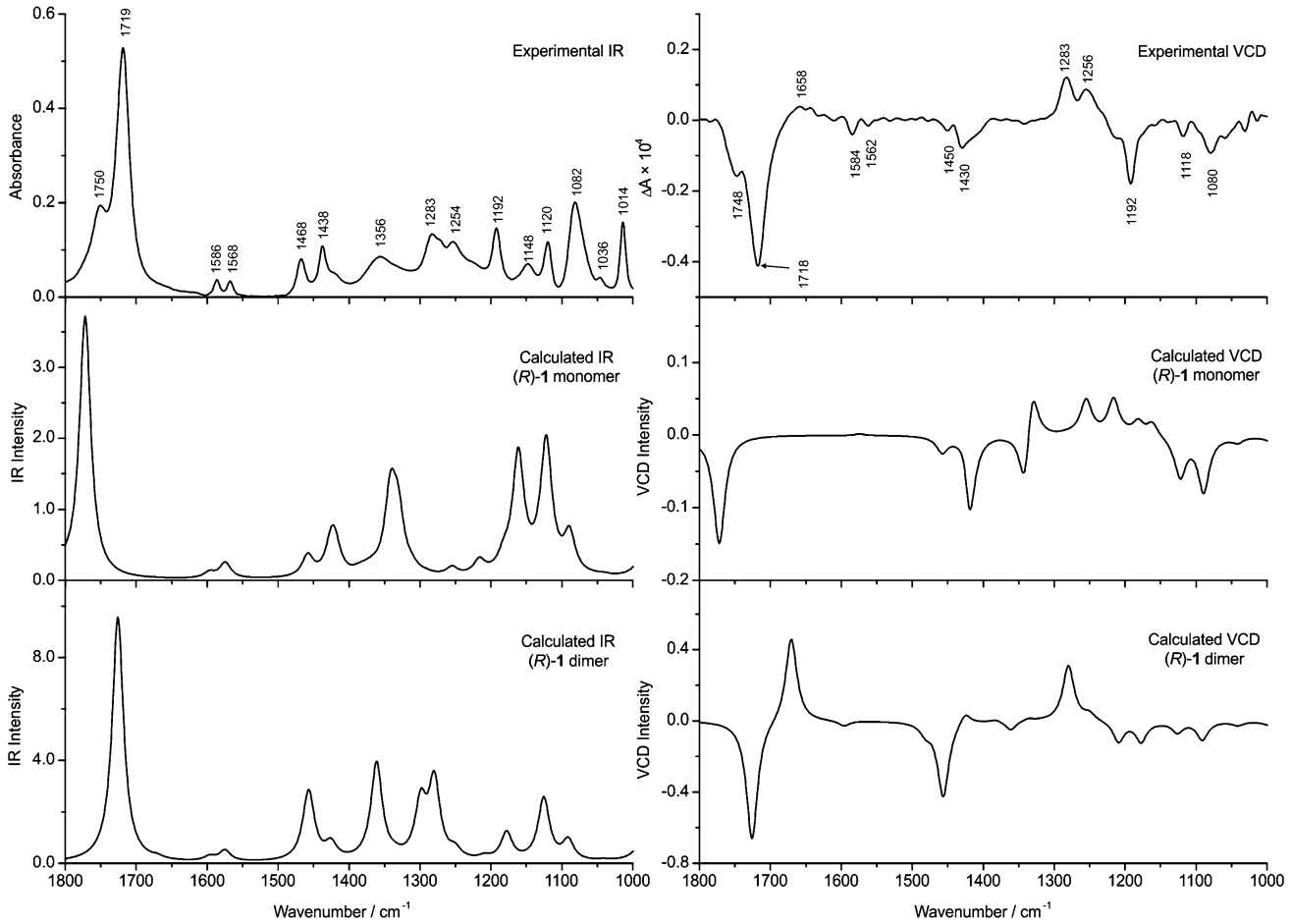


Fig. 4 Experimental IR and VCD spectra of (−)-**1** obtained in $CDCl_3$ in comparison with the calculated spectra of the monomer and H-bonded dimer forms of (*R*)-**1** (at the B3PW91/6-31G(d)/LanL2DZ level of theory)

and 1.1%, respectively. Esterification of the carboxyl group not only reduces the number of conformers to be considered but also eliminates the formation of H-bonded dimers via carboxyl groups, simplifying the interpretation of spectra.

The experimental IR and VCD spectra of (−)-**1** in comparison with the calculated spectra of the monomer and H-bonded dimer form of (*R*)-**1** are shown in Fig. 4. The experimental IR spectrum of (−)-**1** shows a strong absorption band at 1719 cm^{-1}, assigned to the out-of-phase coupled νC = O vibration of the H-bonded dimer, overlapped with a medium intensity νC = O band of the monomer at 1750 cm^{-1}. Similarly, in the VCD spectrum, the strong negative band at 1718 cm^{-1} corresponds to the H-bonded dimer, while the weak negative shoulder at ~ 1748 cm^{-1} is the νC = O contribution of the monomer. The in-phase-coupled νC = O band of the dimer, practically absent from the IR spectrum (due to the local centrosymmetric arrangement of the two carboxyl groups), shows up as a weak-positive band at ~ 1658 cm^{-1} in the VCD spectrum. Despite the often-found non-robust character of the C = O stretching modes in VCD (for a definition of robustness, based on the ratio of rotatory and dipole strengths, see Góbi and Magyarfalvi 2011) the VCD bands measured in the carbonyl region are in very good agreement in terms of both position and sign with the calculated spectral features of the dimer and monomer forms of (*R*)-**1**. In our case the νC = O mode of conformers **a**–**c** is more-or-less robust (with ~ 10.0, 11.1 and 19.7 ppm |R/D| ratios, respectively), and only non-robust for conformer **d** (for which |R/D| = 3.5). Relatively good agreement is also found in the fingerprint region of the VCD spectrum, and similarly, the spectrum shows the contribution of both the monomer and H-bonded dimer forms.

To reduce the complications due to strong intermolecular interactions (e.g., H-bonded dimer formation) and improve the quality of the experimental VCD spectrum (limited by the poor solubility of the sample), the methyl ester derivative (−)-**6** of (−)-2-iodomandelic acid has also been investigated. This compound has a much better solubility in $CDCl_3$,

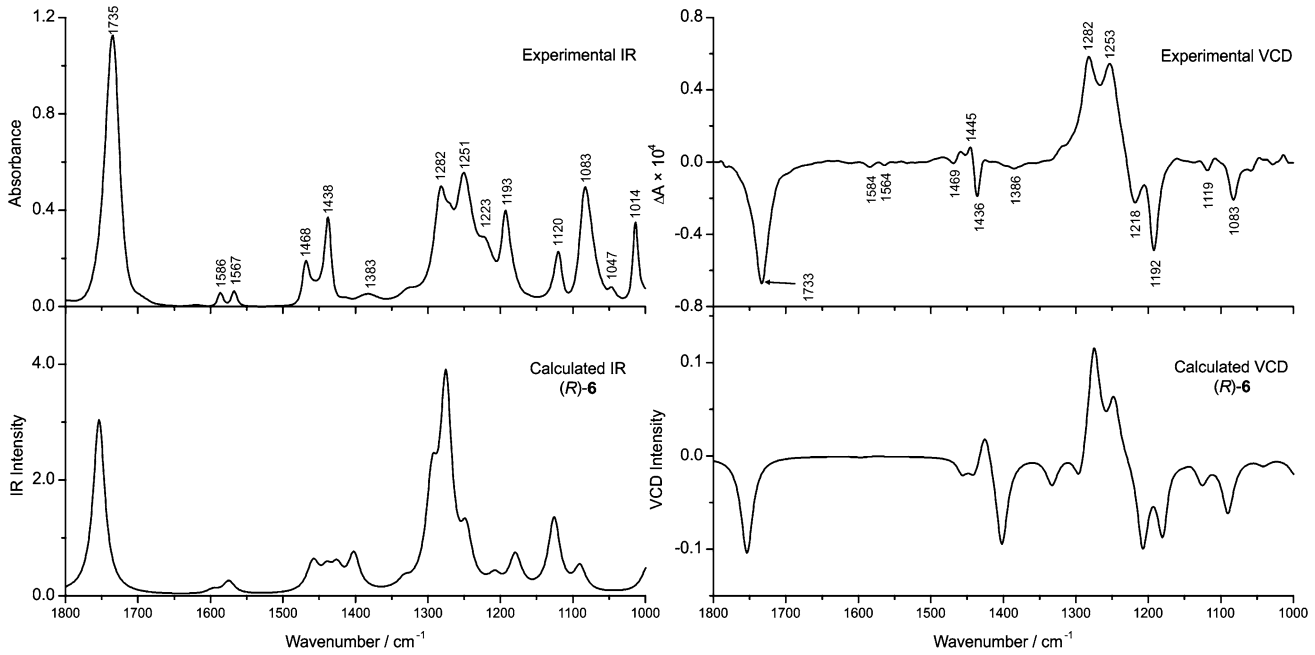


Fig. 5 Experimental IR and VCD spectra of (−)-**6** obtained in $CDCl_3$ in comparison with the calculated spectra of (*R*)-**6** (at the B3PW91/6-31G(d)/LanL2DZ level of theory)

allowing to obtain higher-intensity VCD spectrum under the same experimental setup. The experimental IR and VCD spectra of (−)-**6** in comparison with the calculated spectra of (*R*)-**6** are presented in Fig. 5. Although the band intensity ratios in the calculated IR spectrum do not perfectly match those in the experimental one, which in our opinion is mostly a weakness of the used basis set combination (6-31G(d)/Land2LDZ), the theoretical and experimental VCD spectra are very similar throughout the whole spectral range covered by the measurement, permitting to unambiguously assign the absolute configuration of (−)-**6** to *R*. This is reinforcing the assignment of (−)-**1** to the *R* enantiomer of 2-iodomandelic acid, as esterification of the carboxylic group does not affect the absolute configuration of the compound.

Conclusion

In conclusion, enantiopure 2-iodomandelic acid was synthesized from commercially available 2-iodobenzoic acid. The enantiomeric excess (ee) of the products was determined by ^{1}H NMR spectroscopy using (*S*)-1-methylbenzylamine as chiral solvating agent. The absolute configuration of (−)-**1** was determined to be *R* by VCD spectroscopy, confirmed by the same result obtained for its methyl ester derivative (−)-**6**.

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