Ring opening of activated cyclopropanes with NIS/NaN$_3$: synthesis of C-1 linked pseudodisaccharides

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A R T I C L E   I N F O

A B S T R A C T

NIS/NaN$_3$ mediated ring opening of various donor–acceptor cyclopropanes has been investigated. The study shows the necessity of the donor oxygen lone pair in such ring opening reactions. This methodology has been utilized in the synthesis of C-1 linked pseudodisaccharides through the use of click chemistry.

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1. Introduction

High strain and reactivity of the cyclopropyl systems make them versatile building blocks for various chemical transformations.[1] In certain cases, activation of the strained three-membered ring is also necessary and generally an electron donating or accepting substituents are involved in the reactions, which act as a push–pull systems to make polar processes more favorable.[2] There are reports on ring cleavage of donor–acceptor cyclopropanes, which involve acid mediated ring opening,[3] Lewis acid mediated ring enlargement,[4] or ring opening followed by allylation,[5] NIS/NBS mediated solvolysis,[6] reactions with organometallic species,[7] and a wide range of intermolecular dipolar cycloadditions.[8] Among these reactions, only dipolar cycloaddition reaction takes place under thermal conditions and in principle, proceeds without additional activating reagent. The remaining reactions need some kind of activation. Earlier, we reported from our laboratory an efficient methodology for the synthesis of 2-C-branched glyco-amino-acids by ring opening of 1,2-cyclopropane carboxylated sugar derivatives[9] and it has been successfully applied to the synthesis of unnatural C-2 amino acid nucleosides.[10]

Although ring opening reactions of carbohydrate derived cyclopropyl systems have been widely studied, they are restricted to only selected nucleophiles, such as alcohol or water.[11] We were particularly interested in expanding the scope of our methodology for the synthesis of pseudodisaccharides. There are various types of pseudopolysaccharides known depending on the tether used. For example, alkenyl[12a] or alkynyl[12b] linked glycosides, peptide glycoside,[12c] diol[12d] or triazole[12e,f] linked glycosides have been studied. Among them triazole based pseudopolysaccharides attracted attention in the past few years as their synthesis avoids protection/deprotection and activation. In addition glycosyl azides[12g] and propargyl ethers can be easily prepared. Ferrières et al. reported the synthesis of saccharidyl triazoles and their application as glycosidase inhibitors. They discuss the role of 'glycosyl linkage directly attached to triazole' in inhibitory activity.[13]
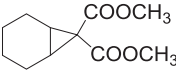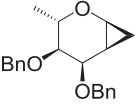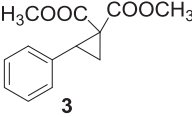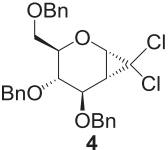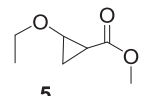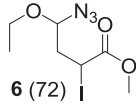
With this background, we report in this paper, studies of reactivity of various activated cyclopropanes with NIS as an activator and sodium azide as a source of nitrogen nucleophile and its application in the synthesis of C-1 linked pseudodisaccharides.

2. Results and discussion

In order to study the reactivity pattern, we synthesized a variety of activated cyclopropanes (1–5, Table 1) using established procedures. Cyclopropane 1[14] having an acceptor and cyclopropane 2[15] having a donor group were treated with 2.5 equiv of NIS/NaN$_3$ (CH$_3$CN, 25 °C, 48 h) separately. Both the cyclopropanes were found to be inert to the reaction conditions and the starting materials

Table 1
Ring opening of various activated cyclopropanes with NIS/NaN$_3$

Substrate	Product (%)[a]
1	No reaction
2	No reaction
3	No reaction
4	No reaction
5 (cis:trans 5:95)	**6** (72) (1:1 mixture diastereomers)

[a] Isolated yield after column chromatography.

Table 2
Ring opening of donor–acceptor cyclopropane carboxylates with NIS/NaN$_3$

Cyclopropane	Iodo-azide (%)[a]
7	**8** (70)
9 (cis)	**10** (74) (cis:trans 2:3)
11	No reaction
12	No reaction

[a] Isolated yield after column chromatography.

Table 3
Ring opening of carbohydrate derived donor–acceptor 1,2-cyclopropane carboxylates with NIS/NaN$_3$

Cyclopropane	Time (h)	Iodo-azide (%)[a]
13	48[b]	**14** (75)
15	14	**16** (75)
17	18	**18** (74)
19	14	**20** (69)

[a] Isolated yield after column chromatography.
[b] ~10% of starting material was recovered after column chromatography.
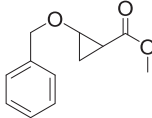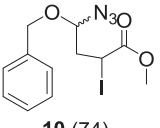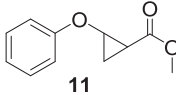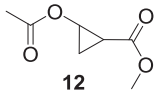
were recovered unchanged. As the cyclopropanes having only one activating group failed to react, we decided to incorporate both the features in the same molecule.
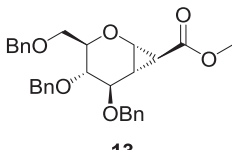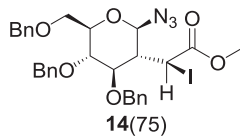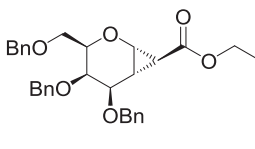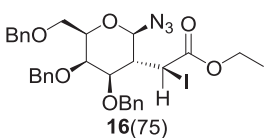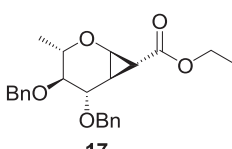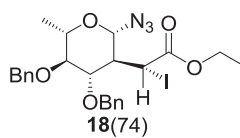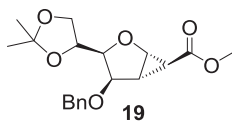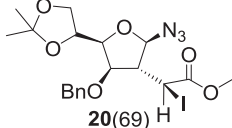
Cyclopropane **3**[16] having phenyl as a donor and di-ester as an acceptor and cyclopropane **4**[17] having oxygen as a donor and dichloro as an acceptor when treated separately with NIS/NaN$_3$ under the same conditions were found to be inert as well. Interestingly, the cyclopropane **5**[18] having an oxygen as a donor and an ester as an acceptor, underwent ring opening reaction to give the expected ring opened iodo-azide **6** in 72% yield after 24 h as a mixture of diastereomers (1:1) (at C1) (Table 1).

The above mentioned reactions clearly demonstrate not only the importance of the donor–acceptor feature in the cyclopropane in electrophilic ring opening reactions, but also the selectivity in its functionality. After successfully standardizing the reaction protocol, we decided to check the generality of this electrophile initiated ring opening reaction with other donor–acceptor substituted cyclopropanes. Dihydropyran derived cyclopropane carboxylate **7**[19] and benzyl vinyl ether derived cyclopropane carboxylate **9** when treated with NIS/NaN$_3$ (CH$_3$CN, 25 °C, 48 h), gave the corresponding iodo azides **8** and **10** in 70% and 74% yield, respectively. However, cyclopropane derivative **11**[20] with a phenoxy substitution, under similar reaction conditions failed to react even after stirring for 2 days. Similar results were observed in the case of cyclopropane **12**[19] with acetoxy substitution (Table 2). The above observations can clearly be accounted for on the basis of non-availability of oxygen lone pair, for the donor–acceptor interaction. This methodology was then extended to the carbohydrate derived 1,2-cyclopropane carboxylates (Table 3). Cyclopropane carboxylates (**13**, **15**, **17**, and **19**)[21] when treated with NIS/NaN$_3$ (CH$_3$CN, 25 °C, 48 h) gave the corresponding iodo-azides **14**, **16**, **18** and **20** respectively, in very good yields (69–75%) with high diastereoselectivity at C1 and C7 centers (carbohydrate nomenclature).

The observed stereochemistry in the product formed after the NIS/NaN$_3$ mediated ring opening of carbohydrate derived cyclopropane, can be explained on the basis of a plausible reaction mechanism depicted in Scheme 1. Initially, cyclopropane **13** undergoes oxygen assisted electrophilic ring opening reaction with NIS from the less hindered 'exo' face to give the corresponding iodo
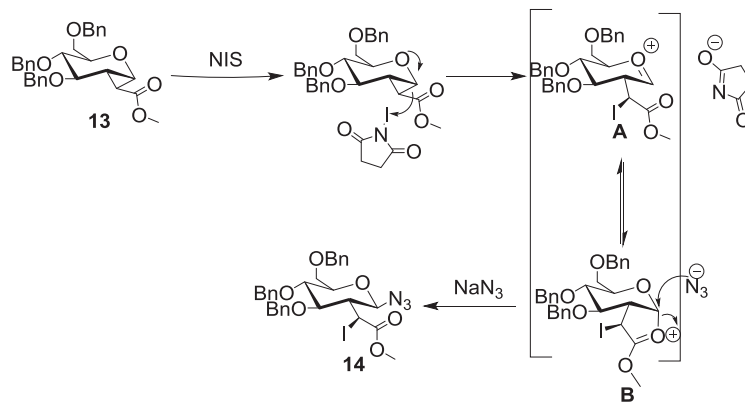
Scheme 1. Plausible mechanism of NIS/NaN$_3$ mediated ring opening of carbohydrate derived cyclopropylcarboxylates.

oxycarbenium intermediate **A**. This oxycarbenium intermediate is stabilized by the neighboring group participation of C-2 ester to get the intermediate **B**. Finally, oxycarbenium **B** is neutralized by the attack of azide. As the alpha face is blocked by the ester moiety, the attack of azide is feasible only from the beta face to give the corresponding iodo-azide **14**.

Among the vast pool of dipolar cycloaddition reactions, the recently developed click chemistry[22] emerges as a powerful tool in synthesis, for the attachment of various groups in a single step to get macromolecules,[23] glycoconjugates[24] or pseudoligosaccharides.[25,12f] There is a report on the tandem epoxide/aziridine ring opening by azide followed by a click reaction.[26] In light of this, we decided to combine our methodology of ring opening of donor–acceptor substituted cyclopropyl derivatives with 'click' reaction to get novel pseudodisaccharides. In preliminary studies, DHP derived cyclopropane **7** was converted to the iodo-azide **8** as described previously (Table 2). When the crude product from this reaction was treated with phenylacetylene (1.5 equiv), CuSO$_4$·5H$_2$O (5 mol %), and sodium ascorbate (15 mol %), in *t*-BuOH/H$_2$O (1:1) after 48 h, the expected triazole **21** was obtained in a poor yield (10%). However, increase in the catalytic loading to 10 mol % of CuSO$_4$·5H$_2$O and 30 mol % of sodium ascorbate helped to get the triazole **21** in 48% yield (Scheme 2). (Stepwise reaction sequence also gave similar results.) The methodology was then extended to the sugar derived donor–acceptor substituted cyclopropyl systems (Table 4).
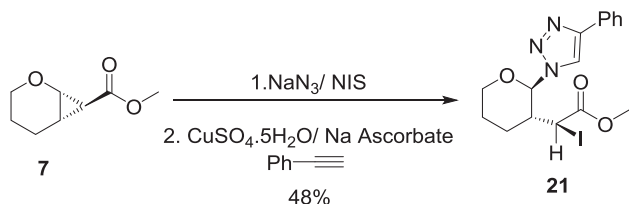
Scheme 2. NIS/NaN$_3$ mediated ring opening of cyclopropane carboxylate followed by a click reaction.

When sugar derived cyclopropane **13** was treated with NIS/NaN$_3$ followed by click reaction using glucose derived alkyne **22**[27] the corresponding C1→C3 linked pseudodisaccharide **23** was obtained in 60% yield. Similar reaction of **15** under the same conditions with alkyne derivative **22** afforded the corresponding pseudodisaccharide **24** in 58% yield. When galactose derived alkyne **25**[27] was used as a partner for the click reaction with the azide derived from compound **15a**[21] the pseudodisaccharide derivative **26** was obtained in 54% yield.

3. Conclusion

In conclusion, we have taken advantage of the NIS/NaN$_3$ mediated ring opening reaction of various donor–acceptor cyclopropanes derived from carbohydrates to synthesize various iodo azides and they have been utilized for the synthesis of C-1 linked pseudodisaccharides through the use of click chemistry. The newly generated active halide (iodide) center could be utilized for further transformations.

4. Experimental section

4.1. Physical properties and spectral measurements

All glassware were oven dried before starting the reaction. *N*-Iodosuccinimide was purchased from Lancaster India and used as such without purification. Solvents like CH$_2$Cl$_2$, DMF, MeOH and THF were purified as mentioned in 'Purification of Laboratory Chemicals' by Perrin & Armarego, Pergamon Press, Third Edition 1988. ^{1}H and ^{13}C NMR spectra were recorded on 300 MHz or 400 MHz, spectrometers. High-resolution mass spectra (HRMS) were recorded on a Q-TOF mass spectrometer. Chemical shifts (δ) are reported in parts per million downfield from the internal reference, tetramethylsilane (TMS) for ^{1}H and CDCl$_3$ for ^{13}C.

4.2. Synthesis of *cis*-methyl 2-(benzyloxy)cyclopropane-1-carboxylate (9)
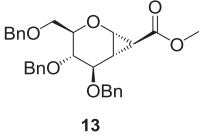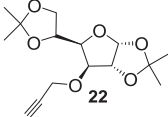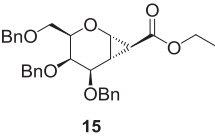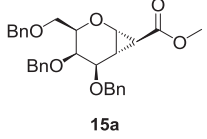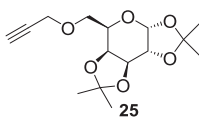
To a stirred suspension of benzyl vinyl ether (0.200 g, 1.4 mmol) and Rh$_2$(OAc)$_4$ (0.013 g, 0.02 mmol) in anhydrous dichloromethane (2 mL) was added dropwise, over a period of 1 h, a solution of methyl diazoacetate (0.298 mg, 2.98 mmol) in dichloromethane (10 mL). After cessation of the nitrogen evolution (5–10 min), the reaction mixture was concentrated in vacuum and the crude product was purified by silica gel column chromatography (eluent: PE/EA 9:1) to get the title compound **9** along with cyclopropane **9a**.

*4.2.1. cis-Methyl 2-(benzyloxy)cyclopropane-1-carboxylate (**9**).* Oil, (0.051 g, 17%); R_f 0.25 (PE/EA 9:1); IR (Neat, cm^{-1}) 2918, 1727, 1440, 1015, 737, 697; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35–7.29 (m, 5H), 4.51 (s, 1H), 3.71 (s, 3H), 3.63 (dq, *J*=1.5, 5.44 Hz, 1H), 1.78–1.73 (m, 1H), 1.65 (dq, *J*=1.54, 5.96 Hz, 1H), 1.10 (dq, *J*=2, 7.52 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.5, 137.0, 128.3, 128.1, 127.8, 73.3, 58.6, 51.8, 20.5, 13.2; HRMS calculated for C$_{14}$H$_{14}$NaO$_3$: 229.0841, found 229.0841.

*4.2.2. trans-Methyl 2-(benzyloxy)cyclopropane-1-carboxylate (**9a**).* Oil, (0.084 g, 27%); R_f 0.25 (PE/EA 9:1); IR (Neat, cm^{-1})

Table 4
Synthesis of C-1 linked pseudodisaccharides from 1,2-cyclopropane carboxylates

Cyclopropane	Reagent	Product(%)[a]
13	1.NaN₃/NIS 2.CuSO₄.5H₂O/Na Ascorbate **22**	**23**(60)
15	1.NaN₃/NIS 2.CuSO₄.5H₂O/Na Ascorbate **22**	**24**(58)
15a	1.NaN₃/NIS 2.CuSO₄.5H₂O/Na Ascorbate **25**	**26** (54)

[a]Isolated yield after column chromatography

2918, 1721, 1443, 1098; ^{1}H NMR (400 MHz, CDCl₃) δ 7.36–7.31 (m, 5H), 4.59 (s, 1H), 3.72–3.69 (m, 1H), 3.68 (s, 3H), 1.86–1.82 (m, 1H), 1.34–1.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl₃) 172.9, 137.0, 128.4, 127.9, 73.3, 60.4, 51.7, 21.0, 15.8; HRMS calculated for C₁₄H₁₄NaO₃: 229.0841, found: 229.0842.

4.3. General procedure for the synthesis of iodo-azides

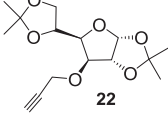To a well stirred solution of cyclopropane carboxylate (1 mmol) and NaN₃ (2.5 mmol) in CH₃CN (3 mL) was added N-iodosuccinimide (2.5 mmol) with powdered 4 Å molecular sieves (0.025 g) under argon atmosphere. The reaction mixture was stirred until the disappearance of starting material at room temperature. After completion of the reaction, solvent was removed under vacuum and the reaction mixture was diluted with chloroform (20 mL). The reaction mixture was then neutralized with dilute Na₂S₂O₃ solution. The organic layer was separated and dried over anhydrous Na₂SO₄. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (230–400 mesh) using ethyl acetate and petroleum ether to obtain the iodo-azide.

4.3.1. Methyl 4-azido-4-ethoxy-2-iodobutanoate (cis:trans mixture) (6). Oil, (0.274 g, 72%); R_f 0.4 (PE/EA 4:1); IR (Neat, cm^{-1}) 2980, 2106, 1736, 1436, 1249, 1102, 739; ^{1}H NMR (400 MHz, CDCl₃) δ 4.52–4.45 (m, 2H), 3.76 (s, 3H), 3.61–3.50 (m, 1H), 2.41–2.32 (m, 2H), 1.28–1.20 (m, 4H); ^{13}C NMR (100 MHz, CDCl₃) δ 171.1, 91.2, 90.8, 65.3, 65.0, 52.9, 41.1, 40.1, 14.8, 14.7, 14.4, 12.8; HRMS calculated for C₇H₁₂IN₃O₃Na: 335.9821, found: 335.9813.

4.3.2. Methyl 2-(2-azidotetrahydro-2H-pyran-3-yl)-2-iodoacetate (8). Gummy solid, (0.260 g, 70%); R_f 0.45 (PE/EA 4:1); IR (Neat, cm^{-1}) 2945, 2105, 1738, 1441, 1252, 1078, 969; ^{1}H NMR (400 MHz, CDCl₃) δ 4.62 (dd, J=6.38, 14.26 Hz, 2H), 4.04–4.00 (m, 1H), 3.76 (s, 3H), 3.63–3.57 (m, 1H), 2.20–2.15 (m, 1H), 1.69–1.52 (m, 4H); ^{13}C NMR (100 MHz, CDCl₃) δ 170.5, 90.2, 66.2, 53.1, 41.6, 27.2, 24.4, 23.5; HRMS calculated for C₈H₁₂IN₃O₃Na: 347.9821, found: 347.9824.

4.3.3. Methyl 4-azido-4-benzyloxy-2-iodobutanoate (10) (cis:trans mixture). Gummy solid (0.274 g, 74%); R_f 0.5 (PE/EA 4:1); IR (Neat, cm^{-1}) 2952, 2109, 1738, 1445, 1241, 1097, 742, 698; ^{1}H NMR (300 MHz, CDCl₃) δ 7.38–7.35 (m, 5H), 4.81 (t, J=12 Hz, 1H), 4.59–4.42 (m, 3H), 3.71 (s, 3H), 3.65 (s, 2H), 2.64–2.55 (m, 1H), 2.47–2.36 (m, 2H); ^{13}C NMR (75 MHz CDCl₃) δ 171.1, 136.2, 128.6, 128.3, 128.1, 90.5, 89.6, 71.4, 71.0, 52.9, 41.2, 40.1, 14.2, 12.3; HRMS calculated for C₁₂H₁₄IN₃O₃Na: 397.9978, found: 397.9976.

4.3.4. 3,4,6-Tri-O-benzyl-2-deoxy-2-C-[(iodo)-(methoxy-carbonyl)-methyl]-β-D-glucopyranosyl azide (14). Gummy solid (0.525 g, 75%); $[\alpha]_D^{25}$ −50 (c 1, CHCl₃); R_f 0.35 (PE/EA 4:1); IR (Neat, cm^{-1}) 2117, 1747, 1455, 1361, 1250, 734, 697. ^{1}H NMR (300 MHz, CDCl₃) δ 7.38–7.07 (m, 15H), 4.96–4.91 (m, 2H), 4.78–4.65 (m, 4H), 4.59 (dd, J=4.2, 5.2 Hz, 1H), 3.90–3.75 (m, 5H), 3.62 (ddd, J=1.8, 3.3, 9.9 Hz, 1H), 3.34 (s, 3H), 1.85 (dt, J=2.1, 9.6 Hz, 1H); ^{13}C NMR (75 MHz, CDCl₃) δ 167.1, 138.0, 137.5, 128.4, 128.1, 127.7, 90.3, 81.5, 79.4, 77.2, 77.1, 74.8, 73.6, 68.2, 53.5, 49.6, 28.4; HRMS calculated for C₃₀H₃₂IN₃O₆Na: 680.1234, found: 680.1241.

4.3.5. 3, 4, 6-Tri-O-benzyl-2-deoxy-2-C-[(iodo)-(ethoxy-carbonyl)-methyl]-β-D-galactopyranosyl azide (16). Gummy solid (0.492 g, 75%); $[\alpha]_D^{25}$ −4 (c 1, CHCl₃); R_f 0.3 (PE/EA 4:1); IR (Neat, cm^{-1}) 2119, 1738, 1448, 1361, 738; ^{1}H NMR (CDCl₃, 400 MHz): 7.42–7.30 (m, 15H), 5.01–5.00 (m, 1H), 4.83 (d, J=11.4 Hz, 1H), 4.70–4.58 (m, 3H), 4.55–4.46 (m, 3H), 3.96–3.90 (m, 3H), 3.71–3.62 (m, 3H), 2.34–2.32 (m, 1H), 1.03 (t, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz,

CDCl$_3$): 166.7, 137.7, 136.9, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 90.8, 81.2, 77.1, 75.6, 74.4, 73.5, 72.3, 71.2, 68.4, 62.6, 44.4, 30.7, 13.7; HRMS calculated for C$_{31}$H$_{34}$IN$_3$O$_6$Na: 694.1390, found: 694.1392.

4.3.6. 3, 4-Di-O-benzyl-2, 6-dideoxy-2-C-[(iodo)-(ethoxy-carbonyl)-methyl]-α-D-glucopyranosyl azide (18). Gummy solid (0.517 g, 74%); [α]$_D^{25}$ −4 (c 1, CHCl$_3$); R$_f$ 0.4 (PE/EA 4:1); IR (Neat, cm^{-1}) 2120, 1725, 1720, 1594, 1451, 1361, 738; ^{1}H NMR (250 MHz, CDCl$_3$) δ 7.34−7.24 (m, 10H), 5.00−4.95 (m, 2H), 4.84 (dd, J=3.25, 10.4 Hz, 2H), 4.71 (t, J=10 Hz, 2H), 3.74−3.94 (m, 3H), 3.6 (dq, J=6.1, 9.4 Hz, 1H), 3.47 (t, J=8.9 Hz, 1H), 1.86 (ddd, J=2.2, 9.4, 10.2 Hz, 1H), 1.44 (d, J=6.1 Hz, 3H), 1.09 (t, J=7.1 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ 166.6, 138.1, 137.5, 128.5, 128.1, 128.0, 127.8, 127.4, 90.2, 85.3, 81.4, 77.6, 77.0, 76.5, 75.4, 74.7, 73.8, 62.9, 49.9, 17.9, 13.8; HRMS calculated for C$_{24}$H$_{28}$IN$_3$O$_5$Na 588.0971, found 588.0961.

4.3.7. 3-O-Benzyl-5,6-O-isopropylidine-2-deoxy-2-C-[(iodo)-(methoxy-carbonyl)-methyl]-β-D-glucopyranosyl azide (20). Gummy solid (0.517 g, 69%); [α]$_D^{25}$ −5 (c 0.2, CH$_2$Cl$_2$); R$_f$ 0.25 (PE/EA 4:1); IR (Neat, cm^{-1}) 2120, 1723, 738. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34−7.29 (m, 5H), 5.03 (d, J=2.28 Hz, 1H), 4.67 (dd, J=11.69 Hz, 2H), 4.45 (q, J=6.39 Hz, 1H), 4.21 (d, J=10.24, 1H), 4.18−4.10 (m, 3H), 4.03−4.0 (m, 1H), 3.77 (s, 3H), 2.94 (dt, J=6.44, 10.24 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 170.1, 137.4, 128.2, 127.9, 127.7, 109.0, 92.5, 83.3, 82.1, 73.0, 71.6, 66.8, 56.0, 53.2, 26.6, 25.3, 17.4; HRMS m/z: calculated for C$_{19}$H$_{24}$IN$_3$O$_6$Na: 540.0607; found: 540.0607.

4.4. General procedure for NIS/NaN$_3$ mediated cyclopropane ring opening followed by click reaction

To a well stirred solution of cyclopropane carboxylate (1 mmol) and NaN$_3$ (2.5 mmol) in CH$_3$CN (3 mL) was added N-iodosuccinimide (2.5 mmol) with powdered 4 Å molecular sieves (0.025 g) under argon atmosphere. The reaction mixture was stirred until the disappearance of starting material at room temperature. After completion of the reaction, solvent was removed under vacuum and the reaction mixture was diluted with chloroform (20 mL). The reaction mixture was then neutralized with dilute Na$_2$S$_2$O$_3$ solution. The organic layer was separated and dried over anhydrous Na$_2$SO$_4$. The filtrate was concentrated and the crude iodo-azide was taken for the next reaction. The crude iodo azide and an alkyne (1.5 equiv) were dissolved in 4 mL of t-BuOH/H$_2$O (1:1) followed by the addition of 10 mol % of CuSO$_4$ and 30 mol % of sodium ascorbate. The reaction mixture was stirred at room temperature for 48 h. The reaction was quenched by addition of water (5 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was separated and dried over anhydrous Na$_2$SO$_4$. The organic layer was concentrated under vacuum to get the crude product, which was purified by column chromatography with appropriate eluent to get the corresponding triazole product.

4.4.1. 4-Phenyl-1-(2′-C-(iodomethyl acetate)-2H-pyranyl)-1,2,3-triazole (21). Gummy solid (0.204 g, 48%); R$_f$ 0.5 (PE/EA 3:7); IR (Neat, cm^{-1}) 2112, 1738, 1461, 1268, 766; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (s, 1H), 7.85 (d, J=7.2 Hz, 2H), 7.44−7.74 (m, 2H), 7.36−7.32 (m, 1H), 5.60 (d, J=8.8 Hz, 1H), 4.28 (d, J=4.8 Hz, 1H), 4.13−4.09 (m, 1H), 3.76−3.68 (m, 1H), 3.60 (s, 3H), 2.42−2.38 (m, 1H), 2.18−2.11 (m, 1H), 1.96−1.88 (m, 1H), 1.78−1.69 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 169.7, 148.0, 130.2, 128.8, 128.4, 125.8, 118.7, 89.2, 68.4, 53.2, 41.9, 28.9, 24.5, 23.8; HRMS calculated for C$_{16}$H$_{18}$IN$_3$O$_3$Na: 450.0291, found: 450.0294.

4.4.2. [1-(3,4,6-Tri-O-benzyl-2-deoxy-2-C-[(iodo)-(methoxy-carbonyl)-methyl]-β-D-glucopyranosyl)-1H-1,2,3-triazol-4-yl]methyl-1,

2:5, 6-O-diisopropylidene-glucofuranoside (23). Gummy solid (0.573 g, 60%); [α]$_D^{25}$ +4.0 (c 1, CHCl$_3$); R$_f$ 0.6 (PE/EA 3:7); IR (Neat, cm-1) 1746, 1452, 1374, 1218, 1079, 847, 753, 699; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (s, 1H), 7.33−7.27 (m, 15H), 5.89 (d, J=3.6 Hz, 1H), 5.80 (d, J=9.9 Hz, 1H), 5.02 (d, J=10.5 Hz, 1H), 4.87−4.76 (m, 4H), 4.64−4.47 (m, 4H), 4.37−4.32 (m, 1H), 4.13−3.93 (m, 7H), 3.82−3.71 (m, 3H), 3.29 (s, 3H), 2.49 (dt, J=1.32, 8.4 Hz, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) 166.6, 145.6, 137.7, 137.5, 137.3, 128.5, 128.4, 128.1, 128.0, 127.86, 127.83, 127.7, 127.5, 121.4, 111.8, 109.1, 105.2, 88.0, 82.6, 82.0, 81.7, 81.1, 79.0, 77.9, 74.9, 73.5, 72.3, 68.1, 67.4, 64.0, 53.6, 49.7, 26.8, 26.7, 26.4, 26.1, 25.4. HRMS calculated for C$_{45}$H$_{54}$IN$_3$O$_{12}$Na: 978.2650, found: 978.2654.

4.4.3. [1-(3,4,6-Tri-O-benzyl-2-deoxy-2-C-[(iodo)-(ethoxy-carbonyl)-methyl]-β-D-galactopyranosyl)-1H-1,2,3-triazol-4-yl]methyl-1, 2:5, 6-O-diisopropylidene-glucofuranoside (24). Gummy solid (0.553 g, 58%); [α]$_D^{23}$ +5.00 (c 0.5, CHCl$_3$); R$_f$ 0.6 (PE/EA 3:7); IR (Neat, cm-1) 1746, 1454, 1374, 1218, 1079, 847, 753, 699; ^{1}H NMR (400 MHz, CDCl$_3$): 7.90 (s, 1H), 7.38−7.26 (m, 15H), 5.87 (d, J=3.2 Hz, 1H), 5.80 (d, J=10 Hz, 1H), 4.86−4.80 (m, 3H), 4.72−4.69 (m, 1H), 4.62−4.42 (m, 6H), 4.30−4.28 (m, 1H), 4.12−4.02 (m, 6H), 3.97−3.85 (m, 5H), 3.78−3.77 (m, 1H), 3.68−3.64 (m, 1H), 3.59−3.57 (m, 1H), 2.89−2.81 (m, 1H), 1.47 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 0.99 (t, J=7 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): 166.2, 145.6, 138.2, 137.4, 136.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.7, 120.7, 111.8, 109.1, 105.2, 88.4, 82.4, 81.7, 81.5, 81.1, 76.7, 76.3, 74.7, 73.5, 72.4, 72.2, 71.2, 67.9, 67.4, 63.9, 62.8, 44.8, 27.9, 26.8, 26.7, 26.1, 25.2, 13.7. HRMS calculated for C$_{46}$H$_{56}$IN$_3$O$_{12}$Na: 992.2806, found: 992.2803.

4.4.4. [6-(3,4,6-Tri-O-benzyl-2-deoxy-2-C-[(iodo)-(methoxy-carbonyl)-methyl]-β-D-galactopyranosyl)-1H-1,2,3-triazol-4-yl]methyl-1,2:3,4-O-diisopropylidene-glucofuranoside (26). Gummy solid (0.515 g, 54%); [α]$_D^{23}$ +5 (c 1, CHCl$_3$); R$_f$ 0.5 (PE/EA 3:7); IR (Neat, cm^{-1}) 1746, 1454, 1374, 1218, 1079, 847, 753, 699; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83 (s, 1H), 7.34−7.26 (m, 15H), 5.77 (d, J=3.3 Hz, 1H), 5.54 (d, J=5.1 Hz, 1H), 5.01 (d, J=10.8 Hz, 1H), 4.83 (s, 1H), 4.79 (s, 1H), 4.75 (t, J=3 Hz, 3H), 4.65 (s, 1H), 4.61 (d, J=1.2 Hz, 1H), 4.58−4.57 (m, 1H), 4.51 (s, 1H), 4.31 (dd, J=2.1, 4.8 Hz, 1H), 4.23 (dd, J=1.8, 7.5 Hz, 1H), 4.15 (d, J=1.8 Hz, 1H), 4.03−4.01 (m, 2H), 3.79 (m, 1H), 3.73−3.70 (m, 4H), 3.30 (s, 3H), 2.61 (t, J=3.5 Hz, 1H), 1.53 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 166.6, 146.0, 137.8, 137.6, 137.3, 128.4, 128.41, 128.1, 127.8, 127.7, 127.6, 121.1, 109.2, 108.5, 96.3, 88.0, 79.1, 74.9, 79.5, 71.1, 70.6, 69.5, 68.1, 66.7, 64.8, 53.5, 49.6, 26.0, 25.9, 24.8, 24.4. HRMS calculated for C$_{45}$H$_{54}$IN$_3$O$_{12}$Na: 978.2650, found: 978.2690.

Supplementary data

Spectroscopic data (^{1}H and ^{13}C) of all new compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.11.005.

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