

CHEMO-ENZYMATIC SYNTHESIS OF NOVEL β -AMINO ACIDS SUBSTITUTED BY (THYMIN-1-YL)METHYL FUNCTIONAL GROUP AT THE α -POSITION[¶]

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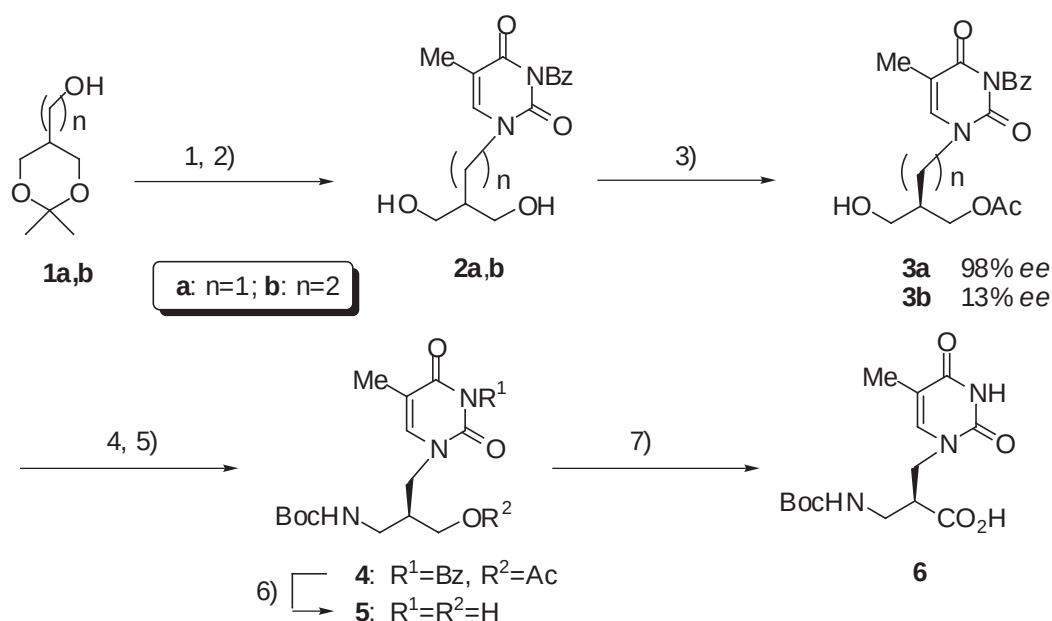
Abstract— A novel β -amino acid having (thymin-1-yl)methyl functionality at the α -position, a useful component of α -substituted β -homoalanyl peptide nucleic acids (β^2 -PNAs), was synthesized as a protected form from 2-(*N*³-benzoylthymin-1-yl)methyl-1,3-propanediol *via* enzymatic desymmetrization catalyzed by lipase PS.

During the past few years, interest in β -amino acids has increased considerably since the discovery of the interesting physical properties associated with β -peptides.^{1,2} The β^2 - and β^3 -peptides respectively derived from α - and β -substituted β -amino acids with a simple alkyl side-chain can fold into well-defined helically or plated-sheet secondary structures.^{2,3} Significant differences in the physical properties between β^2 - and β^3 -peptides are known.^{2d} Moreover, β -peptides are reported to be more stable than α -peptides to enzymatic degradation.⁴

On the other hand, peptide nucleic acids (PNAs), oligomers possessing a polyamide backbone in which the nucleobases of the DNA/RNA function as recognition units, have increased in importance because of their potential use in antigene or antisense therapy.⁵ A number of modifications of the polyamide backbone in PNAs has been recently devised to increase the interaction of PNA/DNA or PNA/RNA.^{5,6} In the light of the characteristic features associated with β -peptides as well as the potential usefulness of PNAs in medicinal chemistry, Diederichsen recently reported synthesis and characterization of β^3 -PNAs derived from β -substituted β -amino acids with a purine nucleobase (Figure 1).⁷ However, the synthesis of α -substituted β -amino acids for components of the β^2 -PNAs as well as elucidation of their physical properties have not been studied.⁷ We herein describe a preparation of an optically active α -substituted β -amino acid having a (thymin-1-yl)methyl side chain, a useful component of the β^2 -PNAs, as a protective form amenable to the peptide synthesis.

[¶]This paper is dedicated to Professor James P. Kutney on the occasion of his 70th birthday.

Our strategy for access to the required nucleo β -amino acids is based on a chemo-enzymatic route as shown in Scheme 1, in which we apply lipase-catalyzed desymmetrization of the 2-substituted 1,3-propanediols as a key reaction. While a number of applications of the lipase-catalyzed desymmetrization of prochiral diols to enantiomerically pure molecules have been reported,¹⁰ to the best of our knowledge, effects of the nucleobases at the terminal position in 2-substituted 1,3-propanediols on discrimination of the enantiotopic diol moiety are unknown.^{10,11}

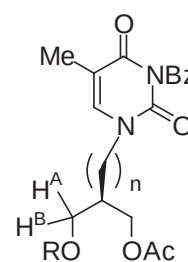


Scheme 1. 1) T(N³-Bz), DEAD, Ph₃P, THF; 2) Amberlyst 15E, MeOH; 3) lipase PS, vinyl acetate, THF; 4) HN₃, DEAD, Ph₃P, THF; 5) H₂, Boc₂O, 10% Pd-C, EtOAc; 6) K₂CO₃, MeOH; 7) Jones reagent, acetone.

Keeping these matters in mind, we first investigated the lipase-catalyzed desymmetrization of 1,3-propanediol derivatives (**2a, b**). Treatment of alcohols (**1a, b**)¹² with *N*³-benzoylthymine (T(*N*³-Bz))¹³ under the Mitsunobu conditions [diethyl azodicarboxylate (DEAD), Ph₃P, THF, rt], followed by

hydrolysis with Amberlyst 15E[®] in MeOH, gave the requisite diols (**2a**) (mp 154-156 °C) and (**2b**) (mp 47-48 °C) in 84 and 85% yields, respectively. The lipase-catalyzed desymmetrization of **2a** and **2b** was carried out in THF in the presence of lipase PS from *Pseudomonas cepacia* and vinyl acetate (1.5 equiv.) at 25 °C. Under the conditions, the transesterification of diol (**2a**) proceeded rapidly (2 h) to give the optically active monoacetate (**3a**), $[\alpha]^{25}_D +3.81^\circ$ (c 1.0, MeOH), in 85% yield. On the contrary, it was verified that the transesterification of the homologous diol (**2b**) requires rather longer time (12 h) to give **3b** of very small amplitude of the specific rotation, $[\alpha]^{25}_D -0.81^\circ$ (c 1.0, MeOH), in 74% yield.

The optical purities of **3a,b** were determined by ¹H NMR (400 MHz, CDCl₃) analysis of the corresponding MTPA esters (**7a,b**) and (**8a,b**) respectively derived from (*S*)- and (*R*)-MTPA. The analyses revealed the acetate (**3a**) to be of high optical purity (>98% *ee*), while optical purity of homologous acetate (**3b**) was proved to be very low (13% *ee*). The enantioselectivity for the transesterification of **3b** was not improved upon using lipases from different origins in place of lipase PS.[†] These experiments clearly show that the length between the methine carbon and the thymin-1-yl moiety in **2a,b** may be a critical factor for discriminating the enantiotopic hydroxyl functionalities.



7a,b: R=(*S*)-MTPA
8a,b: R=(*R*)-MTPA

a: n=1; **b**: n=2

The absolute stereochemistry of **3a** was deduced by analyzing the ¹H NMR spectrum of the MTPA esters (**7a**) and (**8a**) according to the method of Yamaguchi.¹⁴ In the ¹H NMR spectrum (400 MHz, CDCl₃) of **7a**, the signals due to the methylene protons (H^A and H^B) α to the (*S*)-MTPA ester functional group appear at δ 4.39 (dd, *J* = 11.8, 4.6 Hz) and 4.36 (dd, *J* = 11.8, 5.0 Hz), whereas the corresponding H^A- and H^B-protons of (*R*)-MTPA ester (**8a**) resonate at δ 4.50 (dd, *J* = 11.6, 4.6 Hz) and δ 4.27 (dd, *J* = 11.6, 5.2 Hz), respectively. Apparently, the difference (Δδ) of H^A- and H^B-protons of **7a** in chemical shifts is smaller than that of **8a**. On the basis of the coupling patterns and the report of Yamaguchi,¹⁴ the absolute stereochemistry of **3a** was estimated to be *R*-configuration. The determined stereochemistry is consistent with that predicted from the empirical rule regarding enantioselectivity of *Pseudomonas cepacia* lipase toward chiral primary alcohols proposed by Kazlauskas.¹⁵

With monoacetate (**3a**) of high optical purity in hand, transformation of **3a** to the target β-amino acid (**6**) was examined (Scheme 1). Reaction of **3a** with hydrazoic acid under the Mitsunobu conditions, followed by hydrogenation over 10% Pd-C in EtOAc in the presence of Boc₂O,¹⁶ gave *N*-Boc-amino acetate (**4**) in 60% yield for the two-steps. Upon treatment of **4** with excess amounts of potassium carbonate in MeOH, concomitant deacetylation and debenzoylation occurred to give **5**, mp 60-62 °C; $[\alpha]^{25}_D +4.17^\circ$ (c 1.0, MeOH) in virtually quantitative yield. No racemization took place during these transformations; the enantiomeric purity (98% *ee*) of **5** was retained as analyzed by means of ¹H NMR (400 MHz, CDCl₃) after

[†] For example, the diol (**2b**) was transesterified rapidly (2 h) in the presence of lipase AK (*Pseudomonas fluorescens*) and vinyl acetate in THF to give the monoacetate (**3b**) in 94% yield. However, the acetate obtained from this reaction was totally optically inactive. It needs to do further experiments for understanding the remarkable differences between **2a** and **2b** in reactivity toward the transesterification.

transforming to the corresponding (*R*)- and (*S*)-MTPA esters. Oxidation of **5** with the Jones reagent in acetone gave *N*-Boc β -amino acid (**6**) as crystals in 79% yield.

EXPERIMENTAL

Melting points are uncorrected. All NMR data were recorded on a Bruker DPX 400 unless otherwise specified. ^1H and ^{13}C NMR data were collected by operating at 400 and 100 MHz, respectively. The chemical shift data for each signal are given in units of δ relative to tetramethylsilane (δ 0.00) or chloroform (δ 7.26). The chemical shifts of ^{13}C are reported relative to CDCl_3 (δ 77.0). IR spectra were recorded on a JASCO FTIR-620 spectrophotometer. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. MS spectra were measured on a Finnigan TSQ-700 or a VG Auto Spec E spectrometer. Lipase-PS and -AK were purchased from Amano Pharmaceutical Co., Ltd.

3-Benzoyl-1-[3-hydroxy-2-(hydroxymethyl)propyl]-5-methylpyrimidine-2,4(1*H*, 3*H*)-dione (2a). To a stirred solution of alcohol (**1a**)¹² (7.3 g, 50 mmol), *N*³-benzoylthymine (12.6 g, 55 mmol) and Ph_3P (14.4 g, 55 mmol) in THF (100 mL) was added DEAD (40% toluene solution 8.9 mL, 55 mmol) under ice cooling. After being stirred for 12 h at rt, the volatile component of the mixture was removed *in vacuo*. The residue was chromatographed on silica gel (*n*-hexane:EtOAc=2:1) to give an oil, which was dissolved in MeOH (200 mL) and treated with Amberlyst 15E[®] (3 g) for 2 h at rt. The resin was filtered and the filtrate was evaporated. The residue was chromatographed on silica gel. Elution with CHCl_3 gave **2a** (13.3 g, 84 %) as crystals: mp 154-156 °C (EtOAc/*n*-hexane); ^1H NMR (CDCl_3) δ 7.91 (2H, d with small splits, J = 8.4 Hz), 7.66 (1H, t, J = 8.4 Hz), 7.50 (2H, t, J = 7.8 Hz), 7.24 (1H, t, J = 0.8 Hz), 3.99 (2H, d, J = 6.61 Hz), 3.76-3.67 (4H, m), 2.65-2.59 (2H, m), 2.13-2.02 (1H, m), 1.97 (3H, d, J = 0.8 Hz); ^{13}C NMR (CDCl_3) δ 168.6, 162.9, 151.2, 140.7, 135.1, 131.5, 130.4, 129.2, 111.5, 61.9, 46.7, 42.5, 12.4; IR (KBr) 1747, 1691, 1650, 1441, 1252 cm^{-1} ; EIMS m/z 318 (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.01; H, 5.68; N, 8.96.

3-Benzoyl-1-[4-hydroxy-3-(hydroxymethyl)butyl]-5-methylpyrimidine-2,4(1*H*, 3*H*)-dione (2b). The alcohol (**1b**)¹² was condensed with *N*³-benzoylthymine, followed by hydrolysis, in an analogous manner to that for preparation of **2a** to give **2b** as hygroscopic crystals: mp 47-48 °C (ether/*n*-hexane); yield: 42% (for the two-step); ^1H NMR (CDCl_3) δ 7.90 (2H, d with small splits, J = 6.3 Hz), 7.65-7.62 (1H, m), 7.49 (2H, t, J = 8.0 Hz), 7.15 (1H, t, J = 1.1 Hz), 3.81 (2H, t, J = 7.2 Hz), 3.72 (2H, dd, J = 10.9, 4.3 Hz), 3.66 (2H, dd, J = 10.9, 5.6 Hz), 1.94 (3H, d, J = 1.1 Hz), 1.83-1.69 (3H, m); ^{13}C NMR (CDCl_3) δ 169.2, 163.1, 149.6, 140.8, 135.0, 131.0, 120.0, 129.0, 110.21, 63.1, 46.7, 36.6, 27.2, 11.8; EIMS m/z 332 (M^+). HRMS (EI) calcd for $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5$ (M^+): 332.1372. Found: 332.1371.

General procedure for lipase-catalyzed transesterification reaction of 2a,b with vinyl acetate. In a typical experiment, a mixture of **2a** (1 g, 3.1 mmol), vinyl acetate (0.43 mL, 4.7 mmol) and lipase PS (1 g) in THF (15 mL) was stirred at 25 °C for 2 h. The reaction was terminated by filtering off the enzyme. After concentration of the filtrate *in vacuo*, the residue was purified by column chromatography on

silica gel. Elution with CHCl_3 gave the monoacetate (**3a**) as an oil in 85% yield. The transesterification of **2b** with vinyl acetate was carried out in a similar manner.

(2R)-3-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-

(hydroxymethyl)propyl acetate (3a): $[\alpha]^{25}_{\text{D}} +3.81^\circ$ (c 1.0, MeOH); ^1H NMR (CDCl_3) δ 7.88 (2H, d, $J = 7.5$ Hz), 7.63 (1H, t, $J = 7.6$ Hz), 7.45 (2H, t, $J = 7.8$ Hz), 7.17 (1H, br s), 4.15 (1H, dd, $J = 11.4$, 6.3 Hz), 4.06 (1H, dd, $J = 11.4$, 6.4 Hz), 3.84 (1H, dd, $J = 14.1$, 8.1 Hz), 3.77 (1H, dd, $J = 14.1$, 5.8 Hz), 3.56 (2H, d, $J = 3.7$ Hz), 2.96 (1H, br s), 2.28-2.19 (1H, m), 2.04 (3H, s), 1.91 (3H, s); ^{13}C NMR (CDCl_3) δ 171.0, 168.8, 162.9, 150.5, 140.7, 135.1, 131.3, 130.3, 129.1, 111.0, 62.6, 59.3, 47.1, 40.2, 20.7, 12.3; IR (neat) 1743, 1697, 1654, 1440, 1224 cm^{-1} ; EIMS m/z 360 (M^+). HRMS (EI) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_6$ (M^+): 360.1321. Found: 360.1329.

(2R)-4-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-

(hydroxymethyl)butyl acetate (3b): Yield: 74%; an oil; $[\alpha]^{25}_{\text{D}} -0.81^\circ$ (c 1.0, MeOH) (for the sample of 13% ee); ^1H NMR (300 MHz, CDCl_3) δ 7.91 (2H, d, $J = 8.5$ Hz), 7.63 (1H, t, $J = 7.6$ Hz), 7.50 (2H, t, $J = 7.6$ Hz), 7.14 (1H, s with small splits), 4.14 (2H, d, $J = 5.2$ Hz), 3.92-3.78 (2H, m), 3.63 (2H, d, $J = 4.9$ Hz), 2.08 (3H, s), 1.97 (3H, d, $J = 1.2$ Hz), 1.92-1.68 (3H, m); EIMS m/z 374 (M^+).

Preparation of MTPA esters (7a,b) and (8a,b). To a stirred solution of (2R)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid [(S)-MTPA] (91.5 mg, 0.36 mmol), *N,N*-dicyclohexylcarbodiimide (DCC) (74.2 mg, 0.36 mmol), and 4-dimethylaminopyridine (DMAP) (4.4 mg, 0.036 mmol) in CH_2Cl_2 (1 mL) was added a solution of **3a** or **3b** (0.18 mmol) in CH_2Cl_2 (2 mL) at 0 $^\circ\text{C}$. The mixture was stirred at the same temperature for 30 min, and then kept at rt until the starting material disappeared on TLC (3-24 h). The reaction was quenched with 10% HCl (6 mL) at 0 $^\circ\text{C}$. The mixture was extracted with CHCl_3 . The extracts were washed successively with sat. NaHCO_3 and brine, and then dried (MgSO_4). The solution was concentrated *in vacuo*, and diluted with ether. The resulting suspension was passed through silica gel (0.5 g). The filtrate was evaporated to leave crude **7a,b**, which were analyzed by ^1H NMR spectroscopy without purification. The (R)-MTPA-esters (**8a,b**) were prepared in an analogous manner.

(2S)-3-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-[[tert-butoxycarbonyl)amino]methyl]propyl acetate (4). To a stirred solution of **3a** (3.6 g, 10 mmol) and Ph_3P (3.15 g, 12 mmol) in THF (100 mL) were successively added HN_3 [30 mL of benzene solution of HN_3 prepared from NaN_3 (3.00 g, 46 mmol) and 50% H_2SO_4 (20 mL) in benzene (60 mL)] and diethyl azodicarboxylate (40% toluene solution 4.72 mL, 12 mmol) at -35 $^\circ\text{C}$. The mixture was stirred at the same temperature for 30 min, and allowed to warm to room temperature. After being stirred for 2 h, the volatile component of the mixture was evaporated. The residue was dissolved in ether (30 mL), and cooled at -40 $^\circ\text{C}$ for 1 h. The precipitate was filtered and the filtrate was evaporated to give the crude azide (5.6 g), which was used in the next reaction without further purification.

A solution of the azide and Boc_2O (2.26 g, 12 mmol) in EtOAc (100 mL) was hydrogenated over 10% Pd-C (250 mg) for 2 h at rt under atmospheric pressure. The catalyst was removed through Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 2:1 to 1:2) to give **4** (4.48 g, 60%) as an oil. $[\alpha]^{25}_{\text{D}} +3.61^\circ$ (c 1.0, MeOH); ^1H NMR

(CDCl₃) δ 7.91 (2H, d with small splits), 7.65 (1H, t with small splits, $J = 7.5$ Hz), 7.49 (2H, t, $J = 7.8$ Hz), 5.08-5.06 (1H, m), 4.13 (1H, dd, $J = 11.7, 5.5$ Hz), 4.06 (1H, dd, $J = 11.7, 5.8$ Hz), 3.80 (1H, dd, $J = 14.2, 7.2$ Hz), 3.74 (1H, dd, $J = 14.2, 6.1$ Hz), 3.24-3.10 (2H, m), 2.38-2.26 (1H, m), 2.07 (3H, s), 1.95 (3H, s), 1.41 (9H, s); ¹³C NMR (CDCl₃) δ 171.9, 169.9, 164.0, 157.2, 151.4, 141.4, 136.0, 132.4, 131.3, 130.1, 111.9, 80.2, 63.2, 48.3, 39.3, 39.1, 28.5, 21.0, 12.6; IR (neat) 1746, 1698, 1655, 1509 cm⁻¹; EIMS m/z 459 (M⁺); HRMS (EI) calcd for C₂₃H₂₉N₃O₇ (M⁺): 459.2006. Found: 459.2009.

tert-Butyl (2S)-3-hydroxymethyl-2-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl]propylcarbamate (5). A solution of **4** (4.5 g, 10 mmol) in 95% MeOH (100 mL) was treated with K₂CO₃ (2.76 g, 20 mmol) at 25 °C for 1 h. The solvent was evaporated and the residue was partitioned between water and CHCl₃. The aqueous layer was extracted with CHCl₃. The extracts were washed with brine, dried (MgSO₄), and evaporated. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 1:2 to 1:4) to give **5** (2.7 g, 87%) as crystals: mp 60-62 °C (CHCl₃); $[\alpha]_D^{25} +4.17^\circ$ (c 1.0, MeOH); ¹H NMR (CDCl₃) δ 7.07 (1H, d, $J = 0.5$ Hz), 5.29 (1H, t, $J = 6.4$ Hz), 3.79 (1H, dd, $J = 14.0, 7.3$ Hz), 3.59-3.47 (2H, m), 3.43 (1H, dd, $J = 12.0, 5.3$ Hz), 3.28 (1H, ddd, $J = 14.5, 5.2, 5.2$ Hz), 3.08 (1H, ddd, $J = 14.5, 6.5, 6.5$ Hz), 2.04-1.96 (1H, m), 1.91 (3H, d, $J = 0.3$ Hz), 1.44 (9H, s); ¹³C NMR (CDCl₃) δ 164.2, 157.6, 151.8, 140.9, 111.5, 80.2, 46.8, 41.7, 38.2, 28.4 (3-carbons), 12.4; IR (KBr) 1685 cm⁻¹; EIMS m/z 313 (M⁺). Anal. Calcd for C₁₄H₂₃N₃O₅: C, 53.66; H, 7.40; N, 13.41. Found: C, 54.02; H, 7.09; N, 13.07.

(2S)-3-[(tert-Butoxycarbonyl)amino]-2-[(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)methyl]propionic acid (6). To a solution of **5** (2.5 g, 7.9 mmol) in acetone (126 mL) was added Jones reagent (13 mL) under ice cooling. After being stirred for 12 h at rt, the reaction was quenched with 2-propanol. The mixture was diluted in water, and extracted with CHCl₃. The extracts were washed with brine, dried (MgSO₄), and concentrated. The residue was chromatographed on silica gel (CHCl₃:MeOH=500:1 to 200:1) to give **6** (2.46 g, 79%) as crystals: mp 211-214 °C (CHCl₃); $[\alpha]_D^{25} +2.89^\circ$ (c 1.0, MeOH); ¹H NMR (DMSO-*d*₆) δ 12.6 (1H, br s), 11.3 (1H, s), 7.43 (1H, s), 6.89 (1H, t, $J = 5.6$ Hz), 3.79 (1H, dd, $J = 13.9, 6.2$ Hz), 3.69 (1H, dd, $J = 13.9, 8.4$ Hz), 3.19-3.03 (2H, m), 2.93-2.81 (1H, m), 1.72 (3H, s), 1.36 (9H, s); ¹³C NMR (DMSO-*d*₆) δ 173.5, 164.4, 155.7, 151.1, 142.1, 108.3, 78.1, 47.6, 44.6, 28.4 (3 carbons), 12.1; IR (KBr) 3369, 1687, 1521 cm⁻¹; EIMS m/z 327 (M⁺); CIMS (isobutane) m/z 328 (MH⁺), 384 (MC₃H₉⁺). Anal. Calcd for C₁₄H₂₁N₃O₆: C, 51.37; H, 6.47; N, 12.84. Found: C, 51.93; H, 6.59; N, 11.97. HRMS (EI) calcd for C₁₄H₂₁N₃O₆ (M⁺): 327.1430. Found: 327.1425.

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