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Addition of titanium ester enolates to aldimines containing a chiral α-methylbenzylamine moiety: synthesis of chiral *syn*-β-amino esters

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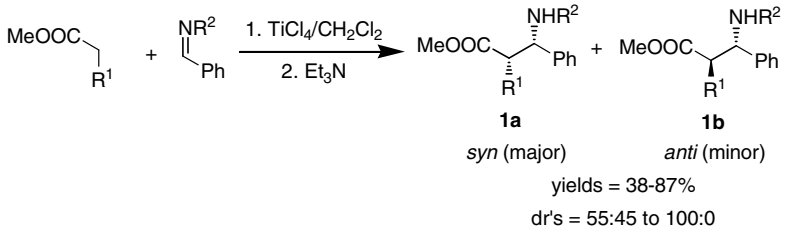
Abstract—Addition of titanium ester enolates to *N*-arylidene derivatives containing a (*R*)-α-methylbenzylamine moiety afforded (2*S*,3*S*,α*R*)-β-amino esters in 73–93% yields with 86:14 to 96:4 diastereomeric ratios.

1. Introduction

In recent years, there has been a large amount of interest in the asymmetric synthesis of β-amino acids and esters as they are useful building blocks for the synthesis of β-lactams[1a–g] and β-peptides that are present in several potent drugs.[1h] Also, β-amino acid moiety is an integral part in numerous biologically and pharmacologically important compounds.[2] Several methods are available for the synthesis of chiral β-amino acids:[3,4] (i) from chiral pool α-amino acids; methods, which include Arndt-Eistert homologation and utilizing aspartic acid, asparagine and their derivatives as starting materials,[5] (ii) classical and enzymatic resolutions of racemic β-amino acids,[6] (iii) selective transformation of one of the carbonyl groups of functionalized succinates into an amino group by means of Curtius rearrangements,[7] (iv) asymmetric conjugate additions of amine nucleophiles to α,β-unsaturated carbonyl compounds,[3c,8] (v) asymmetric hydrogenation of 3-amino acrylates and derivatives,[9] (vi) asymmetric aminohydroxylation of α,β-unsaturated esters,[10] and (vii) asymmetric additions of carbon nucleophiles to imine equivalents, including the addition of metal enolates to C=N, addition of Reformatsky reagents to imines and the addition of carbon nucleophiles to nitrones or oximes (Mannich-type reactions).[3,4,11] Among these methods an asymmetric Mannich-type reaction that leads to β-amino acid derivatives has attracted considerable interest. Herein, we report a *syn*-selective synthesis of chiral β-amino esters by the addition of titanium enolates of prochiral esters to chiral imines.

2. Results and discussion

Previously, it was observed that the titanium enolate-mediated Mannich-type reactions of esters and imines delivered the corresponding *syn*-β-amino esters **1** in good yields and with good selectivity (Scheme 1).[12]



Scheme 1.

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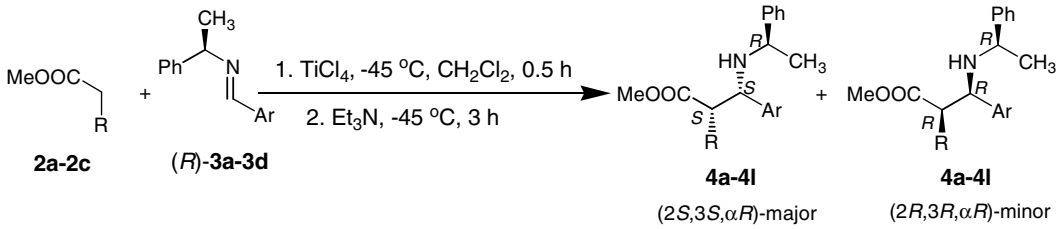


Scheme 2.

We observed that the reaction between different esters **2a**–**2c** and chiral α-methylbenzylamine-derived imines **3a**–**3d** using the $TiCl_4/Et_3N$ reagent system gives the corresponding β-amino esters **4a**–**4l** in good yields and selectivities (Scheme 2). The results are summarized in Table 1.

The ^{13}C NMR data revealed that only two diastereomers are formed in these cases. The diastereomeric ratios (aprox. dr's) of the β-amino esters were estimated by the ^{13}C NMR signals. In some cases, the 3,5-dinitrobenzamide derivatives were prepared (Scheme 3), while the diastereomeric ratios (dr's) of these derivatives were determined by HPLC analysis (Table 2). The structures of these derivatives were also analyzed by single crystal X-ray data.

The single crystal X-ray data of the 3,5-dinitrobenzamide derivatives **6a**,[13] **6b**,[14] and **6c**[15] of the major isomers of the β-amino esters **4a**, **4e**, and **4i**, respectively, revealed that the substituents of the newly formed stereocenters C2 and C3 are in a *syn* relationship to each other with a (2*S*,3*S*,α*R*)-absolute configuration.[16] The ORTEP diagrams of compounds **6a**, **6b**, and **6c** are shown in Figures 1–3, respectively.

Table 1. Mannich-type reactions of esters and chiral imines

Entry	R (ester)	Ar (imine)	Yield of product **4**[a]	dr[f] (approx.)
1	**2a** C_2H_5	**3a** C_6H_5	**4a** 82[b]	92:8
2	**2a** C_2H_5	**3b** *p*-MeC_6H_4	**4b** 79[c]	93:7
3	**2a** C_2H_5	**3c** *p*-$MeOC_6H_4$	**4c** 81[c]	96:4
4	**2a** C_2H_5	**3d** *p*-ClC_6H_4	**4d** 76[c]	89:11
5	**2b** Bn	**3a** C_6H_5	**4e** 79[b]	86:14
6	**2b** Bn	**3b** *p*-MeC_6H_4	**4f** 84[d]	91:9
7	**2b** Bn	**3c** *p*-$MeOC_6H_4$	**4g** 81[d]	95:5
8	**2b** Bn	**3d** *p*-ClC_6H_4	**4h** 80[d]	94:6
9	**2c** ^{i}Pr	**3a** C_6H_5	**4i** 93[b]	93:7
10	**2c** ^{i}Pr	**3b** *p*-MeC_6H_4	**4j** 90[e]	88:12
11	**2c** ^{i}Pr	**3c** *p*-$MeOC_6H_4$	**4k** 85[e]	90:10
12	**2c** ^{i}Pr	**3d** *p*-ClC_6H_4	**4l** 73[e]	86:14

[a] The structures of the products were confirmed by spectral data (IR, ^1H NMR, ^{13}C NMR, and mass spectrometry) and elemental analyses. Yields are for isolated products.

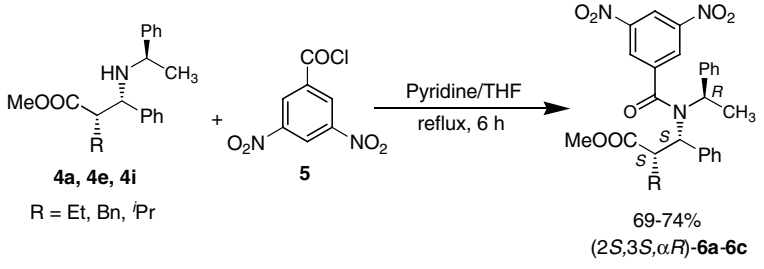
[b] The (2*S*,3*S*,α*R*)-absolute configuration was assigned to the major diastereomers of the products **4a**, **4e**, and **4i** based on the crystal structures of their 3,5-dinitrobenzamide derivatives **6a**, **6b**, and **6c**, respectively.

[c] The *syn* stereochemistry was assigned for the major isomers of the products **4b**–**4d** by comparison of the ^1H NMR (400 MHz) data with those of **4a**.

[d] The stereochemistry of the major products **4f**–**4h** was assigned as *syn* by comparison of the ^1H NMR (400 MHz) data with those of **4e**.

[e] The *syn* stereochemistry was assigned for the major isomers of the products **4j**–**4l** by comparison of the ^1H NMR (400 MHz) data with those of **4i**.

[f] The diastereomeric ratio (dr) was determined by ^{13}C NMR (100 MHz) signals and hence can only be a rough estimate. HPLC analysis of the 3,5-dinitrobenzamide derivatives of the β-amino esters **4a**, **4e**, and **4i** indicated that the amide products **6a**, **6b**, and **6c** are very pure (Table 2). Presumably, further purification occurred during workup in these cases.



Scheme 3.

Table 2. Synthesis of 3,5-dinitrobenzamide derivatives **6**

S. no.	R	Yield of product **6** (%)[a]	de (%)[b]
1	Et	**6a** 74	>98
2	Bn	**6b** 71	>96
3	^{i}Pr	**6c** 69	>94

[a] Yields are for isolated products. The samples were crystallized from DMF for X-ray crystal structure analysis.
[b] The de's were determined by HPLC analysis using Chiralcel OD-H column using 90:10 hexanes/isopropanol as eluent.

The stereochemistry for the major isomers of the β-amino esters **4b–4d** was assigned as *syn* by comparing the ^{1}H NMR data with those of **4a**. The ^{13}C NMR data revealed that only two diastereomers were formed in the reaction. The $[\alpha]_D$ values obtained for all methyl butyrate derived-β-amino esters **4a–4d** were in the range of 40–45. Accordingly, the absolute configuration of the new stereocenters of the major isomers of the β-amino esters **4b–4d** could be assigned tentatively as (*S*,*S*).

In the reactions using methyl hydrocinnamate (Table 1, entries 5–8), the corresponding β-amino esters **4e–4h** were obtained in good yields and selectivities. The configuration of the newly formed stereocenters of **4e** was assigned as (*S*,*S*) by X-ray structure analysis of its amide derivative **6b**. The *syn* stereochemistry was assigned for the β-amino esters **4f–4h** by the comparison of the ^{1}H NMR data with those of **4e**. In these cases, the absolute configuration of the new stereocenters was assigned tentatively as (*S*,*S*). This assignment was made on the basis of the $[\alpha]_D$ values, which are comparable.

The Mannich-type reaction of methyl isovalerate **2c** with chiral imines **3a–3d** (Table 1, entries 9–12) in the presence of the $TiCl_4/Et_3N$ reagent system proceeded in the same way to afford the corresponding β-amino esters **4i–4l** in excellent yields and with good selectivity. The configuration of the newly formed stereocenters of **4i** was assigned as (*S*,*S*) by X-ray structure analysis of the amide derivative **6c**. The configurations of the β-amino esters **4j–4l** were assigned as *syn* by comparison of the ^{1}H NMR data with that obtained for compound **4i**. Here also, the absolute configuration for the new stereocenters can be tentatively assigned as (*S*,*S*) by comparison of the $[\alpha]_D$ values.

We have also carried out the Mannich-type reaction of methyl butyrate **2a** and imine (*S*)-**3a**, containing a (*S*)-α-methylbenzylamine moiety, using the $TiCl_4/Et_3N$ reagent system (Scheme 4). The corresponding β-amino ester **7** was formed in good yield and with good selectivity (Scheme 4). Product **7** would be the enantiomer of the β-amino ester **4a** containing the (*R*)-α-methylbenzylamine moiety.

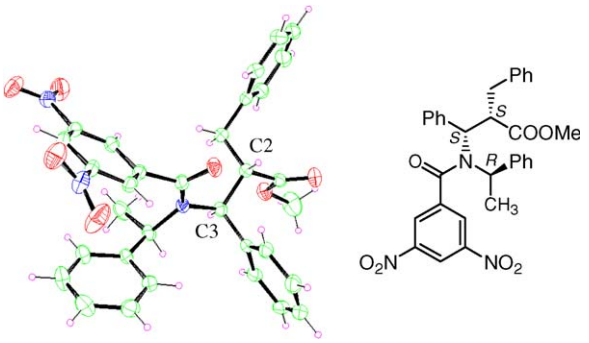


Figure 2. ORTEP representation of the crystal structure of compound **6b** (thermal ellipsoids are drawn at 20% probability).

This is indeed the case as revealed by the $[\alpha]_D$ value, HPLC and single crystal X-ray analyses of the corresponding 3,5-dinitrobenzamide derivative **8** of the β-amino ester **7** (Scheme 5).

The X-ray structural analysis of compound **8** revealed that the new stereocenters C2 and C3 possess the (*R*,*R*)-absolute configuration.[17,16] The ORTEP diagram of compound **8** is shown in Figure 4.

The α-methylbenzyl moiety attached to the nitrogen atom in the β-amino ester **4a** was selectively deprotected by a hydrogenolysis reaction using the Pd/C reagent. The β-amino ester **9** obtained in this way was hydrolyzed using 6 M HCl to give the corresponding β-amino acid hydrochloride salt **10**, which gave the free β-amino acid **11** on treatment with aq $NaHCO_3$ (Scheme 6).

The *syn* diastereoselectivity realized in the Mannich-type reactions of esters and imines (Scheme 1) has been previously explained by considering the reaction of ester titanium enolates formed in situ with achiral imines.[12] The origin of asymmetric induction in the Mannich-type reactions involving chiral α-methyl benzylamine-derived imines can be rationalized considering the following aspects: (i) The geometry of titanium enolate is expected to be *E*, and that of imine is *E*.[18] (ii) Ab initio DFT calculations (at $B_3LYP/6\text{-}31\ G^*$ level) of the conformations **A–F** of imine **3a** revealed that conformation **C** is more stable

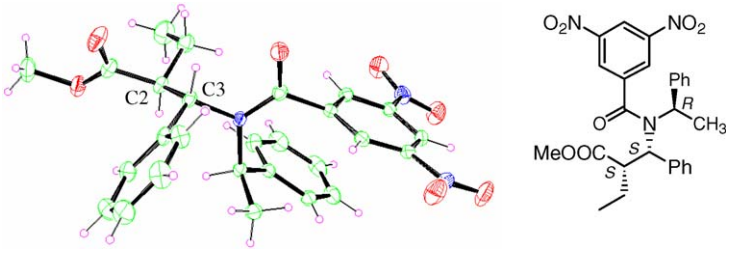


Figure 1. ORTEP representation of the crystal structure of compound **6a** (thermal ellipsoids are drawn at 20% probability).

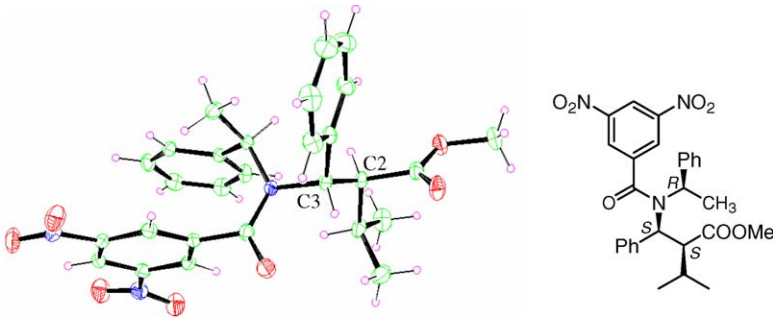
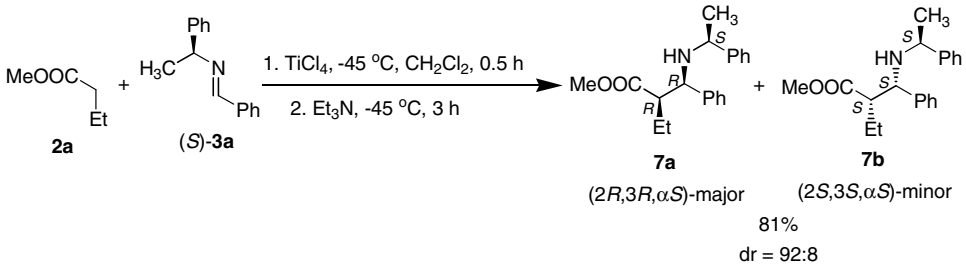
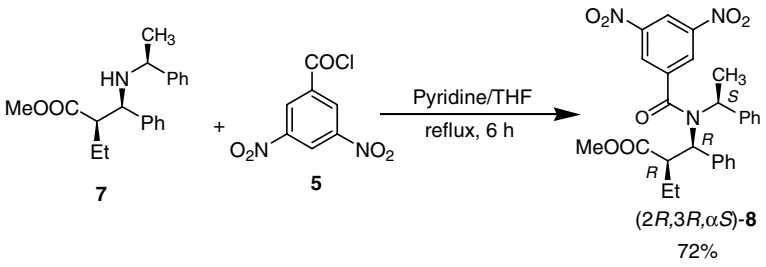


Figure 3. ORTEP representation of the crystal structure of compound **6c** (thermal ellipsoids are drawn at 20% probability).



Scheme 4.



Scheme 5.

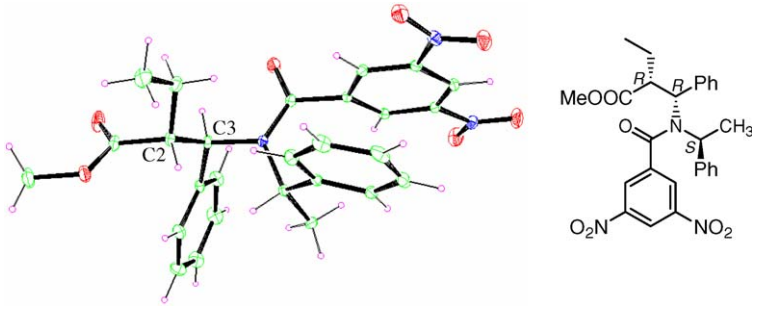
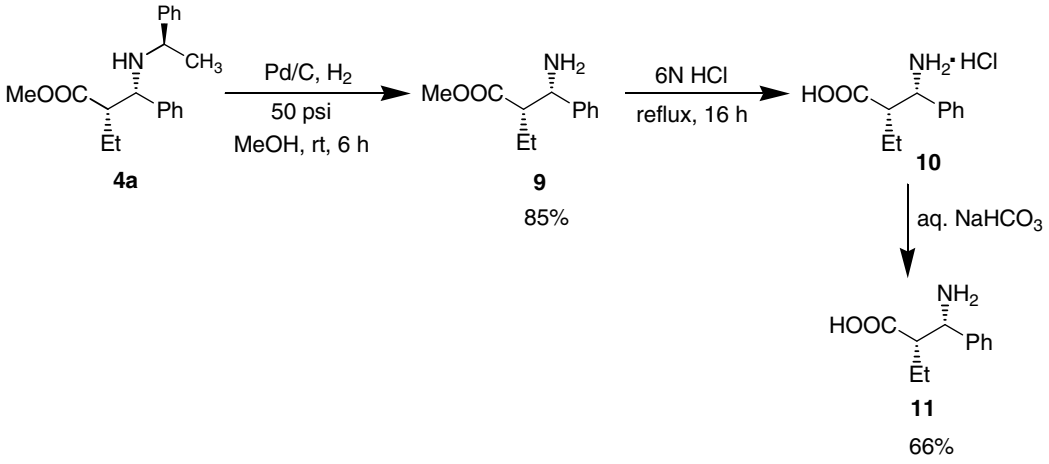


Figure 4. ORTEP representation of the crystal structure of compound **8** (thermal ellipsoids are drawn at 20% probability).

(Fig. 5). Previous theoretical calculations also predicted that conformer **C** is more stable.[19a] The *syn* arrangement of 'H' atoms in the H–C–N–C–H moiety of the imine is the most stable based on the 1,3-allylic strain model.[19] It is well-documented that the bisected conformations are less stable compared to the corresponding eclipsed conformations in the case of olefins and carbonyl compounds (e.g., propene and acetaldehyde).[20]

The stereochemical outcome of the reaction (Scheme 2) can be readily explained by considering the interaction of conformation **C** with the titanium ester enolate. The *Si* face



Scheme 6.

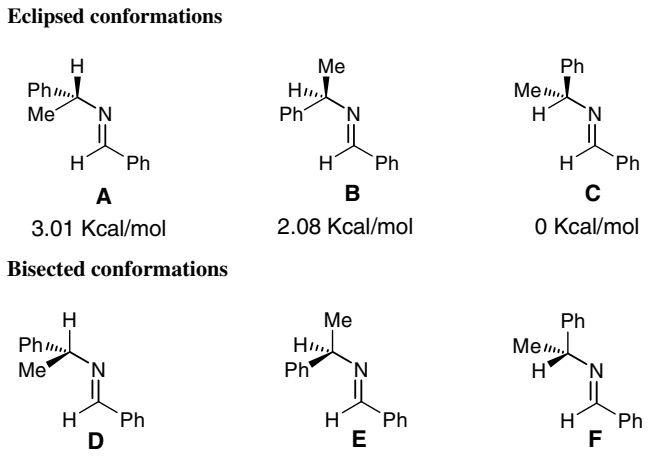


Figure 5. Conformations of imine **3a**.

attack of an ester enolate onto an imine (conformer **C**) in **TS-1** would be more favorable because in this, the large phenyl group is positioned far away from the C–C bond forming side (Fig. 6). Hence, the low-energy transition state **TS-1** would give the major isomer, with a (2*S*,3*S*,α*R*)-absolute configuration, whereas the *Re* face attack of the enolate onto the imine would experience greater repulsions from the large phenyl substituent on the chiral imine, which is positioned on the C–C bond forming side, leading to the high-energy transition state **TS-2** and meaning that the formation of the (2*R*,3*R*,α*R*)-isomer is not favorable (Fig. 6).

3. Conclusions

Chiral *syn* β-amino acid moieties are present in several biologically important compounds, such as onchidin, jasplakinolide and motuporin.[2b] It is noteworthy that taxol, a potent drug with antitumor activity, is composed of a polyoxygenated diterpene and a phenylisoserine.[2b,21] A *syn* β-amino acid moiety with a (2*S*,3*S*)-absolute configuration is an integral part in two synthetic tripeptides, kynostatins (KNI)-227 and (KNI)-272, which are highly potent HIV-1 protease inhibitors and are promising candidates as selective anti-AIDS agents.[22] Hence, the method described here

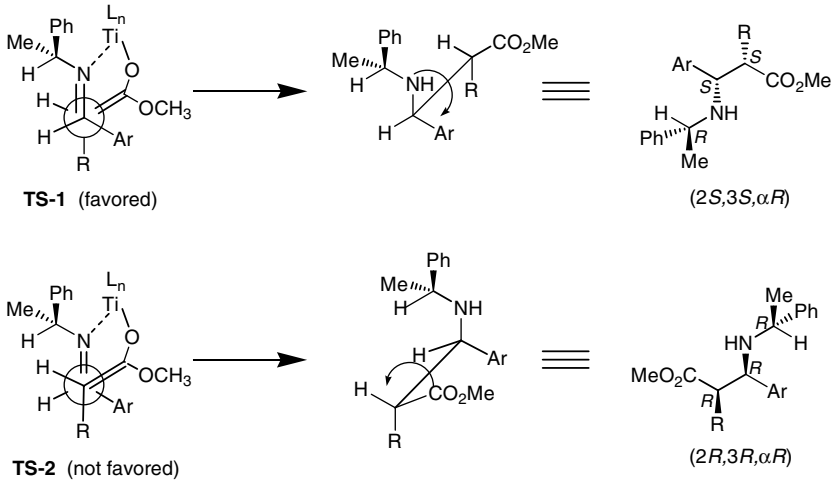


Figure 6. Stereochemical models.

for the synthesis of *syn*-α,β-disubstituted-(2*S*,3*S*)-β-amino esters using the Mannich-type reactions of titanium enolates of prochiral esters with optically active *N*-arylidene-α-methylbenzylamine has good synthetic potential.

4. Experimental

4.1. General procedure for the synthesis of chiral β-amino esters from esters and imines of enantiomerically pure α-methylbenzylamine

The chiral imine (5 mmol) and ester (5.2 mmol) were taken in dichloromethane (40 mL) and $TiCl_4$ (12 mmol, 2.3 mL of a 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (15 mL) was then added at −45 °C dropwise over 15 min under an N_2 atmosphere. After stirring for 0.5 h, triethylamine (0.51 g, 0.70 mL, 5 mmol) was added and the mixture stirred further for 3 h. This was quenched with saturated aq K_2CO_3 (15 mL), brought to room temperature, and filtered through a Buchner funnel. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on neutral alumina, using hexanes/EtOAc (99:1) as eluent, to isolate the products.

4.1.1. Spectral data for the β-amino esters 4a–4l and 7. Compound **4a**: IR (neat): 3329, 3028, 2966, 1732 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 0.90 (t, 3H, $J = 7$ Hz), 1.30 (d, 3H, $J = 7$ Hz), 1.69 (s, NH), 1.75–1.81 (m, 2H), 2.54–2.65 (m, 1H), 3.45 (s, 3H), 3.56–3.62 (m, 1H), 3.96 (d, 1H, $J = 8$ Hz), 7.21–7.30 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): for major diastereomer: 12.2, 22.1, 22.2, 51.1, 54.7, 55.1, 61.7, 126.6, 126.9, 127.2, 127.5, 128.2, 128.4, 142.0, 146.4, 174.6; additional signals for minor diastereomer: 11.2, 21.5, 25.2, 47.5, 51.5, 61.3; Mass: M+1 = 312; Analyses: calcd: C 77.14%, H 8.09%, N 4.50%; found: C 77.03%, H 8.07%, N 4.61%; compound **4b**: IR (neat): 3329, 3026, 2967, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.88 (t, 3H, $J = 7.6$ Hz), 1.28 (d, 3H, $J = 6.4$ Hz), 1.57 (s, br, NH), 1.66–1.88 (m, 2H), 2.32 (s, 3H), 2.52–2.59 (m, 1H), 3.47 (s, 3H), 3.58–3.63 (m, 1H), 3.92 (d, 1H, $J = 7.6$ Hz), 7.03–7.10 (m, 4H), 7.20–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 12.2, 21.1, 22.0, 22.2, 51.2, 54.4, 55.0, 61.2, 126.7, 126.9, 127.3, 127.4, 128.4, 129.0, 136.7, 138.7, 146.4, 174.7; additional signals for minor diastereomer: 21.5, 25.2, 54.8, 55.1, 60.8; Mass: M+1 = 326; Analyses: calcd: C 77.50%, H 8.36%, N 4.30%; found: C 77.68%, H 8.37%, N 3.98%; compound **4c**: IR (neat): 3329, 3063, 2966, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.91 (t, 3H, $J = 8$ Hz), 1.31(d, 3H, $J = 6.4$ Hz), 1.60 (s, br, NH), 1.68–1.76 (m, 2H), 2.55–2.60 (m, 1H), 3.48 (s, 3H), 3.62 (q, 1H, $J = 6.4$ Hz), 3.82 (s, 3H), 3.91 (d, 1H, $J = 8$ Hz), 6.84 (d, 2H, $J = 8$ Hz), 7.13 (d, 2H, $J = 8$ Hz), 7.21–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 12.1, 21.9, 22.4, 51.2, 54.4, 55.1, 55.2, 61.0, 113.6, 126.6, 126.9, 128.3, 128.4, 133.8, 146.4, 158.6, 174.7; additional signal for minor diastereomer: 60.5; Mass: M+1 = 342; Analyses: calcd: C 77.87%, H 7.97%, N 4.10%; found: C 77.76%, H 7.91%, N 3.58%; compound **4d**: IR (neat): 3331, 3061, 2967, 1736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.91 (t, 3H, $J = 8$ Hz), 1.31 (d, 3H, $J = 7$ Hz), 1.58 (s, br, NH), 1.68–1.76 (m, 1H), 1.83–1.92 (m, 1H), 2.53–2.61 (m, 1H), 3.49 (s, 3H), 3.58–3.61 (m, 1H), 3.94 (d, 1H, $J = 8$ Hz), 7.11–7.18 (m, 2H), 7.22–7.32 (7H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 12.1, 22.1, 22.2, 41.4, 51.3, 54.8, 61.1, 126.6, 127.0, 128.4, 128.8, 132.8, 140.5, 146.0, 174.4; additional signals for minor diastereomer: 11.1, 21.4, 25.1; Mass: M+1 = 346; Analyses: calcd: C 69.45%, H 6.99%, N 4.05%; found: C 69.62%, H 6.76%, N 4.46%; compound **4e**: IR (neat): 3327, 3061, 2851, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.34 (d, 3H, $J = 6.4$ Hz), 1.80 (s, br, NH), 2.98–3.01 (m, 2H), 3.24–3.27 (m, 1H), 3.64–3.69 (m, 1H), 4.06 (d, 1H, $J = 6.8$ Hz), 7.13–7.20 (m, 5H), 7.24–7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 21.1, 35.3, 51.2, 54.6, 55.3, 61.8, 126.2, 126.7, 127.0, 127.4, 128.3, 128.6, 128.8, 139.8, 141.4, 146.2, 174.0; additional signals for minor diastereomer: 25.2, 34.1, 52.5, 55.0, 55.5, 60.6; Mass: M+1 = 374; Analyses: calcd: C 80.40%, H 7.29%, N 3.75%; found: C 79.50%, H 7.31%, N 3.58%; compound **4f**: IR (neat): 3323, 3026, 2957, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.30 (d, 3H, $J = 6.4$ Hz), 1.73 (s, NH), 2.33 (s, 3H), 2.96 (d, 2H, $J = 7.2$ Hz), 3.18–3.23 (m, 1H), 3.33 (s, 3H), 3.62–3.67 (m, 1H), 4.01 (d, 1H, $J = 6.8$ Hz), 7.10–7.15 (m, 4H), 7.17–7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 21.2, 22.1, 35.3, 51.1, 54.5, 55.2, 61.4, 126.1, 126.7, 127.0, 127.3, 128.3, 128.4, 128.8, 129.1, 136.9, 138.2, 139.9, 146.3, 174.0; additional signals for minor diastereomer: 25.3, 34.5, 54.9, 55.6, 61.1; Mass: M+1 = 388; compound **4g**: IR (neat): 3325, 3061, 2953, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.33 (d, 3H, $J = 6$ Hz), 1.62 (s, br, NH), 2.97–3.02 (m, 2H), 3.24–3.26 (m, 1H), 3.35 (s, 3H), 3.62–3.67 (m, 1H), 3.82 (s, 3H), 4.01 (d, 1H, $J = 6.4$ Hz), 6.86 (d, 4H, $J = 9$ Hz), 7.11–7.20 (m, 5H), 7.24–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 22.2, 35.5, 51.2, 54.6, 55.2, 55.4, 61.2, 113.7, 126.2, 126.7, 127.0, 128.4, 128.5, 128.9, 133.4, 139.9, 146.3, 158.8, 174.1; additional signals for minor diastereomer: 22.7, 34.7, 51.8, 54.9, 55.7, 60.8; Mass: M+1 = 404; Analyses: calcd: C 77.39%, H 7.24%, N 3.47%; found: C 77.34%, H 7.24%, N 3.60%; compound **4h**: IR (neat): 3024, 2964, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.31 (d, 3H, $J = 6.8$ Hz), 1.73 (s, br, NH), 2.94–3.00 (m, 2H), 3.14–3.19 (m, 1H), 3.33 (s, 3H), 3.58–3.61 (m, 1H), 4.01 (d, 1H, $J = 6.8$ Hz), 7.11 (d, 2H, $J = 7.6$ Hz), 7.15 (d, 2H, $J = 7.2$ Hz), 7.18–7.31 (10H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 22.2, 35.3, 51.3, 54.9, 55.1, 61.3, 126.3, 126.7, 127.1, 128.5, 128.8, 128.9, 129.0, 133.0, 139.5, 140.1, 145.9, 173.8; additional signals for minor diastereomer: 22.7, 34.4, 55.3, 60.1; Mass: M+1 = 408; compound **4i**: IR (neat): 3321, 3063, 2962, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.02 (d, 3H, $J = 7.6$ Hz), 1.12 (d, 3H, $J = 6.8$ Hz), 1.34 (d, 3H, $J = 6.8$ Hz), 1.55 (s, br, NH), 2.45–2.51 (m, 1H), 2.64–2.68 (m, 1H), 3.37 (s, 3H), 3.55–3.60 (m, 1H), 4.08 (d, 3H, $J = 9.6$ Hz), 7.22–7.33 (10H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 17.5, 21.6, 21.7, 27.1, 50.7, 54.2, 58.9, 126.7, 127.0, 127.2, 127.6, 128.2, 128.4, 142.1, 146.5, 173.2; additional signals

for minor diastereomer: 17.2, 21.9, 26.8, 50.6, 54.6, 59.0; Mass: M+1 = 326; compound **4j**: IR (neat): 3319, 3926, 2962, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.98 (d, 3H, $J = 6.8$ Hz), 1.08 (d, 3H, $J = 6.8$ Hz), 1.30 (d, 3H, $J = 6.4$ Hz), 1.47 (s, br, NH), 2.31 (s, 3H), 2.39–2.44 (m, 1H), 2.59–2.63 (m, 1H), 3.37 (s, 3H), 3.52–3.57 (m, 1H), 4.02 (d, 1H, $J = 10$ Hz), 7.03–7.08 (m, 4H), 7.19–7.24 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 17.6, 21.1, 21.6, 21.6, 27.1, 50.7, 54.1, 58.5, 58.9, 126.7, 126.9, 127.2, 127.4, 127.6, 128.3, 128.9, 136.6, 139.0, 146.6, 173.2; additional signals for minor diastereomer: 17.3, 31.9, 26.8, 50.6, 54.5, 59.1; Mass: M+1 = 340; Analyses: calcd: C 77.84%, H 8.61%, N 4.13%; found: C 77.70%, H 8.59%, N 4.88%; compound **4k**: IR (neat): 3320, 3061, 2963, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.98 (d, 3H, $J = 6.8$ Hz), 1.08 (d, 3H, $J = 6.4$ Hz), 1.30 (d, 3H, $J = 6.4$ Hz), 1.43 (s, br, NH), 2.38–2.42 (m, 1H), 2.52–2.62 (m, 1H), 3.37 (s, 3H), 3.52–3.57 (m, 1H), 3.80 (s, 3H), 4.00 (d, 1H, $J = 9.6$ Hz), 6.81 (d, 2H, $J = 8.4$ Hz), 7.12 (d, 2H, $J = 8.4$ Hz), 7.21–7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 17.5, 21.6, 27.1, 50.7, 54.1, 58.2, 59.0, 113.5, 128.3, 128.6, 128.8, 134.2, 146.5, 158.6, 173.3; additional signals for minor diastereomer: 17.2, 21.8, 26.8, 54.5, 59.2; Mass: M+1 = 356; Analyses: calcd: C 74.33%, H 8.22%, N 3.94%; found: C 74.37%, H 8.49%, N 4.61%; compound **4l**: IR (neat): 3324, 3061, 2965, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.98 (d, 3H, $J = 6.8$ Hz), 1.07 (d, 3H, $J = 6.8$ Hz), 1.30 (d, 3H, $J = 6.4$ Hz), 1.49 (s, br, NH), 2.37–2.44 (m, 1H), 2.57–2.61 (m, 1H), 3.38 (s, 3H), 3.49–3.54 (m, 1H), 4.02 (d, 1H, $J = 9.6$ Hz), 7.14 (d, 2H, $J = 8$ Hz), 7.19 (d, 2H, $J = 8$ Hz), 7.22–7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 17.5, 21.5, 21.7, 27.1, 54.4, 58.5, 58.7, 126.6, 127.0, 128.4, 129.0, 129.2, 132.8, 140.8, 146.1, 173.0; additional signals for minor diastereomer: 17.2, 21.9, 26.8, 54.6, 58.2, 58.9; Mass: M+1 = 360; compound **7**: IR (neat): 3329, 3062, 2966, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.91 (t, 3H, $J = 7$ Hz), 1.29 (d, 3H, $J = 7$ Hz), 1.67 (s, NH), 1.74–1.81 (m, 2H), 2.52–2.63 (m, 1H), 3.46 (s, 3H), 3.57–3.61 (m, 1H), 3.95 (d, 1H, $J = 8$ Hz), 7.20–7.28 (10H); ^{13}C NMR (100 MHz, $CDCl_3$): for major diastereomer: 12.2, 22.1, 22.3, 51.1, 54.7, 55.1, 61.7, 126.7, 126.9, 127.2, 127.5, 128.3, 128.4, 141.9, 146.4, 174.6; additional signals for minor diastereomer: 11.3, 21.5, 25.2, 47.5, 51.5, 61.2; Mass: M+1 = 312.

4.2. General procedure for the synthesis of 3,5-dinitrobenzamide derivatives of β-amino esters

To a solution of representative β-amino ester (3 mmol) in THF (20 mL) was added freshly prepared 3,5-dinitrobenzoyl chloride (0.69 g, 3.2 mmol) at 0 °C under an N_2 atmosphere. Then, pyridine (0.28 g, 0.28 mL, 3.5 mmol) was added slowly and the contents were brought to 25 °C and refluxed gently for 6 h. The reaction mixture was then cooled to room temperature and water (10 mL) was added. The organic solvent was evaporated and the crude product extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was subjected to column chromatography on silica gel using hexanes/EtOAc (90:10) as eluent to isolate the products.

4.2.1. Spectral data for compounds 6a–6c and 8. Compound **6a**: mp: 138–140 °C; IR (neat): 3063, 2962, 1734, 1622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.85 (t, 3H, $J = 7$ Hz), 1.15–1.28 (m, 1H), 1.40 (d, 3H, $J = 7$ Hz), 1.58–1.70 (m, 2H), 3.39 (s, 3H), 3.72–4.08 (m, 1H), 4.69–4.74 (m, 1H), 7.00–7.40 (m, 10H), 7.60 (s, 1H), 8.31 (s, 1H), 8.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.8, 18.6, 24.1, 51.4, 58.8, 60.4, 64.5, 118.7, 126.1, 127.6, 128.5, 128.8, 129.0, 138.6, 140.5, 140.8, 141.7, 148.3, 167.9, 174.6; Mass: M+23 = 528; Analyses: calcd: C 64.15%, H 5.38%, N 8.31%; found: C 64.22%, H 5.34%, N 8.04%; compound **6b**: mp: 90–92 °C; IR (neat): 3030, 2949, 1732, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 1.51 (d, 3H, $J = 7$ Hz), 2.12 (s, br, 1H), 2.88–2.91 (m, 1H), 3.11 (s, 3H), 4.39 (s, br, 1H), 4.69 (s, br, 1H), 4.96 (s, br, 1H), 7.09–7.40 (13H), 7.68 (s, br, 2H), 8.44 (s, br, 2H), 9.06 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.5, 37.3, 51.3, 52.6, 59.6, 64.5, 119.0, 126.1, 126.6, 127.9, 128.4, 128.7, 128.8, 129.1, 138.2, 140.4, 141.6, 148.5, 167.5, 174.1; Mass: M−1 = 566; Analyses: calcd: C 67.72%, H 5.15%, N 7.40%; found: C 67.71%, H 5.16%, N 7.50%; compound **6c**: mp: 204–206 °C; IR (neat): 3067, 2961, 1730, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.55–0.56 (m, 3H), 1.06 (s, br, 3H), 1.27 (s, 1H), 1.39–1.40 (m, 3H), 2.18 (s, 1H), 3.45 (s, 3H), 4.86 (s, br, 2H), 6.96 (s, br, 2H), 7.26–7.28 (m, 4H), 7.38–7.40 (m, 2H), 7.68 (s, br, 2H), 8.26 (s, br, 2H), 8.98 (s, br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.4, 18.9, 22.2, 27.4, 51.0, 53.9, 58.1, 62.2, 118.5, 126.2, 127.5, 128.3, 128.9, 139.1, 140.6, 141.9, 148.1, 168.4, 172.0; Mass: M−1 = 518; Analyses: calcd: C 64.73%, H 5.63%, N 8.09%; found: C 64.96%, H 5.77%, N 8.15%; compound **8**: mp: 140–142 °C; IR (neat): 3061, 2965, 1732, 1626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.84 (t, 3H, $J = 7$ Hz), 1.17–1.29 (m, 1H), 1.42 (d, 3H, $J = 7$ Hz), 1.60–1.70 (m, 1H), 3.38 (s, 3H), 3.69–4.06 (m, 1H), 4.70–4.76 (m, 1H), 6.69–7.41 (m, 10H), 7.61 (s, 1H), 8.30 (s, 1H), 9.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 11.8, 18.7, 24.2, 51.4, 58.8, 64.6, 118.7, 126.2, 127.7, 128.5, 128.8, 129.0, 141.8, 148.3, 167.9, 174.5; Mass: M+1 = 506.

4.3. Typical procedure for the synthesis of β-amino acid from the β-amino ester 4a

To a solution of β-amino ester **4a** (1.56 g, 5 mmol) in MeOH (30 mL) was added Pd/C reagent (50 mg), and the mixture was shaken mechanically under hydrogen pressure (50 psi) for 6 h. The reaction mixture was filtered and the filtrate concentrated. The crude product was subjected to column chromatography on neutral alumina using hexane/EtOAc (95:5) as eluent. The free β-amino ester **10** was obtained in 85% yield.

The β-amino ester **9** (1.56 g, 5 mmol) was taken in 6 M HCl (20 mL) and refluxed for 16 h. The β-amino acid hydrochloride salt **10** was obtained after the removal of the solvent by evaporation. The salt **10** was treated with aq $NaHCO_3$ to give the free β-amino acid **11** in 66% yield.

4.3.1. Spectral data for compounds 9–11. Compound **9**: IR (neat): 3381, 3316, 3063, 2966, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 0.90 (t, 3H, $J = 7.4$ Hz), 1.67 (s, 2H),

1.70–1.76 (m, 2H), 2.57–2.60 (m, 1H), 3.49 (s, 3H), 4.15 (d, 1H, $J = 7.1$ Hz), 7.23–7.32 (5H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.0, 21.4, 51.2, 55.7, 57.5, 126.7, 127.3, 128.3, 143.8, 174.7; Mass: M+1 = 208; **10**: IR (KBr): 2962, 1715, 1604, 1498 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): 1.04 (t, 3H, $J = 7.4$ Hz), 1.68–1.82 (m, 2H), 2.91–2.96 (m, 1H), 3.30 (s, br, 2H), 3.35 (s, br, 1H), 4.42 (d, 1H, $J = 9$ Hz), 7.40–7.43 (5H); ^{13}C NMR (100 MHz, CD_3OD): 10.6, 22.1, 51.5, 56.5, 127.5, 128.8, 129.2, 135.4, 173.6; **11**: IR (KBr): 3433, 2968, 1717, 1601 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): 0.92 (t, 3H, $J = 7.5$ Hz), 1.54–1.67 (m, 2H), 2.41–2.48 (m, 1H), 3.30–3.35 (3H), 4.05 (d, 1H, $J = 7.6$ Hz), 7.27–7.32 (m, 2H), 7.39–7.43 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): 13.0, 22.2, 24.3, 59.1, 127.9, 128.2, 129.2, 180.6.

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13. Crystal data: For compound **6a**: molecular formula: $C_{27}H_{27}N_3O_7$, MW = 505.52, monoclinic, space group: $P2(1)$, $a = 11.3587(8)$ Å, $b = 6.7522(5)$ Å, $c = 17.6162(12)$ Å, $\beta = 107.5420(10)°$, $V = 1288.26(16)$ Å^3, $Z = 2$, $\rho_c = 1.303$ mg m^{-3}, $\mu = 0.095$ mm^{-1}, $T = 293(2)$ K. Of the 5792 reflections collected, 3877 were unique ($R_{int} = 0.0000$).

Refinement on all data converged at $R_1 = 0.0490$, $wR_2 = 0.0830$ (deposition number CCDC 265595).

14. Crystal data: For compound **6b**: molecular formula: $C_{32}H_{29}N_3O_7$, MW = 567.60, tetragonal, space group: *P*4(3), $a = 9.1861(2)$ Å, $b = 9.1861(2)$ Å, $c = 34.6903(13)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 2927.32(14)$ Å^3, $Z = 4$, $\rho_c = 1.288$ mg m^{-3}, $\mu = 0.092$ mm^{-1}, $T = 293(2)$ K. Of the 28,207 reflections collected, 5119 were unique ($R_{int} = 0.0720$). Refinement on all data converged at $R_1 = 0.0582$, $wR_2 = 0.0803$ (deposition number CCDC 293264).
15. Crystal data: For compound **6c**: molecular formula: $C_{28}H_{29}N_3O_7$, MW = 519.54, monoclinic, space group: *P*2(1), $a = 11.3739(7)$ Å, $b = 6.7949(5)$ Å, $c = 17.7374(12)$ Å, $\beta = 106.3300(10)°$, $V = 1315.52(15)$ Å^3, $Z = 2$, $\rho_c = 1.312$ mg m^{-3}, $\mu = 0.095$ mm^{-1}, $T = 293(2)$ K. Of the 15,427 reflections collected, 5986 were unique ($R_{int} = 0.0363$). Refinement on all data converged at $R_1 = 0.0439$, $wR_2 = 0.0758$ (deposition number CCDC 293263).
16. X-ray data of compounds **6a**, **6b**, and **6c** revealed that the major isomer possesses *syn* stereochemistry. The absolute configurations at the new stereocenters C2 and C3 were assigned as *S* and *S*, respectively, using the PLATON program, Spek, A. L. version 210103 (Spek, A. L. PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands, 2002). The absolute configurations at the new stereocenters were also further checked relative to the α-methylbenzyl stereocenter.
17. Crystal data: For compound **8**: molecular formula: $C_{27}H_{27}N_3O_7$, MW = 505.52, monoclinic, space group: *P*2(1), $a = 11.365(3)$ Å, $b = 6.7529(19)$ Å, $c = 17.633(5)$ Å, $\beta = 107.620(4)°$, $V = 1289.8(6)$ Å^3, $Z = 2$, $\rho_c = 1.302$ mg m^{-3}, $\mu = 0.095$ mm^{-1}, $T = 293(2)$ K. Of the 15,071 reflections collected, 5937 were unique ($R_{int} = 0.0291$). Refinement on all data converged at $R_1 = 0.0557$, $wR_2 = 0.1130$ (deposition number CCDC 293262).
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