Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 3491–3496

TETRAHEDRON: *ASYMMETRY*

Phenyltrisalanine: a new, C_3-symmetric, trifunctional amino acid

Andreas Ritzén, Basudeb Basu, Andreas Wållberg and Torbjörn Frejd *

Organic Chemistry 1, Department of Chemistry, Lund University, PO Box 124, SE-221 00 Lund, Sweden

Received 26 August 1998; accepted 15 September 1998

Abstract

Two derivatives of phenyltrisalanine, a new, trifunctional amino acid, were synthesised in optically active forms. Two complementary techniques were employed, an HWE olefination reaction or a Heck coupling reaction, and the resulting dehydroamino acids were hydrogenated using a chiral Rh(I)–Et-DuPHOS catalyst. Phenyltrisalanine derivatives of excellent stereoisomeric purities were thus obtained. © 1998 Elsevier Science Ltd. All rights reserved.

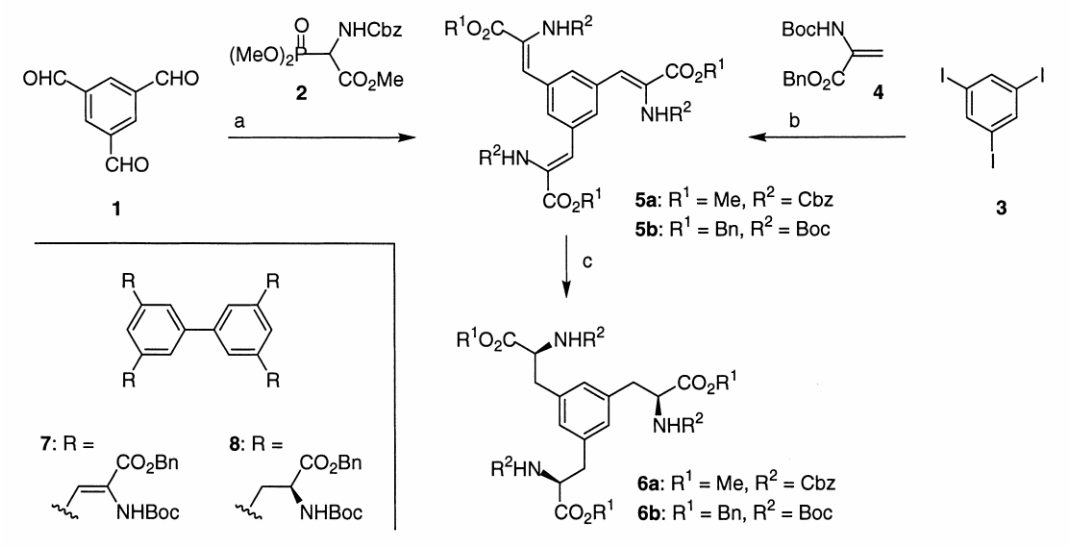
1. Introduction

The synthesis of novel amino acids, naturally and non-naturally occurring, has been the goal of much research in organic chemistry. The interest in such compounds is motivated by the possibility of incorporating them into biologically active peptides to modulate the biochemical properties of such peptides. Moreover, amino acids have in recent years also played an important part as building blocks in various elaborate molecular architectures,[1,2] and as ligands in catalytically active metal complexes for use in asymmetric catalysis.[3]

We have previously synthesised various derivatives of ferrocenylene-bis-alanine,[4] pyridine-2,6-diyl bis-alanine,[5] and phenylene-bis-alanine[6] in optically active forms and with orthogonal protecting groups. These compounds were synthesised by catalytic asymmetric hydrogenation of the corresponding unsaturated derivatives, which were synthesised either by Heck coupling[7,8] or Horner–Wadsworth–Emmons (HWE) olefination.[9] In the present work we have used this methodology to synthesise the hitherto unknown, C_3-symmetric amino acid (**6**), Scheme 1, for which we propose the name phenyltrisalanine, Pta.

* Corresponding author. E-mail: torbjorn.frejd@orgk1.lu.se

PII: S0957-4166(98)00377-2



Scheme 1. (a) *N*,*N*,*N*′,*N*′-Tetramethylguanidine, THF, rt, 4 h, 54%; (b) $NaHCO_3$, Bu_4NCl, $Pd(OAc)_2$, DMF, 80°C, 24 h, 44%; (c) {Rh(COD)[(*S*,*S*)-Et-DuPHOS]}$^+OTf^-$, 40 psi H_2, rt, 6 h, 74–99%

2. Results and discussion

Both the HWE path and the Heck path were used in the synthesis of Pta **6** (Scheme 1). These two paths are complementary with respect to which protecting groups can be introduced. Phosphonate **2** is readily available in three steps from glyoxylic acid, but the reaction conditions limit the choice of protecting groups.[10] If other protecting groups are desired, these must be introduced by deprotection–reprotection of **2**. Acrylate **4**, however, is readily available in three steps from serine with a number of different protecting groups.[7] In our experience, however, the Cbz protecting group interferes with the Heck reaction. The HWE path would thus be the route of choice for Cbz protected derivatives. Also, the HWE condensation typically proceeds with slightly higher yields than the Heck coupling.

The synthesis of Pta **6a** by the HWE path starts with a condensation between 1,3,5-triformylbenzene **1**[11] and **2**. Recrystallisation of the thus obtained derivative **5a** after chromatography substantially increased the purity. The all-*Z* configuration of **5a** was assigned by NOE difference spectroscopy as follows. Irradiation of the core aromatic proton yielded a 19% enhancement of the olefinic CH proton and a 5.6% enhancement of the NH proton. In contrast, irradiation of the CH proton gave no enhancement of the NH proton, but a 15% enhancement of the core CH proton. Finally, irradiation of the NH proton gave no enhancement of the CH proton, but a 5.6% enhancement of the core proton.

Hydrogenation of **5a** using a Rh(I)–(*S*,*S*)-Et-DuPHOS catalyst[12] gave Pta **6a** in 99% isolated yield. For stereochemical analysis, a sample of **5a** was hydrogenated using an achiral Rh(I)–dppe catalyst, which produced **6a** as a ca. 1:3:3:1 mixture of stereoisomers as analysed by chiral stationary phase HPLC and NMR spectroscopy. This is the statistically expected outcome if one assumes that the hydrogenation of each arm is independent of the others, and that the minor diastereomer has the *SSS*/*RRR* configuration, while the major diastereomer has the *SSR*/*SRR* configuration. Note that since **6a** is C_3-symmetric, only four distinct stereoisomers exist, although the molecule has three stereogenic centres.

The diastereomeric ratio of **6a** could be determined with high accuracy by ^1H NMR spectroscopy and a *dr*=99.4:0.6 was found. To evaluate the enantiomeric excess, HPLC using a covalent DNBPG column was used. All four stereoisomers were resolved on this column, but baseline separation between enantiomers

was only obtained for the *SSS*/*RRR* diastereomer. Only one peak was observed for nonracemically hydrogenated **6a**, thus establishing *ee*>98% assuming a 1% detection limit in the HPLC system. For statistical reasons, the *ee* is most likely much higher than the *dr*, since the production of the 'wrong' configuration at all three centres is extremely unlikely, given the high per-centre selectivity of the catalyst. Finally, the absolute configuration is assigned as *SSS* based on the selectivity of the (*S*,*S*)-Et-DuPHOS ligand.[12]

Synthesis of Pta **6b** by the Heck route starts with the Pd-catalysed coupling between 1,3,5-triiodobenzene[13] and acrylate **4**.[7] Attempts to use the commercially available 1,3,5-tribromobenzene were unsuccessful because of the lower reactivity of aryl bromides compared to aryl iodides. Purification of the product **5b** proved difficult. After standard chromatography and recrystallisation, **5b** retained a minor amount of an impurity. Since this impurity could not readily be removed, the mixture was hydrogenated using the Rh(I)–(*S*,*S*)-Et-DuPHOS catalyst to produce **6b** and a minor amount of another compound, which could now be separated by chromatography. Based on NMR spectroscopy and HRMS analysis, we assign structure **8** to this compound, and from this, structure **7** is assigned to the impurity in the preparation of **5b**.

NOE analysis of **5b** was used in the same way as for **5a** to assign the all-*Z* configuration to **5b**. Stereochemical analysis of **6b** was performed as for **6a**, and we found *dr*=98.3:1.7 and *ee*>98%. Although the *dr* is still excellent, it is significantly lower than that of **6a**. The reason for this is not clear, but it seems likely that the protecting groups have a slight influence on the selectivity.

3. Conclusion

Two derivatives of phenyltrisalanine, Pta, a hitherto unknown, trifunctional amino acid, were synthesised using two different, complementary routes. Based on the present work, it should be possible to synthesise various derivatives of Pta, and if both routes are combined, non-C_3-symmetric, orthogonally protected derivatives should be accessible. Applications of Pta in areas such as ligand design, molecular recognition and design of novel molecular architectures are currently being explored in our laboratory.

4. Experimental

NMR spectra were recorded on a Bruker DRX 400 NMR spectrometer in $CDCl_3$. To reduce line broadening resulting from slow rotation around carbamate C–N bonds, spectra were collected at 40–55°C. For ^{1}H experiments, residual $CHCl_3$ at δ 7.27 was used as an internal standard, while the central peak of the $CDCl_3$ triplet at δ 77.23 was used for ^{13}C experiments. Optical rotations were measured on a Perkin–Elmer 241 polarimeter, and melting points were taken with a melting point microscope and are uncorrected. Precoated Merck silica gel 60 F_{254} plates were used for TLC analysis, and retention values (TLC R_f) are given in the same solvent as used in the respective column chromatography unless otherwise stated. Stereochemical HPLC analyses were performed using a covalent DNBPG column (J. T. Baker Inc., 250×4.6 mm; DNBPG=2,4-dinitrobenzoylphenylglycine) or a (*R*,*R*)-Whelk-O1 column (Merck, 250×4.6 mm). Two detectors in tandem were routinely used; one LKB 2142 refractive index detector and one Pye Unicam ultraviolet detector at 254 nm. Compounds **1**,[11] **2**,[10] **3**[13] and **4**[7] were synthesised according to literature procedures, and so was {Rh(COD)[(*S*,*S*)-Et-DuPHOS]}$^+$OTf$^-$.[12] The (*S*,*S*)-Et-DuPHOS ligand is available from Strem Chemicals.

4.1. (Z,Z,Z)-1,3,5-Tri{1-[(benzyloxycarbonyl)amino]-1-(methoxycarbonyl)ethenyl}benzene **5a**

A suspension of 1,3,5-triformylbenzene **1**[11] (0.49 g, 3.0 mmol) in dry THF (15 ml) was added to a stirred solution of **2**[10] (3.28 g, 9.9 mmol) and *N*,*N*,*N*′,*N*′-tetramethylguanidine[9] (1.24 ml, 9.9 mmol) in dry THF (30 ml) at 0°C under N_2. After 4 h at rt the solvent was removed by evaporation and the residue was dissolved in CH_2Cl_2 (50 ml). The solution was washed with half-saturated brine (50 ml) and saturated brine (50 ml) and was then dried over Na_2SO_4. The solution was directly loaded onto a flash chromatography column which was eluted with CH_2Cl_2:MeOH (30:1) to afford crude **5a** (R_f=0.32). If the solvent was removed prior to flash chromatography, it proved impossible to redissolve the crude product in CH_2Cl_2. The chromatographed material was further purified by recrystallisation from EtOAc to yield pure **5a** as a white, amorphous solid (1.26 g, 54%), mp 199–202°C. ^{1}H NMR δ 3.84 (s, 9H), 5.08 (s, 6H), 6.23 (br s, 3H), 7.20 (s, 3H), 7.25–7.32 (m, 15H), 7.58 (s, 3H); ^{13}C NMR δ 52.94, 67.87, 125.75, 128.53, 128.57, 128.78, 130.25, 131.25, 134.85, 136.12, 153.92, 165.55. Calcd for $C_{42}H_{39}N_3O_{12}$: C 64.86, H 5.05, N 5.40, O 24.68. Found C 64.2, H 4.8, N 5.3. HRMS (FAB+) *m*/*z* calcd for $C_{42}H_{39}N_3O_{12}$: 778.2612 [M+H]. Found: 778.2630.

4.2. (Z,Z,Z)-1,3,5-Tri{1-(benzyloxycarbonyl)-1-[(tert-butyloxycarbonyl)amino]ethenyl}benzene **5b**

1,3,5-Triiodobenzene **3**[13] (0.46 g, 1.0 mmol), acrylate **4**[7] (1.0 g, 3.6 mmol), $NaHCO_3$ (0.63 g, 7.5 mmol), Bu_4NCl (0.83 g, 3.0 mmol), and $Pd(OAc)_2$ (22 mg, 0.10 mmol) were mixed in DMF (5 ml) in a screwcap vial. A few crystals of hydroquinone were added to prevent polymerisation of **4**, and the mixture was freed from O_2 by N_2 bubbling for 5 min. The vial was sealed and heated at +80°C for 24 h. The dark reaction mixture was allowed to cool, and was diluted with EtOAc (50 ml). The resulting mixture was washed with water (2×50 ml) and brine (2×50 ml) and was then dried over Na_2SO_4. Evaporation of the solvent followed by flash chromatography using heptane:EtOAc (2:1) as eluent gave crude **5b** as a yellow semisolid (0.75 g), R_f=0.21. Recrystallisation twice from EtOAc:heptane yielded a pale yellow solid (0.40 g, 44%), mp 123–131°C, which contained ca. 20% (by ^{1}H NMR) of an impurity of the same R_f, probably **7** (see text). This material was used in the hydrogenation leading to **6b**. ^{1}H NMR δ 1.35 (s, 27H), 5.29 (s, 6H), 6.26 (br s, 3H), 7.23 (s, 3H), 7.35–7.42 (m, 15H), 7.61 (s, 3H); ^{13}C NMR δ 28.24, 67.83, 81.41, 125.53, 128.50, 128.63, 128.66, 128.72, 128.82, 131.32, 134.77, 135.57, 152.59, 165.38 (one peak at δ 128 originates from **7**; it is not known which one). HRMS (FAB+) *m*/*z* calcd for $C_{51}H_{57}N_3O_{12}$: 926.3840 [M+Na]. Found: 926.3848.

4.3. (S,S,S)-1,3,5-Tri{1-[(benzyloxycarbonyl)amino]-1-(methoxycarbonyl)ethyl}benzene **6a**

Compound **5a** (100 mg, 128 μmol) and {Rh(COD)[(*S*,*S*)-Et-DuPHOS]}$^+$OTf$^-$ (3 mg)[12] were suspended in a 1:1 mixture of MeOH and EtOAc (20 ml) rigorously deoxygenated by N_2 bubbling and sonication for 15 min. This mixture was hydrogenated at 40 psi for 6 h at rt. After this time a clear solution was obtained. The solvents were evaporated, and the residue was dissolved in EtOAc and filtered through a short plug of silica to remove the catalyst. An equal volume of heptane was added to facilitate crystallisation, and the solvents were removed by evaporation to yield pure **6a** as a white, amorphous solid (100 mg, 99%), mp 100–103°C, $[\alpha]_D^{22}$ +62 (*c* 1.0; $CHCl_3$). The reaction could be performed on a 1.0 g scale using 10 mg of catalyst and no less than 150 ml of solvent with the same outcome as above. The very low solubility of **5a** and the low solubility of **6a** necessitate the use of rather large solvent volumes, and the addition of EtOAc as a co-solvent. ^{1}H NMR δ 2.94–3.05 (m, 6H), 3.67 (s, 9H), 4.59 (br q, 3H, *J*=6 Hz), 5.07 (d, 3H, *J*=12 Hz), 5.11 (d, 3H, *J*=12 Hz), 5.20 (br s, 3H), 6.75 (s, 3H), 7.27–7.35 (m,

15H); ^{13}C NMR δ 38.45, 52.49, 55.13, 67.21, 128.36, 128.37, 128.74, 129.42, 136.64, 136.77, 155.85, 171.96. Calcd for $C_{42}H_{45}N_3O_{12}$: C 64.36; H 5.79; N 5.36; O 24.49. Found C 64.9, H 5.7, N 5.2. HRMS (FAB+) *m*/*z* calcd for $C_{42}H_{45}N_3O_{12}$: 784.3082 [M+H]. Found: 784.3063.

A sample of **5a** was racemically hydrogenated using $[Rh(COD)(dppe)]^+BF_4^-$ as catalyst to produce **6a** as a mixture of stereoisomers. The ^{1}H NMR spectrum of this material was similar to that of optically active **6a**, but the diastereomers differed in the region of the aromatic core protons. Since the C_3-symmetry is broken in the *SSR*/*SRR* diastereomer, the three core protons appear as two signals with a 2:1 area, while in the C_3-symmetric *SSS*/*RRR* diastereomer, these three protons appear as a singlet. The chemical shifts were for the *SSS*/*RRR* diastereomer: δ 6.75 (s, 3H), and for the *SSR*/*SRR* diastereomer: δ 6.74 (s, 1H), 6.78 (s, 2H). The peaks at δ 6.75 and 6.78 were almost baseline separated, and this allowed a very accurate determination of the diastereomeric excess of optically active **6a**: *dr*=99.4:0.6. For the racemically hydrogenated **6a**, the *dr* was found to be 1:3 *SSS*/*RRR*:*SSR*/*SRR*.

HPLC analysis (DNBPG, n-hexane:2-propanol=90:10, 1.0 ml/min) of racemically hydrogenated **6a** produced a chromatogram with four peaks with retention times min (area) 34.7 (1), 35.8 (3), 37.6 (3) and 39.7 (1). The peaks were fairly well resolved, but not baseline separated. Since the catalyst is racemic, peaks of equal area must correspond to enantiomeric pairs. Thus, the first and last peaks correspond to one diastereomer, and the second and third peaks correspond to the other. For statistical reasons, the minor diastereomer should be *SSS*/*RRR*. Co-injection with optically active **6a** enhanced the first eluted peak. This was assigned the *SSS* configuration, based on the *S* preference of the (*S*,*S*)-Et-DuPHOS ligand.[12] Only one peak was seen when optically active **6a** was analysed. Assuming a detection limit of 1%, this means that **6a** was formed with *ee*>98%.

*4.4. (*S,S,S*)-1,3,5-Tri{1-(benzyloxycarbonyl)-1-[(*tert*-butyloxycarbonyl)amino]ethyl}benzene **6b***

Compound **5b** (100 mg, 111 μmol) and {Rh(COD)[(*S*,*S*)-Et-DuPHOS]}$^+$OTf$^-$ (3 mg) were dissolved in MeOH rigorously deoxygenated by N_2 bubbling and sonication for 15 min. This mixture was hydrogenated at 40 psi for 6 h at rt. The solvent was evaporated, and the residue was dissolved in EtOAc and filtered through a short plug of silica to remove the catalyst. TLC analysis (heptane:EtOAc=2:1) revealed that this material was a mixture of two compounds, **6b** (R_f=0.31) and a compound tentatively assigned structure **8** (R_f=0.23). After flash chromatography (heptane:EtOAc=5:2) **6b** (74 mg, 74%) and **8** (15 mg) were obtained as pure compounds.

For compound **6b**: mp=42–44°C, $[\alpha]_{365}^{22}$ +10 (*c* 1.0; $CHCl_3$) (optical rotation at longer wavelengths is close to zero), ^{1}H NMR δ 1.41 (s, 27H), 2.89–3.00 (m, 6H), 4.52 (br s, 3H), 4.93 (br s, 3H), 5.12 (d, 3H, *J*=12 Hz), 5.18 (d, 3H, *J*=12 Hz), 6.66 (s, 3H), 7.30–7.35 (m, 15H); ^{13}C NMR δ 28.52, 38.23, 54.87, 67.22, 80.20, 128.63, 128.80, 129.37, 135.71, 136.76, 155.21, 171.71. HRMS (FAB+) *m*/*z* calcd for $C_{51}H_{63}N_3O_{12}$: 932.4309 [M+Na]. Found: 932.4291.

For compound **8**: mp=57–60°C, ^{1}H NMR δ 1.38 (s, 36H), 2.97–3.13 (m, 8H), 4.59 (br s, 4H), 4.97 (br s, 4H), 5.11–5.18 (ABq, 8H), 6.83 (br t, 2 H *J*≈1 Hz), 7.13 (br d, 4H, *J*≈1 Hz), 7.25–7.32 (m, 20H); ^{13}C NMR δ 28.54, 38.61, 54.94, 67.31, 80.26, 127.21, 128.50, 128.61, 128.81, 129.62, 135.67, 137.18, 141.51, 155.24, 171.85. HRMS (FAB+) *m*/*z* calcd for $C_{72}H_{86}N_4O_{16}$: 1285.5937 [M+Na]. Found: 1285.5952.

Stereochemical analysis of **6b** was carried out as for **6a** above. The chemical shifts of the aromatic core protons were for the *SSS*/*RRR* diastereomer: δ 6.66 (s, 3H), and for the *SSR*/*SRR* diastereomer: δ 6.66 (s, 1H, completely overlapped with the signal from the *SSS*/*RRR* diastereomer), 6.69 (br d, 2H, *J*=1.3 Hz). The *dr* for **6b** was found to be 98.3:1.7. HPLC analysis [(*R*,*R*)-Whelk-01, n-hexane:2-propanol 80:20+0.25% HOAc, 1.0 ml/min] of a racemically hydrogenated sample gave only three peaks with

retention times min (area) 12.5 (1), 14.1 (3) and 14.9 (4). The first peak was baseline separated from the other two, and corresponds to the *SSS* isomer by comparison with optically active **6b**. HPLC analysis of optically active **6b** gave two peaks with the following retention times, respectively: min (area) 12.4 (98.3) and 14.6 (1.7) (refractive index detection). This corresponds exactly to the result of the NMR analysis, although the presence of a small amount (<1%) of the *RRR* isomer cannot be ruled out based on this analysis. However, for statistical reasons, only a minute amount is expected. The *ee* is thus >98%.

Acknowledgements

We wish to thank the Knut and Alice Wallenberg Foundation, The Crafoord Foundation, the Royal Physiographical Society, and the Swedish Natural Research Council for financial support and a post doc scholarship to B.B.

References

1. Hartgerink, J. D.; Clark, T. D.; Ghadiri, M. R. *Chem. Eur. J.* **1998**, *4*, 1367.
2. Trojandt, G.; Herr, U.; Polborn, K.; Steglich, W. *Chem. Eur. J*. **1997**, *3*, 1254.
3. Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1635.
4. Basu, B.; Chattopadhyay, S. K.; Ritzén, A.; Frejd, T. *Tetrahedron: Asymmetry* **1997**, *8*, 1841.
5. Basu, B.; Frejd, T. *Acta Chem. Scand.* **1996**, *50*, 316.
6. Ritzén, A.; Basu, B.; Chattopadhyay, S. K.; Dossa, F.; Frejd, T. *Tetrahedron: Asymmetry* **1998**, *9*, 503.
7. Carlström, A.-S.; Frejd, T. *Synthesis* **1989**, 414.
8. Carlström, A.-S.; Frejd, T. *Acta Chem. Scand*. **1992**, *46*, 163.
9. Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487.
10. Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53.
11. Fourmigué, M.; Johannsen, I.; Boubekeur, K.; Nelson, C.; Batail, P. *J. Am. Chem. Soc*. **1993**, *115*, 3752.
12. Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc*. **1993**, *115*, 10125.
13. Schöberl, U.; Magnera, T. F.; Harrison, R. M.; Fleischer, F.; Pflug, J. L.; Schwab, P. F. H.; Meng, X.; Lipiak, D.; Noll, B. C.; Allured, V. S.; Rudalevige, T.; Lee, S.; Michl, J. *J. Am. Chem. Soc*. **1997**, *119*, 3907.