SYNTHESIS OF SUGARS AND STEROID CONJUGATES *VIA* 1,3-DIPOLAR CYCLOADDITION REACTIONS OF NITRILE OXIDES

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Joaquín Plumet
Department of Organic Chemistry, Faculty of Chemistry, Complutense University, 28040 Madrid, Spain
(e-mail: plumety@ucm.es)

Abstract. *The C-glycosyl derivatives of isoxazolines and isoxazoles show important biological activities. The use of the 1,3-dipolar cycloadditions (1,3-DC) of nitrile oxides (NOs) in the synthesis of these compounds will be described in detail, considering both inter- and intramolecular variants of these reactions. On the other hand, steroids are preferred synthons for the development of diverse bioconjugates. The application of novel steroidal NOs as reagent for the synthesis of isoxazole-linked steroidal glycoconjugates will be also described.*

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1. Introduction and objectives

The chemistry of NOs[1] is well documented since the discovery of fulminic acid,[2] the parent compound, in 1800.[3] Benzonitrile oxide (BNO) was generated for the first time in 1886[4] and the intermediacy of NOs in a 1,3-DC reaction was suggested in 1946.[5] The cycloadditions (CAs) of NOs to olefins were developed in 1950[6] and in 1961, Huisgen categorized the NOs as a member of a broader class of 1,3-dipoles that were capable of undergoing 1,3-DC reactions. In the 1960s and 1970s the factors governing the reactivity and selectivity of NOs CAs were brilliantly described and systemized by Huisgen and coworkers.[7] NOs belong to the class of 1,3-dipoles known as "nitrilium betaines". The main aspects related to the structure, stability and preparation of NOs have been recently reviewed.[8]

Glycoconjugates are carbohydrates covalently linked to a non-sugar moiety. In this context, carbohydrate derivatives and, in particular, C-glycosyl compounds have attracted much attention in the last two decades due to the existence of a number of naturally occurring representatives. The biological activities of C-glycosyl derivatives of isoxazolines and isoxazoles as antidiabetic, antioxidants, antiviral, antibacterial, anticancer and antimalarial agents, among others, have been tested. It should be indicated that the synthesis and biological activities of this kind of compounds have been recently reviewed in two excellent accounts.[9]

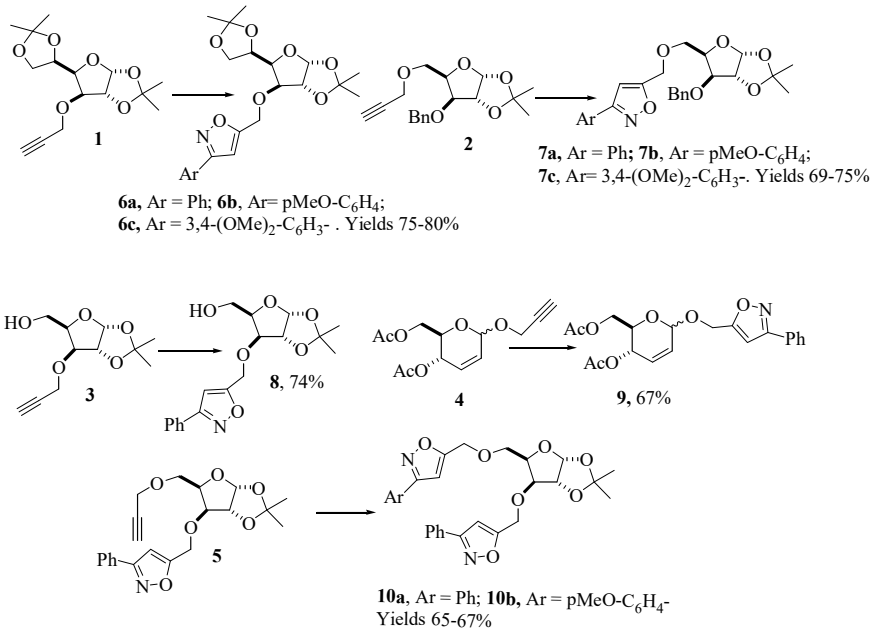
On the other hand, steroids are preferred synthons for the development of diverse bioconjugates.[10] This is because steroids have different functionalization points, broad biological activity profile and ability to penetrate the cell membrane and bind to specific hormonal receptors.

Isoxazoles and isoxazolines are valuable linkers in conjugate chemistry considering that these heterocyclic ring systems are frequently present in biologically active compounds that are designed to treat infections and diseases of different etiologies. On the other hand, they also are used as building blocks in the synthesis of new potential drugs. The 1,3-DC reaction of NOs with carbon dipolarophiles is a versatile and powerful synthetic method to prepare these heterocyclic systems. Consequently, the NOs CA chemistry must playan important role in the construction of sugar and steroids conjugates with isoxazoles and isoxazolines. The most recent and, in our opinion, significant advances in this context are the objective of this report. The literature consulted covers up to February 2019.

2. Sugar conjugates

2.1. Intermolecular cycloadditions

Sugar conjugates of isoxazoles **6-10** were synthesized[11] *via* 1,3-DC of carbohydrate derived alkynes and *in situ* generated NOs from oximes (Scheme 1). The dipolarophiles **1-5** were prepared from D-glucose following standard procedures. NOs were generated from the biphasic oxidation of the corresponding oximes with NaOCl in dichloromethane-triethyl amine.



Scheme 1. Synthesis of isoxazole conjugates of sugars *via* 1,3-DC of NOs.
Reaction conditions: ArCH=NOH, CH_2Cl_2, Et_3N, 0 ºC to r.t., NaOCl, 8-10 h.

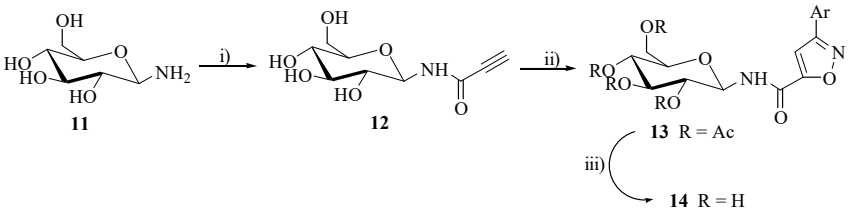
Compounds of general structure **13** and **14**, synthesized[12] as indicate in Scheme 2 have been tested as inhibitor of rabbit muscle glycogen phosphorylase (GP).[13]

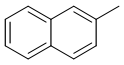
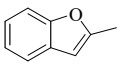
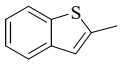
Compound **16**, prepared from 2,3,4,6-tetra-*O*-benzylglucono-1,5-lactone **15** (Scheme 3)[14] *via* Tebbe methylenation,[15] reacts[16] with carbomethoxy NO **17** and ribose NO **18**[17]to give single isoxazolines **19** and **20**, respectively.

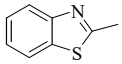
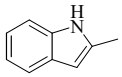
The conversion of hex-5- and pent-4-enofuranosides into six- and five-membered carbocycles respectively has been achieved[18] involving 1,3-DC followed by reductive cleavage of the resulting isoxazolines (Scheme 4). In the case of cycloadducts **22** a single diastereoisomer was formed whereas the glucose analogs provided a 9:1 mixture of diastereoisomers **25** being the major one depicted in Scheme 4. Reductive N-O bond cleavage led carbocyclic products with, in some cases, concomitant missing of MeO and OH groups at position 1. When R=Me, 1,3-diketone compounds **23e** and **26d** were also formed. Enol forms of these compounds are depicted in Scheme 4. The reaction path for the sequence hydrogenation-ring closure may be explained considering the first formation of enaminone **I** which underwent intramolecular aldol-like condensation to give **II**. Hydrogenation of the double bond formed the final product **III** (Scheme 5). In the case of hydrogenation of **22a**, the condensation stops after the first step without subsequent elimination. When R=Me, the enaminones **23c** and **26c** are not enough stable and are partially hydrolysed to diketones **23e** and **26d**.

The synthesis of spiro-isoxazoline C-disaccharides *via* stereoselective 1,3-DC of *exo*-glycals to sugar NOs has been reported.[19] The *exo*-glycals **27-29** (Scheme 6) were prepared by the methylenation from their corresponding sugar lactones with Petasis's reagent.[20] The sugar NOs were generated from oximes **31**, **33**

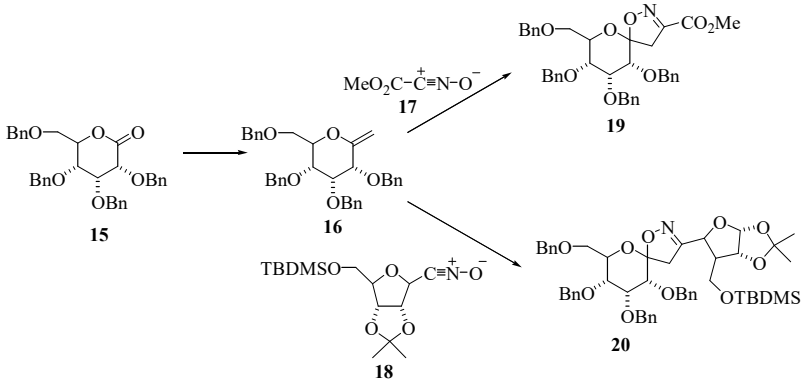
and **35**, synthesized from the corresponding sugar aldehyde derivatives **30**, **32** and **34** (Scheme 6a).[21] The 1,3-DC of glycals **27** and **28** with NOs generated from oximes **32**, **34** and **36** underwent stereospecifically giving exclusively cycloadducts **36-41** (Scheme 6b). However, the CA of the *exo*-galactal **29**with the NO generated from oxime **31** provided an inseparable mixture of two anomeric isomers (diastereoisomers) **42** and **43** in the ratio of 3:2.



Compound	Ar	Yields 13	Yields 14
13a, **14a**	Ph	55	97
13b, **14b**		52	91
13c, **14c**		50	88
13d, **14d**		51	95

Compound	Ar	Yields 13	Yields 14
13e, **14e**		30	90
13f, **14f**		24	76
13g, **14g**		20	70

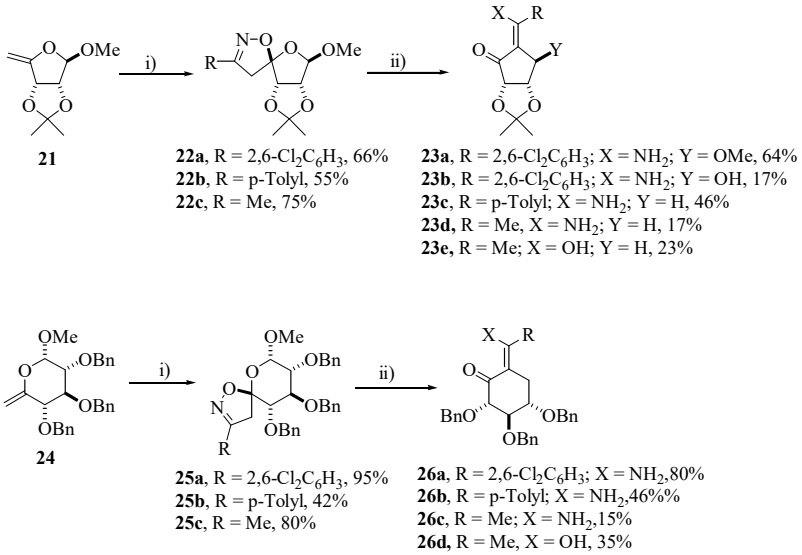
Scheme 2. Synthesis of potential inhibitors of RMGPb. Reaction conditions:i) propiolic acid, DCC, CH_2Cl_2, r.t., 88%; ii) Ar-CH=NOH. NaOCl, THF-H_2O; iii) MeONa, MeOH.



Scheme 3. Synthesis of spiroisoxazolines **19** and **20**.

Debenzylation of cycloadducts **36-43** was carried out by catalytic hydrogenation. In the case of the compounds **44** and **45** they could be readily isolated by flash column chromatography (Scheme 7). The glycosidase inhibitory activities of the debenzoylated compounds were examined on hydrolytic reactions of α-amylase, α-glucosidase, and β-glucosidase by comparison with acarbose.[22] All tested compounds gave low inhibitory effects on the glycosidases contrasted to the positive control, although a certain inhibitory selectivity to the three glycosidases was observed. The inhibitory activities of the compounds against the

enzymes are in the order of α-amylase>β-glucosidase>α-glucosidase.[23] The antiviral activities of the spiro-isoxazoline disaccharides on HIV-1,[24] BVDV[25] and MDBK[26] cells were also evaluated. It was found that the tested compounds had little inhibitory effects in all cases.



Scheme 4. Synthesis of carbocycles **23** and **26** from pent-4-enofuranosides **21** and hex-5-enopyranosides **24**. Reaction conditions: i) 2,6-$Cl_2C_6H_3CNO$, CH_2Cl_2, reflux, 4 h. for compounds **22a** and **25a**; *p*-MeC_6H_4CH=NOH, NCS, pyridine, Et_3N, $CHCl_3$, reflux, 90 min. for compounds **22b** and **25b**; $CH_3CH_2NO_2$, PhNCO, Et_3N, benzene, 20 ºC, 5 days for compounds **22c** and **25c**; ii) Ni-Raney, $MgSO_4$, H_2 (1 atm.), MeOH-CH_3CO_2H, 20 ºC, 90 min.

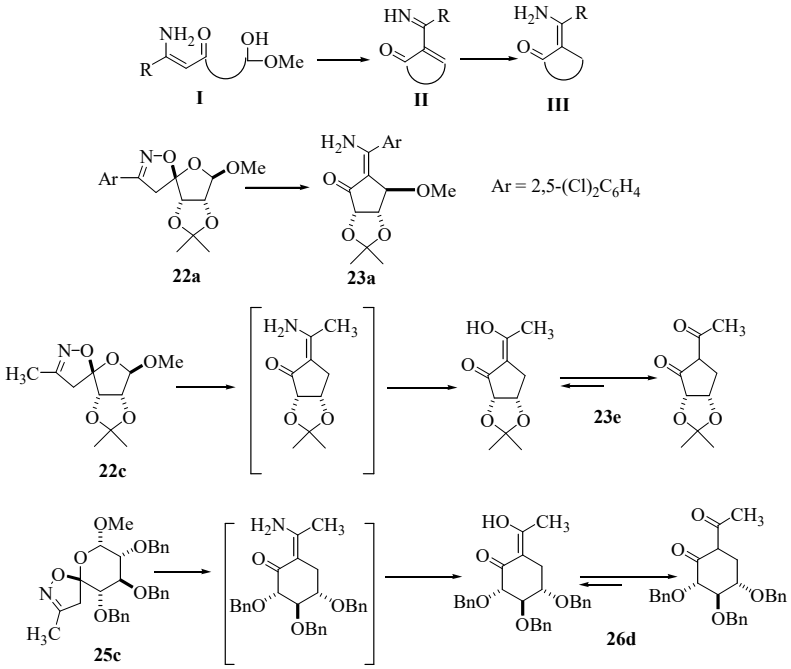
A method for the synthesis of spiroisoxazolines derived from carbohydrates by a sequence involving the Wittig reaction and 1,3-DC as key steps has been published (Scheme 8).[27] Wittig reactions of the phosphonium salt[28] **46** with benzaldehyde and acetaldehyde using n-BuLi in THF furnished the exocyclic enol ethers **47a** and **47b**. The *E* and *Z* isomers could be separated by MPLC on silica gel. The CAs of the olefinated sugars **47** were performed with two NOs: mesitonitrile oxide (compounds **48a** and **48b**) and ethoxycarbonylnitrile oxide (MW irradiation, generated from oxime **50**), to give cycloadducts **49a** and **49b**.

A series of spiro-isoxazolines **53** and **54** were obtained[29] by CA of NOs **51** to the peracetylated *exo*-glucal **52a** and perbenzoylated *exo*-glucal **52b** (Scheme 9).[30] These GP inhibitors exhibited IC50 values in the micromolar range. The 2-naphthyl substituted glucopyranosylidene-spiro-isoxazoline was the best compound identified, lowering glucose levels in blood of nearly 33% at a dose of 30 mg/kg.

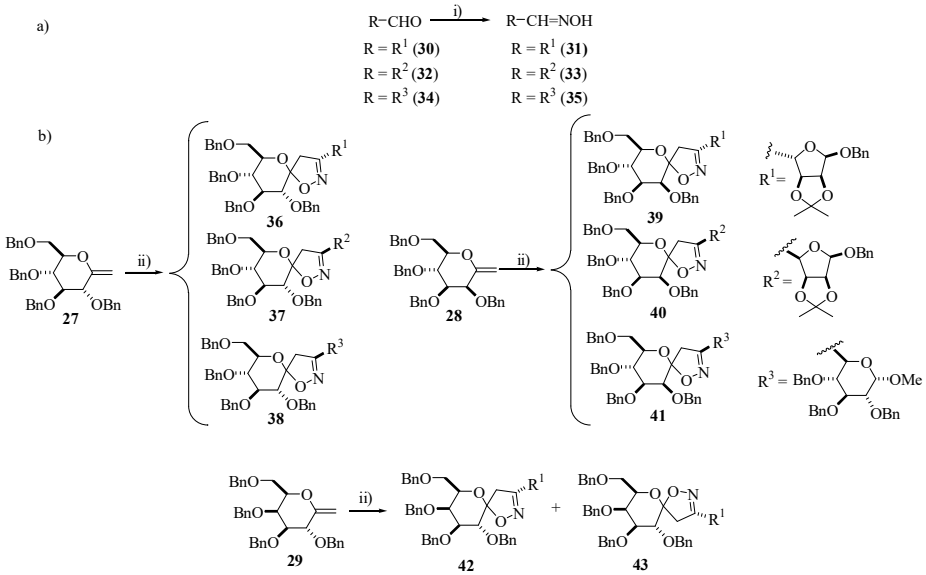
The stereoselective synthesis of 3-(2′-C-3′,4′,6′-tri-*O*-benzylglycal)-Δ2-isoxazolines **56** and **57** (Scheme 10) has been reported.[31] In this case, the NOs derived from the corresponding sugar oximes were generated by means of reaction of these oximes with iodosobenzene[32,33] in neutral aqueous organized media at room temperature and using CTAB (hexadecyltrimethylammonium bromide, ~33 mol %) as surfactant agent.

2.2. Intramolecular cycloadditions

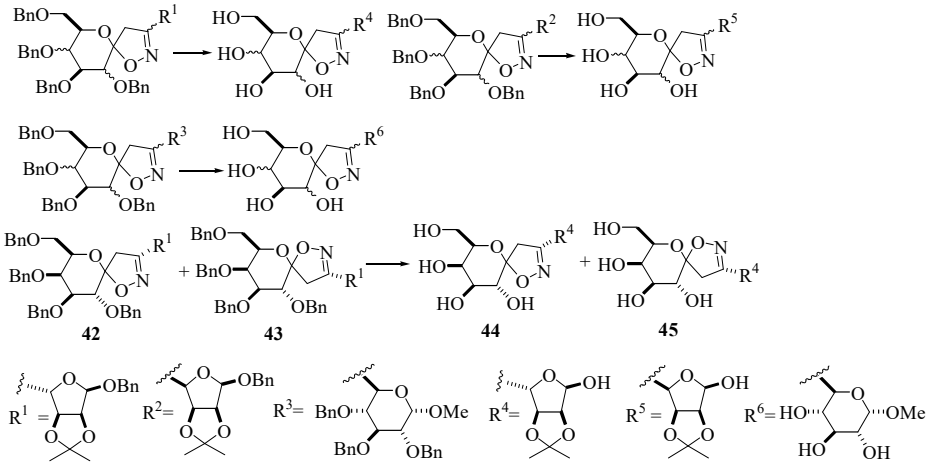
The intramolecular 1,3-DC (IMDC) of NOs[34] and especially with sugar-NOs[35] constitutes a versatile synthetic tool for the fabrication of fully functionalized heterocycles of different ring sizes. Some selected examples on the synthesis of carbohydrate conjugates using IMDC of NOs are disclosed in the following paragraphs.



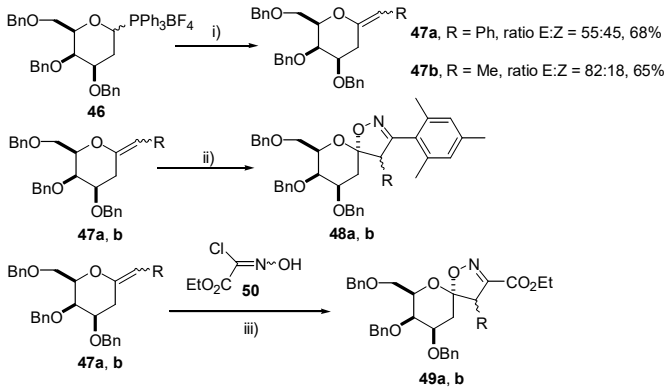
Scheme 5. Reaction path for the hydrogenation of compounds **22** and **25**.



Scheme 6. Synthesis of spiro-isoxazoline C-disaccharides. Reaction conditions: i) $NH_2OH.HCl$, THF, Na_2CO_3, r.t., 1 h.; ii) oximes **31**, **33** and **35**; a. NCS, $ClCH_2CH_2Cl$, reflux, 20 min.; b. Et_3N, r.t.; c. dipolarophiles **27**, **28** and **29**. Yields: **36**, 50%; **37**, 71%; **38**, 65%; **39**, 50%; **40**, 83%; **41**, 81%; **42**+**43**, 52%. Ratio **42**:**43**=3:2.



Scheme 7. Debenzylation of cycloadducts **36**-**43**. Reaction conditions in all cases: H_2, $Pd(OH)_2$/C, MeOH, 2 h. Yields 30-85%.

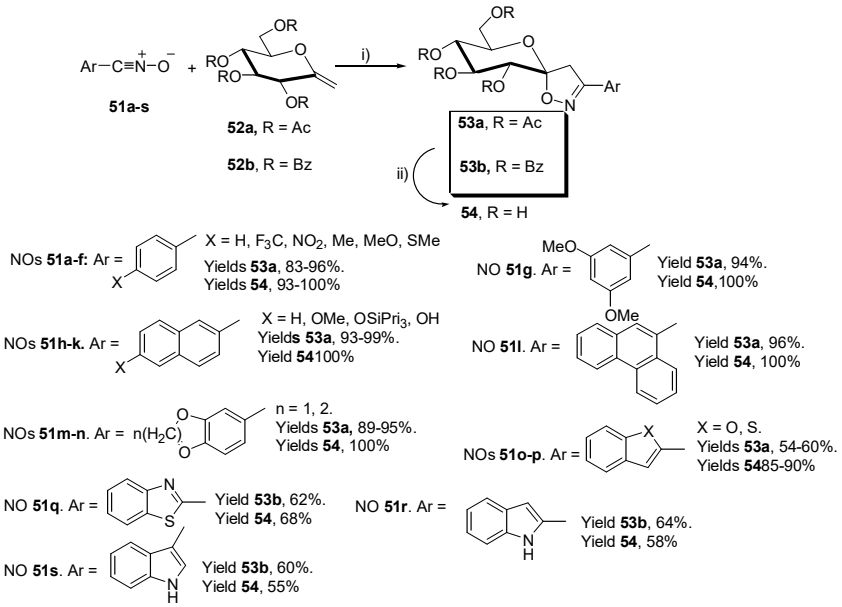


Scheme 8. Synthesis of spiroisoxazolines **48** and **49**. Reaction conditions: i) a. nBuLi, THF, -90 ºC; b. RCHO, -90 ºC to r.t.; ii) Mesitonitrile oxide, CH_2Cl_2. From *E*-**47a**, 20 days, r.t., *trans*-**48a**, 85%. From *Z*-**47a**, 20 days, r.t., *cis*- **48a**, 86%. From *E*-**47b**, reflux, 30 h., *trans*-**48b**, 78%; iii) **50**, Et_3N, MW (400 W), 15 min. From *E*-**47a**, *trans*-**49a**, 42%. From *Z*-**47a**, *cis*-**49a**, 45%. From *E*-**47b**,*trans*-**49b**, 70%.

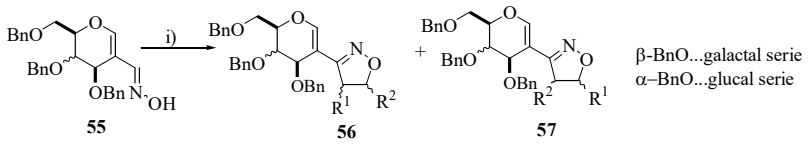
The NO CAs of acyclic 2-*O*- and 4-*O*-allyl and propargyl glucose derivatives has been described.[36] The sugar-NOs were generated from oximes **62**, **65**, **85**, **86**, **87** and **88** and from nitroderivative **63**. The synthesis of these precursors was carried out starting from commercially available glucose dithioacetal **58** and 1,2-isopropylidene glucose derivative **66** (Scheme 11).[37] From these precursors, the IMDC were carried out to give compounds **89**-**95** (Scheme 12).

The mixture silica gel-chloramine-T has been used for the IMDC reactions of substrates having one to four free hydroxyl group(s).[38] The synthesis of the starting sugar derivatives as well as the corresponding intramolecular CAs is summarized in the Schemes 13 and 14, respectively.

Using Montmorillonite K-10 (MK-10) as acidic support, a versatile methodology for the synthesis of isoxazoline fused highly functionalized carbocycles has also been published.[39] The substrates employed for the CA were synthesized from D-ribose as indicated in Scheme 15. Synthesized lactols **136**, **137**, **140**, **145**-**148** were then converted to their corresponding oximes which were oxidized to NOs. The *in situ* intramolecular 1,3-CA afforded the isoxazolines **149**-**155** (Scheme 16).



Scheme 9. Synthesis of spiro-isoxazolines **53** and **54**. Reaction conditions: i) NOs **51a**, **51f-51j** and **51l-51s** were generated from the corresponding α-chloroaldoxime in THF, NaOCl, overnight, r.t.
NOs **51b-51d** were generated from the corresponding α-chloro aldoxime in CH_2Cl_2, Et_3N, r.t., overnight; ii) MeONa, MeOH.

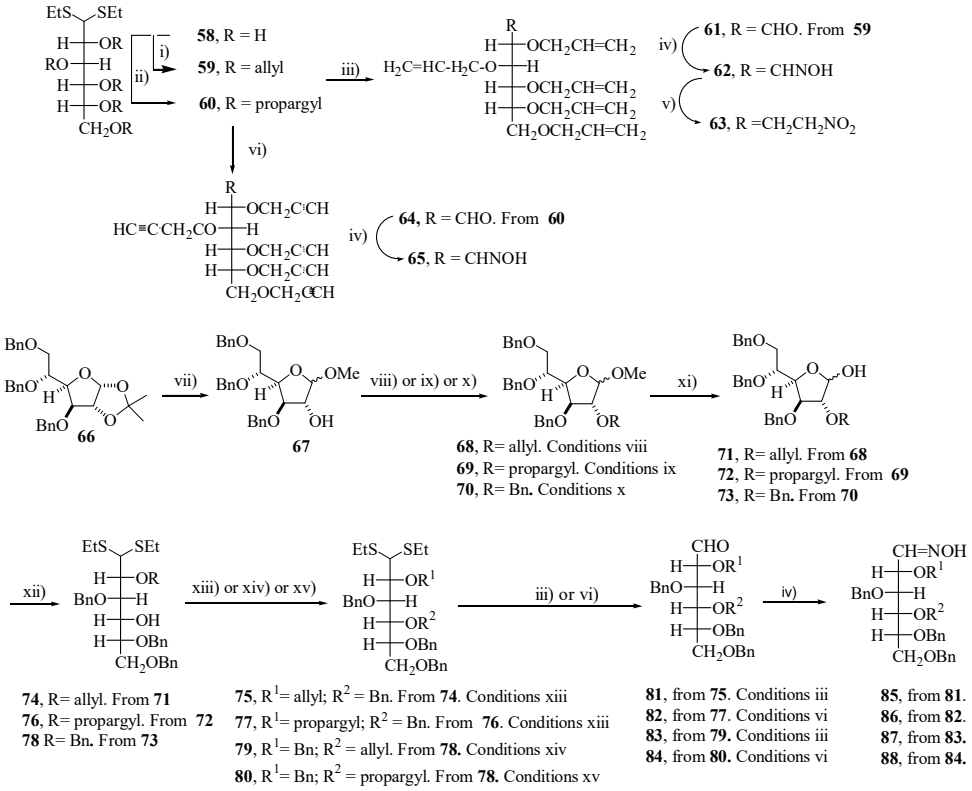


Serie	R^1	R^2	Reaction time (h.)	Selectivity*	Yield
Galactal	H	Ph	3	72:28	58
Galactal	H	CN	3	68:32	58
Galactal	Ph	CO_2Et	3.5	66:34	64
Glucal	H	CN	3	65:35	57

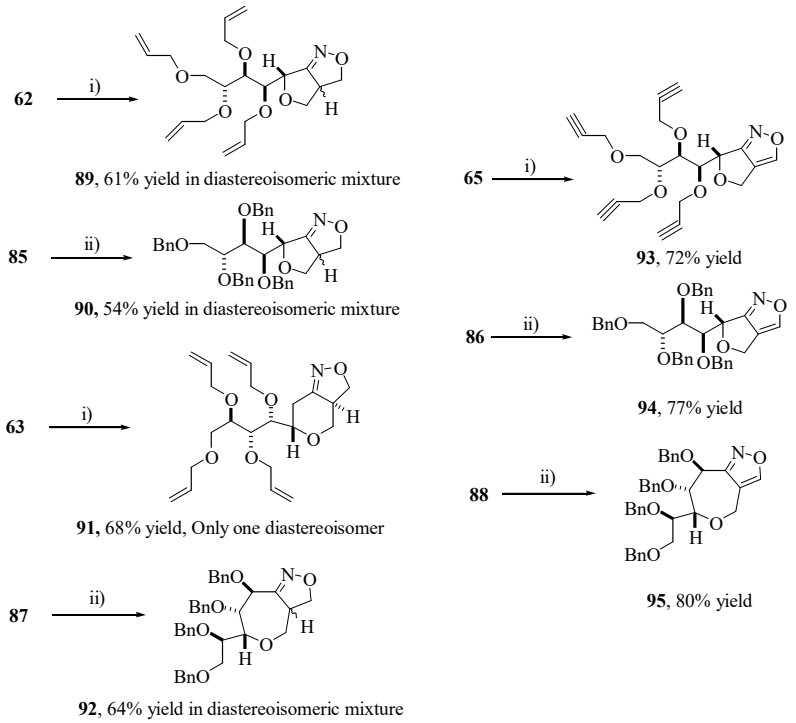
* Major regioisomer was specified.

Scheme 10. Synthesis of glycal derived Δ2-isoxazolines. Reaction conditions: i) PhIO, H_2O, CTAB, dipolarohile R^1-CH=CH-R^2, r.t.

Intramolecular NOs cycloadducts were readily converted[40] into the saturated gabosines[41] F **168** (thereby confirming its absolute configuration), gabosine O **163** and 4-*epi*-gabosine O **160**. Starting from the epimeric mixture of isoxazolines **156**the configuration of the free alcohol in this compoundwas inverted by Mitsunobu reaction followed by ester hydrolysis, resulting in almost quantitative transformation into the mixture of alcohols **157**. Hydrogenolysis of **157** with Raney-Ni/acetic acid,[46] gave the corresponding hydroxy ketone. Martin's sulfurane (a very powerful dehydration reagent: $Ph_2C[O(CF_3)_2Ph]_2$)[47,48,49] reaction followed by catalytic hydrogenation with Raney-Ni at -78 °C afforded **159**in excellent overall yield. Finally, acid hydrolysis of ketone **159** afforded target **160** in a quantitative yield (Scheme 17a).



Scheme 11. Synthesis of NO precursors **62**, **63**, **65**, **66**, **85**, **86**, **87** and **88**.
Reaction conditions: i) NaH, allyl bromide, DMF, 25 ºC, 96%;
ii) NaH, propargyl bromide, DMF, 25 ºC, 12 h., 88%;
iii)[42] $HgCl_2$, $CaCO_3$, CH_3CN:H_2O (4:1), 25 ºC, 6 h., 96% for **61**; 92% for **81**; 91% for **83**;
iv) $NH_2OH.HCl$, pyridine, MeOH, reflux, 72% for **62**; 66% for **65**; 59% for **85**; 64% for **86**; 82% for **87**; 67% for **88**;
v)[43] a. CH_3NO_2, KF, 2-propanol, 25 ºC, 15 h.; b. Ac_2O, DMAP, CH_2Cl_2, 25 ºC, 12 h.; c. $NaBH_4$, EtOH, 0-25 ºC, 6 h., 71% three steps;
vi)[44,45] a. $NaIO_4$, EtOH, 25 ºC, 10 h.; b. H_2SO_4,THF, 25 ºC, 12 h., 72% for **64**, 86% for **82**; 82% for **84**;
vii) TsOH, MeOH, reflux, 6 h., 98%;
viii) allyl bromide, Bu_4NBr,NaOH, CH_2Cl_2, 25 ºC, 12 h., 91%;
ix) propargyl bromide, Bu_4NBr, NaOH, CH_2Cl_2, 25 ºC, 12 h., 88%;
x) benzyl bromide, Bu_4NBr, NaOH, CH_2Cl_2, 25 ºC, 12 h., 90%;
xi) TFA aq., 25 ºC, 24 h., 96% for **71**, 94% for **72**, 89% for **73**;
xii) EtSH, H_2SO_4, 0 ºC, 30 h., 81% for **74**, 76% for **76**, 73% for **78**;
xiii) NaH, benzylbromide, THF, 25 ºC, 12 h., 65% for **75**, 78% for **77**;
xiv) NaH, allyl bromide, THF, 25 ºC, 12 h., 61%;
xv) NaH, propargyl bromide, THF, 25 ºC, 12 h., 73%.



Scheme 12. IMDC reactions of NO substituted allyl and propargyl glucose derivatives. Reaction conditions: i) Chloramine T, EtOH, reflux; ii) 4-chlorophenyl isocyanate, Et_3N, benzene, 25 ºC.

From the mixture of isoxazolines **156** the mixture of ketones **161** was also obtained *via* hydrogenolysis with Raney-Ni in acetic acid (Scheme 17a). Further regioselective dehydration of the primary alcohol with Martin's sulfurane at -78 °C gave enone **162** which bycatalytic hydrogenation with Raney-Ni followed by hydrolysis afforded natural gabosine O **163** (Scheme 17a). On the other hand, the heterocyclic ring in isoxazoline **166** was hydrogenolyzed over Raney-Ni smoothly to give hydroxy ketone **165**. Regioselective acetylation[50] of the primary alcohol in **165** with collidine as base furnished acetate **166** in 87% yield. Elimination of acetic acid from R-acetoxy ketone **166** with triethylamine gave the corresponding exocyclic enonewhich, by catalytic hydrogenation over Raney nickel affored the α-methyl ketone **167**. Removal of the *trans*-diacetal blocking group then furnished the target molecule gabosine F **168** (Scheme 17b).

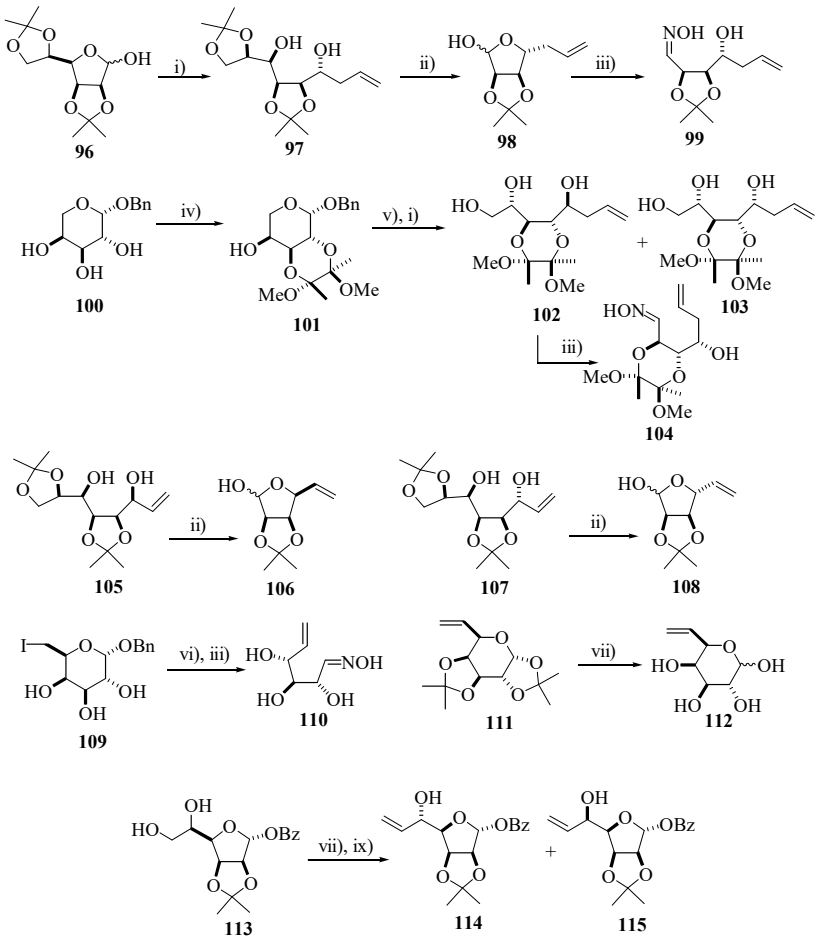
The intramolecular version of the previously described methodology (see reference 34) was explored. Thus, glycal-based aldoximes **169** and **170** were oxidized by PhIO in aqueous media to corresponding NOs and their *in situ* intramolecular CA constructed optically pure 2,8-dioxabicyclo-[4.4.0]decene skeleta **171** and **172** in one step (Scheme 18). Exclusive formation of stereoisomer (+)-(3aS,5aR,6R,7R)-6-allyloxy-7-allyloxymethyl-3a,4,6,7-tetrahydro-3*H*,5a*H*-2,5,8-trioxa-1-aza-cyclopenta[a]naphthalene **171** is in agreement with the results obtained by theoretical calculations.

3. Steroids conjugates

Steroids are preferred synthons for the development of diverse conjugates. This is because steroids have different functionalization points, broad biological activity profile and ability to penetrate the cell membrane and bind to specific hormonal receptors.[56]

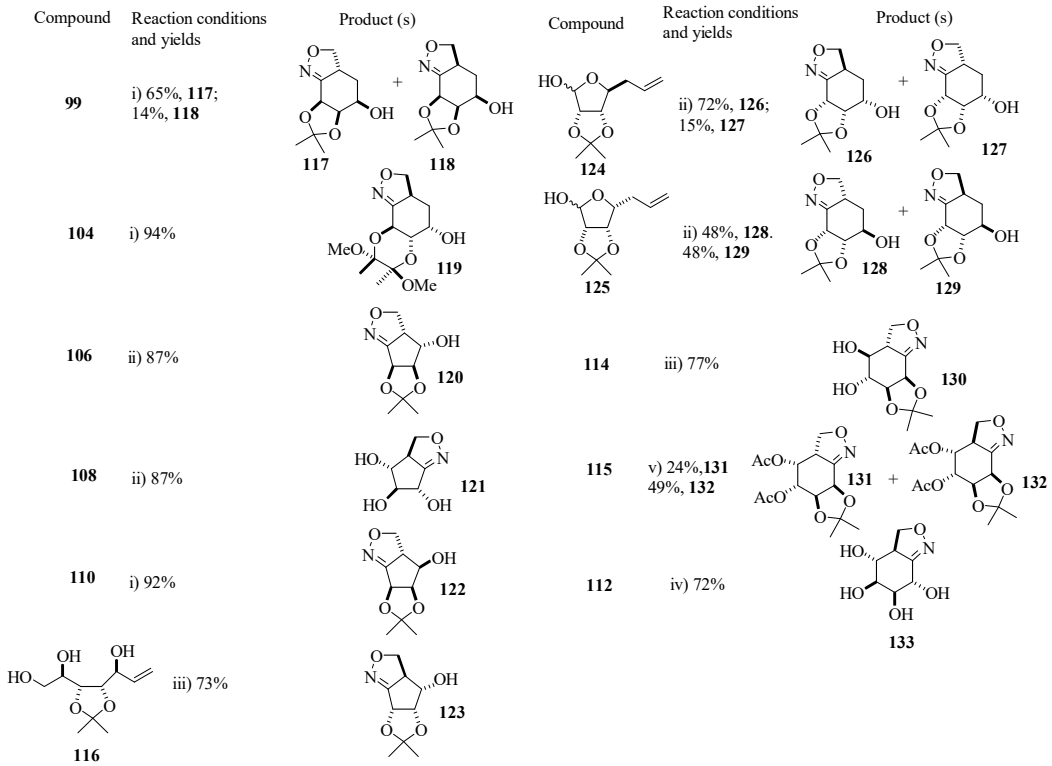
The application of a novel steroidal NO-, as reagent for the synthesis of isoxazole-linked steroidal glycoconjugates, has been reported.[57] Thus, 3β-acetoxy-16α-nitromethyl-5-pregnen-20-one **174** was synthesized from readily available 16-dehydropregnenolone acetate (16-DPA)[58] **173** using DBU and

nitromethane in dry dichloromethane (Scheme 19a). The propargyl ethers of the sugars were prepared from D-glucose, D-mannitol and D-galactose. All the monosaccharides were transformed into the respective alcohols followed by treatment with NaH, propargyl bromide and tetrabutylammonium bromide in THF as a solvent affording the respective propargyl ethers **175-179**. Propargyl ether **178** was obtained by conversion of D-glucose into the D-glucal, using Ferrier rearrangement with propargyl alcohol and bismuth nitrate in acetonitrile.[59]



Scheme 13. Synthesis of starting materials for the intramolecular NO CAs (See Scheme 14).
Reaction conditions: i) allylmagnesium bromide, Et_2O, -78 ºC, 30 min. Then -30 ºC, 12 h., 83%;
ii)[51] $NaIO_4$, H_2O (ap. 80 ºC). Then CH_2Cl_2, 1 h., 79% for **98**, 71% for **106**, 68% for **108**;
iii) $NH_2OH.HCl$, $NaHCO_3$, MeOH, 100% for **99**, 98% for **104**;
iv) 2,2,3,3,-tetramethoxybutane, trimethylchloroformate, (+/-)-10-camphorsulfonic acid, MeOH, reflux, r.t., then $NaHCO_3$, r.t., 5 h., 77%;
v) H_2, 10% Pd-C, EtOH, 12 h. Overall yields: 49% for **102** and 49% for **103**;
vi) Zn powder, THF-H_2O (4:1), sonication, 40 ºC, 45 min. Oximation: $NH_2OH.HCl$, $NaHCO_3$. Overall yield 93%; vii) TFA, H_2O, CH_2Cl_2, r.t., 48 h., 92%.
For the synthesis of compound **96**, see reference.[52] For the synthesis of compounds **105**, **107** and **111**, see reference.[53] For the synthesis of compound **100**, see reference.[54]
For the synthesis of compound **109**, see reference.[55]

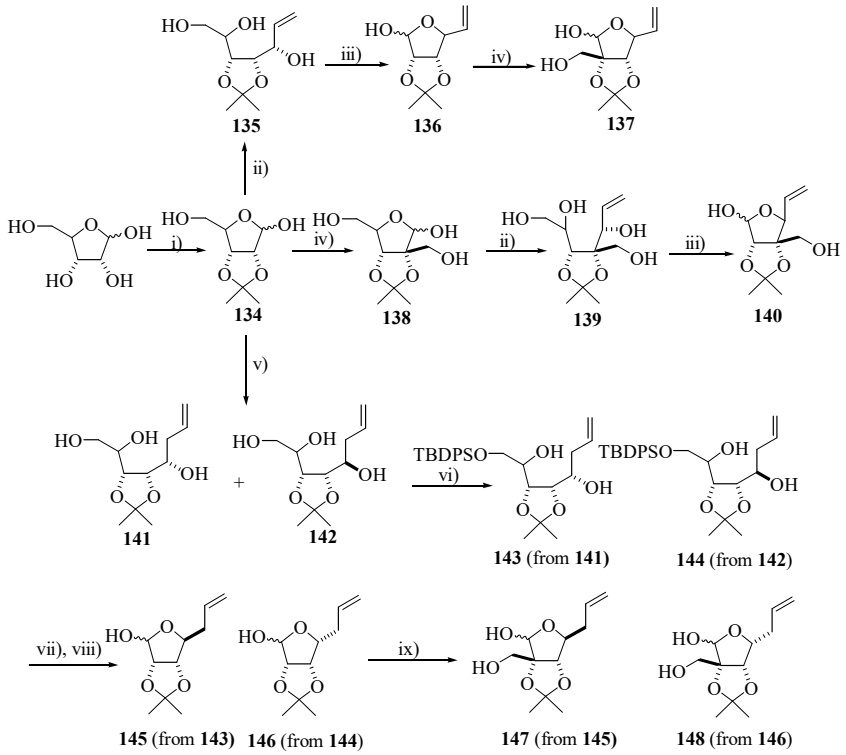
Nitroalkane **174** was treated with propargyl ethers **175-179** under Mukaiyama's conditions. The one-pot reaction proceeds completely regioselectively affording 3,5-disubstituted isoxazoles **180-184** (Scheme 19b). In a related report[60] the 1,4-benzodioxane moiety conjugated with a steroid skeleton *via* isoxazole bridge **185** was synthesized from 2-propynyloxymethyl-1,4-benzodioxane **186**, prepared from 1,2-dihydroxybenzene **187,** as indicated in Scheme 20. Reaction of **174**with **186** provided steroid conjugate **185**.



Scheme 14. Intramolecular NO CAs using Chloramine T-silica gel.Reaction conditions*:
i) Chloramine T, silica gel, EtOH, r.t.; ii) a. NH_2OH; b. Chloramine T, silica gel, EtOH, r.t.; iii) a. $NaIO_4$; b. NH_2OH; c. Chloramine T, silica gel, EtOH, r.t.; iv) a. K_2CO_3, MeOH; b. NH_2OH; c. Chloramine T, silica gel, EtOH, r.t.; v) a. K_2CO_3, MeOH; b. NH_2OH; c. Chloramine T, silica gel, EtOH, r.t.; d. Ac_2O. For the synthesis of compounds **116** see reference.[61] For the synthesis of compounds **124** and **125** see reference.[62]
*The reaction mixture was stirred at room temperature until the disappearance of the oxime (TLC).

A variety of cholesterol conjugates anchored by way of isoxazole nucleus was synthesized starting from cholesterol as indicated as follows[63] (Scheme 21). Steroidal ethers **190** (dipolarophiles) were prepared from cholesterol following a modification of the previously published procedure.[64] Regarding the steroid-coumarin **191j** and steroid-azobenzene **191k** conjugates, it should be pointed out that thesefluorescent derivatives can be used for imaging in cells and tissues and for the construction of thermal and photoresponsive materials[65]including phototriggered drug-delivery vehicles.[66] In the case of conjugate **191j** the NO was generated from coumarin 6-aldoxime[67]and for the photoresponsive azo-conjugated steroid **191k** the NO precursor was the 4-(phenylazo)benzaldehyde oxime.[68] Compound **191k**, initially obtained almost exclusively as the *trans*-isomer, was transformed into a 84:16 mixture of *trans* and *cis* isomers after

exposure to sunlight for 2 h. When the sample was returned to darkness, the original exclusively *trans* geometry was restored.



Scheme 15. Synthesis of precursors **136**, **137**, **140**, **145-148**. Reaction conditions: i) acetone, H_2SO_4 concd., 92%; ii) vinylmagnesium bromide, THF, -78 ºC to r.t., 88%; iii) $NaIO_4$, H_2O, 85% for **136** and 82% for **140**; iv) K_2CO_3, HCHO aq., MeOH, reflux, 90% for **137** and 86% for **138**; v) allylmagnesium bromide, Et_2O, 78 ºC to r.t., 91% for **141** and **142**; vi) TBDPSiCl, Et_3N, DMAP; 23% for **143** and 66% for **144**; vii) TBAF, THF; viii) $NaIO_4$, H_2O, 74% for **145** and 71% for **146** (two steps); ix) K_2CO_3, HCHO aq., MeOH, reflux, 85% for both **147** and **148**.

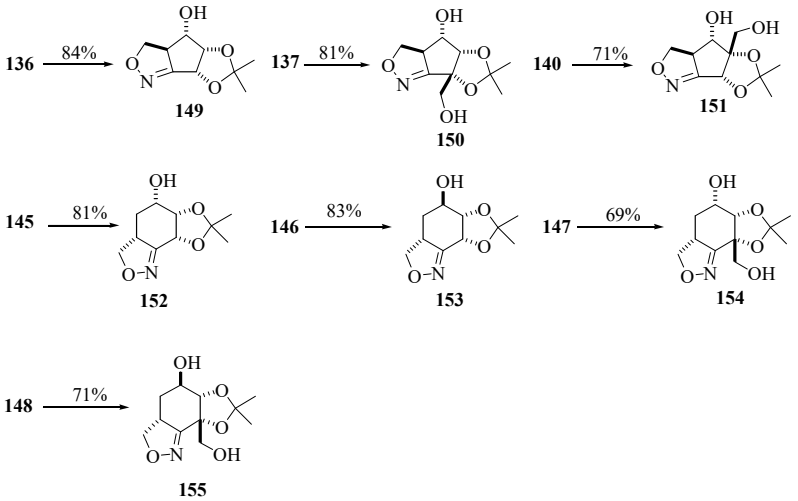
Regioisomeric steroidal oxime ethers **194** were prepared in two steps, as shown in Scheme 22. Reaction of **194** with phenyl propargyl ether **195** furnished the expected isoxazole conjugates **196**. A further improvement in the yield of **196c** to 80% was achieved by adding the steroidal oxime and chloramine-T portionwise to a solution of the dipolarophile in ethanol.

Steroidal glycoconjugate **197** was synthesized by the reaction of oxime **194c** with protected D-galactose **198.** Also, the selective tethering of one or two cholesterol units to a thymidine skeleton was demonstrated by trapping of the same dipole precursor by 5'-protected mono- or bis-propargylated thymidines **199** and **200** to give conjugates **201** and **202**, respectively (Scheme 23).

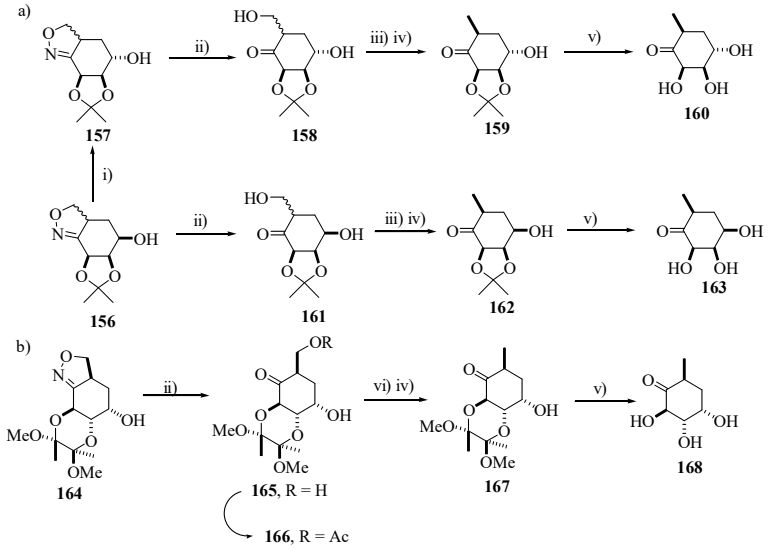
Novel 16-spiroisoxazolinyl-androst-5-ene derivatives have been synthesized[69] from 3β-acetoxy-16-methyleneandrost-5-en-17-one **203**[70] *via* 1,3-DC with aromatic NOs (Scheme 24). Only compounds **204** and **205** were effectively obtained in these CAs.

Several 5α-androstanes containing an isoxazoline moiety condensed to ring A **207** or D **209** were efficiently synthetized[71] by 1,3-DC of aryl nitrile oxides to steroidal α,β-unsaturated ketones. For the synthesis of A ring-fused isosazolines **207** the starting material was the unsaturated ketones 17β-acetoxy-5α-androst-1-en-3-one **206**[72] whereas for the preparation of the corresponding D ring-fused isoxazolines **209**,

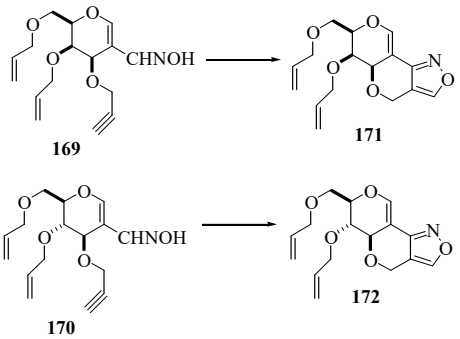
the 1,3-DC was achieved using 3β-acetoxy-5α-androst-15-en-17-one **208**.[73] The results are summarized in Scheme 25.



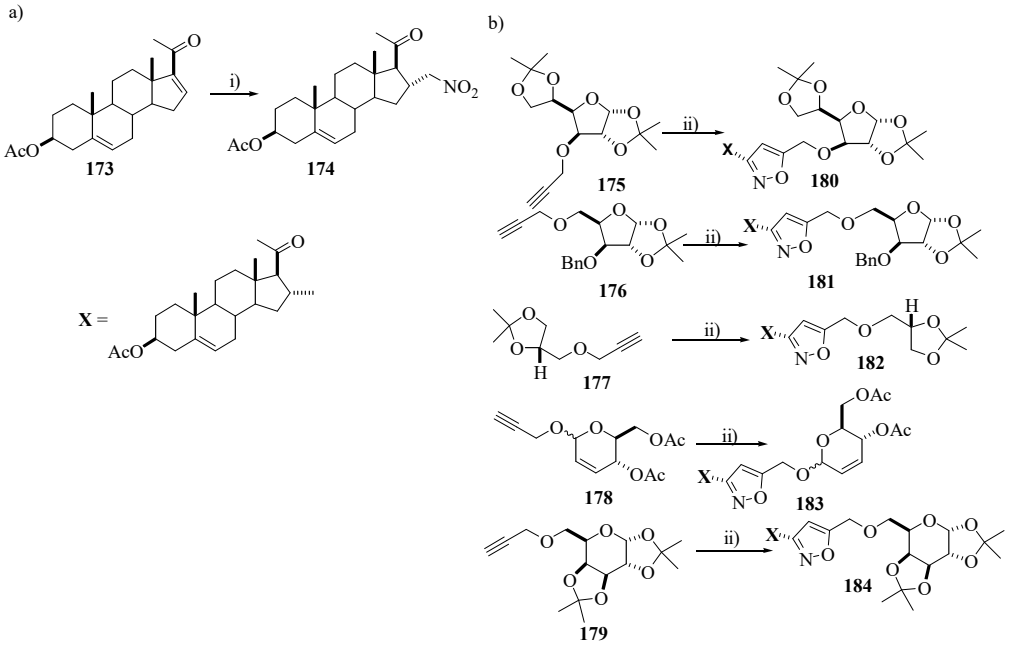
Scheme 16. Intramolecular NO CAs using Chloramine-T hydrate-Montmorillonite K-10.
Reaction conditions (all cases): a. $NH_2OH.HCl$, $NaHCO_3$, MeOH:
b. Chloramine-T hydrate-Montmorillonite K-10, EtOH, r.t.



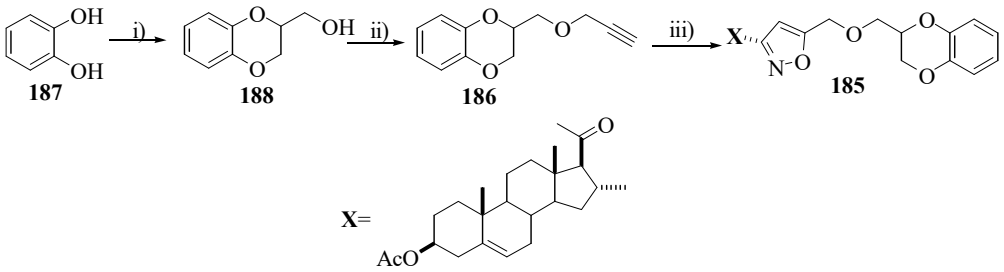
Scheme 17. Synthesis of *epi*-gabosine O **160**, gabosine O **163** and gabosine F **168**.
Reaction conditions: i) a. PPh_3, DIAD, *p*-NO_2-BzOH, r.t., 15 h.; b. LiOH aq., 98% two steps;
ii) H_2, Ni-Raney, AcOH, EtOH/H_2O, dioxane, r.t., 12 h., 93% for **158**; 97% for **161**; 90% for **165**;
iii) Martin's sulfurane, -78 ºC, 10 min.;
iv) H_2, Ni-Raney, AcOH, EtOH/H_2O, dioxane, -78 ºC., 12 h. 88% for **159** from **158**;
v) TFA, CH_2Cl_2, r.t., 5 min.; 100% for **160**; 89% for **163** from **161** (three steps); r.t., 2 h. 100% for **168**;
vi) 2,4,6-collidine, AcCl, CH_2Cl_2, -78ºC, 12 h., 87% for **166**.



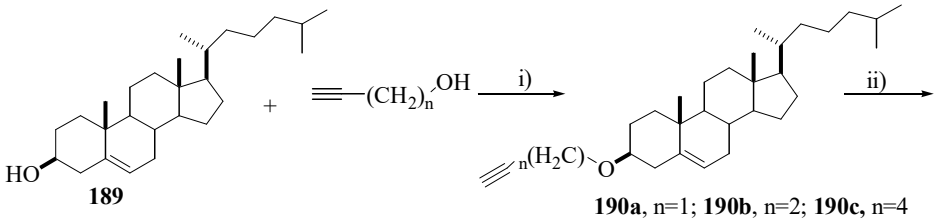
Scheme 18. Intramolecular CAs of oximes **169** and **170**.
Reaction conditions in two cases: aldoximes **169** or **170**,
H_2O, CTAB, 15 min., 0 ºC. Then PhIO, r.t., 3 h.;
64% for **171** and 2.5 h., r.t., 63% for **172**.

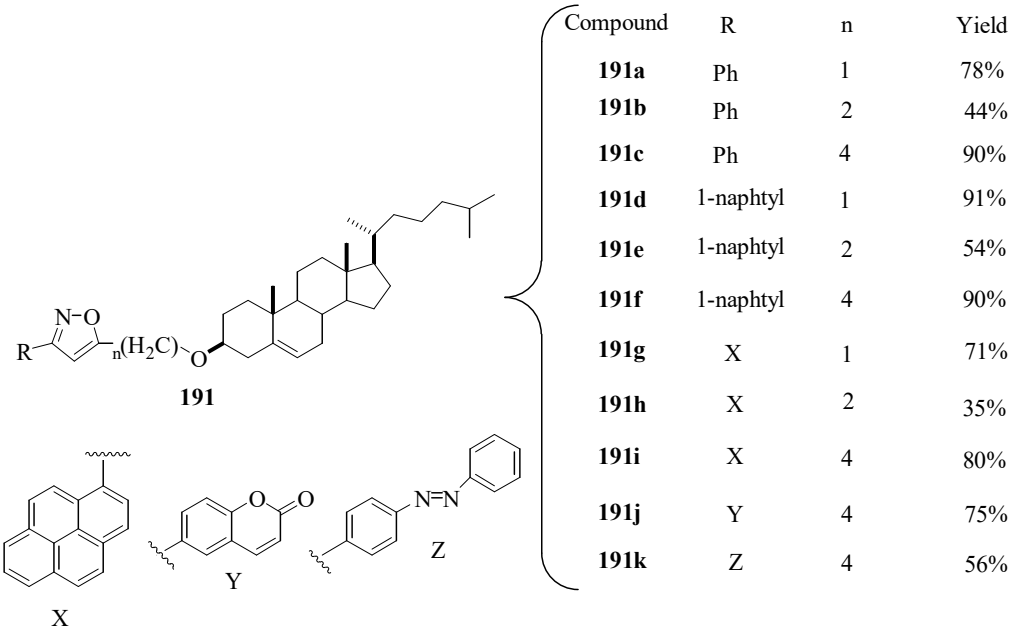


Scheme 19. Synthesis of isoxazole-linked steroidal glycoconjugates.
Reaction conditions: i) DBU, CH_3NO_2, CH_2Cl_2, -15 ºC to r.t., 12 h., 90%;
ii) compounds **175-179**, PhNCO, Et_3N, dry benzene, r.t.
Isolated yields: **180**, 65%; **181**, 62%; **182**, 60%; **183**, 58%; **184**, 64%.
Reaction times were not specified.



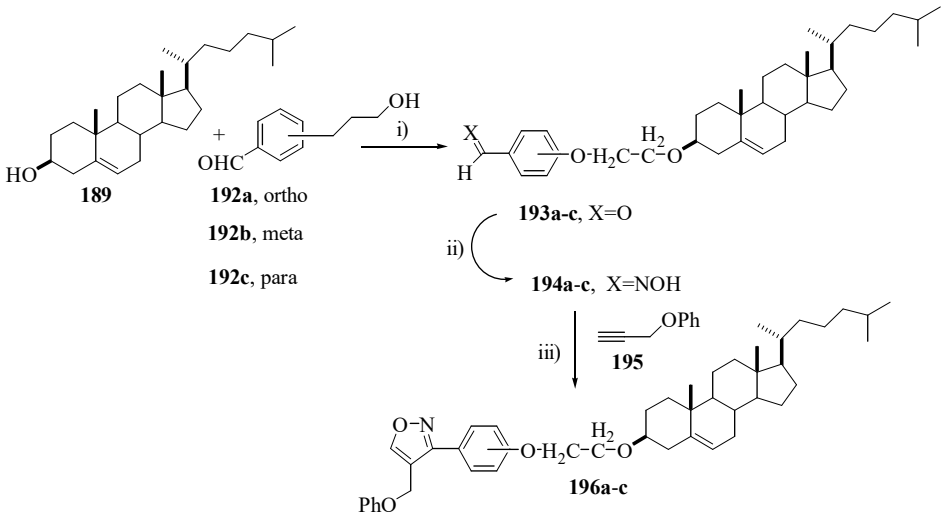
Scheme 20. Synthesis of 1,4-benzodioxan-steroid conjugate.
Reaction conditions: i) K_2CO_3, 1-chloro-2,3-epoxypropane, MeOH, reflux, 8 h.;
ii) NaH, propargyl bromide, TBA bromide, THF, 0º C to r.t., 5 h., 81% two steps;
iii) compound **174** (see Scheme 19), PhNCO, Et_3N, benzene, r.t., 24 h., 64%.



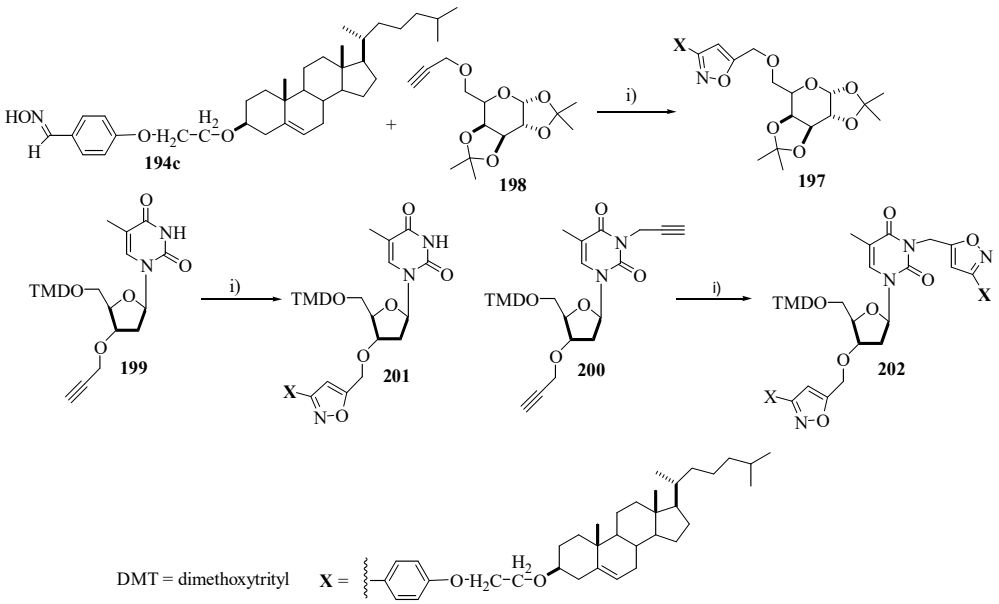


Compound	R	n	Yield
191a	Ph	1	78%
191b	Ph	2	44%
191c	Ph	4	90%
191d	1-naphtyl	1	91%
191e	1-naphtyl	2	54%
191f	1-naphtyl	4	90%
191g	X	1	71%
191h	X	2	35%
191i	X	4	80%
191j	Y	4	75%
191k	Z	4	56%

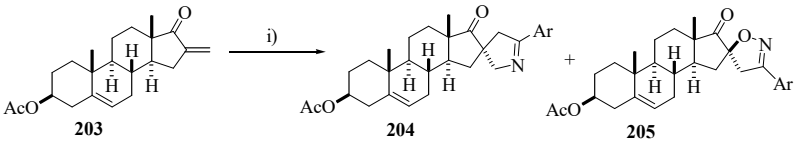
Scheme 21. Synthesis of steroids conjugates **191**.
Reaction conditions: i) Montmorillonite MK-10, $CHCl_3$, 17 h., 90 ºC, MW.
Yields: 68% for **190a**; 62% for **190b**; 70% for **190c**;
ii) RCH=NOH, Chloramine T, EtOH, MW, 100 ºC, 1 h., for R=Ph; 60 ºC,
0.5 h., for the remaining compounds.



Scheme 22. Synthesis of steroids conjugated **196**.
Reaction conditions: i) MK-10, $CHCl_3$, MW, 90 ºC, 8 h.
Yields: **193a**, 35%; **193b**, 58%; **193c**, 58%;
ii) $NH_2OH.HCl$, pyridine, EtOH, 125 ºC, MW.
Quantitative yields in all cases;
iii) Chloramine T, EtOH, r.t.
Yields: **196a**, 25%; **196b**, 35%; **196c**, 58%.



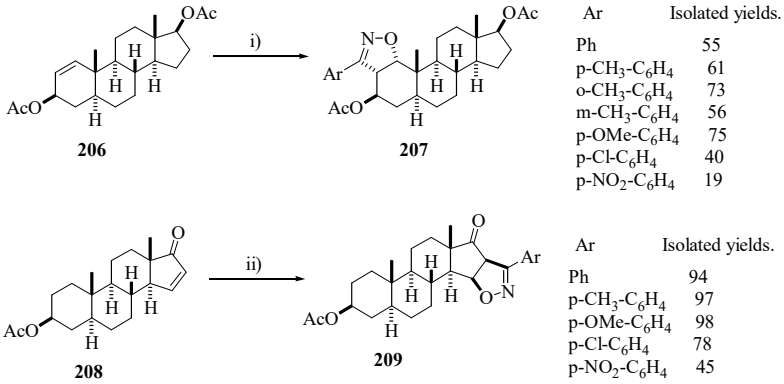
Scheme 23. Synthesis of steroid-glycoconjugates **197**, **201** and **202**.
Reaction conditions: i) oxime **194c**, Chloramine T, EtOH, r.t., 17 h.
Yields: **197**, 85%; **201**, 81%; **202**, 68%.



Ar	Ratio **204**:**205**[a]
Ph	75:10
p-CH_3-C_6H_4	82:9
p-OMe-C_6H_4	89:6
p-Cl-C_6H_4	72:8
p-NO_2-C_6H_4	100:0

a) Isolated yields

Scheme 24. Synthesis of 16-spiroisoxazolinyl androst-5-ene derivatives.
Reaction conditions: i) ArC(Cl)N=OH, DIPEA,[74] toluene, r.t.



Ar	Isolated yields.
Ph	55
p-CH_3-C_6H_4	61
o-CH_3-C_6H_4	73
m-CH_3-C_6H_4	56
p-OMe-C_6H_4	75
p-Cl-C_6H_4	40
p-NO_2-C_6H_4	19

Ar	Isolated yields.
Ph	94
p-CH_3-C_6H_4	97
p-OMe-C_6H_4	98
p-Cl-C_6H_4	78
p-NO_2-C_6H_4	45

Scheme 25. Synthesis of A and D ring-fused isoxazolines.
Reaction conditions: i) ArC(Cl)N=OH, DIPEA, 5 h.; ii) ArC(Cl)N=OH, DIPEA, toluene, 111 ºC, 2 h.

4. Conclusions

The utility of NOs as dipoles in organic synthesis through the 1,3-DC reactions has become valued in industry and academia during the last two decades. These reactions (both inter- and intramolecular variants) has been intensively studied considering that the final cycloadduct products, isoxazoles and their analogues, constitute an important class of heterocyclic compounds which are presents in natural products and drugs. The synthetic applications of NOs CAs have been intensively studied in fields such as heterocyclic bioconjugation, in particular in the case of sugar and steroids conjugates. This article has reviewed some recent advances in these contexts and it can be concluded that NOs CAs are useful reactions with lots of possibilities and will certainly contribute to future creative advances in the domains here considered.

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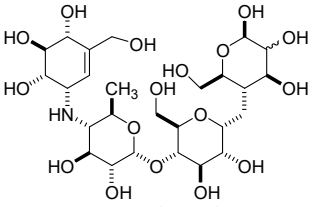

Structure of Acarbose.

23. Glycosidases catalyse the hydrolysis of glycosidic linkages, thereby degrading oligosaccharides and glycoconjugates, the structurally most diverse class of biopolymers. These efficient and highly specific catalysts play important roles in biological processes. The classification of this huge class of enzymes into families on the basis of amino acid sequence has provided a highly valuable tool for the analysis of structure-function relationships. Furthermore, the steady increase in three-dimensional structural information is revealing further evolutionary relationships between glycosidase families. The α-amylases are calcium metalloenzymes. By acting at random locations along the starch chain, α-amylase breaks down long-chain carbohydrates, ultimately yielding maltotriose and maltose from amylose, or maltose, glucoseand "limit dextrin" (a short chained branched amylopectin remnant, produced by hydrolysis of amylopectin with a amylase) from amylopectin. Because it can act anywhere on the substrate, α-amylase tends to be faster-acting than β-amylase. In animals, it is a major digestive enzyme, and its optimum pH is 6.7-7.0. In human physiology, both the salivary and pancreatic amylases are α-amylases.The α-amylases form is also found in plants, fungi (ascomycetes and basidiomycetes) and bacteria (*Bacillus*). β-Glucosidase is located in the brush border of the small intestine that acts upon α(1→4) bonds. α-Glucosidase breaks down starch and disaccharides to glucose. β-Glucosidase catalyzes the hydrolysis of the glycosidic bonds to terminal non-reducing residues in β-D-glucosides and oligosaccharides, with release of glucose. See: Kötzler, M. P; Hancock, S. M.; Withers, S. G. *Glycosidases: functions, families and folds*, John Wiley and Sons, **2014**.
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create the mature protein components of an infectious HIV virion. Aspartil proteases are a catalytic type of protease enzymes. A protease is any enzyme that performs proteolysis by hydrolysis of peptide bonds that use an activated water molecule bound to one or more aspartate residues for catalysis of their peptide substrates. See: (a) Davies, D. R. *Ann. Rev. Biophys. Chem*. **1990**, *19*,189; (b) Brik, A.; Wong, C. H. *Org. Biomol. Chem.* **2003**, *1*, 5.

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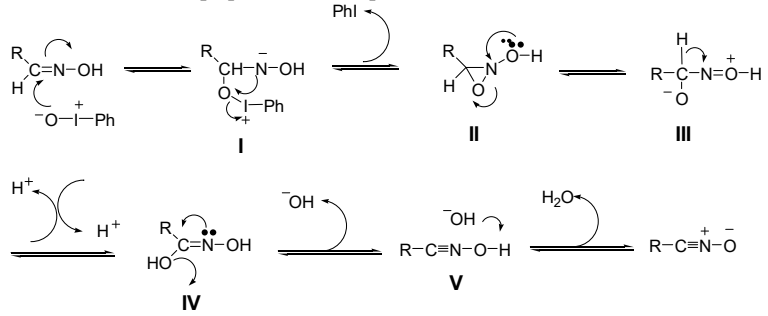

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