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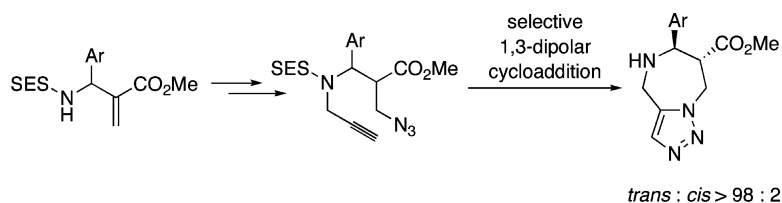
Article

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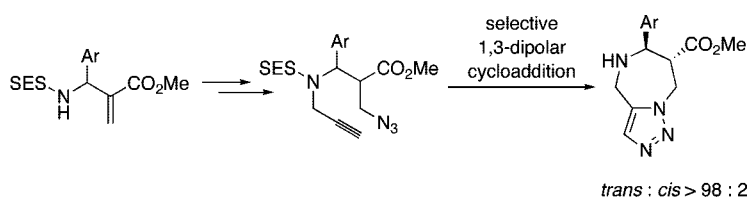
Selective [3 + 2] Huisgen Cycloaddition. Synthesis of *Trans*-Disubstituted Triazolodiazepines from *Aza*-Baylis–Hillman Adducts

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The 1,3-dipolar cycloaddition of linear azido alkynes derived from protected β -amino esters proceeds via diastereomeric differentiation to provide *trans*-disubstituted triazolodiazepines in good yields.

Introduction

The *aza*-Baylis–Hillman reaction^{1–3} is a powerful method for the preparation of densely functionalized small molecules which has attracted the attention of organic chemists. We have recently reported a three-component *aza*-Baylis–Hillman reaction involving a sulfonamide, an aldehyde, and an acrylate for the preparation of highly functionalized 2-(trimethylsilyl)ethanesulfonyl (or SES)-protected^{4,5} α,β -unsaturated β -amino esters which can be used in further transformations.^{6,7}

In an ongoing project dealing with the use of these α,β -unsaturated β -amino esters as building blocks for the synthesis of various heterocyclic structures, we reported the preparation of pyrroles,⁶ pyrrolines,⁸ pyrrolidines,⁸ and benzazepines.^{9,10} We describe herein the synthesis of triazolodiazepines from these β -amino esters involving an intramolecular [3 + 2] Huisgen cycloaddition¹¹ as a keystone.

Triazoles are important molecules due to their unique chemical properties. They possess a wide range of applications in organic, organometallic, medicinal, and material chemistry. Although no product containing the 1,2,3-triazole moiety has been found in nature, this scaffold constitutes an interesting class of pharmacophores since it shows a remarkable resistance to metabolic transformations such as oxidation, reduction, basic or acidic hydrolysis. The 1,2,3-triazole unit is present in various compounds exhibiting interesting antibacterial,¹² anti-HIV,¹³ and antiallergic¹⁴ activities. As examples, cefmatilen¹⁵ exhibit antibacterial activities and tazobactam¹⁶ is a β -lactamase inhibi-

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(1) Balan, D.; Adolffson, H. *J. Org. Chem.* **2001**, *66*, 6498–6501. (a) Balan, D.; Adolffson, H. *J. Org. Chem.* **2002**, *67*, 2329–2334.

(2) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1–48.

(3) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905–2916.

(4) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099–2102.

(5) (a) Ribière, P.; Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2006**, *106*, 2249–2269. (b) Declerck, V.; Ribière, P.; Martinez, J.; Lamaty, F.; Weinreb, S. M.; Ralbovsky, J. L. β -(Trimethylsilyl)ethanesulfonyl Chloride (17 September 2007). *Encyclopedia of Reagents for Organic Synthesis* [Online]; John Wiley & Sons Ltd., www.mrw.interscience.wiley.com/eros/, accessed 20 November 2007, DOI: 10.1002/047084289X.rt300.pub2.

(6) Declerck, V.; Ribière, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372–8381.

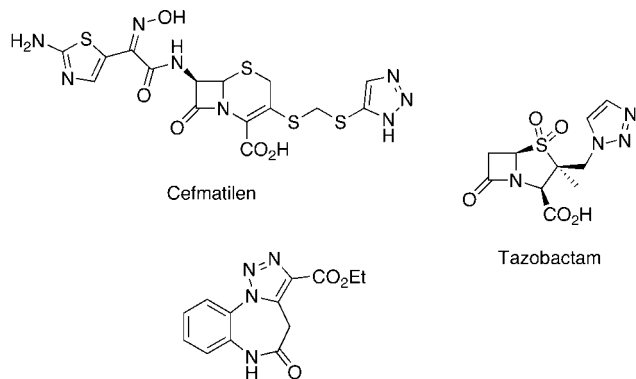
(7) (a) Ribière, P.; Enjalbal, C.; Aubagnac, J.-L.; Yadav-Bhatnagar, N.; Martinez, J.; Lamaty, F. *J. Comb. Chem.* **2004**, *6*, 464–467. (b) Ribière, P.; Yadav-Bhatnagar, N.; Martinez, J.; Lamaty, F. *QSAR Comb. Sci.* **2004**, *23*, 911–914.

(8) Declerck, V.; Allouchi, H.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2007**, *72*, 1518–1521.

(9) Ribière, P.; Declerck, V.; Nédellec, Y.; Yadav-Bhatnagar, N.; Martinez, J.; Lamaty, F. *Tetrahedron Lett.* **2006**, *62*, 10456–10466.

(10) Declerck, V.; Ribière, P.; Nédellec, Y.; Allouchi, H.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2007**, 201–208.

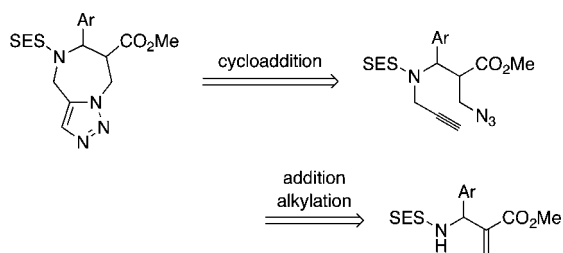
(11) For examples of 7-membered rings, see: (a) Padwa, A.; Ku, A.; Ku, H.; Mazzu, A. *J. Org. Chem.* **1978**, *43*, 66–72. (b) Akritopoulou-Zanze, I.; Gracias, V.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 8439–8441. (c) Tezuka, K.; Compain, P.; Martin, O. R. *Synlett* **2000**, 1837–1839. (d) Dolhem, F.; Al Tahli, F.; Lievre, C.; Demailly, G. *Eur. J. Org. Chem.* **2005**, 5019–5023. (e) Röper, S.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2003**, *5*, 2773–2776. (f) Mohapatra, D. K.; Maity, P. K.; Chorghade, M. S.; Gurjar, M. K. *Heterocycles* **2007**, *73*, 269–274.



[1,2,3]-Triazolobenzodiazepines

FIGURE 1. Biologically active 1,2,3-triazole containing compounds.

SCHEME 1. Retrosynthetic Analysis



tor. Triazolobenzodiazepines¹⁷ have high affinity for the benzodiazepine receptors (Figure 1).

Results and Discussion

As described in the retrosynthetic scheme (Scheme 1), the triazolodiazepines can be obtained by an intramolecular 1,3-dipolar cycloaddition of a linear precursor possessing an azide function and a triple bond. This precursor can be obtained by sequential Michael addition of HN_3 on the α,β -unsaturated β -amino esters and alkylation with propargyl bromide.

Starting from the SES-protected amino ester, we had the choice to perform first either the Michael addition of HN_3 or the alkylation reaction. A disubstituted SES-sulfonamide, which would be obtained after alkylation by propargyl bromide, owns a leaving group character similar to that of acetate¹⁸ and is not suitable for a 1,4-addition (it would provide mainly an elimina-

SCHEME 2. Conjugate Addition of HN_3

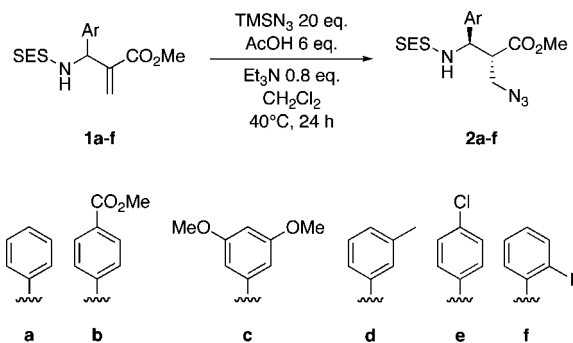


TABLE 1. Yields and Stereoselectivities of Isolated Compounds 2, 3, 5, and 6

substituent	azido- β -amino esters 2		precursors 3	SES-triazoles 5		triazoles 6
	yield (%)	anti/syn ^a	3:4	yield (%) ^b	trans/cis ^a	yield (%)
a	98	83:17	96:4	77	>99	100
b	96	81:19	90:10	68	98:2	100
c	99	83:17	95:5	70	98:2	100
d	94	83:17	96:4	69	>99	100
e	99	78:22	93:7	69	99:1	100
f	95	71:29	96:4	70	99:1	100

^a Determined by ^1H NMR. ^b Yield in two steps: alkylation and 1,3-dipolar cycloaddition.

tion product). Consequently, we have chosen to introduce first the azide function and then the propargyl moiety. Introduction of the azido group on the α,β -unsaturated β -amino ester was realized according to the procedure described by Miller¹⁹ to avoid the use of a toxic and explosive HN_3 solution. This procedure is well-adapted for the 1,4-addition of N_3 to unsaturated ketones, but an intramolecular amine-mediated activation is necessary in the case of α,β -unsaturated esters. Furthermore, to our knowledge no example of the azide addition on a 1,1-disubstituted acrylate has been described. Thus, treatment of the α,β -unsaturated β -amino esters 1a with an excess of TMSN_3 in the presence of acetic acid and triethylamine at 40 °C for 24 h allowed a complete conversion and the azido- β -amino esters 2 were obtained in high yields as a mixture of *anti* and *syn* diastereoisomers, which could not be separated by column chromatography. X-ray analysis of the cyclic compound 5a obtained after the cycloaddition step confirmed that the *anti* isomer was the major one (Scheme 2, Table 1).

The stereochemical outcome of this reaction was governed by the reprotonation of the enolate intermediate formed after the 1,4-addition (Scheme 2). According to the studies of Perlmutter et al. on 1,4-addition of amines to 2-hydroxyalkylpropenoates,²⁰ the two possible conformers A and B of the enolate resulting from the addition of HN_3 are depicted in Scheme 3. Since the bulky SES-NH group does not accommodate easily an interaction with the azidomethylene moiety, conformer A is preferred, leading to the formation of the *anti* product.

The next step was the alkylation of the azido- β -amino ester 2a by propargyl bromide (Table 2). Under classical alkylation conditions using K_2CO_3 in DMF for 6 h (entry 1),⁶ we observed

(12) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953–970.

(13) Alvarez, R.; Velázquez, S.; San-Félix, A.; Aquaro, S.; De Clercq, E.; Perno, C.-F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185–4194.

(14) Brockunier, L. L.; Parmee, E. R.; Ok, H. O.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Tota, L.; Wyratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2111–2114.

(15) (a) Kume, M.; Kubota, T.; Kimura, Y.; Nakashimizu, H.; Motokawa, K.; Nakano, M. *J. Antibiot.* **1993**, *46*, 177–192. (b) Kume, M.; Kubota, T.; Kimura, Y.; Nakashimizu, H.; Motokawa, K. *J. Antibiot.* **1993**, *46*, 316–330. (c) Kume, M.; Kubota, T.; Kimura, Y.; Nakashimizu, H.; Motokawa, K. *Chem. Pharm. Bull.* **1993**, *41*, 758–762.

(16) Tanaka, M.; Yamazaki, T.; Kajitani, M. "Penam Derivatives" Eur. Pat. 158494, 1985; *Chem. Abstr.* **1986**, *104*, 186239d.

(17) (a) Smalley, R. K.; Teguche, M. *Synthesis* **1990**, 654–666. (b) Bertelli, L.; Biagi, G.; Giorgi, I.; Livi, O.; Manera, C.; Scartoni, V.; Martini, C.; Giannaccini, G.; Trincavelli, L.; Barili, P. L. *Farmaco* **1998**, *53*, 305–311.

(18) Declerck, V.; Martinez, J.; Lamaty, F. Unpublished results.

(19) Guerin, D. J.; Horstmann, T. E.; Miller, S. J. *Org. Lett.* **1999**, *1*, 1107–1109.

(20) Perlmutter, P.; Tabone, M. *Tetrahedron Lett.* **1988**, *29*, 949–952.

SCHEME 3. Transition Structure Analysis of the Addition of HN₃ on β -Amino Esters 1

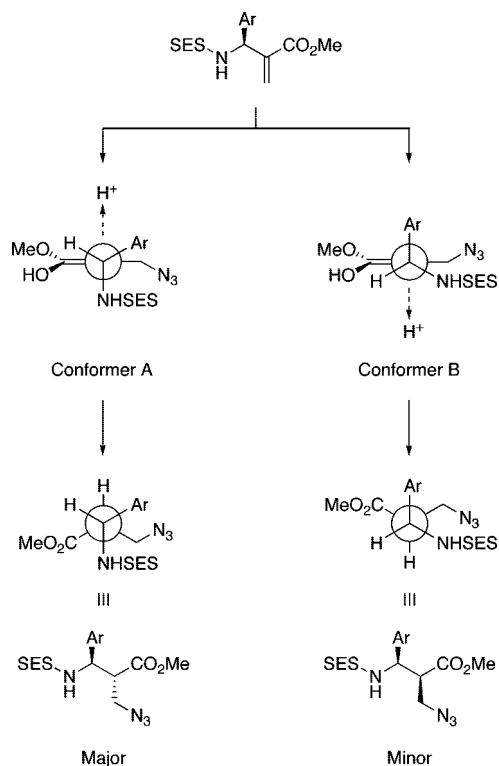
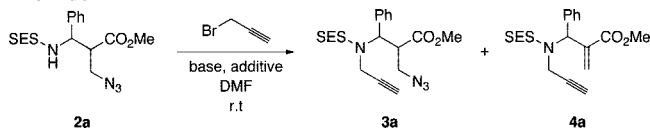


TABLE 2. Optimization of Alkylation of 2a with Propargyl Bromide



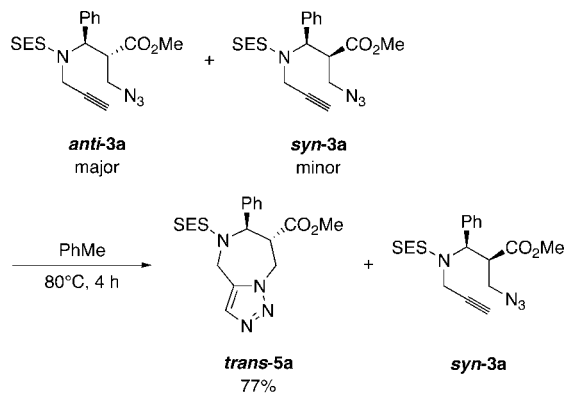
entry	RBr (equiv)	base (equiv)	time (h)	additive (equiv)	proportions ^a		
					2a	3a	4a
1	4	K ₂ CO ₃ (10)	6		0	70	30
2	4	K ₂ CO ₃ (10)	4	18-C-6 (1)	0	82	18
3	4	Cs ₂ CO ₃ , 10	0.5		0	91	9
4	4	Cs ₂ CO ₃ (10)	0.5	NaI (8)	13	83	4
5	8	Cs ₂ CO ₃ (10)	1	NaI (16)	0	96	4

^a Determined by ¹H NMR.

the formation of compound **4a** resulting from elimination of HN₃. The use of a crown ether to accelerate the alkylation decreased the elimination (entry 2). Changing K₂CO₃ for the more basic Cs₂CO₃ decreased the elimination to 9% and the reaction time to 30 min (entry 3). Addition of NaI slowed down the reaction, but the elimination was decreased (entry 4). Finally, using Cs₂CO₃ with NaI in the presence of an excess of propargyl bromide in DMF was a good compromise to obtain compound **3a** in 1 h at rt, along with only 4% of elimination product **4a**. For the other substrates, the linear precursors **3** were obtained along with the elimination compounds **4** in similar proportions except for substrates **2b** and **2e** bearing an electron-withdrawing group on the aryl moiety, for which the elimination was slightly more significant (Table 1). Compounds **3** were obtained as an unseparable mixture of *anti* and *syn* isomers together with compound **4**.

With the compounds **3** in hand, we started to explore the thermal 1,3-dipolar cycloaddition.^{21,22} A first experiment real-

SCHEME 4. 1,3-Dipolar Cycloaddition of Compound 3a



ized by heating the linear precursor **3a** at 80 °C in toluene for 12 h allowed the preparation of the bicyclic triazole **5a**, which was easily separated from the elimination compound **4a** by silica gel chromatography and obtained in a 45% yield. The prolonged reaction time resulted in the degradation of the product. We speculated on the use of the microwave heating to reduce reaction time and probably diminish the degradation. Heating compound **3a** in toluene at 100 °C under microwave irradiation for 30 min did not yield a complete conversion but showed that the linear precursor *anti*-**3a** cyclized more rapidly than the *syn* isomer. By carefully monitoring by ¹H NMR the reaction under classical heating conditions, we found that after 4 h in toluene at 80 °C, only the *anti* diastereoisomer had fully cyclized while the *syn* one did not react. The reaction gave a mixture of bicyclic triazole *trans*-**5a**, linear precursor *syn*-**3a**, and elimination compound **4a** (present in the starting material). The triazolodiazepine *trans*-**5a** was obtained in 77% yield after purification by chromatography on silica gel (Scheme 4). An NOE NMR experiment performed on **5a** did not show any effect between the phenyl group protons and those of the ester group, which implies a *trans* relationship between these substituents. Furthermore, X-ray analysis of **5a** showed that the two substituents are in a *trans* configuration, thus confirming the formation of the *anti* diastereoisomer during the addition of HN₃. Similar results were obtained with the other substrates which allowed the preparation of bicyclic triazoles **5** in good yields with a selectivity higher than 98% for the *trans* isomer (Table 1).

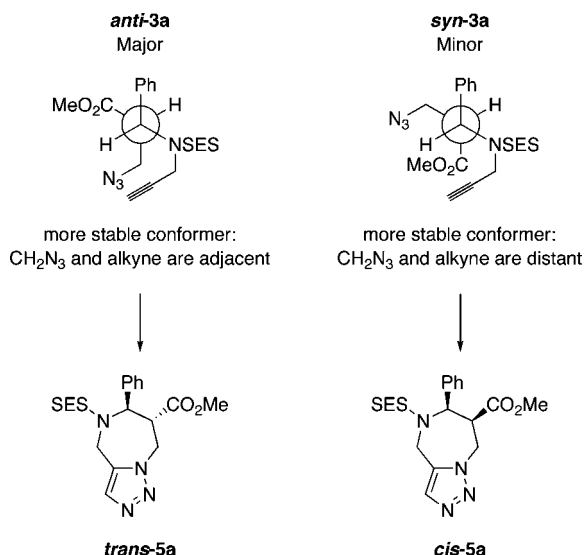
The difference of reactivity between *anti*-**3a** and *syn*-**3a** could be explained by unfavorable interactions between substituents. Newman projections showed that the conformer presenting weaker interactions possess the alkyne and azido substituents in close proximity in the diastereoisomer *anti*-**3a**, whereas these two substituents are in opposite directions in the diastereoisomer *syn*-**3a** (Scheme 5). Diastereomeric differentiation of the two linear diastereomers provided only *trans*-**5a** as a cyclic product.

The last step consisted of the cleavage of the SES group to obtain the free amine. The use of CsF at 80 °C in DMF or *n*-Bu₄NF,⁴ usually employed to deprotect the SES group, yielded only degradation products. We turned our attention to anhydrous HF, a nonbasic fluoride source which has proved to be a very efficient reagent for the deprotection of the SES group in other cyclic β -amino esters.^{8,10} Deprotection of the SES group by anhydrous HF followed by neutralization of the hydrofluoride

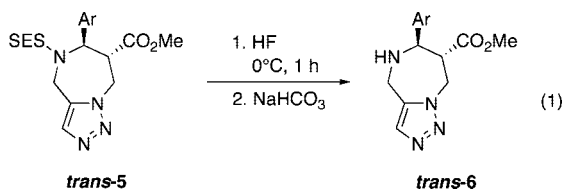
(21) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–598. (b) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604–637.

(22) Huisgen, R.; Knorr, R.; Möbius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014–4021.

SCHEME 5. Conformational Analysis of Compound 3a



salt by NaHCO₃ yielded the deprotected bicyclic triazoles quantitatively (eq 1, Table 1).



In conclusion, we have described an efficient synthesis of new bicyclic triazoles by sequential azidation/alkylation/1,3-dipolar cycloaddition/deprotection starting from SES-protected *aza*-Baylis–Hillman β -amino esters. To our knowledge, we have reported the first example of selective Huisgen cycloaddition, starting from a mixture of diastereoisomers. The bicyclic triazoles are obtained in their *trans* form in good yields and very high diastereomeric ratios.

Experimental Section

General Procedure for HN₃ Addition on β -Amino Esters

1. To a solution of β -amino ester **2** (0.4 mmol, 1 equiv) in toluene were added azidotrimethylsilane (1.06 mL, 8 mmol, 20 equiv), acetic acid (137 μ L, 2.4 mmol, 6 equiv), and triethylamine (45 μ L, 0.32 mmol, 0.8 equiv). The solution was heated for 24 h at 40 °C, and the solvent was evaporated. Silica gel chromatography (Et₂O/cyclohexane) yielded the corresponding azido- β -amino ester **2** as a mixture of *anti* and *syn* diastereoisomers.

Methyl 2-(Azidomethyl)-3-phenyl-3-(2-trimethylsilylthanesulfonylamino)propanoate (2a). Addition of HN₃ on the β -amino ester **1a** yielded 156.1 mg (98%) of the title compound as a white solid (mixture *anti*:*syn* = 81:19) after silica gel chromatography (Et₂O/cyclohexane = 3/7): IR cm⁻¹ 2955 (m), 2108 (s), 1740 (s), 1265 (s); ESIMS *m/z* 399.0 (M + H)⁺, 421.2 (M + Na)⁺; FAB+ *m/z* 398 (M + H)⁺; HRMS calcd for C₁₆H₂₇N₄O₄SSi 399.1522, found 399.1518. **Anti isomer:** ¹H NMR (CDCl₃, Me₄Si) δ -0.21 (s, 9H), 0.45–0.85 (m, 2H), 2.40–2.75 (m, 2H), 3.00–3.15 (m, 1H), 3.53 (s, 3H), 3.60–3.75 (m, 2H), 4.70 (dd, 1H, *J*₃ = 9.8 Hz, *J*₂ = 8.3 Hz), 6.03 (d, 1H, *J*₃ = 9.9 Hz), 7.20–7.40 (m, 5H); ¹³C NMR (CDCl₃, Me₄Si) δ -2.2, 10.1, 49.9, 50.2, 51.8, 52.3, 57.4, 127.0, 128.7, 129.1, 138.4, 171.1. **Syn isomer:** ¹H NMR (CDCl₃, Me₄Si) δ -0.20 (s, 9H), 0.45–0.85 (m, 2H), 2.40–2.75 (m, 2H),

2.95–3.10 (m, 1H), 3.35–3.65 (m, 2H), 3.70 (s, 3H), 4.65–4.75 (m, 1H), 6.07 (d, 1H, *J*₃ = 10.0 Hz), 7.20–7.40 (m, 5H); ¹³C NMR (CDCl₃, Me₄Si) δ -2.2, 10.2, 50.0, 50.7, 51.8, 52.6, 57.1, 126.7, 128.7, 129.2, 138.8, 172.1.

General Procedure for Alkylation of Azido- β -amino Esters 2 and 1,3-Dipolar Cycloaddition of the Intermediate 3. To a mixture of azido- β -amino ester **2** (0.35 mmol, 1 equiv), Cs₂CO₃ (1.14 g, 3.5 mmol, 10 equiv), and NaI (839 mg, 5.6 mmol, 5.6 equiv) in 9.8 mL of DMF was added propargyl bromide (210 μ L, 2.8 mmol, 8 equiv). The mixture was stirred at room temperature for 1 h and then filtered through Celite. The residue was diluted in AcOEt, washed successively with water and brine, dried over MgSO₄, and evaporated to give the alkylated azido- β -amino ester **3** as a mixture of *anti* and *syn* diastereoisomers and enyne **4**. A solution of crude azido- β -amino ester **3** in 10 mL of toluene was heated at 80 °C for 4 h. The solvent was evaporated. Silica gel chromatography (AcOEt/CH₂Cl₂) yielded the SES-triazolodiazepine **trans-5**.

Methyl 6-Phenyl-5-(2-trimethylsilylthanesulfonyl)-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-7-carboxylate (trans-5a). Alkylation of azido- β -amino ester **2a** with propargyl bromide yielded 149.3 mg (quant) of the linear precursor as a yellow oil (mixture *anti*/*syn*/**4a** = 79/17/4). Cyclization of the linear precursor **3a** yielded 118.3 mg (77%, two steps) of the title compound as a white solid (mixture *trans*/*cis* = >99:1) after silica gel chromatography (CH₂Cl₂/AcOEt = 9/1): mp 130–133 °C; IR cm⁻¹ 2956 (m), 1742 (s), 1266 (s); ¹H NMR (CDCl₃, Me₄Si) δ -0.09 (s, 9H), 0.60–0.90 (m, 2H), 2.65–2.90 (m, 2H), 3.64 (s, 3H), 3.79 (dt, 1H, *J*₃ = 8.2 Hz, *J*₂ = 5.0 Hz), 4.47 (d, 1H, *J*₂ = 17.6 Hz), 4.98 (d, 2H, *J*₃ = 5.0 Hz), 5.00 (d, 1H, *J*₂ = 17.6 Hz), 5.74 (d, 1H, *J*₃ = 8.2 Hz), 7.30–7.50 (m, 5H), 7.49 (s, 1H); ¹³C NMR (CDCl₃, Me₄Si) δ -2.0, 10.2, 38.5, 46.8, 48.5, 50.6, 52.9, 61.3, 127.5, 129.2, 129.7, 131.4, 134.1, 136.3, 169.8; ESIMS *m/z* 437.2 (M + H)⁺, 459.1 (M + Na)⁺; FAB+ *m/z* 437 (M + H)⁺; HRMS calcd for C₁₉H₂₉N₄O₄SSi 437.1679, found 437.1704.

General Protocol for the Deprotection of the SES-triazole 5 with HF. SES-triazolodiazepine **5** (0.1 mmol) was treated with 1 mL of anhydrous HF at 0 °C for 1 h in a Teflon vessel. The HF was removed by distillation. The HF·triazolodiazepine thus obtained was neutralized with a saturated aqueous solution of NaHCO₃, and the aqueous phase was extracted three times with AcOEt, dried over MgSO₄, filtered, and evaporated to yield the triazolodiazepine **6**. Caution! HF is a harmful chemical.

Methyl 6-Phenyl-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a]-[1,4]diazepine-7-carboxylate (trans-6a). Deprotection of the compound **trans-5a** according to the general procedure yield 27.2 mg (100%) of the title compound as a white solid (mixture *trans*/*cis* = >99:1): mp >230 °C; IR cm⁻¹ 2982 (m), 1732 (s), 1372 (s); ¹H NMR (CDCl₃, Me₄Si) δ 1.89 (sl, 1H), 3.00 (ddd, 1H, *J*₃ = 10.4 Hz, *J*₂ = 9.1 Hz, *J*₁ = 2.1 Hz), 3.36 (s, 3H), 3.95 (d, 1H, *J*₂ = 15.6 Hz), 4.23 (d, 1H, *J*₃ = 9.1 Hz), 4.33 (d, 1H, *J*₂ = 15.6 Hz), 4.57 (dd, 1H, *J*₂ = 14.6 Hz, *J*₃ = 10.4 Hz), 5.09 (dd, 1H, *J*₂ = 14.6 Hz, *J*₃ = 2.1 Hz), 7.20–7.40 (m, 5H), 7.52 (s, 1H); ¹³C NMR (CDCl₃, Me₄Si) δ 41.8, 50.4, 51.7, 52.0, 69.0, 127.2, 128.6, 128.9, 132.0, 137.7, 141.0, 171.2; ESIMS *m/z* 273.1 (M + H)⁺; FAB+ *m/z* 273 (M + H)⁺; HRMS calcd for C₁₄H₁₇N₄O₂ 273.1352, found 273.1360.

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