Stereospecific synthesis of chiral *N*-(ethynyl)allylglycines and their use in highly stereoselective intramolecular Pauson–Khand reactions

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The first synthesis of an enantiopure *N*-ethynylated allylglycine and its application in the intramolecular Pauson– Khand reaction, which leads to a novel highly functionalised proline derivative with complete control of stereoselectivity, is reported.

N-Functionalised 1-alkynylamides of type **A** are a new class of electronically tuneable acetylenes whose protecting group (PG)



serves both in masking a secondary amine and in tuning the electron density, and hence the reactivity, of the adjacent acetylene moiety.¹ These new building blocks for organic synthesis were designed with the goal of combining the richness and diversity of the chemical reactivity of a carbon–carbon triple bond with one of the most substantial functional groups in chemistry and biology: the amino function.

Recently we described the synthesis of these novel acetylenes based on a two step sequence-ethynylation of secondary amides with trimethylsilylethynyl(phenyl)iodonium triflate² followed by desilylation with TBAF-and the use of the thus derived N-ethynylamides, whose reactivity differs significantly from those of regular ynamines,3 in both the Pauson-Khand reaction¹ and in Rh^I-catalysed cyclotrimerisations.⁴ Given our interest in N-functionalised 1-alkynylamides as versatile building blocks for nitrogen-containing heterocycles, we considered the *N*-ethynylamides **B** derived from α -amino acids as even more attractive targets, because their application in transition metal mediated cycloadditions should allow the asymmetric formation of conformationally constrained amino acids5 and the synthesis of novel proline derivatives that are closely related to the highly potent ACE (angiotensine converting enzyme) inhibitor Ramipril.⁶ Furthermore their use as alkynylogous amino acids in peptide chemistry seems to be an interesting endeavour.7

However, although the previously described route to *N*-functionalised 1-alkynylamides allowed some degree of functional diversity,^{1, 3} α -branched 1-alkynylamides could only be obtained in low yields with trimethylsilylethynyl(phenyl)iodonium triflate **3a**. Furthermore all attempts to *N*-alkynylate the α amino acid derivatives **2a–f** with **3a** (R² = SiMe₃) failed. We assumed that the observed lack of reactivity was caused by increased steric hindrance inherent in α -branched amino acid derivatives interfering with the nucleophilic addition of the amide nitrogen to the β -carbon of the alkyne **3a** (R² = SiMe₃). The ethynyl(phenyl)iodonium triflate⁸ **3b** (R² = H) was therefore thought to be more suitable for the intended *N*ethynylation. Moreover its use would shorten the previously applied sequence effectively by avoiding the desilylation step and directly affording the terminal *N*-functionalised 1-alkynylamide.

With the idea of exploring the scope of the ethynylation sequence based on **3b** and developing a flexible protecting group strategy,⁹ the amides **2a–f** were synthesised starting from allylglycine **1** (Scheme 1, Table 1).[†] Deprotonation of **2a–f** with either KHMDS in toluene or Cs₂CO₃ in DMF, followed by the addition of **3b** (1.3 equiv.) in CH₂Cl₂ at room temperature, yielded the *N*-ethynylamides **5a–d** in 70–95%.[‡] A plausible mechanism for the alkyne formation embodies the *in situ* generation of the alkenylidene carbenes **4**, which immediately rearrange *via* an 1,2-H migration towards the *N*-ethynylamides **5a–d**. The observation that no 1,5-C–H insertion product was formed indicated that the migration aptitude of the hydrogen towards the carbenoid centre in **4** must have been, as anticipated,¹⁰ significantly greater than an alternative intramolecular 1,5-C–H carbene insertion.¹¹ However, following



Scheme 1 Reagents and conditions: i, SOCl₂, MeOH, -10 °C, 24 h; ii, R¹Cl (for 2a–c and 2f) or R¹₂O (for 2d,e), Et₃N, CH₂Cl₂, 0 °C, 6–12 h, for yield of isolated 2a–f (2 steps) see Table 1; iii, Cs₂CO₃ (1.3 equiv.), 3b (1.3 equiv.), DMF–CH₂Cl₂, room temp., 3 h, for yield of isolated 5a–f see Table 1; iv, Co₂(CO)₈ (1.1 equiv.), THF, 30 min. 0–20 °C, then NMO or Me₃NO (6 equiv.), room temp., 25 min, for yield of isolated 6a–d see Table 1.

Table 1 Yield of isolated 2a-f, 5a-f, and 6a-d⁺

Entry	\mathbb{R}^1	2	Yield (%)	5	Yield (%)	6	Yield (%) [de (%)]
1	Ts	2a	88	5a	70	6a	69 [>96]
2	2-pyridyl-SO ₂	2b	71	5b	78	6b	69 [>95]
3	$4-NO_2C_6H_4SO_2$	2c	89	5c	95	6c	35 [>97]
4	Tf	2d	83	5d	94	6d	60 [>95]
5	Boc	2e	80	5e	0	_	
6	Ac	2f	94	5f	0	—	_

this protocol the allylglycines $2e (R^1 = Boc)$ and $2f (R^1 = Ac)$ could not be ethynylated with $3b (R^2 = H)$ and were recovered unchanged. Obviously the increase of basicity¹² and likewise the change of nucleophilicity of the potassium salts of 2e and 2f prevented their addition to 3b and instead caused its decomposition presumably initiated by deprotonation.

Gratifyingly, the application of enantiomerically pure (*S*)-**2a** [ee >98%, $[\alpha]_D$ +13 (*c* 1.0, CHCl₃]¹³ in the outlined protocol afforded enantiomerically pure *N*-(ethynyl)allylglycine methyl ester (*S*)-**5a**, testifying that *N*-ethynylation proceeded without racemisation. HPLC analysis of the crude product with a chiral stationary phase (Chiralpak AD column) stated that (*S*)-**5a** [ee >98%, $[\alpha]_D$ -60 (*c* 2.0, CHCl₃] was obtained essentially enantiomerically pure.¹⁴

Having established a short and efficient route to chiral and enantiopure N-ethynylated allylglycines, we tested their applicability as building blocks for the synthesis of functionalised proline derivatives via the intramolecular Pauson-Khand reaction.¹⁵ Although [2+2+1] cycloadditions of **6a-d** could be affected at 80 °C in toluene in the presence of a stoichiometric amount of Co₂(CO)₈, the mild amine N-oxide promoted protocol developed by Schreiber was most effective with respect to yield and diastereoselectivity.¹⁶ Treatment of 5a-d with $Co_2(CO)_8$ at room temperature for 25 min and subsequent addition of either NMO or Me₃NO in CH₂Cl₂ at room temperature provided the proline derivatives 6a-d in yields of 69, 69, 35 and 60%, respectively. The lower yield achieved with the sulfonamide **5c** was caused by a concurrent reduction of the 4-nitrophenylsulfonyl moiety to the corresponding aniline and led to a mixture of products. Pauson-Khand reactions with 5a-d proceeded with high diastereoselectivity giving almost exclusively one single diastereomer (de >95%, determined by ¹H-NMR, diastereomeric pure **6a-d** were obtained by crystallisation).§ The structural assignment of compound 6a was based on a combination of H, H and C, H COSY experiments and the analysis of distinct NOE relationships. The use of enantiopure (S)-5a afforded the optically active (2S,4R)-6a $[[\alpha]_D + 145$ (c 2.0, CHCl₃)] in 69% yield.

Preliminary attempts to further elaborate the obtained highly functionalised proline derivatives were successful (Scheme 2). Pauson–Khand product **6a** was stereoselectively hydrogenated on Pd-C/(H₂) to the cyclopentanone **7** in 90% yield. Luche reduction of **6a** proceeded with distinctive stereoselectivity giving exclusively the allylic alcohol **8** in 80% yield. Compound **8** was obtained as colorless crystals (mp 139–140 °C, CH₂Cl₂–pentane) after column chromatography on silica gel with CH₂Cl₂ containing 0.5% Et₃N. However, the allylic alcohol **8** being extremely sensitive to traces of acid, rearranged under H⁺ catalysis with ring cleavage to the cyclopentenones **9** (2:1 mixture of two diastereoisomers).



Scheme 2 Reagents and conditions: i, H_2 (1 atm.), (10%) Pd/C, EtOH–AcOH (1:1), room temp., 24 h; ii, NaBH₄ (2 equiv.), CeCl₃· 7 H₂O (1 equiv.), MeOH–CH₂Cl₂, 20 °C, 0.5 h; iii, cat. H⁺, CHCl₃, room temp.

In conclusion, we have established a short and efficient synthesis of a first set of *N*-ethynylated amino acid derivatives and proved, for the example **2a/5a**, that *N*-ethynylation with the alkynyliodonium salt **3b** proceeded without detectable racemisation. Their use in the intramolecular Pauson–Khand reaction

allowed the stereoselective formation of novel proline derivatives. Additional applications of *N*-alkynylated amino acids for the synthesis of conformationally constrained amino acids *via* cycloaddition strategies are part of our ongoing research.

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Footnote and references

[†] All new compounds exhibited satisfactory spectra (¹H, ¹³C NMR, IR and MS) and elemental analyses. The compounds **2b-f**, **5b-d**, **6b-d**, **8** and **9** were synthesised starting from racemic (*rac*)-**1**. The compounds **2a**, **5a**, **6a** and **7** were synthesised starting from both (*rac*)-**1** and enantiopure (*S*)-**1**. [‡] Selected data for (*S*)-**5a**: mp 39–40 °C (Et₂O–hexanes) (Calc. for

² *Selected data* for (5)-5a: mp 39–40 °C (Et₂O–nexanes) (Calc. for $C_{15}H_{17}NO_4S$ (307.37): C, 58.61; H, 5.57; N, 4.56. Found: C, 58.54; H, 5.63; N, 4.61%); $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.79 (d, *J* 8.3, 2H), 7.33 (d, *J* 8.3, 2H), 5.60–5.71 (m, 1H), 5.04–5.19 (m, 2H), 4.53 (dd, *J* 9.8, 5.2, 1H), 3.57 (s, 3H), 2.84 (s, 1H), 2.54–2.74 (m, 2H), 2.45 (s, 3H).

¶ Selected data for (2S,4R)-**6a**: mp 132–134 °C (CH₂Cl₂–hexanes) (Calc. for C₁₆H₁₇NO₅S (335.38): C, 57.30; H, 5.11; N, 4.18. Found: C, 57.01; H, 5.06; N, 4.23%); $\delta_{\rm H}$ (400 MHz, CDCl₃) 7.81 (d, J 8.3, 2H), 7.36 (d, J 8.3, 2H), 5.67 (d, J 1.5, 1H), 4.64 (dd, J 10.3, 5.7, 1H), 3.85 (s, 3H), 2.85–2.95 (m, 1H), 2.56–2.63 (m, 1H), 2.53 (dd, J 17.1, 6.7, 1H), 2.45 (s, 3H), 2.21 (dd, J 17.1, 5.2, 1H), 1.76–1.86 (m, 1H).

§ The stereochemical course of the intramolecular Pauson–Khand reaction with the compounds **5a–d** follows the one previously noticed by us with other *N*-ethynylamides. See ref. 1. A detailed discussion will be presented in the full account of this study.

- 1 B. Witulski and T. Stengel, Angew. Chem., Int. Ed., 1998, 37, 489.
- 2 P. J. Stang and V. V. Zhdankin, Chem. Rev., 1996, 96, 1123.
- 3 G. Himbert, Methoden Org. Chem. (Houben-Weyl), 1993, vol. E15, pp. 3267–3461; J. Ficini, Tetrahedron, 1976, 32, 1448.
- 4 B. Witulski and T. Stengel, Angew. Chem., Int. Ed., 1999, 38, in the press.
- 5 J. Gante, Angew. Chem., Int. Ed. Engl., 1994, 33, 1699; A. E. P. Adang, P. H. H. Hermkens, J. T. M. Linders, H. C. J. Ottenheijm and C. J. van Staveren, Recl. Trav. Chim. Pays-Bas., 1994, 113, 63.
- 6 R. Henning, U. Lerch and H. Urbach, Synthesis, 1989, 265.
- 7 M. T. Reetz, T. J. Strack, J. Kanand and R. Goddard, *Chem. Commun.*, 1996, 733.
- 8 For the preparation of **3b** and its reaction with carbon nucleophiles see: M. Ochiai, T. Ito, Y. Takaoka, Y. Masaki, M. Kunishima, S. Tani and Y. Nagao, *J. Chem. Soc., Chem. Commun.*, 1990, 118; P. J. Stang, in *Modern Acetylene Chemistry*, ed. P. J. Stang and F. Diederich, VCH, Weinheim, 1995.
- 9 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley, New York, 1991; C. Goulaouic-Dubois, A. Guggisberg and M. Hesse, *J. Org. Chem.*, 1995, **60**, 5969; T. Fukuyama, C.-K. Jow and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373.
- 10 M. M. Gallo, T. P. Hamilton and H. F. Schaefer III, J. Am. Chem. Soc., 1990, **112**, 8714; W. Kirmse, Angew. Chem., Int. Ed. Engl., 1997, **36**, 1164.
- 11 K. S. Feldman and D. A. Mareska, J. Am. Chem. Soc., 1998, 120, 4027 and references therein.
- 12 The pK_a values of **2a–e** can be estimated by comparison with the following model compounds (in DMSO): NH₃ (41), PhSO₂NH₂ (16.1), CF₃SO₂NH₂ (9.7), CH₃CONH₂ (25.5), EtOCONH₂ (24.8); all data taken from F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456.
- 13 (S)-Allylglycine is commercially available. For its synthesis, see: Y. N. Belokon, V. I. Bakhmutov, N. I. Chernoglazova, K. A. Kochetkov, S. V. Vitt, N. S. Garbalinskaya and V. M. Belikov, J. Chem. Soc., Perkin Trans 1, 1988, 305.
- 14 Baseline separation of (*S*)-**5a** and (*R*)-**5a** from (*rac*)-**5a** could be achieved by using the Chiralpak AD column.
- 15 For recent reviews, see A. C. Comely and S. E. Gibson, J. Chem. Soc., Perkin Trans 1, 1999, 223; O. Geis and H.-G. Schmalz, Angew. Chem., Int. Ed., 1998, 37, 911; N. E. Schore, Comprehensive Organometallic Chemistry II, ed. L. S. Hegedus, Pergamon, 1995, vol. 12, p. 703.
- 16 S. Shambayati, W. E. Crowe and S. L. Schreiber, *Tetrahedron Lett.*, 1990, **31**, 5289.

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