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Asymmetric Michael reaction between a chiral α,β-dimethyl-β-enamino ester and α-substituted acrylates

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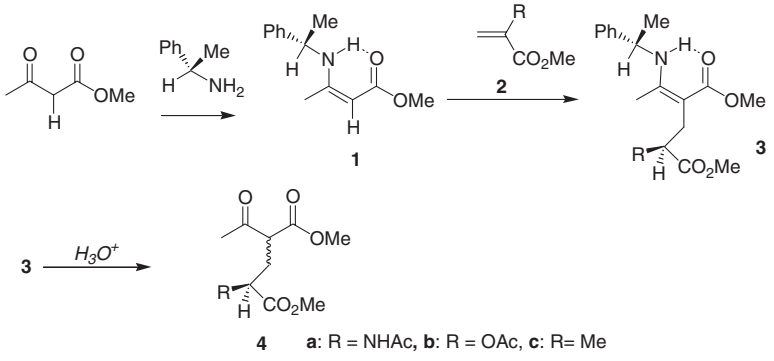
Abstract—An asymmetric Michael reaction between a chiral α,β-dimethyl-β-enamino ester derived from (*S*)-1-phenylethylamine and α-substituted acrylates is reported. Methyl acetamidoacrylate and methyl acetoxyacrylate furnished the expected Michael adduct with good ee's and de's. By contrast, an annulation process of the intermediary imine took place when using methyl methacrylates.

1. Introduction

The Michael-type alkylation of chiral imines, and chiral enamino esters, derived from optically active 1-phenylethylamine, has been documented in numerous reports.[1] In this respect, the addition of α-substituted acrylates to chiral acyclic enamino esters seemed highly promising. In a preliminary report, we established that the addition of chiral β-enamino ester **1** to various α-substituted acrylates **2** furnished Michael adducts **3** in satisfying yields (66–74%) and excellent de's (⩾94%).[2] The hydrolysis of these adducts however proved to be sluggish, furnishing an equimolar mixture of diastereomeric β-keto esters **4** (Scheme 1).

On the other hand, the Michael-type addition of chiral enamino esters **6** to methyl vinyl ketone furnished imines **7**, which were easily hydrolysed into Michael adducts **8**



Scheme 1.

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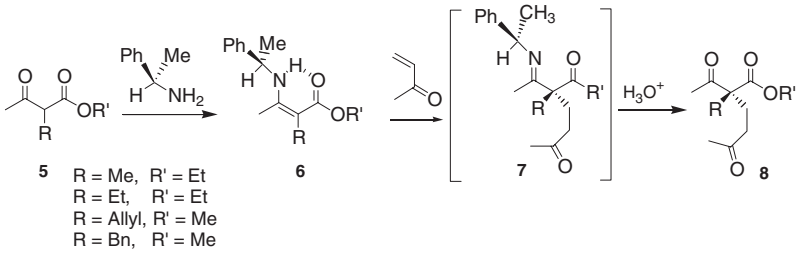


Scheme 2.

(Scheme 2). These were obtained in good yields (68–75%) and excellent ee's (93–96%).[3]

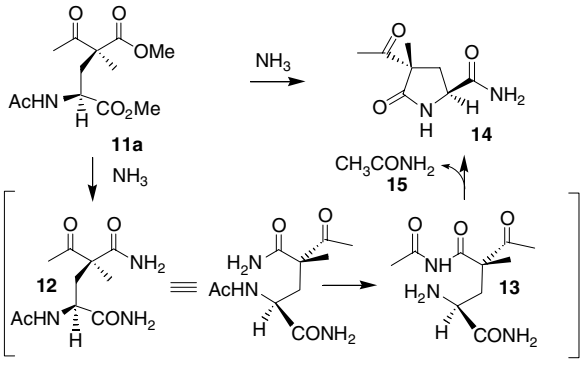
As a part of our research directed towards the synthesis of new chiral building blocks, we recently investigated the reaction between the chiral α,β-dimethyl-β-enamino ester **9** and various α-substituted acrylates **2**.

2. Results and discussion

Additions of enamino ester (*S*)-**9**, of pure (*Z*) geometry (secured by the intramolecular hydrogen bonding) to methyl acetamidoacrylate **2a** was performed under neutral conditions in refluxing THF (3 days). After hydrolytic work-up (10% AcOH in water, 20 °C, 2 h) of the intermediary imines **10**, the Michael adduct (*S*,*S*)-**11a** was isolated in 54% yield with excellent de (>95%) and ee (>95%). Similarly, the addition of methyl acetoxyacrylate **2b** gave **11b** in 50% yield, and with excellent de (>95%) and ee (>95%) (Scheme 3).

Adducts (*S*,*S*)-**11a** and (*S*,*S*)-**11b** proved to be homogeneous by ^{1}H and ^{13}C NMR spectroscopy [including experiments using $Eu(FOD)_3$ and $Eu(hfc)_3$ as shift reagents]. For comparison, **11a** and **11b** were prepared in a nonstereoselective fashion by the addition of methyl methylacetoacetate to acrylates **2a** or **2b** in the presence of Triton® B. The sense of induction of these asymmetric Michael additions was deduced from mechanistic considerations (vide infra).

In order to determine the relative configuration of adducts **11a** and **11b**, ammonia was added (MeOH, NH_3, 20 °C) to these adducts. In the case of **11a**, this reaction unexpectedly gave pyrrolidine (*S*,*S*)-**14** as a single isomer in 90% yield. Formation of **14** can be interpreted by invoking first the attack of ammonia on the ester groups of **11a**, giving the bis-amide **12**, followed by *trans*-amidification into **13**. In turn **13** was cyclised into **14** and acetamide **15**, which was characterised as a side compound (Scheme 4).



Scheme 4.

The structure of **14** was determined through an X-ray crystal structure analysis (Fig. 1).

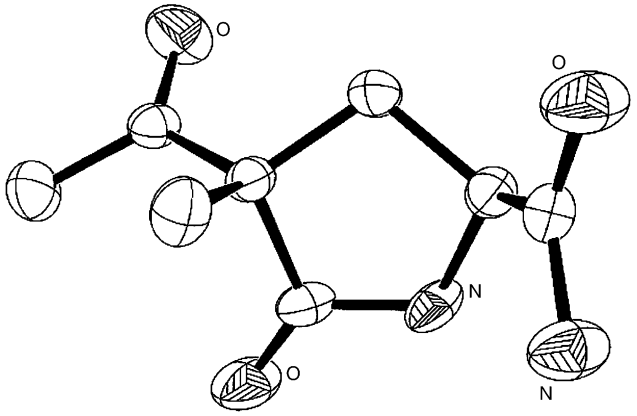
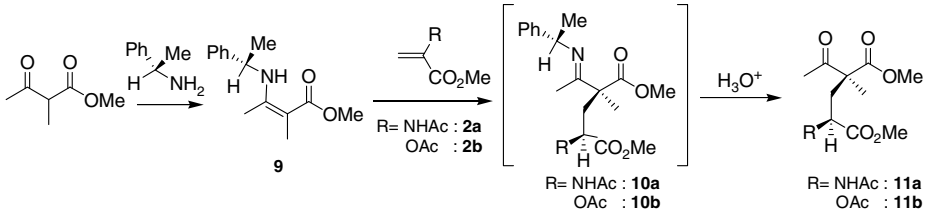
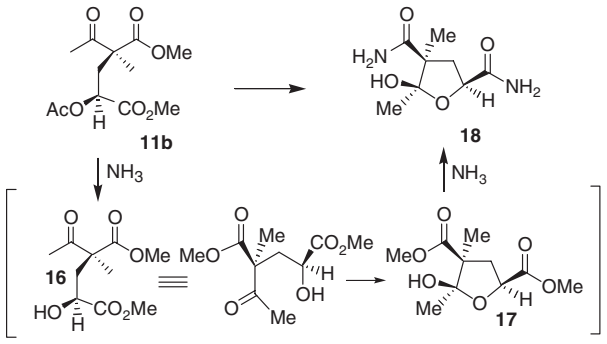


Figure 1. ORTEP view of (−)-**14** with labelled heteroatoms.



Scheme 3.

Surprisingly, the reaction of ammonia with **11b** gave hemiacetal (2*R*,3*S*,5*S*)-**18** as a single isomer (95% yield). Formation of **18**, probably involved the cleavage of the acetoxy group, furnishing **16**, which cyclised into hemiacetal **17**. Attack of ammonia on the ester groups of **17** delivered **18** (Scheme 5).



Scheme 5.

The structure of (−)-**18** was established through an X-ray crystallographic analysis (Fig. 2).

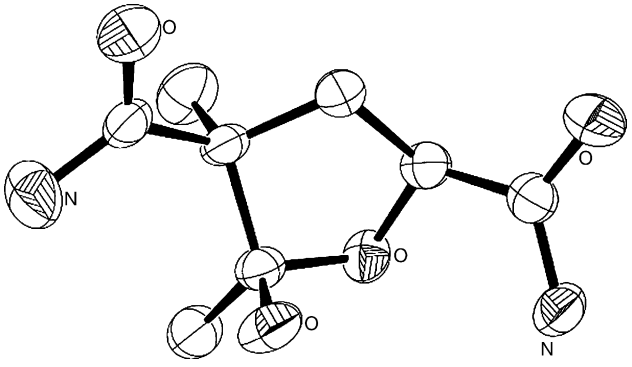


Figure 2. ORTEP view of (−)-**18** with labelled heteroatoms.

In contrast, the addition of (*S*)-**9** to the less reactive methyl methacrylate **2c** required the presence of zinc chloride (1.4 equiv). In this case, only the single cyclohexenone (*S*′,*S*,*S*)-**19** was isolated in 67% yield. This compound results from an annulation process of the intermediary imine **10c** (Scheme 6).

Structure of **19**, including the configuration of the two newly created stereogenic centres was unambiguously determined through X-ray crystallographic analysis (Fig. 3).

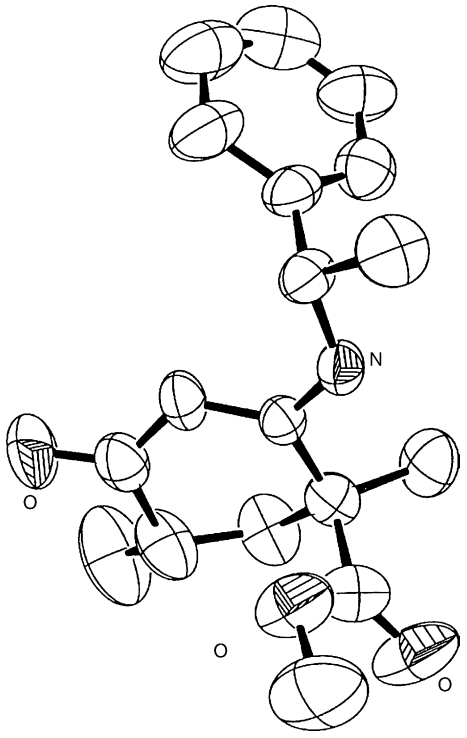
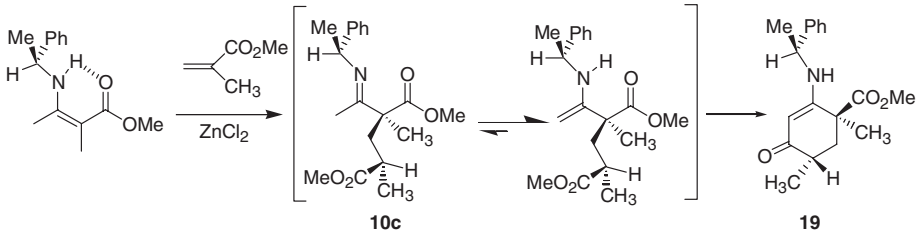
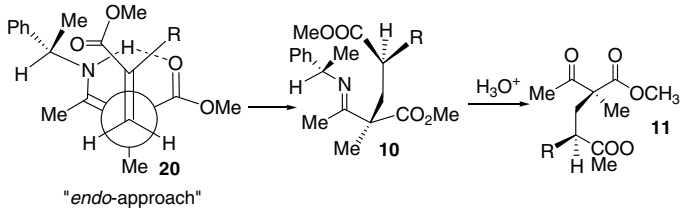


Figure 3. X-ray crystal structure of enaminone (−)-**19**.

The remarkable remote transfer of chirality observed in the previous Michael additions can be interpreted by invoking the *syn*-approach **20** of the two reactants **9** and **2**, with the '*endo*-arrangement' of the ester part of the acrylate partner **2** (the carbomethoxy group facing the nitrogen atom of enamino ester **9**), and the related six-membered 'aza-ene-synthesis-like' transition state. According to such a model,[4] the alkylation took place predominantly on the less hindered π-face of enamino ester **9** (*anti* to the bulky phenyl group of the chiral amine moiety, portrayed in its energetically preferred conformation minimizing the $A^{1,3}$ allylic-type interactions). The transfer of the proton of the enamino ester to the α-vinylic centre of acceptor **2**, more or less concerted with the creation of the C–C bond, then secured the control of the tertiary stereogenic centre in intermediary imines **10**. Hydrolysis of **10** finally delivered the observed Michael adducts **11**. This accounts for the absolute and relative configuration of the two newly



Scheme 6.



Scheme 7.

created stereogenic centres in adducts **11a** and **11b** (Scheme 7).

3. Conclusion

The asymmetric Michael addition of substituted acyclic chiral β-enamino ester to α-substituted acrylates is an efficient methodology for the synthesis of new chiral compounds with simultaneous and complete stereocontrol of a quaternary carbon centre and a tertiary one at the β-position.

4. Experimental section

4.1. General

Melting point were recorded on a Kofler bench. Infrared (IR) spectra were obtained as neat films between NaCl plates or KBr pellets. The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in Bruker AC 200 P or Bruker Avance 300 (200 and 50 MHz, or 300 and 75 MHz, for ^{1}H and ^{13}C, respectively). Optical rotations were measured at 589 nm in a 1 dm-cell at a specified temperature on an Optical Activity Limited AA-10R. Analytical thin-layer chromatography was performed on SDS silica gel $60F_{254}$ aluminium plates (0.2 mm layer). All liquid chromatography separations were performed using SDS silica gel 60. Tetrahydrofuran (THF) was distilled from Na-benzophenone ketyl. Methanol was dried over magnesium and distilled under a nitrogen atmosphere. Organic layers were dried over anhydrous sodium sulfate. Elemental analyses were performed by the service de microanalyse, Centre d'Etudes Pharmaceutiques, Chatenay-Malabry, France, with a Perkin–Elmer 2400 analyser.

4.2. General procedure for the addition of methyl acetamidoacrylate 2a or methyl acetoxyacrylate 2b to the enamino ester 9

A mixture of enamine **9** (5 g, 21.4 mmol), acrylate **2a** or **2b** (28 mmol) and hydroquinone (2 mg) in THF (20 mL) was heated at 70 °C under nitrogen, respectively, for 3 and 5 days after which 5 mL of 10% aqueous acetic acid solution were added. The mixture was stirred for an additional 2 h at 20 °C. The solvents were removed under reduced pressure and 1 M hydrochloric acid (10 mL) then added. The mixture was extracted with ethyl acetate (3 × 10 mL) and the combined organic layers washed with brine, dried over sodium sulfate and concentrated.

4.2.1. (*S*,*S*)-2-Acetyl-4-acetylamino-2-methyl-pentanedioic acid dimethyl ester 11a. Chromatography over silica gel (ethyl acetate–hexane 7:3) afforded keto ester **11a** as a yellow oil; yield 54%; $[\alpha]_D = -5.3$ (*c* 1.7, MeOH); IR (film, cm^{-1}): 3285, 1744, 1720, 1656, 1540; ^{1}H NMR (CD_4O, 300 MHz) δ: 4.45 (dd, $J = 4.5$, 9.2, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 2.47 (dd, $J = 4.5$, 14.9, 1H), 2.14 (dd, $J = 9.2$, 14.9, 1H), 2.12 (s, 3H), 1.88 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (CD_4O, 200 MHz) δ: 204.7 (C), 172.5 (C), 172.0 (C), 171.5 (C), 58.0 (C), 51.7 (CH_3), 51.4 (CH), 47.9 (CH_3), 35.7 (CH_2), 24.7 (CH_3), 20.8 (CH_3), 17.9 (CH_3). Anal. Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.89; H, 7.05; N, 5.29.

4.2.2. (*S*,*S*)-4-Acetoxy-2-acetyl-2-methyl-pentanedioic acid dimethyl ester 11b. Chromatography over silica gel (hexane–ethyl acetate 3:2) afforded pure keto ester **11b** as a yellow oil; yield 50%; $[\alpha]_D = -5.3$ (*c* 1.5, MeOH); IR (film, cm^{-1}): 1747, 1718; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 4.98 (dd, $J = 3.75$, 10.2, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 2.50–2.34 (m, 2H), 2.12 (s, 3H), 1.98 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 203.4 (C), 172.3 (C), 169.8 (C), 169.4 (C), 68.6 (CH), 57.4 (C), 52.5 (CH_3), 52.3 (CH_3), 35.4 (CH_2), 25.8 (CH_3), 19.9 (CH_3), 18.4 (CH_3). Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.31; H, 6.84.

4.3. (*S*′,*S*,*S*)-1,5-Dimethyl-4-oxo-2-(1-phenyl-ethyl-amino)-cyclohex-2-enecarboxylic acid methyl ester 19

Enamino ester **9** (1 g, 4.3 mmol) and methyl methacrylate **2c** (245 μL, 2.23 mmol) were added to a solution of $ZnCl_2$ (1.4 equiv) and hydroquinone in THF (5 mL). The mixture was stirred at 60 °C for 7 days and during this period, additional portions of methyl methacrylate (245 μL, 2.23 mmol) were added every 12 h. The solvent was removed under vacuum and the crude oil purified on chromatography over silica gel (hexane–ethyl acetate 3:7). White crystal mp 110–114 °C; yield 67%; $[\alpha]_D = -316.7$ (*c* 1.68, MeOH); IR (pellet, cm^{-1}): 3229, 3050, 1771, 1518; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31–7.18 (m, 5H), 6.15 (s, 1H), 5.20 (s, 1H), 4.53–4.49 (m,

1H), 3.71 (s, 3H), 2.48–2.40 (m, 1H), 2.32–2.26 (m, 1H), 1.67–1.58 (m, 1H), 1.56 (s, 3H), 1.47 (d, $J = 6.6$, 3H), 1.03 (d, $J = 6.6$, 3H); ^{13}C NMR (CD_4O) δ: 197.9 (C), 173.7 (C), 164.4 (C), 143.0 (C), 129.1 (2CH), 127.7 (CH), 126.1 (2CH), 98.6 (CH), 54.1 (CH), 53.2 (CH_3), 47.2 (CH), 42.7 (C), 36.2 (CH_2), 25.0 (CH_3), 23.4 (CH_3), 15.8 (CH_3). Crystal data: $C_{18}H_{23}NO_3$, Mw = 301.38, white crystal of $0.20 \times 0.30 \times 0.30$ mm, monoclinic, space group $P2_1$, $Z = 2$, $a = 13.589(7)$, $b = 9.914(15)$, $c = 14.000(5)$ Å, $\alpha = \gamma = 90°$, $\beta = 111.24(4)$, $V = 1758(3)$ Å^3, $d = 1.135$ g cm^{-3}, $F(000) = 644$, $\lambda = 0.710693$ Å (Mo Kα), $\mu = 0.077$ mm^{-1}; 4336 reflections measured ($0 \leqslant h \leqslant 16$, $0 \leqslant k \leqslant 13$, $-18 \leqslant l \leqslant 18$) on a Nonius CAD4 diffractometer. The structure was solved with SIR92 and refined with CRYSTALS. Hydrogen atoms riding. Due to the poor quality of crystal, the structure has not been deposited at the Cambridge Crystallographic Data Centre but will be sent for publication in Zeitschrift für Kristallographie.

4.4. General procedure for the addition of ammonia on keto esters 11a and 11b

In a two necked round-bottom flask with a drying tube ($CaCl_2$), a stream of ammonia was bubbled through 10 mL of ice-cooled anhydrous methanol for 10 min. Keto esters **11a** or **11b** (300 mg) previously dissolved in anhydrous methanol (5 mL) were added. The mixture was then stirred at 0 °C for 1.5 h, and the solvent removed under reduced pressure.

4.4.1. (*S*,*S*)-4-Acetyl-4-methyl-5-oxo-pyrrolidine-2-carboxylic acid amide 14. Chromatography purification over silica gel (ethyl acetate–methanol 8:2) gave compound **14** as a white solid; yield 90%; mp 150–154 °C; $[\alpha]_D = -15.8$ (*c* 4.425, MeOH); IR (film, cm^{-1}): 3199 (large), 1666; ^{1}H NMR (200 MHz, CD_4O) δ: 4.23 (dd, $J = 8.30$, 6.70, 1H), 3.08 (dd, $J = 8.30$, 13.40, 1H), 2.31 (s, 3H), 1.91 (dd, $J = 6.70$, 13.40, 1H), 1.50 (s, 3H); ^{13}C NMR (200 MHz, CD_4O) δ: 207.8 (C), 179.1 (C); 177.3 (C), 59.5 (C), 55.4 (CH), 37.8 (CH_2), 26.2 (CH_3), 21.5 (CH_3). Anal. Calcd for $C_8H_{12}N_2O_3$: C, 52.17; H, 6.57; N, 15.21. Found: C, 51.95; H, 6.65; N, 14.88. Crystal data: $C_8H_{12}N_2O_3$, Mw = 184.19, white crystal of $0.20 \times 0.30 \times 0.30$ mm, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 7.115(3)$, $b = 7.138(2)$, $c = 17.375(6)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 882.5(5)$ Å^3, $d = 1.386$ g cm^{-3}, $F(000) = 392$, $\lambda = 0.710693$ Å (Mo Kα), $\mu = 0.107$ mm^{-1}; 2517 reflections measured ($0 \leqslant h \leqslant 9$, $0 \leqslant k \leqslant 10$, $0 \leqslant l \leqslant 24$) on a Nonius CAD4 diffractometer. The structure was solved with SIR92 and refined with CRYSTALS. Hydrogen atoms riding. Refinement converged to $R(gt) = 0.0482$ for the 1310 reflections having $I \geqslant 3\sigma(I)$, and $wR(gt) = 0.0573$, goodness-of-fit $S = 1.1496$. Residual electron density: −0.30 and 0.49 e Å^3. The crystal cohesion is ensured by three hydrogen bonds involving N4, N7 [for N4–H2···O2*i*: 2.060(3) Å, 149°, for N7–H1···O1*ii*: 1.996(2) Å, 167° and for N7–H3···O3*iii*: 2.142(3) Å, 169° (symmetry code *i*: $-x + 2$, $y - 1/2$, $-z + 3/2$; *ii*: $x + 1/2$, $-y - 1/2$, $-z + 2$; *iii*: $x + 1$, y, z)]. Full crystallographic results have been sent for publication in Zeitschrift für Kristallographie.

4.4.2. (2*S*,4*S*,5*R*)-5-Hydroxy-4,5-dimethyl-tetrahydrofuran-2,4-carboxylic acid diamide 18. Chromatography over silica gel (ethyl acetate–methanol 9.5:0.5) afforded **18** as a white solid; mp 161–162 °C; yield 95%; $[\alpha]_D = -12$ (*c* 0.25, MeOH); IR (film, cm^{-1}): 3334, 1645, 1382, 1044; ^{1}H NMR (300 MHz, CD_4O) δ: 4.39 (dd, $J = 7.70$, 10.20, 1H), 2.63 (dd, $J = 10.20$, 12.0, 1H), 2.23 (dd, $J = 7.70$, 12.0, 1H), 1.53 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (300 MHz, CD_4O) δ: 179.5 (C), 178.4 (C), 108.6 (C), 76.8 (CH), 56.7 (C), 40.2 (CH_2), 22.3 (CH_3), 21.20 (CH_3). Anal. Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.29; H, 7.23; N, 14.68.

Crystal data: $C_8H_{14}N_2O_4$, Mw = 202.21, white crystal of $0.20 \times 0.25 \times 0.30$ mm, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 6.489(3)$, $b = 11.556(4)$, $c = 12.904(9)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 967.6(8)$ Å^3, $d = 1.388$ g cm^{-3}, $F(000) = 432$, $\lambda = 0.710693$ Å (Mo Kα), $\mu = 0.112$ mm^{-1}; 1518 reflections measured ($0 \leqslant h \leqslant 9$, $0 \leqslant k \leqslant 16$, $0 \leqslant l \leqslant 18$) on a Nonius CAD4 diffractometer. The structure was solved with SIR92 and refined with CRYSTALS. Hydrogen atoms riding. Refinement converged to $R(gt) = 0.0482$ for the 1323 reflections having $I \geqslant 3\sigma(I)$, and $wR(gt) = 0.0590$, goodness-of-fit $S = 1.1482$. Residual electron density: −0.32 and 0.42 e Å^3. The crystal cohesion is ensured by three hydrogen bonds involving N6, N10 and O2 [for N6–H7···O4*i*: 2.150(3) Å, 175°, for N10–H11···O4*ii*: 2.195(4) Å, 151° and for O2–H3···O5*iii*: 2.024(3) Å, 164° (symmetry code *i*: $x - 1/2$, $-y - 1/2$, $-z + 1$; *ii*: $-x + 3/2$, $-y$, $z + 1/2$; *iii*: $x - 1$, y, z)] and one intramolecular hydrogen bond: O2–H3···O1: 2.438(3) Å, 72°. Full crystallographic results have been deposited as Supplementary Material (CIF file) at the Cambridge Crystallographic Data Centre, UK (CCDC 227084).

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