Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 2333–2338

Application of 1,1,3,3-tetramethylguanidine in the reaction of amino acids with pantolactone

Marek Włostowski, Tomasz Rowicki and Ludwik Synoradzki*

Laboratory of Technological Processes, Faculty of Chemistry, Warsaw University of Technology, ul. Noakowskiego 3, 00-664 Warszawa, Poland

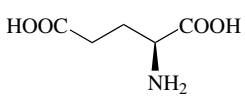
Received 25 March 2004; revised 2 June 2004; accepted 9 June 2004
Available online 23 July 2004

Abstract—1,1,3,3-Tetramethylguanidium salts of selected amino acids were reacted with (*R*)- or (*S*)-pantolactone to gave (*R*)- or (*S*)-*N*-(2,4-dihydroxy-3,3-dimethyl-1-oxobutyl)aminoacids, respectively. No racemisation of the amino acids, and only a slight racemisation of the pantolactone was observed.

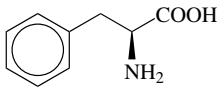
1. Introduction

1,1,3,3-Tetramethylguanidine (TMG) **1** is an efficient reagent for the deprotonation of a wide range of compounds. **1** has been used to generate carbanions from nitro[1–6] and cyano[6–10] compounds, as well as oxoanions from alcohols and phenols.[11,12] Moreover, **1** has been successfully applied in Michael,[13–17] aldol[17–19] and Wittig–Horner[20] type reactions. The use of **1** as a base in reactions with carboxylic,[21–23] hydrazoic[24,25] and hydrocyanic[26] acids has also been described. The application of **1** in converting amino acids into their salts is an easy and convenient method for the amino group activation. Surprisingly, this has been poorly explored with only a few references available.[27–31]

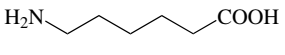
Herein we report the application of **1** in the reaction of amino acids with pantolactone **2**, the compound of our interest. Various easily available amino acids **3a–d** were chosen to show the versatility of this method.



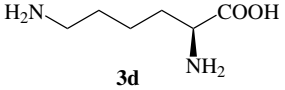
3a



3b



3c



3d

2. Results and discussion

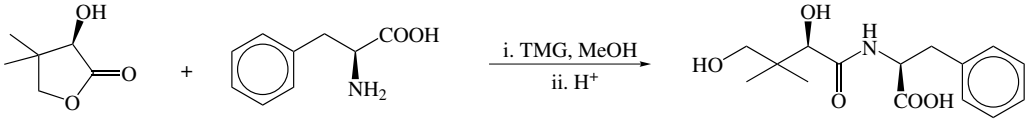
The reactions of **2** with amino acids **3a–c** and **1** were conducted without foregoing the isolation of the tetramethylguanidinium amino acids salts (Scheme 1). Thus, **1** was added to a stirred suspension of amino acid **3** in methanol at room temperature. After a few minutes the amino acid had totally dissolved thus indicating that the salt formation was completed. **2** was then added to the clear solution and the reaction maintained for a given time and conditions (Table 1). Lysine **3d**, because of its basic properties, was used without application of **1**. Such a reaction was carried out analogously to the general procedure, **3d** was suspended in methanol, **2** then added and the reaction mixture stirred for a given time and conditions (Table 1).

Selected reactions were monitored by GC [on an HP-1 column after silylation of the samples with *N*,*O*-bis-(trimethylsilyl)acetamide (BSA)] to determine the optimal reaction times and maximum conversions (Fig. 1).

As can be seen from Figure 1, the rate profiles of amino acids **3** differ significantly. In our opinion the reason for this behaviour is the different sterical hindrances of the amino groups in certain amino acids.[32]

* Corresponding author. E-mail: synsa@ch.pw.edu.pl

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.06.005



(*R*)-**2** (*S*)-**3b** (2′*R*,2S)-**4b**

Scheme 1. Reaction of (*R*)-**2** with an exemplary amino acid (*S*)-**3b**.

In the case of **3d**, where conversions stopped at about 70% (without application of **1**), while for the other amino acids over 90% conversions were achieved, we accelerated the reaction and increased the conversion by carrying out the reaction in the presence of 5% of **1** (**3d′** in Fig. 1).[32]

Comparing the results of the GC analyses for (2′*R*,2*S*)-**4b** and (2′*S*,2*S*)-**4b** syntheses, we noticed a small amount (6–7%) of the main product diastereoisomer present in the reaction mixture. Since the substrates were enantiomerically pure, this clearly showed that a racemisation process must have accompanied the reaction. Therefore, we investigated **4b** by GC analysis as well as HPLC analysis with chiral columns (beta dex 120 and ChiraDex, respectively) to establish, which stereogenic centre was racemised. Our attempts to separate the isomers on a chiral column by GC failed in this case. However, by employing a HPLC chiral column, we were able to solve the problem.[33] The analysis of the chromatograms of all four isomers of **4b** [(2′*R*,2*S*), (2′*S*,2*S*), (2′*R*,2*R*) and (2′*S*,2*R*)] enabled us to establish that only the stereogenic centre in the pantoyl moiety was racemised. Moreover, in experiments when substrates **2** and **3b**, as well as product **4b** were treated with **1**, only in the case of **2** did racemisation occur. The racemisation of **2** was much slower than the formation of product **4b** (the slowest among the studied reactions) therefore high des of all products **4** were observed.

Table 1. Synthesis of amides **4a–d**

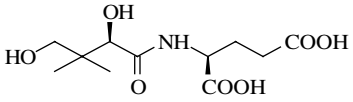
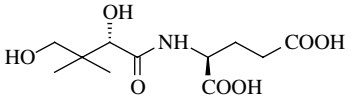
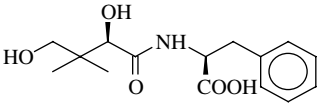
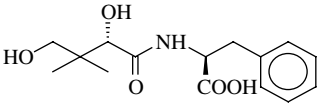
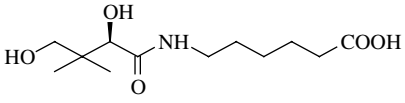
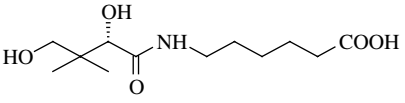
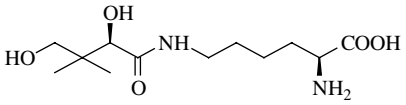
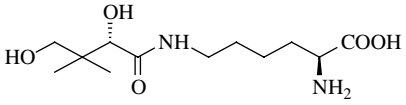
	Equiv of **1**	Reaction time (h)		Yield (%)[c]		De (%)[d]
		a	b	a	b	
 (2′*R*,2*S*)-**4a**	2	12	190	94	98 (45)	90.1
 (2′*S*,2*S*)-**4a**	2		190		97 (56)	96.7
 (2′*R*,2*S*)-**4b**	1	34	500	95	92 (59)	99.2 (99.5)[e]
 (2′*S*,2*S*)-**4b**	1		500		(76)	96.2 (96.4)[e]
 (2′*R*)-**4c**	1	4	40	99	100 (99)	96.8
 (2′*S*)-**4c**	1		40		(99)	96.5

Table 1 (*continued*)

	Equiv of **1**	Reaction time (h)		Yield (%)[c]		De (%)[d]
		a	b	a	b	
 (2′*R*,2*S*)-**4d**	0	15	135	78, 97[f]	79 (75)	99.4
 (2′*S*,2*S*)-**4d**	0		135		(76)	99.0

[a] Reaction temperature = 65 °C.
[b] Reaction temperature = 26 °C.
[c] Yield determined by GC. Isolated yield in parenthesis.
[d] De of isolated products estimated from the ee of **2** obtained after acid hydrolysis of compounds **4**.
[e] In parenthesis de of isolated product determined directly from silylated **4b** by GC with HP-1 column.
[f] Reaction carried out in the presence of 5% of **1**.

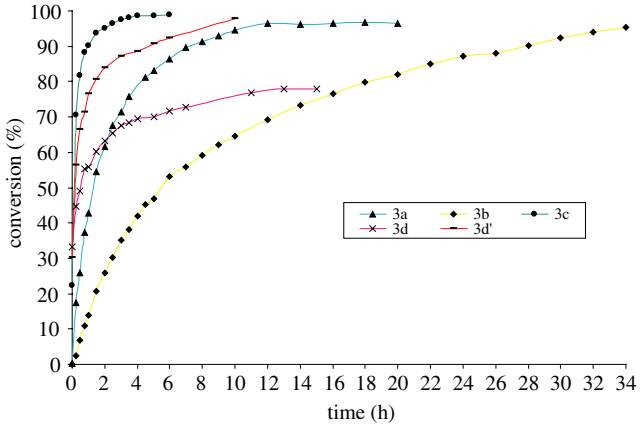


Figure 1. Conversion versus time at 65 °C.

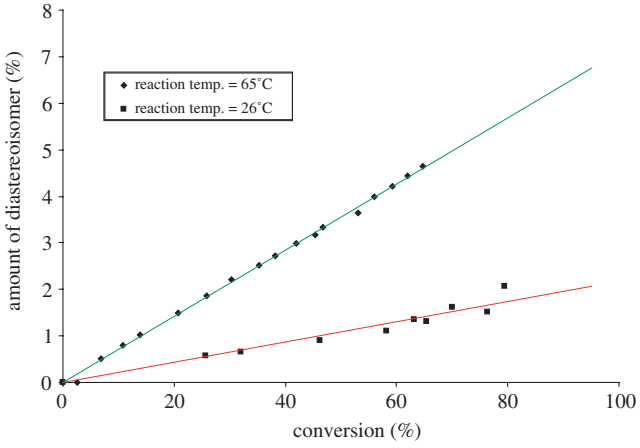


Figure 2. Amount of isomer versus conversion for **4b**.

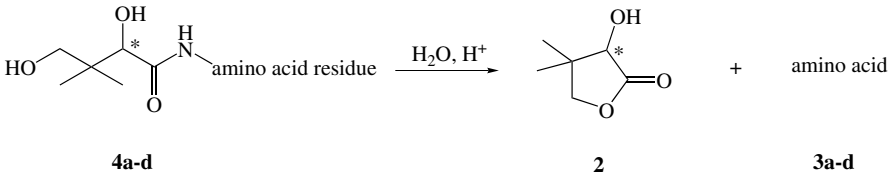
The racemisation of **2** could be minimised by carrying out the reaction at room temperature and by reducing the amount of excess **1** applied. In the case of the product **4b** synthesis, this resulted in a decrease in the amount of the isomer, from about 6% to 2% at 90% conversion (Fig. 2). However, much longer (2–20 days) reaction times were required to achieve adequately good yields.

The GC analysis on an HP-1 column, which allowed us to determine the de of **4b**, and the HPLC analysis on ChiraDex, both failed in the cases of the remaining products **4a**,**c** and **d**. Therefore, an alternative method for estimating the enantiomeric excess was elaborated. Having established that the racemisation of the stereogenic centre in **2** was exclusively responsible for decreasing the products' de, we decided to hydrolyse the purified products **4** back to the substrates (Scheme 2).

Since **2** does not undergo racemisation under acidic conditions[34] the ee of the thus obtained **2** had to be identical with the de of the respective compound **4**. Equal values of the de of product **4b** determined by GC with HP-1 column and the ee of **2** (obtained after hydrolysis of product **4b**) determined directly by GC with a chiral column (beta dex 120) confirmed our assumptions.

The opening of the pantolactone ring by the salt of the amino acid is a well known problem that has been solved on a technical scale in the production of sodium[35,36] or calcium[37,38] pantothenate, where the sodium or calcium salt of β-alanine is applied. However, the application of metallic sodium or calcium in the synthesis of β-alanine salt from β-alanine or obtaining these compounds by hydrolyses of β-alanine esters in the presence of sodium or calcium hydroxide involves many other problems.

The application of **1** in the reaction of the amino acids with **2** eliminates all the disadvantages of the methods with sodium and calcium salts. This procedure seemed to be very general and guaranteed high yields under mild conditions.



4a-d **2** **3a-d**

Scheme 2. Acid hydrolysis of amides **4**.

3. Conclusions

In summary, 1,1,3,3-tetramethylguanidine has been successfully applied in the reaction of the pantolactone ring opening, with various amino acids and new amino acids derivatives being synthesised and characterised. Since no racemisation of the amino acids' stereogenic centre occurred during the reaction, the application of **1** can be considered a general route to the amino group activation in amino acids.

4. Experimental

4.1. Methods and materials

^{1}H and ^{13}C NMR spectra were recorded using Varian Gemini 200 or Mercury 400 instrument. IR spectra were recorded on a Specord 80 Carl Zeiss Jena or Perkin–Elmer 577 spectrophotometer. Optical rotations were measured on an Optical Activity Ltd automatic polarimeter. GC–MS analyses were performed on an Agilent 6890N chromatograph equipped with an Agilent 5973N MS detector. GC analysis: Hewlett Packard 6890 Series chromatograph with FID; (a) HP-1 phase methyl siloxane, capillary column 30 m × 0.32 mm, 2 mL/min helium, temperature programme 100–300 °C, 10 °C/min; (b) Supelco2-4304 phase beta dex 120 (β-cyclodextrin), capillary column 30 m × 0.25 mm, 1 mL/min helium, temperature 140 °C. HPLC analysis: Hewlett Packard 1050 Series chromatograph with UV detector (254 nm), Merck β-ChiraDex column (β-cyclodextrin) 250 × 4 mm, mobile phase 0.02 M NaH_2PO_4 pH = 4.1/MeOH 62/38, 0.8 mL/min, 25 °C. TMG and BSA were supplied by Aldrich; (*R*)-pantolactone, L- and D-phenylalanine as well as 6-aminohexanoic acid were from Fluka; L-glutamic acid from Reanal and (*S*)-pantolactone was obtained from racemic pantolactone with a modified procedure of Delmar and Kubela.[39] Silica gel 60 (0.040–0.063 mm), L-lysine and HPLC grade methanol were from Merck. All solvents and reagents were p.a. grade.

4.2. General procedure for *N*-pantoyl aminoacids 4a–d

Typically, the condensation of the amino acid salts with pantolactone **2** was carried out in methanol under argon at 65 °C or 26 °C. TMG **1** (0–21 mmol) was added to a magnetically stirred suspension of amino acid **3a–c** (10 mmol) in 5 mL of methanol (except for the reactions involving lysine **3d**, in which TMG was not used). After 5–20 min, the mixture became homogeneous indicating the completion of the amino acid TMG salt formation; thus pantolactone **2** (11 mmol) was added. Samples were taken out, and the completion of the reaction determined by GC. The reaction mixture was then diluted with 1,2-dimethoxyethane, acidified to pH = 2–3 with 4 M HCl and dried over magnesium sulfate. After filtering off the $MgSO_4$, a small amount of silica gel was added and the solvent evaporated off to afford a solid residue of the product absorbed on silica gel. The excess of pantolactone **2** was eluted through a short layer of silica gel with dichloromethane, and product **4** with CH_2Cl_2–MeOH (7:1 v/v), respectively. Evaporation of the solvents afforded the products as either solids or viscous oils, pure enough for analysis.

4.2.1. *N*-((*R*)-2,4-Dihydroxy-3,3-dimethyl-1-oxobutyl)-L-glutamic acid (2′*R*,2*S*)-4a. ^{1}H NMR (D_2O, 200 MHz): δ 0.88 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.89–2.37 (m, 2H, CH_2), 2.45 (t, J = 6.8 Hz, 2H, CH_2), 3.36 and 3.48 (AB system J = 11.0 Hz, 2H, CH_2), 3.99 (s, 1H, CH), 4.38 (dd, J = 5.0 Hz, J = 9.2 Hz, 1H, CH). ^{13}C NMR (D_2O, 50 MHz): δ 18.4 (CH_3), 21.6 (CH_3), 25.8 (CH_2), 30.4 (CH_2), 40.8 (C), 54.1 (CH), 75.7 (CH_2), 77.1 (CH), 174.1 (C), 177.5 (C), 180.0 (C). IR (film): 1720, 1640, 1560 cm^{-1}. $[\alpha]_D^{26} = -6.9$ (*c* 1.0, H_2O). GC–MS of silylated compound $C_{23}H_{51}Si_4NO_7$): 565 (1, M^+), 421 (100), 73 (80), 247 (44), 103 (42), 157 (42), 550 (34), 117 (33), 274 (33), 422 (33), 217 (28).

4.2.2. *N*-((*S*)-2,4-Dihydroxy-3,3-dimethyl-1-oxobutyl)-L-glutamic acid (2′*S*,2*S*)-4a. ^{1}H NMR (D_2O, 200 MHz): δ 0.90 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.95–2.31 (m, 2H, CH_2), 2.50 (t, J = 7.2 Hz, 2H, CH_2), 3.39 and 3.51 (AB system J = 11.2 Hz, 2H, CH_2), 4.03 (s, 1H, CH), 4.44 (dd, J = 5.2 Hz, J = 9.0 Hz, 1H, CH). ^{13}C NMR (D_2O, 50 MHz): δ 19.5 (CH_3) 20.7 (CH_3), 25.8 (CH_2), 30.4 (CH_2), 39.1 (C), 52.0 (CH), 68.6 (CH_2); 75.9 (CH), 175.1 (C), 175.5 (C), 177.1 (C). IR (film): 1720, 1650, 1560 cm^{-1}. $[\alpha]_D^{26} = -45.7$ (*c* 1.0, H_2O).

4.2.3. *N*-((*R*)-2,4-Dihydroxy-3,3-dimethyl-1-oxobutyl)-L-phenylalanine (2′*R*,2*S*)-4b. ^{1}H NMR (D_2O, 200 MHz): δ 0.78 (s, 6H, 2·CH_3), 3.18 and 3.31 (AB protons from ABX system J_{AB} = 13.2 Hz, J_{BX} = 8.0 Hz, J_{AX} = 5.4 Hz, 2H, CH_2), 3.28 and 3.41 (AB system J = 11.4 Hz, 2H, CH_2), 3.92 (s, 1H, CH), 4.15 (dd, J = 8.0 Hz, J = 5.4 Hz, 1H, CH), 7.36 (m, 5H, 5·CH). ^{13}C NMR (D_2O, 50 MHz): δ 19.1 (CH_3), 20.5 (CH_3), 36.6 (C), 38.9 (C), 53.8 (C), 68.4 (CH_2), 75.7 (CH), 127.4 (CH), 129.0 (2·CH), 129.4 (2·CH), 136.8 (C), 175.1 (C), 175.3 (C). IR (KBr): 1732, 1636, 1544 cm^{-1}. Mp = 133–134 °C.

$[\alpha]_D^{26} = +10.4$ (c 1.0, H_2O). GC–MS of silylated compound ($C_{24}H_{45}Si_3NO_5$): 511(9, M^+), 367 (100), 73 (87), 247 (49), 103 (48), 157 (47), 368 (47), 117 (37), 496 (27), 158 (24), 147 (21).

4.2.4. *N*-((*S*)-2,4-Dihydroxy-3,3-dimethyl-1-oxobutyl)-L-phenylalanine (2′*S*,2*S*)-4b. ^{1}H NMR (D_2O, 200 MHz): δ 0.66 (s, 3H, CH_3), 0.73 (s, 3H, CH_3), 2.72–3.30 (m, 2H, CH_2), 3.22 and 3.37 (AB system $J = 11.2$ Hz, 2H, CH_2), 3.96 (s, 1H, CH), 4.10 (dd, $J = 8.6$ Hz, $J = 3.6$ Hz, 1H, CH), 7.30 (m, 5H, 5·CH). ^{13}C NMR (D_2O, 50 MHz): δ 19.3 (CH_3), 20.4 (CH_3), 36.8 (C), 38.9 (CH_2), 53.8 (CH), 68.6 (CH_2), 75.8 (CH), 127.4 (CH), 129.0 (2·CH), 129.4 (2·CH), 136.8 (C), 175.1 (C) 175.4 (C). IR (film): 1732, 1648, 1564 cm^{-1}. $[\alpha]_D^{26} = -9.0$ (c 1.0, H_2O).

4.2.5. *N*-((*R*)-2,4-Dihydroxy-3,3-dimethyl-1-oxobutyl)-6-aminohexanoic acid (2′*R*)-4c. ^{1}H NMR (D_2O, 200 MHz): δ 0.89 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.30–1.69 (m, 6H, 3·CH_2), 2.38 (t, $J = 6.8$ Hz, 2H, CH_2), 3.23 (dt, $J = 2.8$ Hz, $J = 6.8$ Hz, 2H, CH_2), 3.40 and 3.51 (AB system $J = 11.2$ Hz, 2H, CH_2), 3.97 (s, 1H, CH). ^{13}C NMR (D_2O, 50 MHz): δ 19.3 (CH_3), 20.8 (CH_3), 24.3 (CH_2), 25.9 (CH_2), 28.4 (CH_2), 34.1 (CH_2), 38.8 (C), 38.9 (CH_2), 68.7 (CH_2), 76.1 (CH), 175.1 (C), 179.6 (C). IR (film) 1720, 1644, 1540 cm^{-1}. $[\alpha]_D^{26} = +16.9$ (c 1.0, H_2O). GC–MS of silylated compound ($C_{21}H_{37}Si_3NO_5$): 467(0, M^+), 333 (100), 73 (64), 462 (46), 103 (44), 157 (41), 117 (33), 186 (31), 247 (30), 334 (26), 304 (21).

4.2.6. *N*-((*S*)-2,4-Dihydroxy-3,3-dimethyl-1-oxobutyl)-6-aminohexanoic acid (2′*S*)-4c. ^{1}H NMR (D_2O, 200 MHz): δ 0.88 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 1.28–1.67 (m, 6H, 3·CH_2), 2.37 (t, $J = 7.2$ Hz, 2H, CH_2), 3.22 (dt, $J = 2.9$ Hz, $J = 6.6$ Hz, 2H, CH_2), 3.38 and 3.50 (AB system $J = 11.3$ Hz, 2H, CH_2), 3.96 (s, 1H, CH). ^{13}C NMR (D_2O, 50 MHz): δ 19.4 (CH_3), 20.8 (CH_3), 24.2 (CH_2), 25.9 (CH_2), 28.4 (CH_2), 33.9 (CH_2), 38.9 (C), 39.0 (CH_2), 68.7 (CH_2), 76.1 (CH), 175.1 (C), 179.3 (C). IR (film) 1716, 1636, 1540 cm^{-1}. $[\alpha]_D^{26} = -16.5$ (c 1.0, H_2O).

4.2.7. N^6-((*R*)-2,4-Dihydroxy-3,3-dimethyl-1-oxobutyl)-L-lysine (2′*R*,2*S*)-4d. ^{1}H NMR (D_2O, 200 MHz): δ 0.90 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.43 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 1.88 (m, 2H, CH_2), 3.26 (t, $J = 6.8$ Hz, 2H, CH_2), 3.40 and 3.52 (AB system $J = 11.2$ Hz, 2H, CH_2), 3.73 (t, $J = 6.0$ Hz, 1H, CH), 3.99 (s, 1H, CH). ^{13}C NMR (D_2O, 50 MHz): δ 19.4 (CH_3), 20.8 (CH_3), 22.1 (CH_2), 28.5 (CH_2), 30.3 (CH_2), 38.7 (C), 38.8 (CH_2), 54.9 (CH), 68.7 (CH_2), 76.1 (CH), 174.9 (C), 175.2 (C). IR (KBr): 1636, 1524 cm^{-1}. Mp = 204–206 °C (dec). $[\alpha]_D^{26} = +24.2$ (c 1.0, H_2O). GC–MS of silylated compound ($C_{24}H_{56}Si_4N_2O_5$): 565 (14, M^+) 447 (100), 247 (73), 73 (71), 420 (62), 549 (42), 156 (41), 448 (38), 157 (32), 103 (26), 564 (25).

4.2.8. N^6-((*S*)-2,4-Dihydroxy-3,3-dimethyl-1-oxobutyl)-L-lysine (2′*S*,2*S*)-4d. ^{1}H NMR (D_2O, 400 MHz): δ 0.86 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 1.38 (m, 2H, CH_2), 1.54 (m, 2H, CH_2), 1.83 (m, 2H, CH_2), 3.21 (t, $J = 6.6$ Hz, 2H, CH_2), 3.36 and 3.48 (AB system $J = 11.2$ Hz, 2H, CH_2), 3.69 (t, $J = 6.0$ Hz, 1H, CH), 3.92 (s, 1H, CH). ^{13}C NMR (D_2O, 100 MHz): δ 19.7 (CH_3), 21.1 (CH_3), 22.4 (CH_2), 28.8 (CH_2), 30.6 (CH_2), 39.0 (C), 39.2 (CH_2), 55.2 (CH), 68.9 (CH_2), 76.4 (CH), 175.3 (C), 175.6 (C). IR (KBr): 1640, 1536 cm^{-1}. Mp = 212–214 °C (dec). $[\alpha]_D^{26} = -17.3$ (c 1.0, H_2O).

4.3. Acid hydrolysis of products 4

A sample (1–5 mmol) of purified compound **4** was placed in a 10 mL round bottomed flask. 1–3 mL of water was then added followed by 2 equiv of concd sulfuric acid. The reaction mixture was stirred overnight at room temperature and then refluxed for 1 h. After adjusting the pH to 4.5 with Na_2CO_3, water was removed in vacuo, after which the residue was taken up in diethyl ether and dried over $MgSO_4$. Solids were filtered off, the filtrate concentrated in vacuo and the enantiomeric excess of pantolactone **2** determined directly by GC on a Supelco2-4304 column.

References and notes

1. Hubbard, C. D.; Wilson, C. J.; Caldin, E. F. *J. Am. Chem. Soc.* **1976**, *98*, 1870–1875.
2. Sasaki, M.; Sugimoto, N.; Osugi, J. *Chem. Lett.* **1980**, 887–890.
3. Kresge, A. J.; Powell, M. F. *J. Am. Chem. Soc.* **1981**, *103*, 201–202.
4. Caldin, E. F.; Mateo, S.; Warrick, P. *J. Am. Chem. Soc.* **1981**, *103*, 202–204.
5. Pruszyński, P.; Jarczewski, A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1117–1120.
6. Gałęzowski, W.; Grześkowiak, J.; Jarczewski, A. *Can. J. Chem.* **1999**, *77*, 1042–1049.
7. Jarczewski, A.; Pruszyński, P.; Leffek, K. T. *Can. J. Chem.* **1983**, *61*, 2029–2032.
8. Hojatti, M.; Leffek, K. T. *Can. J. Chem.* **1984**, *62*, 2653–2656.
9. Hojatti, M.; Leffek, K. T. *Can. J. Chem.* **1986**, *64*, 2365–2367.
10. Leffek, K. T.; Pruszyński, P. *Can. J. Chem.* **1988**, *66*, 1454–1458.
11. Yang, H. B.; Taft, R. W. *J. Am. Chem. Soc.* **1971**, *93*, 1310–1311.
12. Joris, L.; Mitsky, J.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 3438–3442.
13. Nysted, L. N.; Burtner, R. R. *J. Org. Chem.* **1962**, *27*, 3175–3177.
14. Pollini, G. P.; Barco, A.; De Giuli, G. *Synthesis* **1972**, 44–45.
15. Jaworski, T.; Kołodziejek, W.; Prejzner, J.; Włostowski, M. *Pol. J. Chem.* **1981**, *55*, 1321–1328.
16. Hewson, A. T.; MacPherson, D. T. *Tetrahedron Lett.* **1983**, *24*, 647–648.
17. Kozikowski, A. P.; Xia, Y.; Reddy, E. R.; Tucmantel, W.; Hanin, J.; Tang, X. C. *J. Org. Chem.* **1991**, *56*, 4636–4645.
18. Simoni, D.; Invidiata, F. P.; Manfredini, S.; Ferroni, R.; Lampronti, I.; Robertini, M.; Pollini, G. P. *Tetrahedron Lett.* **1997**, *38*, 2749–2752.
19. Simoni, D.; Invidiata, F. P.; Manfredini, S.; Ferroni, R.; Lampronti, I.; Robertini, M.; Pollini, G. P. *Tetrahedron Lett.* **1998**, *39*, 7615–7618.

20. Simoni, D.; Rossi, M.; Rodanin, R.; Mazzali, A.; Baruchello, R.; Malaguti, C.; Roberti, M.; Invidiata, F. P. *Org. Lett.* **2000**, *2*, 3765–3768.
21. Wolfe, S.; Ducep, J.-B.; Tin, K.-C.; Lee, S.-L. *Can. J. Chem.* **1974**, *52*, 3996–3999.
22. Spry, D. O. *Tetrahedron Lett.* **1980**, *21*, 1289–1292.
23. Wolfe, S.; Shaw, C.-C. *Can. J. Chem.* **1982**, *60*, 144–153.
24. Papa, A. J. *J. Org. Chem.* **1966**, *31*, 1426–1430.
25. Sakai, K.; Anselme, J.-P. *J. Org. Chem.* **1971**, *36*, 2387–2388.
26. Dowd, D.; Wilk, B. K.; Włostowski, M. *Synth. Commun.* **1993**, *23*, 2323–2329.
27. Ali, A.; Fahrenholz, F.; Weinstein, B. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 289.
28. Kemp, D. S.; Wang, S.-W.; Rebek, J., Jr.; Mollan, R. C.; Banquer, C.; Subramanyam, G. *Tetrahedron* **1974**, *30*, 3955–3967.
29. Kemp, D. S.; Wrobel, S. J., Jr.; Wang, S.-W.; Bernstein, Z.; Rebek, J., Jr. *Tetrahedron* **1974**, *30*, 3969–3980.
30. Kemp, D. S.; Young, E. C. *Tetrahedron Lett.* **1994**, *35*, 8315–8318.
31. Luo, J.; Smith, M. D.; Lantrip, D. A.; Wang, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1997**, *119*, 10004–10013.
32. The influence of the amino group's steric hindrance and specific catalysis of $TMGH^+$ in a similar process have been noticed for the reaction of various amino acids with 4,4-dimethyl-dihydro-furan-2,3-dione: Włostowski, M.; Rowicki, T.; Grzęda, Ł.; Synoradzki, L. In preparation.
33. Methods of GC and HPLC analysis will be the subject of a separate publication.
34. Effenberger, F.; Eichorn, J.; Roos, J. *Tetahedron: Asymmetry* **1995**, *6*, 271–282.
35. Williams, R. J.; Mitchell, H. K.; Weinstock, H. H., Jr.; Snell, E. E. *J. Am. Chem. Soc.* **1940**, *62*, 1784–1785.
36. Darke, H. C.; Lawson, E. J. *J. Am. Chem. Soc.* **1941**, *63*, 2869–2871.
37. Ford, J. H. *J. Am. Chem. Soc.* **1946**, *68*, 1666–1668.
38. Kagan, F.; Heinzelman, R. V.; Weisblat, D. I.; Greiner, W. *J. Am. Chem. Soc.* **1957**, *79*, 3545–3549.
39. Delmar, G.; Kubela, R. Patent GB 1,183,387, C.A. 1970, 72:132087e.