Enantiomerically Pure β-Amino Acids: A Convenient Access to Both Enantiomers of *trans*-2-Aminocyclohexanecarboxylic Acid

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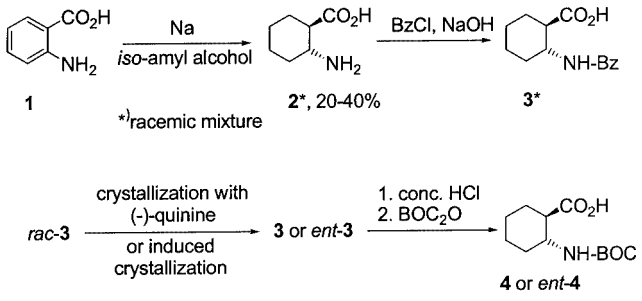
Enantiomerically pure *trans*-2-aminocyclohexanecarboxylic acid is an important building block for helical β-peptides. We report here that this amino acid can be obtained from *trans*-cyclohexane-1,2-dicarboxylic acid in good yield by a simple one-pot procedure comprising cyclization to the anhydride, amide formation with ammonia, and a subsequent Hofmann-type degradation with phenyliodine(III) bis(trifluoroacetate) (PIFA) as the oxidant. The *N*-Fmoc- and *N*-BOC-protected derivatives were obtained by treatment of the amino acid with Fmoc-OSu and BOC_2O, respectively. The *N*-BOC derivative could be prepared in even better overall yield by a one-pot procedure leading directly from *trans*-cyclohexane-1,2-dicarboxylic acid to the *N*-BOC-protected amino acid. Both enantiomers of the starting *trans*-1,2-cyclohexanedicarboxylic acid can be obtained easily and in large quantities by separating commercially available racemic *trans*-1,2-cyclohexanedicarboxylic acid using either (*R*)- or (*S*)-1-phenethylamine. X-ray crystallography of the diastereomerically pure salt obtained from (*R*)-1-phenethylamine revealed that the configuration of the diacid component is (1*R*,2*R*), and not (1*S*,2*S*) as reported in the literature.

Introduction

β-Amino acids have recently attracted considerable attention, mainly due to the bioactivity of β-peptides, which are not subject to peptidase degradation, and due to their ability to form stable tertiary structures.[1−4] In the latter context, Gellman and co-workers have shown that oligomers of *trans*-2-aminocyclohexanecarboxylic acid **2** (Scheme 1) form stable 14-helices.[5,6] Our interest in β-peptides in general, and in the oligomers of the β-amino acids **2** and *ent*-**2** in particular, is related to our work aiming at biomimetic catalysts based on helical peptide scaffolds.[7] The published syntheses of enantiomerically pure **2** or *ent*-**2** are based on the following sequence (Scheme 1): (i) preparation of the racemic amino acid *rac*-**2** by alkali metal reduction of anthranilic acid **1**, (ii) *N*-benzoylation to *rac*-**3**, (iii) separation of the enantiomers either by using (−)-quinine as the chiral auxiliary or by induced crystallization, (iv) *N*-debenzoylation, (v) introduction of an *N*-protecting group suitable for peptide synthesis, such as BOC (Scheme 1).[5,8,9] In our hands, the reduction of **1** proved tedious and relatively low-yielding (10−30%). The isolation of pure *rac*-**3** from the benzoylation requires intermediate esterification, column chromatography and hydrolysis.[5] Furthermore, the separation of the enantiomers **3** and *ent*-**3** by crystallization with (−)-quinine proved capricious,[5] whereas the induced crystallization of **3** or *ent*-**3** is reported to afford varying yields (10−41%) of the individual enantiomers of the *N*-benzoylated amino acids **3** and *ent*-**3**.[5] Finally, it appeared desirable to avoid the change of the *N*-protecting group (benzoyl to BOC).



Scheme 1

It was reported recently that (1*S*,2*S*)-*trans*-cyclohexanedicarboxylic acid (*ent*-**5**) can be obtained readily in enantiomerically pure form by crystallization of the commercially available racemate *rac*-**5** with the inexpensive auxiliary (*R*)-1-phenethylamine (**6**; Scheme 2).[10] In our hands, this procedure afforded the enantiomerically pure (> 99% *ee*) diacid reproducibly in at least 40% yield on a 0.5 mol scale and without any problem. In addition, the racemic starting *trans*-diacid *rac*-**5** can be obtained in one step from even cheaper *cis*-hexahydrophthalic anhydride.[11] We thus reasoned that **5** or *ent*-**5** are excellent starting materials for the preparation of the amino acids **2** and *ent*-**2** on a larger scale.

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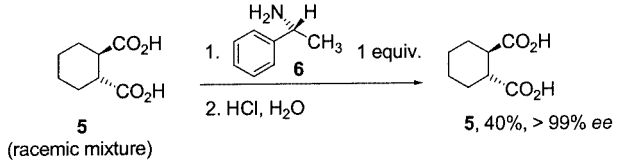
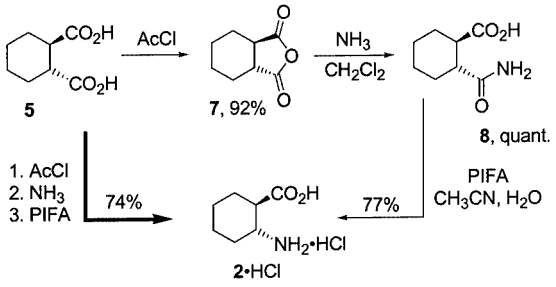
Here we disclose our one-pot procedure for the high-yielding conversion of the diacids **5** and *ent*-**5** to the β-amino acids **2** and *ent*-**2**, respectively. A one-pot conversion leading directly from the diacids **5** and *ent*-**5** to the *N*-BOC-protected amino acids **4** and *ent*-**4** proved possible as well. Furthermore, X-ray crystallography of the diastereomerically pure salt obtained from the crystallization of racemic *trans*-1,2-cyclohexanedicarboxylic acid (*rac*-**5**) with (*R*)-1-phenethylamine **6** revealed that the configuration of the diacid component is in fact (1*R*,2*R*) (**5**, as shown in Scheme 2), and not (1*S*,2*S*) as reported.[10]



Scheme 2

Results and Discussion

We initially tried to convert the enantiomerically pure diacid **5** directly into the BOC-protected amino acid **4** by treatment with *O*,*O*-diphenylphosphoryl azide (DPPA) in *tert*-butyl alcohol.[12] As it turned out, the desired product could not be isolated in reasonable yields under any of the many reaction conditions tried. We thus turned our attention to a Hofmann degradation of the monoamide **8** (Scheme 3). The latter is readily available from **5** by conversion into the *trans*-anhydride **7**[11] and subsequent ring-opening with ammonia.[14] Of the many reagents examined, phenyliodine(III) bis(trifluoroacetate) (PIFA) turned out to give the best results (77%, Scheme 3).[16] Most importantly, we found that all three steps necessary for the conversion of the diacid **5** to the amino acid **2** can be carried out in a one-pot procedure (Scheme 3): First, the diacid **5** is refluxed with acetyl chloride. Dissolution of the diacid indicates the completion of the first step. Excess acetyl chloride and acetic acid are pumped off, and the anhydride **7** is dissolved in dichloromethane. Conversion into the amide **8** is effected within minutes by treatment with gaseous ammonia. Once the precipitation is complete, the dichloromethane solvent is replaced by a solution of the oxidant (PIFA) in a mixture of acetonitrile/water, and the Hofmann degradation proceeds smoothly at room temperature. After ca. 24 h, the desired amino acid **2** can be isolated in 74% yield as the hydrochloride **2·HCl**. The X-ray crystal structure of this hydrochloride is shown in Figure 1. Finally, introduction of the Fmoc group is achieved in the usual way by treatment with Fmoc-OSu, affording the *N*-protected amino acid **9** in 81% yield (Scheme 4).[17] Similarly, the *N*-BOC protected derivative **4** was obtained in 68% yield by treatment of **2·HCl** with di-*tert*-butyl pyrocarbonate (BOC_2O, Scheme 4, Figure 2).[5] In fact, the four-step sequence leading from the diacids **5** and *ent*-**5** to the *N*-BOC-protected amino acids **4** and *ent*-**4** could be performed in a one-pot procedure as well (overall yield 67%).



Scheme 3

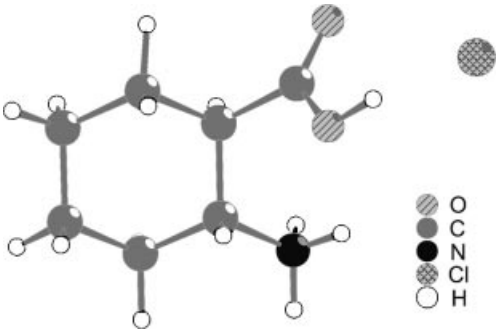
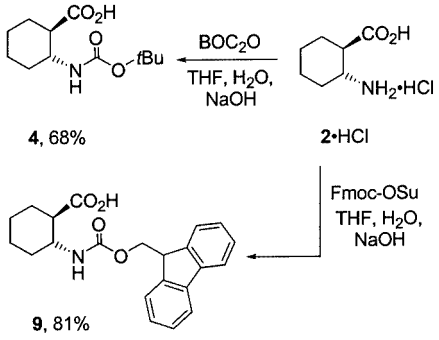


Figure 1. X-ray crystal structure of the amino acid hydrochloride **2·HCl**



Scheme 4

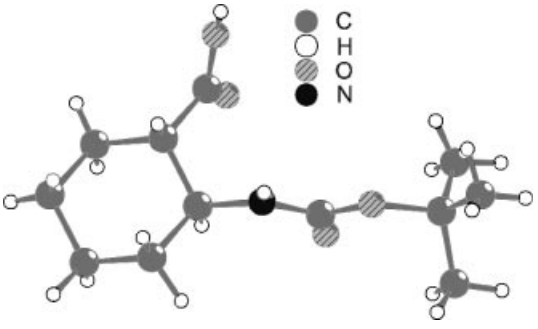


Figure 2. X-ray crystal structure of the *N*-BOC derivative *ent*-**4**

As mentioned in the introduction, (*R*)-1-phenethylamine **6** is reported in the literature to cause the precipitation of

the diastereomeric salt with (1*S*,2*S*)-cyclohexanedicarboxylic acid *ent*-**5** from the racemate *rac*-**5**.[10] In our hands, the dicarboxylate moiety of the precipitate formed was the (1*R*,2*R*)-isomer, as revealed by X-ray crystallography (Figure 3). We found the isolated (1*R*,2*R*)-cyclohexanedicarboxylic acid **5** to be more than 99% optically pure and to be levorotatory. The reported procedure[10] also states a negative specific rotation. Consequently, it appears most likely that just the descriptors for the configuration of the isolated *trans*-cyclohexanedicarboxylic acid were misassigned.[10]

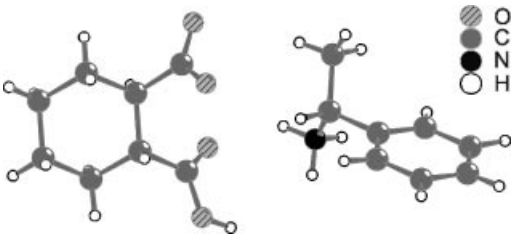


Figure 3. X-ray structure of the salt formed from (*R*)-1-phenethylamine (**6**) and (1*R*,2*R*)-cyclohexanedicarboxylic acid (**5**)

Experimental Section

General: Reagents and solvents were purified by standard procedures. Phenyliodine(III) bis(trifluoroacetate) (PIFA), *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu) and di-*tert*-butylpyrocarbonate (BOC_2O) were purchased from standard suppliers and used as received. Melting points were determined in capillary tubes and are uncorrected. NMR spectra were recorded on a Bruker AC 300 instrument. IR spectra were recorded on a Perkin−Elmer FT-IR 1600 spectrometer (CsI discs). Optical rotations were measured on a Perkin−Elmer polarimeter 343plus. CHN-Analyses were determined on an Elementar Vario EL instrument (Elementaranalysen Systeme GmbH). Capillary gas chromatography was carried out on a Hewlett−Packard-5800 II instrument using a 25 m Hydrodex β-3P column (Macherey−Nagel) or a 25 m WCOT-FS CP-Chiralsil-Dex CB column (Chrompack). X-ray structural analyses were performed on a Nonius Kappa CCD diffractometer.

trans-1,2-Cyclohexanedicarboxylic acid (*rac*-**5**) was obtained in 80% yield as a colorless solid (m.p. 220 °C, ref.[11] m.p. 218−220 °C) from *cis*-hexahydrophthalic anhydride, according to a literature procedure.[11]

Separation of the Enantiomers 5 and *ent*-5 of *trans*-1,2-Cyclohexanedicarboxylic Acid (*rac*-5): Racemic *trans*-1,2-cyclohexanedicarboxylic acid (*rac*-**5**; 2.40 g, 13.9 mmol) was added to a solution of (*R*)-1-phenethylamine (**6**; 1.70 g, 14.0 mol) in EtOH (20 mL) at −78 °C. A colorless precipitate formed, which was filtered off after warming to room temperature. This solid was recrystallized from hot EtOH/toluene (1:1, 40 mL) three times. The product thus obtained was dissolved in 1 N aq. HCl and extracted three times with Et_2O (50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure, affording the enantiomerically pure dicarboxylic acid **5** (or *ent*-**5**, when *ent*-**6** was employed) as colorless crystals; yield: 800 mg (4.66 mmol, 33%, *ee* > 99%); m.p. 177 °C (ref.[13] m.p. 179−183 °C). For the *ee* determination, a sample of **5** (or *ent*-**5**) was converted into the dimethyl ester by treatment with an ethereal solution of diazomethane and analyzed by GC on a 25 m WCOT FS CP-Chiralsil-Dex CB column. $C_8H_{12}O_4$ (172.2): calcd. C 55.81, H 7.02; found C 55.88, H 6.97. ^{1}H NMR ([D$_4$]methanol): δ = 1.16−1.37 (m, 4 H), 1.64−2.05 (m, 4 H), 2.37−2.51 (m, 2 H) ppm. ^{13}C NMR ([D$_4$]methanol): δ = 26.5, 30.2, 46.3, 178.9 ppm. IR: $\tilde{\nu}$ = 2961, 1716, 1458, 1273, 1204, 939 cm^{-1}. $[\alpha]_D^{25}$ = −18.3 (*c* = 1.00, acetone) {ref.[13] $[\alpha]_D^{25}$ = −18.5 (*c* = 1.00, acetone)}.

Enantiomerically pure *trans*-1,2-cyclohexanedicarboxylic acid anhydride **7** was prepared according to a procedure published for the racemic material (*rac*-**7**) using acetyl chloride,[11] affording the anhydride **7** as a colorless solid, yield: 98%; m.p. 162 °C (ref.[13] m.p. 164 °C).

Enantiomerically pure *trans*-1,2-cyclohexanedicarboxylic acid monoamide **8** was prepared according to a procedure published for the racemic material (*rac*-**8**) by ring-opening the anhydride with dry ammonia gas.[14] The product was separated as a white solid. Yield: quant., m.p. 197 °C (ref.[15] m.p. 196 °C, racemic mixture).

Hofmann Degradation of the Monoamide 8 (or *ent*-8) with PIFA: Phenyliodine(III) bis(trifluoroacetate) (PIFA) (1.00 g, 2.32 mmol) was dissolved in acetonitrile/water (8 mL, 1:1 v/v). *trans*-1,2-Cyclohexanedicarboxylic acid monoamide (**8** or *ent*-**8**, 400 mg, 2.32 mmol) was added, and the mixture was stirred at room temperature overnight. The solution was then diluted with water (50 mL) and acidified with concentrated HCl (5 mL). Iodobenzene and unchanged PIFA were extracted with Et_2O. The ether layer was washed with 10% aq. HCl, and the combined aqueous layers were evaporated, yielding the amino acid hydrochloride **2·HCl** (or *ent*-**2·HCl**) as a colorless solid. Recrystallization from EtOH/Et_2O afforded 320 mg (1.78 mmol, 77%, *ee* > 99%) of analytically pure **2·HCl** (or *ent*-**2·HCl**) as colorless crystals; m.p. 208 °C. For the *ee* determination, a sample of **2·HCl** (or *ent*-**2·HCl**) was converted into the *N*-trifluoroacetamide of **2** (or *ent*-**2**) by treatment with trifluoroacetic anhydride and analyzed by GC on a 25 m Hydrodex β-3P column. $C_7H_{14}ClNO_2$ (179.6): calcd. C 46.80, H 7.86, N 7.80; found C 46.83, H 7.54, N 7.92.. ^{1}H NMR ([D$_6$]DMSO): δ = 1.15−1.46 (m, 4 H), 1.58−1.73 (m, 2 H), 1.94−2.06 (m, 2 H), 2.36−2.45 (m, 1 H), 3.07−3.18 (m, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 23.1, 24.1, 28.1, 28.9, 45.5, 49.9, 174.4 ppm. IR: $\tilde{\nu}$ = 2862, 2035, 1720, 1623, 1604, 1514, 1453, 1382, 1249, 1219, 1164, 1055, 874, 670 cm^{-1}. $[\alpha]_D^{25}$ = −46 (*c* = 1.00, water).

One-Pot Procedure for the Conversion of the Diacid 5 (or *ent*-5) to the Amino Acid Hydrochloride 2·HCl (*ent*-2·HCl): Acetyl chloride (25 mL) was added to *trans*-1,2-cyclohexanedicarboxylic acid (**5** or *ent*-**5**, 1.60 g, 9.30 mmol), and the mixture was refluxed until all solids had dissolved. Excess acetyl chloride was removed under reduced pressure, and the solid residue was taken up in dichloromethane (250 mL). Dry ammonia was bubbled through this solution at room temperature. After completion of the precipitation, the solvent was again removed under reduced pressure, and a solution of PIFA (4.00 g, 9.30 mmol) in acetonitrile/water (50 mL, 1:1 v/v) was added. Stirring was continued at room temperature overnight. The reaction mixture was then diluted with water (100 mL), acidified with concentrated HCl (15 mL), and extracted with Et_2O. The ether layer was washed with 10% aq. HCl, and the combined aqueous layers were evaporated to yield the amino acid hydrochloride **2·HCl** (or *ent*-**2·HCl**) as a colorless solid. Recrystallization from EtOH/Et_2O afforded **2·HCl** (or *ent*-**2·HCl**) as colorless crystals (1.22 g, 6.85 mmol, 74%); m.p. 208 °C. All analytical data were identical with those obtained for the material prepared in a stepwise manner.

***N*-Fmoc-*trans*-2-aminocyclohexanecarboxylic Acid (9, or *ent*-9):** *trans*-2-Aminocyclohexanecarboxylic acid hydrochloride **2·HCl** (or *ent*-**2·HCl**; 290 mg, 1.62 mmol) was dissolved in THF (15 mL)

whilst stirring. Sodium hydroxide (81.0 mg, 2.00 mmol) was added, followed by Fmoc-OSu (545 mg, 1.62 mmol). Finally, water (7.5 mL) and additional THF (7.5 mL) were added. After five minutes, sodium bicarbonate (169 mg, 2.0 mmol) and THF (7.5 mL) were added and the reaction mixture was stirred at room temperature overnight. The solution was acidified to pH 1 by addition of 1.5 N aqueous hydrochloric acid. A precipitation occurred, and the mixture was extracted thoroughly with EtOAc. The combined organic layers were washed with 1.5 N aq. hydrochloric acid and water. After drying over $MgSO_4$, the solvent was evaporated under reduced pressure. The solid residue was recrystallized from EtOAc/hexane, affording **9** (or *ent*-**9**) as a colorless solid. Yield: 480 mg (1.31 mmol, 81%); m.p. 222 °C (ref.[17] m.p. 201−203 °C, racemic mixture). $C_{22}H_{23}NO_4$ (365.4): calcd. C 72.31, H 6.34, N 3.83; found C 72.41, H 6.32, N 3.78. ^{1}H NMR ($CDCl_3$): δ = 1.05−1.95 (m, 9 H), 2.18−2.30 (m, 1 H), 4.15−4.25 (m, 3 H), 7.30−7.88 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.2, 24.4, 28.8, 32.1, 46.7, 48.3, 50.7, 65.2, 120.0, 125.1, 125.2, 127.0, 127.5, 175.3 ppm. IR: $\tilde{\nu}$ = 3332, 2934, 1696, 1559, 1540, 1529, 1451, 1424, 1318, 1261, 1231, 1126, 1057, 760, 741 cm^{-1}. $[\alpha]_D^{25}$ = −42 (*c* = 1.00, $CHCl_3$).

***N*-BOC-*trans*-2-aminocyclohexanecarboxylic Acid (4, or *ent*-4):** *N*-Protection of the amino acid hydrochloride **2·HCl** (or *ent*-**2·HCl**) with BOC_2O was performed according to a literature procedure,[5] affording **4** (or *ent*-**4**) as colorless solids. Yield: 68%, m.p. 154 °C (ref.[5] m.p. 154 °C). All analytical data were identical with the literature values.[5] Crystals suitable for X-ray structural analysis were obtained by crystallization from hot ethyl acetate/hexane.

One-Pot Procedure for the Conversion of the Diacid 5 (or *ent*-5) to the *N*-BOC-Protected Amino Acid 4 (or *ent*-4): A mixture of *trans*-1,2-cyclohexanedicarboxylic acid **5** (or *ent*-**5**) (4.66 g, 27.1 mmol) and acetyl chloride (25 mL) was refluxed until the solid was dissolved. Excess acetyl chloride was removed under reduced pressure, and the solid residue was taken up in dichloromethane (500 mL). Dry ammonia was bubbled through this solution at room temperature. After completion of the precipitation, the colorless solid was filtered off, dried in vacuo, and added to a solution of PIFA (12.8 g, 29.8 mmol) in acetonitrile/water (150 mL, 1:1 v/v). Stirring was continued at room temperature overnight. The reaction mixture was then diluted with water (250 mL), acidified with concentrated HCl (50 mL), and extracted with Et_2O. The aqueous layer was concentrated to a volume of 200 mL, and potassium carbonate (29.9 g, 216 mmol) was added, followed by dioxane (400 mL) and BOC_2O (11.8 g, 54.2 mmol). The reaction mixture was stirred at room temperature overnight. It was then acidified to pH 1 by addition of 3 N HCl and extracted three times with EtOAc (250 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The remaining solid was dried at 60 °C and 1 mbar to afford the product **4** (or *ent*-**4**) as a colorless powder; yield: 4.44 g, 67%; m.p. 150−151 °C. The analytical data were identical with those obtained for the material prepared in a stepwise manner (see above).

X-ray Structural Analyses of the Amino Acid Hydrochloride 2·HCl, *ent*-2·HCl, of the *N*-BOC Derivative *ent*-4 and of the salt 5·6: Crystals suitable for X-ray structural analyses were obtained by recrystallization as described in the preparations. Experimental parameters are summarized in Table 1.

CCDC-187726 (**5·6**), -187727 (*ent*-**2**·HCl), -187728 (*ent*-**4**) and -187729 (**2**·HCl) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

Acknowledgments

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Table 1. Experimental parameters of the X-ray structural analyses of **2·HCl** *ent*-**2·HCl**, **5·6**, *ent*-**4**

	2·HCl	*ent*-**2**·HCl	**5·6**	*ent*-**4**
Empirical formula	$C_7H_{14}ClNO_2$	$C_7H_{14}ClNO_2$	$C_{16}H_{23}NO_4$	$C_{12}H_{21}NO_4$
M_r	179.64	179.64	293.35	243.30
Crystal dimensions [mm]	0.2 × 0.15 × 0.15	0.15 × 0.15 × 0.15	0.2 × 0.1 × 0.1	0.2 × 0.2 × 0.1
Crystal system	monoclinic	monoclinic	orthorhombic	orthorhombic
Space group	$P2_1$	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
a [Å]	7.842(1)	7.833(1)	6.091(1)	5.200(1)
b [Å]	6.883(1)	6.883(1)	10.006(1)	20.315(1)
c [Å]	8.803(1)	8.904(1)	26.091(1)	27.003(1)
α [°]	90	90	90	90
β [°]	94.81(1)	94.81(1)	90	90
γ [°]	90	90	90	90
V [Å^3]	473.48(11)	472.99(11)	1590.16(31)	2852.5(6)
$\rho_{calcd.}$ [gcm^{-3}]	1.260	1.261	1.225	1.133
Z	2	2	4	8
Radiation	Mo-K_α	Mo-K_α	Mo-K_α	Mo-K_α
Scan mode	φ/ω	φ/ω	φ/ω	φ/ω
2 Θ_{max} [°]	54	54	54	54
Reflections collected	3063	3807	8868	18526
Independent reflections	1831	1973	3463	6011
Reflections observed	1633	1760	1864	2051
Data/parameters	1831/156	1973/156	3463/283	6011/477
*R*1 (*F*)	0.033	0.029	0.052	0.069
*R*2 (F^2)	0.073	0.062	0.082	0.126
$\rho_{fin.}$ (max) [e·Å^{-3}]	0.185	0.122	0.133	0.155
Absolute structure parameter	0.00(6)	0.03(5)	−	−

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