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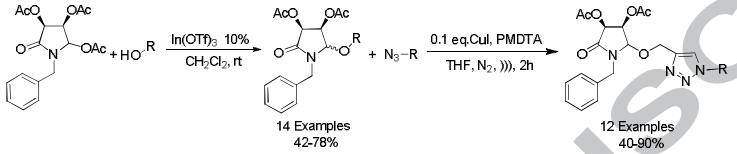

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Ultrasound-assisted Addition of Alcohols to *N*-Acyliminium Ions Mediated by $In(OTf)_3$ and Synthesis of 1,2,3-Triazoles

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ABSTRACT

An easy and mild approach using ultrasound-assisted reaction addition of alcohols to *N*-acyliminium ion mediated by Lewis acid, $In(OTf)_3$, allowed the synthesis of ether pyrrolidinones; next, the products were converted to 1,2,3-triazoles using click chemistry reaction conditions. The products in both reactions were afforded in moderate to good yields.

1. Introduction

N-Acyliminium ions are important intermediates in organic synthesis, mainly in intramolecular reactions;[1] therefore, they have found large use in the synthesis of nitrogen-containing natural and unnatural products of biological interest.[2,3] *N*-Acyliminium ions act as electron-deficient carbocations in reactions with weak nucleophiles.

This reactivity affords exceptionally useful methodologies for carbon–carbon bond formation, both in intermolecular and intramolecular processes.[3] These species have been generated from amides or lactams which bear a good leaving group at the nitrogen atom α-position in acidic media.

Several classes of carbon nucleophiles can react with *N*-acyliminium ions, such as allyl-, alkyl-, aryl-, and alkynylmetals, cyanotrimethylsilane (TMSCN), isonitriles, enol derivatives, and aromatics.[3]

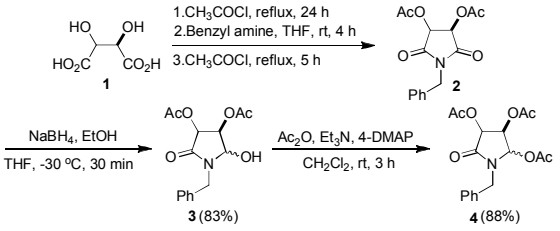
The use of ultrasound to promote chemical reactions is called sonochemistry. The effects of ultrasound observed during organic reactions are due to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressures inside the bubbles (cavities), leading to turbulent flow of the liquid and enhanced mass transfer.[4]

Sonochemistry shares some aims with green chemistry, as it also uses smaller quantities of hazardous chemicals and solvents, reduces energy consumption, and increases product selectivity.

In connection with our research interest on the preparation and reactivity of *N*-acyliminium ions,[5] we wish to report here a general procedure to access various readily available 5-ether-2-pyrrolidinones from the corresponding addition reaction of alcohols to acyliminium ions mediated by $In(OTf)_3$ and further transformation in 1,2,3-triazolyl 2-pyrrolidinone.

Results and Discussion

L-Tartaric acid has proven to be a useful precursor for *N*-acyliminium ion reactions leading to enantiopure pyrrolidine derivatives.[6] The *N*-benzyl imide 2 was prepared from inexpensive *L*-tartaric acid 1, according to a procedure from the literature[7] (Scheme 1).



Scheme 1. Synthesis of *N*-acyliminium ion precursor

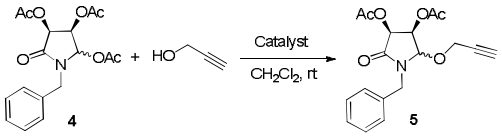
Acid **1** was successively treated with acetyl chloride, benzylamine and acetyl chloride to afford the respective imide **2**. Regio- and stereoselective reduction of imide **2** was accomplished by the reaction with excess sodium borohydride in ethanol/THF at -30°C for 30 min to give the 5-hydroxy- 2-pyrrolidinone derivative **3** as a 95:5 mixture of *syn/anti* diastereoisomers.[7]

After acylation of the alcohol with acetic anhydride, the desired *N*-acyliminium ion precursor **4** was obtained in a good

yield. The stereochemistry of the major *syn*-isomer was determined on thebasis of the *J* (H_4 and H_5) coupling constant of 2.0 Hz.

With the starting material in hand, various Lewis acids were screened for the intermolecular nucleophilic addition to *N*-acyliminium ions by using propargyl alcohol as a model reagent to evaluate the influence of the catalyst in dichloromethane. The most representative results obtained by using Lewis acids are presented in entries 1–7 (Table 1).

Table 1. Screening of the ideal conditions for the addition of propagyl alcohol



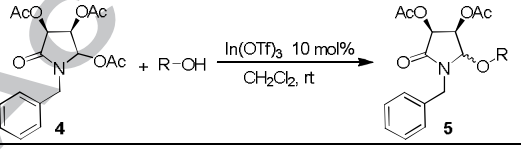
Entry	Catalyst/ mol%	Reaction Time(h)	Yield (%)	Ratio syn/anti
1	$BF_3.Et_2O$/20	4	30	50/50
2	$BF_3.Et_2O$/ 5 equiv	18	60	61/39
3	$Sc(OTf)_3$/10	18	62	30/70
4	$FeCl_3$/10	3	43	36:64
5	$In(OTf)_3$/10	3	75	70:30
6	$Cu(OTf)_3$/10	18	58	16:84
7	$Ag(OTf)_3$/10	18	67	20:80

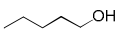
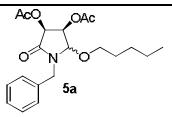
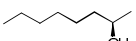
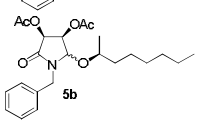
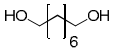
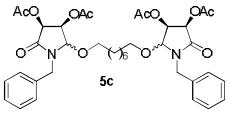
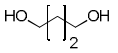
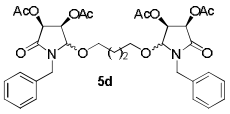
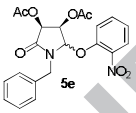
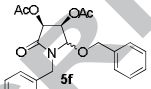
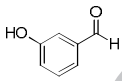
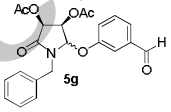
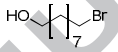
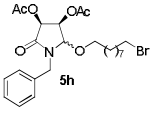
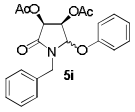
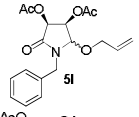
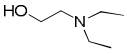
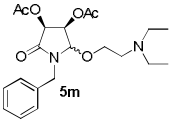
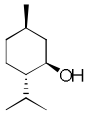
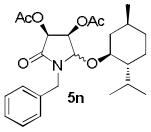
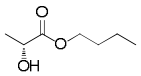
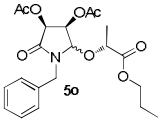
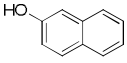
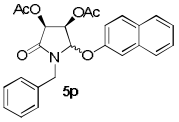
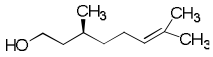
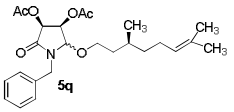
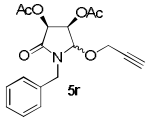
[a]Isolated product

When **4** was reacted with propargyl alcohol in the presence of $BF_3.Et_2O$ (20 mol%), under room temperature in dichloromethane (DCM) for 4 h, the addition product **5** was isolated in 30% yield (entry 1) with a *syn/trans* ratio of 50/50. Increasing the amount of the catalyst $BF_3.Et_2O$ to 5 equiv. observed an increased yield to 60% and a ratio of 61/39, but with a long reaction time (entry 2). In the case of $Sc(OTf)_3$, $FeCl_3$, $Cu(OTf)_3$, and $Ag(OTf)_3$, the yields achieved ranged from 43% to 67% and the ratio of the enantiomer was *anti* majority in all cases. The reaction time was 3 to 18 hours. $In(OTf)_3$ was shown to be the best catalyst, affording the desired product at a yield of 75% and a ratio of 70:30.

Using the conditions from Table 1, entry 5, the scope of the addition reaction was investigated with a variety of alcohols. As shown in Table 2, primary, secondary, and aromatic alcohols were found to react smoothly with *N*-acyliminium ion to give products (**5a**-**5r**) in yields ranging from 42% to 78%.

Table 2 – Scope of the $In(OTf)_3$-catalyzed addition reaction of alcohols and *N*-acyliminium ion



Entry	Alcohol	Compound	Yield(%)[a,b] Ratio *syn/anti*
1		 5a	75 *syn/anti* 10:4
2		 5b	72 *syn/anti* 10:3
3		 5c	54 not determined
4		 5d	42 not determined
5		 5e	nr
6		 5f	78 *syn/anti* 10:7
7		 5g	66 *syn/anti* 10:3
8		 5h	65 *syn/anti* 10:4
9		 5i	70 *syn/anti* 10:2
10		 5l	71 *syn/anti* 10:1
11		 5m	nr
12		 5n	63 *syn/anti* 10:2
13		 5o	67 *syn/anti* 10:2
14		 5p	58 *syn/anti* 10:2
15		 5q	61 *syn/anti* 1:10
16		 5r	75 *syn/anti* 10:7

[a]All the reactions were carried out with **1** (1.2 mmol), **2** (1 mmol), [$In(OTf_3$ 10 %]. [b]Isolated yield. [c]Reaction time: 3 hours.

It was found that the reaction carried out with alkyl alcohols worked well to produce primary and secondary alcohols with almost the same yields (Table 2, entry 1 and 2). The yield dropped when diols with carbon chains with four and eight carbons were reacted, giving yields of 42% and 54% (Table 2, entries 3 and 4). For all other alcohols, the yields were good. Alcohols with another functionality and groups such as phenyl, bromide, allyl, carbocyclic, ester, olefin, and acetylene had yields ranging from 57% to 78% (Table 2, entries 6, 8, 10, 12, 13 and 15, respectively). The reaction was not effective for amino alcohol (Table 2, entry 11).

In the case of aromatic alcohols, including phenols and naphthol (Table 2, entries 5, 7, 9, and 14), the yields ranged from 54% to 70%. The presence of electron-withdrawing groups such as nitro led to no results (Table 2, entry 5) and an acyl group in the aromatic ring was tolerated in the reaction (Table 2, entry 7). The stereochemistry of the newly created stereogenic center in the products was assigned by ^{1}H NMR analysis of the crude reaction mixtures.

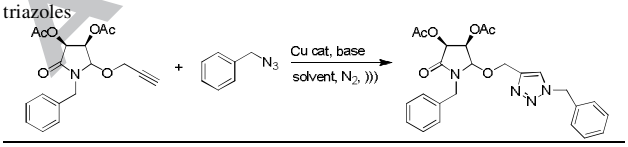
The *syn* relative stereochemistry of the major product was established by analysis of the multiplicity and vicinal coupling constants of the hydrogen attached to the carbon that underwent nucleophilic attack (H-5). In this way, the relative stereochemistry of compounds was assigned by correlation to the chemical shifts and coupling constant data of similar compounds already described in the literature.

For analogous the vicinal coupling constant ^3J (H5–H4) for the *syn*-isomer always has a smaller value than the *anti*-isomer. In addition, the H5 of the *syn*-isomer appears up-field of the *anti*-isomer. These chemical correlations are in full agreement with the major isomer obtained here; thus, the relative stereochemistry of the major isomer was assigned as *syn*.[5b]

As mentioned above, the presence of other functionalities in the alcohols opened up many opportunities for further transformations. Using these advantages, we envisioned the synthesis of 1,2,3-triazole rings through the "click chemistry" approach.[8]

Initially, we focused our attention on the optimization of the reaction conditions, investigating parameters including: copper loading salts, base, additive and solvents. The standard reaction was carried out with propynyl pyrrolidone (Table 2, entry 16) (1.0 mmol), propargyl alcohol (1.5 mmol), CuI (0.1 eq.), PMDETA (1.0 mmol) and dichloromethane (5 mL) as solvent. Using these conditions, the product 1 (Table 4) was obtained in 70% yield. On the other hand, under the same conditions but in the absence of a base, the product was isolated in only 21% yield, thus showing the crucial role of the base in this reaction.

Table 3 - Screening of the ideal reaction condition for synthesize 1,2,3-triazoles.



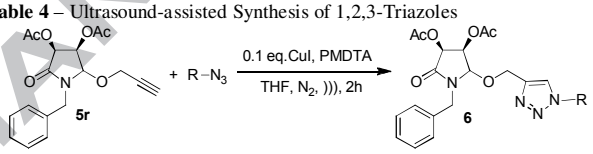
Entry	Cu Cat. (equiv)	Base or additive (1.1 equiv)	Solvent	Yield %
1	CuI (1.0)	-	THF	21
2	CuI (1.0)	PMDTA	THF	68
3	CuCN (1.0)	PMDTA	THF	45
4	$CuSO_4.5H_2O$ (1.0)	PMDTA	THF	37
5	CuI (0.1)	PMDTA	THF	70
6	$Cu(OAc)_2$ (0.1)	PMDTA	THF	58
7	CuCl (0.1)	PMDTA	THF	40
8	$Cu(OTf)_3$ (0.1)	PMDTA	THF	7
9	CuI (0.1)	Na-ascorbate	THF	40
10	$Cu(OAc)_3$	Na-ascorbate	THF	65
11	CuI (0.1)	PMDTA	DCM	67
12	CuI (0.1)	PMDTA	MeOH	28
13	CuI (0.1)	PMDTA	CH_3CN	nr

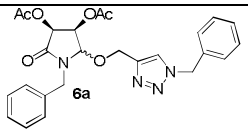
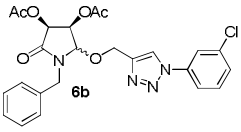
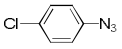
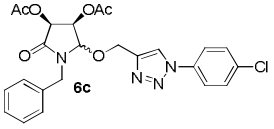
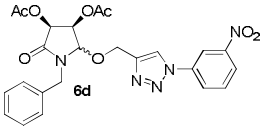
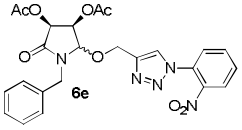
Concerning the amount of copper salt, we carried out the reaction whilst reducing the amount of CuI to 0.1 equiv; the yield was almost the same (70%). Other copper sources were tested, such as CuCl, CuCN, $Cu(OAc)_2$ and $CuSO_4.5H_2O$, but lower results were obtained for all.

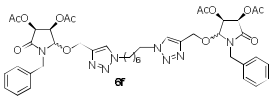
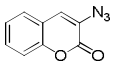
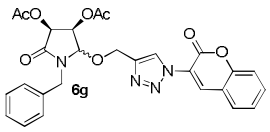
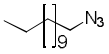
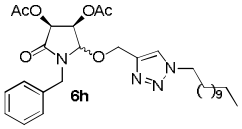
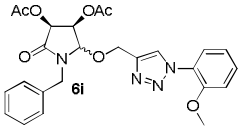
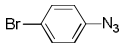
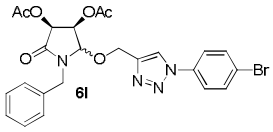
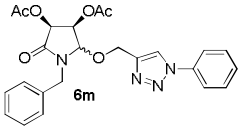
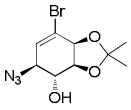
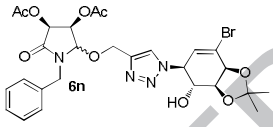
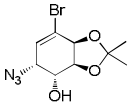
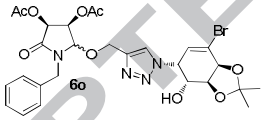
PMDTA was the base only surveyed. The use of sodium ascorbate as an additive did not improve yields, with just low or moderate yields being observed (Table 3, entries 9 and 10), even when 1.1 equivalent was used. The choice of solvent was of paramount importance for the success of the reaction; dichloromethane provided the optimal environment, leading to 67% yield and THF gave a similar yield (Table 3, 70%, entries 5). Low or no yields were obtained with the other solvents such as MeOH and CH_3CN (Table 3, entries 12, 13).

The extension of these conditions to a broader range of organic azides allowed the synthesis of a number of 1,2,3-triazoles in good yields under mild reaction conditions; the most representative results are illustrated in Table 4.

Table 4 – Ultrasound-assisted Synthesis of 1,2,3-Triazoles



Entry	Azide	Product	Yield (%)
1		 6a	70 *syn/anti* 10:7
2		 6b	70 *syn/anti* 10:6
3		 6c	65 *syn/anti* 10:6
4		 6d	63 *syn/anti* 10:7
5		 6e	68 *syn/anti* 10:8

6		 6r	40 *syn/anti* 10:7
7		 6g	nr
8		 6h	78 *syn/anti* 10:7
9		 6i	82 *syn/anti* 10:7
10		 6l	71 *syn/anti* 10:5
11		 6m	90 *syn/anti* 10:7
12		 6n	48 *syn/anti* 10:6
13		 6o	52 *syn/anti* 10:6

When aliphatic azides were employed as the substrates, the corresponding products were obtained in good yields (Table 4, entries 1, 6 and 8). The reaction carried out overnight without ultrasound of benzyl azide (table 4, entry 1) gave a yield of 53%.

Aromatic azides were also used as substrates for Cu(I)-promoted cycloaddition; when phenylazide was employed, the corresponding triazolyl pyrrolidone was obtained in a high yield (90%; Table 4, entry 11). Conversely, substituted aromatic azides, particularly those with electron-withdrawing groups, resulted in good yields ranging from 63% to 71% (Table 4, entries 2-5 and 10). The best result with aromatic azides was achieved with *ortho*-methoxyphenyl azide, which gave the product in an 82% yield (Table 4, entry 9). Substituents in the *ortho, meta* and *para* positions of the aromatic ring seemed to have no effect on the average yield of aromatic azides (Table 4, entries 2-5 and 9-10).

Sugar azides gave only moderate yields of the 1,2,3-triazolyl pyrrolidinone (Table 4, entries 12 and 13). The alkyl diazides afforded the desired product in low yield (40%; Table 4, entry 6), but with a very interesting structure.

Unfortunately, when coumarin azide (Table 4, entry 7) was subjected to this reaction, only starting materials were recovered, even after prolonged reaction times. All of the products[9,10] were characterized by ^{1}H, ^{13}C NMR and high resolution mass spectrometry.

Conclusion

In conclusion, we have demonstrated an efficient addition reaction of primary, secondary, aromatic and alkylic alcohols to *N*-acyliminum anion catalyzed by $In(OTf_3)$, which allows the assembly of a wide range of ethers and 1,2,3-trizole products in moderate to good isolated yields. The transformation in 1,2,3-triazoles by click chemistry is operationally simple, the substrate scope is wide, and the starting materials are readily available. This study not only increased our understanding of the character of the *N*-acyliminum anion but also shed important light on how to further expand its scope and utility.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version.

References and notes

1.Maryanoff, B. E.; Zhang, H-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431-1628.
2.Hubert, J. C.; Wunberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437-1441.
3.a)*N*-acyliminium ion chemistry, see: Koning, H.; Speckamp, W. N. in *Houben-Weyl, Stereoselective Synthesis* (Eds G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann) **1995**, Vol. E21, p. 1953 (Thieme Verlag: Stuttgart). b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817-3856. c) Pilli, R. A.; Russowsky, D. *Trends Org. Chem.* **1997**, *6*, 101-123. d) Zaugg, H. E. *Synthesis* **1984**, 85-110. e) Zaugg, H. E. *Synthesis* **1984**, 181-212.
4.Cella, R.; Stefani, H. A. *Tetrahedron* **2009**, *65*, 2619-2641.
5.a) Vieira, A. S.; Guadagnin, R. C.; Fiorante, P. F.; Ferreira, F. P.; Stefani, H. A. *Tetrahedron* **2008**, *64*, 3306-3314. b) Vieira, A. S.; Ferreira, F. P.; Guarezemini, A. S.; Stefani, H. A. *Aust. J. Chem.* **2009**, *62*, 909-916. c) Caracelli, I.; Ferreira, F. P.; Vieira, A. S.; Stefani, H. A.; De Simone, C. A.; Tiekink, E. R. T. *Acta Cryst. Section E* **2010**, *E66*, o3044. d) Vieira, A. S.; Fiorante, P. F.; Zukerman-Schpector, J.; Alves, D. Botteselle, G. V.; Stefani, H. A. *Tetrahedron* **2008**, *64*, 7234-7241.
6.For reviews of *N*-acyliminium ion chemistry, see: (a) Yazici, A.; Pyne, S. S. *Synthesis* **2009**, *3*, 339–368. (b) Yazici, A.; Pyne, S. S. *Synthesis* **2009**, *4*, 513–541.x.x.209
7.Louwrier, S.; Ostendorf, M.; Bomm, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1996**, *52*, 2603-2628.
8.Wu, P.; Fokin, V. V. *Aldrichim. Acta* **2007**, *40*, 7-17.
9.**General procedure for preparation of** (**2**): To a solution of **1** (1 mmol) in dry dichloromethane (5 mL), $In(OTf)_3$ (0.1 mmol) and propargyl alcohol (1.5 eq) were added at room temperature under N_2. The reaction mixture was stirred at room temperature for 3 h. Then the reaction was washed with water (10 mL), 2-times. The organic phase was dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. The crude product **2** was purified by column chromatography on silica gel using ethyl acetate/hexane (1.5:8.5).

(3*R*,4*R*)-1-benzyl-2-oxo-5-(prop-2-yn-1-yloxy)pyrrolidine-3,4-diyl diacetate - Syn: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.09 (s, 3 H), 2.10 (s, 3 H), 2.35 (t, *J* = 2.35 Hz, 1 H), 4.01 - 4.09 (m, 4 H), 4.93 (t, *J* = 3.20 Hz, 1 H), 5.07 (dd, *J* = 3.49, 1.79 Hz, 1 H), 5.27 (d, *J* = 3.6 Hz, 1 H), 7.25 - 7.29 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 20.5, 20.6, 44.7, 57.6, 71.6, 73.3, 75.7, 78.6, 89.0, 128.0, 128.3 (2C), 128.9 (2C), 135.2, 167.3, 169.8, 170.4.

Anti: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.10 (s, 3 H), 2.11 (s, 3 H), 2.38 (t, *J* = 2.35 Hz, 1 H), 4.01 - 4.09 (m, 4 H), 4.93 (t, *J* = 3.20 Hz, 5 H), 5.00 - 5.05 (m, 1 H), 5.32 (dd, *J* = 7.72, 0.75 Hz, 1 H), 7.25 - 7.29 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 20.5, 20.6, 43.8, 55.8, 72.4, 73.3, 75.7, 78.6, 83.9, 127.9, 128.3 (2C), 128.9 (2C), 135.2, 167.3, 169.6, 169.8. HRMS calcd for $C_{18}H_{19}NO_6$ (M + Na): 368.1116; found: 368.1116. Light yellow oil, yield 75% (260 mg).

10.**General procedure for preparation of 1,2,3-triazoles**: To a solution of (3*R*,4*R*)-1-benzyl-2-oxo-5-(prop-2-ynyloxy)pyrrolidine-3,4-diyl diacetate (1 mmol) in dry THF (5 mL), CuI (0.1 mmol), PMDTA (1.1 mmol) and azide (1.3 mmol) were added at room temperature under N_2. The reaction mixture was sonicated at room temperature for 2 h. The reaction mixture was filtered through Celite®, filtrate was concentrated under reduced vacuum. The concentrate was dissolved in ethyl acetate, extracted with 1 M hydrochloric acid (10 mL x 2). Then organic phase was washed with aqueous $NaHCO_3$ 10 % solution, brine, dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexane (4:6).

(3*R*,4*R*)-1-benzyl-2-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-5-oxopyrrolidine-3,4-diyl diacetate (Table 4, entry 1): ***Syn*** ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.04 (s, 3H), 2.15 (s, 3 H), 4.11 - 4.17 (m, 2 H), 4.68 (s, 2 H), 4.88 (m, 1 H), 5.15 - 5.19 (m, 1H), 5.35 (d, *J* = 3.96 Hz, 1 H), 5.50 (s, 2 H), 7.19 - 7.41 (m, 11 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 20.5, 20.9, 43.8, 54.2, 61.7, 71.6, 73.5, 84.6, 122.8, 127.9 (2C), 128.1 (4C), 129.2 (4C), 129.2(2C), 135.1, 167.1, 169.8, 171.0.

Anti: ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.04 (s, 3 H), 2.18(s, 3H), 4.11 - 4.17 (m, 1H), 4.56 (m, 2H), 4.68 (s, 1H), 4.73-4.74 (m, 1 H), 5.17 - 5.18 (m, 1 H), 5.50 (s, 2 H), 5.71 (d, *J* = 8.90 Hz, 1 H), 7.19 - 7.41 (m, 11 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 20.5, 20.6, 45.0, 54.2, 63.5, 72.6, 75.9, 89.4, 122.5, 127.9 (2C), 128.2 (4C), 129.1 (4C), 134.3(2C), 135.1, 167.2, 169.6, 170.5. HRMS calcd for $C_{25}H_{26}N_4O_6$ (M+Na): 501.1750; found: 501.1759. Light yellow oil, yield 70% (336 mg).