

# Synthesis of novel all-*cis*-functionalized cyclopropane template-assembled collagen models†

Shoko Yamazaki,<sup>\*,a</sup> Mari Sakamoto,<sup>a</sup> Michiko Suzuri,<sup>a</sup> Masamitsu Doi,<sup>b</sup> Takashi Nakazawa<sup>c</sup> and Yuji Kobayashi<sup>d</sup>

<sup>a</sup> Department of Chemistry, Nara University of Education, Takabatake-cho, Nara 630-8528, Japan

<sup>b</sup> Department of Materials Science, Wakayama National College of Technology, Gobo, Wakayama 644-0023, Japan

<sup>c</sup> Department of Chemistry, Nara Women's University, Nara 630-8506, Japan

<sup>d</sup> Graduate School of Pharmaceutical Science, Osaka University, Suita, 565-1871, Japan

Received (in Cambridge, UK) 1st May 2001, Accepted 20th June 2001

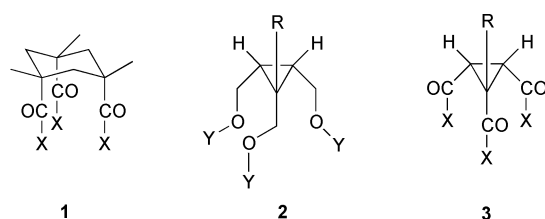
First published as an Advance Article on the web 31st July 2001

An all-*cis*-functionalized cyclopropane template to connect the three peptide chains in a collagen model is designed. Stereoselective synthesis of cyclopropane-assembled collagen-model **2b** with the minimum unit of Gly-Pro-Pro is based on a novel 1-seleno-2-silylethene [2 + 1] cycloaddition strategy. Reaction of the 1-seleno-2-silylethene **4** with triester-substituted olefin **5** in the presence of ZnI<sub>2</sub> gives [2 + 1] cycloadduct **6** stereoselectively. Cyclopropane **6** is selectively transformed into triol **10** in four steps. The reaction of **10** and three equivalents of *N*-Boc-Pro-Pro-Gly-OH in the presence of WSC-DMAP and subsequent deprotection with TFA gives **2b**.

## Introduction

Collagen is the main protein constituent of bone, tendon, and skin, which form the basic skeleton of the human body. This characteristic function of collagen arises from its triple-helix tertiary structure.<sup>1</sup> The primary structure of the peptide chains of collagen are mainly composed of trimer repeats of sequences such as Gly-Pro-Hyp or Gly-Pro-Pro.<sup>2</sup> Understanding the dissociation-association mechanism of the three peptide chains is of biophysical interest in order to elucidate the importance of the triple-helix structure, and also to facilitate the design of potential collagen-like synthetic materials that may have improved properties. Towards this goal, a conformationally constrained template-assembled synthetic collagen model has been studied recently by Goodman.<sup>3</sup> *cis,cis*-1,3,5-Trimethylcyclohexane-1,3,5-tricarboxylic acid (Kemp's triacid, KTA)<sup>4</sup> was utilized as a template for a collagen model consisting of three peptide chains **1** (Scheme 1). This all-*cis* cyclohexane-

Cyclopropanes have more rigid skeletons than the cyclohexane skeleton of Kemp's triacid.<sup>5</sup> An all-*cis*-functionalized cyclopropane template may be more effective at inducing the collagen-like triple-helical structure for very short peptide chains, compared with KTA. *cis,cis*-1,2,3-Tris(hydroxymethyl)cyclopropane derivative **2** and *cis,cis*-cyclopropane-1,2,3-tricarboxylic acid derivative **3** are newly designed cycloalkane templates with potential application as collagen models (Scheme 1).<sup>4,5</sup> Cyclopropanes **2** and **3** have two sets of peptide chains that are distinguishable owing to the presence of a substituent R on the cyclopropane ring. In the resulting desymmetrized peptide chains assembled in the templates **2** and **3**, more detailed structural features may be analyzed by NMR than in KTA-based model **1**. In template model **2**, the three peptide chains are linked *via* the C-termini and in template **3** are linked at the N-termini, respectively. Although a number of stereoselective cyclopropane syntheses are known,<sup>6,7</sup> few methods for all-*cis*-functionalized cyclopropanes are available.<sup>8</sup> In this paper, we describe a stereoselective synthesis of template model **2** based on a novel seleno(silyl)ethene [2 + 1] cycloaddition strategy.<sup>9</sup>



X = NH-CH<sub>2</sub>-CO-, Y = CO-CH<sub>2</sub>-NH-

Scheme 1

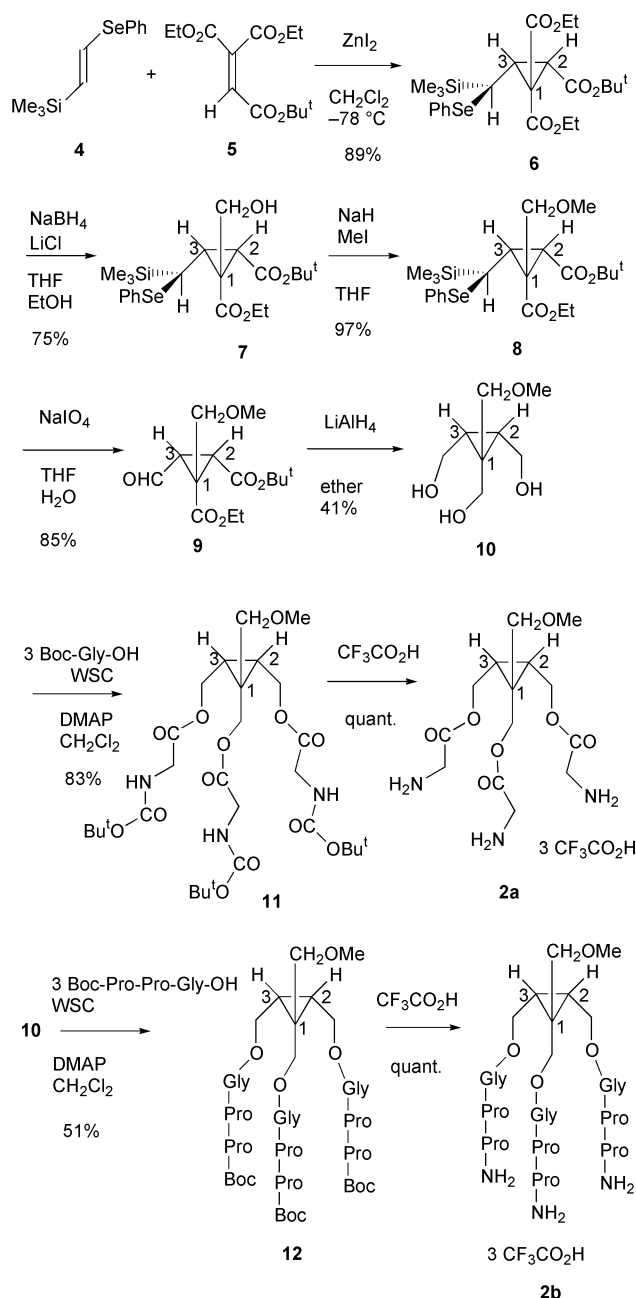
assembled synthetic collagen model effectively induces the collagen-like triple-helical structure for short peptide chains. Examination of the effect on triple-helix formation by changing the ring size of the template is of interest.

## Results and discussion

Reaction of 1-(phenylseleno)-2-(trimethylsilyl)ethene **4** with triester-substituted olefin **5** in the presence of ZnI<sub>2</sub> gave [2 + 1] cycloadduct **6** stereoselectively in 89% yield (Scheme 2). The ethoxycarbonyl group on the least hindered face of cyclopropane **6** was chemoselectively reduced to mono alcohol **7** with NaBH<sub>4</sub>-LiCl in THF-EtOH in 75% yield.‡ Reaction of **7** with NaH-MeI in THF gave methoxymethylcyclopropane **8** in 97% yield. The methoxymethyl group was introduced to the *trans* side and is for synthetic convenience; however, it may be used as a handle for desymmetrization of the molecule and the resulting differentiation of one of the three peptide chains in an

† Electronic supplementary information (ESI) available: <sup>1</sup>H NMR spectra of compounds **2a**, **2b**, **8-13**, **15** and **17**. See <http://www.rsc.org/suppdata/p1/b1/b103887g/>

‡ The racemic alcohol **7** was separable by chiral column (CHIRALCEL OF). This property should allow further development of asymmetric template models.



Scheme 2

NMR study, as described above. Oxidation of **8** with  $\text{NaIO}_4$  in aq. THF gave aldehyde **9** via sila-Pummerer reaction<sup>10</sup> in 85% yield. Aldehyde diester **9** was reduced by  $\text{LiAlH}_4$  in diethyl ether to give triol **10** in 41% yield. The reaction of **10** and three equivalents of *N*-Boc-glycine in the presence of WSC {1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride}–DMAP [4-(dimethylamino)pyridine] in  $\text{CH}_2\text{Cl}_2$  gave **11** in 83% yield. Deprotection of **11** with trifluoroacetic acid then afforded **2a**. The collagen model **2b** with the minimum unit Gly-Pro-Pro was obtained from **10**. Protected derivative **12** was directly prepared in 51% yield by the reaction of triol **10** and three equivalents of *N*-Boc-Pro-Pro-Gly-OH using the same conditions. Deprotection of **12** with trifluoroacetic acid gave **2b**.<sup>§</sup>

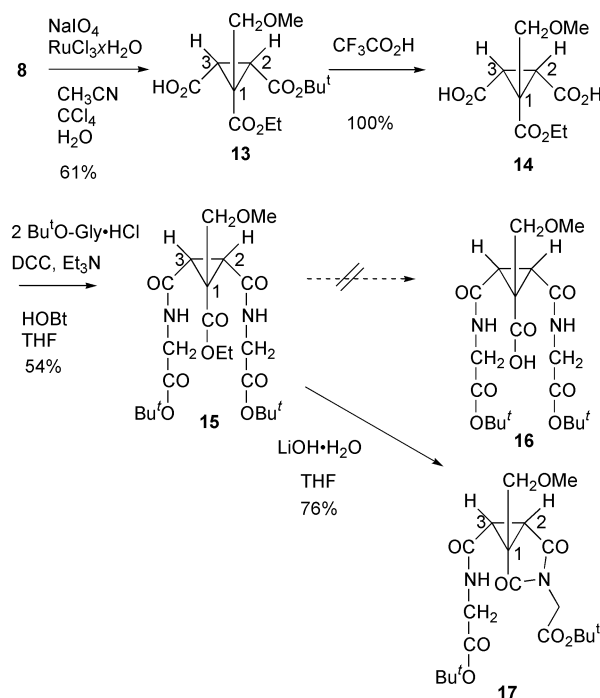
The *cis* stereochemistry of the cyclopropanes in Scheme 2 was confirmed by 2D-NOESY. Thus, NOEs between 2-H and 3-H (the cyclopropane ring-numbering is shown in Scheme 2) and/or between 2-H, 3-H and  $\text{CH}_2\text{OMe}$  were observed. The

<sup>§</sup> Molecular modelling of **2b** shows the chains are too short to form a triple helix. CD spectra of **2b** in aqueous solution showed no positive band at 220–240 nm at 24 °C, which is characteristic for a triple helix.<sup>11</sup>

stereochemistry was also supported by the observed vicinal coupling constants. The coupling constants of vicinal protons in cyclopropane rings are characteristic and the *J*-values are in the region of those for *cis*-vicinal protons (8.9–9.2 Hz for the unsymmetric cyclopropanes **6–9**).<sup>9c,12</sup>

The  $^1\text{H}$  NMR spectra of **2a** and **2b** showed differentiation between two equivalent chains and one chain. For example, in **2b** two sets of glycine  $\alpha$ -H are clearly distinguished [ $\delta$  3.79 (2H), 3.90 (2H) and 3.80 (1H), 3.92 (1H)]. Compounds **2a** and **2b** can be used to connect further tripeptides to create a range of collagen mimetics.

Synthesis of the *cis,cis*-cyclopropane-1,2,3-tricarboxylic acid template **3** was attempted through intermediate **8** (Scheme 3).



Scheme 3

The cyclopropane **8** was directly oxidized to the carboxylic acid by  $\text{NaIO}_4$ – $\text{RuCl}_3$  in  $\text{CH}_3\text{CN}$ – $\text{CCl}_4$ –water,<sup>13</sup> to give *cis,cis*-cyclopropane-1,2,3-tricarboxylic acid derivative **13** in 61% yield. Treatment of **13** with trifluoroacetic acid gave the *cis*-cyclopropane-1,2-dicarboxylic acid **14**. Reaction of **14** with two equivalents of glycine *tert*-butyl ester gave **15**. Attempted removal of the ethyl ester group of **15** to afford the monoacid **16** was not successful. For example, hydrolysis of **15** with  $\text{LiOH}\cdot\text{H}_2\text{O}$  in THF gave imide **17**. The *cis* stereochemistry of the cyclopropanes **13–15** and **17** in Scheme 3 was also confirmed by 2D-NOESY. NOEs between 2-H and 3-H and/or between 2-H, 3-H and  $\text{CH}_2\text{OMe}$  were observed. The stereochemistry was supported by the observed *cis*-vicinal coupling constants (9.3 Hz for **13**, 8.5 Hz for **17**) as well.

Other routes were also attempted for the preparation of all-*cis* three-amino-acid-connected cyclopropanes; however, epimerization of the *tert*-butoxycarbonyl group in addition to undesirable interaction of the *cis*-functional groups has prevented success so far.

In summary, we have described the synthesis and preliminary investigations of cyclopropane templates for collagen models. Further studies on synthesis of collagen models with longer chains and with three differentiated chains, and on synthesis of other three-functionalized cyclopropane templates, are in progress. Furthermore, all-*cis*-functionalized cyclopropanes are also attractive as templates for various chemical libraries and peptidomimetics.<sup>14</sup>

## Experimental

### General methods

Mps were measured on a Yamato MP-21 melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO FT-IR 5000 spectrophotometer. NMR spectra were recorded on a Varian INOVA 400 spectrometer. Chemical shifts are reported in ppm relative to Me<sub>4</sub>Si or residual nondeuterated solvent. *J*-Values are given in Hz. <sup>1</sup>H and <sup>13</sup>C assignments were determined by COSY, TOCSY, NOESY, DEPT, HSQC and HMBC. Mass spectra were recorded on a JEOL JMS700 or JMS-SX-102 spectrometer at an ionizing voltage of 70 eV by EI or FAB. All reactions were carried out under a nitrogen atmosphere.

### 2-*tert*-Butyl 1,1-diethyl 2,3-*cis*-3-[(phenylseleno)(trimethylsilyl)methyl]cyclopropane-1,1,2-tricarboxylate **6**

Optimization of the reaction conditions gave a better yield than that described in ref. 9c. To a solution of **4** (2.66 g, 10.4 mmol) in dichloromethane (24 mL), cooled to –78 °C, was added ZnI<sub>2</sub> (4.99 g, 15.7 mmol), followed by a solution of **5** (3.69 g, 13.6 mmol) in dichloromethane (4 mL). The mixture was allowed to warm to –40 °C and was stirred for 18 h. The reaction was quenched by triethylamine (3.7 mL, 2.70 g, 26.7 mmol), and then saturated aq. NaHCO<sub>3</sub> (10 mL) was added to the mixture, which was extracted with dichloromethane, and the organic phase was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel with hexane–diethyl ether (2 : 1) as eluent to give **6** (4.79 g, 89%), *R*<sub>f</sub> 0.6, as a colorless oil; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) –0.002 (9H, s, SiMe<sub>3</sub>), 1.22 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.27 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.45 (9H, s, 'Bu), 2.00 (1H, dd, *J* 13.5 and 9.4, H-3), 2.62 (1H, d, *J* 9.4, H-2), 3.32 (1H, d, *J* 13.5, CHSeSi), 4.01–4.26 (4H, m, OCH<sub>2</sub>CH<sub>3</sub>), 7.19–7.22 (3H, m, *m*-, *p*-H of Ph) and 7.61–7.64 (2H, m, *o*-H of Ph). The ring numbering is shown in Scheme 2. Selected NOEs were between δ –0.002 and 1.45, δ 1.45 and 3.32, δ 1.45 and 4.01–4.26, and δ 2.00 and 2.62; δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>) –1.54 (SiMe<sub>3</sub>), 14.04 (CH<sub>2</sub>CH<sub>3</sub>), 23.46 (CHSeSi), 28.20 ('Bu), 34.49 (C-2), 35.91 (C-3), 39.51 (C-1), 61.28 (OCH<sub>2</sub>CH<sub>3</sub>), 62.32 (OCH<sub>2</sub>CH<sub>3</sub>), 82.16 (OCMe<sub>3</sub>), 127.29 (*p*-C of Ph), 128.69 (*m*-C of Ph), 129.84 (C of Ph), 135.15 (*o*-C of Ph), 164.60 (CO), 167.99 (CO) and 169.57 (CO). The spectroscopic data are in agreement with those described in ref. 9c.

### 2-*tert*-Butyl 1-ethyl 1-(hydroxymethyl)-*c*-3-[(phenylseleno)(trimethylsilyl)methyl]cyclopropane-*r*-1,*c*-2-dicarboxylate **7**

The cyclopropane **6** (4.52 g, 8.6 mmol) obtained as above was dissolved in THF (24 mL), and anhydrous lithium chloride (1.471 g, 34.2 mmol) and sodium borohydride (1.301 g, 34.2 mmol) were added successively at 0 °C. After addition of ethanol (48 mL), the mixture was allowed to warm to room temperature and was stirred overnight, then refluxed for 4 h before being cooled with ice–water, acidified by the gradual addition of 10% aq. citric acid (37 mL), and concentrated *in vacuo*. Water was added to the residue, which was extracted with dichloromethane; the extract was dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel and elution with hexane–diethyl ether (2 : 1) to give **7** (3.15 g, 75%), *R*<sub>f</sub> 0.2, as a pale yellow oil; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 0.060 (9H, s, SiMe<sub>3</sub>), 1.18 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.46 (9H, s, 'Bu), 1.66 (1H, dd, *J* 13.2 and 8.9, H-3), 2.17 (1H, d, *J* 8.9, H-2), 2.43 (1H, br, OH), 3.47 (1H, dd, *J* 11.8 and 6.4, CHHOH), 3.52 (1H, d, *J* 13.2, CHSeSi), 3.80 (1H, dd, *J* 11.8 and 5.7, CHHOH), 3.96 (2H, q, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>), 7.19–7.23 (3H, m, *m*-, *p*-H of Ph) and 7.55–7.58 (2H, m, *o*-H of Ph). Selected NOEs were between δ 1.66 and 2.17, δ 1.66 and 3.47, δ 1.66 and 3.80, δ 2.17 and 3.47, and δ 2.17 and 3.80; δ<sub>C</sub> (100.6

MHz; CDCl<sub>3</sub>) –1.58 (SiMe<sub>3</sub>), 14.14 (CH<sub>2</sub>CH<sub>3</sub>), 25.28 (CHSeSi), 28.26 ('Bu), 33.92 (C-3), 35.21 (C-2), 37.69 (C-1), 61.30 (OCH<sub>2</sub>CH<sub>3</sub>), 67.71 (CH<sub>2</sub>OH), 81.34 (OCMe<sub>3</sub>), 127.01 (*p*-C of Ph), 128.77 (*m*-C of Ph), 130.87 (C of Ph), 133.92 (*o*-C of Ph), 167.01 (CO<sub>2</sub>'Bu) and 169.46 (CO<sub>2</sub>Et); ν<sub>max</sub> (neat)/cm<sup>–1</sup> 3412, 2980, 1725, 1578, 1479, 1369, 1249, 1151, 862, 841 and 735; MS (EI) *m/z* 486; exact mass M<sup>+</sup>, 486.1319 (Calc. for C<sub>22</sub>H<sub>34</sub>O<sub>5</sub>SeSi: *M*, 486.1341) (Calc. for C<sub>22</sub>H<sub>34</sub>O<sub>5</sub>SeSi: C, 54.42; H, 7.06. Found: C, 53.93; H, 6.88%).

### 2-*tert*-Butyl 1-ethyl 1-(methoxymethyl)-*c*-3-[(phenylseleno)(trimethylsilyl)methyl]cyclopropane-*r*-1,*c*-2-dicarboxylate **8**

After removal of the mineral oil from sodium hydride (60% dispersion in oil; 69 mg, 2.9 mmol) by washing with *n*-pentane, THF (1.4 mL) was added and the mixture was cooled to 0 °C. A THF (2.5 mL) solution of the alcohol **7** (0.93 g, 1.91 mmol) was added dropwise to the mixture. After the reaction mixture had been stirred for 30 min at 0 °C and for 1 h at room temperature, it was cooled to 0 °C and iodomethane (0.18 mL, 412 mg, 2.9 mmol) was added. After the addition, the mixture was stirred for 1.5 h at 0 °C. MeOH (69 μL) and water (1.6 mL) were then added. The mixture was extracted with diethyl ether, the extract was dried (MgSO<sub>4</sub>), and the solvent was evaporated off *in vacuo*. The residue was purified by column chromatography over silica gel and elution with hexane–diethyl ether (2 : 1) to give **8** (926 mg, 97%), *R*<sub>f</sub> 0.6, as a pale yellow oil; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 0.036 (9H, s, SiMe<sub>3</sub>), 1.17 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.46 (9H, s, 'Bu), 1.70 (1H, dd, *J* 13.2 and 8.8, H-3), 2.24 (1H, d, *J* 8.8, H-2), 3.37 (3H, s, OMe), 3.513 (1H, d, *J* 10.3, CHHOMe), 3.515 (1H, d, *J* 13.2, CHSeSi), 3.72 (1H, d, *J* 10.3, CHHOMe), 3.91–4.02 (2H, m, OCH<sub>2</sub>CH<sub>3</sub>), 7.18–7.21 (3H, m, *m*-, *p*-H of Ph) and 7.56–7.58 (2H, m, *o*-H of Ph). Selected NOEs were between δ 1.70 and 2.24, δ 1.70 and 3.513, δ 1.70 and 3.72, δ 2.24 and 3.513, and δ 2.24 and 3.72; δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>) –1.55 (SiMe<sub>3</sub>), 14.10 (CH<sub>2</sub>CH<sub>3</sub>), 25.24 (CHSeSi), 28.27 ('Bu), 31.74 (C-3), 33.24 (C-2), 35.91 (C-1), 58.81 (OCH<sub>3</sub>), 60.92 (OCH<sub>2</sub>CH<sub>3</sub>), 73.75 (CH<sub>2</sub>OMe), 81.04 (OCMe<sub>3</sub>), 126.80 (*p*-C of Ph), 128.66 (*m*-C of Ph), 131.02 (C of Ph), 133.88 (*o*-H of Ph), 167.77 (CO) and 168.72 (CO); ν<sub>max</sub> (neat)/cm<sup>–1</sup> 2980, 1740, 1578, 1479, 1369, 1309, 1249, 1154, 861, 839 and 737; MS (EI) *m/z* 500; exact mass M<sup>+</sup>, 500.1511 (Calc. for C<sub>23</sub>H<sub>36</sub>O<sub>5</sub>SeSi: *M*, 500.1497).

### 2-*tert*-Butyl 1-ethyl *c*-3-formyl-1-(methoxymethyl)-cyclopropane-*r*-1,*c*-2-dicarboxylate **9**

To a solution of **8** (955 mg, 1.91 mmol) in THF (39 mL) were added water (19.5 mL) and NaIO<sub>4</sub> (2.043 g, 9.55 mmol). The mixture was stirred for 4.5 h at room temperature. After removal of THF *in vacuo*, saturated aq. NaHCO<sub>3</sub> was added to the residue. The mixture was extracted with diethyl ether 5 times, and the organic phase was washed with water, dried (MgSO<sub>4</sub>), and evaporated *in vacuo* to give **9** (465 mg, 85%) as a colorless oil; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 1.30 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.46 (9H, s, 'Bu), 2.18 (1H, dd, *J* 9.2 and 6.0, H-3), 2.40 (1H, d, *J* 9.2, H-2), 3.35 (3H, s, OMe), 3.39 (1H, d, *J* 10.3, CHHOMe), 3.85 (1H, d, *J* 10.3, CHHOMe), 4.26 (2H, q, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>) and 9.71 (1H, d, *J* 6.0, CHO). Selected NOEs were between δ 2.18 and 2.40, δ 2.18 and 3.39 and δ 2.40 and 3.39; δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>) 14.12 (CH<sub>2</sub>CH<sub>3</sub>), 28.04 ('Bu), 31.66 (C-2), 35.91 (C-3), 39.74 (C-1), 58.95 (OMe), 62.08 (OCH<sub>2</sub>CH<sub>3</sub>), 73.43 (CH<sub>2</sub>OMe), 82.77 (OCMe<sub>3</sub>), 166.71 (CO), 167.27 (CO) and 197.94 (CHO); ν<sub>max</sub> (neat)/cm<sup>–1</sup> 2984, 2936, 1729, 1715, 1458, 1396, 1373, 1323, 1228, 1152, 1112 and 1023; MS (FAB) *m/z* 287 (M + H)<sup>+</sup>; exact mass (M + H)<sup>+</sup>, 287.1507 (Calc. for C<sub>14</sub>H<sub>23</sub>O<sub>6</sub>: *m/z*, 287.1495).

### *r*-1-(Methoxymethyl)-1,*r*-2,*r*-3-tris(hydroxymethyl)cyclopropane **10**

To LiAlH<sub>4</sub> (89 mg, 2.1 mmol) was added diethyl ether (4.5 mL)



and the mixture was stirred for 1 h at room temperature, then cooled to 0 °C, and a solution of **9** (201 mg, 0.7 mmol) in diethyl ether (6.3 mL) was added with stirring. The resulting mixture was allowed to warm to room temperature and was stirred for 1 h. Saturated aq. Na<sub>2</sub>SO<sub>4</sub> (2 mL) was then added to the mixture, which was then extracted with diethyl ether 5 times, and the organic phase was dried (MgSO<sub>4</sub>), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel with diethyl ether–MeOH (19 : 1) as eluent to give **10** (50 mg, 41%), *R*<sub>f</sub> 0.2, as a colorless oil;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 1.36 (2H, m, H-2,3), 2.88 (2H, br s, OH), 3.34 (1H, m, OH), 3.35 (2H, s, CH<sub>2</sub>OMe), 3.38 (3H, s, OMe), 3.79 (4H, br s, 2,3-CH<sub>2</sub>OH) and 3.88 (2H, d, *J* 5.1, 1-CH<sub>2</sub>OH). Selected NOEs were between  $\delta$  1.36 and 3.35;  $\delta_{\text{C}}$  (100.6 MHz; CDCl<sub>3</sub>) 27.43 (C-2, -3), 30.06 (C-1), 58.68 (2-, 3-CH<sub>2</sub>OH), 59.10 (OMe), 61.50 (1-CH<sub>2</sub>OH) and 81.53 (CH<sub>2</sub>OMe);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3504, 2930, 1456, 1419, 1241, 1195, 1096 and 1023; MS (FAB) *m/z* 177 (M + H)<sup>+</sup>; exact mass (M + H)<sup>+</sup>, 177.1127 (Calc. for C<sub>8</sub>H<sub>17</sub>O<sub>4</sub>; *m/z*, 177.1127).

### Compound 11

To a solution of Boc-Gly-OH (154 mg, 0.88 mmol), DMAP (10 mg, 0.08 mmol) and **10** (50 mg, 0.28 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.2 mL) was added WSC (184 mg, 0.96 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C, allowed to warm to room temperature, and stirred overnight. After removal of the solvent under reduced pressure, diethyl ether (40 mL) and water (2 mL) were added to the residue. The organic phase was extracted, washed successively with saturated aq. NaHCO<sub>3</sub> (4 mL × 2) and water (4 mL × 2), dried (MgSO<sub>4</sub>), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel and elution with diethyl ether–MeOH (19 : 1) to give **11** (150 mg, 83%), *R*<sub>f</sub> 0.4, as a colorless viscous oil;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 1.45 (27H, s, 'Bu), 1.50 (2H, m, H-2, -3), 3.26 (2H, br s, CH<sub>2</sub>OMe), 3.31 (3H, s, OMe), 3.90 (6H, d, *J* 5.9, Gly- $\alpha$ ), 4.26–4.31 (4H, m, 2-, 3-CH<sub>2</sub>OCO), 4.34 (2H, s, 1-CH<sub>2</sub>OCO) and 5.20 (br s, NH). Selected NOEs were between  $\delta$  1.50 and 3.26 and  $\delta$  4.26–4.31 and 4.34;  $\delta_{\text{C}}$  (100.6 MHz; CDCl<sub>3</sub>) 23.24 (C-2, -3), 27.66 (C-1), 28.40 ('Bu), 42.46 (Gly- $\alpha$ ), 58.85 (OMe), 61.16 (2-, 3-CH<sub>2</sub>OCO), 61.71 (1-CH<sub>2</sub>OCO), 76.39 (CH<sub>2</sub>OMe), 80.17 (OCMe<sub>3</sub>), 155.89 (CO<sub>2</sub>'Bu) and 170.30 (HNCH<sub>2</sub>CO);  $\nu_{\text{max}}$  (KBr)/cm<sup>-1</sup> 3400, 2982, 1750, 1725, 1520, 1369 and 1170; MS (EI) *m/z* 647; exact mass M<sup>+</sup>, 647.3229 (Calc. for C<sub>29</sub>H<sub>49</sub>N<sub>3</sub>O<sub>13</sub>; *M*, 647.3265).

### Compound 2a

TFA (0.32 mL) was added to **11** (20 mg, 0.031 mmol) at 0 °C and the solution was stirred for 2 h. Removal of the solvent under reduced pressure gave **2a** quantitatively as a colorless viscous oil;  $\delta_{\text{H}}$  (400 MHz; D<sub>2</sub>O) 1.48 (2H, m, H-2, -3), 3.15 (3H, s, OMe), 3.19 (2H, s, CH<sub>2</sub>OMe), 3.76 (4H, s, Gly- $\alpha$ ), 3.78 (2H, s, Gly- $\alpha$ ), 4.29 (4H, d, *J* 7.8, 2-, 3-CH<sub>2</sub>OCO) and 4.31 (2H, s, 1-CH<sub>2</sub>OCO). Selected NOEs were between  $\delta$  1.48 and 3.76 and  $\delta$  4.29 and 4.31;  $\delta_{\text{C}}$  (100.6 MHz; D<sub>2</sub>O) 24.16 (C-2, -3), 28.02 (C-1), 40.93 (Gly- $\alpha$ ), 41.01 (Gly- $\alpha$ ), 59.01 (OMe), 63.84 (2-, 3-CH<sub>2</sub>OCO), 64.52 (1-CH<sub>2</sub>OCO), 77.82 (CH<sub>2</sub>OMe), 117.24 (C, q, *J*<sub>CF</sub> 291.5, CF<sub>3</sub>), 163.82 (C, q, *J*<sub>CF</sub> 35.9, CF<sub>3</sub>CO), 168.81 (CO) and 169.01 (CO);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3000, 1760, 1748, 1684, 1653, 1634, 1435 and 1417; MS (FAB) *m/z* 370 (M + Na)<sup>+</sup>, 348 (M + H)<sup>+</sup>; exact mass (M + Na)<sup>+</sup>, 370.1596 (Calc. for C<sub>14</sub>H<sub>25</sub>N<sub>3</sub>NaO<sub>7</sub>; *m/z*, 370.1590); (M + H)<sup>+</sup>, 348.1779 (Calc. for C<sub>14</sub>H<sub>26</sub>N<sub>3</sub>O<sub>7</sub>; *m/z* 348.1771).

Boc-Pro-Pro-Gly-OH was prepared by standard liquid-phase peptide-synthesis methods. Reaction of glycine, *p*-TsOH, and benzyl alcohol in benzene gave Gly-OBz·TsOH in 77% yield. Gly-OBz·TsOH was converted to Boc-Pro-Gly-OBz by reaction with Et<sub>3</sub>N, Boc-Pro-OH, and DCC in CH<sub>2</sub>Cl<sub>2</sub> quantitatively. The product was converted to TFA·Pro-Gly-OBz by reaction with TFA in CH<sub>2</sub>Cl<sub>2</sub> in 66% yield. TFA·Pro-Gly-OBz

was converted to Boc-Pro-Pro-Gly-OBz by reaction with Boc-Pro-OH, *N*-methyl morpholine and DCC in CH<sub>2</sub>Cl<sub>2</sub> in 91% yield. The product was converted to Boc-Pro-Pro-Gly-OH by hydrogenation in the presence of Pd/C in methanol in 98% yield.

### Compound 12

To a solution of Boc-Pro-Pro-Gly-OH (184 mg, 0.50 mmol), DMAP (5.6 mg, 0.046 mmol) and **10** (28 mg, 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added WSC (105 mg, 0.5 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C, allowed to warm to room temperature, and stirred overnight. After removal of the solvent under reduced pressure, CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and water (4 mL) were added to the residue. The organic phase was extracted, washed with saturated aq. NaHCO<sub>3</sub> (4 mL × 2) and water (4 mL × 2), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel and elution with diethyl ether–MeOH (19 : 1) to give **12** (101 mg, 51%), *R*<sub>f</sub> 0.3, as colorless crystals; mp 86–88 °C;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 1.39 (s), 1.41 (s), 1.46 (s) (proportions 1 : 0.9 : 1.5, total 27H, 'Bu), 1.46 (2H, m, H-2, -3), 1.82–2.56 (24H, m, Pro- $\beta$ , - $\gamma$ ), 3.16–3.31 (2H, m, CH<sub>2</sub>OMe), 3.30 (3H, s, OMe), 3.40–3.74 (12H, m, Pro- $\delta$ ), 3.84–4.08 (6H, m, Gly- $\alpha$ ), 4.15–4.29 (6H, m, CH<sub>2</sub>OCO), 4.31–4.35 (m), 4.41 (dd, *J* 8.4 and 4.4), 4.50 (dd, *J* 8.3 and 3.9), 4.70 (m) (proportions 1 : 0.8 : 1.0 : 1.5, total 6H, Pro- $\alpha$ ), 7.61–7.64 (2H, m, Gly-NH) and 8.62–8.63 (m, 1H, Gly-NH);  $\delta_{\text{C}}$  (100.6 MHz; CDCl<sub>3</sub>) 22.20 (Pro- $\beta$  or - $\gamma$ ), 23.12 (C-2, -3), 23.74 (Pro- $\beta$  or - $\gamma$ ), 24.31 (Pro- $\beta$  or - $\gamma$ ), 24.69 (Pro- $\beta$  or - $\gamma$ ), 25.01 (Pro- $\beta$  or - $\gamma$ ), 25.29 (Pro- $\beta$  or - $\gamma$ ), 25.67 (Pro- $\beta$  or - $\gamma$ ), 26.79 (Pro- $\beta$  or - $\gamma$ ), 26.92 (Pro- $\beta$  or - $\gamma$ ), 27.54 (C-1), 28.46 ('Bu), 28.55 ('Bu), 29.47 (Pro- $\beta$  or - $\gamma$ ), 29.75 (Pro- $\beta$  or - $\gamma$ ), 30.35 (Pro- $\beta$  or - $\gamma$ ), 31.73 (Pro- $\beta$  or - $\gamma$ ), 34.00 (Pro- $\beta$  or - $\gamma$ ), 41.14 (Gly- $\alpha$ ), 41.47 (Gly- $\alpha$ ), 46.78 (Pro- $\delta$ ), 46.99 (Pro- $\delta$ ), 47.09 (Pro- $\delta$ ), 47.23 (Pro- $\delta$ ), 57.82 (Pro- $\alpha$ ), 58.14 (Pro- $\alpha$ ), 58.80 (OMe), 59.50 (Pro- $\alpha$ ), 59.66 (Pro- $\alpha$ ), 61.02 (Pro- $\alpha$ ), 61.10 (2-, 3-CH<sub>2</sub>OCO), 61.69 (1-CH<sub>2</sub>OCO), 76.25 (CH<sub>2</sub>OMe), 76.59 (CH<sub>2</sub>OMe), 79.59 (OCMe<sub>3</sub>), 79.73 (OCMe<sub>3</sub>), 80.06 (OCMe<sub>3</sub>), 153.75 (CO<sub>2</sub>'Bu), 154.65 (CO<sub>2</sub>'Bu), 154.92 (CO<sub>2</sub>'Bu), 169.27 (CO), 169.58 (CO), 171.50 (CO), 171.84 (CO), 171.94 (CO), 172.01 (CO), 172.08 (CO), 172.70 (CO) and 172.80 (CO);  $\nu_{\text{max}}$  (KBr)/cm<sup>-1</sup> 2978, 2882, 1745, 1688, 1657, 1543, 1402 and 1165; MS (FAB) *m/z* 1252 (M + Na)<sup>+</sup>, 1230 (M + H)<sup>+</sup>; exact mass (M + Na)<sup>+</sup>, 1252.6311 (Calc. for C<sub>59</sub>H<sub>91</sub>N<sub>9</sub>NaO<sub>19</sub>; *m/z*, 1252.6329), (M + H)<sup>+</sup>, 1230.6454 (Calc. for C<sub>59</sub>H<sub>92</sub>N<sub>9</sub>O<sub>19</sub>; *m/z*, 1230.6510), M<sup>+</sup>, 1229.6470 (Calc. for C<sub>59</sub>H<sub>91</sub>N<sub>9</sub>O<sub>19</sub>; *M*, 1229.6431).

### Compound 2b

TFA (0.17 mL) was added to **12** (20 mg, 0.016 mmol) at 0 °C and the solution was stirred for 2 h. Removal of the solvent under reduced pressure gave **2b** (20 mg, 100%) as a pale yellow oil;  $\delta_{\text{H}}$  (400 MHz; D<sub>2</sub>O) 1.41 (2H, t-like, *J* 5.6, H-2, -3), 1.73–1.94 (18H, m, Pro- $\gamma$ , - $\beta$ ), 2.14–2.22 (3H, m, Pro- $\beta$ ), 2.32–2.43 (3H, m, Pro- $\beta$ ), 3.14 (3H, s, OMe), 3.13–3.28 (8H, m, CH<sub>2</sub>OMe, Pro- $\delta$ ), 3.39–3.45 (3H, m, Pro- $\delta$ ), 3.50–3.55 (3H, m, Pro- $\delta$ ), 3.79 (2H, d, *J* 17.9, Gly- $\alpha$ ), 3.80 (1H, d, *J* 17.9, Gly- $\alpha$ ), 3.90 (2H, d, *J* 17.9, Gly- $\alpha$ ), 3.92 (1H, d, *J* 17.9, Gly- $\alpha$ ), 4.18 (4H, d, *J* 5.6, 2-, 3-CH<sub>2</sub>OCO), 4.23 (2H, s, 1-CH<sub>2</sub>OCO), 4.31–4.34 (3H, m, Pro- $\alpha$ ) and 4.43–4.47 (3H, m, Pro- $\alpha$ );  $\delta_{\text{C}}$  (100.6 MHz; D<sub>2</sub>O) 24.10 (C-2, -3), 24.81 (Pro- $\gamma$ ), 25.55 (Pro- $\gamma$ ), 28.00 (C-1), 29.32 (Pro- $\beta$ ), 30.44 (Pro- $\beta$ ), 42.18 (Gly- $\alpha$ ), 47.55 (Pro- $\delta$ ), 48.65 (Pro- $\delta$ ), 58.98 (OMe), 60.05 (Pro- $\alpha$ ), 61.47 (Pro- $\alpha$ ), 63.09 (2-, 3-CH<sub>2</sub>OCO), 63.51 (1-CH<sub>2</sub>OCO), 117.25 (C, q, *J*<sub>CF</sub> 292, CF<sub>3</sub>), 163.83 (C, q, *J*<sub>CF</sub> 35.6, CF<sub>3</sub>CO), 171.92 (CO), 171.98 (CO), 175.10 (CO) and 175.16 (CO);  $\nu_{\text{max}}$  (neat)/cm<sup>-1</sup> 3400, 1734, 1694, 1684, 1667, 1653, 1647, 1634, 1570, 1557, 1541, 1470, and 1456; MS (FAB) *m/z* 930 (M + H)<sup>+</sup>; exact mass (M + H)<sup>+</sup>, 930.4933 (Calc. for C<sub>44</sub>H<sub>68</sub>N<sub>9</sub>O<sub>13</sub>; *m/z*, 930.4937).

### 2-*tert*-Butyl 1-ethyl 3-hydrogen 1-(methoxymethyl)cyclopropane-*r*-1, *c*-2, *c*-3-tricarboxylate **13**

Compound **8** (203 mg, 0.41 mmol) was dissolved in a mixture of CH<sub>3</sub>CN (4.3 mL), CCl<sub>4</sub> (4.3 mL), and water (5.5 mL); NaIO<sub>4</sub> (1.052 g, 4.93 mmol) was then added, followed by RuCl<sub>3</sub>·*x*H<sub>2</sub>O (14 mg, ≈0.067 mmol). After 5 h of stirring at room temperature, the solution was diluted with diethyl ether. The layers were separated, and the aq. layer was extracted with diethyl ether. The combined organic layers were dried (MgSO<sub>4</sub>), and concentrated *in vacuo*. The residue was purified by column chromatography over silica gel and elution with hexane–diethyl ether (1 : 9) to give **13** (75 mg, 61%), *R*<sub>f</sub> 0.6, as pale yellow crystals; mp 108–110 °C; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 1.28 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.48 (9H, s, 'Bu), 2.33 (1H, d, *J* 9.3, H-2), 2.46 (1H, d, *J* 9.3, H-3), 3.36 (3H, s, OMe), 3.57 (1H, d, *J* 10.1, CHHOMe), 3.77 (1H, d, *J* 10.1, CHHOMe) and 4.20–4.27 (2H, m, OCH<sub>2</sub>CH<sub>3</sub>). The ring numbering is shown in Scheme 3. Selected NOEs were between δ 2.33 and 2.46, δ 2.33 and 3.57, δ 2.33 and 3.77, δ 2.46 and 3.57, and δ 2.46 and 3.77; δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>) 13.86 (CH<sub>2</sub>CH<sub>3</sub>), 27.92 ('Bu), 29.26 (C-3), 29.99 (C-2), 36.46 (C-1), 58.92 (OMe), 62.34 (OCH<sub>2</sub>CH<sub>3</sub>), 72.05 (CH<sub>2</sub>OMe), 83.96 (OCMe<sub>3</sub>), 168.39 (CO), 169.18 (CO) and 169.20 (CO); ν<sub>max</sub> (KBr)/cm<sup>-1</sup> 2990, 1745, 1731, 1371 and 1154; MS (FAB) *m/z* 303 (M + H)<sup>+</sup>; exact mass (M + H)<sup>+</sup>, 303.1435 (Calc. for C<sub>14</sub>H<sub>23</sub>O<sub>7</sub>, *m/z*, 303.1444).

### 1-Ethyl 2,3-dihydrogen 1-(methoxymethyl)cyclopropane-*r*-1, *c*-2, *c*-3-tricarboxylate **14**

TFA (0.37 mL) was added to **13** (32 mg, 0.11 mmol) at 0 °C and the solution was stirred for 15 min. Removal of the solvent under reduced pressure gave **14** (29 mg, 100%) as colorless crystals, mp 106–108 °C; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 1.25 (3H, t, *J* 6.7, CH<sub>2</sub>CH<sub>3</sub>), 2.55 (2H, s, H-2, -3), 3.40 (3H, s, OMe), 3.71 (2H, s, CH<sub>2</sub>OMe) and 4.24 (2H, q, *J* 6.7, OCH<sub>2</sub>CH<sub>3</sub>). Selected NOEs were between δ 2.55 and 3.71; δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>) 13.51 (CH<sub>2</sub>CH<sub>3</sub>), 29.39 (C-2, -3), 37.26 (C-1), 59.10 (OMe), 63.09 (OCH<sub>2</sub>CH<sub>3</sub>), 72.60 (CH<sub>2</sub>OMe), 168.44 (CO<sub>2</sub>Et) and 172.80 (CO<sub>2</sub>H); ν<sub>max</sub> (KBr)/cm<sup>-1</sup> 3400, 3000, 2900, 1740, 1713, 1439, 1234, 1201 and 1110; MS (FAB) *m/z* 247 (M + H)<sup>+</sup>; exact mass (M + H)<sup>+</sup>, 247.0821 (Calc. for C<sub>10</sub>H<sub>15</sub>O<sub>7</sub>, *m/z*, 247.0818) (Calc. for C<sub>10</sub>H<sub>14</sub>O<sub>7</sub>: C, 48.78; H, 5.73; O, 45.49. Found: C, 48.54; H, 5.74; O, 45.14%).

### Compound **15**

Et<sub>3</sub>N (0.125 mL, 90.4 mg, 0.83 mmol) was added to glycine *tert*-butyl ester hydrochloride (139 mg, 0.83 mmol) in THF (0.76 mL). To the solution were added HOBt (223 mg, 1.65 mmol) and **14** (108.5 mg, 0.41 mmol). The mixture was cooled to 0 °C and a solution of DCC (177 mg, 0.86 mmol) in THF (0.38 mL) was added. The reaction mixture was stirred for 1 h at 0 °C, allowed to warm to room temperature, and stirred overnight. After removal of the insoluble dicyclohexylurea (DCU), the filtrate was concentrated under reduced pressure. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and the organic phase was washed successively with saturated aq. NaHCO<sub>3</sub>, 2 M aq. citric acid, saturated aq. NaHCO<sub>3</sub>, and water (2 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel with diethyl ether–MeOH (19 : 1) as eluent to give **15** (106 mg, 54%), *R*<sub>f</sub> 0.3, as colorless crystals, mp 91–93 °C; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 1.17 (3H, t, *J* 7.1, CH<sub>2</sub>CH<sub>3</sub>), 1.45 (18H, s, 'Bu), 2.33 (2H, s, H-2, -3), 3.36 (3H, s, OMe), 3.64 (2H, s, CH<sub>2</sub>OMe), 3.88 (2H, dd, *J* 18.3 and 4.9, Gly-α), 3.95 (2H, dd, *J* 18.3 and 5.2, Gly-α), 4.13 (2H, q, *J* 7.1, OCH<sub>2</sub>CH<sub>3</sub>) and 7.67 (2H, dd, *J* 5.2 and 4.9, NH). Selected NOEs were between δ 2.33 and 3.64; δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>) 13.95 (CH<sub>2</sub>CH<sub>3</sub>), 28.09 ('Bu), 31.59 (C-2, -3), 35.14 (C-1), 42.42 (Gly-α), 59.01 (OMe), 61.65 (OCH<sub>2</sub>CH<sub>3</sub>), 73.36 (CH<sub>2</sub>OMe), 82.14 (OCMe<sub>3</sub>), 167.18 (CO), 168.55 (CO) and 168.67 (CO);

ν<sub>max</sub> (KBr)/cm<sup>-1</sup> 3280, 3000, 1750, 1735, 1628, 1549, 1369, 1228 and 1154; MS (FAB) *m/z* 495 (M + Na)<sup>+</sup>, 473 (M + H)<sup>+</sup>; exact mass (M + H)<sup>+</sup>, 473.2491 (Calc. for C<sub>22</sub>H<sub>37</sub>N<sub>2</sub>O<sub>9</sub>, *m/z*, 473.2499).

### Compound **17**

To a solution of **15** (40 mg, 0.085 mmol) in THF (1 mL) was added LiOH·H<sub>2</sub>O (3.6 mg, 0.085 mmol) at room temperature. The mixture was stirred overnight. After removal of the solvent under reduced pressure, CH<sub>2</sub>Cl<sub>2</sub> and water were added to the residue and acidified with KHSO<sub>4</sub>. The organic phase was extracted, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel and elution with diethyl ether–MeOH (9 : 1) to give **17** (27.5 mg, 76%), *R*<sub>f</sub> 0.7, as a colorless oil; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 1.45 (9H, s, 'Bu), 1.46 (9H, s, 'Bu), 2.71 (1H, d, *J* 8.5, H-3), 2.82 (1H, d, *J* 8.5, H-2), 3.38 (3H, s, OMe), 3.82 (1H, d, *J* 10.6, CHHOMe), 3.87 (2H, d, *J* 5.0, HNCH<sub>2</sub>CO), 3.97 (1H, d, *J* 10.6, CHHOMe), 3.99 (2H, s, NCH<sub>2</sub>CO) and 6.46 (1H, *J* 5.0, t, NH). Selected NOEs were between δ 2.71 and 2.82, δ 2.71 and 3.82, δ 2.71 and 3.97, δ 2.82 and 3.82, δ 2.82 and 3.97, and δ 2.71 and 6.46; δ<sub>C</sub> (100.6 MHz; CDCl<sub>3</sub>) 28.02 ('Bu), 28.05 ('Bu), 29.65 (C-3), 36.57 (C-2), 37.63 (C-1), 40.62 (NCH<sub>2</sub>CO), 42.41 (HNCH<sub>2</sub>CO), 59.17 (OMe), 67.16 (CH<sub>2</sub>OMe), 82.46 (OCMe<sub>3</sub>), 82.70 (OCMe<sub>3</sub>), 165.08 (CO), 166.05 (CO), 168.50 (CO), 170.89 (CO) and 171.81 (CO); ν<sub>max</sub> (neat)/cm<sup>-1</sup> 3320, 2982, 2940, 1742, 1725, 1715, 1684, 1541, 1419, 1373, 1232 and 1158; MS (FAB) *m/z*, 449 (M + Na)<sup>+</sup>, 427 (M + H)<sup>+</sup>.

### Acknowledgements

We are grateful to Dr K. Yamamoto (Osaka University) and Dr Shigeo Umetani (Kyoto University) for measurement of mass spectra and elemental analysis. We thank Ms Etsuko Tanigawa for experimental assistance.

### References

- (a) P. Bornstein and W. Traub, in *The Proteins*, ed. H. Neurath and R. L. Hill, Academic Press, New York, 1979, vol. 2, pp. 412–632; (b) G. N. Ramachandran, in *Aspects of Protein Structure*, ed. G. N. Ramachandran, Academic Press, New York, 1963, p. 39.
- (a) W. Traub and K. Piez, *Adv. Protein Chem.*, 1971, **25**, 243; (b) *Biochemistry of Collagen*, ed. G. N. Ramachandran and A. H. Reddi, Plenum, New York, 1976.
- (a) M. Goodman, Y. Feng, G. Melacini and J. P. Taulane, *J. Am. Chem. Soc.*, 1996, **118**, 5156; (b) G. Melacini, Y. Feng and M. Goodman, *J. Am. Chem. Soc.*, 1996, **118**, 10359.
- D. S. Kemp and K. S. Petrakis, *J. Org. Chem.*, 1981, **46**, 5140.
- J. Baum and B. Brodsky, in *Mechanisms of Protein Folding*, ed. R. H. Pain, Oxford University Press, Oxford, 2nd edn., 2000, pp. 330–351.
- (a) *The Chemistry of the Cyclopropyl Group*, ed. Z. Rappoport, Wiley, New York, 1987; (b) *The Chemistry of the Cyclopropyl Group*, ed. Z. Rappoport, Wiley, New York, 1995, vol. 2.
- (a) J. Salaün, *Chem. Rev.*, 1989, **89**, 1247; (b) A. B. Charette and J.-F. Marcoux, *Synlett*, 1995, 1197; (c) H.-U. Reissig, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 971; (d) M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911.
- (a) S. Hanessian, D. Andreotti and A. Gomtsyan, *J. Am. Chem. Soc.*, 1995, **117**, 10393; (b) M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M. Y. Kwan, S. Liras, C. J. Oalman, R. J. Pieters, M. N. Protopopova, C. E. Raab, G. H. P. Roos, Q.-L. Zhou and S. F. Martin, *J. Am. Chem. Soc.*, 1995, **117**, 5763; (c) D. Romo and A. I. Meyers, *J. Org. Chem.*, 1992, **57**, 6265; (d) A. Monpert, J. Martelli, R. Grée and R. Carrière, *Tetrahedron Lett.*, 1981, **22**, 1961; (e) V. Michelet, I. Besnier and J. P. Genêt, *Synlett*, 1996, 215.
- (a) S. Yamazaki, M. Tanaka, A. Yamaguchi and S. Yamabe, *J. Am. Chem. Soc.*, 1994, **116**, 2356; (b) S. Yamazaki, M. Tanaka, T. Inoue, N. Morimoto, H. Kumagai and K. Yamamoto, *J. Org. Chem.*, 1995, **60**, 6546; (c) S. Yamazaki, H. Kumagai, T. Takada, S. Yamabe and K. Yamamoto, *J. Org. Chem.*, 1997, **62**, 2968; (d) S. Yamazaki, T. Takada, T. Imanishi, Y. Moriguchi and S. Yamabe, *J. Org. Chem.*,

- 1998, **63**, 5919; (e) S. Yamazaki, H. Kataoka and S. Yamabe, *J. Org. Chem.*, 1999, **64**, 2367.
- 10 (a) H. J. Reich and S. K. Shah, *J. Org. Chem.*, 1977, **42**, 1773; (b) A. G. Brook and D. G. Anderson, *Can. J. Chem.*, 1968, **46**, 2115; (c) F. A. Carey and M. Mullins, *Tetrahedron Lett.*, 1975, 2017.
- 11 K. Inouye, S. Sakakibara and D. J. Prockop, *Biochim. Biophys. Acta*, 1976, **420**, 133.
- 12 (a) K. L. Williamson, C. A. Lanford and C. R. Nicholson, *J. Am. Chem. Soc.*, 1964, **86**, 762; (b) C. Gey, R. Perraud, J. L. Pierre, H. Cousse, L. Dussourd D'Hinterland and G. Mouzin, *Org. Magn. Reson.*, 1977, **10**, 75; (c) J. D. White and M. S. Jensen, *J. Am. Chem. Soc.*, 1995, **117**, 6224.
- 13 (a) P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936; (b) S. Yamazaki, T. Inoue, T. Hamada, T. Takada and K. Yamamoto, *J. Org. Chem.*, 1999, **64**, 282.
- 14 (a) P. Kocis, O. Issakova, N. Sepetov and M. Lebl, *Tetrahedron Lett.*, 1995, **36**, 6623; (b) M. Pátek, B. Drake and M. Lebl, *Tetrahedron Lett.*, 1994, **35**, 9169.