Synthesis and Structural Characteristics of Geminally Disubstituted β-Amino Acids

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We dedicate this to Professor Clayton Heathcock on the occasion of his retirement.

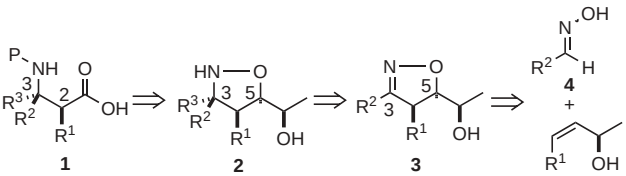
Abstract: The syntheses of seven new β-amino acids containing aryl, alkyl, and heteroaryl substituents are outlined. The synthetic strategy employs densely functionalized chiral isoxazolines as key intermediates, enabling the preparation of single stereoisomers of these challenging targets. Solid-state characterization of two of the sterically encumbered targets is also reported.

Key words: cycloadditions, β-amino acid, diastereoselectivity, isoxazolidine, amino alcohol

Stereoisomerically pure β-amino acids (**1**) serve as important constituents of both natural and non-natural materials and, as a result, have been the focal point of much synthetic effort.[1,2] β-Peptides (oligomers of β-amino acids) often adopt stable secondary structures such as helices, beta turns and beta sheets and have successfully been used to mimic the structure and function of naturally occurring α-amino acid oligomers.[1b,c,g] An additional attractive feature of β-amino acids is their increased resistance to proteolysis relative to α-amino acids, increasing their utility in biological settings.[3] Both the propensity to adopt secondary structure and the proteolytic stability of β-peptides are dependent on the substitution patterns of the β-amino acid constituents. The selective synthesis of β-amino acids with specific substitution patterns thus continues to inspire the development of novel synthetic methods.[1–7]

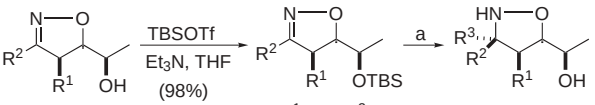
A class of β-amino acids that has proven particularly difficult to access as single stereoisomers are those highly substituted at the C3 position (e.g., $\beta^{3,3}$- and $\beta^{2,3,3}$-amino acids).[2c,4–7] This is especially true in cases where the substituents (R_2 and R_3 in Scheme 1) are either sterically similar[6] and/or are bulky in size.[7] Consequently, although $\beta^{3,3}$- and $\beta^{2,3,3}$-amino acids are predicted to impart interesting structural and thus functional properties to oligomers, they have remained largely unexplored.[2c] In this report we describe the selective preparation of seven new β-amino acids of this class incorporating alkyl, aryl, and heteroaryl substituents, expanding the diversity of β-amino acids available for application and study. In addition, solid-state structures of two of these densely functionalized amino acids are provided, confirming the stereochemical assignments and revealing packing arrangements of infinite sheets or helices dictated by hydrogen bonding.

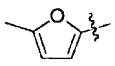
Isoxazolines (**3**) provide an excellent starting point for the preparation of β-amino acids[7] as they are easily prepared as single isomers from the 1,3-dipolar cycloaddition of nitrile oxides and allylic alcohols (Scheme 1).[8] Addition of a nucleophile to the C=N moiety of **3** then provides isoxazolidines (**2**) that contain the substitution patterns and stereochemical relationships present in the β-amino acid target.



Scheme 1 Retrosynthetic analysis of β-amino acids

Table 1 Organolithium Addition Reactions[14]



Product[a]	R^1	R^2	R^3	Yield (%)[15]	dr[b]
10a	H	*i*-Bu	Me	80	20:1[c]
10b	H	*i*-Bu	Ph	60	20:1[c]
10c	H	*i*-Bu		80	13:1
10d	H	*i*-Bu		80	10:1
10e	H	*i*-Bu		82	15:1
11a	Ph	Et	Me	70	20:1[c]
11b	Ph	Et	Ph	49	20:1[c]

[a] (i) R^3Li, $BF_3{\cdot}OEt_2$, toluene, –78 °C, 2–6 h; (ii) TBAF, THF, 0 °C to r.t., 3 h.
[b] From ^1H NMR spectral integration of the crude product mixture.
[c] A single stereoisomer observed by ^1H NMR.

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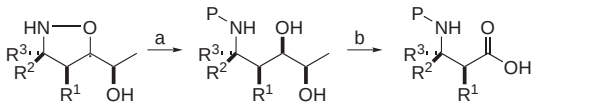
Transformation to the final β-amino acid product then proceeds through cleavage of the N-O bond and protection of the free amine followed by an oxidative cleavage of the diol moiety. A primary advantage of this approach is that judicious choice of the readily available starting materials (allylic alcohol, oxime, and nucleophile) can in principle provide access to a wide variety of β-amino acids as single stereoisomers.

There were several points to be investigated regarding the application of the strategy outlined above to the synthesis of $\beta^{3,3}$- and $\beta^{2,3,3}$-amino acids incorporating alkyl, aryl, and heteroaryl substituents. Although preliminary results indicated that methyl and phenyl groups could be added selectively to a C3-substituted isoxazoline via the corresponding organolithium reagents if the 2° hydroxyl group on the C5 substituent were masked,[7] this had yet to be explored with the heteroaryl nucleophiles needed to produce the target products.[9,10]

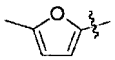
Table 2 Conversion to β-Amino Acids



10a-e: R^1 = H, R^2 = *i*-Bu
11a-b: R^1 = Ph, R^2 = Et

12a-e
13a-b

14a-e: R^1 = H, R^2 = *i*-Bu
15a-b: R^1 = Ph, R^2 = Et

β-Amino acid[a,b]	R^3	Yield of **12**/**13** (%)[c]	Yield of **14**/**15** (%)[16]	$[\alpha]_D$ **14** ($CHCl_3$)
14a	Me	78	70	–12.2
14b	Ph	71	82	+11.8
14c		70	84	– 3.2
14d		78	75	– 5.1
14e		75	80	+17.8
15a	Me	68	95	–
15b	Ph	46	71	–

[a] (i) $LiAlH_4$, Et_2O, 0 °C to r.t., 8 h; (ii) BOC_2O, THF–H_2O, pH 10, 12 h.
[b] (i) $NaIO_4$, MeCN–H_2O (1:1), r.t., 30 min; (ii) $NaClO_2$, 2-methyl-2-butene, KH_2PO_4, *t*-BuOH, H_2O, r.t. 2.5 h.
[c] Amine diol protected as the benzyl carbamate: CbzCl, THF–H_2O (5:1), Na_2CO_3, r.t., 12 h.

Of particular interest was the incorporation of functional groups such as 2-methylfuran that could serve as a masked carboxylic acid, key for future recognition applications. In addition, the resulting isoxazolidine products would be densely functionalized, quite hindered about the nitrogen, and, in most cases, the nitrogen would be benzylic, presenting a potential challenge for chemoselectivity in the N-O bond reduction. With aryl or heteroaryl substituents at the C3 position, reduction conditions which would be robust enough to reduce this difficult to access functional group without promoting over-reduction would thus need to be identified.

To initiate the synthesis, two isoxazolines (**6** and **7**) were prepared from the corresponding oximes and allylic alcohols in excellent yields (Table 1). In preparation for the formation of the C3 quaternery center, the 2° hydroxyl groups of **6** and **7** were protected as *t*-butyldimethylsilyl ethers as this group provides the best combination of stability to the Lewis acidic reaction conditions and ease of removal. In the case of isoxazoline **8**, PhLi and MeLi both provided the desired adducts in good to excellent yields and with high diastereoselectivity. Success was not limited to these two nucleophiles as 2-furyllithium, 5-methyl-2-furyllithium, and 2-thienyllithium also added efficiently and selectively to **8**. Furthermore, the more highly substituted isoxazoline (**7**) also served as a good substrate under these conditions, although longer reaction times were typically required for complete consumption of starting material. As shown in Table 1, this provided densely functionalized isoxazolidine products (**11a** and **11b**) in excellent diastereoselectivity. Among the various nucleophiles examined, PhLi provided the lowest yields. This result is most likely due to steric considerations as changes in solvent, Lewis acid, reaction temperature, and concentration had little impact. The facial selectivity of the addition is evidently dictated by steric considerations as NOE difference experiments carried out on a peracetylated derivative of **10a** indicated the new C3 group resides *trans* to the C5 substituent.

A number of reaction conditions were investigated for reduction of the N-O bond. In a related synthesis of a (hindered) $\beta^{2,3,3}$-amino acid,[7] hydrogenolysis was successfully employed for the N-O bond reduction. For these substrates, however, the use of 10% Pd/C with NH_4O_2CH provided poor conversion to the desired amine diol, likely due to steric hindrance; complete consumption of starting material was achieved under more forcing conditions [$Pd(OH)_2$, HCl–MeOH] but the target amine diol was isolated in low yields.[11] SmI_2 was also investigated as a reductant[12] with inconsistent results. Of the conditions examined, $LiAlH_4$ in diethyl ether produced the most consistent yields and in situ protection of the intermediate free amine provided the protected amino diols **12** and **13** (Table 2).[13] While the Boc group was suitable for the protection of most of our substrates, the sterically hindered amine diol precursor to **13b** proved resistant to protection under a variety of reaction conditions. For this substrate, protection as the less hindered benzyl carbamate proceeded more smoothly. Oxidative cleavage of the protected amine diols was then achieved using $NaIO_4$, and the resulting aldehydes were immediately oxidized to the final β-amino acids in good yields (70–95%) under standard conditions.

Two of the β-amino acids, **14b** and **15a**, were subjected to a solvent screen in order to produce single crystals for solid state analysis (Figure 1).[17] Compound **14b** is arranged through a hydrogen-bonded heterodimer motif between the carbamate of one molecule and the carboxylic acid of

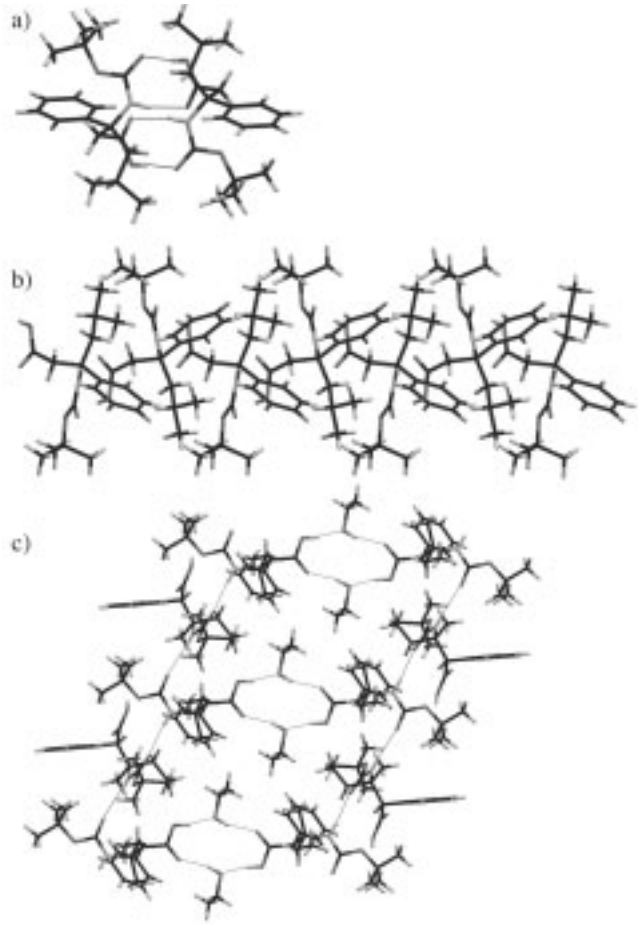


Figure 1 X-ray crystallographic structures of β-amino acids **14b** (panels a and b) and **15a** (panel c). Hydrogen bonds are indicated by light gray lines.

another, creating a very compact geometry that gives rise to infinite chains (Figure 1, a). This motif efficiently accommodates the hydrogen-bonding requirements of each functional group and results in an overall helical repeat of the *t*-butyl, phenyl, and *i*-butyl functional groups along the exterior of the columns (Figure 1, b). In the case of **15a**, the carboxylic acids dimerize through an expanded hydrogen bonding motif mediated by two ethanol molecules to form a 12-membered ring, accommodating steric congestion at the C2 and C3 positions (Figure 1, c). The chains are organized along one axis via hydrogen bonds between the carbamates and the carboxylic acids alternate position, providing space for the bridging solvent molecules and connecting adjacent chains into an infinite network.

In summary, we have outlined the selective synthesis of a series of highly substituted $\beta^{3,3}$- and $\beta^{2,3,3}$-amino acid targets employing isoxazolines as key synthetic intermediates. X-ray crystallographic studies of two of the β-amino acids provided final of structural assignments and revealed highly compact hydrogen bonding motifs leading to infinite networks in the solid state. We anticipate that these new β-amino acids will rapidly find application in peptidomimetic studies as they are among the most densely functionalized β-amino acids yet produced. In addition to serving as essential building blocks for novel β-peptides, the synthetic intermediates prepared contain up to four contiguous stereocenters, including an amine-bearing quaternary center, and thus may serve as valuable intermediates for the stereoselective preparation of other interesting targets such as amino alcohols, β-lactams, and alkaloid natural products.

Acknowledgment

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(14) **General Procedure for Preparation of 10a–e, 11a–b:** To a solution of **8** or **9** (0.8 mmol, 1 equiv) in toluene (5 mL) cooled in a dry ice–acetone bath, $BF_3{\cdot}OEt_2$ (O.31 mL, 2.5 mmol, 3.1 equiv) was added dropwise, and the resulting solution was stirred for 0.5 h with continued cooling. A solution of the organolithium reagent (5.8 mmol, 7.2 equiv) was then added over 15 min. After TLC analysis indicated complete consumption of starting material (typically 3–5 h), the reaction was quenched with 15 mL sat. $NaHCO_3$. The mixture was extracted with Et_2O (3 × 20 mL), and the combined extracts were washed with H_2O (3 × 15 mL), brine (1 × 15 mL), dried over Na_2SO_4, and concentrated. The crude mixture was passed through a short plug of silica (9:1 hexanes–EtOAc) and after concentration, the residue was dissolved in 4 mL THF, cooled in an ice–H_2O bath, and TBAF (4 equiv) was added dropwise. The reaction was allowed to warm to ambient temperature while monitoring by TLC. Following the consumption of starting material, the reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O or EtOAc. Combined extracts were washed with brine (1 × 10 mL), dried over Na_2SO_4, concentrated, and purified by flash chromatography. Only the major diastereomer was carried on in subsequent steps.

(15) **10a**: Mp 73–75 °C; $[\alpha]_D$ = –85.0 (*c* 0.44, $CHCl_3$).
10b: $[\alpha]_D$ = –85.0 (*c* 0.44, $CHCl_3$).
10c: $[\alpha]_D$ = –97.3 (*c* 0.70, $CHCl_3$). IR (thin film): 3392, 2956, 2930, 2871, 1469, 1368 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.78 (d, 3 H, *J* = 6.6 Hz), 0.82 (d, 3 H, *J* = 7.0 Hz), 1.21 (d, 3 H, *J* = 6.6 Hz), 1.43–1.49 (m, 1 H), 1.79–1.81 (m, 2 H), 1.91 (dd, 1 H, *J* = 12.5, 8.1 Hz), 2.84 (dd, 1 H, *J* = 12.8, 7.7 Hz), 3.70–3.77 (m, 1 H), 3.89–3.94 (m, 1 H), 6.32–6.34 (m, 2 H), 7.36–7.37 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.53, 23.66, 23.88, 25.57, 43.59, 46.31, 68.53, 69.73, 85.40, 106.72, 110.52, 141.77, 155.97. HRMS (ESI): *m/z* calcd for $[C_{13}H_{21}NO_3 + Na]^+$: 262.1419; found: 262.1420.
10d: $[\alpha]_D$ = –86.8 (*c* 0.59, $CHCl_3$). IR (thin film): 3392, 2955, 2926, 2871, 1565, 1453, 1368 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.80 (d, 3 H, *J* = 6.8 Hz), 0.85 (d, 3 H, *J* = 6.6 Hz), 1.21 (d, 3 H, *J* = 6.3 Hz), 1.49–1.52 (m, 1 H), 1.72–1.87 (m, 3 H), 2.19–2.26 (br s, 1 H), 2.29 (s, 3 H), 2.62–2.92 (m, 1 H), 3.64–3.82 (m, 1 H), 3.91–3.95 (m, 1 H), 5.45 (br s, 1 H), 5.91 (s, 1 H), 6.17 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.80, 19.44, 23.70, 23.98, 25.57, 43.36, 46.31, 68.41, 69.85, 85.72, 106.34, 107.49, 151.54, 153.79. HRMS (ESI): *m/z* calcd for $[C_{14}H_{23}NO_3 + Na]^+$: 276.1576; found: 276.1575.
10e: $[\alpha]_D$ = –52.6 (*c* 1.26, $CHCl_3$). IR (thin film): 3402, 2955, 2929, 2870, 1446, 1368 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.82–0.85 (m, 6 H), 1.20 (d, 3 H, *J* = 6.3 Hz), 1.46–1.54 (m, 1 H), 1.73 (m, 1 H), 1.85 (dd, 1 H, *J* = 13.9, 5.6 Hz), 2.04–2.06 (m, 1 H), 2.11–2.17 (m, 1 H), 2.80–2.88 (m, 1 H), 3.74 (m, 1 H), 3.89–3.94 (m, 1 H), 5.54 (br s, 1 H), 6.96–6.99 (m, 2 H), 7.23 (dd, 1 H, *J* = 4.6, 1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.68, 23.93, 24.03, 25.27, 46.88, 49.25, 69.71, 70.43, 85.22, 124.10, 124.54, 126.87, 148.85. HRMS (ESI): *m/z* calcd for $[C_{13}H_{21}NO_2S + Na]^+$: 278.1191; found: 278.1182.
11a: Mp 72–74 °C. IR (thin film): 3343, 3217, 2969, 1455 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.73 (t, 3 H, *J* = 7.4 Hz), 0.86 (d, 3 H, *J* = 6.2 Hz), 0.88–0.99 (m, 1 H), 1.09–1.22 (m, 1 H), 1.41 (s, 3 H), 2.00–2.50 (br s, 1 H), 3.16 (d, 1 H, *J* = 5.5 Hz), 3.71–3.74 (m, 1 H), 4.24–4.27 (m, 1 H), 5.54–6.02 (br s, 1 H), 7.12–7.18 (m, 2 H), 7.24–7.35 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.70, 18.19, 24.91, 27.74, 59.28, 67.96, 68.53, 89.18, 127.10, 128.34, 129.80, 136.16. HRMS (ESI): *m/z* calcd for $[C_{14}H_{21}NO_2 + Na]^+$: 258.1470; found: 258.1469.
11b: IR (thin film): 3441, 2969, 1494 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.44 (t, 3 H, *J* = 7.6 Hz), 0.76 (d, 3 H, *J* = 6.1 Hz), 0.84–0.93 (m, 1 H), 1.49–1.57 (m, 1 H), 1.96 (s, 1 H), 3.57 (d, 1 H, *J* = 4.9 Hz), 3.85–3.91 (m, 1 H), 3.73 (dd, 1 H, *J* = 4.9, 9.0 Hz), 6.14 (br s, 1 H), 7.24–7.35 (m, 4 H), 7.39–7.42 (m, 4 H), 7.66 (d, 2 H, *J* = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.35, 18.91, 29.53, 61.01, 68.25, 74.98, 87.95, 126.59, 127.11, 127.62, 128.54, 129.05, 129.73, 136.22, 143.41. HRMS (ESI): *m/z* calcd for $[C_{19}H_{23}NO_2 + H]^+$: 298.1807; found: 298.1797.

(16) **14a**: IR (thin film): 3316, 2956, 1712, 1166 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 0.93 (d, 6 H, *J* = 6.6 Hz), 1.32 (s, 3 H), 1.42 (s, 9 H), 1.52 (dd, 1 H, *J* = 13.9, 5.1 Hz), 1.69–1.78 (m, 1 H), 1.86 (dd, 1 H, *J* = 13.5, 6.3 Hz), 2.48 (d, 1 H, *J* = 13.9 Hz), 2.80 (d, 1 H, *J* = 14.2 Hz). ^{13}C NMR (125 MHz, CD_3OD): δ = 24.67, 25.14, 25.28, 28.85, 31.12, 44.68, 47.42, 54.80, 79.55, 156.57, 174.88. HRMS (ESI): *m/z* calcd for $[C_{13}H_{25}NO_4 + Na]^+$: 282.1681; found: 282.1684.
14b: mp 136–138 °C. IR (thin film): 3305, 2926, 1712, 1651, 1165 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 0.65 (s, 3 H), 0.78 (s, 3 H), 1.37 (s, 9 H), 1.51–1.60 (m, 1 H), 1.83–1.92 (m, 1 H), 2.13 (dd, 1 H, *J* = 13.8, 5.0 Hz), 3.03 (d, 1 H, *J* = 14.2 Hz), 3.21 (d, 1 H, *J* = 14.2 Hz), 7.19 (t, 1 H, *J* = 7.2 Hz), 7.27–7.31 (m, 2 H), 7.32–7.36 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.67, 24.43, 27.76, 29.69, 41.58, 49.32, 59.67, 81.46, 125.37, 126.32, 127.77, 144.83, 157.74, 175.28. HRMS (ESI): *m/z* calcd for $[C_{18}H_{27}NO_4 + Na]^+$: 344.1838; found: 344.1848.
14c: mp 108–110 °C. IR (thin film): 3361, 29.18, 1714, 1490, 1043 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 0.72 (d, 3 H, *J* = 6.6 Hz), 0.76 (d, 3 H, *J* = 6.6 Hz), 1.40 (s, 9 H), 1.57–1.66 (m, 1 H), 1.95–2.03 (m, 2 H), 3.02 (d, 1 H, *J* = 14.4 Hz), 3.16 (d, 1 H, *J* = 14.4 Hz), 6.22 (dd, 1 H, *J* = 3.2, 0.7 Hz), 6.35 (dd, 1 H, *J* = 3.2, 1.7 Hz), 7.40 (dd, 1 H, *J* = 1.7, 0.7 Hz). ^{13}C NMR (125 MHz, CD_3OD): δ = 24.40, 25.05, 28.68, 31.12, 41.16, 46.84, 57.60, 80.15, 106.77, 111.35, 142.02, 156.37, 157.42, 173.88. HRMS (ESI): *m/z* calcd for $[C_{16}H_{25}NO_5 + Na]^+$: 334.1630; found: 334.1629.
14d: mp 95–97 °C. IR (thin film): 3313, 2956, 1714, 1165 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 0.74 (d, 3 H, *J* = 6.6 Hz), 0.77 (d, 3 H, *J* = 6.6 Hz), 1.40 (s, 9 H), 1.58–1.64 (m, 1 H), 1.90–1.99 (m, 2 H), 2.23 (s, 3 H), 2.99 (d, 1 H, *J* = 15.0 Hz), 3.09 (d, 1 H, *J* = 14.6 Hz), 5.90 (dd, 1 H, *J* = 2.9, 1.1 Hz), 6.04 (d, 1 H, *J* = 3.3 Hz). ^{13}C NMR (125 MHz, CD_3OD): δ = 13.40, 24.31, 24.45, 25.08, 28.71, 41.63, 46.82, 57.57, 80.23, 107.17, 107.38, 151.57, 155.45, 156.37, 174.53. HRMS (ESI): *m/z* calcd for $[C_{17}H_{27}NO_5 + Na]^+$: 348.1787; found: 348.1784.
14e: mp 127–129 °C. IR (thin film): 3024, 2924, 1712, 1649, 1394, 1170 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 0.71 (d, 3 H, *J* = 6.6 Hz), 0.85 (d, 3 H, *J* = 6.6 Hz), 1.37 (s, 9 H), 1.61–1.70 (m, 1 H), 1.87 (dd, 1 H, *J* = 14.0, 5.5 Hz), 2.20 (dd, 1 H, *J* = 13.9, 5.5 Hz), 3.00 (d, 1 H, *J* = 1.4 Hz), 3.24 (d, 1 H, *J* = 14.4 Hz), 6.88–6.91 (m, 2 H), 7.23 (dd, 1 H, *J* = 4.6, 1.5 Hz). ^{13}C NMR (125 MHz, C_6D_6): δ = 23.99, 24.35, 24.69, 27.90, 30.17, 50.33, 58.83, 81.56, 123.13, 123.55, 126.15, 151.49, 158.20, 174.61. HRMS (ESI): *m/z* calcd for $[C_{13}H_{25}NO_4 + Na]^+$: 350.1402; found: 350.1401.
15a: mp 100–102 °C. IR (thin film): 3304, 2974, 1706, 1164 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ = 0.84 (t, 3 H, *J* = 7.5 Hz), 1.18 (s, 3 H), 1.44 (s, 9 H), 1.52–1.61 (m, 1 H), 2.37–2.46 (m, 1 H), 4.49 (s, 1 H), 7.23–7.29 (m, 3 H), 7.36–7.39 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.84, 20.29, 28.38, 28.77, 56.47, 57.62, 79.11, 127.52, 128.00, 130.06, 134.84, 154.24, 177.18. HRMS (ESI): *m/z* calcd for $[C_{17}H_{25}NO_4 + Na]^+$: 330.1681; found: 330.1672.

15b: mp 204–206 °C. IR (thin film): 3440, 2973, 1703, 1498, 1166 cm^{-1}. ^1H NMR (500 MHz, acetone-d_6): δ = 0.53–0.56 (m, 3 H), 1.93–2.02 (m, 1 H), 2.62–2.64 (m, 1 H), 4.59 (s, 1 H), 4.97–5.04 (m, 2 H), 7.26–7.51 (m, 15 H). ^{13}C (for methyl ester derived from **15b**, 125 MHz, $CDCl_3$): δ = 8.77, 29.48, 29.70, 51.83, 59.33, 64.84, 66.03, 125.99, 127.06, 127.97, 128.08, 128.17, 128.23, 128.46, 129.97, 133.81, 136.93, 142.95, 154.78, 172.81. HRMS (ESI): *m/z* calcd for $[C_{25}H_{25}NO_4 + Na]^+$: 426.1681; found: 426.1691.

(17) Crystallographic data for **14b**: $C_{18}H_{27}NO_4$, colorless square rods crystallized from EtOH at 22 °C, orthorhombic, space group P2 (1)2 (1)2 (1), *a* = 7.9578 (15) Å, *α* = 90°, *b* = 11.135 (2) Å, *β* = 90°, *c* = 20.543 (4) Å, *γ* = 90°, *U* = 1820.3 (6) $Å^3$, *Z* = 4, D_c = 1.173 mg/m^3, μ = 0.082 mm^{-1}, *R* = 0.0300, *wR2* = 0.0737, *GOF* = 1.034, *T* = 113 (2) K, *F*(000) = 696, 2590 independent reflections were collected on a Bruker SMART CCD-based X-ray diffractometer with an LT-2 low temperature device and a MoKα source (wavelength = 0.71073 Å).
Crystallographic data for **15a**: $C_{17}H_{25}NO_4 \cdot (C_2H_5OH)$, colorless needles crystallized from EtOH at 4 °C, monoclinic, space group P2 (1)/c, *a* = 9.7981 (9) Å, *α* = 90°, *b* = 22.641 (2) Å, *β* = 112.690 (2)°, *c* = 9.7517 Å, *γ* = 90°, *U* = 1995.8 (3) $Å^3$, *Z* = 4, D_c = 1.176 mg/m^3, μ = 0.084 mm^{-1}, *R* = 0.0397, *wR2* = 0.0867, *GOF* = 1.011, *T* = 113 (2) K, *F*(000) = 768, 4948 independent reflections were collected on a Bruker SMART CCD-based X-ray diffractometer with an LT-2 low temperature device and a MoKα source (wavelength = 0.71073 Å).