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Desymmetrisation of C_2-symmetric (2*S*,3*S*)-diazidobutane-1,4-diol with benzaldehyde

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Dedicated to Prof. Hans Hofmann on the occasion of his 75th birthday

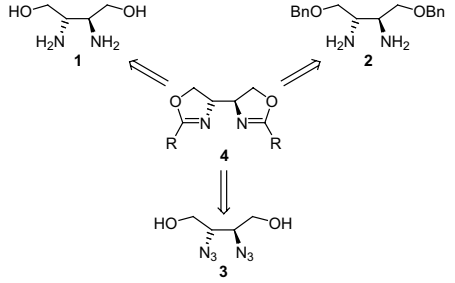
Abstract—Surprisingly, doubly functionalised (2*S*,3*S*)-diazidobutane-1,4-diol under modified Boyer conditions reacted with only 1 equiv of benzaldehyde yielding a mono oxazoline, whereas quantum chemical studies favour the formation of the C_2-symmetric bioxazoline. In addition, the oxazoline formation was indirectly confirmed via detailed NMR studies and X-ray structure analysis of the oxazoline *p*-nitrobenzoic acid ester derivative.

1. Introduction

The first synthesis of achiral bisoxazolines was established in the early sixties by Witte and Seeliger.[1] Phenyl-spaced, achiral bisoxazolines were obtained by reacting aromatic dinitriles with amino alcohols in the presence of a catalytic amount of different M(II)-salts. Subsequently, due to their good donor properties, a large number of optically active enantiomerically pure bisoxazolines were generated and widely used in metal-catalysed asymmetric syntheses.[2]

2. Results and discussion

The initial step in the preparation of bisoxazoline ligands is the condensation of oxalic, malonic or succinic acid chlorides and esters with enantiomerically pure amino alcohols. The intermediate bis(hydroxyl)diamides are subsequently cyclised to the corresponding bisoxazolines with the help of different activating reagents ($SOCl_2/OH^-$,[3a] $MsCl/OH^-$,[3b] Bu_2SnCl_2,[2b] $ZnCl_2$,[1,3c] DAST,[3d] $BF_3{\cdot}OEt_2$,[3e] TfOH,[3f]...). Over the course of our catalysis studies, we intended to prepare novel substituted bioxazolines, where the chirality is incorporated in the backbone of the ligand. Starting from L-tartaric acid, the three differently functionalised chiral building blocks **1**–**3** are accessible.[4] These are potential educts for the synthesis of C_2-symmetric bioxazolines **4** (Scheme 1). Whereas a synthesis starting with diaminodiol **1** did not lead to the parent products **4** (Witte–Seeliger conditions),[5] several substituted bioxazolines **4** (R = alkyl, aryl) were synthesised in a three step sequence starting from **2**,[6] involving a debenzylation reaction, which does not tolerate sensitive functional groups in R.



Scheme 1. Retrosynthetic analysis for the preparation of bioxazolines (*S*,*S*)-**4**.

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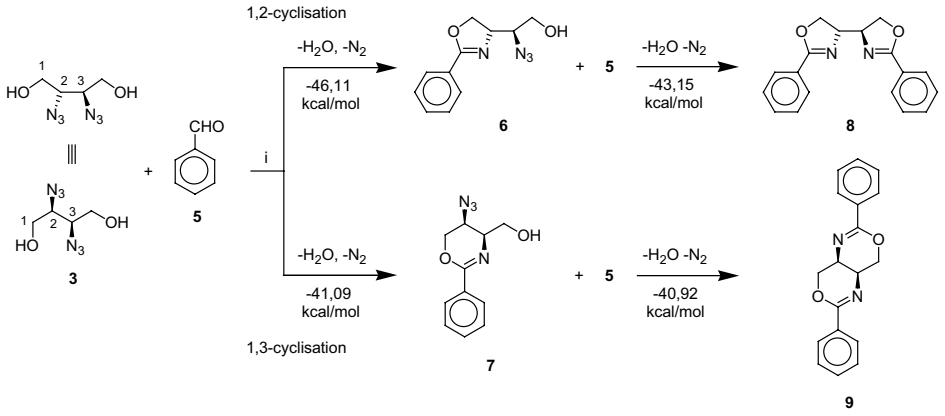


Scheme 2. Synthesis, structures and calculated energies (PM3) for compound **6**–**8**. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, 0 °C to rt, 18 h, CH_2Cl_2.

In order to introduce functionalities in the final step, our attention was drawn to the modified Boyer reaction, reported in 1996 by Aubé.[7] In this case, aldehydes and 1,2- or 1,3-azidoalcohols were converted in the presence of Lewis acids to oxazolines or 5,6-dihydro-4*H*-1,3-oxazines, respectively. Interestingly, for the reaction of C_2-symmetric (2*S*,3*S*)-diazidobutane-1,4-diol **3** with carbonyl compounds, two pathways are conceivable (Scheme 2): reaction as a 1,2-azidoalcohol, leading to five-membered ring product **6**, or as a 1,3-azidoalcohol, resulting in the formation of six-membered ring **7**. Subsequently, in both cases a second carbonyl addition may take place, giving rise to a product with two five-membered rings **8** or with two fused six-membered rings **9**, respectively.

2.1. Quantum chemical calculations

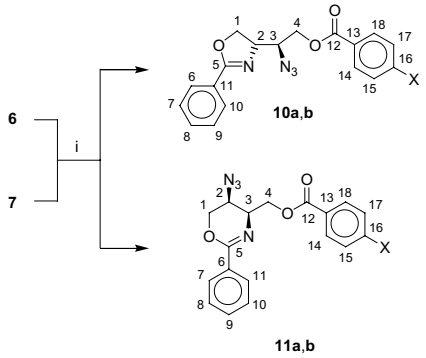
We investigated the two pathways, 1,2- and 1,3-cyclisation leading to **6** or **7** (Scheme 2), using PM3 semi-empirical MO calculations.[8,9] Both pathways are computed to be exothermic. However, five-membered **6** is computed to be 5 kcal/mol more stable than six-membered **7**. The energy difference of 2 kcal/mol between **8** and **9**, generated in the second reaction step, is less pronounced, but still significant. The thermodynamic preference of **8** over **9** amounts to 7.3 kcal/mol starting from **3**. Furthermore, the formation of **6** in the first step is calculated to be only 3 kcal/mol more exothermic than the formation of **8** in the second step. Therefore, a two-step reaction of **3** with benzaldehyde **5** was expected to lead to the desired bioxazoline **8**. Note that these calculations refer to isolated molecules in the gas phase, so computed reaction energies may be inaccurate. Relative energies for the isomeric products, however, can be compared reliably.

2.2. Synthesis

The calculations prompted us to react **3** (CH_2Cl_2 at 0 °C) with 2 equiv of benzaldehyde **5** in the presence of 4 equiv of $BF_3{\cdot}OEt_2$.[7a] To our surprise, the analysis of the spectroscopic data of the purified reaction product indicated that only 1 equiv of benzaldehyde **5** had reacted with (2*S*,3*S*)-diazidobutane-1,4-diol **3** (yield: 86%).[10] This was evident from the MS-CI-spectrum {(CH_4) $[M+H]^+ = 233$}, from the IR-spectrum (remaining OH- and N_3-function, $\tilde{\nu}$ = broad 3369, 2102 cm^{-1}) and from the NMR data (e.g., four signals were observed for the aliphatic carbons in the ^{13}C spectrum). Unfortunately, these spectroscopic data did not allow us to unequivocally distinguish between the two possible mono condensation isomers **6** and **7**. Therefore, the reaction product was esterified with benzoic acid chlorides with either the oxazoline esters **10** or the oxazine esters **11** being expected (Scheme 3).

2.3. NMR studies

A detailed NMR study was carried out in order to distinguish between the formation of **10a** or **11a** (for assignment, use the numbering given in Scheme 3). The experimental ^{13}C NMR data recorded for the reaction product (166.0, 126.9 ppm) almost matched exactly with the values simulated for C5 and C6 of hypothetical **10a** (165.2, 127.1 ppm) by using the CSEARCH software package by Robien.[11] However, the experimental data mismatched the values calculated for C5 and C6 of



Scheme 3. Conversion of hypothetical **6** or **7** into the corresponding benzoic ester derivatives **10a** and **b** or **11a** and **b**. Reagents and conditions: (i) *p*-$NO_2C_6H_4COCl$, NEt_3, CH_2Cl_2, rt, 76%; **10a**, **11a**: X = NO_2; *p*-BrC_6H_4COCl, NEt_3, CH_2Cl_2 rt, 69%; **10b**, **11b**: X = Br.

hypothetical **11a** (156.2, 137.2 ppm). A combination of $^{1}H,^{1}H$-COSY, $^{1}H,^{13}C$-HMQC and $^{1}H,^{13}C$-HMBC allowed complete assignment of all carbon and proton resonances and coupling pathways. The diastereotopic protons at C4 were easily assigned both from their splitting pattern (Fig. 1) as well as from a cross peak in the $^{1}H,^{13}C$-HMBC-spectrum between the carbonyl signal C12 and the protons at C4. Since the COSY coupling pattern leads to a circular argument, an unequivocal differentiation between **10a** and **11a** was not possible. The definite proof for only the formation of **10a** was achieved from a $^{1}H,^{15}N$-HMBC spectrum (natural abundance ^{15}N). An expanded region of this spectrum is depicted in Figure 1.

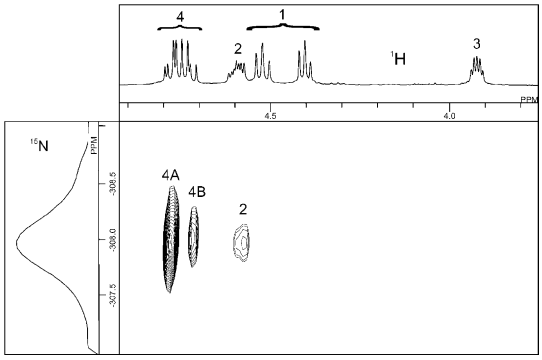


Figure 1. $^{1}H,^{15}N$-HMBC spectrum ($CDCl_3$, 26 °C) of **10a**, expanded region; natural abundance ^{15}N. The one-dimensional ^{1}H-spectrum is a high-resolution spectrum, the one-dimensional ^{15}N-spectrum is a projection along f_2.

With respect to the ^{15}N-chemical shifts of the three nitrogen atoms in an azido group, the shift of the proximal C-bound nitrogen is −321.2 ppm in H_3CN_3 and −287.9 ppm in PhN_3.[12] The ^{15}N–C azido signal recorded at −308 ppm and the cross peak 2 in Figure 1 is compatible with both structures **10a** and **11a** (interchange of positions 2 and 3). However, the cross peaks 4A and 4B in Figure 1 unequivocally prove the validity of structure **10a**. The peaks 4A and 4B arise from ^{3}J-coupling between the N–C azido nitrogen and protons 4A/4B. In case that **11a** were the species present, these cross peaks would involve a long-range ^{4}J-coupling, incompatible with the cross peak intensity found. Thus, species **10a** indirectly proves the formation of **6** instead of **7** during the reaction discussed in Scheme 2.

2.4. X-ray structure analysis

The NMR based structure of **10a** was unequivocally confirmed by single crystal X-ray determination. Crystals of **10a** suitable for X-ray diffraction were grown from $CDCl_3$.[13,14] Compound **10a** crystallises in the chiral space group $P2_1$ with two independent molecules in the unit cell (Fig. 2, Table 1).

In the crystal, two structural motifs determine the stacking of **10a** (Fig. 3), which is mainly due to the *p*-nitrobenzoic ester group.[16] Compound **10a** is vertically stacked like an angle steel caused by weak π–π interactions.[17] The interplanar distance of the nitro benzoic moiety is 3.44 Å with an interplanar shift of the molecules of 3.64 Å, and a lateral shift of 0.77 Å. The angular staples of **10a** are horizontally connected via weak H-bonds.[18] The aromatic hydrogens interact with oxygens of the nitro and ester function (N–O···H–C = 2.45 Å and C=O···H–C = 2.42 Å), while aliphatic hydrogens adjacent to the ester group are directed to the N_3-functions (C–N_3···H–C = 2.58 Å).

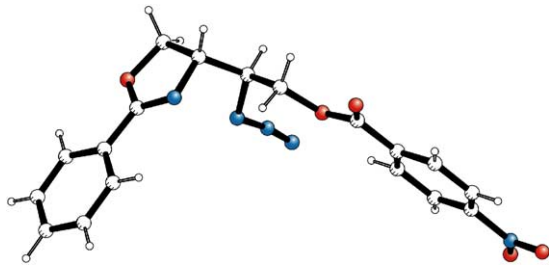


Figure 2. Molecular structure of **9a** (PLUTON presentation[15]). H: void; C: shaded; N: blue; O: red.

Table 1. Crystallographic data for compound **10a**

Formula	$C_{18}H_{15}N_5O_5$
M_r	381.35
Crystal size [mm]	0.30×0.30×0.25
Crystal system	monoclinic
Space group	$P2_1$
T [K]	173(2)
a [Å]	5.0702(2)
b [Å]	30.3384(11)
c [Å]	5.63050(10)
α [°]	90°
β [°]	94.589(2)
γ [°]	90°
V [Å^3]	863.32(5)
Z	2
P_{calcd} [Mg m^{-3}]	1.467
θ range [°]	3.87–27.49°
Reflections collected	2462
Unique reflections	2462
Refl. observed [$I > 2\sigma(I)$]	1317
Parameters	253
Final $R1$ [$I > 2\sigma(I)$]	0.0467
$wR2$ (all data)	0.0881
Largest residuals [e Å^{-3}]	0.175/−0.184

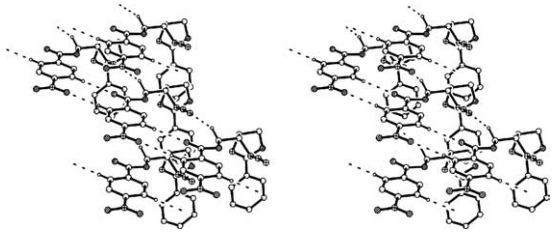


Figure 3. Crystal packing of **10a** (stereoview, PLUTON presentation[15]). H: void, C: shaded; N: net; O: diagonal. X···H–C H-bonds, highlighted via dots. H omitted for clarity except hydrogens involved in weak H-bonds.

3. Conclusion

To the best of our knowledge, this contribution describes for the first time the asymmetric cyclisation of a C_2-symmetric bis-functionalised 2,3-diazido-1,4-diol with benzaldehyde under modified Boyer conditions. In addition, the formation of oxazoline **6** was indirectly proven via **10a** by detailed NMR studies and X-ray structure determination. Due to the remaining functionalities, mono condensation product **6** should allow the synthesis of new unsymmetric ligands, thus be interesting for enantioselective catalysis.

4. Experimental

4.1. General

CH_2Cl_2 was distilled over CaH_2 before use. All reagents employed were commercially available, high-grade purity materials (Fluka, Aldrich), were used as supplied. All moisture-sensitive and oxygen-sensitive reactions were conducted under nitrogen. Flash chromatography was carried out using silica gel 60 (70–230 mesh). Melting points are not corrected. IR spectra were recorded with NaCl plates on a Nicolet 204 FT-IR spectrometer. NMR spectra were obtained in dilute $CDCl_3$ solutions, using Me_4Si as an internal standard at 400 MHz for ^1H and 100 MHz for ^{13}C on a BRUKER ARX 400 spectrometer; δ values are given in ppm. Low-resolution mass spectra were carried out at the Institut für Organische Chemie in Erlangen on a MICROMASS ZAB-Spectrometer (8 kV). Spectral parameters of Figure 1 (*Jeol Alpha 500* spectrometer): $B_0 = 11.7$ T ($^1H = 500$ MHz). Inverse gradient probehead, $CDCl_3$, +24 °C, inverse gradient enhanced ^1H,^{15}N-HMBC, 512 data points in f_2, spectral width in f_2 5200 Hz, 64 scans per t_1-increment, acquisition time 0.1 s, relaxation delay 2.0 s, spectral width in f_1 25,250 Hz, 256 t_1-increments, 90°-pulses = 6.2 μs (^1H) and 32.0 μs (^{15}N), delay in HMBC sequence = 62.5 ms, equivalent to a J-coupling of 8 Hz, exponential window in t_2 and Gaussian window in t_1. Single crystal X-ray structure analysis: Details for crystal data, data collection and refinement are given in Table 1. X-ray data for **10a** were collected on a Nonius Kappa CCD area detector, using Mo-Kα radiation ($\lambda = 0.71073$ Å). Scalepack absorption correction was employed. The structure was solved by direct methods with SHELXS-97[13] and refined with full-matrix least-squares against F^2 with SHELXL-97.[13]

4.2. Synthesis of (2*S*)-azido-2-[2-phenyl-4,5-dihydro-oxazol-(4*S*)-yl]-ethanol,[19] 6

A suspension of diazidodiol **3**[20] (0.172 g, 1.00 mmol) and benzaldehyde (0.203 mL, 2.00 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. After addition of 5–10 drops of the $BF_3{\cdot}OEt_2$-complex (0.503 mL, ca. 48% BF_3, 4.00 mmol) a clear solution was obtained. Further addition of $BF_3{\cdot}OEt_2$-complex was accompanied by gas evolution, which stopped after 1 h. The reaction mixture was then allowed to warm to 20 °C and stirred for a further 18 h. Saturated $NaHCO_3$-solution was added slowly for hydrolysis (30 mL) and the two-phase system stirred until the end of gas evolution. The aqueous layer was extracted with EtOAc (3 × 30 mL), the organic phase washed with brine, dried over Na_2SO_4 and concentrated. The crude reaction product was purified by silica gel chromatography (solvent gradient from CH_2Cl_2 to CH_2Cl_2/MeOH 98/2) affording oxazole **6** as a colourless oil (0.200–0.225 g, 86–97%, $R_f = 0.22$ (CH_2Cl_2/MeOH 98/2), colourless crystals after prolonged storage in refrigerator (0 °C), mp 55–57 °C); IR (neat): $\tilde{\nu}$ 3370 (broad), 2960, 2928, 2905, 2103, 1732, 1645, 1604, 1580, 1496, 1471, 1451, 1370, 1262, 1092, 1060, 1027, 971, 783, 698 cm^{-1}; ^1H NMR: δ 7.97–7.92 (m, 2H, Ar–CH_{ortho}), 7.51 (tt, 1H, $J = 7.4$, 1.6 Hz, Ar–CH_{para}), 7.46 (tm, 2H, $J = 7.4$ Hz, Ar–CH_{meta}), 4.60 (ddd, 1H, $J = 9.9$, 7.5, 4.0 Hz, COCH$_2$CH), 4.51 (dd, 1H, $J = 9.9$, 8.4 Hz, COCH_2CH), 4.38 (dd, 1H, $J = 8.4$, 7.5 Hz, COCH_2CH), 4.04 (d, 2H, $J = 4.7$ Hz, HOCH_2CH), 3.53 (td, 1H, $J = 4.7$, 4.0 Hz, HOCH$_2$CH), 3.48 (s, 1H, OH); ^{13}C NMR: δ 166.00 (1C, O–C=N), 131.98 (1C, Ar–CH$_{para}$), 128.54 and 128.46 (4C, Ar–CH$_{ortho\ and\ meta}$), 126.75 (1C, Ar–C$_{ipso}$), 69.71 (1C, COCH$_2$CH, correlates with protons at 4.51 and 4.38 ppm), 68.32 (1C, COCH$_2$$C$H, correlates with proton at 4.60 ppm), 64.14 (1C, HOCH$_2$$C$H, correlates with proton at 3.53 ppm), 63.37 (1C, HOCH$_2$CH, correlates with protons at 4.04 ppm); MS (CI, CH_4) m/z (%): calcd for $C_{11}H_{12}N_4O_2$ 233.1 [M+H]$^+$, found 233.2 (100) [M+H]$^+$; $[\alpha]_D^{25} = -105$, $[\alpha]_{578}^{25} = -108$, $[\alpha]_{546}^{25} = -125$, $[\alpha]_{436}^{25} = -222$ (c 1.6, $CHCl_3$); $C_{11}H_{12}N_4O_2$ (232.24).

4.3. General method for the synthesis of oxazoline esters 10a and b

To a solution of alcohol **6** (0.093 g, 0.40 mmol), NEt_3 (0.11 mL, 0.80 mmol) and a cat. amount of DMAP (0.002–0.004 g) in CH_2Cl_2 (1.6 mL) was added at 0 °C a solution of *p*-nitrobenzoyl chloride (0.104 g, 0.56 mmol; for **10b**: *p*-bromobenzoyl chloride: 0.123 g, 0.56 mmol) in CH_2Cl_2 (1.0 mL). After removal of the ice bath, the reaction mixture was stirred for a further 18 h at ca. 25 °C. After addition of H_2O (1 mL) and phase separation, the aqueous phase was extracted with EtOAc (3 × 5 mL), and the collected organic layers dried over Na_2SO_4 and concentrated. The crude reaction product was purified by silica gel chromatography.

4.4. Spectroscopic data for *p*-nitro-benzoic acid (2*S*)-azido-2-[2-phenyl-4,5-dihydro-oxazol-(4*S*)-yl]-ethyl ester,[19] 10a

Solvent gradient from CH_2Cl_2 to CH_2Cl_2/MeOH 98/2. Yellow crystals, 0.116 g, 76%, $R_f = 0.45$ (CH_2Cl_2/MeOH 99/1), mp 116–118 °C; IR (Nujol): $\tilde{\nu}$ 3113, 3081, 3057, 2173, 2148, 2121, 2097, 1721, 1642, 1607, 1527, 1456, 1371, 1348, 1295, 1274, 1086, 1024, 981, 877, 824, 719 cm^{-1}; ^1H NMR: δ 8.31 (pseudo dt, 2H, $J = 9.0$, 2.1 Hz, *p*-NO$_2$C$_6$H$_4$–CH), 8.24 (pseudo dt, 2H, $J = 9.0$,

2.1 Hz, *p*-$NO_2C_6H_4$–C*H*), 7.97–7.92 (m, 2H, Ar–CH_{ortho}), 7.51 (ddt, 1H, $J = 8.2$, 6.6, 1.4 Hz, Ar–CH_{para}), 7.42 (m, 2H, Ar–CH_{meta}), 4.79 (dd, 1H, $J = 11.8$, 4.1 Hz, CH_2CH–N_3), 4.73 (dd, 1H, $J = 11.8$, 8.2 Hz, CH_2CH–N_3), 4.61 (ddd, 1H, $J = 9.9$, 7.0, 3.9 Hz, OCH_2CH), 4.54 (dd, 1H, $J = 9.9$, 8.4 Hz, OCH_2CH), 4.41 (dd, 1H, $J = 8.4$, 7.0 Hz, OCH_2CH), 3.94 (ddd, 1H, $J = 8.2$, 4.1, 3.9 Hz, CH_2CH–N_3); ^{13}C NMR: δ 166.03 (1C, O–*C*=N), 164.37 (1C, *C*O_2), 150.74 (1C, C_{ipso} α to NO_2), 134.78 (1C, C_{ipso} α to CO_2), 131.91 (1C, Ar–*C*H_{para}), 130.94 (2C, *p*-$NO_2C_6H_4$–*C*H), 128.52 and 128.44 (4C, Ar–*C*$H_{ortho\ and\ meta}$), 126.91 (1C, C_{ipso} α to O–*C*=N), 123.69 (2C, *p*-$NO_2C_6H_4$–*C*H), 69.32 (1C, OCH_2CH, correlates with protons at 4.54 and 4.41 ppm), 67.39 (1C, OCH_2CH, correlates with proton at 4.61 ppm), 65.77 (1C, *C*H_2CH–N_3, correlates with protons at 4.79 and 4.73 ppm), 62.61 (1C, CH_2CH–N_3, correlates with proton at 3.94 ppm); MS (FAB, *m*-NBA) *m*/*z* (%): calcd for $C_{18}H_{16}N_5O_5$ 382.12 $[M+H]^+$, found 393 (52), 382 (43) $[M+H]^+$, 322 (100), 250 (34); HRMS (ESI, MeCN, 4 kV) *m*/*z* (%): calcd for $C_{18}H_{16}N_5O_5$ 389.1151 $[M+H]^+$, found 389.1149 (100); $[\alpha]_D^{20} = -12.6$, $[\alpha]_{578}^{20} = -13.3$, $[\alpha]_{546}^{20} = -14.9$ (*c* 1.0, $CHCl_3$); $C_{18}H_{15}N_5O_5$ (381.34). Crystals suitable for X-ray analysis were obtained by slow $CDCl_3$ evaporation of the NMR sample (Table 1).

4.5. Spectroscopic data for *p*-bromo-benzoic acid (2*S*)-azido-2-[2-phenyl-4,5-dihydro-oxazol-(4*S*)-yl]-ethyl ester,[19] 10b

Solvent gradient from CH_2Cl_2 to CH_2Cl_2/MeOH 99/1. White crystals, 0.115 g, 69%, $R_f = 0.62$ (CH_2Cl_2), mp 100–101 °C; IR (Nujol): $\tilde{\nu}$ 3099, 3066, 2169, 2125, 2097, 1718, 1646, 1589, 1456, 1370, 1349, 1329, 1292, 1271, 1179, 1132, 1116, 1105, 1086, 1070, 1026, 1011, 977, 849, 831, 755, 700, 689 cm^{-1}; ^{1}H NMR: δ 7.98–7.90 (m, 4H, *p*-BrC_6H_4–C*H* and Ar–CH_{ortho}), 7.60 (pseudo dt, 2H, $J = 8.9$, 2.1 Hz, *p*-BrC_6H_4–C*H*), 7.50 (ddt, 1H, $J = 8.3$, 6.5, 1.3 Hz, Ar–CH_{para}), 7.45–7.38 (m, 2H, Ar–CH_{meta}), 4.73 (dd, 1H, $J = 11.8$, 4.0 Hz, CH_2CH–N_3), 4.65 (dd, 1H, $J = 11.8$, 8.3 Hz, CH_2CH–N_3), 4.59 (ddd, 1H, $J = 9.9$, 7.0, 4.1 Hz, OCH_2CH), 4.52 (dd, 1H, $J = 9.9$, 8.2 Hz, OCH_2CH), 4.39 (dd, 1H, $J = 8.2$, 7.0 Hz, OCH_2CH), 3.90 (ddd, 1H, $J = 8.3$, 4.1, 4.0 Hz, CH_2CH–N_3); ^{13}C NMR: δ 165.93 (1C, O–*C*=N), 165.52 (1C, *C*O_2), 131.90 (2C, *p*-BrC_6H_4–*C*H), 131.84 (1C, Ar–*C*H_{para}), 131.30 (2C, *p*-BrC_6H_4–*C*H), 128.61 (1C, *p*-BrC_6H_4–C_{ipso}), 128.53 and 128.41 (4C, Ar–*C*$H_{ortho\ and\ meta}$), 128.33 (1C, *p*-BrC_6H_4–C_{ipso}), 126.97 (1C, C_{ipso} α to O–*C*=N), 69.36 (1C, OCH_2CH, correlates with protons at 4.52 and 4.39 ppm), 67.42 (1C, OCH_2CH, correlates with proton at 4.59 ppm), 65.12 (1C, *C*H_2CH–N_3, correlates with protons at 4.73 and 4.65 ppm), 62.77 (1C, CH_2CH–N_3, correlates with proton at 3.90 ppm); MS (FAB, *m*-NBA) *m*/*z* (%): calcd for $C_{18}H_{16}N_4O_3{}^{79}Br$ 415.04 $[M+H]^+$, gef.: 417 (100) $[M(^{81}Br)+H]^+$, 415 (99) $[M(^{79}Br)+H]^+$, 337 (11) $[M-C_6H_5]^+$; HRMS (ESI, MeOH, 4 kV) *m*/*z* (%): calcd for $C_{19}H_{19}N_4O_4{}^{79}BrNa$ 469.0487 $[M+CH_3OH+Na]^+$, found 469.0531 (5), calcd for $C_{18}H_{15}N_4O_3{}^{79}BrK$ 452.9965 $[M+K]^+$, found 452.9992 (12), calcd for $C_{18}H_{15}N_4O_3{}^{79}BrNa$ 437.0225 $[M+Na]^+$, found 437.0223 (100), calcd for $C_{18}H_{16}N_4O_3{}^{79}Br$ 415.0406 $[M+H]^+$, found 415.0404 (10); $[\alpha]_D^{20} = -14.5$, $[\alpha]_{578}^{20} = -15.3$, $[\alpha]_{546}^{20} = -17.4$ (*c* 2.5, $CHCl_3$); $C_{18}H_{15}N_4O_3Br$ (415.24).

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10. The reaction was carried out several times under the same reaction conditions (yields: 86–97% after purification).

Doubling of the reagents compared to **3** did not lead to **4** and was accompanied with lower yields of **6**. Reaction of **3** with picolinaldehyde or salicylaldehyde instead of **5** failed to give any condensation product.

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20. In spite of the high N/C ratio of **3**, suggesting a potential explosive hazard, no problem was encountered. However, caution is recommended in handling **3**.