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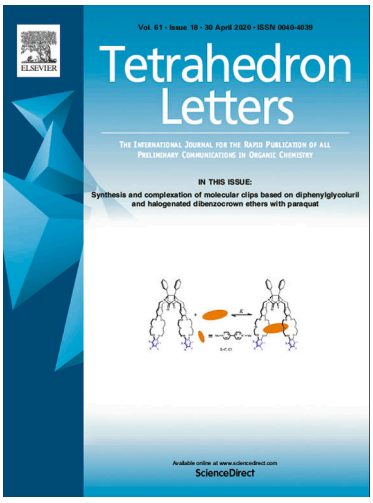

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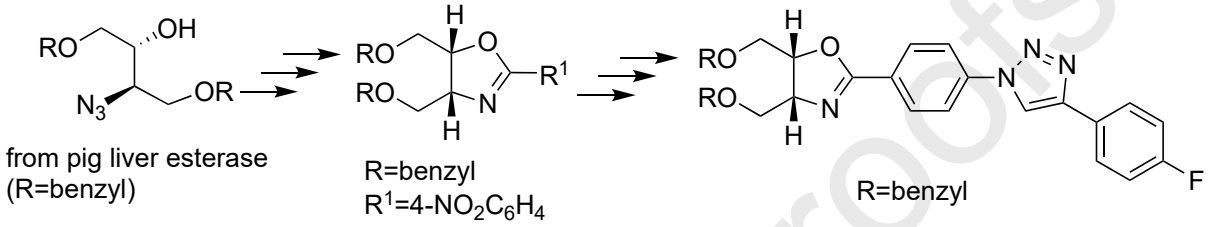

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Chemoenzymatic route to stereodefined 2-(azidophenyl)oxazolines for click chemistry

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ABSTRACT

Aryl-substituted esters of a racemic diprotected 2-azido-1-alkanol were submitted to the Staudinger/aza-Wittig reaction in order to assess scope and establish conditions for their cyclization to the corresponding 2,4,5-trisubstituted oxazolines. Following the cyclization study, the (2*R*,3*R*)-antipode of the azidoalkanol was obtained in high ee by incubation of the corresponding racemic azidoacetate with pig liver esterase (PLE). The *p*-nitrobenzoate of the enantioenriched 2-azido-1-alcohol was cyclized by the Staudinger/aza-Wittig to give the corresponding (4*R*,5*R*)-disubstituted-2-(4-nitrophenyl) oxazoline. Selective reduction of the nitrophenyloxazoline to the corresponding aminophenyloxazoline using aluminum amalgam followed by direct azidation of the 2-(4-aminophenyl) moiety provided the corresponding (4*R*,5*R*)-2-(4-azidophenyl) oxazoline derivative. The azidophenyl oxazoline was reacted with a proven click partner 4-ethynylfluorobenzene under copper/sodium ascorbate mediation to provide the click triazole product in high yield.

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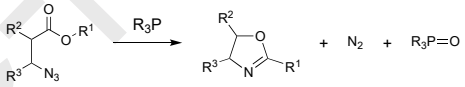
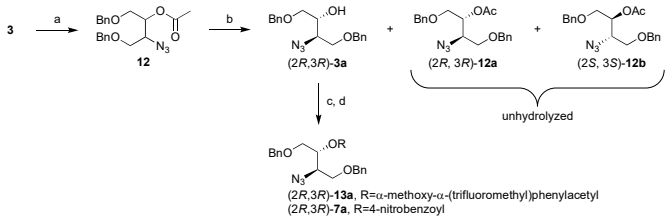
1. Introduction

Oxazolines and their substituted derivatives occupy a unique niche in the realm of nitrogen-oxygen heterocycles. Oxazoline-derived structural cores are found in natural products, medicinals, experimental therapeutics and polymers and are also functional molecules as they have been employed as chiral directing groups, ligands and protecting groups in synthetic chemistry.[1] Our research efforts have involved the design and development of oxazole-derived azides as reacting partners with arylacetylenes in the so called "click" reaction.[2] The product triazoles of interest have evolved from the development of *oxazole*-based peptidomimetic inhibitors of *Porphyromonas gingivalis* adherence to *Streptococcus gordonii* using click chemistry.[3] The adherence between *P.gingivalis* and *S. gordonii* is mediated by a protein-protein interaction which results in the generation of a dental biofilm. In turn the microbial community becomes resistant to many types of antibacterial therapy and ultimately leads to degradation of bone and dental structure. Consequently, any synthetic inhibitors of the adherence process will provide a unique therapy for the treatment of gingival disease propagated by *P. gingivalis* and the associated microbes. In the quest for adherence inhibitors with increased potency, we are presently exploring the replacement of the 2,4,5-trisubstituted oxazole motif with the corresponding 2,4,5-trisubstituted oxazolines (dihydrooxazoles). As evidenced by recent reports, oxazoline-based scaffolds are beginning to gain ground as functional peptidomimetics.[4] In contrast to the more planar trisubstituted oxazoles, the corresponding oxazolines offer a more three-dimensional motif with two ring stereocenters. Therefore, our goals were to develop a synthesis of stereodefined trisubstituted oxazolines which will constitute the basic scaffold of new adherence inhibitors. The stereodefined oxazolines should have potential for further synthetic elaboration[5] at the 4- and 5- positions, with the aid of suitable protecting groups,[5] as well as suitably-positioned azide functionality for the 'click' cycloaddition. We carefully considered several of the more common routes to 2-substituted oxazolines which included the dehydration of *N*-acylaminoalcohols[6a] and the bimolecular cyclocondensation routes involving aminoalcohols and imidates[6b] or aminoalcohols and nitriles.[6c] Finally, we decided on the pursuit of an oxazoline synthesis based on the relatively mild Staudinger/aza-Wittig reaction of azido esters (Scheme



Scheme 1. Staudinger/aza-Wittig route to oxazolines.

1).[7] The advantages of the Staudinger/aza-Wittig scheme are the effective access to the azidoester intermediates as well as the straightforward accommodation of their stereocenters which will ultimately be expressed in the oxazoline product. Moreover, through enzyme-mediated enantioselective hydrolysis of azido acetate derivatives, access to either antiopodal intermediate en route to the target oxazoline can be realized.

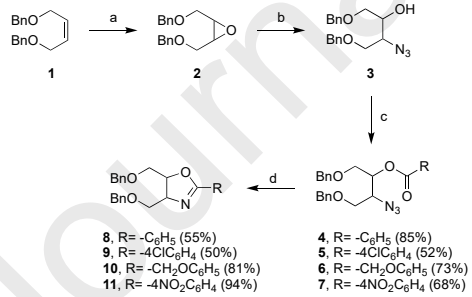


Scheme 3. Pig liver esterase-mediated hydrolysis of azidoacetate **12** giving (2*R*,3*R*)-**3a** followed by Mosher ester derivatization and acylation with 4-nitrobenzoyl chloride. Reagents/Conditions: (a) Ac_2O/pyridine/rt/1.5 h, 89%. (b) PLE/phosphate buffer/35 °C/7 days, 42%. (c) *R*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid/DCC/DCM/rt/48 h, 61% (d) 4-nitrobenzoyl chloride/pyridine/DMAP/DCM/rt/16 h, 97%.

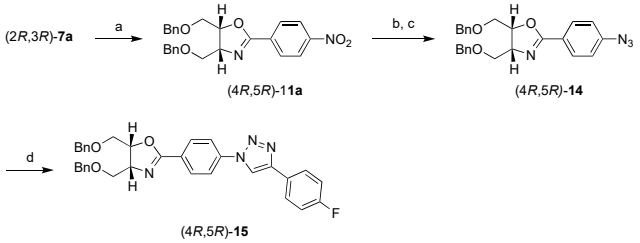
2. Results and Discussion

Our synthesis begins with the readily-available unsaturated dibenzyl ether **1** in which each benzyloxymethyl group is positioned to become the substituent groups at positions 4 and 5 of the oxazoline target (Scheme 2).[8] Epoxidation of **1** (mCPBA/CH_2Cl_2)[9] gave the (dibenzyloxy)epoxide **2** (80%) which upon treatment with sodium azide (DMF/100 °C/24 h) gave the (dibenzyloxy) azido alcohols **3** (97%). In order to establish conditions and explore the scope of the Staudinger/aza-Wittig reaction the dibenzyloxyazidoester substrates **4**, **5**, **6**, **7** were prepared from **3**. Hence, (dibenzyloxy) azido alcohol **3** was esterified with the appropriate acid chlorides (RCOCl) in the presence of base to give azido esters **4-7** which were purified by column chromatography on silica gel. Treatment of the azidoesters **4-7** with triphenylphosphine (1.5 eq.) in tetrahydrofuran (rt to 40 °C/16 h) gave the corresponding oxazolines **8-11** in 50-94% isolated yield. Thus, the reagents/conditions of the Staudinger/aza-Wittig reaction for conversions of azidoesters **4-7** to oxazolines **8-11** were found to be of general applicability.

With the conditions of the Staudinger/aza-Wittig cyclization now established, we then prepared the (dibenzyloxy)azidoalcohol (2*R*,3*R*)-**3a** generated from enantioselective esterase hydrolysis of the racemic acetate derivative **12** (Scheme 3).[10] Hence, the (dibenzyloxy)azidoalcohol **3** was then acetylated (acetic anhydride/pyridine/1.5 h/rt) to provide the (dibenzyloxy)-azidoacetate **12** (89%). Addition of the (dibenzyloxy)azidoacetate **12** to a suspension of pig liver esterase (PLE) in aqueous phosphate buffer (pH=7.4, 35 °C/7 days) gave the chromatographically-separable mixture of (2*R*,3*R*)-azidoalcohol **3a** $[\alpha]_D^{20}$ –14.2 (*c*=0.4, $CHCl_3$) (42% based on racemic **12**) and unhydrolyzed azidoacetates **12a**/**12b**. We were satisfied that the aqueous conditions offered by the pH=7.4 buffer ensured the optimum performance of the esterase as was the case in our previous work with esterase enzyme systems.[11] For comparison, we explored the enzymatic resolution of the azidoalcohol mixture using various lipases and vinyl acetate in organic solvents and found that the "reverse" enzymatic



Scheme 2. Preparation of oxazolines **8**-**11** from azidoesters **4**-**7**. Reagents/Conditions: (a) mCPBA/DCM/0 °C to rt/24 h, 80%. (b) NaN_3/DMF/100 °C, 24 h, 97%. (c) ROCl/Et_3N or pyridine/DMAP/DCM/rt/16-48 h. (d) PPh_3/THF/rt to 40 °C/16 h.



Scheme 4. Conversion of 4-nitrobenzoyl ester (2*R*,3*R*)-**7a** to oxazoline (4*R*,5*R*)-**11** followed by azidation to give click partner (4*R*,5*R*)-**14** and subsequent click reaction to afford (4*R*,5*R*)-**15**. Reagents/Conditions: (a) PPh_3/THF/rt to 40 °C/16 h, 78%. (b) Al(Hg)/THF/H_2O/rt/30 min. (c) $NaNO_2$/ NaN_3/AcOH/H_2O/0 °C to rt/1.5 h, 69% (two steps). (d) 4-ethynylfluorobenzene/$CuSO_4{\cdot}5H_2O$/sodium ascorbate/THF/H_2O/rt/16 h, 94%.

esterification mode was unsuccessful with these substrates. The absolute configuration of azidoalcohol (2*R*,3*R*)-**3a** was confirmed by correlation with products prepared in two separate previously reported syntheses from tartaric acid derivatives.[12a-d] Interestingly, after several enzymatic runs, our (2*R*,3*R*)-**3a** consistently gave a somewhat higher rotation than the azidoalcohol product obtained in one reported synthesis (Lit. $[\alpha]_D^{20}$ –10.5, *c*=0.4, $CHCl_3$).[12a] The enantiomeric purity of (2*R*,3*R*)-**3a** was determined by preparation of its Mosher ester **13a**[13] (See Supplementary Data) from (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(DCC/DMAP/ CH_2Cl_2), $[\alpha]_D^{20}$ +19.0 (*c*=0.18, $CHCl_3$)] and the ee was found to be >99% by ^{19}F NMR analysis. After chromatographic separation of azidoalcohol **3a** from the unhydrolyzed azidoesters, the presence of unhydrolyzed azidoester **12a** was confirmed by saponification ($LiOH/H_2O$) of the recovered azidoacetate mixture and revealed material of lower rotation, presumably due to the presence of the antipodal azidoalcohol derived from **12b**. Therefore, the **12a/12b** mixture could be recycled with fresh esterase to provide additional azidoalcohol (2*R*,3*R*)-**3a**. Starting with the esterase product azidoalcohol (2*R*,3*R*)-**3a**, treatment with 4-nitrobenzoyl chloride (pyridine/DMAP/CH_2Cl_2) afforded the corresponding 4-nitrobenzoyl ester (2*R*,3*R*)-**7a** [97%, $[\alpha]_D^{20}$ –21.8 (*c*=0.57, $CHCl_3$)]. Staudinger/aza-Wittig cyclization of 4-nitrobenzoyl ester (2*R*,3*R*)-**7a** (PPh_3/THF) gave the (4*R*,5*R*)-2-(nitrophenyl)oxazoline **11a** [78%, $[\alpha]_D^{20}$ +12.1 (*c*=0.34, $CHCl_3$)] after purification by flash-column chromatography. The reduction-azidation of the (nitrophenyl)oxazoline (4*R*,5*R*)-**11a** involved a two-step sequence whereby the arylnitro group was reduced with aluminum amalgam (THF/H_2O)[14,15] followed by direct treatment with sodium nitrite/sodium azide ($AcOH/H_2O$) to give azidophenyl-oxazoline (4*R*,5*R*)-**14** [69% over two steps, $[\alpha]_D^{20}$ +8.0 (*c*=0.07, $CHCl_3$)]. The (4*R*,5*R*)-2-(azidophenyl)-oxazoline **14** responded well to the click reaction with 1-ethynyl-4-fluorobenzene, a common co-reactant with several of our azidophenyloxazoles from previous studies.[3a-c] Thus, admixture of copper sulfate pentahydrate and sodium ascorbate to a solution of azidophenyloxazoline (4*R*,5*R*)-**14** and 1-ethynyl-4-fluorobenzene in THF/H_2O followed by stirring (16 h) gave the (4*R*,5*R*)-(oxazolinylphenyl)triazole click product (4*R*,5*R*)-**15** [94%, $[\alpha]_D^{20}$ +4.5 (*c*=0.16, CH_2Cl_2)] as a white solid after flash column chromatography on silica gel. The click product (4*R*,5*R*)-**15** was characterized by ^1H NMR as the 1,4-'anti'-disubstituted triazole whereby the regiochemistry of the cycloaddition is consistent with the copper (I)-catalyzed dipolar cycloaddition mechanism.[16]

3. Conclusions

The employment of a stereoselective enzymatic hydrolysis using pig liver esterase (PLE) combined with the Stauginger/aza-Wittig cyclization proves to be a mild and effective route to stereodefined 2-aryl-4,5-disubstituted oxazolines. Under the ideal conditions using aqueous phosphate buffer, the key intermediary β-azidoacetate is a substrate which yields the corresponding non-racemic azido alcohol in good yield and high ee. The use of aqueous conditions in the enzymatic step is a noteworthy example in of "green chemical" transformation and an otherwise eco-friendly step. The reduction-azidization sequence involving the aluminum amalgam reduction of the nitrophenyloxazoline was noteworthy and is an effective application to click chemistry as a result of our previous studies. The application of the esterase hydrolysis scheme will be applied to the complete stereochemical array of 4,5-disubstituted oxazolinyl intermediates followed by their conversion to adherence inhibitors and will be reported in due course.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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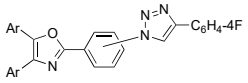

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Supplementary Data

Supplementary data features detailed experimental procedures, characterization data (^1H, ^{13}C and ^{19}F NMR, FTIR, and HRMS data), and copies of spectra is provided.

TETL-D-20-01402
Luzzio/Monsen
"Chemoenzymatic route to stereodefined 2-(azidophenyl)oxazolines for click chemistry"

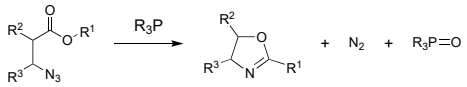
Highlights

- Cyclization under Mild Conditions
- Enzyme Hydrolysis under Aqueous Conditions
- High ee's

Luzzio, Monsen

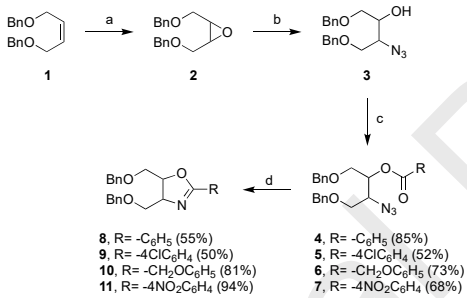
Figures:

Scheme 1



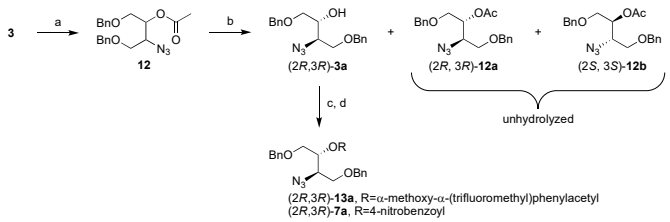
Scheme 1. Staudinger/aza-Wittig route to oxazolines.

Scheme 2



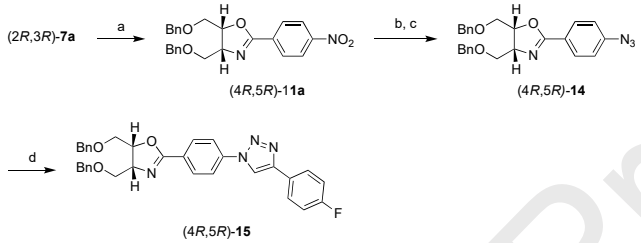
Scheme 2. Preparation of oxazolines **8**-**11** from azidoesters **4**-**7**. Reagents/Conditions: (a) mCPBA/DCM/0 °C to rt/24 h, 80%. (b) NaN_3/DMF/100 °C, 24 h, 97%. (c) ROCl/Et_3N or pyridine/DMAP/DCM/rt/16-48 h. (d) PPh_3/THF/rt to 40 °C/16 h.

Scheme 3



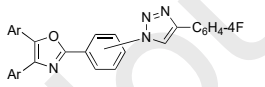
Scheme 3. Pig liver esterase-mediated hydrolysis of azidoacetate **12** giving (2*R*,3*R*)-**3a** followed by Mosher ester derivatization and acylation with 4-nitrobenzoyl chloride. Reagents/Conditions: (a) Ac_2O/pyridine/rt/1.5 h, 89%. (b) PLE/phosphate buffer/35 °C/7 days, 42%. (c) *R*-(+)- α-methoxy-α-(trifluoromethyl)phenylacetic acid/DCC/DCM/rt/48 h, 61% (d) 4-nitrobenzoyl chloride/pyridine/DMAP/DCM/rt/16 h, 97%.

Scheme 4

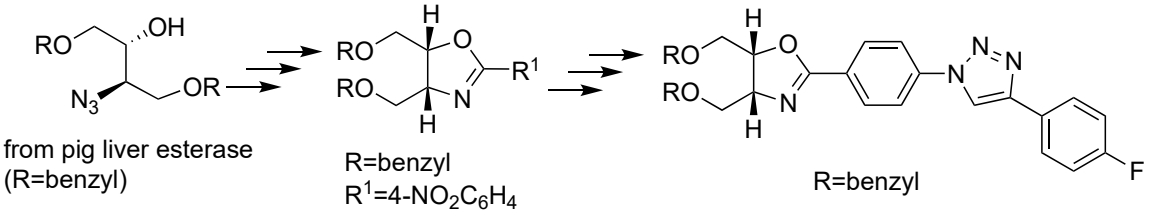


Scheme 4. Conversion of 4-nitrobenzoyl ester (2*R*,3*R*)-**7a** to oxazoline (4*R*,5*R*)-**11** followed by azidation to give click partner (4*R*,5*R*)-**14** and subsequent click reaction to afford (4*R*,5*R*)-**15**. Reagents/Conditions: (a) PPh_3/THF/rt to 40 °C/16 h, 78%. (b) Al(Hg)/THF/H_2O/rt/30 min. (c) $NaNO_2$/ NaN_3/AcOH/H_2O/0 °C to rt/1.5 h, 69% (two steps). (d) 4-ethynylfluorobenzene/$CuSO_4 \cdot 5H_2O$/sodium ascorbate/THF/H_2O/rt/16 h, 94%.

Reference 3 Figure



TETL-D-20-01402
Luzzio/Monsen
Abstract Graphic



from pig liver esterase
(R=benzyl)

R=benzyl
R^1=4-$NO_2C_6H_4$

R=benzyl