Fast Microwave-Assisted Preparation of Aryl and Vinyl Nitriles and the Corresponding Tetrazoles from Organo-halides

Mathias Alterman and Anders Hallberg*

Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, Uppsala University, Box 574, SE-751 23 Uppsala, Sweden

Anders.Hallberg@farmkemi.uu.se

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Aryl and vinyl nitriles have been prepared in very high yields from the corresponding bromides using palladium-catalyzed reactions with microwave irradiation employed as the energy source. Furthermore, flash heating was used successfully for the conversion of these nitriles into aryl and vinyl tetrazoles by cycloaddition reactions. One-pot transformation of aryl halides directly to the aryl tetrazoles could be accomplished both in solution and on solid support. All reactions were completed in minutes rather than in hours or days as previously reported with the standard thermal heating technique. A very potent HIV-1 protease inhibitor ($K_i = 0.56$ nM), comprising two tetrazole heterocycles as carboxyl group bioisosteres, was prepared in one pot by microwave-promoted cyanation of a bromo precursor and a subsequent cycloaddition reaction. The temperature−time profiles at 13, 20, and 60 W magnetron input power in DMF are presented.

Introduction

Nitriles are valuable intermediates in organic synthesis and can be transformed to yield a broad spectrum of functionalities, e.g., thiazoles, oxazolidones, triazoles, and tetrazoles.[1] Tetrazoles are of particular interest to the medicinal chemist since they probably constitute the most commonly used bioisostere of the carboxyl group.[2] Thus, a retained pharmacological effect and a more favorable pharmacokinetic profile are often achieved by the replacement of a carboxyl group with a metabolically stable tetrazole.

There are several methods available for the preparation of nitriles,[1a,3] and among these, considerable research efforts have been devoted to the direct transition metal-catalyzed conversion of aryl halides to aryl nitriles.[3e−n] Aryl halides are attractive as starting materials in lead optimization processes since they can serve as precursors for a plethora of diverse reactions. In 1994, Tschaen et al. reported an improvement of the palladium-catalyzed cyanation of aryl bromides where zinc cyanide was exploited as the cyanide source.[3h] Reaction times of 5−7 h were reported. Also the subsequent transformation to tetrazoles need long reaction times for completion, often days when electron-rich aryl nitriles were employed.[2a,4]

The rapid development of combinatorial and robotized parallel synthesis has led to a growing demand for fast reactions and efficient purification procedures. We herein report that flash heating by microwave irradiation[5] allows for the formation of aryl and vinyl nitriles[6] from the corresponding halides and the further conversion of

(1) (a) Larock, R. C. *Comprehensive Organic Transformations. A Guide to Functional Group Preparations*; VCH Publishers: New York, 1989. (b) Khanna, I. K.; Weier, R. M.; Yu, Y.; Xu, X. D.; Koszyk, F. J.; Collins, P. W.; Koboldt, C. M.; Veenhuizen, A. W.; Perkins, W. E.; Casler, J. J.; Masferrer, J. L.; Zhang, Y. Y.; Gregory, S. A.; Seibert, K.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1634−1647. (c) Judkins, B. D.; Allen, D. G.; Cook, T. A.; Evans, B.; Sardharwala, T. E. *Synth. Commun.* **1996**, *26*, 4351−4367. (d) Chihiro, M.; Nagamoto, H.; Takemura, I.; Kitano, K.; Komatsu, H.; Sekiguchi, K.; Tabusa, F.; Mori, T.; Tominaga, M.; Yabuuchi, Y. *J. Med. Chem.* **1995**, *38*, 353−358. (e) Diana, G. D.; Cutcliffe, D.; Volkots, D. L.; Mallamo, J. P.; Bailey, T. R.; Vesico, N.; Oglesby, R. C.; Nitz, T. J.; Wetzel, J.; Giranda, V.; Pevear, D. C.; Dutko, F. J. *J. Med. Chem.* **1993**, *36*, 3240−3250. (f) Medwid, J. B.; Paul, R.; Baker, J. S.; Brockman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A.; Tarrant, M. E.; Torley, L. W.; Wrenn, S. *J. Med. Chem.* **1990**, *33*, 1230−1241.

(2) (a) Wittenberger, S. J. *Org. Prep. Proced. Int.* **1994**, *26*, 499−531. (b) Hodges, J. C.; Hamby, J. M.; Blankley, C. J. *Drugs Future* **1992**, *17*, 575−593. (c) Singh, H.; Chawla, A. S. C.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151−183.

(3) (a) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1992. (b) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779−794. (c) Friedrich, K., Wallenfels, K., Rappoport, Z., Ed.; Interscience: New York, 1970; pp 92−93. (d) Patai, S., Zabicky, J., Ed.; John Wiley & Sons: New York, 1970. (e) Okano, T.; Kiji, J.; Toyooka, Y. *Chem. Lett.* **1998**, 435−426. (f) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224−8228. (g) Andersson, Y.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1395−1400. (h) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887−890. (i) Sosnovsky, G.; Krogh, J. A. *Synthesis* **1978**, 703−705. (j) Yamamura, K.; Murahashi, S. *Tetrahedron Lett.* **1977**, *50*, 4429−4430. (k) Sekiya, A.; Ishikawa, N. *Chem. Lett.* **1975**, 277−278. (l) Takagi, K.; Okamoto, T.; Sakaibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298−3301. (m) Fizet, C.; Streith, J. *Tetrahedron Lett.* **1974**, *36*, 3187−3188. (n) Corey, E. J.; S., H. L. *J. Am. Chem. Soc.* **1969**, *91*, 1233−1234.

(4) (a) Curran, D. P.; Hadida, S.; Kim, S. *Tetrahedron* **1999**, *55*, 8997−9006. (b) Jursic, B. S.; LeBlanc, B. W. *J. Heterocycl. Chem.* **1998**, *35*, 405−408. (c) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis* **1998**, 910−914. (d) LeBlanc, B. W.; Jursic, B. S. *Synth. Commun.* **1998**, *28*, 3591−3599.

(5) (a) The dissipation factor (tan δ) expresses the ability of a material to transform electromagnetic energy into thermal energy at a given temperature and frequency. A higher value for the tan δ indicates a higher susceptibility to microwave energy. Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, M. P. *Chem. Soc. Rev.* **1998**, *27*, 213−223. (b) Langa, F.; De La Cruz, P.; De La Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* **1997**, 373−386. (c) Caddick, S. *Tetrahedron* **1995**, *51*, 10403−10432. (d) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev.* **1991**, *20*, 1−47.

(6) For microwave-promoted synthesis of aryl nitriles (1) from aldehydes, see (a) Das, B.; Madhusudhan, P.; Venkataiah, B. *Synlett* **1999**, *10*, 1569−1570. (b) Chakraborti, A. K.; Kaur, G. *Tetrahedron* **1999**, *55*, 13265−13268. (c) Feng, J.; Liu, B.; Dai, L.; Bain, N. *Synth. Commun.* **1998**, *28*, 3765−3768. (d) Bose, D. S.; Narsaiah, A. V. *Tetrahedron Lett.* **1998**, *39*, 6533−6534. (2) From amides, see (e) Bose, D. S.; Jayalakshimi, B. *J. Org. Chem.* **1999**, *64*, 1713−1714. (3) From aldoximes, see (f) Sabitha, G.; Syamala, M. *Synth. Commun.* **1998**, *28*, 4577−4580.

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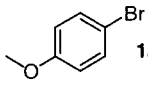
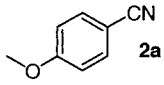
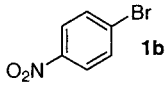
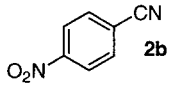
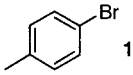
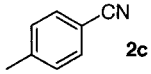
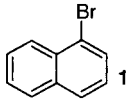
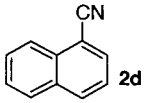
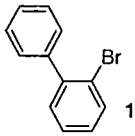
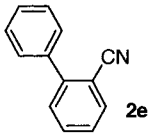
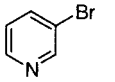
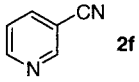
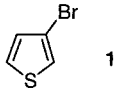
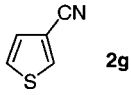
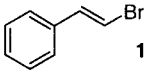
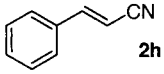
Table 1. Microwave-Promoted Cyanation Reactions with Organo-bromides

Entry	Organo Bromide	Time (min)/ Effect (W)	Product	Isolated Yield (%)	Thermal heating Time (h)	Thermal heating Yield (%)
1	 **1a**	2/60	 **2a**	81	7	95[3h]
2	 **1b**	2/60	 **2b**	78	6	92[3h]
3	 **1c**	2/60	 **2c**	90	6	84[3h]
4	 **1d**	2/60	 **2d**	90	4	97[3f]
5	 **1e**	2/60	 **2e**	95		
6	 **1f**	2/60	 **2f**	88	4	71[3f]
7	 **1g**	2.5/60	 **2g**	80	16	89[18]
8	 **1h**	2/60	 **2h**	93	2	94[3j]

these nitriles to tetrazoles,[7] either in solution or on solid phase, in minutes rather than hours or days. Furthermore, the microwave-assisted synthesis of a potent HIV-1 protease inhibitor, comprising tetrazole rings, which is a target in an ongoing medicinal chemistry program,[8] is reported.

Results

The reactions were performed in a commercially available single-mode microwave cavity in sealed heavy-walled Pyrex tubes. The organo-bromides **1a**−**h** were reacted with 1 equiv of $Zn(CN)_2$ in DMF with $Pd(PPh_3)_4$ as catalyst. All bromides were consumed after 2 min at a magnetron input power of 60 W, with the exception of the electron-rich thiophene **1g** that required a somewhat longer reaction time, 2.5 min, for full conversion. A reaction temperature of 175 °C was reached after 2.5 min at 60 W, as deduced by temperature measurement using a fluoroptic probe. The preparative results are summarized in Table 1. After chromatography the nitriles **2a**−**h** were isolated in good yields. Corresponding reaction times and yields from reports on the preparation of the nitriles from the corresponding bromides by thermal heating, and in some cases by alternative methods are presented in the table for comparison.

The nitriles **2a**−**h** were converted to tetrazoles by treatment with sodium azide and ammonium chloride in DMF, rather than by employing alkyltin or alkylsilicon azide reagents, which would require a subsequent deprotection step. The sodium azide procedure allowed for a facile purification but is known to be accompanied by the sublimation of explosive ammonium azide.[9] The results are presented in Table 2. A microwave power of 20 W was applied to avoid formation of the side products that tended to be produced with greater irradiation. Despite the relatively low power, a temperature of 220 C° was reached already after 10 min, most likely attributed to the high salt concentration.[10] The reaction times varied from 10 to 25 min. The yields were generally good and comparable to those previously reported, although the sterically hindered ortho-substituted biphenyl **3e**, comprising the common fragment in many angiotensin II antagonists,[2b] was isolated in only moderate yield. The yield with **3e** was considerably lower than that achieved by other methods, i.e., using trimethylsilyl azide/trimethyaluminum, and standard thermal heating.[11] Starting material (**2e**) remained after 25 min of microwave heat-

(7) For a microwave-promoted preparation of a tetrazole from a 2-azido-4-methylquinoline, see Kidwai, M.; Goel, Y.; Kumar, R. *Indian J. Chem.* **1998**, *37B*, 174−179.

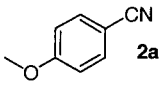
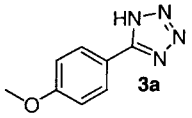
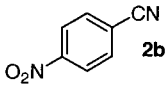
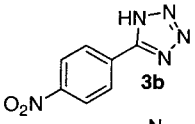
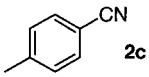
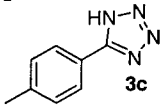
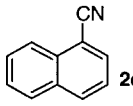
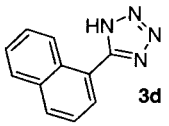
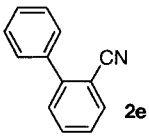
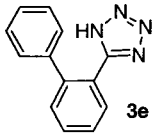
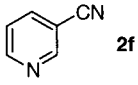
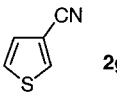
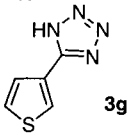
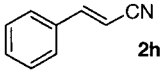
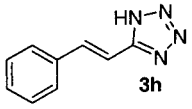
(8) (a) Alterman, M.; Andersson, H. O.; Garg, N.; Ahlsén, G.; Lövgren, S.; Classon, B.; Danielson, U. H.; Kvarnström, I.; Vrang, L.; Unge, T.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 3835−3844. (b) Alterman, M.; Björsne, M.; Mühlman, A.; Classon, B.; Kvarnström, I.; Danielson, H.; Markgren, P. O.; Nillroth, U.; Unge, T.; Hallberg, A.; Samuelsson, B. *J. Med. Chem.* **1998**, *41*, 3782−3792.

(9) Although no explosion occurred in any of the described examples only microwave cavities enclosed in a safety metal case and a reaction vessel with a pressure releasing septa should be used. In fact, even experiments with no inert atmosphere were safely performed.

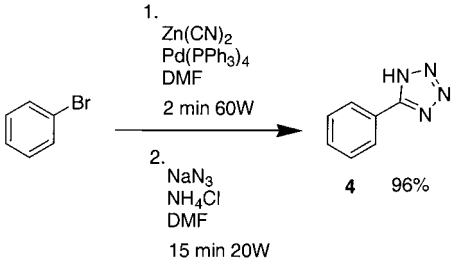
(10) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665−1692.

(11) Huff, B. E.; Staszak, M. A. *Tetrahedron Lett.* **1993**, *34*, 8011−8014.

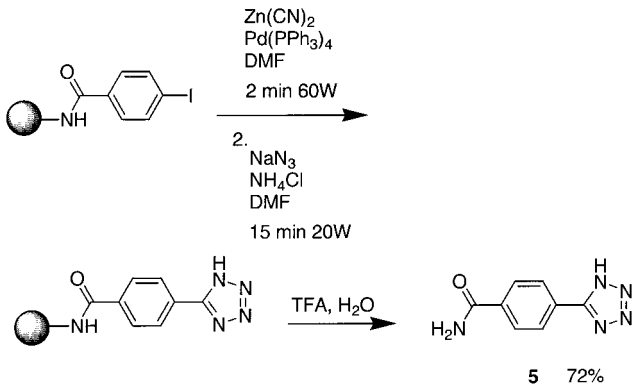
Table 2. Microwave-Promoted Cycloaddition Reactions with Organo-nitriles

Entry	Organo nitrile	Time (min)/ Effect (W)	Product	Isolated Yield (%)	Thermal heating Time (h)	Thermal heating Yield (%)
1	 **2a**	25/20	 **3a**	96	24	68[12]
2	 **2b**	10/20	 **3b**	95	3	97[19]
3	 **2c**	15/20	 **3c**	91	7	97[4c]
4	 **2d**	15/20	 **3d**	48	96	35[20]
5	 **2e**	25/20	 **3e**	36	72	72[11]
6	 **2f**	15/20	 **3f**	75	7	75[12]
7	 **2g**	15/20	 **3g**	98		
8	 **2h**	15/20	 **3h**	60		

Scheme 1



Scheme 2



ing. A longer reaction time or alternatively higher power input led to the formation of side products, and no improvement of the isolated yield was observed. On the other hand the microwave irradiation provided the electron rich tetrazole **3a** from **2a** in a better yield than previously reported.[12]

Bromobenzene can be converted to 5-phenyltetrazole **4** by a convenient one-pot procedure, which delivers a very high total yield (Scheme 1). The microwave-promoted heating technique is apparently also suitable for conversions of iodides to tetrazoles on solid support as demonstrated in Scheme 2 where a Rink linker on Tentagel was used as solid support. A high yield of the aryl tetrazole **5** was isolated after cleavage from the resin, and only a negligible decomposition of the solid support had occurred.

A potent C_2-symmetric HIV-1 protease inhibitor (**7**, K_i = 0.56 nM) with two carboxyl group bioisosteres, designed to interact with Arg 8/Arg 108 of the enzyme,[8a] was prepared in one pot from the corresponding aryl bromo precursor **6** (Scheme 3). It is notable that the bisfunctionalization could be accomplished smoothly in good yield and that no side products derived by, for example, elimination of water were detected. Cycloaddition with ammonium azide in DMF is recognized to

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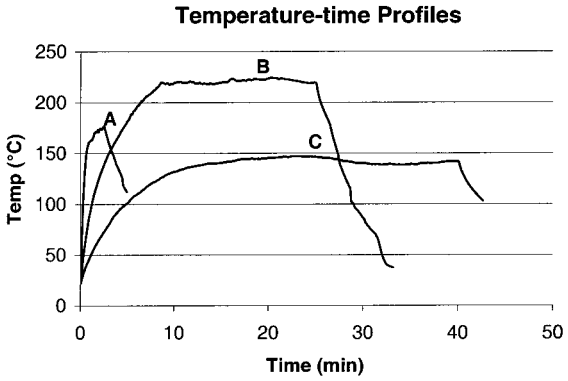


Figure 1. Curve A: 60 W, 2.5 min, DMF, 4-bromoanisole, $Zn(CN)_2$, $Pd(PPh_3)_4$; Curve B: 20 W, 25 min, DMF, 4-methoxybenzonitrile, NaN_3, NH_4Cl; Curve C: 13 W, 40 min, DMF, **6**, NaN_3, NH_4Cl.

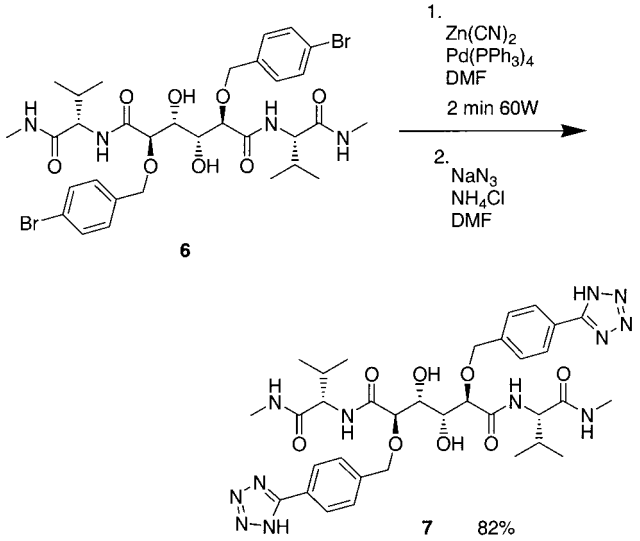
produce side products and to provide a less suitable combination for the preparation of larger polyfunctional molecules.[4b]

Discussion

Microwave irradiation has been much exploited as a heating source for organic reactions. Recently, the Heck, Stille, and Suzuki reactions, that often need hours or days for completion with the standard thermal heating technique, as deduced from literature data, were executed in a few minutes and delivered high yields by employing flash heating with microwave irradiation.[13] These reactions involve labile organopalladium complexes as key intermediates. The related cyanation, proceeding by an oxidative addition of palladium(0) and a subsequent reductive elimination, could be accomplished in DMF (tan $\delta = 0.16$)[5a] at the same relatively high magnetron input power (60 W) as the other palladium-catalyzed reactions. On the other hand, cycloaddition reactions performed with the same power input (60 W) led to complex mixtures of products, with low power and somewhat longer reaction times providing a more satisfying outcome. Thus, the best balance between microwave power and irradiation time must be carefully determined for each individual reaction type. Even though a power of only 20 W was employed for cycloaddition reactions, a high reaction temperature (220 °C after 10 min) and a considerable superheating (bp of DMF = 153 °C) were noted. In Figure 1 the temperature profiles in the septum-sealed reaction mixtures at 60, 20, and 13 W in DMF are presented.

By the in situ mode of energy conversion, microwaves enable the heating of a reaction mixture very rapidly, directly and uniformly if single-mode microwave cavities are used.[14] No problems related to heat transfer through the walls of the reaction vessels are to be expected.[15] The overall advantage of microwave heating is attributable to the direct rapid in situ heating and the bulk superheating that easily can be achieved.[10] These factors alone are thought to account for the accelerated reaction rates. The energy transmitted by the microwave is too small,

Scheme 3



< 0.3 kcal/mol at a output frequency of 2450 MHz, to be responsible for any noteworthy direct molecular activation.[15]

Conclusion

In conclusion, aryl and vinyl nitriles have been prepared very efficiently from the corresponding bromides in palladium-catalyzed reactions where microwave irradiation was employed as the energy source. Flash heating was also used successfully for the fast conversion of these nitriles into aryl and vinyl tetrazoles by cycloaddition reactions. The transformation of aryl halides directly to the aryl tetrazoles in one pot could be accomplished both in solution and on solid support. The reactions were completed in a few minutes and considerably faster than previously reported with standard heating technique. Although only a limited number of examples are given herein, we believe that the flash heating methodology should provide a very attractive alternative to standard thermal heating procedures when organonitriles or tetrazoles are required using aryl and vinyl halides as starting materials.

Experimental Section

General Information. ^1H and ^{13}C NMR spectra were recorded at 270.2 and 67.8 MHz, respectively. Chemical shifts are given as δ values (ppm) downfield from tetramethylsilane. Infrared spectra were recorded on a FTIR instrument equipped with a Microfocus Beam Condenser and compression cell. Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden, and were within ±0.4% of calculated values. Circular chromatography was performed with 1 mm thick silica gel 60 (0.04−0.063 mm) plates and gradient elution. FPLC reversed phase chromatography was performed with a PepRPC 15 μm 30 × 100 mm column. Thin-layer chromatography was performed on precoated silica gel F-254 plates (0.25 mm) and visualized with UV light or H_2SO_4 in ethanol, or ninhydrin. The palladium tetrakis triphenylphosphine was freshly made according to procedure described by Heck.[16] All microwave reactions were carried out in heavy-walled Pyrex tubes, inner diameter 9 mm and height 147 mm, sealed with screw cap fitted Teflon septa. Microwave heating was carried out with a MicroWell 10 single-mode cavity (Labwell AB, Uppsala, Sweden), producing continuous irradiation at 2450 MHz. It is not recommended to repeat these reactions in a

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multimode domestic microwave oven producing nonuniform irradiation. **Caution! It is important to note that when carrying out microwave-heated reactions in closed vessels, quite large pressures may build up, and therefore it is imperative that an appropriate septum is utilized as a pressure relief device.** Temperature profiles were recorded using a NoEMI-TS Reflex (NortechFibronic, Inc.) utilizing temperature-sensitive fluoroptic probes (TPP-01-M2.5-A; Nortech Fibronic). The probe was positioned at the bottom of the reaction tube. Standard workup: organic layers were dried with $MgSO_4$ and concentrated in vacuo. The isolated compounds **2a**,[21] **b**,[22] **c**,[23] **d**,[24] **e**,[25] **f**,[26] **g**,[27] **h**,[28] **3a**,[29] **b**,[29a,30] **c**,[29a,30] **d**,[31] **e**,[32] and **4**[33] have previously been characterized and corresponded satisfactory with NMR literature data. The isolated compounds **3f**,[34]**g**,[35]**h**,[36] have previously been characterized and corresponded satisfactory with literature melting point data, NMR data are provided in Supporting Information. **Caution! Ammonium azide, which might sublimate in reactions with sodium azide and ammonium chloride, is in dry form explosive at temperatures above 136 °C.**

General Procedures for Nitrile-Coupling Reaction (Table 1). A dried heavy-walled Pyrex tube was charged with organo-bromide (0.2 mmol), $Zn(CN)_2$ (23.5 mg, 0.2 mmol), and $Pd(PPh_3)_4$ (6.9 mg, 6.0 μmol) in DMF (1 mL). The reaction mixture was flushed with nitrogen and the screw cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was exposed to microwave irradiation (60 W) for 2 min (for **2g** 2.5 min). The reaction tube was allowed to reach room temperature before the reaction mixture was diluted in EtOAc (60 mL) and washed with water. The organic phase was dried, and the solvent was removed under reduced pressure. The crude product was purified on circular chromatography to give the pure nitrile **2a**,[21] **b**,[22] **c**,[23]**d**,[24] **e**,[25] **f**,[26] **g**,[27] **h**.[28]

General Procedures for Tetrazole Formation (Table 2). A dried heavy-walled Pyrex tube was charged with organo-nitrile (0.1 mmol), NaN_3 (78 mg, 1.2 mmol), and NH_4Cl (64 mg, 1.2 mmol) in DMF (1 mL). The reaction mixture was flushed with nitrogen and the screw cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was exposed to microwave irradiation (20 W) for 10−25 min. The reaction tube was allowed to reach room temperature before the reaction mixture was diluted in saturated $NaHCO_3$ (60 mL) and washed with EtOAc. The water phase was acidified to pH < 1 with concentrated HCl and extracted with $CHCl_3$. The combined organic phases were dried, and the solvent was removed under reduced pressure to give the pure compounds **3a**,[29]**b**,[29a,30] **c**,[29a,30] **d**,[31] **e**,[32] **f**,[34] **g**,[35] **h**.[36]

5-Phenyltetrazole (4), A dried heavy-walled Pyrex tube was charged with bromobenzene (10.5 μL, 0.1 mmol), $Zn(CN)_2$ (11.7 mg, 0.1 mmol), and $Pd(PPh_3)_4$ (11.6 mg, 10 μmol) in DMF (1 mL). The reaction mixture was flushed with nitrogen and the screw cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was exposed to microwave irradiation (60 W) for 2 min. The reaction tube was allowed to reach room temperature. Thereafter the tube was charged with NaN_3 (78 mg, 1.2 mmol) and NH_4Cl (64 mg, 1.2 mmol). The reaction mixture was flushed with nitrogen and the screw cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was once again exposed to microwave irradiation (20 W) for 15 min. The reaction tube was allowed to reach room temperature before the reaction mixture was diluted in sat. $NaHCO_3$ (60 mL) and washed with EtOAc. The water phase was acidified to pH < 1 with concentrated HCl and extracted with $CHCl_3$. The combined organic phase was dried, and the solvent was removed under reduced pressure to give the pure compound **4**.[33]

4-(5-Tetrazolyl)benzenecarboxamide (5), 4-Iodobenzoic acid coupled to TentaGel S Ram (100 mg, 0.25 mmol/g capacity) was added to a dried heavy-walled Pyrex tube.[17] The resin was swollen in DMF (1 mL) for 15 min. Then $Zn(CN)_2$ (2.9 mg, 0.025 mmol) and $Pd(PPh_3)_4$ (2.9 mg, 2.5 μmol) were added. The reaction mixture was flushed with nitrogen and the screw cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was exposed to microwave irradiation (60 W) for 2 min. The reaction tube was allowed to reach room temperature. Thereafter the tube was charged with NaN_3 (19.5 mg, 0.3 mmol) and NH_4Cl (16.0 mg, 0.3 mmol). The reaction mixture was flushed with nitrogen and the screw cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was once again exposed to microwave irradiation (20 W) for 15 min. The reaction tube was allowed to reach room temperature. The resin was collected on a polypropylene filter and washed with DMF, water, DMF, MeOH, and CH_2Cl_2. The resin was transferred to a polypropylene tube, and a TFA:water mixture (25:1, 1 mL) was added. The reaction mixture was turned for 5 min and then filtered through a polypropylene filter. The resin was washed with CH_2Cl_2 and MeOH. The combined filtrate was evaporated and coevaporated with acetonitrile. The residue was dissolved in saturated NH_4OH and was purified using Waters Oasis Extraction Cartridges (HLB6cc) with water (20 mL) as eluent, to give pure **5** in 72% yield: IR (compression cell) ν 3355, 3170, 1658, 1625 cm^{-1}; ^1H NMR (CD_3OD) δ 8.14 (m, 2H), 7.99 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 167.0, 155.5, 136.2, 128.4, 127.2, 126.7. Anal. Calcd for $C_8H_7N_5O$ + 0.3 TFA: C, 46.1; H, 3.3; N, 31.2. Found: C, 46.1; H, 3.6; N, 30.8.

***N*1,*N*6-Bis[(1*S*)-2-methyl-1-(methylcarbamoyl)propyl]-(2*R*,3*R*,4*R*,5*R*)-2,5-bis[4-(5-tetrazolyl)benzyloxy]-3,4-dihydroxyhexanediamide (7),** A dried heavy-walled Pyrex tube was charged with **6**[8a] (30 mg, 0.04 mmol), $Zn(CN)_2$ (13.7 mg, 0.12 mmol), and $Pd(PPh_3)_4$ (5.4 mg, 4.7 μmol) in DMF (1 mL). The reaction mixture was flushed with nitrogen and the screw cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was exposed to microwave irradiation (60 W) for 2.5 min. The reaction tube was allowed to reach room temperature. Thereafter the tube was charged with NaN_3 (61 mg, 0.9 mmol) and NH_4Cl (50 mg, 0.9 mmol). The reaction mixture was flushed with nitrogen and the screw cap tightened thoroughly before mixing with a Whirlimixer. The reaction mixture was once again exposed to microwave irradiation (13

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W) for 40 min. The reaction tube was allowed to reach room temperature before the reaction mixture was diluted in CH_3Cl (60 mL) and washed with 1 M HCl. The organic phase was dried, and the solvent was removed under reduced pressure. The crude product was purified on FPLC, with water:2-propanol 0.1% TFA (1:9 to 3:7), to give 24 mg (82%) of the titled compound as a white solid: IR (KBr) ν 3302, 2927, 2874, 1625, 1539 cm^{-1}; $[\alpha]^{22}_D = -8.3$ ($c = 2.15$, DMSO); ^1H NMR (CD_3OD) δ 7.7 (d, $J = 8.3$ Hz, 4H), 7.57 (d, $J = 8.3$ Hz, 4H), 4.65 (s, 2H), 4.19 (d, $J = 6.9$, 2H), 4.11 (m, 4H), 2.75 (s, 6H), 2.09 (m, 2H), 0.94 (d, $J = 6.8$ Hz, 6H), 0.92 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (DMSO-d_6) δ 171.1, 170.4, 155.2, 141.4, 128.2, 126.9, 123.2, 79.4, 70.5, 69.6, 57.7, 30.5, 25.4, 19.3, 18.1. Anal. Calcd for $C_{34}H_{46}N_{12}O_8 + H_2O$: C, 53.1; H, 6.3; N, 21.9. Found: C, 53.3; H, 6.1; N, 21.5.

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Supporting Information Available: ^{13}C NMR spectra for the compounds **3e**; ^1H and ^{13}C NMR spectra for the compounds **3f**−**h**. This material is available free of charge on the Internet at http://pubs.acs.org.

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