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

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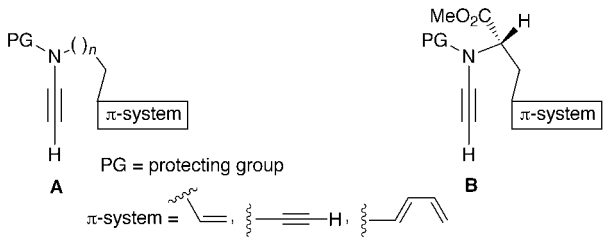
The first synthesis of an enantiopure *N*-ethynylated allylglycine and its application in the intramolecular Pauson–Khand reaction, which leads to a novel highly functionalised proline derivative with complete control of stereoselectivity, is reported.

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

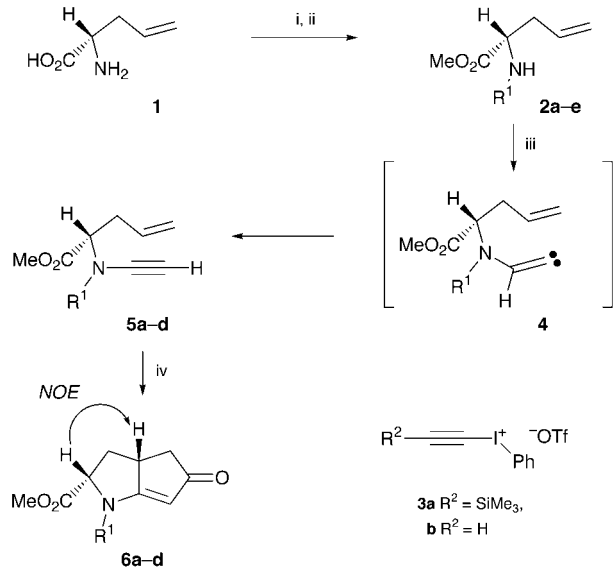


serves both in masking a secondary amine and in tuning the electron density, and hence the reactivity, of the adjacent acetylene moiety.[1] These new building blocks for organic synthesis were designed with the goal of combining the richness and diversity of the chemical reactivity of a carbon–carbon 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 triflate[2] 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 reaction[1] 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 acids[5] 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** (R^2 = $SiMe_3$) 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** (R^2 = $SiMe_3$). The ethynyl(phenyl)iodonium triflate[8] **3b** (R^2 = 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 Cs_2CO_3 in DMF, followed by the addition of **3b** (1.3 equiv.) in CH_2Cl_2 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, $SOCl_2$, MeOH, −10 °C, 24 h; ii, R^1Cl (for **2a–c** and **2f**) or $R^1{}_2O$ (for **2d**,**e**), Et_3N, CH_2Cl_2, 0 °C, 6–12 h, for yield of isolated **2a–f** (2 steps) see Table 1; iii, Cs_2CO_3 (1.3 equiv.), **3b** (1.3 equiv.), DMF–CH_2Cl_2, room temp., 3 h, for yield of isolated **5a–f** see Table 1; iv, $Co_2(CO)_8$ (1.1 equiv.), THF, 30 min. 0–20 °C, then NMO or Me_3NO (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**†

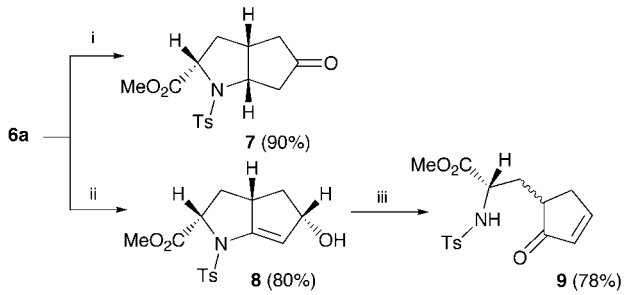
Entry	R^1	**2**	Yield (%)	**5**	Yield (%)	**6**	Yield (%) [de (%)]
1	Ts	**2a**	88	**5a**	70	**6a**	69 [> 96]
2	2-pyridyl-SO_2	**2b**	71	**5b**	78	**6b**	69 [> 95]
3	4-$NO_2C_6H_4SO_2$	**2c**	89	**5c**	95	**6c**	35 [> 97]
4	Tf	**2d**	83	**5d**	94	**6d**	60 [> 95]
5	Boc	**2e**	80	**5e**	0	—	—
6	Ac	**2f**	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 basicity[12] 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, $CHCl_3$][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, $CHCl_3$] 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 $Co_2(CO)_8$, 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 Me_3NO in CH_2Cl_2 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 ^{1}H-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 (2*S*,4*R*)-**6a** [$[\alpha]_D$ +145 (*c* 2.0, $CHCl_3$)] 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/(H_2) 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, CH_2Cl_2–pentane) after column chromatography on silica gel with CH_2Cl_2 containing 0.5% Et_3N. 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, $NaBH_4$ (2 equiv.), $CeCl_3 \cdot 7\ H_2O$ (1 equiv.), MeOH–CH_2Cl_2, 20 °C, 0.5 h; iii, cat. H^+, $CHCl_3$, 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 (^{1}H, ^{13}C 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 (Et_2O–hexanes) (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%); δ_H (400 MHz, $CDCl_3$) 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 (2*S*,4*R*)-**6a**: mp 132–134 °C (CH_2Cl_2–hexanes) (Calc. for $C_{16}H_{17}NO_5S$ (335.38): C, 57.30; H, 5.11; N, 4.18. Found: C, 57.01; H, 5.06; N, 4.23%); δ_H(400 MHz, $CDCl_3$) 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): NH_3 (41), $PhSO_2NH_2$ (16.1), $CF_3SO_2NH_2$ (9.7), CH_3CONH_2 (25.5), $EtOCONH_2$ (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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