One-Pot Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from Aldehydes and Amines

Stéphane Maisonneuve, Juan Xie*

PPSM, Institut d'Alembert, ENS de Cachan, CNRS UMR 8531, 61 Avenue du Président Wilson, 94235 Cachan, France
Fax +33(1)47405586; E-mail: joanne.xie@ens-cachan.fr

Received 17 July 2009

Abstract: A one-pot, three-step synthesis of 1,4-disubstituted 1,2,3-triazoles from aldehyde and amine has been developed by in situ transformation of aldehyde into alkyne, followed by diazo-transfer of amine into azide and subsequent cycloaddition. This procedure allowed the synthesis of fluorescent amino acid derivatives as well as glycoconjugate mimetics.

Key words: aldehydes, amines, cycloadditions, one-pot reaction, triazoles

The Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition[1] between terminal alkynes and organic azides (also known as 'click chemistry') has been extensively used and found wide application in organic synthesis, medicinal chemistry, molecular biology, polymer and materials science because of its high efficiency, versatility, regioselectivity, and excellent functional-group compatibility.[2] The copper-catalyzed alkyne–azide cycloaddition (CuAAC) usually proceeds at room temperature in water with a variety of organic co-solvents, such as *t*-BuOH, EtOH, THF, DMSO, MeCN, CH_2Cl_2, or PEG-400. In addition, the 1,2,3-triazole ring is resistant to hydrolysis, oxidation, reduction, or other modes of cleavage. Due to their electronic properties, 1,2,3-triazoles have been employed as rigid linking units to mimic amide and ester bonds.[2d,3] These important features have allowed the synthesis of complex molecules including dendrimers, bioconjugates, functionalized polymers, and various bioactive compounds.

Many organic azides and terminal alkynes are not commercially available. Moreover, low molecular weight organic azides can be unstable[4] and difficult to handle. To avoid the isolation of azide partner and in searching for step-economic synthesis, one-pot CuAAC with in situ generated organic azides has been developed for alkyl or aryl halides,[5] α-haloketones,[6] tosylates,[7] boronic acids,[8] epoxides,[9] secondary alcohols,[10] glucals,[11] unprotected monosaccharides,[12] alkyl[13] and aromatic amines.[14] One-pot synthesis of triazoles with in situ generated terminal alkynes[15] or benzyne[16] has also been explored. However, to the best of our knowledge, there is only one report concerning an in situ generated aromatic azide and benzyne for benzyne click chemistry.[17]

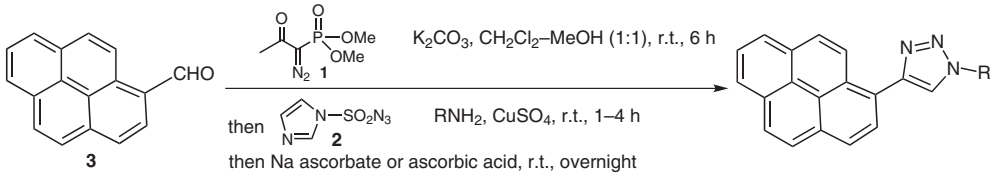
With a continuing interest in click chemistry,[18] we decided to investigate a one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from aldehydes and amines, in light of the great variety of commercially available aldehydes and amines. Such chemistry should not only circumvent the isolation of the alkyne and azide intermediates, hence saving time, reagents, and solvents, but also broaden the scope and application of the CuAAC. Herein, we report a one-pot, three-step synthesis of triazoles from alkyl amines and aryl or alkyl aldehydes.

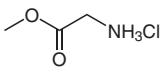
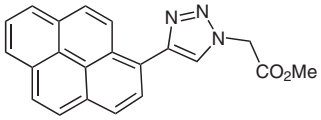
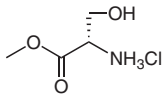
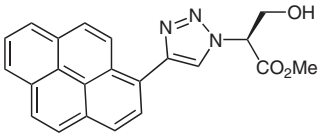
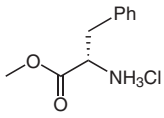
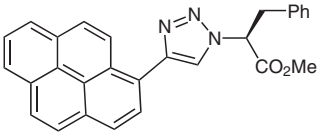
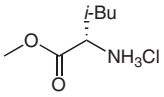
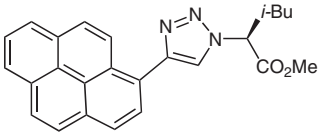
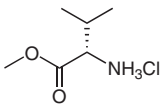
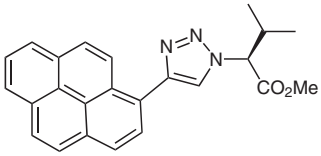
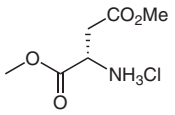
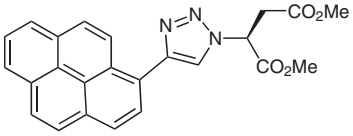
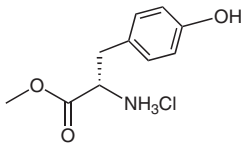
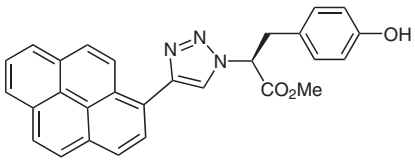
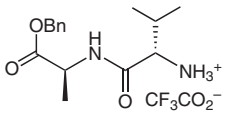
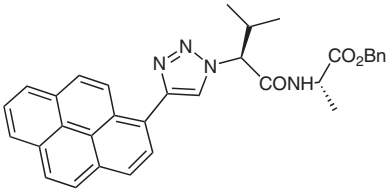
Homologation of an aldehyde to the corresponding alkyne can be easily realized using the Bestmann–Ohira reagent under mild basic conditions.[15,19] One-step transformation of an amine to azide is possible with the diazo-transfer reaction, usually catalyzed by transition-metal ions such as Cu(II), Ni(II), or Zn(II) under basic conditions. Trifluoromethanesulfonyl (triflyl) azide has been successfully used to convert various amines to organic azides in the presence of Cu(II) as an efficient catalyst.[13,20] However, triflyl azide is hard to handle because of its inherent tendency to explode. Furthermore, excess triflyl azide usually has to be used since it is difficult to determinate its exact concentration in CH_2Cl_2 solution.[13] In 2007, Goddard–Borger and Stick reported the synthesis of imidazole-1-sulfonyl azide hydrochloride as an efficient and shelf-stable diazo-transfer reagent.[21] This reagent, as an efficient alternative to triflyl azide, converted a diverse range of amines into the corresponding azides with excellent yield.[21,22] We thus decided to use imidazole-1-sulfonyl azide **2** as the diazo-transfer reagent in order to control the quantity of **2** (1 equiv/amine), which is of crucial importance to realize a one-pot reaction. It should be noted that, in the presence of catalytic Cu(I), sulfonyl azide itself can react with terminal alkyne to *N*-sulfonyltriazole which can then rearrange to a keteneimine intermediate, leading to amidines, imidates, or amides in the presence of amines, alcohols, or water, respectively.[23] Our preliminary experiments indicated that ethynyl pyrene did not react with imidazole-1-sulfonyl azide **2** in the presence of $CuSO_4$ and K_2CO_3 in a mixture of CH_2Cl_2–MeOH; conditions generally used for the one-pot diazo-transfer reaction. Another advantage to use **2** is its easy detection on TLC which is useful to follow the diazo-transfer reaction.

We started our investigation with fluorescent pyrene carboxaldehyde **3** because pyrenyl-substituted molecules exhibited attractive fluorescent properties[24] useful for the labeling of biomolecules[25] or for the detection of metal

SYNLETT 2009, No. 18, pp 2977–2981
Advanced online publication: 08.10.2009
DOI: 10.1055/s-0029-1218267; Art ID: D19109ST
© Georg Thieme Verlag Stuttgart · New York

Table 1 One-Pot, Three-Step Synthesis of 1,2,3-Triazoles from Pyrene Carboxaldehyde and Amino Esters



Entry	Amine	Product	Yield (%)[a,b]	Yield (%)[a,c]
1	 **4**	 **12**	45	57
2	 **5**	 **13**	32	67
3	 **6**	 **14**	30	92
4	 **7**	 **15**	27	46
5	 **8**	 **16**	26	52
6	 **9**	 **17**		51
7	 **10**	 **18**		51
8	 **11**	 **19**		32

[a] Isolated yield.
[b] Conditions: 1.2 equiv of Na ascorbate were used.
[c] Conditions: 4 equiv of ascorbic acid were used.

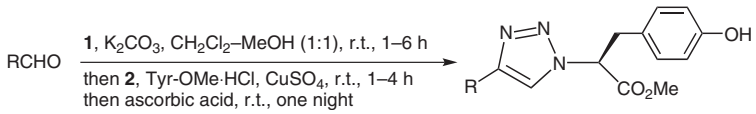
ions.[26] As azide precursors, natural amino acids derivatives were chosen in order to obtain fluorescent amino acids derivatives. Compound **3** was treated with 1.8 equivalents of the Bestmann–Ohira reagent (**1**) and 4 equivalents of K_2CO_3 in a 1:1 mixture of CH_2Cl_2 and MeOH at room temperature. Upon complete homologation of the aldehyde (TLC monitoring, 6 h), amine·HCl (1.2 equiv), $CuSO_4$ (1.2 equiv), and imidazole-1-sulfonyl azide **2** (1.2 equiv) were then added to the reaction mixture. After disappearance of **2** on TLC (1–4 h), sodium ascorbate (1.2 equiv) was then introduced to accomplish the cycloaddition. As shown in the Table 1, for amino esters **4**–**8**, the corresponding triazoles were isolated in 27–45% yields (entries 1–5). Careful examination of the literature data showed that basic conditions could influence the CuAAC and favor the formation of byproducts.[27] Since the CuAAC is usually realized under neutral conditions with $CuSO_4$/Na ascorbate as catalyst, we decided to introduce ascorbic acid in place of sodium ascorbate during the third step, to neutralize the reaction mixture (K_2CO_3 in excess) and reduce Cu(II) to Cu(I). Improved yields were thus obtained; compounds **12**–**16** being isolated in 46–92% yield.[28] For the amino esters of Asp and Tyr **9** and **10** (entries 6 and 7), the corresponding triazoles were obtained in 51% yield. One-pot reaction of the dipeptide **11** led also to the corresponding triazole **19** in 32% yield (entry 8).

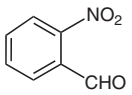
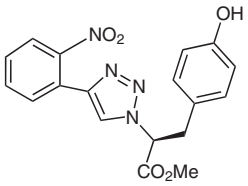
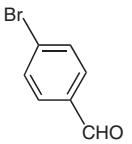
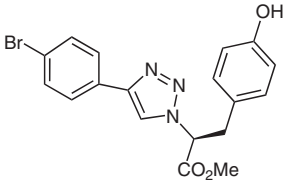
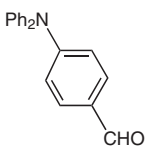
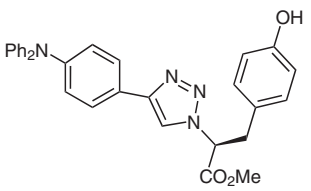
We subsequently tested the scope of this one-pot process with other aromatic aldehydes (Table 2). Reaction of aldehydes **20**–**22** with Tyr-OMe led successfully to the corresponding triazoles **23**–**25** in 45–75% yields.

Synthesis of triazole-linked glycopeptides and oligosaccharides has recently been reported, providing useful building blocks or mimetics of natural ones.[29] We therefore also examined the possibility of preparing glycoconjugates by this one-pot procedure. Treatment of galactosyl aldehyde **26** with Tyr-OMe led to the desired glycosyl derivative **27** in 49% yield (Scheme 1). Reaction of aldehyde **26** with the *C*-glycosyl ethylamine **28**[30] afforded the corresponding triazole-linked *C*-disaccharide **29**.

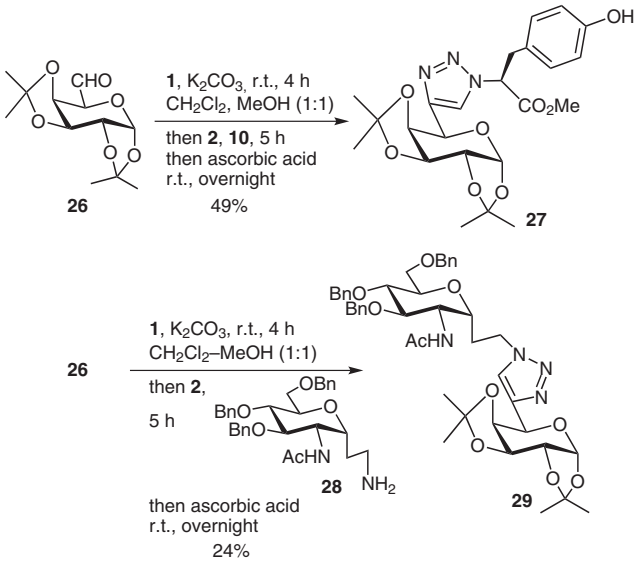
In summary, a one-pot, three-step sequential synthesis of triazoles has been developed from various aldehydes and amines. To the best of our knowledge, the present work is the first example of in situ generation of both terminal alkyne and organic azide for the click reaction. Not only aryl aldehydes, but also glycosyl aldehydes can be used as alkyne precursors. As azide precursors, amino esters, dipeptides as well as *C*-glycosyl amines have been proven successful. We have demonstrated that this procedure can be used for the synthesis of fluorescent amino acid and peptide derivatives and for the synthesis of glycoconjugate mimetics.

Table 2 One-Pot, Three-Step Synthesis of 1,2,3-Triazoles from Tyr-OMe·HCl and Aldehydes



Entry	Aldehyde	Product	Yield (%)[a]
1	 **20**	 **23**	75
2	 **21**	 **24**	57
3	 **22**	 **25**	45

[a] Isolated yield.



Scheme 1 One-pot, three-step synthesis of glycoconjugates

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

(2) Selected reviews: (a) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51. (b) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (c) Lutz, J. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1018. (d) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278. (e) Moorhouse, A. D.; Moses, J. E. *ChemMedChem* **2008**, *3*, 715.

(3) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674.

(4) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188.

(5) (a) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897. (b) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223. (c) Demaray, J. A.; Thuener, J. E.; Dawson, M. N.; Sucheck, S. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4868. (d) Durugkar, K. A.; Gonnade, R. G.; Ramana, C. V. *Tetrahedron* **2009**, *65*, 3974.

(6) (a) Odlo, K.; Høydahl, E. A.; Hansen, T. V. *Tetrahedron Lett.* **2007**, *48*, 2097. (b) Sudhir, V. S.; Baig, R. B. N.; Chandrasekaran, S. *Eur. J. Org. Chem.* **2008**, 2423. (c) Kumar, D.; Patel, G.; Reddy, V. B. *Synlett* **2009**, 399.

(7) Kumar, D.; Reddy, V. B.; Varma, R. S. *Tetrahedron Lett.* **2009**, *50*, 2065.

(8) Tao, C.-Z.; Cui, X.; Li, J.; Liu, A.-X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, *48*, 3525.

(9) (a) Yadav, J. S.; Reddy, B. V. S.; Reddy, G. M.; Chary, D. N. *Tetrahedron Lett.* **2007**, *48*, 8773. (b) Kumaraswamy, G.; Ankamma, K.; Pitchaiah, A. *J. Org. Chem.* **2007**, *72*, 9822.

(10) Sreedhar, B.; Reddy, P. S.; Krishna, V. R. *Tetrahedron Lett.* **2007**, *48*, 5831.

(11) Yadav, J. S.; Reddy, B. V. S.; Chary, D. N.; Reddy, Ch. S. *Tetrahedron Lett.* **2008**, *49*, 2649.

(12) Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331.

(13) Beckmann, H. S. G.; Wittmann, V. *Org. Lett.* **2007**, *9*, 1.

(14) Moorhouse, A. D.; Moses, J. E. *Synlett* **2008**, 2089.

(15) (a) Luvino, D.; Amalric, C.; Smietana, M.; Vasseur, J.-J. *Synlett* **2007**, 3037. (b) Baxendale, I. R.; Ley, S. V.; Mansfield, A. C.; Smith, C. D. *Angew. Chem. Int. Ed.* **2009**, *48*, 4017.

(16) (a) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett.* **2008**, *10*, 2409. (b) Campbell-Verduyn, L.; Elsinga, P. H.; Mirfeizi, L.; Dierckx, R. A.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, *6*, 3461.

(17) Zhang, F.; Moses, J. E. *Org. Lett.* **2009**, *11*, 1587.

(18) (a) David, O.; Maisonneuve, S.; Xie, J. *Tetrahedron Lett.* **2007**, *48*, 6527. (b) Maisonneuve, S.; Fang, J.; Xie, J. *Tetrahedron* **2008**, *64*, 8716. (c) Lin, L.; Shen, Q.; Chen, Q.-R.; Xie, J. *Bioorg. Med. Chem.* **2008**, *16*, 9757. (d) Cheng, K. G.; Liu, J.; Liu, X. F.; Li, H. L.; Sun, H. B.; Xie, J. *Carbohydr. Res.* **2009**, *344*, 841. (e) Li, C.; Tang, J.; Xie, J. *Tetrahedron* **2009**, *65*, 7935.

(19) (a) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. (b) Pietruszka, J.; Witt, A. *Synthesis* **2006**, 4266.

(20) (a) Alper, P. B.; Hung, S.-C.; Wong, C.-H. *Tetrahedron Lett.* **1996**, *34*, 6029. (b) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773.

(21) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797.

(22) During the preparation of this manuscript, Smith et al. published the one-pot synthesis of triazoles from amines and alkynes with imidazole-1-sulfonyl azide hydrochloride as diazo-transfer reagent: Smith, N. M.; Greaves, M. J.; Jewell, R.; Perry, M. W. D.; Stocks, M. J.; Stonehouse, J. P. *Synlett* **2009**, 1391.

(23) (a) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038. (b) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046. (c) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347. (d) Cassidy, M. P.; Raushel, J.; Fokin, V. V. *Angew. Chem. Int. Ed.* **2006**, *45*, 3154. (e) Yoo, E. J.; Ahlquist, M.; Kim, S. H.; Bae, I.; Fokin, V. V.; Sharpless, K. B.; Chang, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 1730.

(24) (a) Winnik, F. M. *Chem. Rev.* **1993**, *93*, 587. (b) Abreu, A. S.; Castanheira, E. M. S.; Ferreira, P. M. T.; Monteiro, L. S.; Pereira, G.; Queiroz, M.-J. R. P. *Eur. J. Org. Chem.* **2008**, 5697.

(25) Wang, G.; Bobkov, G. V.; Mikhailov, S. N.; Schepers, G.; Van Aerschot, A.; Rozenski, J.; Van der Auweraer, M.; Herdewijn, P.; De Feyter, S. *ChemBioChem* **2009**, *10*, 1175.

(26) Xie, J.; Ménand, M.; Maisonneuve, S.; Métivier, R. *J. Org. Chem.* **2007**, *72*, 5980.

(27) Angell, Y.; Burgess, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 3649.

(28) **General Procedure**
To a solution of aldehyde (1 equiv) in a mixture MeOH–CH_2Cl_2 (4 mL/4 mL for 0.5 mmol of aldehyde) were added K_2CO_3 (4 equiv) and the Bestmann–Ohira reagent (1.8 equiv). The mixture was stirred at r.t. until complete conversion of aldehyde to alkyne (TLC monitoring – 6 h maximum). Amine hydrochloride salt (1.2 equiv), $CuSO_5{\cdot}5H_2O$ (1.2 equiv) and the imidazole-1-sulfonyl azide (1.2 equiv) were then added to the reaction mixture and stirred at r.t. to transform the amine into the azide intermediate. Reaction was judged to be complete when imidazole-1-sulfonyl azide spot disappeared on TLC (4 h maximum). Finally, ascorbic acid (4 equiv) was added, and the reaction was stirred at r.t. overnight. The mixture was filtered through a pad of Celite, washed with MeOH, and the

solvents evaporated under vacuum. The residue was purified by column chromatography on silica gel (40–63 μM) to afford the triazoyl compound.

Analytical Data for Selected Compounds

Compound **12**: mp 191 °C; R_f = 0.55 (EtOAc–cyclohexane = 1:1); $[\alpha]_D$ –89.2 (*c* 0.48, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 5.37 (s, 2 H, CH_2), 8.01–8.29 (m, 9 H), 8.67 (d, 1 H, *J* = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.0 (CH_2), 53.3 (CH_3), 124.3, 124.7, 125.0, 125.3, 126.2, 127.3, 127.5, 128.0, 128.4, 128.7 (CH), 131.0, 131.4, 131.5, 148.0, 166.9 (C). ESI-HRMS: *m/z* calcd for $C_{21}H_{15}N_3NaO_2$: 364.1062; found: 364.1057.

Compound **29**: mp 114 °C; R_f = 0.48 (EtOAc); $[\alpha]_D$ –35.2 (*c* 0.47, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 3 H), 1.36 (s, 3 H), 1.45 (s, 3 H), 1.60 (s, 3 H), 1.83 (s, 3 H), 1.83–2.01 (m, 2 H), 3.52–3.53 (m, 1 H), 3.61–3.63 (m, 1 H), 3.67 (dd, 1 H, *J* = 6.4, 10.1 Hz), 3.90 (dd, 1 H, *J* = 7.4, 10.1 Hz), 3.95–3.97 (m, 1 H), 4.11–4.13 (m, 1 H), 4.25 (t, 1 H, *J* = 6.8 Hz), 4.37 (dd, 1 H, *J* = 2.8, 5.0 Hz), 4.39–4.51 (m, 6 H), 4.55–4.59 (m, 3 H), 4.70 (dd, 1 H, *J* = 2.3, 7.8 Hz), 5.19 (d, 1 H, *J* = 1.8 Hz), 5.60 (d, 1 H, *J* = 5.0 Hz), 6.60 (d, 1 H, *J* = 9.6 Hz), 7.20–7.33 (m, 15 H), 7.65 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4, 24.3, 25.1, 26.1, 26.3 (CH_3), 32.4, 46.9 (CH_2), 47.8, 64.7, 65.3 (CH); 67.6 (CH_2), 70.8, 70.9 (CH); 72.0, 72.3 (CH_2), 72.7, 73.2 (CH), 73.4 (CH_2), 74.2, 75.1, 77.3 (CH), 96.7 (CH), 109.0, 109.3 (C), 123.6, 127.8, 127.9, 128.6, 128.7 (CH), 137.3, 137.5, 138.2, 145.1, 170.0 (C). ESI-HRMS: *m/z* calcd for $C_{44}H_{54}N_4NaO_{10}$: 821.3738; found: 821.3732.

(29) Dondoni, A. *Chem. Asian J.* **2007**, *2*, 700.
(30) Xie, J.; Thellend, A.; Becker, H.; Vidal-Cros, A. *Carbohydr. Res.* **2001**, *334*, 177.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.