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Synthesis of complex alkoxyamines using a polymer-supported *N*-hydroxyphthalimide

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Abstract—The synthesis of a polymer-supported *N*-hydroxyphthalimide is described. The polystyrene-bound *N*-hydroxyphthalimide resin **1** has been used to prepare complex alkoxyamines exhibiting both stereochemical and positional diversity. Methods for efficient condensation of complex alkoxyamines with aldehydes and ketones are also outlined.

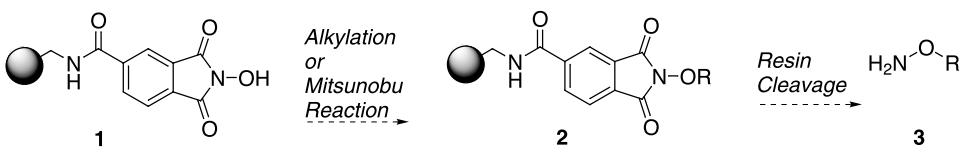
1. Introduction

The oxime functional group is present in several natural products and biologically active molecules.[1] The oxime ether is an attractive functionality to incorporate into library synthesis due to the chemoselective reaction of alkoxyamines[2] with aldehydes and ketones.[3] However, only a limited number of alkoxyamines are commercially available[4] and relatively few methods have been reported for the preparation of chiral variants.[5]

As part of our general interest to construct complex chemical libraries that contain both stereochemical[6] and positional diversification elements, we devised an approach towards the synthesis of stereochemically diverse alkoxyamines employing a polymer-supported *N*-hydroxyphthalimide (Scheme 1).[7,8] Alkylation of the phthalimide hydroxyl group using alkyl halides[9] or alcohols via Mitsunobu etherification[10] would provide the corresponding polymer-supported *N*-alkoxyphthalimides. These products could be further modified using solid-phase synthesis. Hydrazine-mediated cleavage of the alkylation products would afford the corresponding alkoxyamines. This paper reports the synthesis of a polystyrene-based *N*-hydroxyphthalimide resin and its utility in preparing stereochemically and structurally diverse alkoxyamines. The alkoxyamines were utilized to synthesize complex oxime ethers from aldehydes and ketones.

2. Results and discussion

A report from Aronov and Gelb[11] describing the preparation of a polystyrene-bound phthalimide reagent served as a starting point for preparation of *N*-hydroxyphthalimide resin **1**. The synthesis of **1** began by transformation of commercially available anhydride **4** to the *N*-hydroxyphthalimide **5** using hydroxylammonium chloride in refluxing pyridine[12] (Scheme 2). Protection of the hydroxyl group with trityl chloride afforded protected phthalimide **6**. Attachment of the protected phthalimide **6** to aminomethyl polystyrene (PS-NH_2, 1.30 mmol/g, Argonaut) using HATU-mediated amide bond formation afforded resin **7**. Deprotection of the trityl group using 10:1 CH_2Cl_2:TFA completed the synthesis of *N*-hydroxyphthalimide resin **1**. Unfortunately, extensive screening of reaction conditions



Scheme 1. Preparation of complex alkoxyamines using a polymer-supported *N*-hydroxyphthalimide.

Keywords: Polymer-supported; *N*-Hydroxyphthalimide; Alkoxyamine; Stereochemical diversity; Positional diversity.
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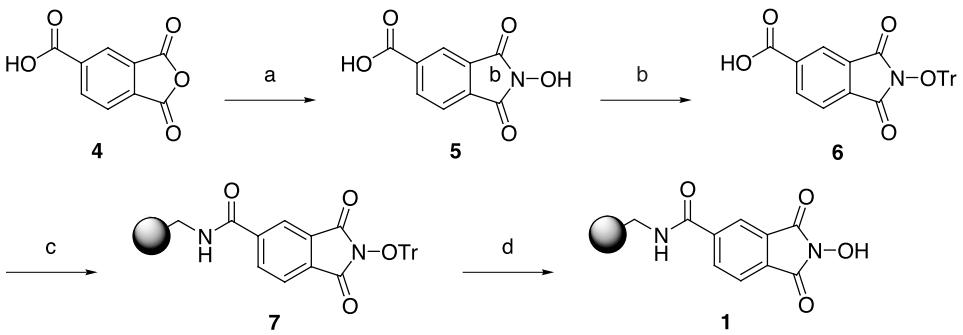


Scheme 2. Initial synthesis of an *N*-hydroxyphthalimide resin. Reagents and conditions: (a) $H_2NOH{\cdot}HCl$, pyridine, 95 °C, 66%. (b) TrCl, DIEA, CH_3CN, reflux, 34%. (c) HATU, DIEA, PS-NH_2, DMF. (d) 10:1 CH_2Cl_2:TFA.

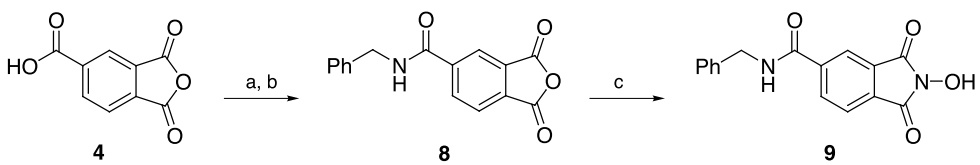
failed to improve the yield for trityl protection of *N*-hydroxyphthalimide **5**. Other protecting groups (e.g., TMS, TBS, and THP) were also evaluated and found to be less effective than the trityl group. Attempts to directly condense anhydride **4** with *O*-trityl hydroxylamine or *O*-(tetrahydro-2*H*-pyran-2-yl) hydroxylamine were likewise unsuccessful.

To improve the synthesis of resin **1**, amide bond formation in the presence of the anhydride moiety, followed by transformation to the hydroxyphthalimide, was investigated (Scheme 3). A model study was initiated to determine the effectiveness of amide bond formation with the acid chloride of compound **4**.[13] In order to potentially minimize reaction with the anhydride moiety, we employed benzylamine hydrochloride as a protected form of the amine. Slow addition of triethylamine gradually liberated the benzylamine to selectively react with the more reactive acid chloride. According to ^1H NMR analysis, no reaction of the anhydride was observed using 1 equiv. of the amine salt. Although this transformation provided only moderate yields, it was anticipated that by using an excess of acid chloride, high levels of chemoselectivity should be achievable using a solid-supported amine. Following a literature procedure,[12] anhydride **8** was reacted with hydroxylamine hydrochloride to provide the desired model compound **9**.

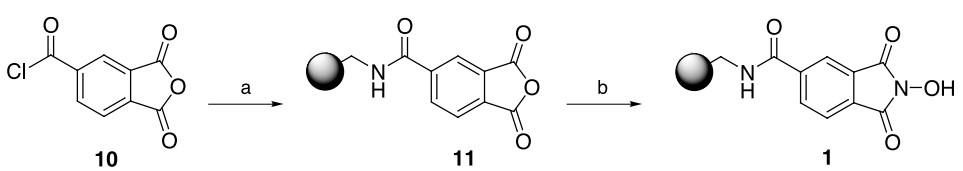
Following solution phase model studies, solid-phase synthesis was initiated by condensation of acid chloride **10** and PS-$NH_2{\cdot}HCl$, prepared from commercially available aminomethylated polystyrene (1.10 mmol/g, Novabiochem) and 4 M HCl in dioxane. The reaction was monitored by both bead staining with bromophenol blue[14] and single-bead IR analysis. A negative result from the bromophenol blue stain test and strong carbonyl absorptions (1858, 1781, 1673 cm^{-1}) by IR analysis clearly indicated the formation of anhydride resin **11**.[15] After resin washing, **11** was successfully transformed to *N*-hydroxyphthalimide resin **1** as indicated by the shift of the carbonyl stretches (1788, 1728, 1603 cm^{-1}) and the appearance of a strong hydroxyl stretch by single-bead IR (Scheme 4).

In order to determine the loading of *N*-hydroxyphthalimide resin **1**, a Mitsunobu reaction was employed for resin derivatization (Scheme 5). 4-Biphenylmethanol was reacted with resin **1** using TMAD/PBu_3.[16] After resin washing and subsequent cleavage using NH_2NH_2 (2 equiv.), the corresponding biaryl alkoxyamine[17] was obtained after solvent removal. The yield was determined by HPLC analysis of the acetone oxime derivative **13** employing 4-biphenylmethanol as an internal standard. The loading of resin **1** was thus determined to be 0.68 mmol/g (75% of theoretical loading). Further efforts to improve the loading of the resin were investigated. To minimize potential crosslinking of the anhydride with aminomethyl sites on the resin, other variables including use of a secondary amine resin[15] and alternative solvents (e.g., THF) were evaluated. However, none of these variations afforded improved resin loading.

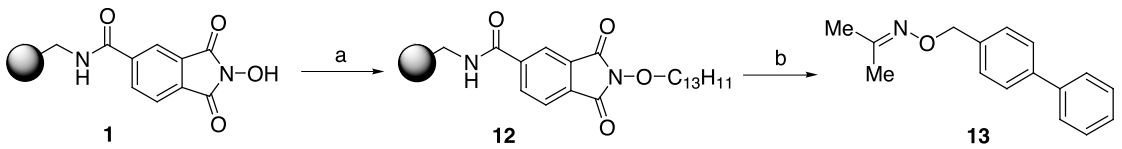
A recent report[18] prompted us to investigate an alternative



Scheme 3. Synthesis of *N*-hydroxyphthalimide resin via a direct condensation pathway. Reagents and conditions: (a) oxalyl chloride, CH_2Cl_2, cat. DMF. (b) $PhCH_2NH_2{\cdot}HCl$, Et_3N, CH_2Cl_2. (c) $H_2NOH{\cdot}HCl$, pyridine, 95 °C, 45% from **4**.



Scheme 4. Second synthesis of *N*-hydroxyphthalimide resin. Reagents and conditions: (a) PS-NH_2, Et_3N, CH_2Cl_2. (b) $H_2NOH{\cdot}HCl$, pyridine:$ClCH_2CH_2Cl$ 3:1, 75 °C.



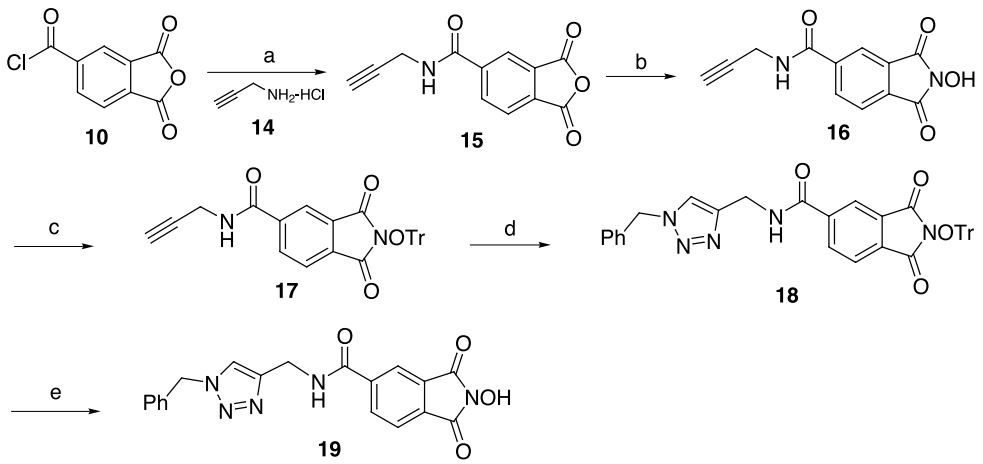
Scheme 5. Characterization of the *N*-hydroxyphthalimide resin. Reagents and conditions: (a) 4-biphenylmethanol, PBu_3, TMAD, THF:CH_2Cl_2=1:1, rt. (b) H_2NNH_2, CH_2Cl_2, then acetone.

polymer-supported reagent synthesis involving 1,2,3-triazole formation (Scheme 6). Selective condensation of acid chloride **10** and propargyl amine hydrochloride **14** afforded anhydride **15**, which was converted to hydroxyphthalimide **16** using microwave conditions (150 W, 100 °C, 60 min).[19] At this stage, both CuI-catalyzed[23a] and thermal triazole formations were evaluated and failed to provide any desired product. Further studies indicated that the trityl-protected compound **17**[20] (prepared from **16** and trityl chloride) readily underwent cycloaddition using Cu(I) catalysis. Interestingly, a mixture of 1.4:1 mixture of 1,2,3-triazole regioisomers (unassigned) was obtained instead of the expected head-to-tail regioisomer.[23] Subsequent deprotection of both isomers using 10:1 CH_2Cl_2/TFA successfully afforded the desired model 1,2,3-triazole **19**.

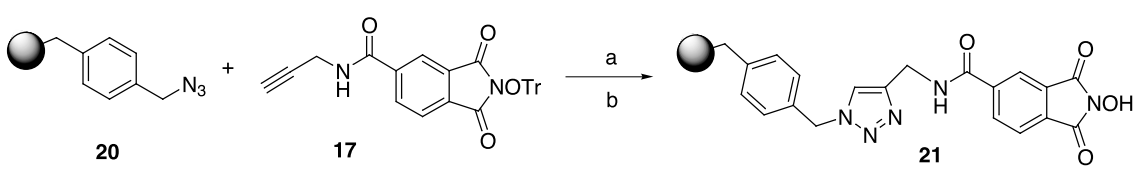
Following the solution phase model studies, compound **17** was employed for solid-phase synthesis (Scheme 7). Copper (I)-mediated dipolar cycloaddition of benzyl azide resin **20**[18,21] and propargylamide **17**, followed by TFA-mediated detritylation, afforded the desired resin **21**.[22] Although Mitsunobu reactions proceeded smoothly using **21**, subsequent functionalization reactions to produce complex alkoxyamines (acetylenic Mannich reaction, vide infra) produced inconsistent results leading to general concern about 1,2,3-triazole regioisomers and potential for compromised reactivity. Accordingly, we selected *N*-hydroxyphthalimide resin **1** for further studies to prepare structurally and stereochemically diverse alkoxyamines.

Due to the high efficiency of the Mitsunobu reaction and the numerous transformations that potentially can be applied on tethered alkynes, we focused on attachment of alkyne-containing alcohols to resin **1**. Three diversification pathways were selected for terminal alkyne modification: Cu-catalyzed 1,2,3-triazole formation,[23] isoxazole synthesis,[24] and acetylenic Mannich reactions[25] (Scheme 8).

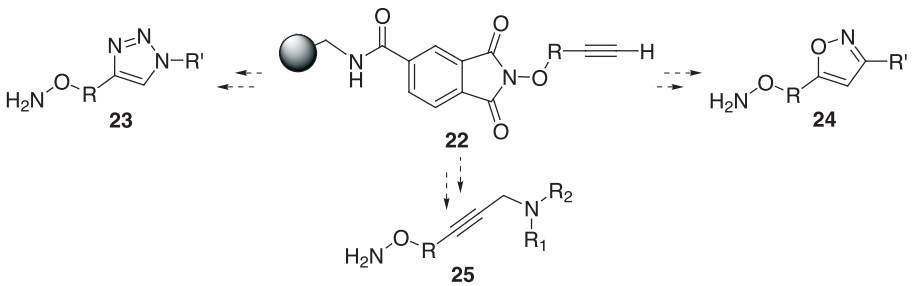
Condensation of *N*-hydroxyphthalimide resin **1** and diverse terminal alkyne-containing alcohols was effected using a Mitsunobu conditions[16] to afford alkyne resins **26** (Scheme 9). At this stage, Cu-catalyzed 1,2,3-triazole formation was investigated.[23] A number of Cu(I) sources were tested along with variation of base, additives, and ligands. The cycloaddition was monitored by the disappearance of alkyne C–H stretch (3292 cm^{-1}) using single-bead IR. Optimal reaction conditions were found using a combination of $Cu(MeCN)_4PF_6$, 2,6-lutidine, and CH_2Cl_2 as solvent. Resin washing with 10% *N*,*N*,*N*′,*N*′-tetramethylethylenediamine efficiently removed the copper



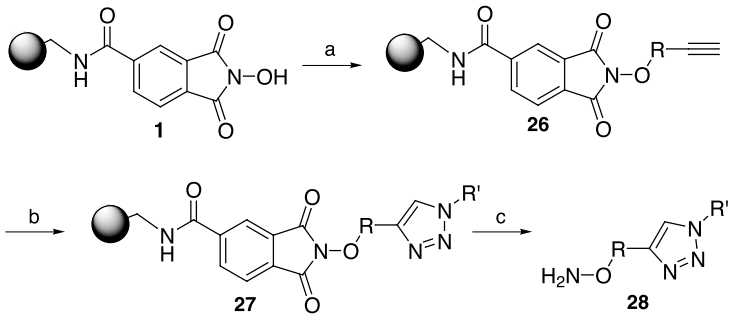
Scheme 6. Model studies towards the synthesis of an *N*-hydroxyphthalimide resin using 1,2,3-triazole linkage (only one regioisomer of **18** and **19** are shown for clarity). Reagents and conditions: (a) pyridine, THF. (b) $NH_2OH{\cdot}HCl$, pyridine, microwave 100 °C, 150 W, 60 min 75%. (c) TrCl, DIEA, MeCN. (d) CuI, DIEA, THF, $PhCH_2N_3$. (e) 10:1 CH_2Cl_2:TFA, 90% from **16**.



Scheme 7. Synthesis of an *N*-hydroxyphthalimide resin using a triazole linker (only one regioisomer **21** is shown for clarity). Reagents and conditions: (a) CuI, DIEA, THF. (b) 10:1 CH_2Cl_2:TFA.



Scheme 8. Plan for synthesis of complex alkoxyamines using the *N*-hydroxyphthalimide resin.



Scheme 9. Synthesis of 1,2,3-triazole-containing alkoxyamines. Reagents and conditions: (a) alkyne-containing alcohol, TMAD, Bu_3P, THF/CH_2Cl_2=1:1, rt. (b) R'N_3, Cu(MeCN)$_4PF_6$, 2,6 lutidine, CH_2Cl_2. (c) NH_2NH_2, CH_2Cl_2.

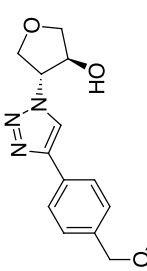
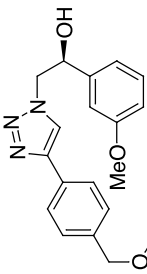
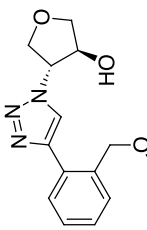
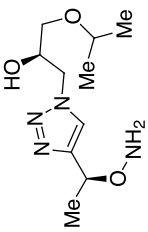
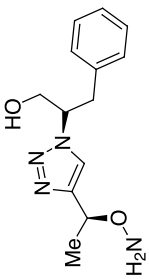
salts from the polystyrene support. Subsequent cleavage using anhydrous hydrazine provided the desired products. Using this protocol, several alkoxyamine triazoles (Table 1, **29**–**33**) containing both positional and stereochemical diversity were prepared in yields ranging from 95 to 98% (71–74% based on loading of the aminomethylated polystyrene) and high purities (>99%, HPLC-ELSD).

Isoxazoles are heterocycles which are present in a number of therapeutic agents.[26] Thus, the cycloaddition of nitrile oxides with alkynes was investigated for preparation of diverse isoxazole-containing alkoxyamines (Scheme 10).[24] Dipolar cycloaddition of alkyne resin **26** was best performed using in situ generation of a nitrile oxide prepared from oxime **35**, NBS, and $NaHCO_3$[27] in CH_2Cl_2 at 35 °C. Other conditions[24c,28] employing NCS,[24a] NaOCl,[24b] and $(Bu_3Sn)_2O$[29] lead to incomplete reactions as evidenced by single bead IR. Regioisomers were observed for some of the substrates (Table 2) and the ratio was determined by ^1H NMR. Due to the limited availability of diverse oximes, we have developed a practical method for the synthesis of oximes starting from commercially available aldehydes (inset, Scheme 10). Treatment of aldehydes **34** with hydroxylamine hydrochloride in the presence of Et_3N in CH_2Cl_2 provided the desired oximes **35**, which can be readily separated from the hydrochloride salts by eluting though an SLE[30] cartridge containing 1 N HCl. The resulting oximes were reacted with NBS in CH_2Cl_2 for 3 h and then incubated with diverse alkyne resins ($NaHCO_3$, 12 h) to afford the corresponding isoxazole-containing resins. After hydrazinolysis, the desired isoxazole-containing alkoxyamines (Table 2, **38**–**42**) were obtained in yields ranging from 92 to 96% (69–72% based on loading of the aminomethylated polystyrene) and high purities (≥92%, HPLC-ELSD).

Since tertiary propargylic amines are also of significant pharmaceutical interest,[31] the preparation of propargylic amine-containing alkoxyamines was next explored (Scheme 11). Initial reactions employing conventional reaction conditions (e.g., CuCl/1,4-dioxane[25]) were not satisfactory and led to incomplete reactions. After extensive experimentation, we found that pretreating the secondary amine with paraformaldehyde and *p*-toluenesulfonic acid, followed by addition of CuBr in DMF, provided the desired Mannich products in high yield and purity after cleavage with NH_2NH_2. The washing regimen developed for the solid phase 1,2,3-triazole synthesis (Scheme 9) was also employed for removal of copper salts from the polystyrene support. Following this general procedure, several propargylic amine-containing alkoxyamines (Table 3, **46**–**50**) were synthesized employing commercially available amines in yields ranging from 95 to 99% (71–74% based on loading of the aminomethylated polystyrene) and high purities (≥97%, HPLC-ELSD).

The condensation of alkoxyamines with aldehydes or ketones via oxime formation is an efficient method for the ligation of two complex fragments (Scheme 12). A small collection of oxime–ether containing molecules was targeted to demonstrate the utility of the complex alkoxyamines for preparation of compounds with stereochemical and positional diversity. Microwave irradiation[32] was employed to facilitate expedient product formation. General conditions for the preparation of oxime ethers employed a slight excess of alkoxyamine (1.2 equiv.) relative to ketone or aldehyde. Aldehydes (**51**–**53**) reacted cleanly with alkoxyamines in 1,2-dichloroethane to produce the desired oxime products (**57**–**59**) within minutes (Table 4). Excess alkoxyamine was scavenged using a solid-supported methyl isatoic anhydride resin[33] to afford the

Table 1. Synthesis of 1,2,3-triazole-containing alkoxyamines

Substrate					
	29	**30**	**31**	**32**	**33**
Yield (%)[a]	97	98	96	95	98
Purity (%)[b]	>99	>99	>99	>99	>99

[a] Isolated yield based on the loading of the *N*-hydroxyphthalimide resin **1** (0.68 mmol/g).
[b] Purity determined by HPLC-ELSD analysis of the corresponding acetone oxime.

desired products in high yield and purity. The stereochemistry of oxime ethers was determined by ^{1}H NMR analysis.[1a] Higher reaction temperatures and use of acetic acid improved the rate of oxime condensations with ketones such as estrone **54** and (+)-griseofulvin[34] **55** to afford compounds **60** and **61**. Production of structures such as **57**–**61** using oxime ligation illustrates the potential for future synthesis of complex hybrid molecule libraries using convergent approaches.[35]

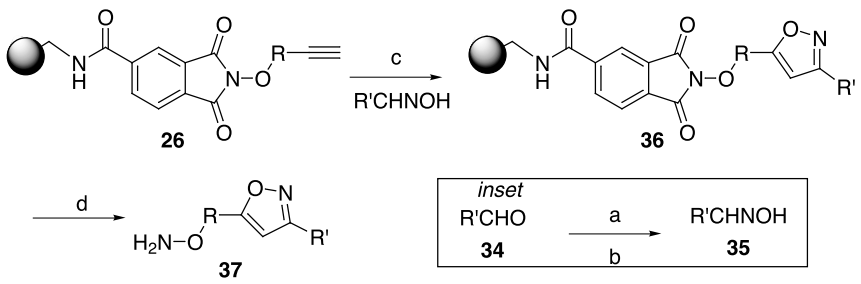
3. Conclusion

In summary, the synthesis of a polymer-supported *N*-hydroxyphthalimide has been accomplished. In initial studies, the supported *N*-hydroxyphthalimide reagent has been used to prepare complex alkoxyamines containing stereochemical and positional diversity elements. Attachment of alkynols to the *N*-hydroxyphthalimide resin using Mitsunobu reactions has facilitated the synthesis of complex 1,2,3-triazole-, isoxazole- and propargylamine-containing alkoxyamines via branching reaction pathways. Finally, methods for efficient condensation of the diverse alkoxyamines with both aldehydes and ketones have been developed leading to the production of highly complex, hybrid molecules. Further studies concerning the construction of complex oxime-based libraries using convergent approaches is currently in progress and will be reported in due course.

4. Experimental

4.1. General experimental procedures

^{1}H NMR spectra were recorded on a 400 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on a 75.0 MHz spectrometer (unless otherwise stated) at ambient temperature. Chemical shifts are reported in parts per million relative to chloroform (^{1}H, δ 7.24; ^{13}C, δ 77.23). Data for ^{1}H NMR are reported as follows: chemical shift, integration, multiplicity (app=apparent, par obsc=partially obscure, ovrlp=overlapping, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet) and coupling constants. All ^{13}C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. Single-bead IR was performed on Nicolet Nexus 470 FT-IR+ContinuμM microscope. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and are recorded as $[\alpha]_D$ (concentration in grams/100 mL solvent). HPLC-ELSD-MS analysis was performed on a Waters HPLC-MS system equipped with Waters 600 HPLC pump, Waters 2996 photodiode array detector, Micromass ZQ Quadrupole Mass Spectrometer, Sedere Sedex 75 ELS reverse phase column (XTerra®RP_8, 5 μm, 4.6×30 mm). Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200–400 mesh silica gel (Scientific Absorbents, Inc.). Solid-phase synthesis was performed using Quest 210 and Quest 205 synthesizer (Argonaut Technologies, Foster City, CA). Liquid–liquid extraction



Scheme 10. Synthesis of isoxazole-containing alkoxyamines. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, CH_2Cl_2, Et_3N. (b) SLE, 1 N HCl. (c) NBS, CH_2Cl_2, then $NaHCO_3$, 35 °C. (d) NH_2NH_2, CH_2Cl_2.

for oxime formation was performed using 5.0 mL ISOLUTE® HM-N SPE Columns (Argonaut Technologies). Aminomethylated polystyrene (cat. No. 01-64-0143, 1.10 mmol/g) was obtained from Novabiochem. Polystyrene-NH_2 resin (PS-NH_2, part. no. 800263, 1.30 mmol/g) was obtained from Argonaut Technologies. Solid-supported methyl isatoic anhydride resin (PL-MIA, part # 3405-3679, 2.57 mmol/g) was obtained from Polymer Laboratories. All other reagents were used as supplied by Sigma-Aldrich, Lancaster Synthesis, Strem, and Argonaut Technologies. Methylene chloride, tetrahydrofuran, methanol, benzene were purified by passing through two packed columns of neutral alumina (Glass Contour, Irvine, CA).

4.1.1. *N*-Hydroxyphthalimide resin (1). Pre-swelled aminomethylated polystyrene resin (5.0 g, 5.50 mmol, loading: 1.10 mmol/g,) was mixed with 40 mL CH_2Cl_2 in an 80 mL reaction vessel on the Quest 205 parallel synthesizer. After addition of 6.9 mL HCl in dioxane (4.0 M, 27.4 mmol), the mixture was agitated for 1 h. Upon filtration, the PS-$NH_2{\cdot}HCl$ resin was washed with CH_2Cl_2 (3×30 mL) and transferred to a pre-silylated 250 mL two-neck flask equipped with a mechanical stirrer. Trimellitic anhydride chloride (5.75 g, 27.4 mmol) was added followed by 30 mL CH_2Cl_2 and the reaction was cooled to 0 °C using an ice bath. A solution of Et_3N (5.26 mL, 38.5 mmol) in 20 mL CH_2Cl_2 was added to the reaction mixture over 2 h via syringe pump. The reaction was stirred at 0 °C for an additional 3 h, warmed to rt, and stirred for an additional 2 h. After the reaction mixture was transferred to a reaction vessel on the Quest 205 synthesizer, the resulting anhydride resin was washed with CH_2Cl_2 (2×20 mL), DMF (2×20 mL), THF (2×20 mL), and CH_2Cl_2 (2×20 mL). Following washing, $NH_2OH{\cdot}HCl$ (1.91 g, 27.5 mmol) and 40 mL 3:1 pyridine: 1,2-dichloroethane were added and the reaction was agitated for 24 h at 75 °C. The reaction was cooled to rt, the resin was filtered, washed with MeOH (2×20 mL), DMF (2×20 mL), DMF–H_2O=1:1 (2×30 mL), DMF (1×20 mL), THF (3×20 mL), CH_2Cl_2 (2×20 mL), Et_2O (2×20 mL), and dried under high vacuum at 50 °C for 12 h. IR (single bead): 3385, 3060, 3027, 2925, 1788, 1728, 1669, 1601, 1514, 1494, 1453, 1374, 1299, 1194, 1141, 1115, 1021, 998, 913, 827, 761, 709 cm^{-1}.

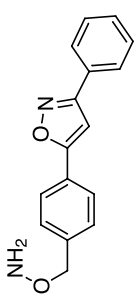
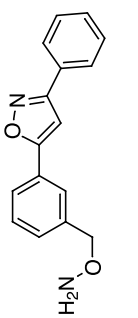
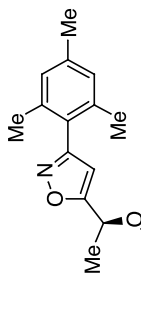
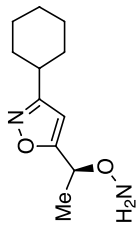
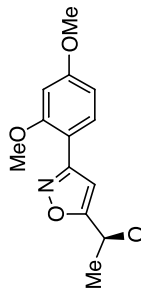
4.2. Loading determination

Resin **1** (100 mg) was pre-swelled with CH_2Cl_2 in a 5 mL reaction vessel on the Quest-210 synthesizer and 4-biphenylmethanol (55.2 mg, 0.30 mmol) and azodicarboxylic acid bis[dimethylamide] (51.6 mg, 0.30 mmol) were added as solids under N_2 followed by 2 mL 1:1 THF–CH_2Cl_2. After mixing to dissolve the reagents, P(*n*-Bu)$_3$ (43.2 μL, 0.30 mmol) was added and reaction mixture was agitated for 6 h. After filtering the reaction mixture, the resulting resin was washed with DMF (2×3 mL), MeOH (2×3 mL), THF (3×3 mL), CH_2Cl_2 (3×3 mL). Following the addition of 2 mL CH_2Cl_2, NH_2NH_2 (6.3 μL, 0.20 mmol) was added and the reaction was agitated for 1 h. The filtration was collected and treated with 2 mL acetone. After concentration, the resulting sample was subjected to an HPLC analysis using a Waters AutoPure HPLC systemand an XTerra®RP_8, 5 μm, 4.6×30 mm column (4-biphenylmethanol as internal standard). The loading was determined to be 75% (0.68 mmol/g).

Note. For compounds **29**–**33**, **38**–**42**, and **46**–**50** (a) all yields were calculated based on the experimentally determined loading of the *N*-hydroxyphthalimide resin (**1**, cf. Section 4.1.2); (b) purity and NMR studies were conducted on the corresponding acetone oxime derivatives.

4.2.1. Representative procedure for synthesis of 1,2,3-triazole-containing alkoxyamines (acetone oxime of 33). Resin **1** (56 mg, 0.0385 mmol) was pre-swelled with CH_2Cl_2 in a 5 mL reaction vessel on the Quest-210 synthesizer. Azodicarboxylic acid bis[dimethylamide] (20 mg, 0.116 mmol) was added as a solid under N_2 followed by 2 mL 1:1 THF–CH_2Cl_2 and (*R*)-(+)-3-butyne-2-ol (9.1 μL, 0.116 mmol). After mixing to dissolve the reagents, P(*n*-Bu)$_3$ (16.4 μL, 0.116 mmol) was added and reaction mixture was agitated for 6 h. After filtering the reaction mixture, the resulting resin was washed with DMF (2×3 mL), MeOH (2×3 mL), THF (3×3 mL), and CH_2Cl_2 (3×3 mL). After resin washing, $Cu(CH_3CN)_4PF_6$ (4.5 mg, 0.012 mmol, 30 mol%) was added to the reaction vessel followed by the addition of 2 mL CH_2Cl_2, 2*S*-2-azido-3-phenyl-propan-1-ol[36] (20.5 mg, 0.116 mmol) and 2,6-lutidine (13.5 μL, 0.116 mmol). The reaction was agitated at rt for 12 h and filtered. After resin washing with 10% *N*,*N*,*N*′,*N*′-tetramethylethylenediamine in CH_2Cl_2 (2×3 mL), CH_2Cl_2 (1×3 mL), 5% AcOH in CH_2Cl_2 (2×3 mL), THF (3×3 mL) and CH_2Cl_2 (3×3 mL), 2 mL CH_2Cl_2 and NH_2NH_2 (2.5 μL, 0.077 mmol) were added and the reaction was agitated for 1 h. The reaction was filtered, the resin was washed with CH_2Cl_2, and the filtrate collected and evaporated to afford 9.9 mg (0.0377 mmol, 73.5%) of (2*R*)-[4-[(1*S*)-aminooxy-ethyl)-[1,2,3]triazol-1-yl]-3-phenyl-propan-1-ol **33** as a colorless oil. **33** was treated with 2 mL of acetone and then concentrated and the

Table 2. Synthesis of isoxazole-containing alkoxyamines

Substrate					
	38	**39**[a]	**40**[b]	**41**	**42**
Yield (%)[c]	95	92	93	96	95
Purity (%)[d]	>99	>99	92	>99	>99

[a] 2:1 mixture of regioisomers (major isomer shown).
[b] >10:1 mixture of regioisomers (major isomer shown).
[c] Isolated yield based on the loading of the *N*-hydroxyphthalimide resin **1** resin (0.68 mmol/g).
[d] Purity determined by HPLC-ELSD analysis of the corresponding acetone oxime.

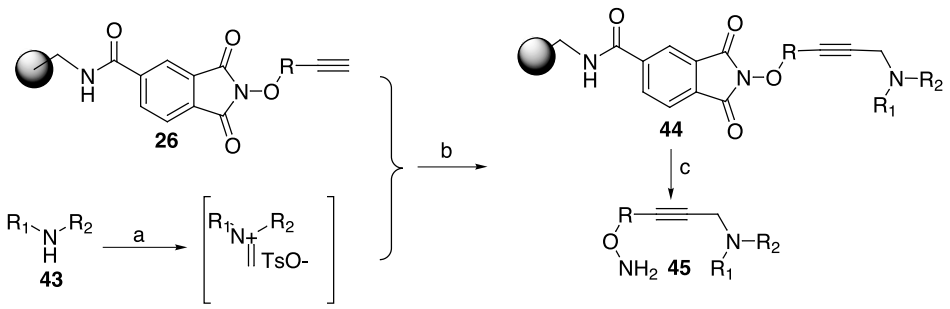
resulting sample was subjected to HPLC-ELSD analysis using a Waters HPLC-MS system (XTerra®RP_8, 5 μm, 4.6×30 mm column) to determine the purity (>99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.20 (m, 3H), 7.08 (d, 2H, J=7.2 Hz), 5.32 (q, 1H, J=7.2 Hz), 4.67 (m, 1H), 4.07 (m, 2H), 3.25 (m, 2H), 2.01 (m, 1H), 1.84 (s, 3H), 1.83 (s, 3H), 1.61 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 155.3, 149.4, 136.6, 129.1, 128.8, 127.0, 122.1, 73.1, 64.7, 63.6, 37.9, 21.8, 19.8, 15.7; IR (thin film) ν_{max} 3333, 3029, 2926, 2857, 1454, 1372, 1079, 935, 702, 670 cm^{-1}; LRMS $[M]^+$ calculated for $C_{16}H_{22}N_4O_2$: 302.4, found: 302.5; $[\alpha]_D^{23}=-57.8°$ (c=0.58, CH_2Cl_2).

4.2.2. (4*R*)-[4-(4-Aminooxymethyl-phenyl)-[1,2,3]triazol-1-yl]-tetrahydro-furan-(3*R*)-ol (acetone oxime of 29). White solid. Mp 125.0–126.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.73 (d, 2H, J=7.6 Hz), 7.39 (d, 2H, J=7.6 Hz), 5.18 (m, 1H), 5.06 (s, 2H), 4.61 (m, 1H), 4.35 (dd, 1H, J=5.2, 10.0 Hz), 4.29 (dd, 1H, J=5.6, 10.0 Hz), 4.20 (dd, 1H, J=2.0, 10.8 Hz), 3.84 (dd, 1H, J=3.2, 9.6 Hz), 1.88 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 155.8, 148.0, 138.9, 129.1, 128.5, 125.7, 118.5, 74.7, 74.0, 70.8, 68.5, 21.8, 15.7; IR (thin film) ν_{max} 3409, 3137, 2960, 2930, 2882, 2856, 1639, 1620, 1496, 1442, 1416, 1364, 1232, 1074, 1012, 882, 803, 739 cm^{-1}; LRMS $[M]^+$ calculated for $C_{16}H_{20}N_4O_3$: 316.4, found: 316.0; $[\alpha]_D^{23}=-54.5°$ (c=0.67, CH_2Cl_2).

4.2.3. 2-[4-(4-Aminooxymethyl-phenyl)-[1,2,3]triazol-1-yl]-(1*R*)-(3-methoxy-phenyl)-ethanol (acetone oxime of 30). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.70 (s, 1H), 7.65 (d, 1H, J=8.0 Hz), 7.30 (m, 3H), 6.98 (m, 2H), 6.86 (m, 1H), 5.22 (dd, 1H, J=3.2, 8.8 Hz), 5.05 (s, 1H), 4.66 (dd, 1H, J=3.2, 14.0 Hz), 4.44 (dd, 1H, J=8.8, 13.6 Hz), 3.79 (s, 3H), 1.98 (s, 1H), 1.89 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 160.1, 155.7, 147.3, 141.9, 139.0, 130.4, 130.0, 128.9, 127.7, 125.1, 124.9, 121.4, 118.1, 114.1, 111.3, 75.0, 72.8, 57.5, 55.2, 21.8, 15.7; IR (thin film) ν_{max} 3305, 3141, 2923, 1601, 1489, 1458, 1434, 1367, 1266, 1073, 10489, 790, 699 cm^{-1}; LRMS $[M]^+$ calculated for $C_{21}H_{24}N_4O_3$: 380.4, found: 380.2; $[\alpha]_D^{23}=-24.4°$ (c=0.54, CH_2Cl_2).

4.2.4. (4*R*)-[4-(2-Aminooxymethyl-phenyl)-[1,2,3]triazol-1-yl]-tetrahydro-furan-(3*R*)-ol (acetone oxime of 31). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.88 (dd, 1H, J=1.2, 7.6 Hz), 7.41 (m, 3H), 5.20 (m, 1H), 5.04 (m, 2H), 4.61 (m, 1H), 4.36 (dd, 1H, J=5.2, 10.4 Hz), 4.24 (dd, 1H, J=5.6, 10.4 Hz), 4.18 (dd, 1H, J=3.2, 10.4 Hz), 3.83 (dd, 1H, J=3.2, 10.0 Hz), 1.98 (s, 1H), 1.88 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 156.4, 146.3, 134.1, 131.0, 130.3, 129.0, 128.8, 128.5, 121.5, 74.0, 73.97, 70.8, 68.3, 21.8, 15.7; IR (thin film) ν_{max} 3362, 2925, 2880, 1648, 1435, 1368, 1269, 1227, 1074, 914, 767 cm^{-1}; LRMS $[M]^+$ calculated for $C_{16}H_{20}N_4O_3$: 316.4, found: 316.0; $[\alpha]_D^{23}=-52.8°$ (c=0.59, CH_2Cl_2).

4.2.5. 1-[4-[(1*S*)-Aminooxy-ethyl)-[1,2,3]triazol-1-yl]-3-isopropoxy-propan-(2*R*)-ol (acetone oxime of 32). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 5.37 (q, 1H, J=6.8 Hz), 4.52 (dd, 1H, J=3.6, 14.0 Hz), 4.39 (dd, 1H, J=6.4, 14.0 Hz), 4.13 (m, 1H), 3.56 (m, 1H), 3.44 (dd, 1H,



Scheme 11. Synthesis of propargylic amine-containing alkoxyamines. Reagents and conditions: (a) CH_2Cl_2, *p*-TsOH·H_2O, $(CH_2O)_n$. (b) CuBr, DMF, 50 °C. (c) NH_2NH_2, CH_2Cl_2.

J=5.2, 9.6 Hz), 3.34 (dd, 1H, J=6.0, 9.6 Hz), 1.83 (s, 6H), 1.63 (d, 3H, J=8.4 Hz), 1.13 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 155.2, 150.0, 122.8, 73.2, 72.4, 69.3, 68.7, 52.7, 21.9, 21.8, 19.9, 15.7; IR (thin film) ν_{max} 3333, 2972, 2924, 1457, 1371, 1262, 1130, 1078, 935, 668 cm^{-1}; LRMS $[M]^+$ calculated for $C_{13}H_{24}N_4O_3$: 284.4, found: 284.5; $[\alpha]_D^{23}$=+11.9° (c=0.55, CH_2Cl_2).

4.2.6. Representative procedure for synthesis of isoxazole-containing alkoxyamines (acetone oxime of 41). Cyclohexanecarboxaldehyde (21.6 mg, 0.193 mmol), hydroxylamine hydrochloride (26.7 mg, 0.385 mmol) were mixed with 1 mL CH_2Cl_2 in the presence of Et_3N (79 μL, 0.578 mmol). The reaction mixture was stirred for 1 h, diluted with CH_2Cl_2, and subsequently applied to an SLE cartridge (5.0 mL) containing 1 N HCl. After elution with 15 mL CH_2Cl_2, the resulting oxime solution was concentrated and reacted with NBS in CH_2Cl_2 for 3 h. The reaction mixture was transferred to a 5 mL reaction vessel on the Quest-210 synthesizer containing the alkyne resin (0.0385 mmol, see procedure for preparation of **33**) and $NaHCO_3$ (16.4 mg, 0.193 mmol). The reaction was agitated at 35 °C for 12 h to afford the corresponding isoxazole-containing resin. After filtration and resin washing with H_2O (2×3 mL), MeOH (1×3 mL), DMF (2×3 mL), THF (3×3 mL) and CH_2Cl_2 (3×3 mL), 2 mL CH_2Cl_2 and NH_2NH_2 (2.5 μL, 0.077 mmol) were added and the reaction was agitated for 1 h. The reaction was filtered, the resin washed with CH_2Cl_2, and the filtrate collected and evaporated to provide 7.8 mg (0.0374 mmol, 72.4%) of *O*-[(1*S*)-(3-cyclohexyl-isoxazol-5-yl)-ethyl]-hydroxylamine **41** as a colorless oil. **41** was treated with 2 mL acetone and then concentrated, and the resulting sample was subjected to HPLC-ELSD analysis using a Waters HPLC-MS system (XTerra®RP_8, 5 μm, 4.6×30 mm column) to determine the purity (>99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (s, 1H), 5.27 (q, 1H, J=7.2 Hz), 2.70 (m, 1H), 1.96 (m, 2H), 1.86 (s, 3H), 1.84 (s, 3H), 1.75 (m, 3H), 1.38 (m, 5H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 172.9, 168.3, 156.1, 99.4, 72.9, 35.8, 31.9, 25.88, 25.77, 21.7, 18.8, 15.7; IR (thin film) ν_{max} 2985, 2929, 2854, 1603, 1450, 1423, 1371, 1343, 1269, 1155, 1087, 986, 933, 891, 803 cm^{-1}; LRMS $[M]^+$ calculated for $C_{14}H_{22}N_2O_2$: 250.3, found: 250.4; $[\alpha]_D^{23}$=−2.9° (c=0.28, CH_2Cl_2).

4.2.7. *O*-[4-(3-Phenyl-isoxazol-5-yl)-benzyl]-hydroxylamine (acetone oxime of 38). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 4H), 7.46 (m, 5H), 6.80 (s, 1H), 5.10 (s, 2H), 1.91 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 170.4, 163.1, 155.9, 140.9, 130.1, 129.1, 129.0, 128.3, 127.5, 126.9, 126.7, 125.9, 97.4, 74.5, 21.8, 15.7; IR (thin film) ν_{max} 3106, 2922, 2856, 1620, 1566, 1503, 1463, 1367, 1074, 950, 816, 767, 671 cm^{-1}; LRMS $[M]^+$ calculated for $C_{19}H_{18}N_2O_2$: 306.4, found: 306.2.

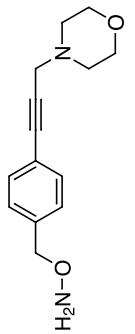
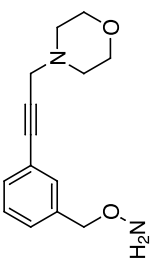
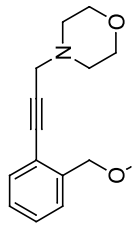
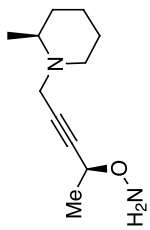
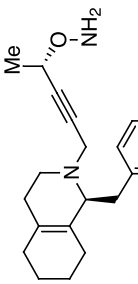
4.2.8. *O*-[3-(3-Phenyl-isoxazol-5-yl)-benzyl]-hydroxylamine (acetone oxime of 39). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) (spectrum of the major isomer reported) δ 7.85 (m, 2H), 7.84 (s, 1H), 7.76 (d, 1H, J=6.8 Hz), 7.46 (m, 5H), 6.82 (s, 1H), 5.12 (s, 2H), 1.91 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) (spectrum of the mixture of both isomers reported) δ 170.5, 163.1, 155.9, 155.8, 139.6, 138.7, 137.0, 130.1, 129.7, 129.1, 129.0, 128.8, 128.5, 128.4, 128.3, 127.5, 126.9, 125.2, 125.1, 121.4, 103.0, 97.6, 74.62, 74.56, 21.8, 15.7; IR (thin film) ν_{max} 3063, 2920, 2869, 1608, 1573, 1484, 1468, 1447, 1401, 1366, 1271, 1073, 1019, 921, 791, 767, 694 cm^{-1}; CIHRMS $[M]^+$ calculated for $C_{19}H_{18}N_2O_2$: 306.4, found: 306.2.

4.2.9. *O*-{(1*S*)-[3-(2,4,6-Trimethyl-phenyl)-isoxazol-5-yl]-ethyl}-hydroxylamine (acetone oxime of 40). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 6.07 (s, 1H), 5.38 (q, 1H, J=6.8 Hz), 2.29 (s, 3H), 2.12 (s, 6H), 1.88 (s, 3H), 1.85 (s, 3H), 1.66 (d, 3H, J=7.2 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 173.5, 161.9, 156.1, 138.7, 137.3, 128.3, 102.75, 102.67, 72.9, 21.6, 21.0, 20.1, 18.7, 15.6; IR (thin film) ν_{max} 2986, 2923, 1613, 1445, 1373, 1268, 1090, 1030, 986, 933, 890, 671, 656 cm^{-1}; LRMS $[M]^+$ calculated for $C_{17}H_{22}N_2O_2$: 286.4, found: 286.6; $[\alpha]_D^{23}$=+12.1° (c=1.57, CH_2Cl_2).

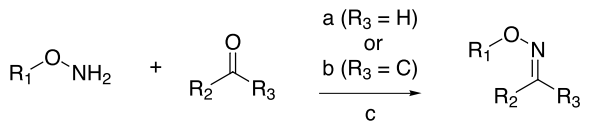
4.2.10. *O*-{(1*S*)-[3-(2,4-Dimethoxy-phenyl)-isoxazol-5-yl]-ethyl}-hydroxylamine (acetone oxime of 42). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 1H, J=2.8 Hz), 6.92 (m, 2H), 6.67 (s, 1H), 5.36 (q, 1H, J=6.8 Hz), 3.82 (s, 3H), 3.79 (s, 3H), 1.87 (s, 3H), 1.84 (s, 3H), 1.64 (d, 3H, J=7.2 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 172.9, 159.8, 156.1, 153.7, 151.7, 118.6, 117.2, 113.6, 113.1, 102.9, 72.7, 56.1, 55.8, 21.7, 18.6, 15.7; IR (thin film) ν_{max} 2990, 2937, 1602, 1511, 1471, 1438, 1372, 1275, 1226, 1045, 857, 745, 669 cm^{-1}; LRMS $[M]^+$ calculated for $C_{16}H_{20}N_2O_4$: 304.3, found: 304.2; $[\alpha]_D^{23}$=+4.5° (c=1.33, CH_2Cl_2).

4.2.11. Representative procedure for synthesis of propargylic amine-containing alkoxyamines (acetone oxime of 50). (*R*)-(+)-1-(4-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinolline (49.6 mg, 0.193 mmol) was mixed with

Table 3. Diverse propargylamine-containing alkoxyamines

Substrate					
	46	**47**	**48**	**49**	**50**
Yield (%)[a]	99	99	96	95	95
Purity (%)[b]	>99	>99	>99	>99	97

[a] Isolated yield based on the loading of the *N*-hydroxyphthalimide resin **1** resin (0.68 mmol/g).
[b] Purity determined by HPLC-ELSD analysis of the corresponding acetone oxime.



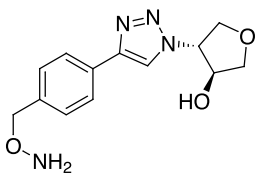
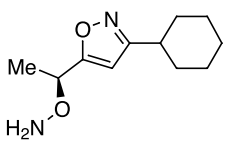
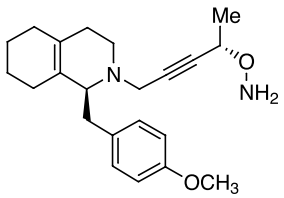
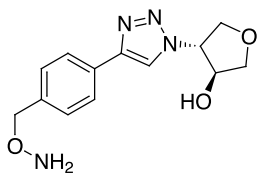
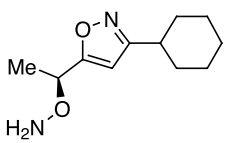
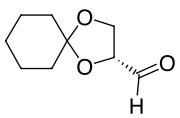
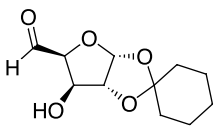
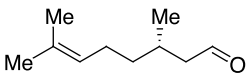
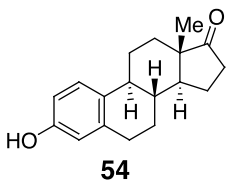
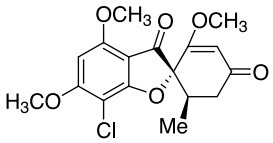
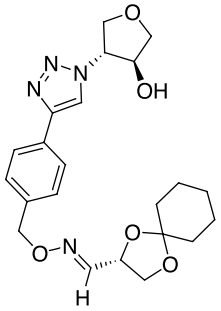
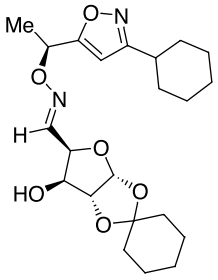
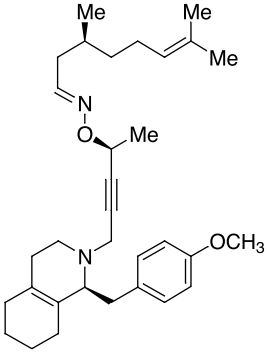
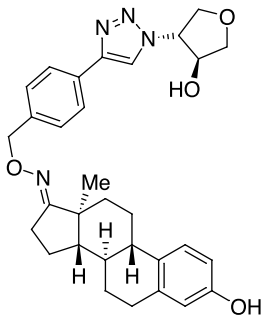
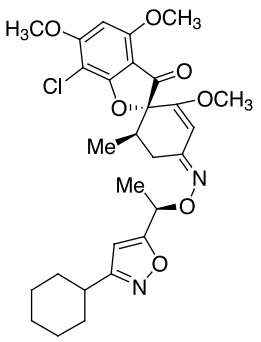
Scheme 12. Oxime formation. Reagents and conditions: (a) $ClCH_2CH_2Cl$, 120 °C, 150 W, 15 min. (b) HOAc, EtOAc, 150 °C, 150 W, 30 min. (c) PL-MIA, CH_2Cl_2, 4 h.

paraformaldehyde (9.2 mg, 0.29 mmol), *p*-TsOH·H_2O (36.7 mg, 0.193 mmol), and 1 mL CH_2Cl_2. The reaction mixture was stirred for 3 h and then concentrated. The resulting solid was mixed with 2 mL DMF and transferred to a 5 mL reaction vessel on the Quest-210 synthesizer containing the alkyne resin (0.0385 mmol, see procedure for preparation of **33**) and CuBr (2.7 mg, 0.0193 mmol, 50 mol%). The reaction was agitated at 50 °C for 12 h to afford the corresponding propargylic amine-containing resin. After filtration and resin washing with H_2O (2×3 mL), MeOH (1×3 mL), DMF (2×3 mL), MeOH (1×3 mL), 10% *N*,*N*,*N*′,*N*′-tetramethylethylenediamine in CH_2Cl_2 (2×3 mL), CH_2Cl_2 (1×3 mL), 5% AcOH in CH_2Cl_2 (2×3 mL), THF (3×3 mL) and CH_2Cl_2 (3×3 mL), 2 mL CH_2Cl_2 and NH_2NH_2 (2.5 μL, 0.077 mmol) was added and the reaction was agitated for 1 h. The reaction was filtered, the resin was washed with CH_2Cl_2, and the filtrate was collected and evaporated to provide 12.9 mg (0.0363 mmol, 70.7%) of *O*-{4-[(1*R*)-(4-methoxy-benzyl)-3,4,5,6,7,8-hexahydro-1*H*-isoquinolin-2-yl]-(1*S*)-methyl-but-2-ynyl}-hydroxylamine **50** as a pink oil. **50** was treated with 2 mL acetone, concentrated, and the resulting sample subjected to HPLC-ELSD analysis using a Waters HPLC-MS system (XTerra®RP_8, 5 μm, 4.6×30 mm column) to determine the purity (97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, 2H, *J*=8.4 Hz), 6.77 (d, 2H, *J*=8.4 Hz), 4.81 (q, 1H, *J*=6.7 Hz), 3.75 (s, 3H), 3.51 (dd, 2H, *J*=16.4, 38.0 Hz), 3.26 (s, 1H), 2.90 (m, 1H), 2.78 (m, 3H), 1.90 (m, 2H), 1.85 (s, 3H), 1.84 (s, 3H), 1.64 (m, 8H), 1.44 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 157.8, 155.4, 132.6, 130.2, 129.1, 127.7, 113, 68.4, 62.3, 55.1, 45.3, 43.5, 35.7, 30.0, 28.1, 27.9, 23.0, 22.7, 21.8, 21.1, 15.7; IR (thin film) ν_{max} 2086, 2928, 2832, 1613, 1512, 1440, 1368, 1326, 1247, 1176, 1072, 1038, 931, 824, 659 cm^{-1}; CIHRMS $[M]^+$ calculated for $C_{25}H_{34}N_2O_2$: 394.5, found: 394.3; $[\alpha]_D^{23}=-4.3°$ (*c*=0.55, CH_2Cl_2).

4.2.12. *O*-[4-(3-Morpholin-4-yl-prop-1-ynyl)-benzyl]-hydroxylamine (acetone oxime of 46). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 2H, *J*=8.0 Hz), 7.27 (d, 2H, *J*=8.4 Hz), 5.02 (s, 2H), 3.77 (t, 4H, *J*=4.8 Hz), 3.50 (s, 2H), 2.65 (t, 4H, *J*=3.6 Hz), 1.86 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 155.7, 138.7, 131.7, 127.7, 122.1, 85.7, 83.6, 74.7, 66.7, 52.2, 48.0, 21.8, 15.7; IR (thin film) ν_{max} 2922, 2855, 2814, 1510, 1454, 1367, 1117, 1072, 1012, 828, 669, 655 cm^{-1}; LRMS $[M]^+$ calculated for $C_{17}H_{22}N_2O_2$: 286.4, found: 285.9.

4.2.13. *O*-[3-(3-Morpholin-4-yl-prop-1-ynyl)-benzyl]-hydroxylamine (acetone oxime of 47). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.29 (m, 1H), 7.20 (m, 1H), 5.21 (s, 2H), 3.77 (t, 4H, *J*=4.4 Hz), 3.56 (s, 2H), 2.67 (t, 4H, *J*=4.4 Hz), 1.90 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 155.6, 140.2, 132.4, 128.4, 127.7, 127.3, 121.5, 88.2, 83.5, 73.4, 66.7, 52.1, 48.0, 21.8, 15.7;

Table 4. Synthesis of complex oximes

Alkoxyamines					
	29	**41**	**50**	**29**	**41**
Aldehyde/ketone					
	51	**52**	**53**	**54**	**55**
Products					
	57[a]	**58**[b]	**59**[c]	**60**	**61**[b]
Yield (%)	95	96	93	86	89
Purity (%)[d]	98	99	99	97	98

[a] Isolated as a 2:1 (*E*:*Z*) mixture of oximes, as determined by ^{1}H NMR (see Ref. 1a).
[b] Isolated as a 1:1 (*E*:*Z*) mixture of oximes, as determined by ^{1}H NMR (see Ref. 1a).
[c] Isolated as a 7:1 (*E*:*Z*) mixture of oximes, as determined by ^{1}H NMR (see Ref. 1a).
[d] Purity determined by HPLC-ELSD analysis.

IR (thin film) ν_{max} 2958, 2921, 2855, 2815, 1484, 1452, 1366, 1117, 1072, 1011, 761, 666 cm^{-1}; CIHRMS $[M]^+$ calculated for $C_{17}H_{22}N_2O_2$: 286.4, found: 285.9.

4.2.14. *O*-[2-(3-Morpholin-4-yl-prop-1-ynyl)-benzyl]-hydroxylamine (acetone oxime of 48). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.29 (m, 3H), 5.00 (s, 2H), 3.78 (t, 4H, J=4.0 Hz), 3.51 (s, 2H), 2.65 (m, 4H), 1.87 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 155.6, 138.7, 131.1, 131.0, 128.3, 127.8, 122.9, 85.8, 83.6, 74.6, 66.7, 52.3, 48.0, 21.8, 15.7; IR (thin film) ν_{max} 2956, 2924, 2855, 1484, 1453, 1367, 1267, 1118, 1073, 1006, 797, 692, 671 cm^{-1}; LRMS $[M]^+$ calculated for $C_{17}H_{22}N_2O_2$: 286.4, found: 285.9.

4.2.15. *O*-{(1*S*)-Methyl-4-[(2*S*)-methyl-piperidin-1-yl]-but-2-ynyl}-hydroxylamine (acetone oxime of 49). Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.83 (q, 1H, J=5.3 Hz), 3.69 (dd, 1H, J=2.0, 15.2 Hz), 3.36 (par obsc, 1H), 2.77 (m, 1H), 2.44 (m, 1H), 2.36 (m, 1H), 1.86 (s, 3H), 1.84 (s, 3H), 1.61 (m, 4H), 1.46 (d, 3H, J=6.8 Hz), 1.26 (m, 2H), 1.06 (d, 3H, J=6.0 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 155.6, 86.0, 78.4, 68.3, 54.7, 53.2, 43.5, 34.5, 26.0, 24.4, 21.8, 21.2, 19.8, 15.7; IR (thin film) ν_{max} 3283, 2931, 2855, 2801, 1650, 1544, 1440, 1372, 1322, 1157, 1074, 990, 932, 892, 656 cm^{-1}; LRMS $[M]^+$ calculated for $C_{14}H_{24}N_2O$: 236.4, found: 236.0; $[\alpha]_D^{23}$=+6.0° (c=0.61, CH_2Cl_2).

4.2.16. Representative procedure for the synthesis of oxime ethers from aldehydes. To a standard microwave reaction vessel (CEM Corp.) equipped with a stir bar was charged (*S*)-citronellal **53** (0.0044 mL, 0.024 mmol), *O*-{4-[(3*R*)-(4-methoxy-benzyl)-3,4,5,6,7,8-hexahydro-1*H*-isoquinolin-2-yl]-(1*S*)-methyl-but-2-ynyl}-hydroxylamine **50**, (0.0104 g, 0.0293 mmol, 1.2 equiv.), and dichloroethane (0.075 mL, 0.3 M). The mixture was heated under microwave irradiation for 15 min at 120 °C (300 W). The reaction mixture was cooled to rt and charged with PL-MIA resin (0.0063 g, 0.0162 mmol, 3 equiv.) and stirred at room temperature for 4 h. The resin was filtered and rinsed with CH_2Cl_2 (3×1 mL). The filtrate was concentrated under reduced pressure to yield (3*S*),7-dimethyl-oct-6-enal *O*-{4-[(1*R*)-(4-methoxy-benzyl)-3,4,5,6,7,8-hexahydro-1*H*-isoquinolin-2-yl]-(1*S*)-methyl-but-2-ynyl}-oxime **59** (0.0109 g, 0.0222 mmol, 93% yield) as a pink oil (7:1 mixture of *E*:*Z* oxime ethers). The product was subjected to an HPLC-ELSD analysis using a Waters HPLC-MS system (XTerra®RP_8, 5 μm, 4.6×30 mm column) to determine the purity (99%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, 1H, J=6.6 Hz, *E*), 7.16 (d, 2H, J=8.6 Hz), 6.76 (d, 2H, J=8.6 Hz), 6.69 (t, 1H, J=5.4 Hz, *Z*), 5.07–5.03 (m, 1H), 4.84–4.79 (m, 1H), 3.76 (s, 3H), 3.44 (dd, 2H, J=17.0, 42.4 Hz), 3.21 (m, 1H), 2.89–2.87 (m, 1H), 2.76 (m, 3H), 2.22–2.15 (m, 1H), 2.06–1.80 (m, 6H), 1.66 (s, 3H), 1.58, (s, 3H), 1.43 (d, 3H, J=6.6 Hz), 1.39–1.27 (m, 2H), 1.23–1.14 (m, 3H), 0.90 (d, 3H, J=6.6 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 151.1, 130.6, 130.2, 127.8, 124.4, 113.4, 77.2, 68.6, 62.3, 55.1, 45.3, 43.4, 36.7, 36.6, 36.3, 35.7, 32.6, 30.8, 30.5, 30.1, 29.6, 28.1, 25.6, 25.3, 23.0, 22.7, 21.0, 19.6, 19.3, 17.5; IR (thin film) ν_{max} 2926, 2834, 2739, 1613, 1512, 1458, 1376, 1327, 1247, 1177, 1072, 1040, 935, 830, 775, 661; LRMS $[M]^+$ calculated for $C_{32}H_{46}N_2O_2$: 490.4, found: 490.6; $[\alpha]_D^{23}$=+4.2° (c=0.28, CH_2Cl_2).

4.2.17. 1,4-Dioxa-spiro[4.5]decane-2-carbaldehyde *O*-{4-[1-[(4*R*)-hydroxy-tetrahydro-furan-(3*R*)-yl]-1*H*-[1,2,3]triazol-4-yl]-benzyl}-oxime 57. Pale yellow oil isolated as a 2:1 mixture of *E*:*Z* oxime ethers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.78 (d, 2H, J=7.9 Hz), 7.39 (m, 2H), 7.36 (d, 1H, J=8.2 Hz, *E*), 6.93 (d, 1H, J=4.3 Hz, *Z*), 5.14 (m, 1H), 5.09 (s, 2H, *E*), 5.08 (s, 2H, *Z*), 4.69 (m, 1H), 4.61 (dd, 1H, J=6.3, 12.9 Hz), 4.38 (dd, 1H, J=5.4, 10.4 Hz), 4.30 (dd, 1H, J=5.4, 10.1 Hz), 4.23 (dd, 1H, J=2.5, 10.4 Hz, 1H), 4.13 (dd, 1H, J=6.6, 8.6 Hz, *E*), 3.86–3.83 (m, 2H), 3.72 (dd, 1H, J=6.8, 8.4 Hz, *Z*), 1.59 (m, 8H), 1.38 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 153.0, 149.3, 147.9, 137.8, 137.6, 129.6, 128.9, 128.7, 128.4, 125.8, 125.7, 118.5, 110.9, 110.4, 77.1, 76.6, 75.9, 75.7, 74.0, 72.8, 70.8, 70.5, 68.5, 67.6, 67.0, 60.4, 36.0, 35.5, 34.8, 34.7, 29.6, 25.7, 24.9, 23.76, 23.72, 23.68, 20.9, 14.0; IR (thin film) ν_{max} 3410, 3137, 2933, 2856, 1447, 1366, 1232, 1164, 1110, 1076, 1041, 1014, 975, 930, 803, 696, 655 cm^{-1}; LRMS $[M]^+$ calculated for $C_{22}H_{28}N_4O_5$: 428.2, found: 428.2; $[\alpha]_D^{23}$=−20.2° (c=0.67, CH_2Cl_2).

4.2.18. 1,2-*O*-Cyclohexylidene-α-D-xylopentodialdo-1,4-furanose *O*-[(1*S*)-(3-cyclohexyl-isoxazol-5-yl)-ethyl]-oxime 58. Pale yellow oil isolated as a 1:1 mixture of *E*:*Z* oxime ethers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 1H, J=5.3 Hz, *E*), 6.85 (d, 1H, J=3.0 Hz, *Z*), 6.0 (s, 1H), 5.97 (d, 1H, J=3.6 Hz), 5.37 (dd, 1H, J=6.9, 13.7 Hz, *Z*), 5.31 (dd, 1H, J=6.9, 13.7 Hz, *E*), 5.01 (t, 1H, J=3.0 Hz, *Z*), 4.67 (m, 1H), 4.55 (t, 1H, J=3.3 Hz), 4.34 (d, 1H J=2.6 Hz, *E*), 2.74–2.67 (m, 1H), 1.96–1.94 (m, 2H), 1.81–1.78 (m, 2H), 1.72–1.64 (m, 4H), 1.60 (dd, 3H, J=6.9, 8.2 Hz), 1.57–1.52 (m, 4H), 1.49–1.31 (m, 6H), 1.28–1.23 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 172.2, 172.0, 168.9, 168.8, 150.7, 148.2, 113.1, 113.0, 105.1, 104.6, 100.7, 100.4, 85.0, 84.9, 78.4, 78.0, 76.7, 76.0, 74.3, 74.1, 36.8, 36.7, 36.1, 35.9, 32.3, 32.2, 32.1, 26.2, 26.1, 26.0, 25.1, 24.2, 24.1, 23.8, 18.8, 18.7; IR (thin film) ν_{max} 3415, 2934, 2865, 1604, 1451, 1371, 1341, 1291, 1232, 1076, 1019, 940, 867, 808, 759, 696, 674 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{22}H_{32}N_2O_6$: 420.2, found: 420.2; $[\alpha]_D^{23}$=−11.1° (c=1.22, CH_2Cl_2).

4.2.19. Representative procedure for synthesis of oxime ethers from ketones. To a standard microwave reaction vessel (CEM Corp.) equipped with a stir bar was charged estrone **54** (0.0079 g, 0.029 mmol), *O*-alkylhydroxylamine **30**, (0.0097 g, 0.035 mmol, 1.2 equiv.), acetic acid (0.025 mL, 0.44 mmol, 15 equiv.), and ethyl acetate (0.50 mL, 0.06 M). The mixture was heated under microwave irradiation for 30 min at 150 °C (300 W). The cooled reaction mixture was concentrated under reduced pressure. The mixture was re-suspended in dichloromethane (0.20 mL), and charged with PL-MIA (0.0071 g, 0.018 mmol, 3 equiv) and stirred at room temperature for 4 h. The resin was filtered and rinsed with CH_2Cl_2 (3×1 mL). The filtrate was concentrated under reduced pressure to yield 3-hydroxylestra-1,3,5(10)-triene-17-one *O*-{4-[1-[(4*R*)-hydroxy-tetrahydro-furan-(3*R*)-yl]-1*H*-[1,2,3]-triazol-4-yl]-benzyl}-oxime **60** (0.0133 g, 0.025 mmol, 86% yield) as a clear, yellow oil. The product was subjected to an HPLC-ELSD analysis using a Waters HPLC-MS system (XTerra®RP_8, 5 μm, 4.6×30 mm column) to determine the purity (97%). ^1H NMR (400 MHz, $CDCl_3$)

δ 7.80 (s, 1H), 7.68 (d, 2H, J=8.2 Hz), 7.30 (d, 2H, J=7.9 Hz), 6.99 (d, 1H, J=8.6 Hz), 6.52 (dd, 1H, J=2.6, 8.6 Hz), 6.46 (s, 1H), 5.01 (m, 1H), 4.97 (s, 2H), 4.47 (m, 1H), 4.25 (dd, 1H, J=5.6, 10.2 Hz), 4.16–4.11 (m, 2H), 3.71 (dd, 1H, J=3.3, 9.9 Hz), 2.73–2.69 (m, 2H), 2.48–2.38 (m, 2H), 2.24–2.20 (m, 1H), 2.14–2.09 (m, 1H), 1.95–1.90 (m, 1H), 1.81–1.75 (m, 2H), 1.52–1.22 (m, 6H), 1.16–1.12 (m, 2H), 0.82 (s, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 171.5, 153.7, 138.9, 138.1, 132.3, 129.1, 128.6, 128.4, 128.3, 126.5, 125.6, 118.5, 115.3, 112.8, 77.1, 74.9, 74.1, 70.1, 68.4, 52.8, 44.3, 43.8, 38.0, 34.0, 29.6, 29.4, 27.1, 26.0, 22.9, 17.2; IR (thin film) ν_{max} 3314, 3147, 3056, 2927, 2868, 1732, 1652, 1612, 1583, 1501, 1453, 1418, 1371, 1285, 1247, 1232, 1099, 1078, 1048, 1015, 983, 915, 853, 736, 667 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{31}H_{36}N_4O_4$: 528.3, found: 528.5; $[\alpha]_D^{23}=-3.8°$ (c=0.16, CH_2Cl_2).

4.2.20. (2*S*)-*trans*-7-Chloro-2′,4,6-trimethoxy-(6′*S*)-methyl spiro(benzofuran-2[3*H*], 1′-[2]cyclohexene)-3,4′-dione-4′ *O*-[(1*S*)-(3-cyclohexyl-isoxazol-5-yl)-ethyl]-oxime 61. Pale yellow oil isolated as a 1:1 mixture of *E*:*Z* oxime ethers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (s, 1H, *Z*), 6.08 (s, 1H), 6.01 (s, 1H), 5.56 (s, 1H, *E*), 5.28 (m, 1H), 3.99 (s, 3H), 3.94 (s, 3H), 3.58 (s, 3H, *E*), 3.51 (s, 3H, *Z*), 3.03 (dd, 1H, J=4.9, 16.8 Hz, *Z*), 2.92 (dd, 1H, J=13.2, 15.0 Hz, *E*), 2.74–2.65 (m, 1H), 2.64 (d, 1H, J=16.8 Hz, *Z*), 2.58–2.50 (m, 1H), 2.36 (dd, 1H, J=4.1, 15.0 Hz, *E*), 1.95 (m, 2H), 1.81–1.68 (m, 3H), 1.61 (d, 3H, J=6.6 Hz), 1.49–1.25 (m, 5H), 0.91 (d, 3H, J=6.3 Hz); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 194.3, 194.2, 172.7, 172.6, 169.6, 168.4, 164.5, 161.4, 158.8, 157.6, 157.5, 155.3, 152.0, 105.6, 99.7, 99.6, 99.0, 97.1, 93.2, 91.4, 91.3, 89.2, 89.1, 73.5, 73.4, 56.9, 56.3, 56.1, 55.9, 36.4, 35.8, 35.2, 31.9, 31.0, 29.6, 26.2, 25.9, 25.8, 18.7, 18.6, 14.2, 14.1; IR (thin film) ν_{max} 2930, 2853, 1707, 1613, 1590, 1466, 1351, 1220, 1141, 1099, 949, 912, 881, 733 cm^{-1}; CIHRMS $[M+H]^+$ calculated for $C_{28}H_{33}ClN_2O_7$: 544.2, found: 544.1; $[\alpha]_D^{23}=+85.6°$ (c=0.76, CH_2Cl_2).

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