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Synthesis of Polyacetylene Glycosides and Thioglycosides

by

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ABSTRACT

Polyacetylene glycosides are natural products isolated from a variety of natural sources, primarily terrestrial plants and fungi. Polyacetylene glycosides isolated to date feature a linear and conjugated polyacetylene chain and a mono di-, or trisaccharide group in their structures. These compounds have been shown to possess a host of different biological activities, including anti-inflammatory effects, inhibition of nitric oxide production and histamine release, anti-bacterial activity, and the ability to inhibit the enzyme 12-lipoxygenase. The project described in this thesis focuses on polyacetylene glycosides and polyacetylene thioglycosides by glycosylating or thioglycosylating mono-, di-, or triyne alcohols, which have been synthesized using the Cadiot-Chodkiewicz reaction and Fritcsh-Buttenberg-Wiechell rearrangement. Twenty-seven polyacetylene glycosides and thioglycosides have been synthesized. Given the structural similarity of these compounds to bioactive natural products, we expected the molecules should have interesting biological activities. Thirty compounds have thus been assayed for cytotoxicity against MCF-7 breast lines, as well as anti-bacterial activity.

ACKNOWLEDGEMENT

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

LIST OF ABBREVIATIONS

HIV……..……Human Immunodeficiency Virus

IC_{50}……..…….……half maximal inhibitory concentration

HCT-15…….……colon carcinoma

UISO……..…….……uterine-cervix cancer

KB……..…….……nasopharyngeal carcinoma

ED_{50}……..……..…Effective dose 50%

NMR……..…….……Nuclear Magnetic Resonance

nm……..……nanometer

Me……..…….Methyl

rt. ……..……..…..……room temperature

TBAF……..……...…Tetrabutylammonium fluoride

TBDPS……..……Tert-butyldiphenylsilyl

THF……..……..…….……Tetrahydrofuran

4 Å MS……..…….……4 Å Molecular Sieves

TMS……..…….…….Trimethylsilyl

Et……..……..…..…..……..…Ethyl

Bu..……..……..……Butyl

Me.……..……..…..…….……Methyl

NBS……..……..……N-Bromosuccinimide

DMF……..……...…N,N-Dimethylformamide

Ac_2O……..…….……..Acetic anhydride

DBU……..……1,8-Diazabicyclo[5.4.0]undec-7-ene

TMSOTf……..……Trimethylsilyl trifluoromethanesulfonate

TLC……..…….……..Thin Layer Chromotography

DTBMP……..…….....…2,6-Di-*tert*-butyl-4-methylpyridine

DMAP……..……...…….4-(Dimethylamino)pyridine

MsCl……..……...…Methanesulfonyl chloride

TsCl……..…….……Toluenesulfonyl chloride

Tf_2O……..……..…Trifluoroacetic anhydride

UV……..…….…….…Ultraviolet-Visible

IR……..……..…Infrared

COSY……..…….……..…Correlation Spectroscopy

HMQC……..…….…..…Heteronuclear Multiple Quantum Coherence

ESI-MS……..……..…..……Electrospray Ionization Mass Spectrometry

TE……..……..……..…Trypsin-EDTA

EDTA……..……ethylenediaminetetraacetic acid

LB……..…….……...…..…Luria-Burtani

NB……..……..…Nutrient Broth

MHA……..…….……..…Mueller-Hinton Agar

Mp……..…….…….…Melting point

DMEM F-12…..…..…Dulbcco's Modified Eagle Medium: Nutrient mixture F-12

ATCC……..……..…American Type Culture Collection

Chapter 1. Introduction

1.1 Introduction

Polyacetylenic products have long been known to exist in natural sources, and thousands have been isolated in the past hundred years from a wide range of terrestrial plant species, fungi, sponges, corals, and bacteria.[1] Many of these compounds have interesting biological activities, such as antibacterial, antimicrobial, anticancer, anti-HIV, antifeedant, and pesticidal properties.[1-16] Despite their significant numbers present in nature, polyacetylenes pale in comparison to that of the carbohydrates, which is one of the most abundant families of natural products. Carbohydrates are involved in a wide range of biological processes, including energy storage and transport, modulation of protein function, cell-cell adhesion, and signal transduction.[17-19] Consequently, carbohydrate-containing molecules have attracted attention as novel pharmaceuticals; indeed, many drugs in common use (e.g., erythromycin, doxorubicin) are functionalized with sugars. Over the past few years we have developed an interest in molecules that posses both a polyacetylenic moiety and a carbohydrate and one class of molecules of this type are polyacetylene glycosides (polyyne glycosides). These species consist of a carbohydrate group attached via an acetal linkage to a polyacetylenic alcohol.

In 1960, the first natural polyacetylenic glycoside was found in the metabolites of the wood destroying fungus *Basidiomycete* B-841.[20] Since then, about fifty polyacetylenic glycosides have been isolated from natural sources. Similar to polyacetylenes lacking a carbohydrate group, several of these natural products display interesting biological properties, including antibacterial activity,[21] the ability to inhibit nitric oxide production,[22] and the power to modulate blood glucose levels.[23] The majority of polyacetylene glycosides have been isolated from plants, and they are particularly common in species such as *Panax* and *Bidens,* which have been used for centuries as traditional medicines in many

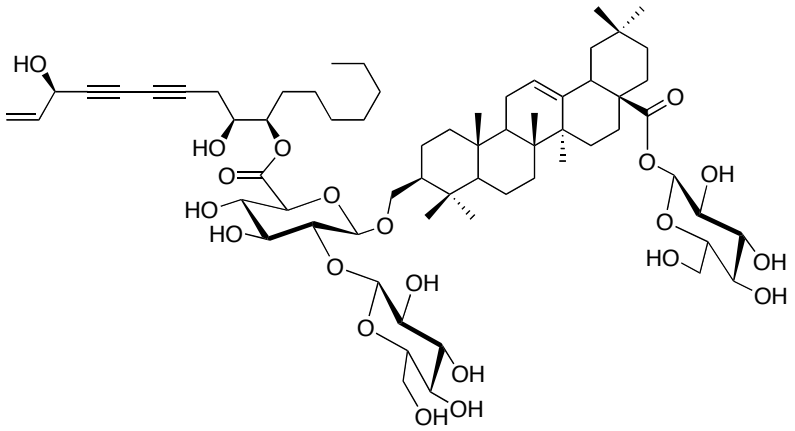
countries. While biological testing has often not been reported in conjunction with their isolation, it is likely that polyacetylene glycosides from these sources possess useful activities.

Synthetic analogues of polyacetylene glycosides might also have significant biological activity, yet virtually no efforts in this direction have been undertaken.[24] Therefore, the synthesis of polyacetylene glycosides and an evaluation of their biological activity are the subject of this thesis. The first chapter represents a review of polyacetylene glycosides that have been isolated from natural sources. This review also includes, where possible, information on the biological activity of these compounds. It concludes with a description of known syntheses of naturally occurring polyacetylene glycosides, natural products analogues, and several molecules that while strictly speaking are not polyacetylene glycosides, they are nevertheless composed of polyacetylene and carbohydrate moieties.

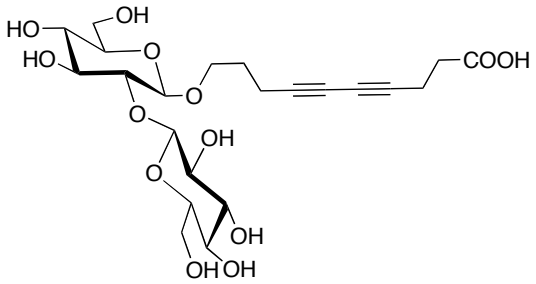
1.2. Polyacetylene glycosides isolated from plants

1.2.1 Family *Araliaceae* – Ginseng family

Red ginseng, the steamed and dried root of *Panax ginseng* C. A. Meyer, has been used extensively in Asian traditional medicine.[25] From this plant and other ginseng species,[26] a host of polyacetylenes have been identified, and this class of compounds has received substantial synthetic attention.[1] To date, however, only one polyacetylene glucoside has been isolated from *P. ginseng,* the oleanolic acid-derived saponin, ginsenoside-Ro **1.1** (Figure 1.1). Studies on natural product **1.1** showed that it inhibited the replication of human immunodeficiency virus type 1 (HIV-1) with an IC_{50} value of 13.4 mg/mL (11.1 mM).[27] It should be mentioned that the ester functionality of **1.1** contains the natural polyacetylene panaxytriol, one of the most studied of all known natural occurring polyacetylenes.[1]



1.1 *ginsenoside-Ro*



1.2 *notoginsenic acid β-sophoroside*

Figure 1.1 Polyacetylene glucoside from the genus *Panax.*

In another study, guided by the hepatoprotecting activity of fractions extracted from *P. notoginseng*, Yoshikawa and coworkers isolated and characterized notoginsenic acid b-sophoroside, (**1.2**, Figure 1.1) as fine, colorless crystals.[28] Unfortunately, nothing further has been reported on the bioactivity of this compound.

1.2.2 Family *Asteraceae* - Aster family

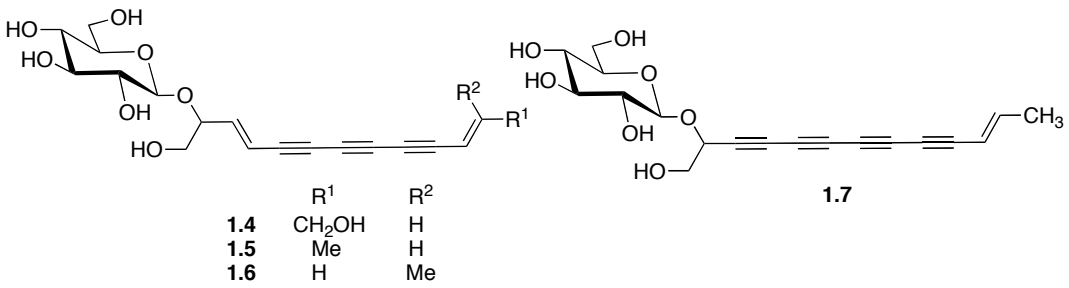
Polyacetylenes are widely distributed in the plant family Asteraceae,[9,29-32] and they are particularly common in the species *Bidens*, commonly referred to as beggarticks in North America.[33] Species of the genus *Bidens* have long been used as traditional Chinese medicinal plants, and many of them have afforded polyacetylenic natural products.[34-36] In 1970, Romussi and Pagani isolated a

polyacetylene glycoside from the species devil's beggarticks, *B. frondosa*, and the structure was initially determined to be a D-glycoside of trideca-4,6,8,10-tetrayn-2-en-1,12,13-triol, although neither the attachment point of the sugar moiety, nor the stereochemistry of the glycosidic linkage was established (the aglycone was also isolated).[37] In subsequent papers, the authors reported on their efforts to confirm the structure of this natural product as **1.3** (Figure 1.2), but they did not provide any information about its biological activity.[38,39]

1.3

Figure 1.2 Polyacetylene glycoside from the species *B. frondosa* (devil's beggarticks).

More than two decades later, Davis and coworkers reported, in 1992, the isolation of four polyacetylene glucosides **1.4**–**1.7** from polar extracts of the dried aerial parts of viper beggarticks, *B. campylotheca* (Figure 1.3).[40] This herb is found only on the Hawaiian islands and has been used in traditional Hawaiian folk medicine as an appetite stimulant, as well as a treatment of general debility, throat and stomach afflictions, and severe cases of asthma.[41] There was no reported study of the bioactivity of **1.4**–**1.7** at the time. It was suggested, however, that glycosylation of the polyacetylene may facilitate the transportation of the typically lipophilic polyacetylenes that are commonly isolated from the many members of this genus.[42] Subsequently, the aglycone of **1.5** was isolated from the same species, and this compound showed a weak inhibitory affect on prostaglandin biosynthesis.[43] In 1999, de Moraes and coworkers reported that tetrayne **1.7** was also present in the methanolic extract of hairy beggarticks (*B. pilosa*) and also examined its bioactivity.[44] Their investigations showed that both the methanolic extract and polyacetylene glycoside **1.7** suppressed human lymphocyte proliferation, with the pure compound **1.7** being 10-fold more potent than the crude extract.



	R^1	R^2
1.4	CH_2OH	H
1.5	Me	H
1.6	H	Me

1.7

Figure 1.3 Polyacetylene glycosides from the species *Bidens campylotheca* (viper beggarticks).

Another *Bidens* species, *B. pilosa,* is a wildly distributed weed in tropical and subtropical regions, and its leaves and flowers are commonly used as a traditional medicine. In Cuba, for example, it is used for treating renal and respiratory problems, as well as inflammation,[35] while it is used in China to treat inflammation,[45] in South Africa for diarrhea,[46] and in Brazil to combat malaria.[47] Alvarez and coworkers have isolated triyne glucoside **1.8** from the methanolic extract of the whole plants of *B. pilosa* in 1996 (Figure 1.4).[48] Although **1.8** did not show activity against a range of bacterial and fungal species including *Staphylococcus aureus, Salmonella typhimurium, Escherichia coli, Pseudomonas aeruginosa, Microspoum gypseum, and Candida albicans*, it did have moderate activity against *Trichophyton mentagrophytes* (MIC = 100 mm/mL), a fungus that causes scalp infections in children.[49] The cytotoxicity of **1.8**, and the parent polyacetylene, were also evaluated against several cancer cell lines, including HCT-15 (colon carcinoma), UISO (uterine-cervix cancer), KB (nasopharyngeal carcinoma), and W138 (lung embryonic fibroblasts), and in all cases the ED_{50} was greater than 4 μg/mL, indicating moderate potency. Interestingly, however, was that **1.8** enhanced the growth of cells, particularly the W138 cells. It was suggested that this proliferative activity might be related to cocarcinogenic action found for dried leaves of *B. pilosa* for esophageal tumors induced in rats.[50]

Two polyacetylene glucosides, **1.9** and **1.10**, were isolated from the African shrub *Microglossa pyrifolia* by Rücker and coworkers in 1992,[21] and were obtained as a

3:2 mixture from *B. pilosa* in 2000 by Fort and coworkers (Figure 1.4).[23] Compounds **1.9** and **1.10** were not separated and tested individually because of their instability during purification. Instead, the mixture of **1.9** and **1.10** was used to study their effect on blood glucose levels, which were demonstrated to drop significantly. In another investigation, Chang et al. have explored the bioactivity of **1.9** and **1.10** and found that both prevent diabetes development in non-obese diabetic mice.[51]

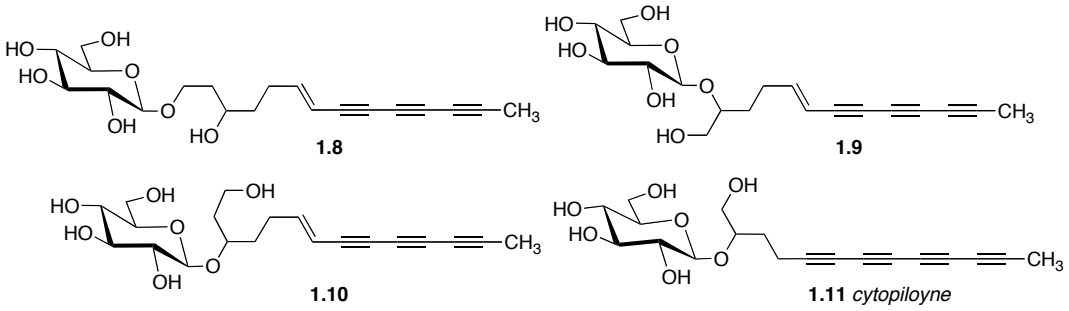


Figure 1.4 Polyacetylene glycosides from *Bidens pilosa.*

Tetrayne **1.11** (cytopiloyne, Figure 1.4) was recently isolated from the methanolic extract of *B. pilosa*, together with the known triyne glucosides **1.9** and **1.10**.[52,53] Similar to the triyne glucosides **1.8**–**1.10**, it was found that cytopiloyne was able to control or prevent type I diabetes in non-obese diabetic mice. More detailed investigations on cytopiloyne revealed that it was capable of inducing the selective differentiation of T helper (Th0) cells into type II T helper (Th2) cells, over type I T helper (Th1) cells. Thus, cytopiloyne suppressed IFN-γ expression and promoted IL-4 expression. These studies therefore demonstrated that cytopiloyne is a T cell modulator, and this function may explain, in part, why *B. pilosa* extracts prevent diabetes. Very recently, cytopiloyne was also found to suppress the maturation of human dendritic cells.[54] The corresponding triyne glycosides were not, however, evaluated in this study and thus the immunomodulatory potential of these compounds is unknown.

In addition to *B. frondosa, B. campylotheca*, and *B. pilosa*, two other *Bidens* species have afforded polyacetylenic glucosides, *B. parviflora* and *B. bipinnata.* Both species have been used in traditional Chinese medicine for treatment of, for example, inflammatory and rheumatism.[55] In 2001, polyacetylenic glucosides **1.12**–**1.16** (Figure 1.5), the bidensyneosides, were isolated from *B. parviflora*. These molecules were characterized as part of a study designed to identify antiallergic agents,[22] and all five were shown to inhibit both histamine release and nitric oxide production. Subsequently, in 2004, Okuyama and coworkers reported the isolation of bidensyneoside C **1.15** and bidensyneoside D **1.17** from *B. bipinnata* (Spanish needles) through extraction of the aerial parts with hot ethanol. Although **1.15** was known from the work described above,[19] **1.17** was a new compound whose biological activity remains unexplored.[56]

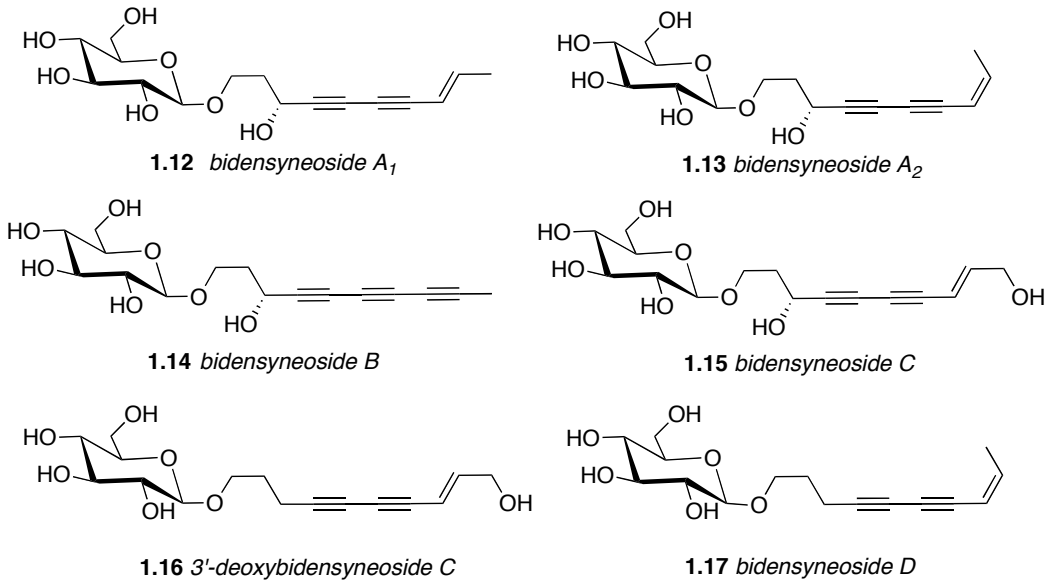


Figure 1.5 Polyacetylene glycosides from *Bidens parviflora* and *B. bipinnata.*

The isolation of polyacetylene glycosides from other genera of the Asteraceae family, such as *Microglossa pyrifolia,* has also been reported. Parts of this shrub are used as a traditional medicine in Ghana for treating fever and impotence,[34] while hunters in the Ivory Coast have used the leaf extract as an arrow poison.[57]

In 1992, Rücker reported the isolation of acetylenic glucosides from the leaves of this species, including triynes **1.9** and **1.10** (Figure 1.4), as well as a tetrayne **1.18** and, remarkably, the pentayne **1.19** (Figure 1.6). All of these molecules are β-glucopyranosides and were characterized spectroscopically through comparisons to their aglycones, which were generated via enzymatic hydrolysis. These four polyacetylene glycosides were then evaluated for their antimicrobial properties against five bacterial stains, and it was determined that only pentayne **1.19** possessed any substantial activity, in particular against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[21]

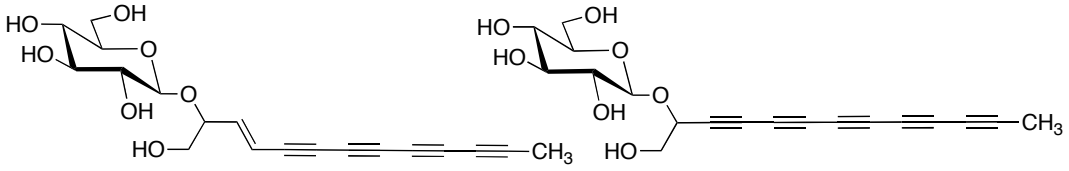


Figure 1.6 Polyacetylene glycosides from *Microglossa pyrifolia.*

In 1993, Yoshihara, and coworkers isolated two new methyl β-D-glucopyranosyl helianthenates **1.20** and **1.21** from a 70% aqueous ethanol extract of the leaves of Jerusalem artichoke (*Helianthus tuberosus*),[58] which, despite its name, is a species of sunflower (Figure 1.7).[31] Both **1.20** and **1.21** showed tuber-forming activity in potatoes. Later, the same group reported four additional methyl β-D-glucopyranosyl helianthenates **1.22**–**1.25**, which were isolated from the same plant species.[59] It is worth noting that the helianthenates A–E share a similar substructure with falcarinol and falcarindiol, two of the most widely studied, naturally occurring polyacetylenes.[1,26,60]

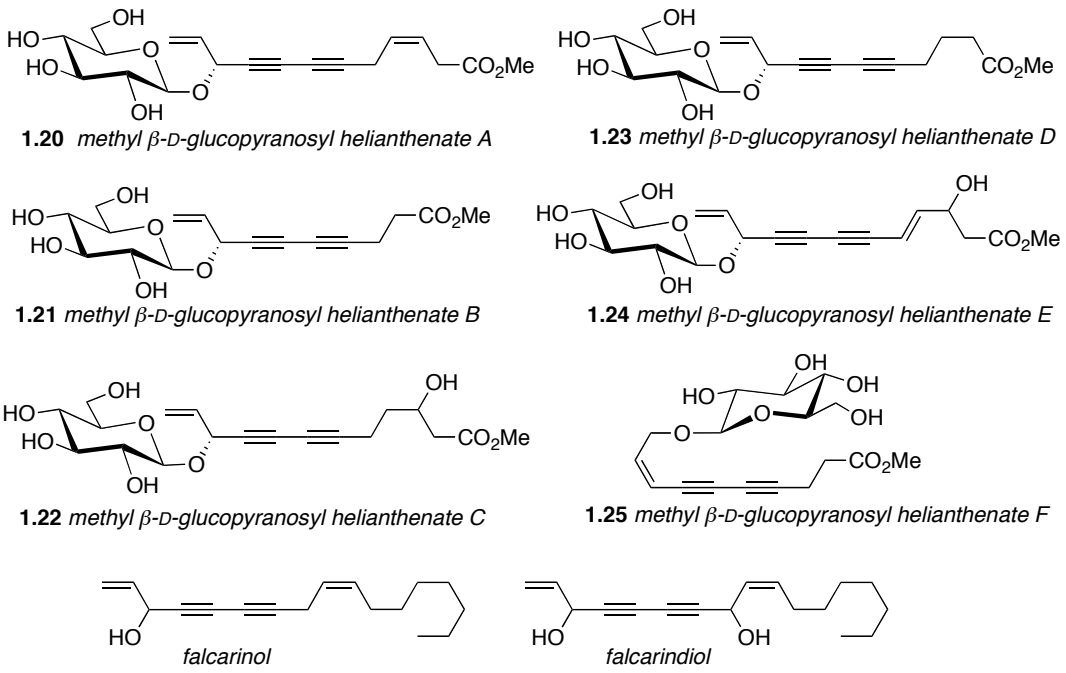


Figure 1.7 Polyacetylene glycosides **1.20–1.25** from *Helianthus tuberosus.*

Members of the *Aster* genus have been used in traditional medicine for the treatment of, for example, fever, colds, snakebites, and bee stings.[61] As part of their study of *Aster* species as sources of bioactive compounds, Zhou and coworkers have isolated asteryunnanoside I **1.26** (Figure 1.8) from the *n*-butanol-soluble portion of a 70% ethanol extract of *Aster yunnanensis* roots.[62]

In a similar investigation, Yu and coworkers isolated four glycosidic constituents, **1.27**–**1.30**, from the 70% ethanol extract of the roots of the species *A. auriculatus*.[63] Compounds **1.27** and **1.28** are both disaccharides that possess the same aglycone, but differ in the structure of the carbohydrate moiety. In contrast, compounds **1.29** and **1.30** are both β-D-glucopyranosides, but differ in the position of the double bond in their aglycone. Compound **1.29** resembles bidensyneoside D **1.17** (Figure 1.5), which was isolated by Okuyama and coworkers from *Bidens bipinnata*, except that the configuration of the olefin at the distal end of the aglycone is *E*, rather than *Z*.[56]

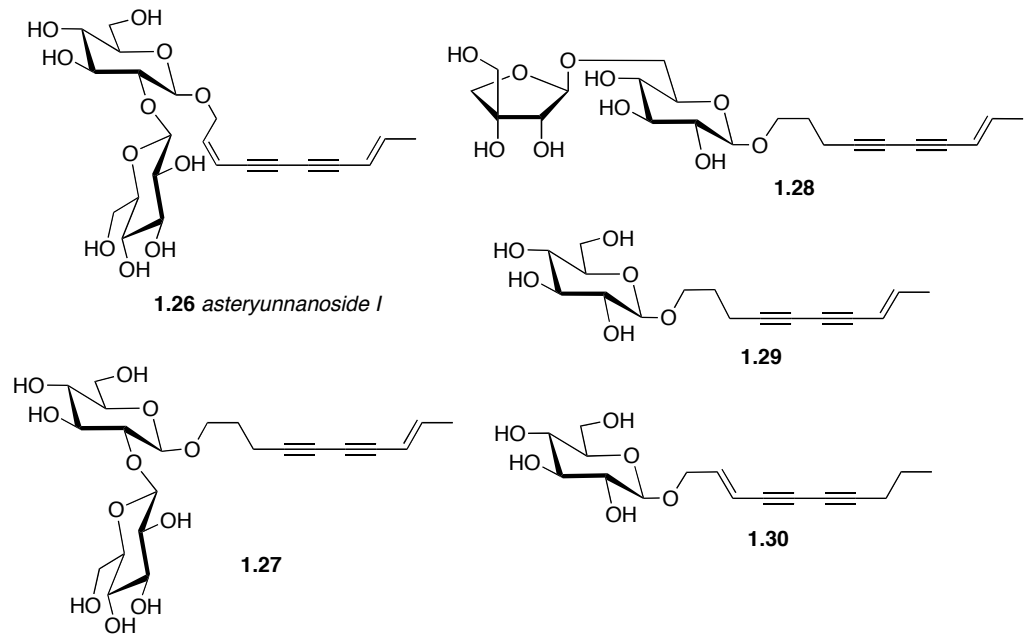


Figure 1.8 Polyacetylene glycosides from *Aster yunnanensis* and *A. auriculatus.*

Another member of the aster family is *Gymnaster koraiensis*, which is a common plant species in Korea. Several polyacetylenes have been isolated from *G. koraiensis*, including gymnasterkoreaynes A–G (not shown).[64,65] To find pharmacologically active constituents from this plant, Bae and coworkers analyzed root extracts from *G. koraiensis* and isolated two polyacetylene glycosides, gymnasterkoreasides A (**1.12**, Figure 1.5) and B (**1.31**, Figure 1.9**)**.[66] Compound **1.12** had been previously isolated from *Bidens parviflora* by Wang and co-worker, who christened it bidensyneoside A_1.[22] Compound **1.31**, which, like **1.28** (Figure 1.9) possesses a β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyl moiety, represented a new polyacetylene disaccharide.

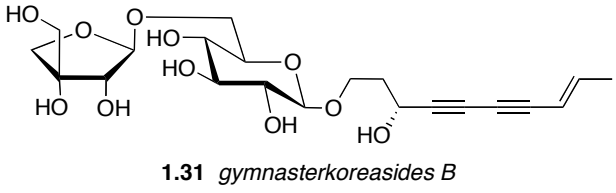


Figure 1.9 Polyacetylene glycoside from *Gymnaster koraiensis.*

The rhizomes of another genus of the aster family, *Atractylodes,* have long been used in Japanese traditional medicine.[67] A number of polyacetylene natural products have been discovered in this genus, including glucoside derivative **1.32** (Figure 1.10) identified from *A. lancea* by Kitajima and coworkers.[68] It is worth noting that the aglycone of **1.32** has also been isolated from the aerial parts of the ornamental knapweed (*Centaurea ruthenica*) by Bohlmann and coworkers.[69] From a related species, *A. ovata*, the polyacetylene glycoside **1.33** was isolated and identified by the same group.[70] To date, there are no reports on the biological activity of either **1.32** or **1.33**.

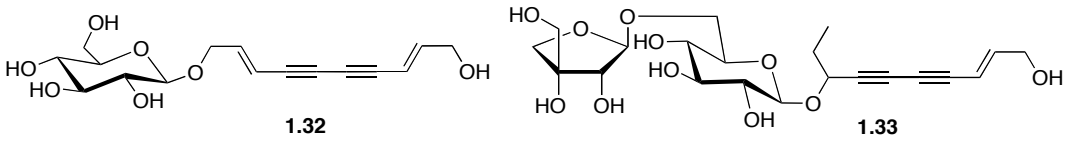


Figure 1.10 Polyacetylene glycosides from *Atractylodes lancea* and *A. ovata.*

The aster family species *Artemisia monosperma* is a desert shrub native to a number of countries in the Middle East, for example, Egypt, Libya, Israel, Jordan, and Lebanon. Phytochemical studies on this species have resulted in the isolation of polyacetylene, sesquiterpene, and acetophenone natural products.[71,72] In 2005, Gibbons and coworkers reported the isolation of additional bioactive constituents from *A. monosperma*, including a new polyacetylene glucoside **1.34a** and its aglycone **1.34b** (Figure 1.11).[73] Diol **1.34b** had been isolated previously from the same plant[74] and it was proposed, but not established, that the stereochemistry of the aglycone of **1.34a** was the same. These two compounds were tested for their ability to inhibit the enzyme 12-lipoxygenase, and both exhibited moderate activity against the enzyme at 30mg/mL.

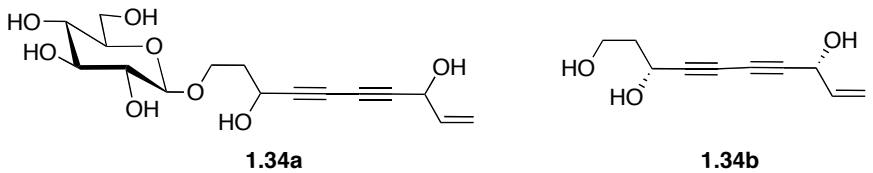
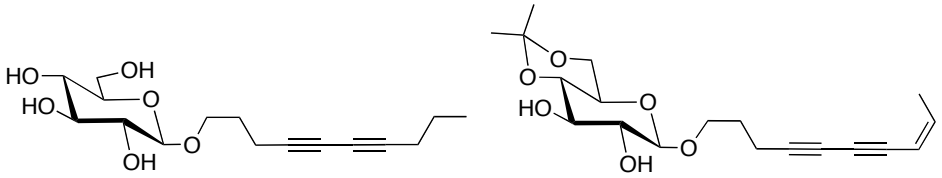


Figure 1.11 Polyacetylene glycoside from *Artemisia monosperma.*

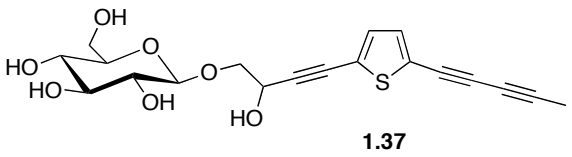
In addition to its cultivation for its seed oil, the dried flower petals of the safflower plant (*Carthamus tinctorius*) are widely used in traditional Chinese medicine to, for example, promote blood circulation.[75] Two new compounds, carthamoside A_1 **1.35** and A_2 **1.36** (Figure 1.12) were isolated from *C. tinctorius*, as well as **1.17** (bidensyneoside D, Figure 1.5).[76] Similar to bidensyneoside D, whose biological activity has not been reported, the ability of either **1.35** or **1.36** to modulate biological processes has seemingly not been investigated.



1.35 *carthamoside* A_1 **1.36** *carthamoside* A_2

Figure 1.12 Polyacetylene glycosides from *Carthamus tinctorius.*

Pluchea indica (Indian fleabane or Indian camphorweed) is a native plant of India, South China, Malaysia and Australia, and recently it has been classified as an invasive species in the Hawaiian Islands.[77] The species has been used traditionally to remedy a variety of ailments; for example, in Thailand and Java the chopped stem bark is smoked as cigarettes to relieve the pain of sinusitis.[78] From the aerial parts of this plant, the thiophene based polyacetylene glycoside **1.37** has been isolated, together with several other polyacetylenes including the aglycone (Figure 1.13).[79] The antimicrobial properties of these derivatives have been explored, and, using a standard disk diffusion assay, it was shown that **1.37** was active against *Staphylococcus aureus* and *Bacillus subtilis*. By way of comparison, the aglycone of **1.37** was active against not only *S. aureus* and *B. Subtilis*, but also *S. cerevisiae*. Neither was active against *Escherichia coli* or *Bacillus thuringiensis*. The aglycone of **1.37** has been previously identified from several sources, including *Pterocaulon allopecuroides* (blackroot),[80] *Onoseris alata*,[81] and *Pluchea suaveolens* (wingstem camphorweed).[82]

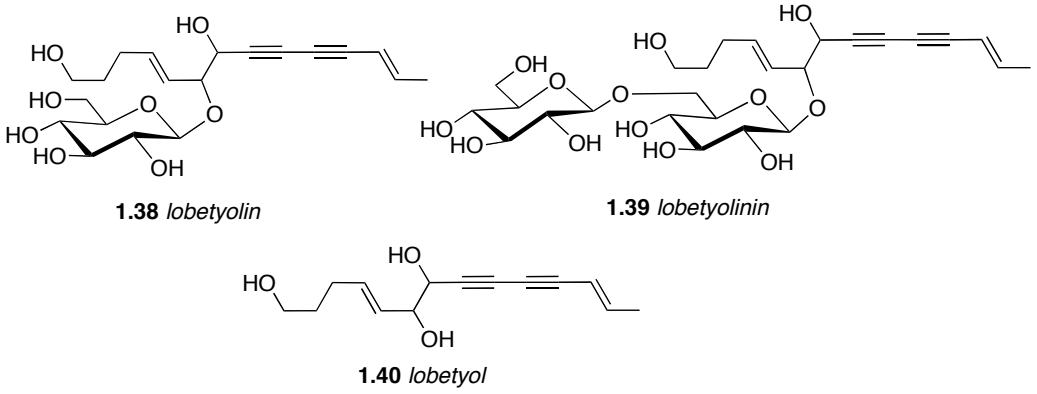


1.37

Figure 1.13 Polyacetylene glycoside from *Pluchea indica*.

1.2.3 Family *Campanulaceae* – Bellflower family

Of the known polyacetylene glycosides from this family of plants, two have been particularly well studied, lobetyolin **1.38** and lobetyolinin **1.39** (Figure 1.14); the aglycone of both glycosides, lobetyol **1.40**, has also been included in these investigations. In 1990, Tanaka and coworkers first identified lobetyolin **1.38**, along with a number of other glucosides, from the herb *Codonopsis tangshen*,[83] a very common drug plant in China (known as dangshen) whose root is widely used as a substitute for ginseng.[84] In 1994, Nörr and Wagner also reported the isolation of lobetyolin from *C. pilosula*, a related species that is sometimes called "poor man's ginseng".[85]



1.38 *lobetyolin* **1.39** *lobetyolinin*

1.40 *lobetyol*

Figure 1.14 Polyacetylenes glycosides lobetyolin (**1.38**), lobetyolinin (**1.39**), and lobetyol (**1.40**).

In 1991, Ishimaru and coworkers isolated lobetyolin **1.38** and lobetyol **1.40** from *Lobelia inflata*, a common North American plant, typically called Indian tobacco

or puke weed.[86] In the following year, 1992, lobetyolinin **1.39**, was isolated from this same species.[87] Ishimaru and coworkers also isolated lobetyol, lobetyolin, and lobetyolinin from hairy root cultures of *Lobelia sessilifolia*, *Lobelia chinensis,* and *Lobelia cardinalis*.[88,89,90] Bálvànyos and coworkers analyzed for these three compounds in hairy root culture of *Lobelia inflata* cultivated in a bioreactor by direct infection of the sterile plants with *Agrobacterium rhizogenes* strain R1601.[91]

In 1995, Ishiruma and coworkers infected the cultured hairy roots of *Platycondon grandiflorum* with *Agrobacterium rhizogenes* to produce lobetyol, lobetyolin, and lobetyolinin.[92] Over the next few years, this group reported the use of the same method to culture hairy roots of *Platycodon grandiflorum* (Korean balloon flower) and *Trachelium caeruleum* with the goal of obtaining larger amounts of the polyacetylenes and polyacetylene glycosides.[93,94] The isolation of **1.38**–**1.40** from hairy root cultures of *Campanula medium*,[95] *Cladophora glomerata,*[96] *Wahlenbergia marginata,*[97,98] *Dialypetalum floribundum*[99] has also been reported.

Interestingly, despite the significant amount of work directed at producing and isolating lobetyolin, lobetyolinin, or lobetyol from various sources, in none of studies, has their biological been reported. Indeed, the only report on the biological activity of these compounds comes from Dumlu et al. who isolated five known compounds, including lobetyol and lobetyolin, from the methanolic extract of the ivory bellflower (*Campanula alliariifolia*) and studied their antioxidant (free radical scavenging) activity. These investigations revealed that lobetyolin (**1.38**) showed antioxidant activity at a concentration of 500 mg/L; the activity of lobetyol (**1.40**) was similar.[100]

In 2008, another plant species used in Chinese herbal remedies, *Codonopsis cordifolioidea*, was shown to produce three polyacetylene glycosides, cordifolioidynes A–C (**1.41**–**1.43**, Figure 1.15), as well as lobetyolin **1.38**. The antibacterial activity of these compounds was assessed against eight microbial

strains by the agar dilution method, and none exhibited antibacterial effects at concentrations up to 100 μg/mL.[101]

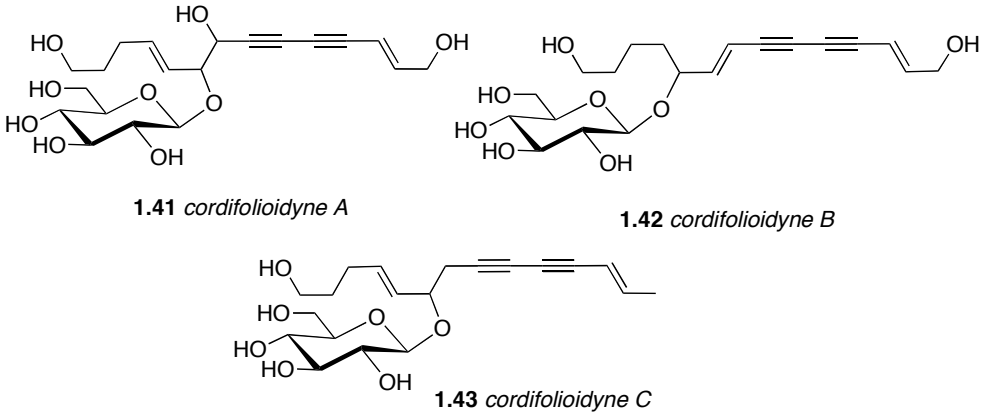


Figure 1.15 Polyacetylene glycosides from *Codonopsis cordifolioidea.*

Pratia nummularia is a perennial plant found at high altitudes in China, India, Malaysia, Thailand, Myanmar, Australia and South America. The whole plant has been commonly used as a traditional medicine for the treatment of contusions, cough, and inflammation.[102] From the hairy root cultures of *P. nummularia*, Ishimaru and coworkers isolated two unique glycosides, pratialin-A (**1.44**, Figure 1.16) and pratialin-B (**1.45**) as well as lobetyolin and lobetyolinin.[103] Their report did not include any biological testing of these complex glycolipids.

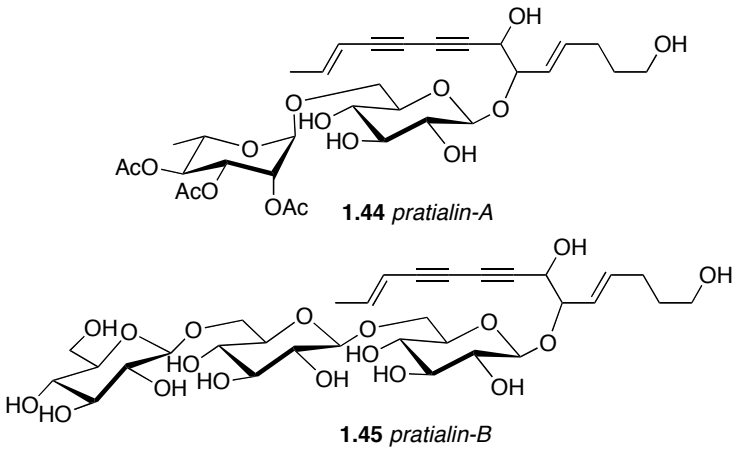


Figure 1.16 Polyacetylene glycosides from *Pratia nummularia.*

1.3 Polyacetylene glycosides isolated from fungi

While polyacetylenes are rather commonly found in fungi,[8,12,15] only two reports describe polyacetylene glycosides isolated from this class of organisms. The first comes from species of the fungus *Fistulina*, which are known to produce polyacetylenes both in mycelia cultures[104] and in fruiting bodies in the field.[105] In 1974, it was demonstrated that extracts from the culture fluids of the pale beefsteak fungus (*Fistulina pallida*) grown in surface cultures produced small amount of several triyne products, including a polyacetylene glucoside and the corresponding aglycone. Unfortunately, this glucoside could not be isolated in a pure state, but on the basis of their analyses on the impure materials, the compound was determined to be one of two isomeric structures, triyne **1.46** or **1.47**.[106] No biological activity of these compounds was reported.

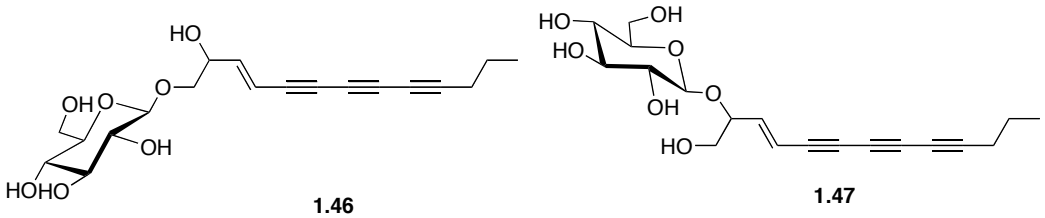


Figure 1.17. Polyacetylene glycosides from *Fistulina pallida.*

Bu'Lock and coworkers have examined the polyacetylene metabolites obtained from of *Basidiomycete* B-841 and identified the unusual allene-diyne **1.48**, the β-D-xylopyranoside of nemotinic acid **1.49** (Figure 1.18).[20] While the configuration of the allene group remains unknown, the identification of **1.48** is very impressive given that structural assignment was achieved in 1955, through chemical analysis and degradation, rather than NMR spectroscopic analysis. The aglycone, nemotinic acid, has been identified in extracts of the fungi *Poria corticola* and *Poria tenuis*, the liquid cultures of which showed antibiotic activity against a number of microorganisms, including *Mycobacterium tuberculosis*.[107-109]

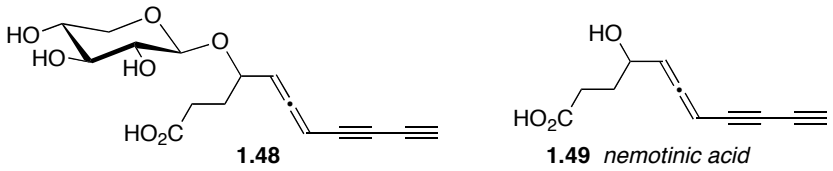


Figure 1.18 Polyacetylene glycosides from *Basidiomycete* B-841.

1.4 Polyacetylene glycosides isolated from algae

The unicellular alga *Prymnesium parvum* is one of the most damaging red tide species,[110,111] and its bloom has been responsible for devastating fish kills.[112] It has been known for over three decades that the organism produces a potent ichthyotoxcin named prymnesin, although the structure of this toxin was unknown at the time this discovery was made.[113] In 1996, 10 mg of prymnesin-1 (**1.50**) and 15 mg of prymnesin-2 (**1.51**) were isolated by Yasumoto and coworkers from 400 L of *P. parvum* cultures. Initially, only the structure of the major component, prymnesin-2, was reported, albeit without the stereochemistry established; the structure of prymnesin-1 remained unknown.[114] However, in 1999, Yasumoto and coworkers reported the structural elucidation of both prymnesins, including stereochemical assignments, on the basis of extensive NMR spectroscopic analyses.[115] The relative configuration of two stereogenic centers of these initial structures (at the E/F ring junction) have subsequently been reassigned.[116] The toxicity of both molecules is quite impressive: both are toxic to fish at concentrations less than 10 nM, and they also lead to complete lysis of mouse cells at a concentration of 3 nM.[117]

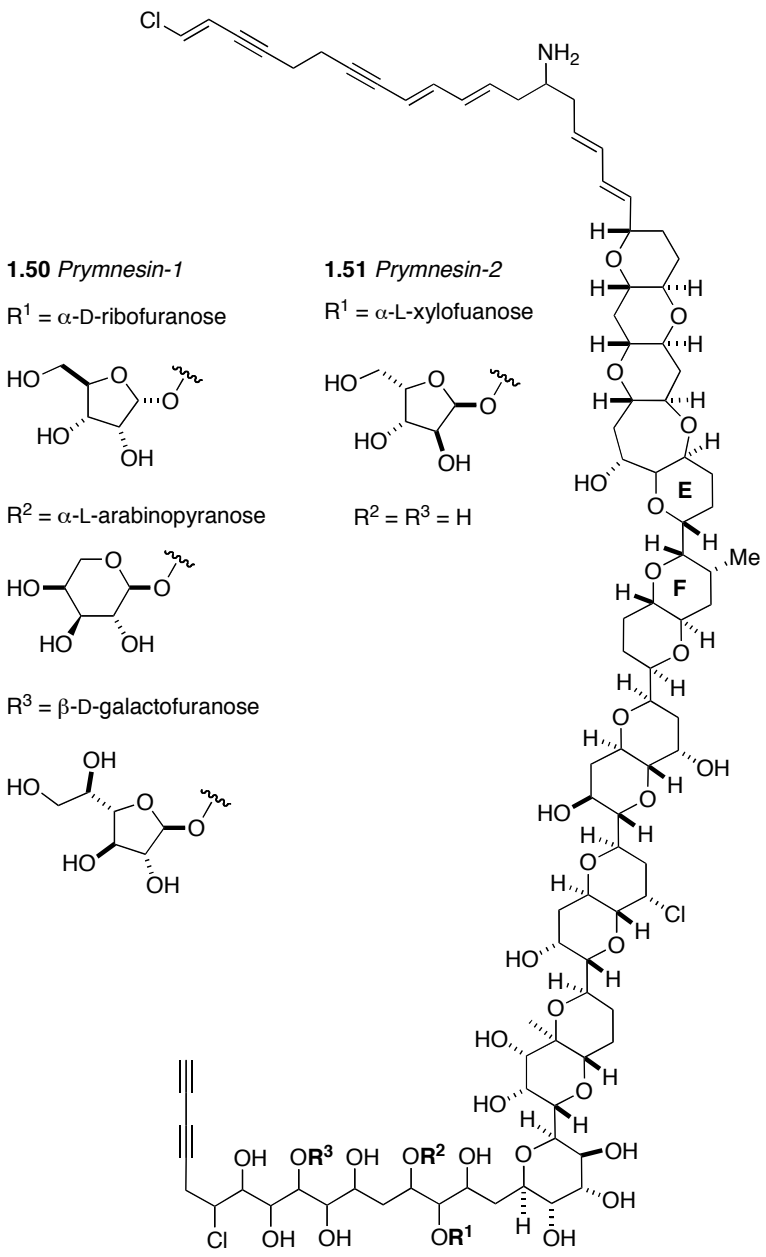
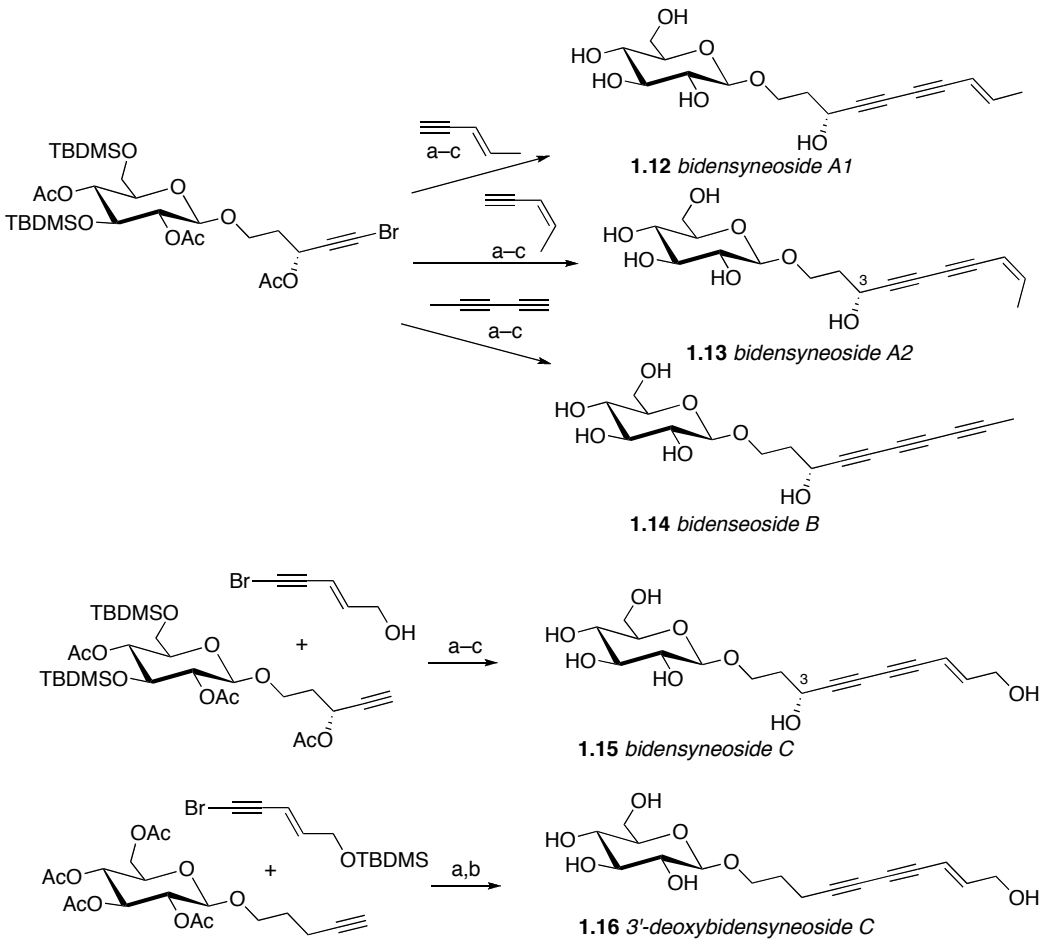


Figure 1.19 Polyacetylene glycosides prymnesin-1 (**1.50**) and prymnesin-2 (**1.51**) from alga *Prymnesium parvum.*

1.5 Synthesis of polyacetylene glycosides

1.5.1 Synthesis of natural products.

Although many polyacetylene glycosides have been isolated from natural sources, and some of them have been shown to possess a range of biological activities, there has been surprisingly little interest in their synthesis. To date, only two reports have described the synthesis of naturally occurring polyacetylene glycosides. Gung and Fox have reported the syntheses of bidensyneosides A_1, A_2, B, and C (**1.12–1.15**, respectively), and an analogue bidensyneoside C (**1.16**, Scheme 1.1).[118,119] Although the protecting group strategy employed for the sugar moiety varied among the individual syntheses, the general approach for construction of the polyyne segment remained constant. In each case, the di- or triyne segment of the bidensyneoside was completed with a Cadiot–Chodkiewicz coupling between a glycosyl bromoacetylene derivative and a mono or diyne, which depending on the coupling partners proceeded in yields between 31% and 91%. Global deprotection, in one or two steps then afforded the desired products. It should be mentioned that the synthesis of these glycosides also allowed for the confirmation of the stereochemistry at C3 of the aglycone of **1.12–1.15**, which had not yet been established.



Scheme 1.1 Bidensyneoside syntheses from Gung and co-workers.

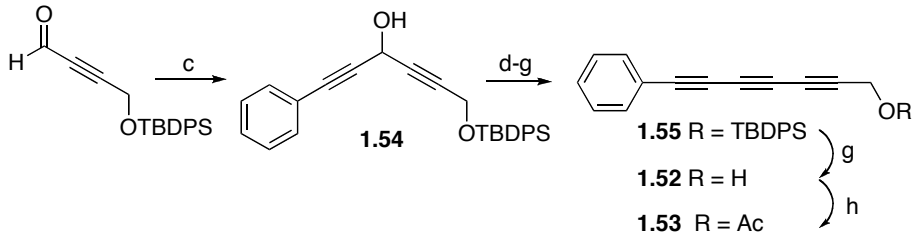
a) CuCl, Et_2NH, NH_2OH•HCl, MeOH, H_2O, 0 °C, 91% (**1.12**), 86% (**1.13**), 46% (**1.14**), 56% (**1.15**), 31% (**1.16**); b) HF–pyr, THF, 0 °C, 87% (**1.12**), 85% (**1.13**), 53% (**1.14**), 50% (**1.15**), 51% (**1.16**); c) MeOH, K_2CO_3, rt, 50% (**1.15**) over two steps.

1.5.2 Synthesis of natural product analogues

As is the case described above for naturally occurring polyacetylene glycosides, there has also been surprisingly little effort amongst synthetic chemistry toward the assembly of natural product analogues. The synthesis of polyacetylene glycosides, particularly derivatives with a tri-, tetra-, or pentayne skeleton can be challenging,

in part due to the inherently unstable nature of these longer polyynes.[1] Presumably this instability, and the dearth of effective methods for making polyynes, are factors that have limited synthesis of compounds in this class of molecules. To date, there has been a single report that has specifically targeted the synthesis of natural product analogues of polyacetylene glycosides.

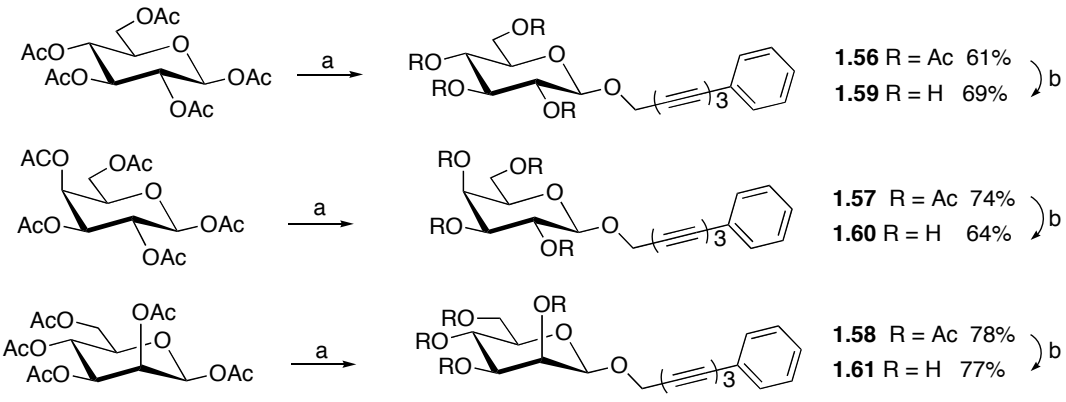
In 2005, Tykwinski and Lowary described[120] the first syntheses of triyne glycosides using triynol **1.52**, which together with its acetate derivative **1.53** (Scheme 1.2) were isolated from several species of *Bidens* (beggarticks), including *Bidens pilosus* and *Bidens leucanthus*.[121] The synthesis of **1.52** and **1.53** started from 1,4-butynediol.[120] Mono-protection of this diol with TBDPS chloride followed by oxidation gave the corresponding aldehyde, which was then reacted with lithium phenylacetylide to provide alcohol **1.54** in 71% yield over the two steps. A sequence of oxidation, dibromoolefination, and Fritsch–Buttenberg–Wiechell rearrangement gave the triyne core **1.55** in 68% overall yield. Finally, liberation of the alcohol with TBAF gave a 90% yield of triynol **1.52**, which was then acetylated affording an 81% yield of **1.53**.



Scheme 1.2 Synthesis of triynol **1.52** by Luu et al.

a) [111] TBDPSCl, THF, Et_3N, DMAP, rt, 84%; b) $BaMnO_4$, CH_2Cl_2, rt, 85%; c) PhC≡CLi, THF, –78 °C, 85%; d) $BaMnO_4$, CH_2Cl_2, rt, 89%; e) CBr_4, PPh_3, CH_2Cl_2, Et_3N, 0 °C, 53%; f) *n*-BuLi, hexanes, –78 °C to 10 °C, 90%; g) TBAF, THF, rt, 96%; h) Ac_2O, DMAP, CH_2Cl_2, Et_3N, rt, 81%.

In theory, coupling triynol **1.52** to different sugar moieties could be achieved through the use of a number of different glycosylation protocols. In this study, three standard methods, each employing a different class of glycosylating agent – glycosyl acetates, glycosyl halides and glycosyl imidates were investigated. The reaction rate and yields were both low when glycosyl bromides were used as donors, while the coupling reactions using trichloroacetimidates as donors led to multiple products. In contrast, using glycosyl acetates as donors gave the desired products **1.56–1.58** in modest to good (61–78%) yields. Deacetylation of the protected sugars afforded the triynol glycosides **1.59–1.61** (Scheme 1.3).[120]



Scheme 1.3 Synthesis of triynol glycosides by Luu et al.

a) [111] **1.52**, BF_3•OEt_2, 4 Å MS, CH_2Cl_2, rt; b) K_2CO_3, CH_3OH, –78 °C to rt.

In addition to the natural product analogues just described, there have been several forays into combining the conjugated framework of a polyacetylene with that of a carbohydrate. Although these studies have not always targeted natural products or their analogues (indeed most are not, strictly speaking, polyacetylene glycosides) several are mentioned here to show the broad and evolving scope of this area of chemistry.[24]

Vasella and coworkers have explored a number of potential mimics of cellulose, such as **1.62**, which possesses two cellooctaosyl chains with a C-glycosidic mono-

or diyne linkage between the "reducing" end of the oligosaccharide and an anthraquinone core (Figure 1.20).[122] The anthraquinone template was used to ensure a parallel orientation of the oligosaccharide chains, and the distance between the two chains was designed to correspond to that determined crystallographically for the two independent chains of cellulose I. The ethynyl and butadiynyl linker units enforced an appropriate phase shift between the two chains. Key steps in the synthesis of these compounds involved the formation of a carbon-linked glycosyl acetylene or diacetylene derivative, which was the coupled via a Sonagashira coupling to anthraquinone triflates. The use of a selective protection–deprotection sequence on 1,8-dihydroxyanthraquinone facilitated the introduction of two different carbohydrate substitutents. The Vasella group has also used butadiyne-linked saccharide oligomers as cellulose analogues in which intrachain-interesidue hydrogen bonding can be avoided. This has led to the development of efficient methodology for the formation of monodisperse oligomers such as **1.63**, which relies on palladium-catalyzed coupling of carbohydrate building blocks functionalized at C1 and C4 (or C4') with ethynyl fragments to form the diyne linkers.[123-128]

4-Ethynyl-α-D-glucopyranosylacetylenes has also been used by this same group for the preparation of cyclodextrin analogues free of interresidue hydrogen bonds (**1.64**, **1.65**). In the synthesis of these compounds, a series of sequential Cadiot–Chodkiewicz cross-couplings was used to form linear oligomers, which were then cyclized via an intramolecular Cadiot–Chodkiewicz coupling to provide tri-, tetra-, penta-, and hexamers.[129-131] In other cases, oxidative homocoupling has been used to assemble the cyclic acetylenosaccharides.[132] One example involves the formation of **1.65** via reaction of a 4-ethynyl-□-D-pyranosylacetylene monomer under Eglinton conditions.[133] In addition to their synthesis, the host-guest properties of these cyclic structures were investigated and indeed they have been shown to act as hosts for small molecules. For example, the D2-symmetric tetramer **1.64** forms complexes of approximately the same strength with D- or L-adenosine in D_2O, albeit with rather low affinity (K_a = 40 M^{-1})[129,130]

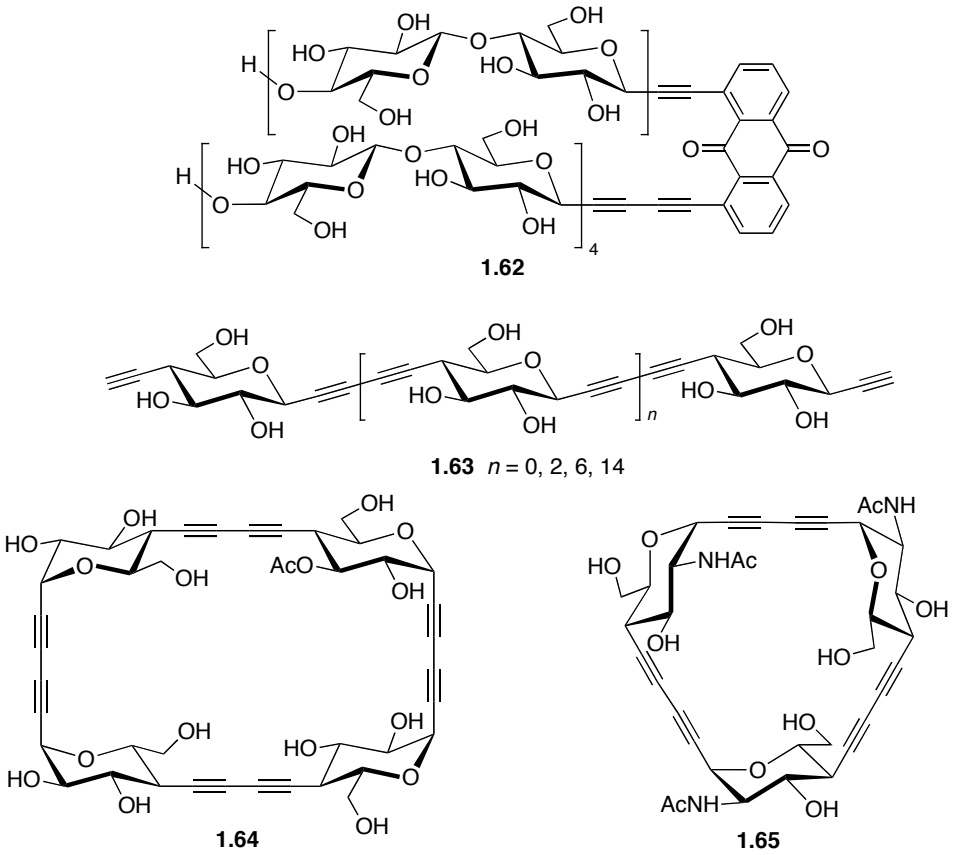


Figure 1.20 Polyacetylene glycoside oligomers by Vasella and co-workers.

The use of two acetylene moieties to connect carbohydrate residues has also been explored by Roy and coworkers who have reported the use of a mild homocoupling method for the formation of conjugated carbohydrate diynes **1.66** based on Pd-catalyzed homocoupling of the corresponding monomer **1.67** (Figure 21). Five derivatives were reported, with yields ranging from 65–85%. The mannose terminated dimer was subsequently deacylated and its ability to cross-link the tetrameric plant lectin concanavalin (Con A) was examined.[134]

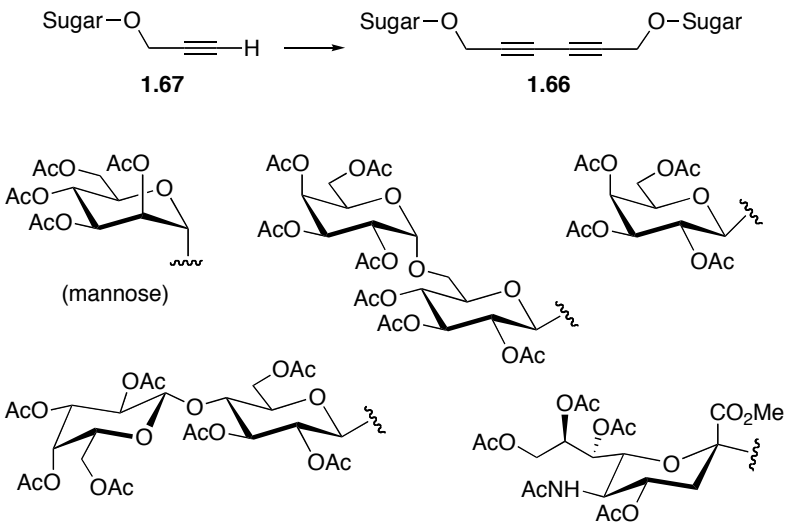


Figure 1.21 Glycoside dimers by Roy and co-workers.

Conjugates of carbohydrates and polyynes have also been synthesized as potential biological sensors. An example are diynes **1.68** and **1.69**, which were synthesized and then incorporated into self-assembled monolayer of polydiacetylenes by Charych and coworkers (Figure 1.22).[135] The sialic acid component of **1.68** acts as a ligand for molecular recognition for the influenza virus, while the photochromic conjugated polymer backbone serves to signal the binding event, which is visible to the naked eye as a blue to red color change. The lactose analogue **1.69** was also prepared and used to test for nonspecific binding.

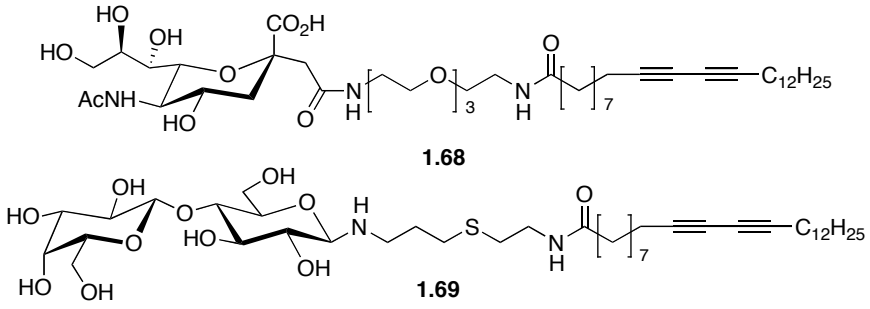
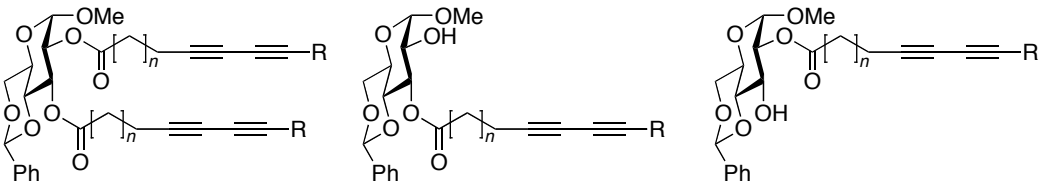


Figure 1.22 Glycoside diynes from Charych and co-workers.

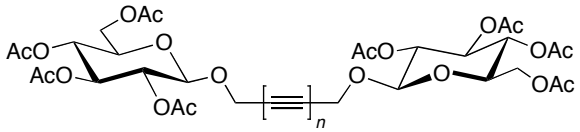
In work related to that of Charych and co-workers, Wang and Nie have synthesized a series of 24 diacetylene-containing sugar lipids **1.70** that incorporated a range of different chain lengths, substituents, as well as varied positioning of diyne moiety (Figure 1.23).[136] The self-assembling properties of these diynes were then explored in several solvents including hexane, ethanol, and ethanol–water mixtures. Many of these derivatives exhibited excellent gelation properties in ethanol or ethanol–water mixtures, and this behavior was dependent both on the position of the diyne on the carbohydrate and the chain length. The production of new materials, via diacetylene polymerization of the resulting gels, was also explored.



1.70 *n* = 1, 2, 4, 6; R = H, alkyl, phenyl, trialkylsilyl

Figure 1.23 Glycoside dimers synthesized by Wang and Nie.

Most recently, Frauenrath and Hoheisel, have expanded on the concept of polyacetylene tethered saccharides through the construction of two derivatives, a hexayne and octayne (**1.71**, Figure 1.24).[137] The formation of these extended molecules relied on a newly devised cross-coupling method using the combination of a zinc-acetylide and a bromoacetylene in the presence of $Pd(Cl_2)dppf$. Despite their highly unsaturated polyyne skeleton, both molecules were stable for days under ambient conditions.[138]



1.71 *n* = 6, 8

Figure 1.24 Glycoside polyynes prepared by Frauenrath and Hoheisel.

1.6 Conclusion

Polyacetylene glycosides are an intriguing class of compounds with important biological activities including antibacterial and anti-inflammatory properties, as well as the ability to modulate blood glucose levels. Even though about fifty polyacetylene glycoside natural products have been isolated and some of their biological activities have been studied, identifying new polyacetylene glycosides remains an important area of research, as is the synthesis of polyacetylene glycoside natural product analogues. Our approach was to synthesize analogues of these natural products that possess a polyacetylene side chain. In Chapter 2, the synthesis of polyacetylene glycosides and their subsequent screening for cytotoxic activity towards cancer cell lines and several bacterial strains will be presented and discussed.

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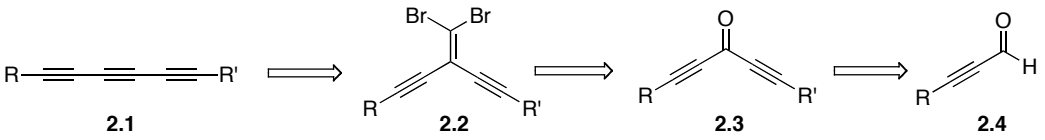
Chapter 2. Synthesis of polyacetylene glycosides and polyacetylene thioglycosides

2.1 Introduction

Hundreds of compounds bearing a conjugated polyyne framework have been identified in nature.[1] Biological studies have revealed that they have a broad scope of activities, including larvicidal,[2] antimicrobial,[3] anti-viral (HIV),[4] and cytotoxic properties.[5] Unfortunately, the isolation of these kinds of compounds from natural sources is difficult due to the unstable nature of polyynes. To date, a number of strategies have been used to synthesize the polyyne framework: the Cadiot–Chodkiewicz reaction, the Sonogashira reaction, and oxidative homocouplings such as those reported by Eglinton, Glaser and Hay.[6] However, the challenges with these strategies include the instability of the precursors, the formation of byproducts and low yields of the products. An alternative synthetic method, the Fritsch–Buttenberg–Wiechell rearrangement,[7] has been developed to allow for the use of readily available starting materials. For example, a retrosynthetic analysis for triyne **2.1** is shown in Scheme 2.1, where a new triple bond is formed via a rearrangement of the dibromoolefin **2.2** as a precursor.[8,9] The dibromoolefin **2.2** can be accessed from ketone **2.3**, which can be obtained from aldehyde **2.4** in a few steps.



Scheme 2.1 Retrosynthesis of polyyne **2.1**.

Polyyne glycosides are also natural products that have been shown to have a host of different biological activities.[10] The syntheses of natural polyyne glycosides and their analogues have not been widely investigated. Indeed, to date, only three studies have described the synthesis of such species. In 2004, Gung and

coworkers described the synthesis of bidensyneoside A_2 and C (Figure 2.1) based on a glycosylation and subsequent Cu(I)-catalyzed cross coupling of the right hand enyne fragment to the main framework.[11] In 2005, Tykwinski, Lowary and their coworkers synthesized several triyne glycosides by glycosylating triynols with different carbohydrate donors.[12] Finally, in 2006, the Gung group reported the synthesis of bidensyneosides A_1 and B, as well as the 3′-deoxy-analogue of bidensyneoside C with the same strategy they used in 2004.[13]

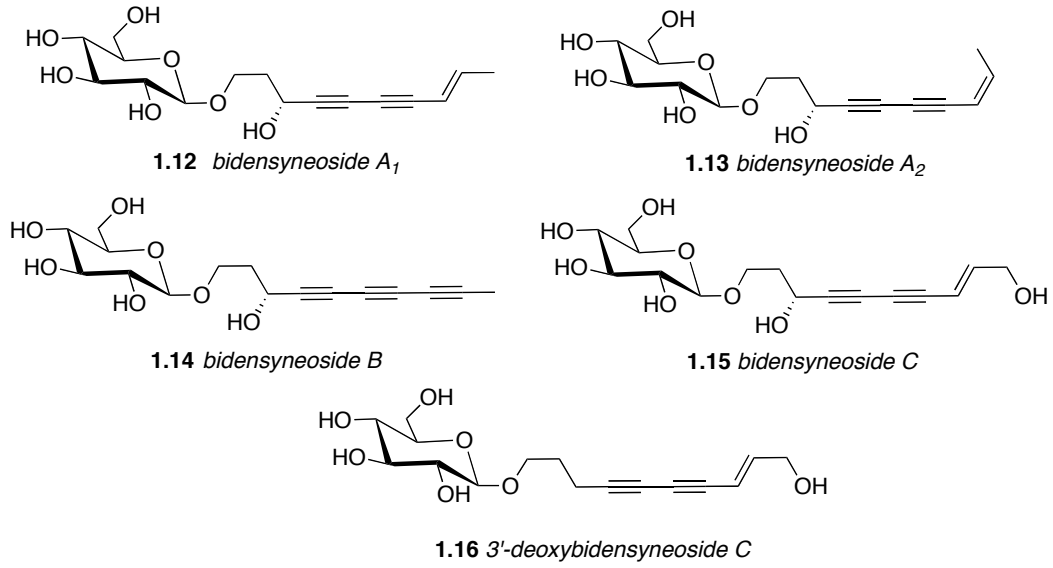


Figure 2.1 Structures of bidensyneoside A_1, A_2, B, C and an analogue of C.

Described in this chapter is the successful synthesis of two polyyne alcohols, **2.5** and **1.52** (Figure 2.2), using a Cadiot–Chodkiewicz reaction and a Fritsch–Buttenberg–Wiechell rearrangement as key steps, respectively. The synthesis of polyyne glycosides and polyyne thioglycosides based on these alcohols is then described, using BF_3•OEt_2 as promoter and various carbohydrates as donors.

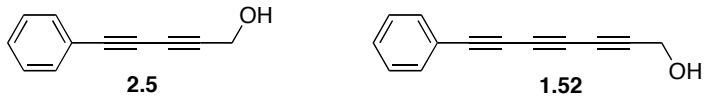
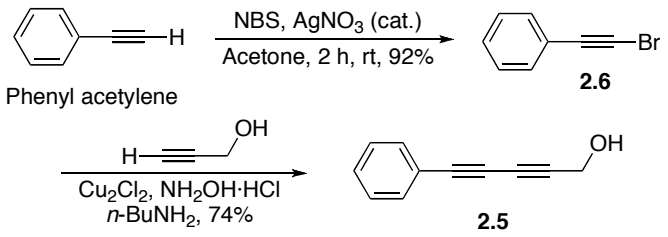


Figure 2.2 Structures of **2.5** and **1.52**.

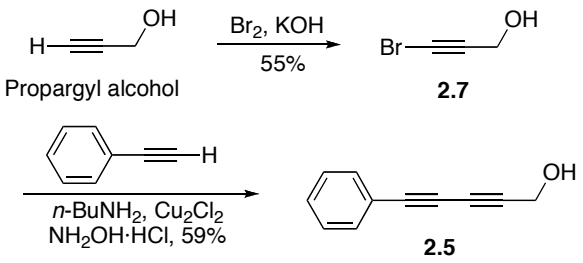
2.2 Synthesis of polyyne alcohols 2.5 and 1.52

5-Phenyl-2,4-pentadiyn-1-ol (**2.5**) has been previously synthesized using an alkyne–iodoalkyne cross-coupling reaction.[14] We explored another approach and attempted to access this compound from commercially available phenyl acetylene and propargyl alcohol by a bromination reaction followed by Cadiot–Chodkiewicz reaction. Using this strategy, either phenylacetylene or propargyl alcohol can be brominated and then coupled with another starting material to obtain **2.5** (Schemes 2.2 and 2.3). In fact, both routes were tried to provide the target molecule.

The sequence beginning with bromination of phenylacetylene gave **2.5** in an overall yield of 68% (Scheme 2.2), whereas, the one beginning with bromination of propargyl alcohol gave **2.5** in an overall yield of 32% (Scheme 2.3). The first method gave better yield, and using Br_2 as a reagent in the bromation of propargyl alcohol in the second method was a more technically difficult reaction than bromination of phenylacetylene with NBS. Hence, bromination of phenylacetylene was used, rather than bromination of propargyl alcohol. The yield obtained is higher than that reported by Wityak and Chan,[14] who used phenyl acetylene iodide, not phenyl acetylene bromide.

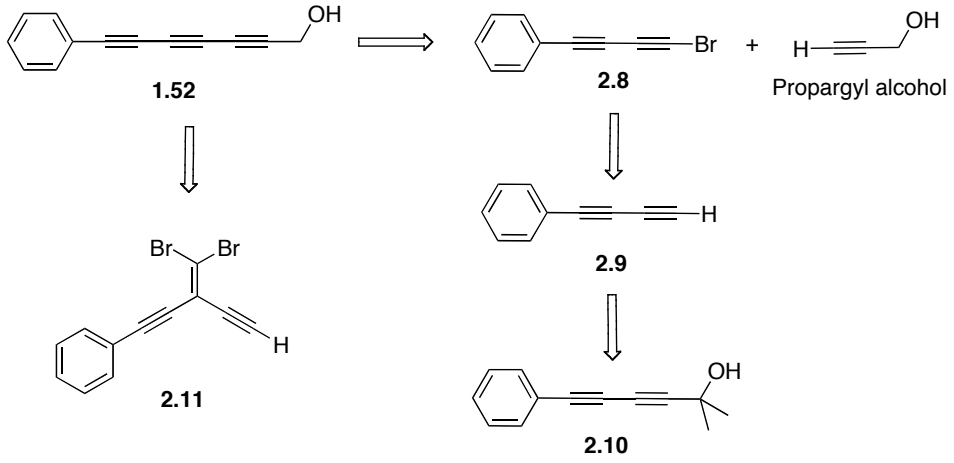


Scheme 2.2 Synthesis of 5-phenyl-2,4-pentadiyn-1-ol (**2.5**) by bromination of phenyl acetylene.



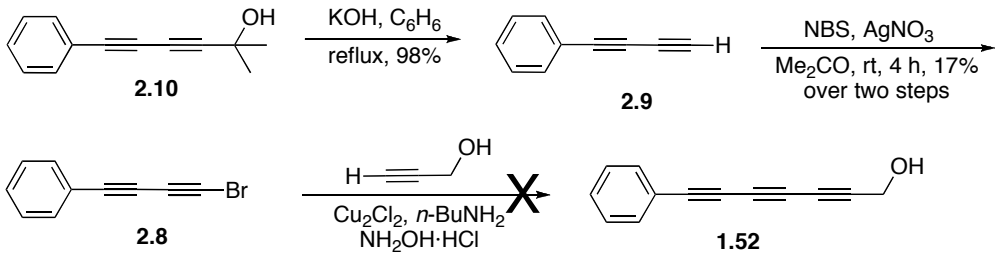
Scheme 2.3 Synthesis of 5-phenyl-2,4-pentadiyn-1-ol (**2.5**) by bromination of propargyl alcohol.

With diyne alcohol **2.5** in hand, we turned our attention to the preparation of triyne alcohol **1.52**. From the retrosynthetic analysis (Scheme 2.4), 7-phenyl-2,4,6-heptatriyn-1-ol **1.52** can be acquired either via Cadiot–Chodkiewicz coupling of propargyl alcohol and alkynyl bromide **2.8** or via Fritsch–Buttenberg–Wiechell rearrangement of dibromoolefin **2.11**. Alkynyl bromide **2.8** could arise from 1-phenyl-1,3-tetradiyne **2.9**, and this diyne could be prepared from commercially available 2-methyl-6-phenyl-3,5-hexadiyn-2-ol **2.10**. Conversely, dibromoolefin **2.11** could be prepared from the corresponding ketone, which can be obtained from commercially available phenylacetylene in three steps.



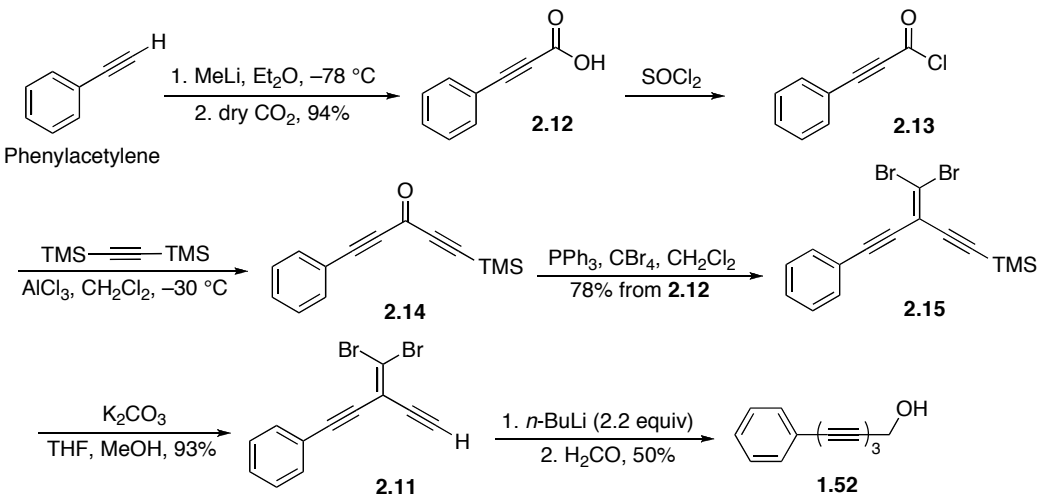
Scheme 2.4 Retrosynthesis of 7-phenyl-2,4,6-heptatriyn-1-ol (**1.52**).

When comparing these two routes, the one using the Fritsch–Buttenberg–Wiechell rearrangement as the key step is longer than the one employing the Cadiot–Chodkiewicz reaction. Thus, the Cadiot–Chodkiewicz route was attempted first (Scheme 2.5). Diyne **2.9** was prepared by treating **2.10** with KOH. The terminal alkyne **2.9** was then brominated with NBS to yield alkynyl bromide **2.8** in a low yield of 17% over two the steps. The following step, conversion of diyne bromide to triyne alcohol with a Cadiot–Chodkiewicz reaction, failed to give the desired product **1.52**.



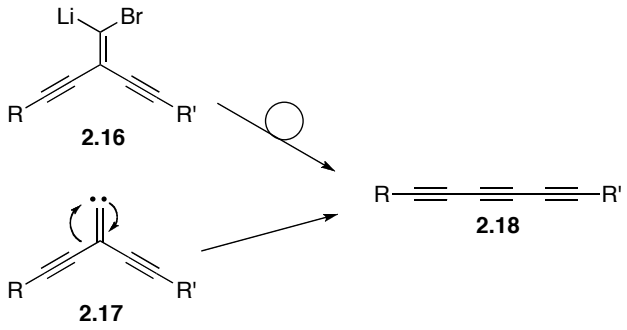
Scheme 2.5 Attempted synthesis of 7-phenyl-2,4,6-heptatriyn-1-ol (**1.52**) using a Cadiot–Chodkiewicz reaction.

The other approach, involving a Fritsch–Buttenberg–Wiechell rearrangement as the key step, was then used to synthesize triynol **1.52**.[12,15] In comparison with the reported route to **1.52**,[12] the same key step was used, but **2.11** was assembled from different precursors (Scheme 2.6). First, phenylacetylene was converted to the lithium acetylide and then trapped with CO_2 to give **2.12** in 94% yield. This carboxylic acid was then treated with thionyl chloride to provide acyl chloride **2.13**, and this intermediate was converted to ketone **2.14** using a Friedel–Crafts acylation reaction with bis(trimethylsilyl)acetylene.[16] Ketone **2.14** was treated with PPh_3 and CBr_4 to give dibromoolefin **2.15** in an overall yield of 78% from **2.13**. The trimethylsilyl (TMS) end cap of dibromoolefin **2.15** was then removed to yield **2.11** by treatment with K_2CO_3. Reaction of **2.11** with *n*-BuLi provided a lithium acetylide intermediate, which was trapped with paraformaldehyde in a one-pot reaction to give **1.52** in 50% yield.



Scheme 2.6 Synthesis of 7-phenyl-2,4,6-heptatriyn-1-ol (**1.52**) using a Fritsch–Buttenberg–Wiechell rearrangement.

The proposed mechanism of the Fritsch–Buttenberg–Wiechell rearrangement is shown below (Scheme 2.7).[17] Either an alkylidene carbene, or carbenoid species (**2.16** or **2.17**, respectively) is the reactive intermediate. The 1,2-migration of a pendent alkynyl moiety from either of these species forms a triyne product **2.18**.

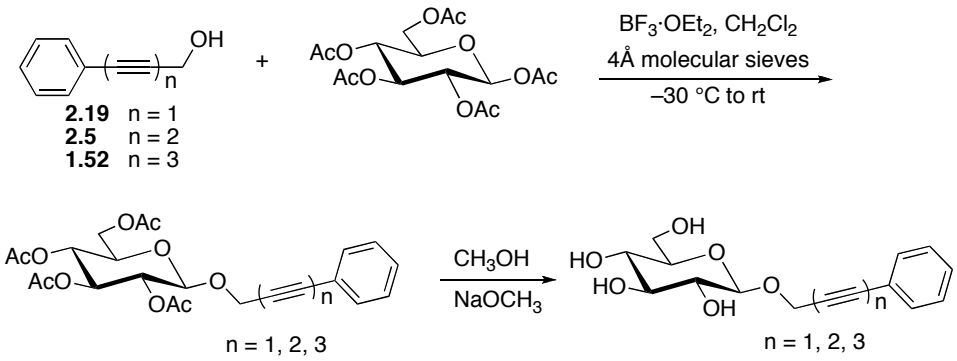


Scheme 2.7 Proposed mechanism of Fritsch–Buttenberg–Wiechell rearrangement.

2.3 Synthesis of polyacetylene glycosides

To synthesize polyacetylene glycosides, a number of different glycosylation protocols can, in principle, be used to couple carbohydrates with polyyne alcohols. For example, glycosyl acetates,[18] glycosyl halides[19] and glycosyl

imidates[20] could be used. In earlier work from the Tykwinski and Lowary groups, a variety of methods were investigated to couple carbohydrates and polyyne alcohols, and it was determined that the reaction rate and yield were both low when glycosyl bromides were used as donors, and the coupling reactions using trichloroacetimidate donors led to multiple products. However, when glycosyl acetates were used as donors, the desired products were obtained in good yields.[12] Therefore, glycosyl acetates were used as the donors and BF_3•OEt_2 as a promoter in the synthesis of polyyne glycosides (Scheme 2.8). Nine glycosyl acetates were used as precursors, and an acetyl group was used as a protecting group at C-2 to ensure good selectivity for the 1,2-*trans*-glycoside product via the initial formation of dioxolenium ion intermediate.



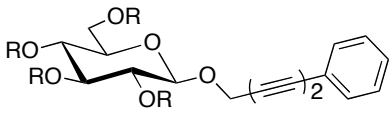
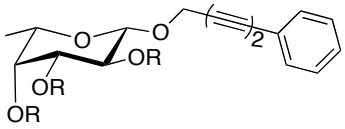
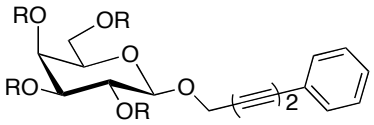
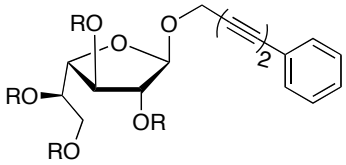
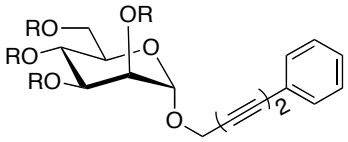
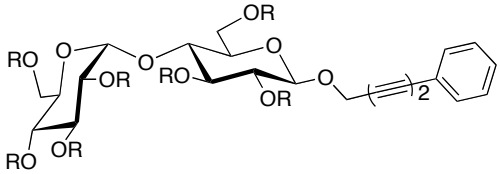
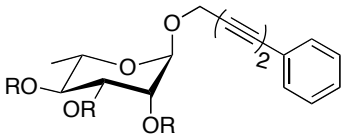
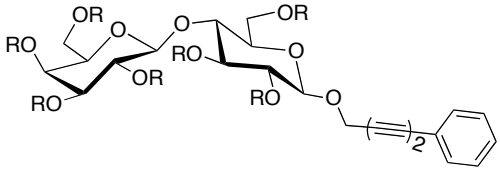
Scheme 2.8 General approach for the synthesis of polyyne glycosides.

2.3.1 Synthesis of diyne glycosides

Using the conditions outlined in Scheme 2.8, diynol **2.5**, triynol **1.52**, and 3-phenyl-2-propyn-1-ol (**2.19**) were successfully coupled with various glycosyl acetates to yield the corresponding glycosides. Diyne glycosides were synthesized first, using alcohol **2.5** and the appropriate glycosyl donors; the products are summarized in Table 2.1. Most of the protected diyne glycosides could be purified by silica gel chromatography with hexanes–EtOAc as the eluent, except for **2.22**. Compound **2.22** could be purified using CH_2Cl_2–EtOAc as the eluent.

The products were obtained in 31–82% yields (Table 2.1), depending on the donor used.

Table 2.1 Synthesis of diyne glycosides from peractylated glycosyl donors and **2.5** using $BF_3{\cdot}OEt_2$.

Compound and yield	Compound and yield
	
2.20 R = Ac, 71%, β only	**2.28** R = Ac, 77%, β only
2.21 R = H, 94%	**2.29** R = H, 63%
	
2.22 R = Ac, 80%, β only	**2.30** R = Ac, 70%, β only
2.23 R = H, 95%	**2.31** R = H, 97%
	
2.24 R = Ac, 31%, α only	**2.32** R = Ac, 74%, β only
2.25 R = H, 90%	**2.33** R = H, 81%
	
2.26 R = Ac, 82%, α only	**2.34** R = Ac, 54%, β only
2.27 R = H, 96%	**2.35** R = H, 98%

With the majority of the glycosyl donors, the reactions were highly selective for the formation of the 1,2-*trans*-glycoside. However, the glycosylation using 1,2,3,4-tetra-*O*-acetyl-β-L-fucopyranose gave an α,β-mixture (α:β = 2:3) when the reaction time was 36 hours. When the reaction time was reduced to 17 hours, however, only the 1,2-*trans* product, the β-anomer (**2.28**), was obtained. The stereochemistry was proved by ^{1}H NMR and coupled HMQC NMR spectroscopies.

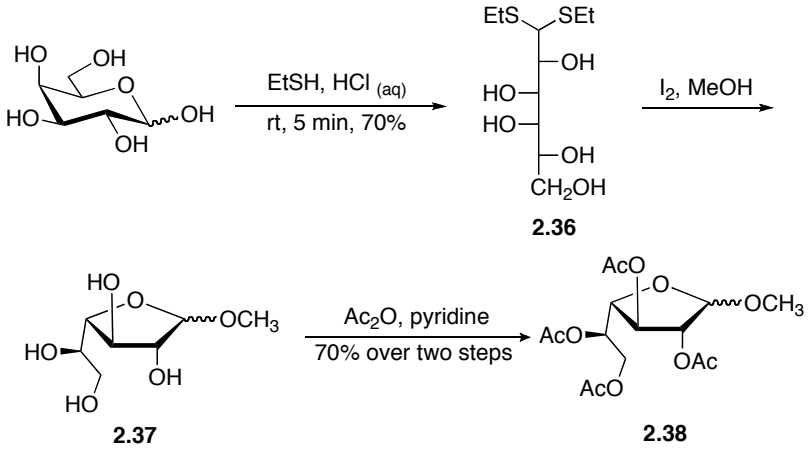
Having completed the glycosylations of diynol **2.5** with the corresponding glycosyl acetates, removal of the acetate groups in compounds **2.20**, **2.22**, **2.24**, **2.26**, **2.28**, **2.30**, **2.32** and **2.34** with $NaOCH_3$ in CH_3OH yielded the expected products **2.21**, **2.23**, **2.25**, **2.27**, **2.29**, **2.31 2.33** and **2.35**, respectively, in 63–98% yield.

2.3.2 Synthesis of galactofuranosyl donor

Most of the diyne glycosides synthesized were pyranosides; only compound **2.30** was a furanoside. In all cases, the hexoses precursors used were commercially available, and only needed to be converted to glycosyl acetate donors by simple acetylation. However, the furanose precursor was not commercially available and thus its synthesis was necessary. The most common method for obtaining the furanose form of monosaccharides is Fisher glycosylation.[21] When the reaction is carried out under kinetic control, it affords the higher-energy furanoside isomers. However, in the case of galactose, both of the furanoside and pyranoside isomers are obtained, which cannot be separated easily. There are also other methods to prepare glycofuranoses, such as Fisher glycosylation in the presence of strontium and calcium ions,[22] ring opening of pyranoses to form furanoses using a boron[23] or Fe(III) catalyst,[24] and the cyclization of open-chain dithioacetals with mercuric ions.[25] There are, however, typically problems with all of these methods - yields are low, they produce multiple products, or use toxic reagents. Szarek and coworkers have reported an alternate method for the cyclization of acyclic

dithioacetals that employs iodine in the presence of an alcohol to produce glycofuranosides.[26] Through the use of this less toxic promoter, the synthesis of glucofuranosides, mannofuranosides, and arabinofuranosides was accomplished. While the initial Szarek protocol used only 0.5% iodine (by weight), the Lowary group modified this method by using 2–5% iodine (by weight) and successfully applied it to synthesis galactofuranose derivatives.[27]

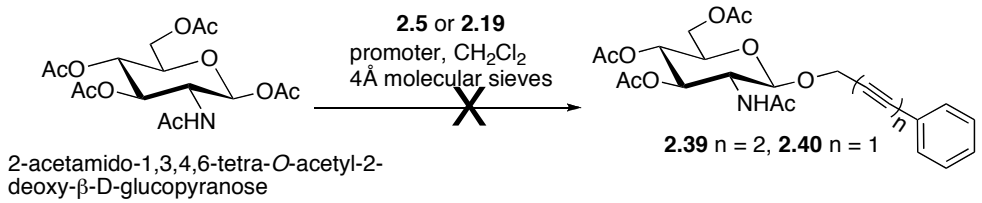
The preparation of a galactofuranose species that we could couple to a polyyne was carried out using galactopyranose as starting material. Treatment of galactopyranose with ethanethiol in the presence of hydrogen chloride produced the dithioacetal **2.36** in 70% yield (Scheme 2.9). The dithioacetal **2.36** was then reacted with 5% iodine (by weight) in methanol to provide the kinetic product, methyl galactofuranoside **2.37**. Compound **2.37** was then acetylated to give **2.38** in an overall yield of 70% from **2.36**. It should be noted that methyl galactofuranoside **2.38** was used as the glycosyl donor to couple with polyyne alcohols rather than galactofuranosyl acetate.



Scheme 2.9 Preparation of donor **2.38**.

2.3.3 Synthesis of polyacetylene 2-acetamido-2-deoxy glucopyranoside

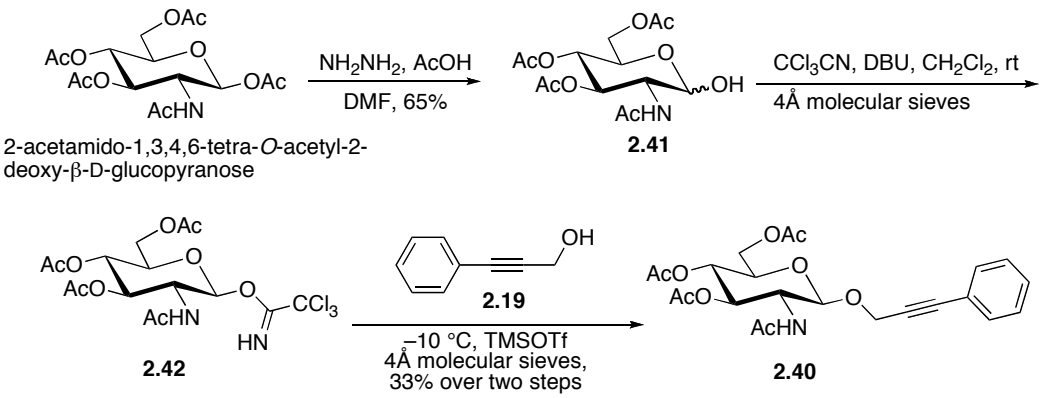
It was also interest to synthesize analogs that contained an *N*-acetamido group at C-2. However, unlike the other saccharides discussed above, the glycosylation of diynol **2.5** with 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose under the general glycosylation conditions did not lead to the expected diyne glycoside **2.39** (Scheme 2.10). To determine if there was a problem with the acceptor alcohol, our attention was turned to the glycosylation of monoynol **2.19**. However, when glycosylation of **2.19** was attempted under the general coupling conditions, no product (**2.40**) was obtained either. We considered that the promoter, BF_3•OEt_2, was not strong enough. Thus, the stronger Lewis acid $SnCl_4$ and triflic acid were tried as promoters to circumvent this problem, but again no desired products were obtained.



2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose

Scheme 2.10 Attempted preparation of **2.39** and **2.40** using different promoters.

Faced with this problem, we changed the donor from a glycosyl acetate to a more reactive donor, a glycosyl trichloroacetimidate.[28] Thus, 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose was treated with hydrazine acetate to remove the acetate group on the anomeric position to give **2.41** in 65% yield (Scheme 2.11). Compound **2.41** was then reacted with trichloroacetonitrile in the presence of DBU to give trichloroacetimidate **2.42**. Compound **2.42** was then coupled with monoynol **2.19** to give the desired product **2.40** in 33% yield over two steps. To date, this reaction has not yet been extended to diynol **2.5** and triynol **1.52**.

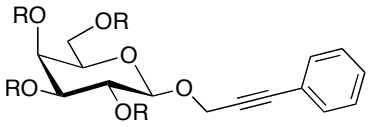
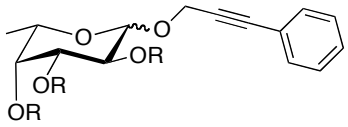
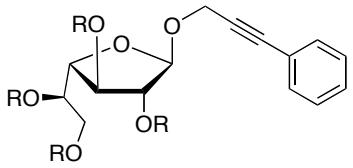
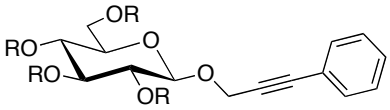
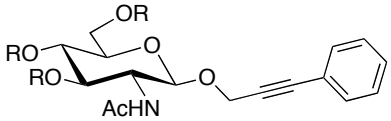
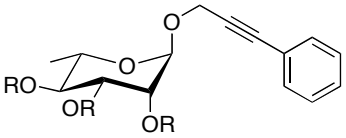


Scheme 2.11 Preparation of **2.40** using a trichloroacetimidate donor.

2.3.4 Synthesis of monoyne glycosides

Having been successful in synthesizing glycosides of diyne alcohol **2.5**, our efforts were then focused on the preparation of products from monoynol **2.19**. As was observed for the glycosylation of diynol **2.5**, reaction of **2.19** with several monosaccharide glycosyl acetate donors using BF_3•OEt_2 as promoter was successful. The yield (Table 2.2) for galactoside **2.43** was 70%, for glucoside **2.45**, 57%, for rhamnoside **2.47**, 73%, and for galactofuranoside **2.50**, 77%. The glycosylation of 1,2,3,4-tetra-*O*-acetyl-β-L-fucopyranose once again gave an α,β mixture of products **2.49** (α:β = 2:3), which could not be separated by column chromatography. The other products were all 1,2-*trans*-glycosides. Removal of the acetate groups of these compounds gave the deprotected glycosides **2.44**, **2.46**, **2.48**, **2.51** and **2.52** in 90–98% yield. Compound **2.49** was not deacylated because it was an α,β mixture.

Table 2.2 Synthesis of monoyne glycosides from peractylated glycosyl donors and monoynol **2.19** using BF_3•OEt_2 or TMSOTf.[a]

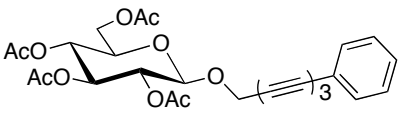
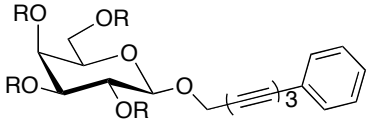
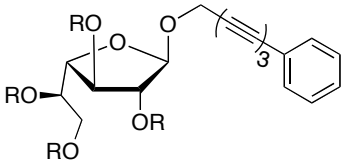
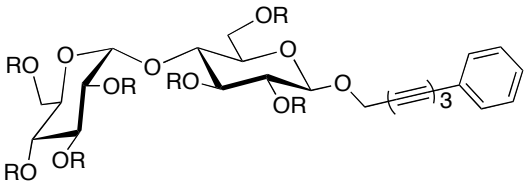
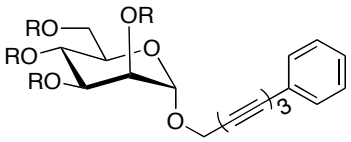
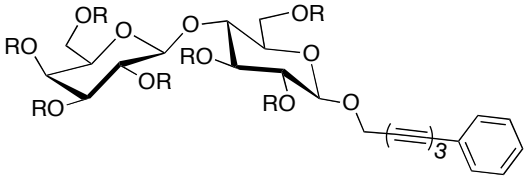
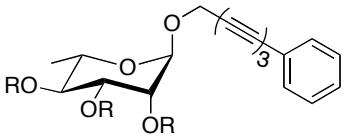
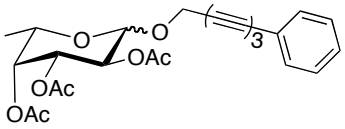
Compound and yield	Compound and yield
	
2.43 R = Ac, 70%, β only	**2.49** R = Ac, 74%, α:β = 2:3
2.44 R = H, 98%	
	**2.50** R = Ac, 77%, β only
2.45 R = Ac, 57%, β only	**2.51** R = H, 97%
2.46 R = H, 93%	
	**2.40** R = Ac, 33%, β only
2.47 R = Ac, 73%, α only	**2.52** R = H, 90%
2.48 R = H, 98%	

[a] Compound **2.40** was synthesized using TMSOTf.

2.3.5 Synthesis of triyne glycosides

Next, we investigated the preparation of the triynol glycosides. Their synthesis was carried out by glycosylation of triynol **1.52** with BF_3•OEt_2 as the promoter, using the same donors employed in the synthesis of the monoynol and diynol glycosides. In general, the reaction yields were good (61–80%), except for the synthesis of triyne mannoside **1.58**, which was formed in a yield of 33% (Table 2.3).

Table 2.3 Synthesis of triyne glycosides from peractylated glycosyl donors and triynol **1.52** using BF_3•OEt_2.[a]

Compound and yield	Compound and yield
 **1.56** 61%, β only	 **1.57** R = Ac, 78%, β only **1.60** R = H, 64%
 **2.53** R = Ac, 74%, β only **2.54** R = H, 51%	 **2.57** R = Ac, 77%, β only **2.58** R = H, 65%
 **1.58** R = Ac, 33%, α only **1.61** R = H, 64%	 **2.59** R = Ac, 74%, β only **2.60** R = H, 97%
 **2.55** R = Ac, 80%, α only **2.56** R = H, 65%	 **2.61** 13%, α anomer **2.62** 19%, β anomer, α:β = 1:1.4

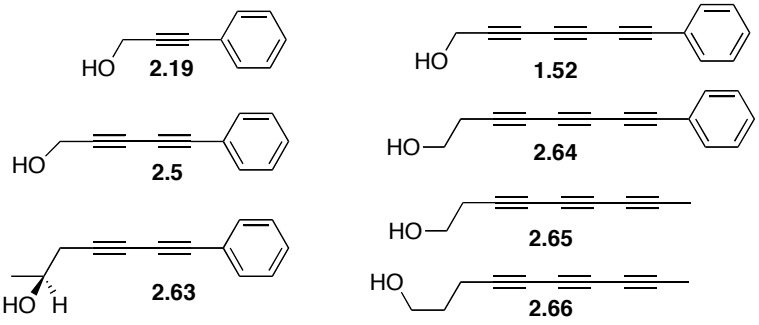
[a] Compound **2.61** was formed from the corresponding imidate donor.

Most of the triyne glycosides were a single anomer, but, as was found with the reaction of **2.5** and **2.19**, the glycosylation of **1.52** with 1,2,3,4-tetra-*O*-acetyl-β-L-

fucopyranose (not shown) gave an α,β mixture (α:β = 1:1.4). We also explored an alternate method to make the triyne fucoside by converting 1,2,3,4-tetra-*O*-acetyl-β-L-fucopyranose to an imidate, following by coupling with triynol **1.52**. However, two products, **2.61** and **2.62** were produced and separated by column chromatography to give a 1:1.4 α:β mixture, respectively. Because this method did not give single anomer product, the diyne fucoside and monoyne fucoside were not synthesized using this method.

Once synthesized, all these triyne glycosides were treated with $NaOCH_3$ in CH_3OH to remove the protecting groups, as with previous derivatives. Yields for these deacylation reactions are summarized in Table 2.3. Compound **1.56**, **2.61** and **2.62** were not deacylated, because too small amount of **2.61** and **2.62** were obtained to carry forward to next step.

In addition to using alcohols **1.52**, **2.5** and **2.19** to prepare glycosides, several other polyyne alcohols (**2.63**-**2.66**, Scheme 2.12), were also glycosylated with carbohydrate donors (Table 2.4). These alcohols were synthesized by Dr. Thanh Luu.[15,29]

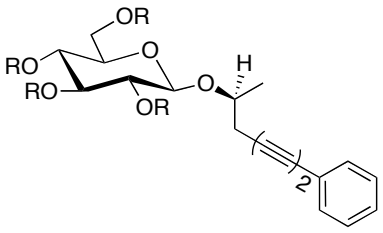
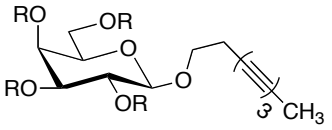
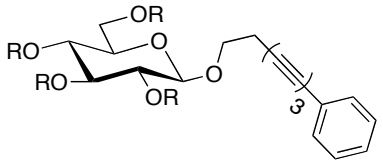
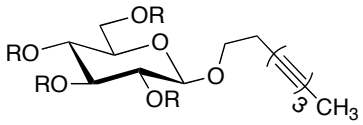
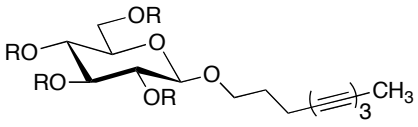


Scheme 2.12 Polyyne alcohols used to synthesize other polyyne glycosides.

Glycosides of these alcohols (**2.67**, **2.69**, **2.71**, **2.73** and **2.75**) were synthesized to determine the effect of varying the number of methylene groups between the glycosidic group and polyyne skeleton, and the effect of different end capping

groups on the biological activity of these compounds. As illustrated in Table 2.4, the more methylene groups between the alcohol and the polyyne, the lower the yield of the glycosylation step. Moreover, the alcohol with a methyl end cap was less stable under ambient condition than the corresponding alcohol with a phenyl end cap. As before, removal of the acetyl protecting groups was done in the present of $NaOCH_3$ and CH_3OH to give **2.68**, **2.70**, **2.72**, **2.74** and **2.76**.

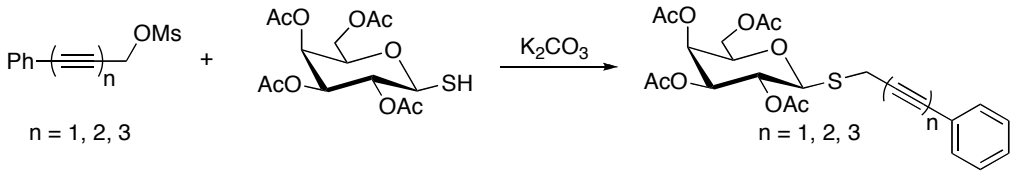
Table 2.4 Glycosylation products of polyyne alcohols **2.63**, **2.64**, **2.65** and **2.66**.

Compound and yield	Compound and yield
 **2.67** R = Ac, 61%, β only **2.68** R = H, 86%	 **2.71** R = Ac, 38%, β only **2.72** R = H, 44%
 **2.69** R = Ac, 30%, β only **2.70** R = H, 68%	 **2.73** R = Ac, 48%, β only **2.74** R = H, 76%
	 **2.75** R = Ac, 26%, β only **2.76** R = H, 70%

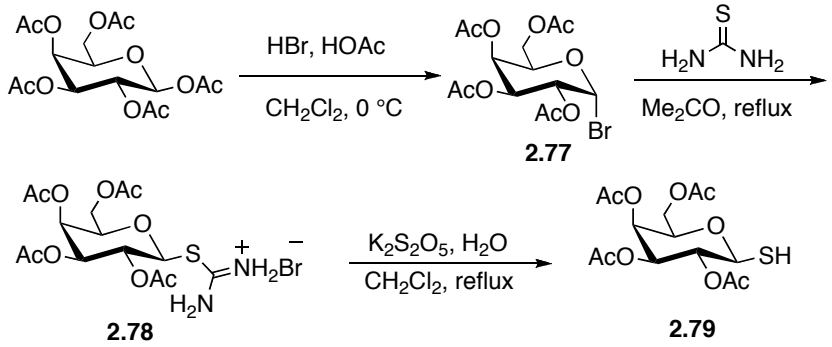
2.4 Synthesis of polyyne thioglycosides

2.4.1 Synthesis of glycosyl thiols

With a panel of polyyne glycosides in hand, we next focused on the preparation of the corresponding thioglycosides. To access these polyyne thioglycosides, we chose a route in which a polyyne methanesulfonate would be coupled with a glycosyl thiol using K_2CO_3 as a base (Scheme 2.13). Three glycosyl thiols were synthesized using the general approach shown below (Scheme 2.14). Starting from the glycosyl acetate, conversion to the glycosyl bromide (e.g., **2.77**) was effected through reaction with HBr–HOAc.[30] Then, the glycosyl bromide was treated with thiourea to provide the thio–iminium salt (e.g., **2.78**). The glycosyl thiol (e.g., **2.79**) was then produced by reaction with potassium metabissulfite.[31] The yields of these three glycosyl thiols (Table 2.5) ranged from 54% to 75% over the three steps. Maltose octaacetate and lactose octaacetate were not tried with this method because we expected that the acidic conditions of the first step would hydrolyze these disaccharides into monomers.

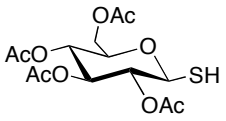
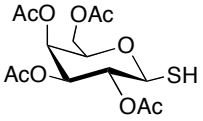
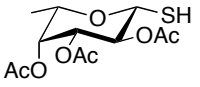


Scheme 2.13 General approach for the synthesis of polyyne thioglycosides.



Scheme 2.14 General approach for synthesis of glycosyl thiols.

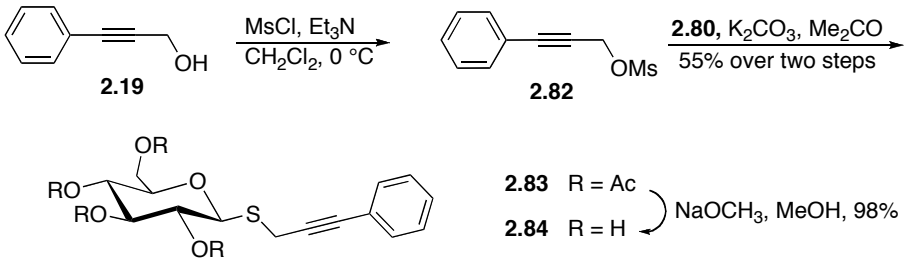
Table 2.5 Synthesis of glycosyl thiols.

Compound and yield[a]	Compound and yield[a]	Compound and yield[a]
		
2.80 68%, β only	**2.79** 75%, β only	**2.81** 54%, β only

[a] Over three steps from the corresponding glycosyl acetate (see Scheme 2.14).

2.4.2 Synthesis of monoyne thioglycoside

With three glycosyl thiols in hand, we next focused on the syntheses of the alkynyl thioglycosides.[32] Compound **2.19** was treated with methanesulfonyl chloride and triethylamine to give 3-phenylprop-2-ynyl methanesulfonate **2.82**. Compound **2.82** was then coupled with 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl thiol **2.80** to give thioglycoside **2.83** in 55% yield over two steps (Scheme 2.15). Removal of the acetate groups of **2.83** gave **2.84** in 98% yield.

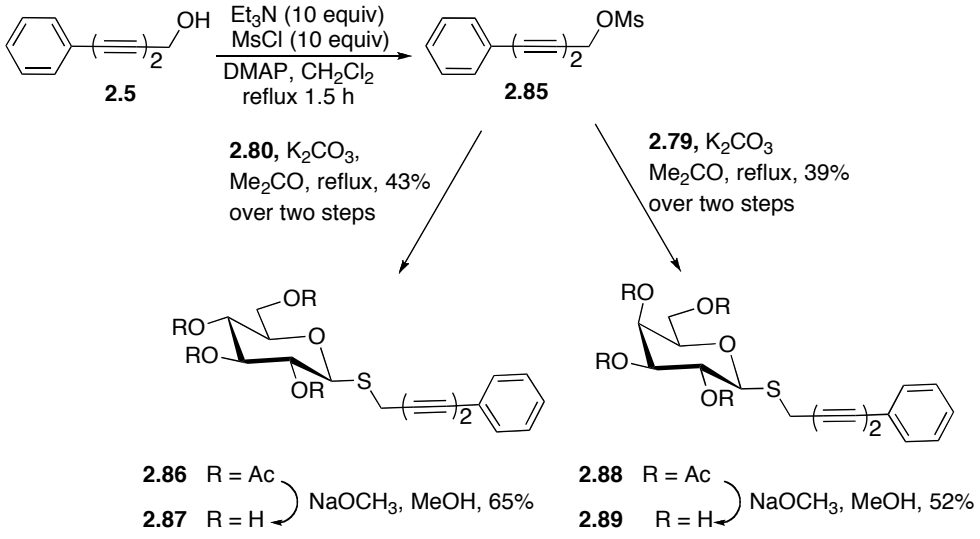


Scheme 2.15 Synthesis of thioglycoside **2.84**.

2.4.3 Synthesis of diyne thioglycosides

Having succeeded in preparing a mesylate from **2.19**, the same reaction was attempted on diynol **2.5** to generate the diyne methanesulfonate **2.85**. At low temperature (0 °C), the reaction was very slow, and TLC analysis indicated that

there was a significant amount of starting material remaining after three hours. More methanesulfonyl chloride and triethylamine were added, and the reaction was heated to reflux for 1.5 hours, at which point TLC analysis indicated that it was complete. Crude product **2.85** was obtained and was then coupled with glycosyl thiols **2.80** and **2.79** to give **2.86** in 43% and **2.88** in 39% yield over the two steps (Scheme 2.16). Removal of the acetate groups of polyyne thioglycosides **2.86** and **2.88** gave the free glycosides **2.87** in 65% yield and **2.89** in 52% yield.

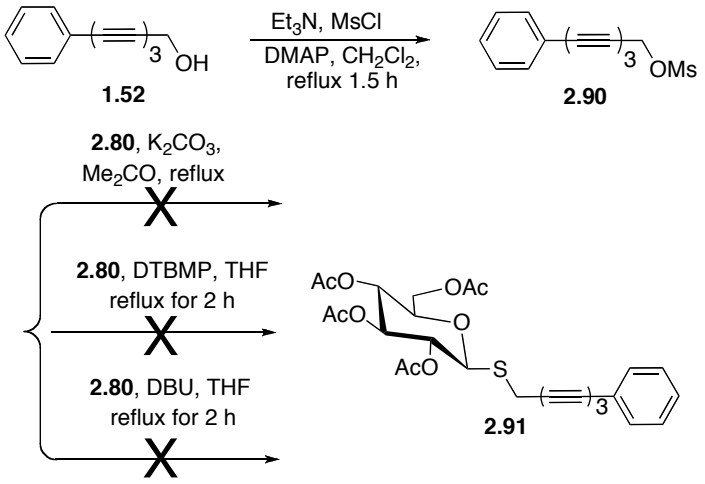


Scheme 2.16 Preparation of thioglycosides **2.87** and **2.89**.

2.4.4 Synthesis of triyne glycosides

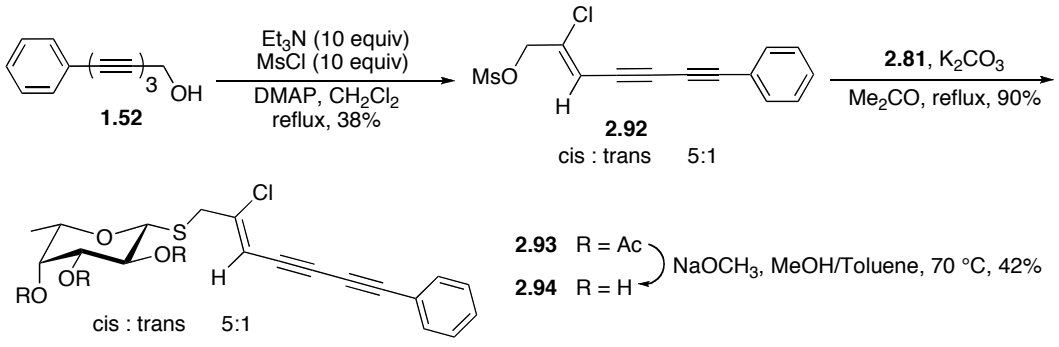
With the successful syntheses of monoyne and diyne thioglycosides completed, we next turned our attention to the synthesis of the triyne thioglycosides. Triynol **1.52** was treated with methanesulfonyl chloride and triethylamine at reflux for 1.5 hours to give triyne methanesulfonate **2.90**, which was then coupled with glycosyl thiol **2.80** using potassium carbonate as a base (Scheme 2.17). However, the reaction failed to give the desired product **2.91**. Even when soluble organic bases such as 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) or 1,8-diazabicyclo[5.4.0]

undec-7-ene (DBU) were used instead of insoluble inorganic salt K_2CO_3 to promote the reaction, there was still no desired product formed in the reaction.



Scheme 2.17 Attempted synthesis of triyne thioglycoside using triyne methanesulfonate **2.90**.

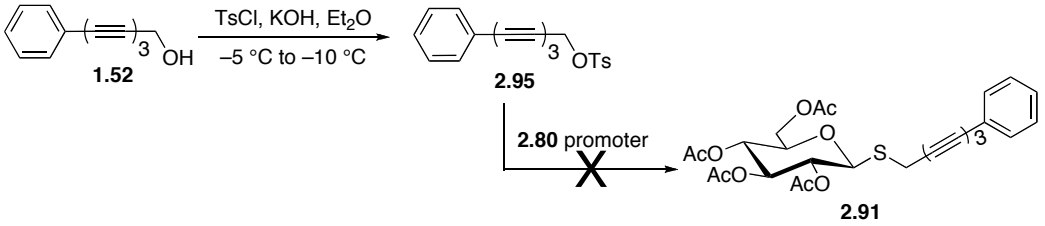
During the course of these experiments, an unexpected result was observed. In the attempted formation of mesylate **2.90**, the desired product was not formed; instead, a reaction occurred at one of the acetylenic bonds to yield allyl mesylate **2.92** (*Z:E* = 5:1) in 38% yield (Scheme 2.18). With suitable quantities of this compound available, it was then coupled with **2.81** to give a new polyacetylene thioglycoside **2.93** in 90% yield.



Scheme 2.18 Synthesis of thioglycoside **2.94**.

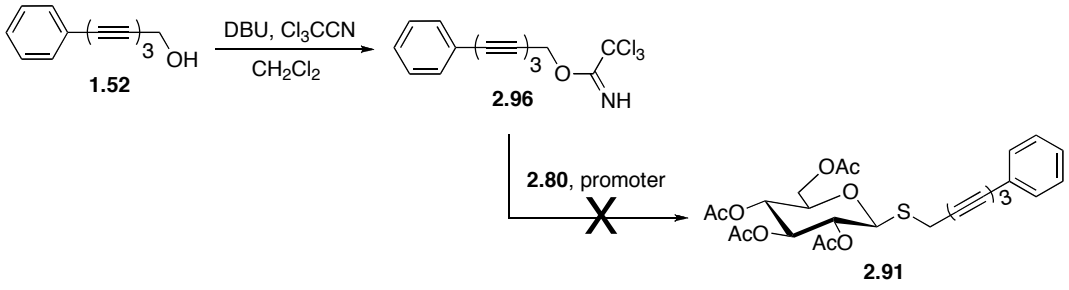
In order to reform the triple bond and remove all the acetate groups, compound **2.93** was treated with 1.2 equivalents of $NaOCH_3$ at 70 °C for 24 hours. However, an elimination reaction of HCl from the double bond to generate the alkyne did not occur. The reaction gave the deacetylated product **2.94** in 42% yield.

To overcome the unreactive nature of methanesulfonate **2.90** toward the thioglycosylation, triynol **1.52** was treated with tosyl chloride in the presence of potassium hydroxide to give triyne tosylate **2.95**.[33] Potassium carbonate and DBU were tried as promoters in the reaction of **2.95** and **2.80**, but again none of thioglycoside **2.91** was obtained (Scheme 2.19).



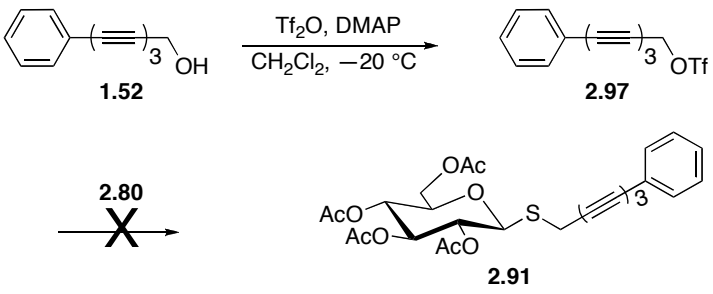
Scheme 2.19 Attempted preparation of triyne thioglycoside using triyne tosylate **2.95**.

In an attempt to make the electrophile more reactive, triynol **1.52** was converted to a trichloroacetimidate **2.96** and its reaction with glycosyl thiol **2.80** was explored (Scheme 2.20).



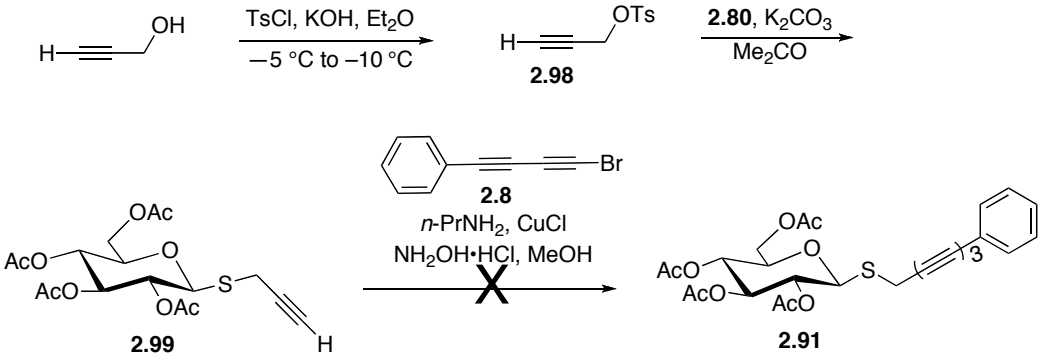
Scheme 2.20 Attempted preparation of triyne thioglycoside using triyne trichloroacetimidate **2.96**.

Lanthanum trifluoromethanesulfonate,[34] BF_3•OEt_2, silver triflate and Trimethylsilyl trifluoromethanesulfonate (TMSOTf) were all tried as promoters. However, these reactions all failed to give the desired product. Triynol **1.52** was also converted to triflate **2.97** (Scheme 2.21), but the reaction with **2.80** also failed to produce **2.91**.



Scheme 2.21 Attempted preparation of triyne thioglycoside using triyne triflate **2.97**.

Another approach to the triyne thioglycoside was attempted via coupling a glycosyl thiol with a propargyl alcohol and then extending the polyyne chain via a Cadiot–Chodkiewicz reaction with a diyne bromide (Scheme 2.22).



Scheme 2.22 Attempted preparation of triyne thioglycoside using the Cadiot–Chodkiewicz reaction.

Propargyl alcohol was treated with tosyl chloride in the presence of potassium carbonate to give tosylate **2.98**. The tosylate was coupled with **2.80** to give **2.99** in 98% yield. The reaction of **2.99** with diyne bromide **2.8** was then attempted, but the reaction failed to provide the desired product **2.91**.

Given our failure to synthesize a triyne thioglycosides via a number of different approaches, their preparation was abandoned and we turned out attention to testing the biological activity of the compounds we had prepared.

2.5 Determination of anti-cancer and anti-bacterial activity of target molecules.

2.5.1 Anti-cancer activity of target molecules.

The first set of biological studies involved testing 29 compounds against two cancer cell lines: MCF-7 breast cancer and HT-29 colon cancer. These studies were done using a standard cell viability assay based on the ability of living cells to reduce the colorless 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophen-yl)-2H-tetrazolium, inner salt (MTS) to a purple formazan product, which can be quantitated.[35]

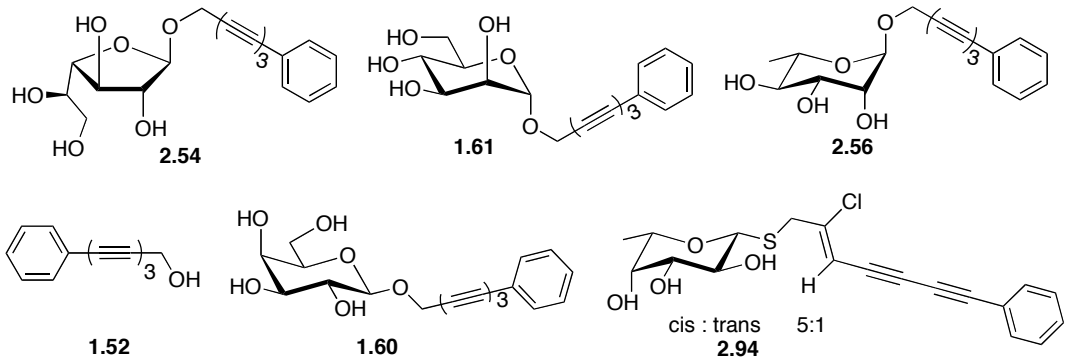


Figure 2.3 Structure of compounds with bioactivity towards MCF-7 breast cancer and HT-29 colon cancer cell lines.

Initially each compound was tested at a 100 μM concentration and the concentration was then lowered to 50 μM, 25 μM and 12.5 μM. Six compounds showed good activity at 50 μM and lower concentrations, they were **1.52**, **2.54**, **1.61**, **2.56**, **1.60** and **2.94** (Figure 2.3). It is interest to note that, except **2.94**, all of the active compounds possessed a triyne aglycon.

The potency of these compounds against the two cell lines is shown in Table 2.6 (MCF-7) and Table 2.7 (HT-29). The lower the number, indicating a lower number of alive cells, the better the result. When the concentration was 12.5 μM, compound **2.56** and **1.60** were found to show very good activity against breast cancer cell MCF-7 (Table 2.6), with only 6 and 11% of the cells remaining alive. However, when the concentration was decreased further the activity dropped off significantly. For example, it was found the percentage of allive cells was 83% for compound **2.56** and 76% for compound **1.60** at a concentration of 10 μM. At even lower concentrations (5 μM, 2.5 μM and 0.625 μM, no cytotoxicity was observed.

Table 2.6 Cytotoxicity against MCF-7 breast cancer cell line.

Allive cells (%) / Concentration	Compounds					
	1.52	**2.54**	**1.61**	**2.56**	**1.60**	**2.94**
50 μM	–[a]	7.0	6.2	3.1	–[a]	6.7
25 μM	24	77	44	3.5	9.8	27
12.5 μM	52	–[a]	69	6.4	11	41
10 μM	72	–[a]	–[a]	83	76	–[a]

[a] not tested.

Although some of the compounds were active against MCF-7 cell, less impressive results were seen against the HT-29 cancer cell lines. Some compounds were active at 50 μM concentration but this potency was reduced as the concentration was decreased. At 12.5 μM concentration, the most potent compounds, **2.56** and **1.60**, resulted in 54% and 59% of the cells surviving. Given this poor activity tests at lower concentration were not carried out.

Table 2.7 Cytotoxicity against HT-29 colon cancer cell line.

Allive cells (%) / Concentration	Compounds					
	1.52	**2.54**	**1.61**	**2.56**	**1.60**	**2.94**
50 μM	4.6	10	4.1	4.6	3.8	11
25 μM	47	69	28	11	10	20
12.5 μM	– [a]	100	71	54	59	72

[a] not tested

2.5.2 Anti-bacterial activity of target molecules.

We next tested the anti-bacterial activity of the 29 compounds using a routine paper disk diffusion assay.[35] The concentration tested was 100 μM using Penicillin G, streptomycin and tetracycline as positive controls. None of these compounds showed activity against the Gram-negative bacteria *Escherichia coli*. On the other hand, five compounds **1.52**, **1.61**, **1.60**, **2.54** and **2.56** showed weak activity against the Gram-positive bacteria *Bacillus Subtilis*. The results are summarized in Table 2.8, at the same concentration, the bigger the inhibition zone, the better the activity (Figure 3).

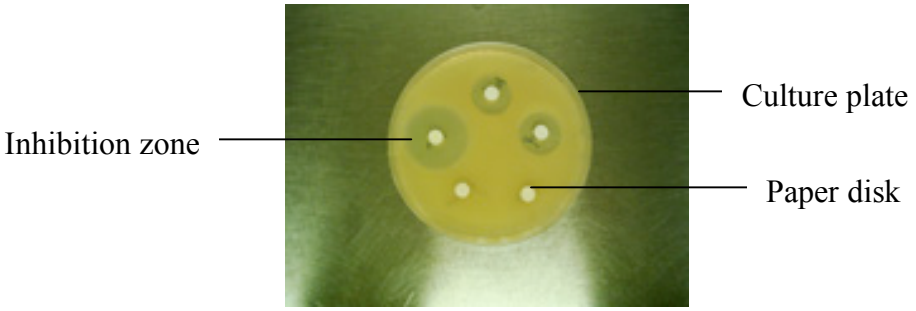


Figure 2.4 Picture of anti-bacterial activity test result.

Table 2.8 Anti-bacterial activity against *Bacillus Subtilis*.

	Positive control			Active target molecules				
Compound	**a***	**b***	**c***	**1.52**	**1.61**	**1.60**	**2.54**	**2.56**
Zone diameter (mm)	27.9	19	30.8	10.4	8.1	9.7	9.4	10.5

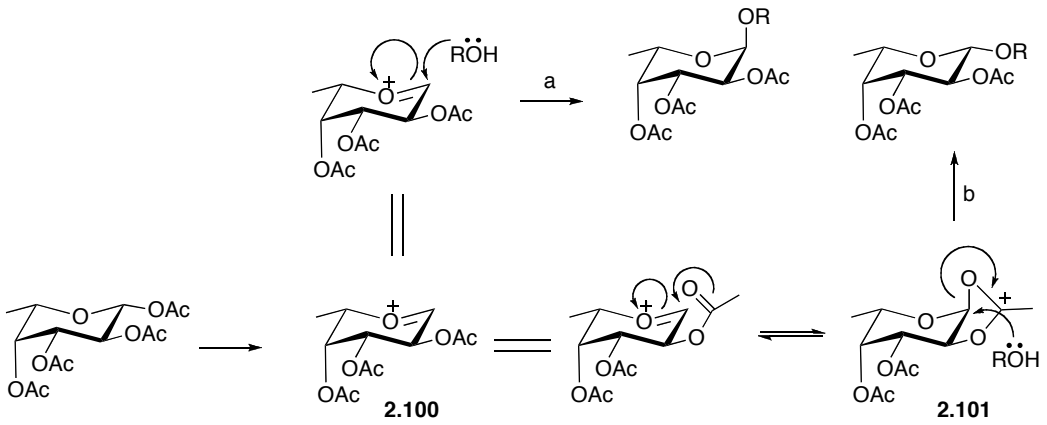
***a**: Penicillin. G.; **b**: Streptomycin; **c**: Tetracycline.

2.6 Conclusion

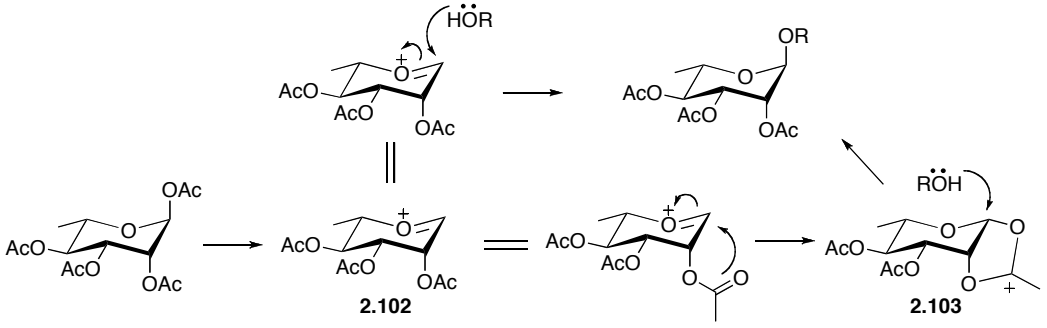
In summary, 27 polyyne glycosides and four polyyne thioglycosides were synthesized. Due to difficulties in their synthesis, no triyne thioglycosides were prepared. The yields of polyyne glycosides were similar for the same carbohydrate moiety, regardless of the polyynol used. In the synthesis of the thioglycosides, the yield of monoyne thioglucoside **2.83** was better than that for the diyne thioglucoside **2.87**, which suggested the sulfonate esters generated from the monoynol were more reactive electrophiles than those formed from the diynol. The inability to prepare the triynol thioglycosides is consistent with this trend and it appears that electrophiles derived from the triynol have lower reactivities. While surprising, it appears that the electron deficient nature of the three triple bonds in **2.90**, **2.95**, **2.96** and **2.97** somehow suppresses the reactivity of these

molecules. In contrast, the double bond in **2.92** makes the conjugated system more reactive; hence a good yield in the coupling reaction is observed.

Although the acetyl group at C-2 helps to give a single anomer in the preparation of the *O*-glycosides, the 1,2-*trans*-isomer, the glycosylation of polyyne alcohols with 1,2,3,4-tetra-*O*-acetyl-β-L-fucopyranose gave α,β-mixtures. This may be due to the competition between the oxacarbenium ion **2.100** and the dioxolenium ion **2.101**, which are in equilibrium during the course of the reaction (Scheme 2.23). Deoxygenation of C-6 makes the oxacarbenium ion **2.100** more stable than in one derived from a fully oxygenated carbohydrate. If the oxacarbenium ion **2.100** is present in sufficient quantity, the α-glycoside (route a in Scheme 2.23) is produced by the attack of the alcohol on this species. If the alcohol attacks the dioxolenium ion **2.101**, the β-isomer is produced (route b in Scheme 2.23). It should be mentioned that glycosylation of polyyne alcohols with 1,2,3,4-tetra-*O*-rhamnopyranose gave only the 1,2-*trans*-product, the α-glycoside. Deoxygenation of C-6 in rhamnose also makes the oxacarbenium ion **2.102** more stable, and both of the oxacarbenium ion **2.102** and dioxolenium ion **2.103** should be in equilibrium during the reaction. However, the product produced from either the oxacarbenium ion **2.102** or the dioxolenium ion **2.103** is the same product, the α-glycoside (Scheme 2.24).

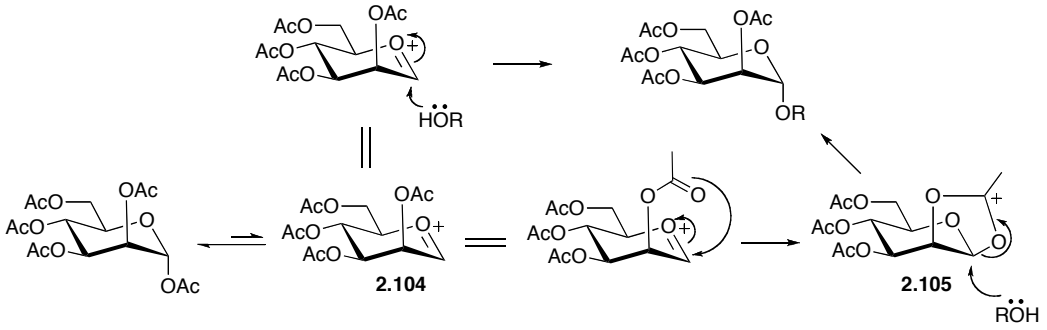


Scheme 2.23 Proposed mechanism for the formation of α-glycoside of polyyne 2,3,4-tri-*O*-acetyl-L-fucopyranosides **2.28**, **2.49** and **2.61**/**2.62**.



Scheme 2.24 Proposed mechanism for the formation of the α- glycoside of polyyne rhamnoside **2.26**, **2.47** and **2.55**.

In contrast to the other glycosides, the yields of polyyne mannosides **2.24** and **1.58** are much lower. The low yield may be the result of the anomeric effect and dipole-dipole repulsion, which favor the α-configuration of the starting material 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose and make it more difficult to form an oxacarbenium ion intermediate **2.104** (Scheme 2.25). Attack of the alcohol on either the oxacarbenium ion **2.104** or dioxolenium ion **2.105** would lead to the α-glycoside.



Scheme 2.25 Proposed mechanism for the formation of the α-isomers of polyyne mannosides **2.24** and **1.58**.

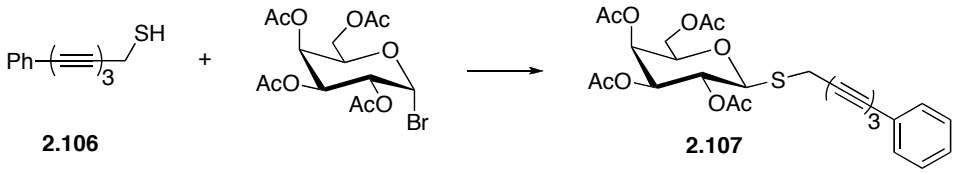
After their synthesis, the 30 of the synthetic targets, including triynol **1.52**, were screened for their ability to kill two cancer cell lines, MCF-7 and HT-29, as well as gram negative bacteria *Escherichia coli* and the gram positive bacteria *Bacillus*

Subtilis. From these results it is clear that only triyne compounds showed any cytotoxic or antibacterial activity.

2.7 Future work

The synthesis of polyyne glycosides has been finished, bacterial tests and cancer cell lines tests have been done. But neither the synthesis of polyyne thioglycosides nor their biological activity testing has been accomplished. Since the synthesis of monoyne thioglycosides and diyne thioglucosides using the general approach (Scheme 2.13) succeeded, future work should therefore include the synthesis of triyne thioglycosides through the development of other methods.

The coupling of the triynyl thiol **2.106** with glycosyl bromide (Scheme 2.26) is a method should be tried. The modifications of other function group on the end cap aromatic ring (**2.108** and **2.109**) could also be examined (Figure 2.5). The electron-donating groups on the phenyl ring could increase the electron density of the conjugated system, and make them more reactive for coupling with thioglycosides and glycosides to give desired products.



Scheme 2.26 Alternate approach to the synthesis of triynol thioglycosides.

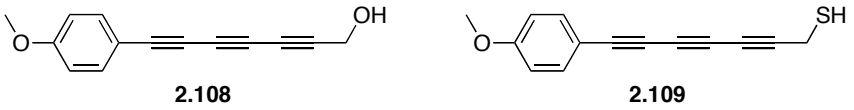


Figure 2.5 End cap functionalized polyynol and polyyne thiol.

In a comparison of the yields and structures of compound **2.73** and **2.69** (Figure 2.6), it was found that when the aromatic endcapping group was replaced by a methyl group, the yield was better. Since the reactivity of compound **2.65** appears greater than that of **2.64**, it is also possible that the reactivity of **2.110** would be better than that of **1.52**. Thus, modification of the endcapping group from phenyl ring to aliphatic groups should also be examined.

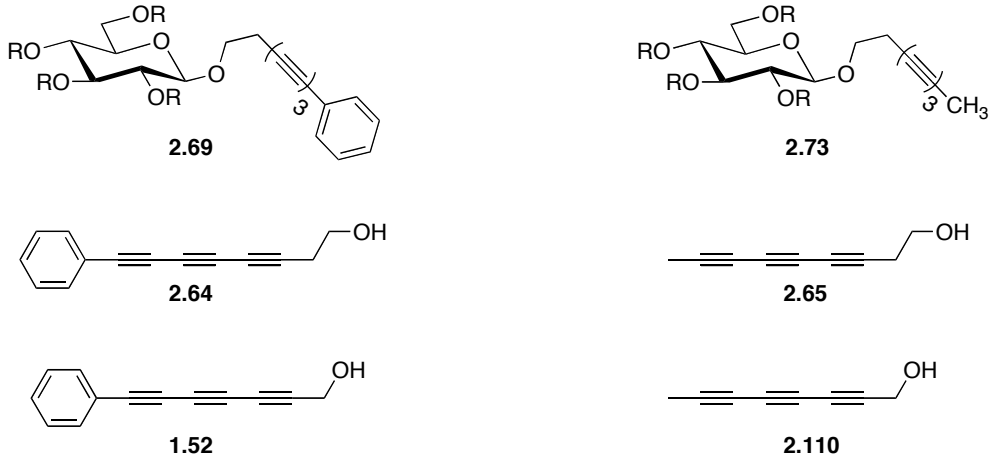


Figure 2.6 comparison of reactivity of compounds with similar structures.

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Chapter 3. Experimental

3.1 General

All reagents for the synthetic chemistry were purchased from commercial suppliers and were used without further purification. CH_2Cl_2 and hexanes were distilled from CaH_2, Et_2O was distilled from sodium/benzophenone ketyl immediately prior to use. All reactions were carried out under a positive pressure of nitrogen and were monitored by TLC analysis on silica gel G-25 UV_{254} from Macherey-Nagel. Spots were visualized by UV light or acidified ethanolic anisaldehyde stain. Anhydrous $MgSO_4$ was used as the drying agent after aqueous work-up. Solvents were evaporated under H_2O-aspirator reduced pressure and the water bath was kept below 40 °C (water bath). Column chromatography was performed on silica gel 60 (230–400 mesh) from General Intermediates of Canada. Melting points were recorded on a Fisher-Johns melting point apparatus. IR spectra were recorded on Nicolet Magna-IR 750 (neat) or Nic-Plan IR microscope (solids) spectrometers. ^{1}H NMR spectra were recorded on Varian Inova-NMR spectrometers at 300, 400 or 500 MHz at rt in $CDCl_3$ (chemical shift: 7.26 ppm) or CD_3OD (chemical shift: 3.30 ppm). ^{13}C NMR spectra were recorded on Varian Inova-NMR spectrometers at 100 or 125 MHz at rt in $CDCl_3$ (chemical shift: 77.0 ppm) or CD_3OD (chemical shift: 49.0 ppm). Peak assignments for ^{1}H NMR and ^{13}C NMR spectra were made by coupling constants in ^{1}H NMR and 2D-NMR spectra (^{1}H–^{1}H COSY and HMQC). The anomeric configuration of glycosides was determined experimentally from the $^1J_{C1,H1}$ by C–H coupled HMQC.[1] ESI-MS spectra were recorded on samples dissolved in $CHCl_3$ or CD_3OD and added NaCl. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at the sodium D line (589 nm) and were in unit of deg·mL(dm·g)$^{-1}$.

All chemicals, biochemicals, reagents, cancer cell lines (MCF-7 breast cancer and HT-29 colon cancer) and bacterial strains for bioactivity tests were purchased from commercial suppliers. Cell lines were grown in Nuaire US autoflow CO_2

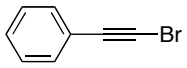
water-jacketed incubator and cell culture media and TE (trypsin-EDTA) were warmed in a Memmert water bath. Plate readings were performed on Molecular Devices SPETRAmax® 340 PC^{384} microplate spectrophotometer. LB (Luria–Burtani), NB (Nutrient Broth) and MHA (Mueller–Hinton Agar) media were autocleaved in a Steris Amsco Eagle SG-3031 scientific gravity sterilizer and kept in a Lab-Line laboratory water bath. Bacterial incubations were done in an Innova 4330 refrigerated incubator shaker. Concentrations of bacterial suspensions were determined using a Hewlett Packard 8451A diode array spectrophotometer.

3.2 Procedures for the synthesis of diynols and triynols

3.2.1 Procedure for preparation of bromoalkyne

To a solution of the polyyne (15.0 mmol) in acetone (100 mL) at rt was added NBS (5.34 g, 30.0 mmol) and $AgNO_3$ (250 mg, 1.50 mmol). After stirring for 4 h, the reaction was complete according to TLC analysis. The solvent acetone was removed by evaporation under reduced pressure. The reaction mixture was then diluted with hexanes (100 mL) and the crystals formed were filtered off. The filtrate was concentrated under reduced pressure and passed though a pad of silica gel using hexanes as the eluent. The filtrate was collected and evaporated under reduced pressure to afford the pure bromoalkyne 2.6 and 2.8 as pale yellow oil. The data for bromoalkyne 2.6 and 2.8 are below.

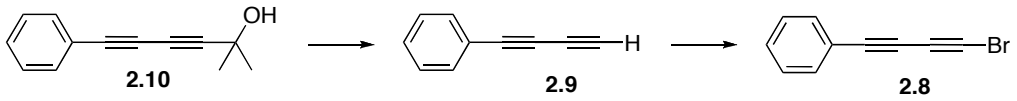
1-Bromo-2-phenyl-acetylene (2.6)



To a solution of phenylacetylene (3.00 g, 29.4 mmol) in acetone (200 mL) was added NBS (6.34 g, 35.6 mmol) and $AgNO_3$ (0.500 mg, 2.90 mmol) at rt as described in the general procedure. A light yellow oil **2.6**[2] was obtained (4.90 g,

92%), R_f = 0.40 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.44 (m, 2H, Ar), 7.38–7.29 (m, 3H, Ar).

1-Bromo-4-phenyl-1,3-butyldiyne (2.8)

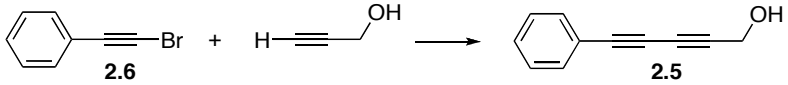


2.10 **2.9** **2.8**

To a solution of 2-methyl-6-phenyl-3,5-hexadiyn-2-ol[3] (4.97 g, 27.0 mmol) in C_6H_6 was added fresh powdered KOH (3.33 g, 59.5 mmol). The reaction solution was heated at reflux for 1 h and was then filtered through Celite. The solvent was removed to afford crude 4-phenyl-1,3-tetradiyne **2.9**[4], R_f = 0.62 (hexanes–EtOAc, 4:1), which was used immediately in the next step. To a solution of the crude 4-phenyl-1,3-tetradiyne in acetone (100 mL) was added NBS (5.10 g, 28.0 mmol) and $AgNO_3$ (0.420 g, 2.50 mmol) at rt as described in the general procedure. Compound **2.8**[5] (0.450 g, 17%) was obtained as a light yellow oil: R_f = 0.30 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.59 (m, 2H), 7.35-7.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4 (2 × Ar), 129.1 (Ar), 128.4 (2 × Ar), 121.7 (Ar), 81.5 (2 × C≡C), 73.8 (2 × C≡C).

3.2.2 Procedures for the synthesis of diynols and triynols

5-Penyl-2,4-pentadiyn-1-ol (2.5)

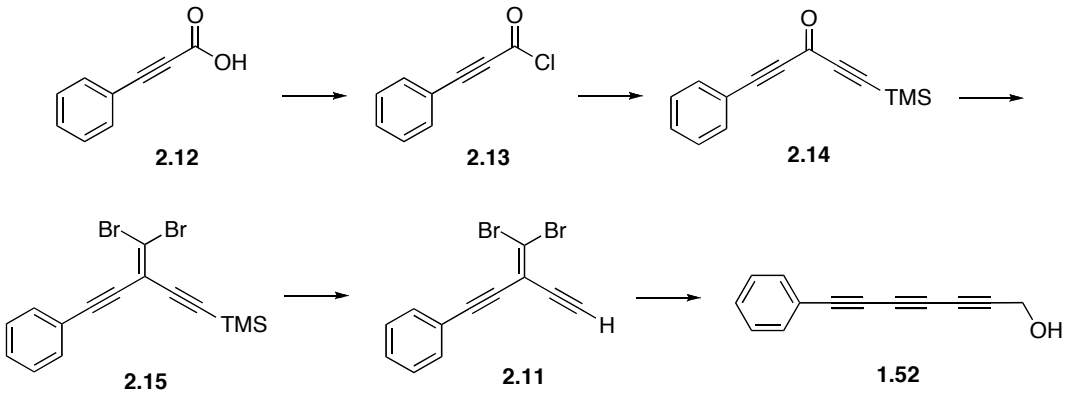


2.6 **2.5**

To a mixture of CH_3OH (6.8 mL), and H_2O (3.40 mL) was added *n*-butylamine (6.70 mL, 68.0 mmol), propargyl alcohol (1.85 g, 33.0 mmol), copper (I) chloride (0.410 g, 4.10 mmol) and NH_2OH•HCl (0.470 g, 6.76 mmol) in that order. A solution of **2.6** (4.90 g, 27.1 mmol) diluted in CH_3OH (3.40 mL) was added dropwise to the reaction mixture. After 20 h stirring at rt, the reaction was

completed according to TLC analysis and was quenched by the addition of H_2O (30.0 mL) and extracted with Et_2O (4 × 40.0 mL). The organic layers were combined and washed with water, brine and then dried over $MgSO_4$. After removing the solvent and purification by a silica gel column (hexanes–EtOAc, 5:1), 5-phenyl-2,4-pentadiyn-1-ol[6] **(2.5)** was obtained (3.00 g, 74%) as a pale yellow oil: R_f = 0.32 (hexanes–EtOAc, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H, Ar), 7.40–7.30 (m, 3H, Ar), 4.43 (s, 2H, C<u>H</u>$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.6 (2 × Ar), 129.4 (Ar), 128.4 (2 × Ar), 121.4 (Ar), 80.4 (<u>C</u>≡C), 78.6 (<u>C</u>≡C), 73.1 (<u>C</u>≡C), 70.5 (<u>C</u>≡C), 51.7 (<u>C</u>H$_2$).

7-Penyl-2,4,6-heptatriyn-1-ol (1.52)



To a solution of phenylacetylene (3.40 g, 33.3 mmol) in Et_2O (25.0 mL) was added *n*-BuLi (16.0 mL, 40.0 mmol) at –78 °C. The reaction was stirred at –78 °C for 2 h. CO_2 was bubbled through a drying tube filled with Drierite and then through the reaction solution for 30 min. Icy diluted NaOH solution (2.50 M, 15.0 mL) was added to quench to the reaction. The aqueous layer was separated and the organic layer was extracted with H_2O (4 × 10.0 mL). The aqueous layers were combined and diluted HCl solution (1.1 mol/L) was added until the solution was pH<1. The aqueous layer was then extracted with Et_2O (4 × 20.0 mL). The organic layers were combined, dried over $MgSO_4$ and solvent was evaporated to afford a crude product **2.12**[7] (4.50 g, 94%) as a white solid, Mp: 135–137 °C (lit.

135–137 °C) To **2.12** (2.00 g, 13.7 mmol) was added thionyl chloride (11.3 g, 94.9 mmol) and the reaction was stirred at rt overnight protected from moisture by a drying tube filled with $CaSO_4$. The excess thionyl chloride was removed in vacuo to obtain the crude acyl chloride **2.13** as a liquid. To the acyl chloride **2.13** in CH_2Cl_2 (100 mL) was added bis(trimethylsilyl)acetylene (2.39 g, 14.0 mmol), and the temperature was lowered to –30 °C. Powdered $AlCl_3$ (2.38 g, 17.8 mmol) was then slowly added. The reaction was stirred and warmed to rt. After 2 h, the reaction mixture was carefully quenched by pouring into diluted ice-cold HCl (1.1 mol/L, ice 50.0 mL, HCl 5.00 mL). The organic layer was separated, washed with saturated NH_4Cl, and dried over $MgSO_4$. The crude mixture was purified by passing through a pad of silica gel, and the resulting solution was concentrated to afford the ketone **2.14**,[8] R_f = 0.60 (hexanes–EtOAc, 4:1), which was carried on without further purification. CBr_4 (5.40 g, 16.4 mmol), and PPh_3 (8.60 g, 32.8 mmol) were added to CH_2Cl_2 (200 mL). The mixture was then added to a solution of the crude ketone **2.14** in CH_2Cl_2 (30.0 mL) at rt and stirred for 30 min. The reaction mixture was reduced; CH_2Cl_2 (6.00 mL) and hexanes (60.0 mL) were added. The mixture was filtered through a short silica gel column to afford **2.15**[7] (4.20 g, 78% based on **2.12**) as a pale yellow solid. Mp 78.5–79.5 °C (lit. 76–78 °C). R_f = 0.62 (hexanes–EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.52–7.55 (m, 2H, Ar), 7.32–7.40 (m, 3H, Ar), 0.27 (s, 9H, Si(C$\underline{H}_3$)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.7 (2 × Ar), 129.2 (Ar), 128.4 (2 × Ar), 122.1 (Ar), 114.3 (C=C), 109.1 (C=C), 102.6 (C≡C), 100.2 (C≡C), 95.8 (C≡C), 85.9 (C≡C), –0.4 (3 × $\underline{C}H_3$).

To a solution of dibromoolefin **2.15** (0.810 g, 2.10 mmol) in THF (20.0 mL) and CH_3OH (20.0 mL) at rt was added pulverized K_2CO_3 (0.190 g, 1.38 mmol). TLC analysis was used to monitor the reaction. After 30 min, diluted HCl (40.0 mL) and Et_2O (80.0 mL) were added. The organic layer was separated, washed with H_2O, and dried over $MgSO_4$. The $MgSO_4$ was filtered off and the solvent was partially evaporated. The solution was passed through a short silica gel column to afford **2.11**[8] (0.610 g, 93%) as a pale yellow liquid. R_f = 0.38 (hexanes–EtOAc, 6:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.51–7.54 (m, 2H, Ar), 7.34–7.37 (m, 3H,

Ar), 3.52 (s, 1H, (C≡C<u>H</u>); ^{13}C NMR (125 Hz, $CDCl_3$) δ 131.6 (2 × Ar), 129.3 (Ar), 128.4 (2 × Ar), 121.9 (Ar), 113.4 (C=C), 109.5 (C=C), 96.2 (<u>C</u>≡C), 85.8 (<u>C</u>≡C), 83.9 (<u>C</u>≡C), 79.7 (<u>C</u>≡C).

To a solution of **2.11** (0.610 g, 1.97 mmol) in toluene (4.00 mL) was added hexanes (20.0 mL). The reaction solution was cooled to –20 °C and *n*-BuLi (2.5 M in hexanes, 1.70 mL, 4.30 mmol) was added slowly. After stirring for 40 min, Et_2O (20.0 mL) was added to dilute the reaction solution. After 15 min, paraformaldehyde (0.700 g, 23.0 mmol, suspended in 7.00 mL Et_2O) was added through a cannula at –20 °C. the reaction was slowly warmed to rt and stirred overnight. Saturated NH_4Cl (30.0 mL) and Et_2O (30.0 mL) were added; the organic layer was separated and dried over $MgSO_4$. The $MgSO_4$ was filtered off, and the solvent was partially evaporated. The solution was passed through a silica gel column to afford **1.52**[9] (0.180 g, 50%) as a pale yellow liquid. R_f = 0.49 (hexanes–EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ 7.52–7.55 (m, 2H, Ar), 7.32–7.42 (m, 3H, Ar), 4.40 (s, 2H, C<u>H</u>$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.0 (2 × Ar), 129.8 (Ar), 128.5 (2 × Ar), 120.7 (Ar), 77.8 (<u>C</u>≡C), 77.3 (<u>C</u>≡C), 74.1 (<u>C</u>≡C), 70.9 (<u>C</u>≡C), 65.8 (<u>C</u>≡C), 63.5 (<u>C</u>≡C), 51.6 (<u>C</u>H$_2$).

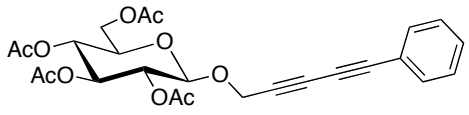
3.3 General procedure for the synthesis of polyyne glycosides and deacetylation of polyyne glycosides

To a solution of the polyyne alcohol (0.850 mmol) in CH_2Cl_2 (10.0 mL) was added the carbohydrate donor (1.70 mmol) and crushed activated 4 Å molecular sieves (100 mg). The reaction mixture was cooled to –30 °C and BF_3•OEt_2 (320 μL, 2.50 mmol) was added slowly over 3 min. The reaction mixture was slowly warmed to rt and stirred for 24 h. Solid K_2CO_3 (675 mg), water (7.00 mL), satd. aq. solution of $NaHCO_3$ (7.50 mL) and CH_2Cl_2 (20.0 mL) were added to the solution. The organic layer was separated, washed with a satd. aq. solution of NaCl (25.0 mL), and dried over $MgSO_4$. Solvent evaporation and purification by column chromatography afforded the polyyne glycoside.

To a solution of the polyyne glycoside (0.400 mmol) in CH_3OH (15.0 mL) was added 1 M $NaOCH_3$ (60.0 μL, 0.060 mmol). After stirring for 2 h at rt, the solution was concentrated. Purification by column chromatography afforded the deprotected polyyne glycoside.

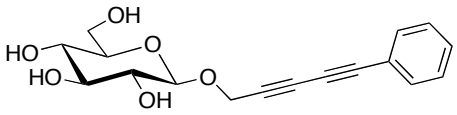
3.3.1 Procedure for the synthesis of diyne glycosides

5-Phenylpenta-2,4-diynyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (2.20)



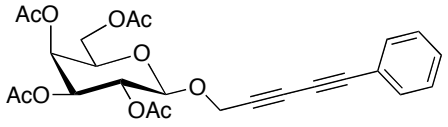
Alcohol 2.5 (104 mg, 0.667 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (500 mg, 1.31 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (100 mg) and BF_3•OEt_2 (280 μL, 1.79 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 5:1) afforded 2.20 (232 mg, 71%) as a white solid: Mp 126.5–127.5 °C; R_f = 0.48 (hexanes–EtOAc, 1:1); IR (CH_2Cl_2, cast) 2960, 2243 (C≡C), 1756 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.55 (m, 2H, Ar), 7.35–7.42 (m, 3H, Ar), 5.27 (t, 1H, $J_{2,3} = J_{3,4} = 9.7$ Hz, H-3), 5.11 (t, 1H, $J_{3,4} = J_{4,5} = 9.7$ Hz, H-4), 5.04 (dd, 1H, $J_{2,3} = 9.7$ Hz, $J_{1,2} = 8.0$ Hz, H-2), 4.80 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 4.55 (d, 1H, $J = 16.7$ Hz, propargyl C$\underline{H}_2$), 4.50 (d, 1H, $J = 16.7$ Hz, propargyl C$\underline{H}_2$), 4.28 (dd, 1H, $J_{6a,6b} = 12.2$ Hz, $J_{5,6a} = 4.7$ Hz, H-6a), 4.17 (dd, 1H, $J_{6a,6b} = 12.2$ Hz, $J_{5,6b} = 2.2$ Hz, H-6b), 3.76 (ddd, 1H, $J_{4,5} = 9.7$ Hz, $J_{5,6a} = 4.7$ Hz, $J_{5,6b} = 2.2$ Hz, H-5), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.09 (s, 3H, C=OC$\underline{H}_3$), 2.04 (s, 3H, C=OC$\underline{H}_3$), 2.02 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 Hz, CD_3OD) δ 170.6 (C=O), 170.2 (C=O), 169.5 (C=O), 169.4 (C=O), 132.6 (2 × Ar), 129.6 (Ar), 128.5 (2 × Ar), 121.1 (Ar), 98.4 (C-1), 78.7 (C≡C), 73.0 (C≡C), 72.8, 72.0, 71.9 (C≡C), 71.0, 68.3, 61.8, 56.7, 20.7 (2 × C=O$\underline{C}H_3$), 20.6 (2 × C=O$\underline{C}H_3$), (one C≡C not observed); HRMS (ESI) calcd. for $C_{25}H_{26}O_{10}Na$ $[M + Na]^+$ 509.1418, found 509.1420.

5-Phenylpenta-2,4-diynyl β-D-glucopyranoside (2.21)



To a solution of **2.20** (195 mg, 0.383 mmol in CH_3OH (15.0 mL) at rt was added 1 M $NaOCH_3$ solution (57.0 μL, 0.057 mmol) as described in the general procedure. Purification by column chromatography (EtOAc–CH_3OH, 15:1) afforded **2.21** (120 mg, 94%) as a yellow solid: Mp: 143.5–144.5 °C; R_f = 0.56 (CH_3OH–EtOAc, 1:6); $[\alpha]_D$ –106.8 (*c* = 0.4, CH_3OH); IR (microscope) 3322 (O–H), 2931, 2244 (C≡C) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.46–7.49 (m, 2H, Ar), 7.32–7.42 (m, 3H, Ar), 4.58 (s, 2H, propargyl C$\underline{H}_2$), 4.45 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 3.87 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 3.66 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 5.6 Hz, H-6b), 3.38 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.2 Hz, H-3), 3.28-3.30 (m, 2H, H-4, H-5), 3.20 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{1,2}$ = 7.6 Hz, H-2); ^{13}C NMR (125 Hz, CD_3OD) δ 133.5 (2 × Ar), 130.7 (Ar), 129.7 (2 × Ar), 122.5 (Ar), 102.4 (C-1, $^1J_{C1,H1}$ = 159.2 Hz), 79.3 (C≡C), 78.9 (C≡C), 78.1 (C-4), 78.0 (C-3), 74.9 (C-2), 73.9 (C≡C), 71.6 (C-5), 71.5 (C≡C), 62.8 (C-6), 57.2 (propargyl $\underline{C}H_2$); HRMS (ESI) calcd. for $C_{17}H_{18}O_6Na$ $[M + Na]^+$ 341.0996, found 341.0996.

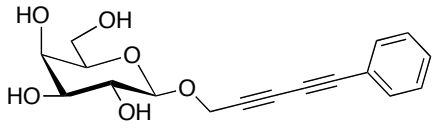
5-Phenylpenta-2,4-diynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (2.22)



Alcohol **2.5** (50.0 mg, 0.320 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (163 mg, 0.417 mmol) in CH_2Cl_2 (5.00 mL) in the presence of crushed activated 4 Å molecular sieves (50.0 mg) and BF_3•OEt_2 (122 μL, 0.960 mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 45:1) afforded **2.22** (125 mg, 80%) as a yellow

solid: Mp: 44.5–45.5 °C; R_f = 0.34 (CH_2Cl_2–EtOAc, 12:1); IR (microscope) 2936, 2866, 2243 (C≡C), 1748 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.52 (m, 2H, Ar), 7.32–7.42 (m, 3H, Ar), 5.42 (dd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 5.24 (dd, 1H, $J_{2,3}$ = 10.4 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 5.08 (dd, 1H, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 4.76 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 5.56 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 5.51 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 4.20 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{5,6a}$ = 6.4 Hz, H-6a), 4.15 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{5,6b}$ = 6.4 Hz, H-6b), 3.97 (dt, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 6.4 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 2.16 (s, 3H, C=OC$\underline{H}_3$), 2.11 (s, 3H, C=OC$\underline{H}_3$), 2.07 (s, 3H, C=OC$\underline{H}_3$), 2.00 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (C=O), 170.1 (C=O), 170.0 (C=O), 169.5 (C=O), 132.5 (2 × Ar), 129.4 (Ar), 128.4 (2 × Ar), 121.0 (Ar), 98.8 (C-1), 78.6 (C≡C), 76.8 (C≡C), 72.9 (C≡C), 71.7 (C≡C), 70.8, 70.7, 68.4, 66.9, 61.2, 56.6, 20.7 (C=O$\underline{C}H_3$), 20.6 (C=O$\underline{C}H_3$), 20.5 (C=O$\underline{C}H_3$), 20.4 (C=O$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{25}H_{26}O_{10}Na$ $[M + Na]^+$ 509.1418, found 509.1405.

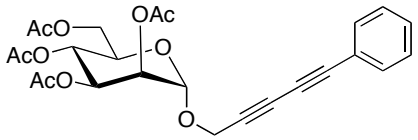
5-Phenylpenta-2,4-diynyl β-D-galactopyranoside (2.23)



To a solution of **2.22** (105 mg, 0.216 mmol) in CH_3OH (10.0 mL) at rt was added 1 M $NaOCH_3$ solution (32.0 μL, 0.032 mmol) as described in the general procedure. Purification by column chromatography (CH_3OH–EtOAc, 12:1) afforded **2.23** (65.0 mg, 95%) as a yellow solid: Mp: 99–100 °C; R_f = 0.40 (CH_3OH–EtOAc, 1:4); $[\alpha]_D$ –72.7 (c = 0.2, CH_3OH); IR (microscope) 3364 (O–H), 2922, 2244 (C≡C) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.47–7.49 (m, 2H, Ar), 7.35–7.42 (m, 3H, Ar), 4.58 (s, 2H, propargyl C$\underline{H}_2$), 4.42 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1), 3.83 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 1.2 Hz, H-4), 3.78 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{5,6a}$ = 6.8 Hz, H-6a), 3.72 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{5,6b}$ = 5.0 Hz, H-6b), 3.52–3.56 (m, 1H, H-5), 3.53 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{1,2}$ = 7.2 Hz, H-2), 3.49 (dd,

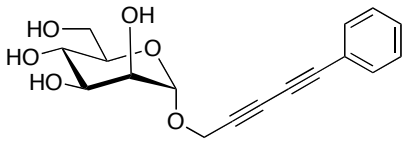
1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 3.2 Hz, H-3); ^{13}C NMR (125 Hz, CD_3OD) δ 133.5 (2 × Ar), 130.6 (Ar), 129.7 (2 × Ar), 122.6 (Ar), 103.0 (C-1), 79.5 (C≡C), 78.8 (C≡C), 76.9 (C-5), 74.9 (C-3), 73.9 (C≡C), 72.3 (C-2), 71.5 (C≡C), 70.3 (C-4), 62.6 (C-6), 57.1 (propargyl CH_2); HRMS (ESI) calcd. for $C_{17}H_{18}O_6Na$ $[M + Na]^+$ 341.0996, found 341.0994.

5-Phenylpenta-2,4-diynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (2.24)



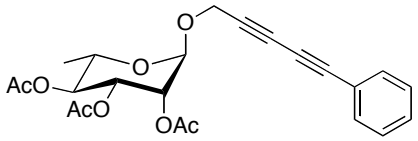
Alcohol **2.5** (102 mg, 0.654 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose (690 mg, 1.70 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (80.0 mg) and BF_3•OEt_2 (240 μL, 1.96 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 9:1) afforded **2.24** (98.0 mg, 31%) as a yellow syrup: R_f = 0.19 (hexanes–EtOAc, 3:1); IR (microscope) 2959, 2245 (C≡C), 1741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.50 (m, 2H, Ar), 7.32–7.41 (m, 3H, Ar), 5.29–5.36 (m, 3H, H-2, H-3, H-4), 5.04 (s, 1H, H-1), 4.45 (d, 1H, J = 16.5 Hz, propargyl CH_2), 4.40 (d, 1H, J = 16.5 Hz, propargyl CH_2), 4.30 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6a}$ = 5.0 Hz, H-6a), 4.14 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6b}$ = 2.5 Hz, H-6b), 4.03–4.06 (m, 1H, H-5), 2.16 (s, 3H, C=OCH_3), 2.11 (s, 3H, C=OCH_3), 2.04 (s, 3H, C=OCH_3), 1.99 (s, 3H, C=OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C=O), 169.8 (C=O), 169.7 (C=O), 169.6 (C=O), 132.6 (2 × Ar), 129.4 (Ar), 128.3 (2 × Ar), 121.0 (Ar), 96.6 (C-1), 78.8 (C≡C), 76.5 (C≡C), 72.9 (C≡C), 71.8 (C≡C), 69.2, 69.0, 68.8, 65.9, 62.2, 55.7, 20.7 (C=OCH_3), 20.6 (2 × C=OCH_3), 20.5 (C=OCH_3); HRMS calcd. for $C_{25}H_{26}O_{10}Na$ $[M + Na]^+$ 509.1418, found 509.1420.

5-Phenylpenta-2,4-diynyl α-D-mannopyranoside (2.25)



To a solution of **2.24** (69.0 mg, 0.140 mmol) in CH_3OH (5.00 mL) at rt was added $NaOCH_3$ solution (21.0 μL, 0.021 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 1:4) afforded **2.25** (40.0 mg, 90%) as a yellow solid: Mp: 107–108 °C; R_f = 0.38 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ +76.9 (*c* = 0.3, CH_3OH); IR (microscope) 3354 (O–H), 2930, 2244 (C≡C) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.46–4.78 (m, 2H, Ar), 7.32–7.41 (m, 3H, Ar), 4.97 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 4.46 (d, 1H, *J* = 16.8 Hz, propargyl C$\underline{H}_2$), 4.42 (d, 1H, *J* = 16.8 Hz, propargyl C$\underline{H}_2$), 3.85 (dd, 1H, $J_{6a,6b}$ = 11.6 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 3.83 (dd, 1H, $J_{2,3}$ = 2.4 Hz, $J_{1,2}$ = 2.0 Hz, H-2), 3.74 (dd, 1H, $J_{6a,6b}$ = 11.6 Hz, $J_{5,6b}$ = 5.6 Hz, H-6b), 3.63–3.70 (m, 2H, H-3, H-4), 3.53 (ddd, 1H, $J_{4,5}$ = 9.2 Hz, $J_{5,6b}$ = 5.6 Hz, $J_{5,6a}$ = 2.0 Hz, H-5); ^{13}C NMR (125 MHz, CD_3OD) δ 133.6 (2 × Ar), 130.7 (Ar), 129.7 (2 × Ar), 122.5 (Ar), 100.4 (C-1, $^1J_{C1,H1}$ = 170.0 Hz), 79.3 (C≡C), 79.0 (C≡C), 75.2 (C-5), 73.8 (C≡C), 72.4 (C-3), 72.0 (C-2), 71.4 (C≡C), 68.4 (C-4), 62.6 (C-6), 55.7 (propargyl $\underline{C}H_2$); HRMS calcd. for $C_{17}H_{18}O_6Na$ $[M + Na]^+$ 341.0996, found 341.0995.

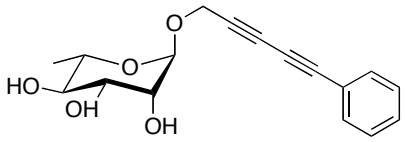
5-Phenylpenta-2,4-diynyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (2.26)



Alcohol **2.5** (100 mg, 0.641 mmol) was coupled with 1,2,3,4-tetra-*O*-acetyl-L-rhamnopyranose (360 mg, 1.30 mmol) in CH_2Cl_2 (8.00 mL) in the presence of crushed activated 4 Å molecular sieves (80.0 mg) and BF_3•OEt_2 (192 μL, 1.92

mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 9:1) afforded **2.26** (226 mg, 82%) as a yellow oil: R_f = 0.28 (hexanes–EtOAc, 3:1); IR (CH_2Cl_2, cast) 2984, 2244 (C≡C), 1749 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.50 (m, 2H, Ar), 7.30–7.38 (m, 3H, Ar), 5.28–5.30 (m, 2H, H-2, H-3), 5.09 (t, 1H, $J_{3,4} = J_{4,5}$ = 10.0 Hz, H-4), 4.94 (s, 1H, H-1), 4.42 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 3.38 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 3.90–3.95 (m, 1H, H-5), 2.16 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 1.98 (s, 3H, C=OC$\underline{H}_3$), 1.25 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (2 × $\underline{C}$=O), 169.9 ($\underline{C}$=O), 132.6 (2 × Ar), 129.4 (Ar), 128.4 (2 × Ar), 121.2 (Ar), 96.5 (C-1), 78.6 ($\underline{C}$≡C), 73.1 ($\underline{C}$≡C), 71.5 ($\underline{C}$≡C), 70.9, 69.6, 69.0, 67.0, 55.6, 20.9 (C=O$\underline{C}H_3$), 20.8 (C=O$\underline{C}H_3$), 20.7 (C=O$\underline{C}H_3$), 17.3 (C-6), (one $\underline{C}$≡C not observed); HRMS (ESI) calcd. for $C_{23}H_{24}O_8Na$ $[M + Na]^+$ 451.1363, found 451.1367.

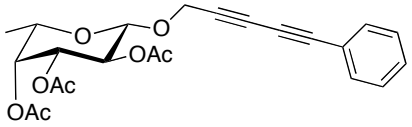
5-Phenylpenta-2,4-diynyl α-L-rhamnopyranoside (2.27)



To a solution of **2.26** (190 mg, 0.444 mmol) in CH_3OH (22.0 mL) at rt was added 1 M $NaOCH_3$ solution (84.0 μL, 0.084 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 1:3) afforded **2.27** (129 mg, 96%) as a brown solid: Mp: 48.5–49.5 °C; R_f = 0.33 (EtOAc); $[\alpha]_D$ –101.1 (c = 0.4, CH_3OH); IR (CH_2Cl_2, cast) 3369 (O–H), 2930, 2244 (C≡C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.47–7.49 (m, 2H, Ar), 7.34–7.42 (m, 3H, Ar), 4.86 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.41 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 4.37 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 3.81(1H, dd, $J_{2,3}$ = 3.5 Hz, $J_{1,2}$ = 1.5 Hz, H-2), 3.62 (t, 1H, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 3.5 Hz, H-3), 3.60 (dq, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6}$ = 6.5 Hz, H-5), 3.39 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 1.28 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, CD_3OD) δ 133.6 (2 × Ar), 130.7

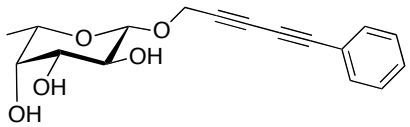
(Ar), 129.7 (2 × Ar), 122.5 (Ar), 100.8 (C-1, $^{1}J_{C1,H1}$ = 158.5 Hz), 79.4 (C≡C), 78.9 (C≡C), 73.8 (C-4, C≡C), 72.3 (C-3), 72.1 (C-2), 71.2 (C≡C), 70.5 (C-5), 55.8 (propargyl CH_2), 17.9 (C-6); HRMS (ESI) calcd. for $C_{17}H_{18}O_5Na$ $[M + Na]^+$ 325.1046, found 325.1048.

5-Phenylpenta-2,4-diynyl 2,3,4-tri-*O*-acetyl-β-L-fucopyranoside (2.28)



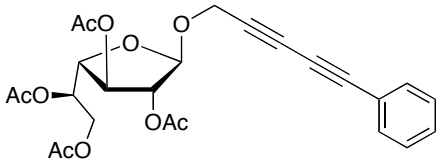
Alcohol **2.5** (100 mg, 0.641 mmol) was coupled with 1,2,3,4-tetra-*O*-acetyl-β-L-fucopyranose (348 mg, 1.28 mmol) in CH_2Cl_2 (8.00 mL) in the presence of crushed activated 4 Å molecular sieves (80.0 mg) and BF_3•OEt_2 (192 μL, 1.92 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 8:1) afforded **2.28** (212 mg, 77%) yield as a white solid: Mp: 129–130 °C; R_f = 0.22 (hexanes–EtOAc, 3:1); IR (CH_2Cl_2, cast) 2986, 2243 (C≡C), 1750 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.52 (m, 2H, Ar), 7.31–7.40 (m, 3H, Ar), 5.25 (d, 1H, $J_{3,4}$ = 3.5 Hz, H-4), 5.21 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 5.07 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.72 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.56 (d, 1H, J = 17.0 Hz, propargyl CH_2), 4.51 (d, 1H, J = 17.0 Hz, propargyl CH_2), 3.86 (q, 1H, $J_{5,6}$ = 6.5 Hz, H-5), 2.18 (s, 3H, C=OCH_3), 2.10 (s, 3H, C=OCH_3), 1.99 (s, 3H, C=OCH_3), 1.24 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C=O), 170.1 (C=O), 169.7 (C=O), 132.6 (2 × Ar), 129.5 (Ar), 128.5 (2 × Ar), 121.2 (Ar), 98.7 (C-1), 78.5 (C≡C), 77.2 (C≡C), 73.1 (C≡C), 71.6 (C≡C), 71.3, 70.2, 69.4, 68.6, 56.5, 20.8 (C=OCH_3), 20.7 (C=OCH_3), 20.6 (C=OCH_3), 16.0 (C-6); HRMS (ESI) calcd. for $C_{23}H_{24}O_8Na$ $[M + Na]^+$ 451.1363, found 451.1366.

5-Phenylpenta-2,4-diynyl β-L-fucopyranoside (2.29)



To a solution of **2.28** (43 mg, 0.080 mmol) in CH_3OH (4.00 mL) at rt was added 1 M $NaOCH_3$ solution (0.120 mL, 0.120 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.29** (15.0 mg, 63%) as a syrup: R_f = 0.31 (EtOAc); $[\alpha]_D$ –68.8 (*c* = 0.7, CH_3OH); IR (CH_2Cl_2, cast) 3396 (O–H), 2934, 2244 (C≡C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.47–7.49 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 4.53 (d, 1H, *J* = 17.0 Hz, propargyl C$\underline{H}_2$), 4.51 (d, 1H, *J* = 17.0 Hz, propargyl C$\underline{H}_2$), 4.39 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 3.66 (qd, 1H, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.5 Hz, H-5), 3.60 (d, 1H, $J_{4,5}$ = 1.5 Hz, H-4), 3.49–3.50 (m, 2H, H-2, H-3), 1.28 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (100 MHz, CD_3OD) δ 133.4 (2 × Ar), 130.5 (Ar), 129.5 (2 × Ar), 122.4 (Ar), 102.7 (C-1, $^1J_{C1,H1}$ = 164.5 Hz), 79.2 (C≡C), 78.6 (C≡C), 74.9 (C-2), 73.8 (C≡C), 72.8 (C-4), 72.0 (C-3), 71.9 (C-5), 71.3 (C≡C), 56.8 (propargyl $\underline{C}H_2$), 16.5 (C-6); HRMS (ESI) calcd. for $C_{17}H_{18}O_5Na$ $[M + Na]^+$ 325.1046, found 325.1044.

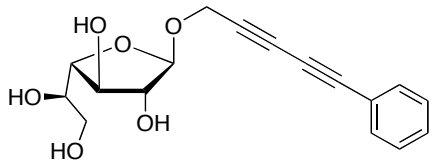
5-Phenylpenta-2,4-diynyl 2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranoside (2.30)



Alcohol **2.5** (97.0 mg, 0.620 mmol) was coupled with methyl 2,3,5,6-tetra-*O*-acetyl-D-galactofuranoside (450 mg, 1.24 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (100 mg) and BF_3•OEt_2 (230 μL, 1.86 mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 40:1) afforded **2.30** (210 mg, 70%) as a yellow

oil: R_f = 0.56 (CH_2Cl_2–EtOAc, 8:1); IR (microscope) 2955, 2244 (C≡C), 1745 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.51 (m, 2H, Ar), 7.32–7.42 (m, 3H, Ar), 5.39 (dt, 1H, $J_{5,6a}$ = 7.0 Hz, $J_{4,5}$ = $J_{5,6b}$ = 4.2 Hz, H-5), 5.26 (s, 1H, H-1), 5.12 (d, 1H, $J_{2,3}$ = 2.0 Hz, H-2), 5.04 (dd, 1H, $J_{3,4}$ = 6.0 Hz, $J_{2,3}$ = 2.0 Hz, H-3), 4.41 (s, 2H, propargyl C$\underline{H}_2$), 4.37 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 4.2 Hz, H-6b), 4.30 (dd, 1H, $J_{3,4}$ = 6.0 Hz, $J_{4,5}$ = 4.2 Hz, H-4), 4.25 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 7.0 Hz, H-6a), 2.15 (s, 3H, C=OC$\underline{H}_3$), 2.13 (s, 3H, C=OC$\underline{H}_3$), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.07 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (C=O), 169.9 (C=O), 169.8 (C=O), 169.4 (C=O), 132.5 (2 × Ar), 129.3 (Ar), 128.3 (2 × Ar), 121.2 (Ar), 104.2 (C-1), 81.2, 80.5, 78.4 (C≡C), 76.5, 73.0 (C≡C), 71.3 (C≡C), 69.2, 62.5, 55.0, 20.7 (C=OCH$_3$), 20.6 (3 × C=OCH$_3$), (one C≡C not observed); HRMS (ESI) calcd. for $C_{25}H_{26}O_{10}Na$ $[M + Na]^+$ 509.1418, found 509.1420.

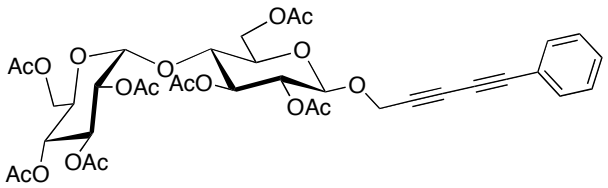
5-Phenylpenta-2,4-diynyl β-D-galactofuranoside (2.31)



To a solution of **2.30** (187 mg, 0.385 mmol) in CH_3OH (10.0 mL) at rt was added 1 M $NaOCH_3$ solution (55.0 μL, 0.055 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.31** (118 mg, 97%) as a syrup: R_f = 0.43 (CH_3OH–EtOAc, 1:6); $[\alpha]_D$ –111.9 (c = 0.2, CH_3OH); IR (microscope) 3302 (O–H), 2926, 2245 (C≡C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.47–7.49 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 5.07 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.43 (d, 1H, J = 16.5 Hz, propargyl C$\underline{H}_2$), 4.40 (d, 1H, J = 16.5 Hz, propargyl C$\underline{H}_2$), 4.03 (dd, 1H, $J_{3,4}$ = 6.5 Hz, $J_{2,3}$ = 3.5 Hz, H-3), 3.99 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{1,2}$ = 1.5 Hz, H-2), 3.94 (dd, 1H, $J_{3,4}$ = 6.5 Hz, $J_{4,5}$ = 3.5 Hz, H-4), 3.73 (ddd, 1H, $J_{5,6a}$ = 7.0 Hz, $J_{5,6b}$ = 5.5 Hz, $J_{4,5}$ = 3.5 Hz, H-5), 3.65 (dd, 1H,

$J_{6a,6b}$ = 11.0 Hz, $J_{5,6b}$ = 5.5 Hz, H-6b), 3.62 (dd, 1H, 1H, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6a}$ = 7.0 Hz, H-6a); ^{13}C NMR (125 MHz, CD_3OD) δ 133.6 (2 × Ar), 130.6 (Ar), 129.7 (2 × Ar), 122.6 (Ar), 107.9 (C-1), 85.0 (C-4), 53.4 (C-2), 79.7 (C≡C), 79.0 (C-3), 78.7 (C≡C), 73.9 (C≡C), 72.4 (C-5), 71.1 (C≡C), 64.5 (C-6), 55.5 (propargyl CH_2); HRMS (ESI) calcd. for $C_{17}H_{18}O_6Na$ $[M + Na]^+$ 341.0996, found 341.0994.

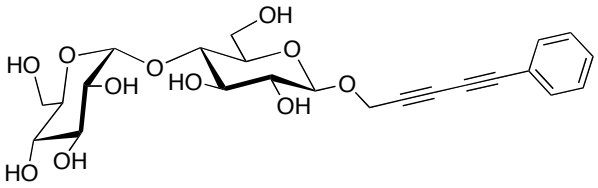
5-Phenylpenta-2,4-diynyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranoside (2.32)



Alcohol **2.5** (72.0 mg, 0.460 mmol) was coupled with 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranose (380 mg, 0.691 mmol) in CH_2Cl_2 (6.00 mL) in the presence of crushed activated 4 Å molecular sieves (60.0 mg) and BF_3•OEt_2 (175 μL, 1.38 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 4:1) afforded **2.32** (263 mg, 74%) as a yellow syrup: R_f = 0.35 (hexanes–EtOAc, 1:1); IR (CH_2Cl_2, cast) 2961, 2244 (C≡C), 1754 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.53 (m, 2H, Ar), 7.32–7.42 (m, 3H, Ar), 5.42 (d, 1H, $J_{1',2'}$ = 4.0 Hz, H-1′), 5.36 (dd, 1H, $J_{2',3'}$ = 10.5 Hz, $J_{3',4'}$ = 9.5 Hz, H-3′), 5.30 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 5.06 (dd, 1H, $J_{4',5'}$ = 10.0 Hz, $J_{3',4'}$ = 9.5 Hz, H-4′), 4.87 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 4.86 (dd, 1H, $J_{2',3'}$ = 10.5 Hz, $J_{1',2'}$ = 4.0 Hz, H-2′), 4.81 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.52 (dd, 1H, $J_{6a,6b}$ = 12.3 Hz, $J_{5,6a}$ = 3.0 Hz, H-6a), 4.52 (d, 1H, J = 17.0 Hz, propargyl CH_2), 4.48 (d, 1H, J = 17.0 Hz, propargyl CH_2), 4.26 (dd, 1H, $J_{6'a,6'b}$ = 12.5 Hz, $J_{5',6'a}$ = 4.0 Hz, H-6′a), 4.25 (dd, 1H, $J_{6a,6b}$ = 12.3 Hz, $J_{5,6b}$ = 4.8 Hz, H-6b), 4.05 (dd, 1H, $J_{6'a,6'b}$ = 12.5 Hz, $J_{5',6'b}$ = 2.5 Hz, H-6′b), 4.03 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 3.96 (ddd, 1H, $J_{4',5'}$ = 10.0 Hz, $J_{5',6'a}$ = 4.0 Hz, $J_{5',6'b}$ = 2.5 Hz, H-5′), 3.74 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6b}$ = 4.8

Hz, $J_{5,6a}$ = 3.0 Hz, H-5), 2.16 (s, 3H, C=OC$\underline{H}_3$), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.07 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 2.03 (s, 3H, C=OC$\underline{H}_3$), 2.02 (s, 3H, C=OC$\underline{H}_3$), 2.00 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (2 × $\underline{C}$=O), 170.4 ($\underline{C}$=O), 170.2 ($\underline{C}$=O), 169.9 ($\underline{C}$=O), 169.7 ($\underline{C}$=O), 169.4 ($\underline{C}$=O), 132.6 (2 × Ar), 129.5 (Ar), 128.4 (2 × Ar), 121.1 (Ar), 97.9, 95.5, 78.7 ($\underline{C}$≡C), 76.7 ($\underline{C}$≡C), 75.3, 73.0 ($\underline{C}$≡C), 72.6, 72.4, 71.9 ($\underline{C}$≡C), 71.8, 70.0, 69.3, 68.5, 68.0, 62.6, 61.5, 56.7, 20.9 (C=O$\underline{C}$H$_3$), 20.8 (C=O$\underline{C}$H$_3$), 20.7 (2 × C=O$\underline{C}$H$_3$), 20.6 (3 × C=O$\underline{C}$H$_3$); HRMS (ESI) calcd. for $C_{37}H_{42}O_{18}Na$ $[M + Na]^+$ 797.2263, found 797.2264.

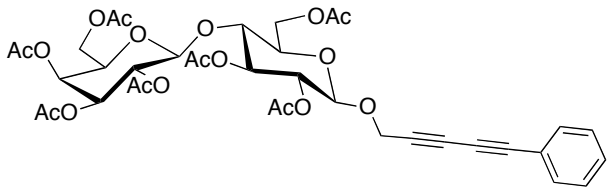
5-Phenylpenta-2,4-diynyl 4-*O*-(α-D-glucopyranosyl)-β-D-glucopyranoside (2.33)



To a solution of **2.32** (220 mg, 0.284 mmol) in CH_3OH (13.5 mL) at rt was added 1 M $NaOCH_3$ solution (84.0 μL, 0.083 mmol) as described in the general procedure. Purification by column chromatography (CH_3OH–EtOAc, 1:12) afforded **2.33** (111 mg, 81%) yield as a yellow solid: Mp: 106.5–107.5 °C; R_f = 0.20 (CH_3OH–EtOAc, 1:4); $[\alpha]_D$ –70.0 (*c* = 0.8, CH_3OH); IR (microscope) 3326 (O–H), 2925, 2244 (C≡C) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.47–7.49 (m, 2H, Ar), 7.33–7.40 (m, 3H, Ar), 5.16 (d, 1H, $J_{1',2'}$ = 4.0 Hz, H-1′), 4.58 (s, 2H, propargyl C$\underline{H}_2$), 4.48 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 3.90 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 3.82 (dd, 1H, $J_{6'a,6'b}$ = 12.5 Hz, $J_{5',6'a}$ = 4.5 Hz, H-6′a), 3.81 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6b}$ = 5.0 Hz, H-6b), 3.64–3.70 (m, 2H, H-5′, H-6′b), 3.65 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.5 Hz, H-3), 3.61 (t, 1H, $J_{2',3'} = J_{3',4'}$ = 9.5 Hz, H-3′), 3.54 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 3.43 (dd, 1H, $J_{2',3'}$ = 9.5 Hz, $J_{1',2'}$ = 4.0 Hz, H-2′), 3.40 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6b}$ = 5.0 Hz, $J_{5,6a}$ = 2.0 Hz, H-5), 3.26 (t, 1H, $J_{3',4'}$ =

$J_{4',5'}$ = 9.5 Hz, H-4′), 3.25 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 7.8 Hz, H-2); ^{13}C NMR (125 MHz, CD_3OD) δ 133.6 (2 × Ar), 130.7 (Ar), 129.7 (2 × Ar), 122.8 (Ar), 102.9 (C-1′, $^1J_{C1',H1'}$ = 169.0 Hz), 102.4 (C-1, $^1J_{C1,H1}$ = 160.5 Hz), 81.1 (C-4), 79.3 (C≡C), 78.9 (C≡C), 77.7 (C-3), 76.8 (C-5), 75.1 (C-3′), 74.8 (C-5′), 74.5 (C-2), 74.2 (C-2′), 74.1 (C≡C), 71.8 (C≡C), 71.5 (C-4′), 62.8 (C-6′), 62.2 (C-6), 57.2 (propargyl CH_2); HRMS (ESI) calcd. for $C_{23}H_{28}O_{11}Na$ $[M + Na]^+$ 503.1524, found 503.1530.

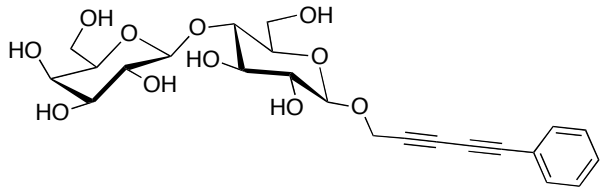
5-Phenylpenta-2,4-diynyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (2.34)



Alcohol **2.5** (109 mg, 0.699 mmol) was coupled with 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranose (461 mg, 0.838 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (100 mg) and BF_3•OEt_2 (264 μL, 2.10 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 4:1) afforded **2.34** (294 mg, 54%) as a yellow oil: R_f = 0.23 (hexanes–EtOAc, 1:1); IR (CH_2Cl_2, cast) 2963, 2244 (C≡C), 1751 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.53 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 5.34 (dd, 1H, $J_{3',4'}$ = 3.2 Hz, $J_{4',5'}$ = 1.2 Hz, H-4′), 5.24 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H-3), 5.11 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, $J_{1',2'}$ = 8.0 Hz, H-2′), 4.96 (dd, 1H, $J_{2',3'}$ = 10.4 Hz, $J_{3',4'}$ = 3.2 Hz, H-3′), 4.93 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{1,2}$ = 7.6 Hz, H-2), 4.76 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.51 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.4 Hz, H-6a), 4.51 (d, 1H, J = 16.4 Hz, propargyl CH_2), 4.49 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1′), 4.46 (d, 1H, J = 16.4 Hz, propargyl CH_2), 4.06-4.15 (m, 3H, H-6b, H-6′a, H-6′b), 3.88 (td, 1H, $J_{5',6'a}$ = 7.6 Hz, $J_{4',5'}$ = 1.2 Hz, H-5′), 3.82 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 3.66 (ddd, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6b}$ =

5.2 Hz, $J_{5,6a}$ = 2.0 Hz, H-5), 2.15 (s, 3H, COC$\underline{H}_3$), 2.13 (s, 3H, COC$\underline{H}_3$), 2.08 (s, 3H, COC$\underline{H}_3$), 2.06 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 2.04 (s, 3H, C=OC$\underline{H}_3$), 1.96 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (2 × $\underline{C}$=O), 170.1 ($\underline{C}$=O), 170.0 ($\underline{C}$=O), 169.8 ($\underline{C}$=O), 169.7 ($\underline{C}$=O), 169.0 ($\underline{C}$=O), 132.6 (2 × Ar), 129.5 (Ar), 128.5 (2 × Ar), 121.1 (Ar), 101.0, 98.1, 78.7 ($\underline{C}$≡C), 76.1, 73.0 ($\underline{C}$≡C), 72.8, 72.7, 71.9 ($\underline{C}$≡C), 71.4, 71.0, 70.7, 69.1, 66.6, 61.8 60.8, 56.7, 20.8 (2 × C=O$\underline{C}$H$_3$), 20.7 (C=O$\underline{C}$H$_3$), 20.6 (3 × C=O$\underline{C}$H$_3$), 20.5 (C=O$\underline{C}$H$_3$), (one $\underline{C}$≡C not observed); HRMS (ESI) calcd. for $C_{37}H_{42}O_{18}Na$ $[M + Na]^+$ 797.2263, found 797.2270.

5-Phenylpenta-2,4-diynyl 4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranoside (2.35)

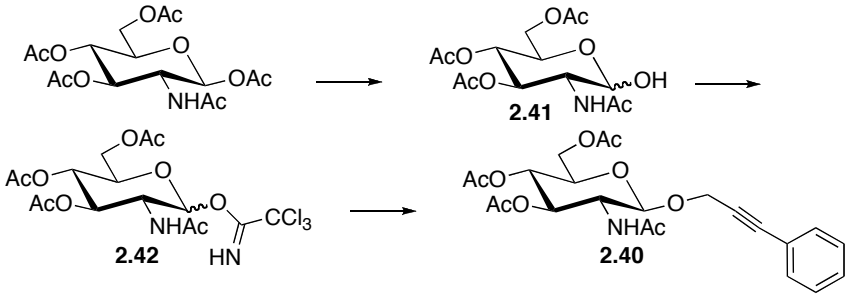


To a solution of **2.34** (57.0 mg, 0.074 mmol) in CH_3OH (3.50 mL) at rt was added 1 M $NaOCH_3$ solution (21.0 μL, 0.021 mmol) as described in the general procedure. Purification by column chromatography (CH_3OH–EtOAc, 1:10) afforded **2.35** (35.0 mg, 98%) as a yellow solid: Mp: 177–178 °C; R_f = 0.20 (CH_3OH–EtOAc, 1:4); $[\alpha]_D$ –80.0 (c = 0.2, CH_3OH); IR (microscope) 3311 (O–H), 2919, 2243 (C≡C) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.47–7.49 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 4.58 (s, 2H, propargyl C$\underline{H}_2$), 4.50 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.35 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1′), 3.92 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, $J_{5,6a}$ = 2.5 Hz, H-6a), 3.84 (dd, 1H, $J_{6a,6b}$ = 12.2 Hz, $J_{5,6b}$ = 4.5 Hz, H-6b), 3.80 (d, 1H, $J_{3',4'}$ = 3.5 Hz, H-4′), 3.77 (dd, 1H, $J_{6'a,6'b}$ = 11.5 Hz, $J_{5',6'a}$ = 7.5 Hz, H-6′a), 3.69 (dd, 1H, $J_{6'a,6'b}$ = 11.5 Hz, $J_{5',6'b}$ = 4.5 Hz, H-6′b), 3.52–3.60 (m, 4H, H-3, H-5′, H-4, H-2′), 3.47 (dd, 1H, $J_{2',3'}$ = 9.5 Hz, $J_{3',4'}$ = 3.5 Hz, H-3′), 3.43–3.45 (m, 1H, H-5), 3.28 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 8.0 Hz, H-2); ^{13}C NMR (100 MHz, CD_3OD) δ 133.4

(2 × Ar), 130.5 (Ar), 129.5 (2 × Ar), 122.4 (Ar), 104.9 (C-1′), 102.1 (C-1), 80.3 (C-3), 79.0 (C≡C), 78.7 (C≡C), 76.9 (C-5′), 76.5 (C-5), 76.2 (C-2′), 74.6 (C-3′), 74.4 (C-2), 73.7 (C≡C), 72.4 (C-4), 71.4 (C≡C), 70.1 (C-4′), 62.3 (C-6′), 61.7 (C-6), 57.0 (propargyl CH_2); HRMS (ESI) calcd. for $C_{23}H_{28}O_{11}Na$ $[M + Na]^+$ 503.1524, found 503.1525.

3.3.2 Procedure for the synthesis of monoyne glycosides

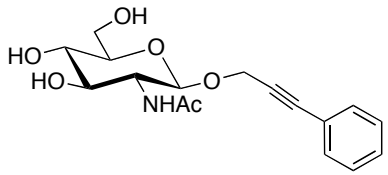
3-Phenylprop-2-ynyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (2.40)



To a solution of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-galactopyranose (209 mg, 0.540 mmol) was added hydrazine acetate (67.0 mg, 0.730 mmol) in DMF (2.00 mL). The reaction mixture was stirred at 60 °C for 1 h. EtOAc (10.0 mL) was added to dilute the solution. The solution was washed with brine and dried over $MgSO_4$. The $MgSO_4$ was filtered off and solvent was evaporated. The residue was purified by column chromatography (hexanes–EtOAc, 1:1) to afford 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranose **2.41**[10] (121 mg, 65%) as a syrup: R_f = 0.22 (EtOAc). 4 Å Molecular sieves (100 mg) and trichloroacetonitrile (0.350 mL, 3.50 mmol) were added to a solution of **2.41** (104 mg, 0.290 mmol) in CH_2Cl_2 (2.50 mL). The reaction mixture was stirred at 0 °C for 1 h, then DBU (20.0 μL, 0.130 mmol) was added slowly. After stirring for 2 h, EtOAc (15.0 mL) was added and the solution was passed through a short silica gel column and the solvent was evaporated to afford the crude 2-acetamido-2-

deoxy-3,4,6-tri-*O*-acetyl-β-D-galactopyranose trichloroacetimidate **2.42**[11] as a syrup: R_f = 0.51 (EtOAc). 3-Phenyl-2-propyn-1-ol (52.0 mg, 0.400 mmol) was added to a solution of the crude **2.42** in CH_2Cl_2 (2.50 mL) at –10 °C in the presence of crushed activated 4 Å molecular sieves (50.0 mg) and TMSOTf (9.00 mg, 0.038 mmol). The reaction mixture was stirred for 1 h, quenched with H_2O (5 mL), and CH_2Cl_2 (15 mL) was added. The organic layer was separated, washed with sat. aq. $NaHCO_3$ solution (10 mL) and H_2O (10 mL), and then dried over $MgSO_4$. After concentration of the organic layer, the residue was purified by column chromatography (hexanes–EtOAc, 2:1) afford **2.40** (44.0 mg, 33% over two steps from **2.41**) as a syrup: R_f = 0.62 (EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.46 (m, 2H, Ar), 7.31–7.36 (m, 3H, Ar), 5.52 (d, 1H, $J_{2,NH}$ = 8.5 Hz, NH), 5.34 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 5.10 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 4.96 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 4.62 (d, 1H, J = 16.0 Hz, propargyl CH$_2$), 4.58 (d, 1H, J = 16.0 Hz, propargyl CH$_2$), 4.29 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6a}$ = 4.5 Hz, H-6a), 4.16 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6b}$ = 2.5 Hz, H-6b), 3.93 (dt, 1H, $J_{2,NH}$ = $J_{1,2}$ = 8.5 Hz, $J_{2,3}$ = 10.5 Hz, H-2), 3.76 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6a}$ = 4.5 Hz, $J_{5,6b}$ = 2.5 Hz, H-5), 2.08 (s, 3H, C=OCH$_3$), 2.03 (s, 3H, C=OCH$_3$), 2.02 (s, 3H, C=OCH$_3$), 1.93 (s, 3H, C=OCH$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9 (C=O), 170.7 (C=O), 170.3 (C=O), 169.4 (C=O), 131.8 (2 × Ar), 128.8 (Ar), 128.4 (2 × Ar), 122.1 (Ar), 98.4 (C-1), 87.0 (C≡C), 83.6 (C≡C), 72.4, 72.0, 68.5, 62.0, 56.8, 54.6, 23.4 (C=OCH$_3$), 20.7 (2 × C=OCH$_3$), 20.6 (C=OCH$_3$).

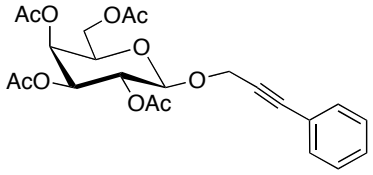
3-Phenylprop-2-ynyl 2-acetamido-2-deoxy-β-D-glucopyranoside (2.52)



To a solution of **2.40** (44.0 mg, 0.095 mmol) in CH_3OH (3.00 mL) at rt was added 1 M $NaOCH_3$ solution (40.0 μL, 0.040 mmol) as described in the general

procedure. Purification by column chromatography (CH_3OH–EtOAc, 1:10) afforded **2.52** (32.0 mg, 90%) as an oil: R_f = 0.06 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ – 18.4 (*c* = 1.2, CH_3OH); IR (CH_2Cl_2 cast) 3375 (O–H, N-H), 2925 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.41–7.39 (m, 2H, Ar), 7.33–7.38 (m, 3H, Ar), 4.67 (d, 1H, $J_{1,2}$ = 8.5 Hz, H-1), 4.61 (d, 1H, *J* = 16.5 Hz, propargyl C$\underline{H}_2$), 4.57 (d, 1H, *J* = 16.5 Hz, propargyl C$\underline{H}_2$), 3.90 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 3.70 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 5.5 Hz, H-6b), 3.68 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{1,2}$ = 8.5 Hz, H-2), 3.52 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 8.5 Hz, H-3), 3.31–3.35 (m, 2H, H-4, H-5), 1.88 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, CD_3OD) δ 180.4 ($\underline{C}$=O), 132.7 (2 × Ar), 129.7 (Ar), 129.5 (2 × Ar), 124.0 (Ar), 100.7 (C-1, $^1J_{C1,H1}$ = 149.5 Hz), 87.2 ($\underline{C}$≡C), 85.5 ($\underline{C}$≡C), 78.1 (C-4), 75.9 (C-3), 72.1 (C-5), 62.8 (C-6), 57.2 (propargyl $\underline{C}H_2$, C-2), 24.3 (C=O$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{17}H_{21}O_6Na$ $[M + Na]^+$ 358.1261, found 358.1256.

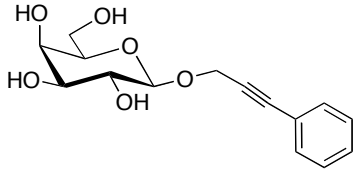
3-Phenylprop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (2.43)



3-Phenyl-2-propyn-1-ol (109 mg, 0.820 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (380 mg, 0.970 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (95.0 mg) and BF_3•OEt_2 (312 μL, 2.50 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 6:1) afforded **2.43** (267 mg, 70%) as a syrup: R_f = 0.36 (hexanes–EtOAc, 2:1); IR (CH_2Cl_2 cast) 2981, 2235 (C≡C), 1748 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.45 (m, 2H, Ar), 7.26–7.36 (m, 3H, Ar), 5.41 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 0.7 Hz, H-4), 5.25 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 5.07 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.81 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.61 (s, 2H, propargyl C$\underline{H}_2$), 4.21 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz,

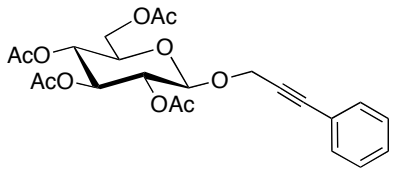
$J_{5,6a}$ = 6.5 Hz, H-6a), 4.15 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6b}$ = 6.5 Hz, H-6b), 3.97 (dt, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, $J_{4,5}$ = 0.7 Hz, H-5), 2.16 (s, 3H, C=OC<u>H</u>$_3$), 2.06 (s, 3H, C=OC<u>H</u>$_3$), 2.04 (s, 3H, C=OC<u>H</u>$_3$), 1.99 (s, 3H, C=OC<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (<u>C</u>=O), 170.2 (<u>C</u>=O), 170.1 (<u>C</u>=O), 169.6 (<u>C</u>=O), 131.7 (2 × Ar), 128.8 (Ar), 128.4 (2 × Ar), 122.2 (Ar), 98.9 (C-1), 87.0 (<u>C</u>≡C), 83.5 (<u>C</u>≡C), 70.9, 70.8, 68.7, 67.0, 61.3, 56.9, 20.8 (C=O<u>C</u>H$_3$), 20.6 (3 × C=O<u>C</u>H$_3$); HRMS (ESI) calcd. for $C_{23}H_{26}O_{10}Na$ $[M + Na]^+$ 485.1418, found 485.1425.

3-Phenylprop-2-ynyl β-D-galactopyranoside (2.44)



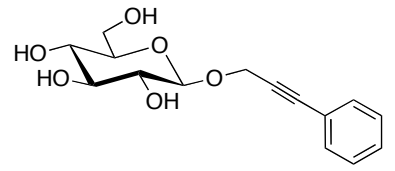
To a solution of **2.43** (240 mg, 0.520 mmol) in CH_3OH (10.0 mL) at rt was added 1 M $NaOCH_3$ solution (160 μL, 0.160 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.44** (150 mg, 98%) as a pale yellow solid: Mp: 82–83 °C; R_f = 0.51 (CH_3OH–EtOAc, 1:4); $[\alpha]_D$ –56.2 (*c* = 0.6, CH_3OH); IR (microscope) 3367 (O–H stretch), 2873, 2224 (C≡C stretch) cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.40–7.42 (m, 2H Ar), 7.29–7.36 (m, 3H, Ar), 4.66 (d, 1H, *J* = 15.6 Hz, propargyl C<u>H</u>$_2$), 4.61 (d, 1H, *J* = 15.6 Hz, propargyl C<u>H</u>$_2$), 4.48 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 3.83 (dd, 1H, $J_{4,5}$ = 1.2 Hz, $J_{3,4}$ = 3.2 Hz, H-4), 3.77 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{5,6a}$ = 6.8 Hz, H-6a), 3.73 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{5,6b}$ = 5.2 Hz, H-6b), 3.56 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{1,2}$ = 7.6 Hz, H-2), 3.52-3.58 (m, 1H, H-5), 3.48 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 3.2 Hz, H-3); ^{13}C NMR (125 MHz, CD_3OD) δ 132.7 (2 × Ar), 129.6 (Ar), 129.4 (2 × Ar), 124.0 (Ar), 103.0 (C-1, $^1J_{C1,H1}$ = 159.2 Hz), 87.2 (<u>C</u>≡C), 85.7 (<u>C</u>≡C), 76.9 (C-5), 74.4 (C-3), 72.4 (C-2), 70.3 (C-4), 62.6 (C-6), 57.3 (propargyl <u>C</u>H$_2$); HRMS (ESI) calcd. for $C_{15}H_{18}O_6Na$ $[M + Na]^+$ 317.0996, found 317.0993.

3-Phenylprop-2-ynyl 2,3,5,6-tetra-*O*-acetyl-β-D-glucopyranoside (2.45)



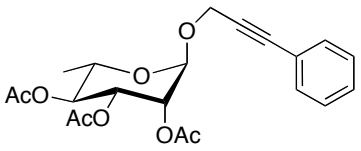
3-Phenyl-2-propyn-1-ol (104 mg, 0.788 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (380 mg, 0.980 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (95.0 mg) and $BF_3 \bullet OEt_2$ (312 μL, 2.50 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 8:1) afforded **2.45** (208 mg, 57%) as a white solid: Mp: 98–99 °C; R_f = 0.35 (hexanes–EtOAc, 2:1); IR (microscope) 2957, 2106 (C≡C), 1753 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.46 (m, 2H, Ar), 7.30–7.38 (m, 3H, Ar), 5.26 (t, 1H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3), 5.12 (t, 1H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 5.05 (dd, 1H, $J_{2,3} = 9.5$ Hz, $J_{1,2} = 8.0$ Hz, H-2), 4.86 (d, 1H, $J_{1,2} = 8.0$ Hz, H-1), 4.60 (s, 2H, propargyl C$\underline{H}_2$), 4.29 (dd, 1H, $J_{6a,6b} = 12.0$ Hz, $J_{5,6a} = 4.5$ Hz, H-6a), 4.17 (dd, 1H, $J_{6a,6b} = 12.0$ Hz, $J_{5,6b} = 2.5$ Hz, H-6b), 3.76 (ddd, 1H, $J_{4,5} = 9.5$ Hz, $J_{5,6a} = 4.5$ Hz, $J_{5,6b} = 2.5$ Hz, H-5), 2.08 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 2.03 (s, 3H, C=OC$\underline{H}_3$), 2.01 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 Hz, $CDCl_3$) δ 170.6 (C=O), 170.2 (C=O), 169.4 (2 × C=O), 131.7 (2 × Ar), 128.8 (Ar), 128.4 (2 × Ar), 122.2 (Ar), 98.4 (C-1), 87.2 (C≡C), 83.4 (C≡C), 72.9, 71.9, 71.1, 68.4, 61.8, 56.9, 20.7 (2 × C=O$\underline{C}H_3$), 20.6 (2 × C=O$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{23}H_{26}O_{10}Na$ $[M + Na]^+$ 485.1418, found 485.1420.

3-Phenylprop-2-ynyl β-D-glucopyranoside (2.46)



To a solution of **2.45** (183 mg, 0.396 mmol) in CH_3OH (10.0 mL) at rt was added 1 M $NaOCH_3$ solution (120 μL, 0.120 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.46** (109 mg, 93%) as a pale yellow solid: Mp: 59–60 °C; R_f = 0.62 (CH_3OH–EtOAc, 1:4); $[\alpha]_D$ –76.3 (*c* = 0.3, CH_3OH); IR (microscope) 3350 (O–H), 2925, 2241 (C≡C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.40–7.42 (m, 2H, Ar), 7.30–7.37 (m, 3H, Ar), 4.66 (d, 1H, *J* = 15.6 Hz, propargyl C$\underline{H}_2$), 4.61 (d, 1H, *J* = 15.6 Hz, propargyl C$\underline{H}_2$), 4.52 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 3.88 (dd, 1H, $J_{6a,6b}$ = 11.8 Hz, $J_{5,6a}$ = 1.8 Hz, H-6a), 3.67 (dd, 1H, $J_{6a,6b}$ = 11.8 Hz, $J_{5,6b}$ = 5.6 Hz, H-6b), 3.38 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.2 Hz, H-3), 3.28–3.30 (m, 2H, H-4, H-5), 3.22 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{1,2}$ = 8.0 Hz, H-2); ^{13}C NMR (125 Hz, CD_3OD) δ 132.7 (2 × Ar), 129.6 (Ar), 129.5 (2 × Ar), 124.0 (Ar), 102.4 (C-1, $^1J_{C1,H1}$ = 159.2 Hz), 87.3 (C≡C), 85.6 (C≡C), 78.1 (C-4), 78.0 (C-3), 75.0 (C-2), 71.7 (C-5), 62.8 (C-6), 57.4 (C-7); HRMS (ESI) calcd. for $C_{15}H_{18}O_6Na$ $[M + Na]^+$ 317.0996, found 317.0998.

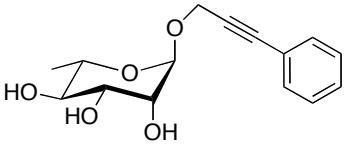
3-Phenylprop-2-ynyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (2.47)



3-Phenyl-2-propyn-1-ol (100 mg, 0.758 mmol) was coupled with 1,2,3,4-tetra-*O*-acetyl-L-rhamnopyranose (380 mg, 1.14 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (100 mg) and BF_3•OEt_2 (285 μL, 2.50 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 8:1) afforded **2.47** (222 mg, 73%) as a white solid: Mp: 138–139 °C; R_f = 0.29 (hexanes–EtOAc, 3:1); IR (microscope) 2982, 1742 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.46 (m, 2H, Ar), 7.28–7.37 (m, 3H, Ar), 5.34 (dd, 1H, $J_{3,4}$ = 10.0 Hz, $J_{2,3}$ = 3.5 Hz, H-3), 5.31 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{1,2}$ = 1.5 Hz, H-2), 5.10 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H-4), 5.02 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.48 (s, 2H, propargyl C$\underline{H}_2$), 3.97 (dq, 1H, $J_{4,5}$ = 10.0 Hz,

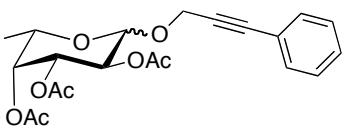
$J_{5,6}$ = 6.5 Hz, H-5), 2.16 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 1.99 (s, 3H, C=OC$\underline{H}_3$), 1.25 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (3 × $\underline{C}$=O), 131.8 (2 × Ar), 128.6 (Ar), 128.3 (2 × Ar), 122.3 (Ar), 96.2 (C-1), 86.8 ($\underline{C}$≡C), 83.5 ($\underline{C}$≡C), 71.1, 69.8, 69.1, 66.9, 55.6, 20.9 (C=O$\underline{C}H_3$), 20.8 (C=O$\underline{C}H_3$), 20.7 (C=O$\underline{C}H_3$), 17.4 (C-6); HRMS (ESI) calcd. for $C_{21}H_{24}O_8Na$ [M + Na]$^+$ 427.1363, found 427.1361.

3-Phenylprop-2-ynyl α-L-rhamnopyranoside (2.48)



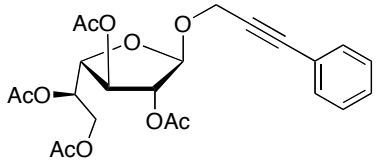
To a solution of **2.47** (190 mg, 0.470 mmol) in CH_3OH (5.00 mL) at rt was added 1 M $NaOCH_3$ solution (140 μL, 0.140 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 1:3) afforded **2.48** (128 mg, 98%) as a pale yellow solid: Mp: 34–35 °C; R_f = 0.59 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ –94.1 (*c* = 0.3, CH_3OH); IR (microscope) 3356 (O–H), 2922, 2101 (C≡C) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.41–7.43 (m, 2H, Ar), 7.30–7.38 (m, 3H, Ar), 4.92 (d, 1H, $J_{1,2}$ = 1.7 Hz, H-1), 4.47 (d, 1H, *J* = 16.0 Hz, propargyl C$\underline{H}_2$), 4.43 (d, 1H, *J* = 16.0 Hz, propargyl C$\underline{H}_2$), 3.83 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{1,2}$ = 1.7 Hz, H-2), 3.62–3.68 (m, 2H, H-3, H-5), 3.40 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 1.27 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, CD_3OD) δ 132.7 (2 × Ar), 129.7 (Ar), 129.5 (2 × Ar), 123.9 (Ar), 100.4 (C-1), 87.0 ($\underline{C}$≡C), 85.6 ($\underline{C}$≡C), 73.9 (C-4), 72.3 (C-3), 72.2 (C-2), 70.3 (C-5), 55.8 (propargyl $\underline{C}H_2$), 18.0 (C-6); HRMS (ESI) calcd. for $C_{15}H_{18}O_5Na$ [M + Na]$^+$ 301.1046, found 301.1046.

3-Phenylprop-2-ynyl 2,3,4-tri-*O*-acetyl-L-fucopyranoside (2.49)



3-Phenyl-2-propyn-1-ol (100 mg, 0.758 mmol) was coupled with 1,2,3,4-tetra-*O*-acetyl-L-fucopyranose (380 mg, 1.14 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (100 mg) and BF_3•OEt_2 (285 μL, 2.50 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 8:1) afforded **2.49** (α:β = 2:3, 240 mg, 74%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) β : δ 7.43–7.46 (m, 2H, Ar), 7.32–7.35 (m, 3H, Ar), 5.25 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 0.5 Hz, H-4), 5.23 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 5.07 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.79 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.61 (s, 2H, propargyl C$\underline{H}_2$), 3.86 (m, 1H, H-5), 2.18 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 1.99 (s, 3H, C=OC$\underline{H}_3$), 1.25 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6); α: δ 7.43–7.46 (m, 2H, Ar), 7.32–7.35 (m, 3H, Ar), 5.32 (s, 1H, H-1), 5.18 (m, 1H, H-5), 5.13 (d, 1H, $J_{2,3}$ = 1.5 Hz, H-2), 5.04 (dd, 1H, $J_{3,4}$ = 6.0 Hz, $J_{2,3}$ = 1.5 Hz, H-3), 4.48 (d, 1H, J = 16.0 Hz, propargyl C$\underline{H}_2$), 4.52 (d, 1H, J = 16.0 Hz, propargyl C$\underline{H}_2$), 4.16 (dd, 1H, $J_{3,4}$ = 6.0 Hz, $J_{4,5}$ = 4.0 Hz, H-4), 2.11 (s, 3H, C=OC$\underline{H}_3$), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.08 (s, 3H, C=OC$\underline{H}_3$), 1.33 (d, 3H, $J_{5,6}$ = 7.0 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2 ($\underline{C}$=O), 167.7 (2 × $\underline{C}$=O), 167.5 ($\underline{C}$=O), 167.2 ($\underline{C}$=O), 167.1 ($\underline{C}$=O), 129.3 (Ar), 129.2 (2 × Ar), 126.2 (Ar), 126.1 (Ar), 125.9 (2 × Ar), 125.8 (Ar), 119.9 (Ar), 119.8 (Ar), 101.4, 96.2, 84.3, 84.0, 81.4, 81.3, 80.7, 79.2, 68.9 (2 ×), 67.7(2 ×), 66.8, 66.3(2 ×), 66.2, 54.2, 52.6, 20.4 (6 × C=O$\underline{C}$H$_3$), 18.2 (2×).

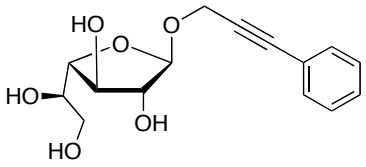
3-Phenylprop-2-ynyl 2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranoside (2.50)



3-Phenyl-2-propyn-1-ol (101 mg, 0.765 mmol) was coupled with methyl 2,3,5,6-tetra-*O*-acetyl-D-galactofuranoside (330 mg, 0.990 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (100 mg) and BF_3•OEt_2

(285 μL, 2.30 mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 50:1) afforded **2.50** (272 mg, 77%) as a syrup: R_f = 0.32 (CH_2Cl_2–EtOAc, 12:1); IR (microscope) 2953, 2240 (C≡C), 1748 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.45 (m, 2H, Ar), 7.30–7.39 (m, 3H, Ar), 5.40 (dt, 1H, $J_{5,6a}$ = 6.8 Hz, $J_{4,5}$ = $J_{5,6b}$ = 4.0 Hz, H-5), 5.33 (s, 1H, H-1), 5.14 (d, 1H, $J_{2,3}$ = 2.0 Hz, H-2), 5.04 (dd, 1H, $J_{3,4}$ = 6.0 Hz, $J_{2,3}$ = 2.0 Hz, H-3), 4.51 (d, 1H, J = 16.0 Hz, propargyl C$\underline{H}_2$), 4.47 (d, 1H, J = 16.0 Hz, propargyl C$\underline{H}_2$), 4.36 (dd, 1H, $J_{6a,6b}$ = 11.6 Hz, $J_{5,6b}$ = 4.0 Hz, H-6b), 4.32 (dd, 1H, $J_{3,4}$ = 6.0 Hz, $J_{4,5}$ = 4.0 Hz, H-4), 4.25 (dd, 1H, $J_{6a,6b}$ = 11.6 Hz, $J_{5,6a}$ = 6.8 Hz, H-6a), 2.14 (s, 3H, C=OC$\underline{H}_3$), 2.12 (s, 3H, C=OC$\underline{H}_3$), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.06 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C=O), 170.0 (2 × C=O), 169.5 (C=O), 131.8 (2 × Ar), 128.6 (Ar), 128.3 (2 × Ar), 122.3 (Ar), 103.9 (C-1), 86.7 (C≡C), 83.4 (C≡C), 81.3 80.4, 76.7, 69.3, 62.6, 55.2 (propargyl $\underline{C}H_2$), 20.8 (2 × C=O$\underline{C}H_3$), 20.7 (2 × C=O$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{23}H_{26}O_{10}Na$ $[M + Na]^+$ 485.1418, found 485.1419.

3-Phenylprop-2-ynyl β-D-galactofuranoside (2.51)

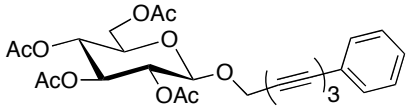


To a solution of **2.50** (250 mg, 0.540 mmol) in CH_3OH (10.0 mL) at rt was added $NaOCH_3$ solution (54.0 μL, 0.054 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.51** (145 mg, 97%) as an oil: R_f = 0.24 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ –83.8 (c = 1.0, CH_3OH); IR (microscope) 3338 (O–H), 2930, 2272 (C≡C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.40–7.42 (m, 2H, Ar), 7.30–7.34 (m, 3H, Ar), 5.16 (d, 1H, $J_{1,2}$ = 2.0 Hz, H-1), 4.48 (s, 2H, propargyl C$\underline{H}_2$), 4.04 (dd, 1H, $J_{3,4}$ = 6.0 Hz, $J_{2,3}$ = 3.5 Hz, H-3), 4.00 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{1,2}$ = 2.0 Hz, H-2), 3.97 (dd, 1H, $J_{3,4}$ = 6.0 Hz, $J_{4,5}$ = 3.5

Hz, H-4), 3.73 (ddd, 1H, $J_{5,6a}$ = 7.0 Hz, $J_{4,5}$ = 3.5 Hz, $J_{5,6b}$ = 6.0 Hz, H-5), 3.64 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6b}$ = 6.0 Hz, H-6b), 3.62 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6a}$ = 7.0 Hz, H-6a); ^{13}C NMR (125 MHz, CD_3OD) δ 132.7 (2 × Ar), 129.6 (2 × Ar), 129.5 (Ar), 124.0 (Ar), 107.6 (C-1), 86.9 (C≡C), 85.7 (C≡C), 84.9, 83.5, 79.1, 72.5, 64.5 (C-6), 55.5 (propargyl CH_2); HRMS (ESI) calcd. for $C_{15}H_{18}O_6Na$ $[M + Na]^+$ 317.0996, found 317.0992.

3.3.3 Procedure for the synthesis of triyne glycosides

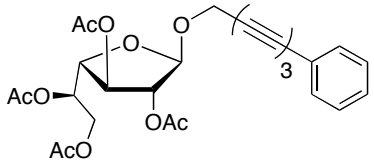
7-Phenylhepta-2,4,6-triynyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (1.56)



Alcohol **1.52** (40.0 mg, 0.220 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (113 mg, 0.290 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (60.0 mg) and BF_3•OEt_2 (96.0 μL, 0.750 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 4:1) afforded **1.56** (68.0 mg, 61%) as a syrup: R_f = 0.48 (hexanes–EtOAc, 1:1); IR (CH_2Cl_2, microscope) 2957, 2191 (C≡C), 1755 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55–7.57 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 5.25 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.6 Hz, H-3), 5.11 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.6 Hz, H-4), 5.02 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 4.75 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.52 (d, 1H, J = 17.2 Hz, propargyl CH_2), 4.47 (d, 1H, J = 17.2 Hz, propargyl CH_2), 4.28 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6a}$ = 4.8 Hz, H-6a), 4.16 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6b}$ = 2.4 Hz, H-6b), 3.75 (ddd, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{5,6b}$ = 2.4 Hz, H-5), 2.10 (s, 3H, C=OCH_3), 2.09 (s, 3H, C=OCH_3), 2.04 (s, 3H, C=OCH_3), 2.02 (s, 3H, C=OCH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 170.6 (C=O), 170.2 (C=O), 169.4 (2 × C=O), 133.1 (2 × Ar), 129.9 (Ar), 128.5 (2 × Ar), 120.6 (Ar), 98.5 (C-1), 77.6 (C≡C), 74.4 (C≡C), 73.9 (C≡C), 72.7, 72.2 (C≡C), 72.1, 71.0, 68.2, 65.5 (C≡C), 63.7 (C≡C), 61.7, 56.7, 20.7 (2 × C=OCH_3), 20.6 (2 ×

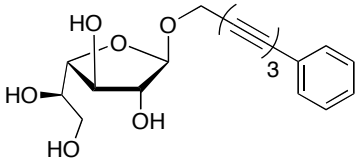
C=O<u>C</u>H$_3$); HRMS (ESI) calcd. for $C_{27}H_{26}O_{10}Na$ [M + Na]$^+$ 533.1418, found 533.1417.

7-Phenylhepta-2,4,6-triynyl 2,3,5,6-tetra-*O*-acetyl-β-D-galactofuranoside (2.53)



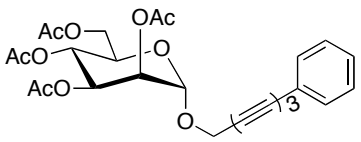
Alcohol **1.52** (84.0 mg, 0.460 mmol) was coupled with methyl 2,3,5,6-tetra-*O*-acetyl-D-galactofuranoside (430 mg, 1.19 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (80.0 mg) and BF_3•OEt_2 (107 μL, 1.47 mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 50:1) afforded **2.53** (176 mg, 74%) as a syrup: R_f = 0.37 (CH_2Cl_2–EtOAc, 12:1); IR (CH_2Cl_2, microscope) 2956, 2192 (C≡C), 1748 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.54 (m, 2H, Ar), 7.32–7.42 (m, 3H, Ar), 5.38 (dt, 1H, $J_{5,6a}$ = 7.0 Hz, $J_{5,6b}$ = $J_{4,5}$ = 4.0 Hz, H-5), 5.22 (br s, 1H, H-1), 5.10 (dd, 1H, $J_{2,3}$ = 2.0 Hz, $J_{1,2}$ = 0.5 Hz, H-2), 5.04 (ddd, 1H, $J_{3,4}$ = 5.5 Hz, $J_{2,3}$ = 2.0 Hz, $J_{1,3}$ = 0.5 Hz, H-3), 4.40 (d, 1H, J = 17.0 Hz, propargyl C<u>H</u>$_2$), 3.36 (d, 1H, J = 17.0 Hz, propargyl C<u>H</u>$_2$), 3.45 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 4.0 Hz, H-6b), 4.29 (dd, 1H, $J_{3,4}$ = 5.5 Hz, $J_{4,5}$ = 4.0 Hz, H-4), 4.24 (dd, 1H, $J_{6a,6b}$ = 12.0, $J_{5,6a}$ = 7.0 Hz, H-6a), 2.15 (s, 3H, C=OC<u>H</u>$_3$), 2.13 (s, 3H, C=OC<u>H</u>$_3$), 2.10 (s, 3H, C=OC<u>H</u>$_3$), 2.08 (s, 3H, C=OC<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (<u>C</u>=O), 169.9 (2 × <u>C</u>=O), 169.5 (<u>C</u>=O), 133.0 (2 × Ar), 129.9 (Ar), 128.5 (2 × Ar), 120.7 (Ar), 104.4 (C-1), 81.2, 80.6, 76.6, 74.9 (<u>C</u>≡C), 74.0 (<u>C</u>≡C), 71.7 (<u>C</u>≡C), 69.3, 65.8 (<u>C</u>≡C), 63.4 (<u>C</u>≡C), 62.5, 55.0, 20.8 (C=O<u>C</u>H$_3$), 20.7 (3 × C=O<u>C</u>H$_3$), (one <u>C</u>≡C not observed); HRMS (ESI) calcd. for $C_{27}H_{26}O_{10}Na$ [M + Na]$^+$ 533.1418, found 533.1417.

7-Phenylhepta-2,4,6-triynyl β-D-galactofuranoside (2.54)



To a solution of **2.53** (162 mg, 0.318 mmol) in CH_3OH (6.00 mL) at rt was added 1 M $NaOCH_3$ solution (93.0 μL, 0.093 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.54** (56.0 mg, 51%) as an oil: R_f = 0.64 (CH_3OH–EtOAc, 1:4); $[\alpha]_D$ –101.2 (*c* = 0.44, CH_3OH); IR (CH_2Cl_2 cast) 3317 (O–H), 2926, 2449, 2194 (C≡C) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.51–7.54 (m, 2H, Ar), 7.34–7.46 (m, 3H, Ar), 5.03 (d, 1H, $J_{1,2}$ = 1.2 Hz, H-1), 4.42 (d, 1H, *J* = 17.2 Hz, propargyl C$\underline{H}_2$), 4.37 (d, 1H, *J* = 17.2 Hz, propargyl C$\underline{H}_2$), 4.04 (dd, 1H, $J_{3,4}$ = 8.0 Hz, $J_{2,3}$ = 4.0 Hz, H-3), 3.98 (dd, 1H, $J_{2,3}$ = 4.0 Hz, $J_{1,2}$ = 1.2 Hz, H-2), 3.94 (dd, 1H, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 4.0 Hz, H-4), 3.71–3.75 (m, 1H, H-5), 3.62–3.64 (m, 2H, H-6a, H-6b); ^{13}C NMR (100 MHz, CD_3OD) δ 133.9 (2 × Ar), 131.1 (Ar), 129.6 (2 × Ar), 121.5 (Ar), 107.9 (C-1, $^1J_{C1,H1}$ = 173.0 Hz), 84.8 (C-4), 83.3 (C-2), 78.8 (C-3), 77.9 (C$\underline{\equiv}$C), 77.6 (C$\underline{\equiv}$C), 74.2 (C$\underline{\equiv}$C), 72.2 (C-5), 71.0 (C$\underline{\equiv}$C), 66.4 (C$\underline{\equiv}$C), 64.3 (C-6), 63.1 (C$\underline{\equiv}$C), 55.2 (propargyl C$\underline{H}_2$); HRMS (ESI) calcd. for $C_{19}H_{18}O_6Na$ $[M + Na]^+$ 365.0996, found 365.0998.

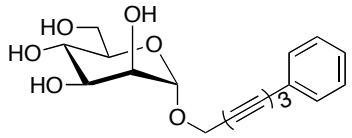
7-Phenylhepta-2,4,6-triynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (1.58)



Alcohol **1.52** (54.0 mg, 0.300 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-D-mannopyranose (148 mg, 0.380 mmol) in CH_2Cl_2 (7.00 mL) in the presence of

crushed activated 4 Å molecular sieves (50.0 mg) and BF_3•OEt_2 (115 μL, 1.47 mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 60:1) afforded **1.58** (50.0 mg, 33%) as a syrup: R_f = 0.22 (CH_2Cl_2–EtOAc, 30:1); IR (CH_2Cl_2, cast) 2955, 2192 (C≡C), 1752 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.54 (m, 2H, Ar), 7.31–7.42 (m, 3H, Ar), 5.27-5.33 (m, 3H, H-2, H-3, H-4), 5.00 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1), 4.44 (d, 1H, J = 17.2 Hz, propargyl C$\underline{H}_2$), 4.37 (d, 1H, J = 17.2 Hz, propargyl C$\underline{H}_2$), 4.31 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6a}$ = 5.2 Hz, H-6a), 4.12 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6b}$ = 2.4 Hz, H-6b), 4.02–4.05 (m, 1H, H-5), 2.18 (s, 3H, C=OC$\underline{H}_3$), 2.13 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 2.00 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C=O), 169.9 (C=O), 169.8 (C=O), 169.7 (C=O), 133.1 (2 × Ar), 129.9 (Ar), 128.5 (2 × Ar), 120.6 (Ar), 96.9 (C-1), 77.6 (C≡C), 74.2 (C≡C), 74.0 (C≡C), 72.2 (C≡C), 69.3, 69.2, 68.9, 66.0, 65.5 (C≡C), 63.8 (C≡C), 62.3, 55.8, 20.8 (C=OCH$_3$), 20.7 (2 × C=OCH$_3$), 20.6 (C=OCH$_3$); HRMS (ESI) calcd. for $C_{27}H_{26}O_{10}Na$ $[M + Na]^+$ 533.1418, found 533.1418.

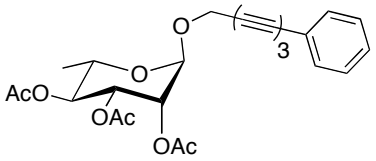
7-Phenylhepta-2,4,6-triynyl α-D-mannopyranoside (1.61)



To a solution of **1.58** (45.0 mg, 0.088 mmol) in CH_3OH (3.00 mL) at rt was added 1 M $NaOCH_3$ solution (31.0 μL, 0.030 mmol) as described in the general procedure. Purification by column chromatography (CH_3OH–EtOAc, 1:20) afforded **1.61** (22.0 mg, 64%) as an oil: R_f = 0.29 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ +110.3 (c = 0.1, CH_3OH); IR (microscope) 3356 (O–H), 2927, 2191 (C≡C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.52–7.54 (m, 2H, Ar), 7.35–7.46 (m, 3H, Ar), 4.92 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.45 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 4.41 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 3.84 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.5 Hz, H-6a), 3.80 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{1,2}$ = 1.5 Hz, H-2), 3.71 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz,

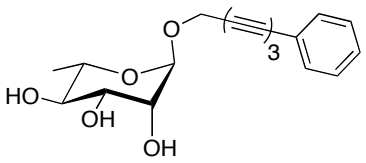
$J_{5,6b}$ = 5.5 Hz, H-6b), 3.66 (dd, 1H, $J_{3,4}$ = 9.5 Hz, $J_{2,3}$ = 3.0 Hz, H-3), 3.63 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 3.50 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6b}$ = 5.5 Hz, $J_{5,6a}$ = 2.5 Hz, H-5); ^{13}C NMR (125 MHz, CD_3OD) δ 134.0 (2 × Ar), 131.3 (Ar), 129.8 (2 × Ar), 121.7 (Ar), 100.6 (C-1, $^{1}J_{C1,H1}$ = 171.7 Hz), 78.2 (C≡C), 77.4 (C≡C), 75.3 (C-5), 74.2 (C≡C), 72.4 (C-3), 71.9 (C-2), 71.4 (C≡C), 68.4 (C-4), 66.4 (C≡C), 63.4 (C≡C), 62.8 (C-6), 55.5 (propargyl CH_2); HRMS (ESI) calcd. for $C_{21}H_{20}O_7Na$ [M + Na]$^+$ 365.0996, found 365.0998.

7-Phenylhepta-2,4,6-triynyl 2,3,4-tri-*O*-acetyl-α-L-rhamnopyranoside (2.55)



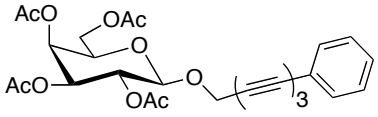
Alcohol **1.52** (54.0 mg, 0.300 mmol) was coupled with 1,2,3,4-tetra-*O*-acetyl-L-rhamnopyranose (150 mg, 0.450 mmol) in CH_2Cl_2 (5.00 mL) in the presence of crushed activated 4 Å molecular sieves (50.0 mg) and BF_3•OEt_2 (100 μL, 0.900 mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 70:1) afforded **2.55** (109 mg, 80%) as a syrup: R_f = 0.50 (CH_2Cl_2–EtOAc, 30:1); IR (microscope) 2985, 2938, 2192 (C≡C), 1749 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.55 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 5.26-5.30 (m, 2H, H-2, H-3), 5.10 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H-4), 4.91 (s, 1H, H-1), 4.42 (d, 1H, J = 16.8 Hz, propargyl CH_2), 4.34 (d, 1H, J = 16.8 Hz, propargyl CH_2), 3.92 (dq, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6}$ = 6.4 Hz, H-5), 2.17 (s, 3H, C=OCH_3), 2.06 (s, 3H, C=OCH_3), 1.99 (s, 3H, C=OCH_3), 1.25 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9 (3 × C=O), 133.0 (2 × Ar), 129.8 (Ar), 128.5 (2 × Ar), 120.6 (Ar), 96.8 (C-1), 77.4 (C≡C), 74.6 (C≡C), 74.1 (C≡C), 71.8 (C≡C), 70.8, 69.5, 68.9, 67.1, 65.6 (C≡C), 63.5 (C≡C), 55.6, 20.9 (C=OCH_3), 20.8 (C=OCH_3), 20.7 (C=OCH_3), 17.3 (C-6); HRMS (ESI) calcd. for $C_{25}H_{24}O_8Na$ [M + Na]$^+$ 475.1361, found 475.1363.

7-Phenylhepta-2,4,6-triynyl α-L-rhamnopyranoside (2.56)



To a solution of **2.55** (100 mg, 0.221 mmol) in CH_3OH (7.00 mL) at rt was added 1 M $NaOCH_3$ solution (66.0 μL, 0.066 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.56** (47.0 mg, 65%) as an oil: R_f = 0.59 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ –15.9 (*c* = 0.8, CH_3OH); IR (CH_2Cl_2 cast) 3380 (O–H), 2926, 2192 (C≡C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.55–7.57 (m, 2H, Ar), 7.38–7.44 (m, 3H, Ar), 4.81 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.41 (d, 1H, *J* = 17.2 Hz, propargyl C$\underline{H}_2$), 4.36 (d, 1H, *J* = 17.2 Hz, propargyl C$\underline{H}_2$), 3.80 (dd, 1H, $J_{2,3}$ = 3.5 Hz, $J_{1,2}$ = 1.5 Hz, H-2), 3.61 (dd, 1H, $J_{3,4}$ = 10.0 Hz, $J_{2,3}$ = 3.5 Hz, H-3). 3.57–3.60 (m, 1H, H-5), 3.39 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H-4), 1.27 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, CD_3OD) δ 134.0 (2 × Ar), 131.3 (Ar), 129.8 (2 × Ar), 121.7 (Ar), 101.1 (C-1), 78.2 (C≡C), 77.6 (C≡C), 74.2 (C≡C), 73.8 (C-4), 72.2 (C-3), 72.0 (C-2), 71.1 (C≡C), 70.5 (C-5), 66.4 (C≡C), 63.4 (C≡C), 55.8 (propargyl $\underline{C}H_2$), 17.9 (C-6); HRMS (ESI) calcd. for $C_{19}H_{18}O_5Na$ $[M + Na]^+$ 349.1046, found 349.1047.

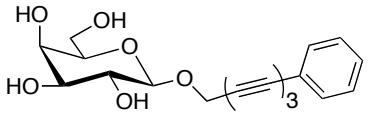
7-Phenylhepta-2,4,6-triynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (1.57)



Alcohol **1.52** (88.0 mg, 0.490 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (330 mg, 0.840 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (60.0 mg) and BF_3•OEt_2 (186 μL, 1.47

mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 50:1) afforded **1.57** (194 mg, 78%) as a syrup: R_f = 0.48 (CH_2Cl_2–EtOAc, 12:1); IR (CH_2Cl_2, cast) 2980, 2192 (C≡C), 1752 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.54 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 5.41 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 5.22 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 5.07 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.71 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 5.52 (d, 1H, J = 17.5 Hz, propargyl C$\underline{H}_2$), 4.48 (d, 1H, J = 17.5 Hz, propargyl C$\underline{H}_2$), 4.18 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6a}$ = 6.5 Hz, H-6a), 4.15 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6b}$ = 6.5 Hz, H-6b), 3.95 (dt, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 2.16 (s, 3H, C=OC$\underline{H}_3$), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.07 (s, 3H, C=OC$\underline{H}_3$), 1.99 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (C=O), 170.2 (C=O), 170.0 (C=O), 169.6 (C=O), 133.1 (2 × Ar), 129.9 (Ar), 128.5 (2 × Ar), 120.6 (Ar), 99.1 (C-1), 77.6 (C≡C), 74.5 (C≡C), 74.0 (C≡C), 72.1 (C≡C), 71.0, 70.8, 68.5, 66.6, 65.6 (C≡C), 63.6 (C≡C), 61.3, 56.7, 20.8 (C=OC$\underline{H}_3$), 20.7 (C=OC$\underline{H}_3$), 20.6 (2 × C=OC$\underline{H}_3$); HRMS (ESI) calcd. for $C_{27}H_{26}O_{10}Na$ $[M + Na]^+$ 533.1418, found 533.1417.

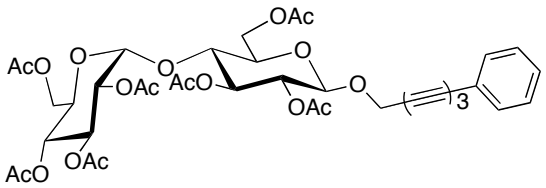
7-Phenylhepta-2,4,6-triynyl β-D-galactopyranoside (1.60)



To a solution of **1.57** (161 mg, 0.316 mmol) in CH_3OH (5.00 mL) at rt was added 1 M $NaOCH_3$ solution (93.0 μL, 0.090 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **1.60** (68.0 mg, 64%) as a pale brown solid: Mp: 138–139 °C; R_f = 0.53 (CH_3OH–EtOAc, 1:4); $[\alpha]_D$ –83.0 (c = 0.4, CH_3OH); IR (microscope) 3498 (O–H), 2958, 2192 (C≡C) 688 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.53–7.55 (m, 2H, Ar), 7.37–7.47 (m, 3H, Ar), 4.57 (s, 2H, propargyl C$\underline{H}_2$), 4.38 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1), 3.83 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 3.77 (dd, 1H, $J_{6a,6b}$ = 11.4 Hz, $J_{5,6a}$

= 7.0 Hz, H-6a), 3.71 (dd, 1H, $J_{6a,6b}$ = 11.4 Hz, $J_{5,6b}$ = 5.0 Hz, H-6b), 3.53 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{1,2}$ = 7.2 Hz, H-2), 3.51–3.55 (m, 1H, H-5), 3.48 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 3.2 Hz, H-3); ^{13}C NMR (125 MHz, CD_3OD) δ 134.0 (2 × Ar), 131.2 (Ar), 129.8 (2 × Ar), 121.7 (Ar), 103.2 (C-1, $^1J_{C1,H1}$ = 158.5 Hz), 78.2 (C≡C), 77.6 (C≡C), 77.0 (C-5), 74.9 (C-3), 74.3 (C≡C), 72.3 (C-2), 71.5 (C≡C), 70.3 (C-4), 66.6 (C≡C), 63.4 (C≡C), 62.6 (C-6), 57.0 (propargyl CH_2); HRMS (ESI) calcd. for $C_{19}H_{18}O_6Na$ $[M + Na]^+$ 365.0996, found 365.0997.

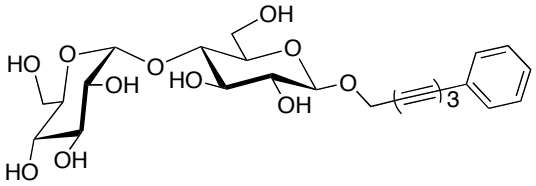
7-Phenylhepta-2,4,6-triynyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranoside (2.57)



Alcohol **1.52** (81.0 mg, 0.450 mmol) was coupled with 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-β-D-glucopyranose (460 mg, 0.840 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (100 mg) and BF_3•OEt_2 (100 μL, 1.38 mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 30:1) afforded **2.57** (277 mg, 77%) as a brown solid: R_f = 0.28 (CH_2Cl_2–EtOAc, 6:1); IR (microscope) 2960, 2192 (C≡C), 1754 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.58 (m, 2H, Ar), 7.32–7.41 (m, 3H, Ar), 5.42 (d, 1H, $J_{1',2'}$ = 4.5 Hz, H-1′), 5.36 (dd, 1H, $J_{2',3'}$ = 10.5 Hz, $J_{3',4'}$ = 9.8 Hz, H-3′), 5.29 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.3 Hz, H-3), 5.06 (t, 1H, $J_{3',4'}$ = $J_{4',5'}$ = 9.8 Hz, H-4′), 4.86 (dd, 1H, $J_{2',3'}$ = 10.5 Hz, $J_{1',2'}$ = 4.5 Hz, H-2′), 4.87 (dd, 1H, $J_{2,3}$ = 9.3 Hz, $J_{1,2}$ = 7.5 Hz, H-2), 4.77 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 4.51 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6a}$ = 2.7 Hz, H-6a), 4.49 (d, 1H, J = 17.0 Hz, propargyl CH_2), 4.45 (d, 1H, J = 17.0 Hz, propargyl CH_2), 4.26 (dd, 1H, $J_{6'a,6'b}$ = 12.5 Hz, $J_{5',6'a}$ = 3.5 Hz, H-6′a), 4.24 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6b}$ = 4.2 Hz, H-6b), 4.05 (dd, 1H, $J_{6'a,6'a}$ = 12.5 Hz, $J_{5',6'b}$ = 2.0 Hz, H-

6′b), 4.02 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.3 Hz, H-4), 3.96 (ddd, 1H, $J_{4',5'}$ = 9.8 Hz, $J_{5',6'a}$ = 3.5 Hz, $J_{5',6'b}$ = 2.0 Hz, H-5′), 3.74 (ddd, 1H, $J_{4,5}$ = 9.3 Hz, $J_{5,6b}$ = 4.2 Hz, $J_{5,6a}$ = 2.7 Hz, H-5), 2.16 (s, 3H, C=OC$\underline{H}_3$), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.06 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 2.03 (s, 3H, C=OC$\underline{H}_3$), 2.02 (s, 3H, C=OC$\underline{H}_3$), 2.00 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, CD_3OD) δ 170.5 (2 × $\underline{C}$=O), 170.4 ($\underline{C}$=O), 170.1 ($\underline{C}$=O), 169.9 ($\underline{C}$=O), 169.7 ($\underline{C}$=O), 169.4 ($\underline{C}$=O), 133.1 (2 × Ar), 129.9 (Ar), 128.5 (2 × Ar), 120.6 (Ar), 98.0, 95.6, 77.6 ($\underline{C}$≡C), 75.3, 74.3 ($\underline{C}$≡C), 74.0 ($\underline{C}$≡C), 72.6, 72.4, 72.2 ($\underline{C}$≡C), 71.8, 70.0, 69.4, 68.5, 68.0, 65.6 ($\underline{C}$≡C), 63.7 ($\underline{C}$≡C), 62.6, 61.5, 56.6, 20.9 (C=O$\underline{C}H_3$), 20.8 (C=O$\underline{C}H_3$), 20.7 (2 × C=O$\underline{C}H_3$), 20.6 (3 × C=O$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{39}H_{42}O_{18}Na$ $[M + Na]^+$ 821.2263, found 821.2263.

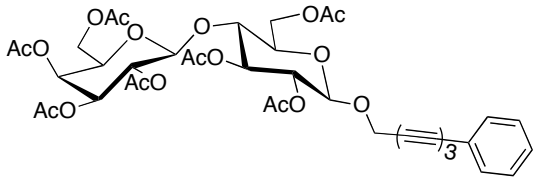
7-Phenylhepta-2,4,6-triynyl 4-*O*-(α-D-glucopyranosyl)-β-D-glucopyranoside (2.58)



To a solution of **1.60** (260 mg, 0.320 mmol) in CH_3OH (10.0 mL) at rt was added 1 M $NaOCH_3$ solution (96.0 μL, 0.096 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.58** (107 mg, 65%) as a brown solid: Mp: 101–102 °C; R_f = 0.40 (CH_3OH–EtOAc, 1:4); $[\alpha]_D$ –26.2 (*c* = 0.2, CH_3OH); IR (microscope) 3350 (O–H), 2927, 2191(C≡C) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.54–7.56 (m, 2H, Ar), 7.37–7.45 (m, 3H, Ar), 5.16 (d, 1H, $J_{1',2'}$ = 4.0 Hz, H-1′), 4.57 (s, 2H, propargyl C$\underline{H}_2$), 4.44 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 3.90 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 3.79–3.83 (m, 2H, H-6b, H-6′a), 3.64–3.70 (m, 2H, H-5′, H-6′b), 3.65 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.3 Hz, H-3), 3.61 (t, 1H, $J_{2',3'} = J_{3',4'}$ = 9.5 Hz, H-3′), 3.54 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.3 Hz, H-4), 3.44 (dd, 1H, $J_{2',3'}$ = 9.5 Hz, $J_{1',2'}$ = 4.0 Hz, H-2′), 3.40 (ddd, 1H, $J_{4,5}$ = 9.3

Hz, $J_{5,6b}$ = 4.5 Hz, $J_{5,6a}$ = 2.0 Hz, H-5), 3.26 (t, 1H, $J_{3',4'} = J_{4',5'}$ = 9.5 Hz, H-4′), 3.25 (dd, 1H, $J_{2,3}$ = 9.3 Hz, $J_{1,2}$ = 8.0 Hz, H-2); ^{13}C NMR (125 MHz, CD_3OD) δ 134.0 (2 × Ar), 131.3 (Ar), 129.8 (2 × Ar), 121.7 (Ar), 102.9 (C-1′, $^1J_{C1',H1'}$ = 170.0 Hz), 102.6 (C-1, $^1J_{C1,H1}$ = 161.0 Hz), 81.1 (C-4), 78.2 (C≡C), 77.7 (C-3), 77.4 (C≡C), 76.8 (C-5), 75.1 (C-3′), 74.8 (C-5′), 74.5 (C-2), 74.3 (C≡C), 74.2 (C-2′), 71.6 (C≡C), 71.5 (C-4′), 66.6 (C≡C), 63.5 (C≡C), 62.8 (C-6′), 62.2 (C-6), 57.2 (propargyl CH_2); HRMS (ESI) calcd. for $C_{25}H_{28}O_{11}Na$ $[M + Na]^+$ 527.1524, found 527.1522.

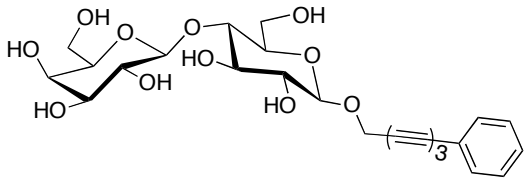
7-Phenylhepta-2,4,6-triynyl 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside (2.59)



Alcohol **1.52** (85.0 mg, 0.460 mmol) was coupled with 1,2,3,6-tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranose (460 mg, 0.840 mmol) in CH_2Cl_2 (10.0 mL) in the presence of crushed activated 4 Å molecular sieves (100 mg) and BF_3•OEt_2 (100 μL, 1.38 mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 50:1) afforded **2.59** (278 mg, 74%) as a brown solid: R_f = 0.19 (CH_2Cl_2–EtOAc, 4:1); IR (microscope) 2961, 2192 (C≡C), 1753 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.55 (m, 2H, Ar), 7.31–7.42 (m, 3H, Ar), 5.35 (dd, 1H, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 1.0 Hz, H-4′), 5.24 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.5 Hz, H-3), 5.12 (dd, 1H, $J_{2',3'}$ = 10.5 Hz, $J_{1',2'}$ = 7.5 Hz, H-2′), 4.96 (dd, 1H, $J_{2',3'}$ = 10.5 Hz, $J_{3',4'}$ = 3.5 Hz, H-3′), 4.92 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 4.71 (d, 1H, $J_{1',2'}$ = 7.5 Hz, H-1′), 4.52 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.5 Hz, H-6a), 4.49 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.47 (d, 1H, J = 17.5 Hz, propargyl CH_2), 4.44 (d, 1H, J = 17.5 Hz, propargyl CH_2), 4.07–4.16 (m, 3H, H-6b, H-6′a, H-6′b), 3.88 (td, 1H, $J_{5',6'a} = J_{5',6'b}$ = 7.0 Hz,

$J_{4',5'}$ = 1.0 Hz, H-5′), 3.82 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 3.66 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6b}$ = 5.0 Hz, $J_{5,6a}$ = 2.5 Hz, H-5), 2.16 (s, 3H, C=OC$\underline{H}_3$), 2.14 (s, 3H, C=OC$\underline{H}_3$), 2.08 (s, 3H, C=OC$\underline{H}_3$), 2.07 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 6H, 2 × C=OC$\underline{H}_3$), 1.97 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (2 × $\underline{C}$=O), 170.1 ($\underline{C}$=O), 170.0 ($\underline{C}$=O), 169.7 ($\underline{C}$=O), 169.6 ($\underline{C}$=O), 169.0 ($\underline{C}$=O), 133.1 (2 × Ar), 129.9 (Ar), 128.5 (2 × Ar), 120.6 (Ar), 101.0, 98.3, 77.6 ($\underline{C}$≡C), 76.0, 74.4 ($\underline{C}$≡C), 74.0 ($\underline{C}$≡C), 72.9, 72.6, 72.2 ($\underline{C}$≡C), 71.3, 71.0, 70.7, 69.1, 66.6, 65.5 ($\underline{C}$≡C), 63.7 ($\underline{C}$≡C), 61.8, 60.8, 56.6, 20.8 (2 × C=O$\underline{C}$H$_3$), 20.7 (C=O$\underline{C}$H$_3$), 20.6 (3 × C=O$\underline{C}$H$_3$), 20.5 (C=O$\underline{C}$H$_3$); HRMS (ESI) calcd. for $C_{39}H_{42}O_{18}Na$ [M + Na]$^+$ 821.2263, found 821.2263.

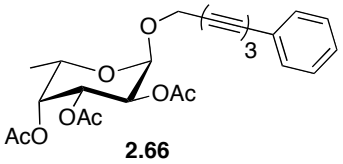
7-Phenylhepta-2,4,6-triynyl 4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranoside (2.60)



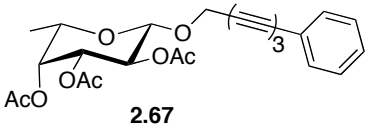
To a solution of **2.59** (252 mg, 0.320 mmol) in CH_3OH (10.0 mL) at rt was added 1 M $NaOCH_3$ solution (103 μL, 0.100 mmol) as described in the general procedure. Purification by column chromatography (CH_3OH–EtOAc, 1:8) afforded **2.60** (156 mg, 97%) as a brown solid: R_f = 0.26 (CH_3OH–EtOAc, 1:4); $[\alpha]_D$ –54.4 (*c* = 0.1, CH_3OH); IR (microscope) 3366 (O–H), 2885, 2190 (C≡C) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.53–7.55 (m, 2H, Ar), 7.36–7.45 (m, 3H, Ar), 4.56 (s, 2H, propargyl C$\underline{H}_2$), 4.46 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.36 (d, 1H, $J_{1',2'}$ = 8.0 Hz, H-1′), 3.92 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.5 Hz, H-6a), 3.84 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 4.5 Hz, H-6b), 3.80 (dd, 1H, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 1.0 Hz, H-4′), 3.77 (dd, 1H, $J_{6'a,6'b}$ = 11.5 Hz, $J_{5',6'a}$ = 7.5 Hz, H-6′a), 3.68 (dd, 1H, $J_{6'a,6'b}$ = 11.5 Hz, $J_{5',6'b}$ = 5.0 Hz, H-6′b), 3.52–3.59 (m, 4H, H-3, H-4, H-2′, H-5′), 3.47 (dd, 1H, $J_{2',3'}$ = 9.5 Hz, $J_{3',4'}$ = 3.5 Hz, H-3′), 3.44 (ddd, 1H, $J_{4,5}$ = 9.5 Hz, $J_{5,6b}$

= 4.5 Hz, $J_{5,6a}$ = 2.5 Hz, H-5), 3.27 (t, 1H, $J_{1,2} = J_{2,3}$ = 8.0 Hz, H-2); ^{13}C NMR (125 MHz, CD_3OD) δ 134.0 (2 × Ar), 131.2 (Ar), 129.8 (2 × Ar), 121.7 (Ar), 105.1 (C-1′), 102.5 (C-1), 80.5 (C-3), 78.2 (C≡C), 77.3 (C≡C), 77.1 (C-5′), 76.7 (C-2′), 76.3 (C-4), 74.8 (C-3′), 74.6 (C-2), 74.2 (C≡C), 72.6 (C-5), 71.6 (C≡C), 70.3 (C-4′), 66.5 (C≡C), 63.4 (C≡C), 62.5 (C-6′), 61.9 (C-6), 57.2 (propargyl CH_2); HRMS (ESI) calcd. for $C_{25}H_{28}O_{11}Na$ $[M + Na]^+$ 527.1524, found 527.1520.

7-Phenylhepta-2,4,6-triynyl 2,3,4-tri-*O*-acetyl-α-L-fucopyranoside (2.61) and 7-phenylhepta-2,4,6-triynyl 2,3,4-tri-*O*-acetyl-β-L-fucopyranoside (2.62)



2.66

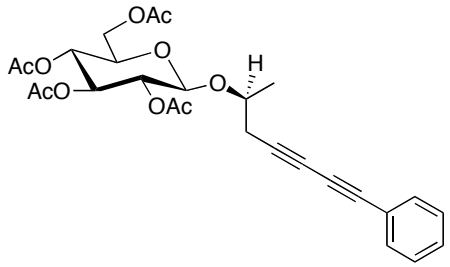


2.67

Alcohol **1.52** (54.0 mg, 0.300 mmol) was coupled with 1,2,3,4-tetra-*O*-acetyl-L-fucopyranose (150 mg, 0.450 mmol) in CH_2Cl_2 (5.00 mL) in the presence of crushed activated 4 Å molecular sieves (50.0 mg) and BF_3•OEt_2 (100 μL, 0.900 mmol) as described in the general procedure. Purification by column chromatography (CH_2Cl_2–EtOAc, 70:1) afforded **2.61** (18.0 mg, 13%) and **2.62** (26 mg, 19%) both as oils. **2.61**: R_f = 0.39 (CH_2Cl_2–EtOAc, 30:1); IR (CH_2Cl_2, cast) 2986, 2192 (C≡C), 1747 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.57 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 5.36 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{1,2}$ = 3.5 Hz, H-2), 5.32 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 5.21 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 5.17 (dd, 1H, $J_{2,3}$ = 11.0 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.43 (d, 1H, J = 17.0 Hz, propargyl CH_2), 4.35 (d, 1H, J = 17.0 Hz, propargyl CH_2), 4.21 (qd, 1H, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 2.17 (s, 3H, C=OCH_3), 2.11 (s, 3H, C=OCH_3), 1.99 (s, 3H, C=OCH_3), 1.25 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C=O), 170.4 (C=O), 169.9 (C=O), 133.0 (2 × Ar), 129.9 (Ar), 128.5 (2 × Ar), 120.6 (Ar), 95.9 (C-1), 77.4 (C≡C), 75.0 (C≡C), 74.0 (C≡C), 71.4 (C≡C), 71.1, 67.8 (2 ×), 65.6 (C≡C), 65.3, 63.5 (C≡C), 56.2, 20.8 (C=OCH_3), 20.7

(C=O<u>C</u>H$_3$), 20.6 (C=O<u>C</u>H$_3$), 15.8 (C-6); HRMS (ESI) calcd. for $C_{25}H_{24}O_8Na$ [M + Na]$^+$ 475.1363, found 475.1357. **2.62**: R_f = 0.38 (CH_2Cl_2–EtOAc, 30:1); IR (CH_2Cl_2, cast) 2987, 2193 (C≡C), 1749 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.57 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 5.26 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 5.20 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 5.06 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.67 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.52 (d, 1H, J = 17.0 Hz, propargyl C<u>H</u>$_2$), 4.48 (d, 1H, J = 17.0 Hz, propargyl C<u>H</u>$_2$), 3.85 (qd, 1H, $J_{5,6}$ = 6.5 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 2.18 (s, 3H, C=OC<u>H</u>$_3$), 2.10 (s, 3H, C=OC<u>H</u>$_3$), 1.99 (s, 3H, C=OC<u>H</u>$_3$), 1.24 (d, 3H, $J_{5,6}$ = 6.5 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (<u>C</u>=O), 170.1 (<u>C</u>=O), 169.7 (<u>C</u>=O), 133.0 (2 × Ar), 129.9 (Ar), 128.5 (2 × Ar), 120.6 (Ar), 98.9 (C-1), 77.4 (<u>C</u>≡C), 74.9 (<u>C</u>≡C), 74.0 (<u>C</u>≡C), 71.9 (<u>C</u>≡C), 71.3, 70.1, 69.5, 68.6, 65.7 (<u>C</u>≡C), 63.4 (<u>C</u>≡C), 56.4, 20.8 (C=O<u>C</u>H$_3$), 20.7 (C=O<u>C</u>H$_3$), 20.6 (C=O<u>C</u>H$_3$), 16.0 (C-6); HRMS (ESI) calcd. for $C_{25}H_{24}O_8Na$ [M + Na]$^+$ 475.1363, found 475.1358.

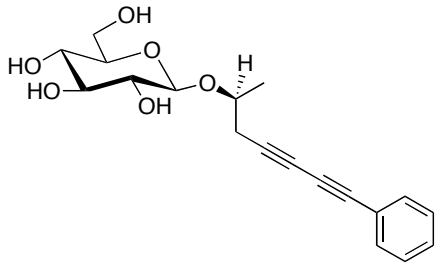
(6*S*)-1-Phenylhepta-1,3-diyn-6-yl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (2.67)



(6*S*)-1-Phenylhepta-1-3-diyn-6-ol **(2.63)** (38.0 mg, 0.210 mmol) was glycosylated with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (160 mg, 0.294 mmol) in CH_2Cl_2 (4.00 mL) in the presence of crushed activated 4 Å molecular sieves (40.0 mg) and BF_3•OEt_2 (112 μL, 0.840 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 4:1) afforded **2.67** (65.0 mg, 61%) as a syrup: R_f = 0.46 (hexanes–EtOAc, 1:1); IR (CH_2Cl_2, cast) 2980, 2936, 2246 (C≡C), 1752 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–

7.49 (m, 2H, Ar), 7.29–7.36 (m, 3H, Ar), 5.39 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 5.19 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 5.03 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.56 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.20 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6a}$ = 6.5 Hz, H-6a), 4.13 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, $J_{5,6b}$ = 6.5 Hz, H-6b), 3.94–3.98 (m, 1H, C<u>H</u>CH$_3$), 3.92 (dt, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 2.82 (dd, 1H, J = 17.0 Hz, J = 5.0 Hz, propargyl C<u>H</u>$_2$), 2.54 (dd, 1H, J = 17.0 Hz, J = 8.0 Hz, propargyl C<u>H</u>$_2$), 2.15 (s, 3H, C=OC<u>H</u>$_3$), 2.06 (s, 3H, C=OC<u>H</u>$_3$), 2.05 (s, 3H, C=OC<u>H</u>$_3$), 1.98 (s, 3H, C=OC<u>H</u>$_3$), 1.32 (d, 3H, J = 6.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 (<u>C</u>=O), 170.3 (<u>C</u>=O), 170.1 (<u>C</u>=O), 169.3 (<u>C</u>=O), 132.5 (2 × Ar), 129.0 (Ar), 128.4 (2 × Ar), 121.8 (Ar), 100.6 (C-1), 80.4 (<u>C</u>≡C), 75.4 (<u>C</u>≡C), 75.1, 74.0 (<u>C</u>≡C), 70.9, 70.8, 68.9 (<u>C</u>≡C), 67.0, 66.9, 61.3, 28.2 (propargyl <u>C</u>H$_2$), 20.7 (C=O<u>C</u>H$_3$), 20.6 (3 × C=O<u>C</u>H$_3$), 19.8 (CH<u>C</u>H$_3$); HRMS (ESI) calcd. for $C_{27}H_{30}O_{10}Na$ $[M + Na]^+$ 537.1731, found 537.1731.

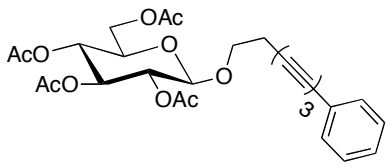
(6*S*)-1-Phenylhepta-1,3-diyn-6-yl β-D-galactopyranoside (2.68)



To a solution of **2.67** (52.0 mg, 0.100 mmol) in CH_3OH (5.00 mL) at rt was added $NaOCH_3$ 1 M solution (15.0 μL, 0.015 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 1:3) afforded **2.68** (31.0 mg, 86%) as a syrup: R_f = 0.17 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ +10.9 (c = 0.4, CH_3OH); IR (CH_3OH cast film, microscope) 3383 (O–H), 2928, 2245 (C≡C) cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.44–7.46 (m, 2H, Ar), 7.30–7.38 (m, 3H, Ar), 4.33 (d, 1H, $J_{1,2}$ = 7.0 Hz, H-1), 4.02–4.06 (m, 1H, C<u>H</u>CH$_3$), 3.83 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 3.77 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6a}$ = 6.5 Hz, H-6a), 3.72 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6b}$ = 5.5 Hz, H-6b), 3.52 (ddd,

1H, $J_{5,6a}$ = 6.5 Hz, $J_{5,6b}$ = 5.5 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 3.50 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 7.0 Hz, H-2), 3.45 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 2.79 (dd, 1H, J = 17.0 Hz, J = 4.5 Hz, propargyl C$\underline{H}_2$), 2.60 (dd, 1H, J = 17.0 Hz, J = 7.5 Hz, propargyl C$\underline{H}_2$), 1.33 (d, 3H, J = 6.5 Hz, CHC$\underline{H}_3$); ^{13}C NMR (125 MHz, CD_3OD) δ 133.4 (2 × Ar), 130.2 (Ar), 129.6 (2 × Ar), 123.2 (Ar), 104.0 (C-1, $^1J_{C1,H1}$ = 157.8 Hz), 82.3 (C≡C), 76.6 (C-5), 75.7 (C≡C), 75.0 (C≡C, C-3), 74.9 (CHCH$_3$), 72.5 (C-2), 70.3 (C-4), 67.4 (C≡C), 62.5 (C-6), 29.0 (propargyl $\underline{C}H_2$), 19.8 (CH$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{19}H_{22}O_6Na$ $[M + Na]^+$ 369.1309, found 369.1310.

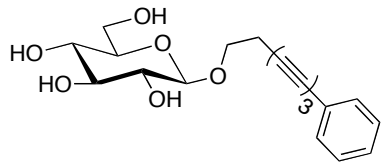
8-Phenylocta-3,5,7-triyn-1-yl 2,3,5,6-tetra-*O*-acetyl-β-D-glucopyranoside (2.69)



8-Phenylocta-3,5,7-triyn-1-ol **2.64** (100 mg, 0.520 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (260 mg, 0.670 mmol) in CH_2Cl_2 (5.00 mL) in the presence of crushed activated 4 Å molecular sieves (100 mg) and BF_3•OEt_2 (196 μL, 1.56 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc, 6:1) afforded **2.67** (83.0 mg, 30%) as a syrup: R_f = 0.50 (hexanes–EtOAc, 1:1); IR (CH_2Cl_2, cast) 2958, 2890, 2216 (C≡C), 1756 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.54 (m, 2H, Ar), 7.31–7.40 (m, 3H, Ar), 5.23 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H-3), 5.09 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 5.01 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{1,2}$ = 7.8 Hz, H-2), 4.58 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 4.28 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6a}$ = 4.6 Hz, H-6a), 4.16 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6b}$ = 2.4 Hz, H-6b), 3.97 (dt, 1H, J = 9.6 Hz, J = 6.0 Hz, C$\underline{H}_2$CH$_2$C≡C), 3.71 (ddd, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 4.6 Hz, $J_{5,6b}$ = 2.4 Hz, H-5), 3.69 (dt, 1H, J = 9.6 Hz, J = 7.2 Hz, C$\underline{H}_2$CH$_2$C≡C), 2.64 (t, 2H, J = 6.6 Hz, propargyl C$\underline{H}_2$), 2.11 (s, 3H, C=OC$\underline{H}_3$), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.03 (s, 3H,

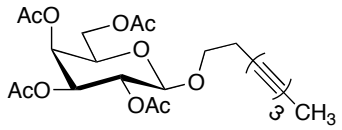
C=OC$\underline{H}_3$), 2.02 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 ($\underline{C}$=O), 170.2 ($\underline{C}$=O), 169.4 (2 × $\underline{C}$=O), 133.0 (2 × Ar), 129.6 (Ar), 128.5 (2 × Ar), 120.9 (Ar), 100.8 (C-1), 78.4 ($\underline{C}$≡C), 75.8 ($\underline{C}$≡C), 74.4 ($\underline{C}$≡C), 72.7, 71.9, 71.0, 68.4, 67.2, 66.8 ($\underline{C}$≡C), 66.7 ($\underline{C}$≡C), 61.8, 60.3 ($\underline{C}$≡C), 21.1 (propargyl $\underline{C}H_2$), 20.7 (C=O$\underline{C}H_3$), 20.6 (3 × C=O$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{28}H_{28}O_{10}Na$ $[M + Na]^+$ 547.1575, found 547.1576.

8-Phenylocta-3,5,7-triyn-1-yl β-D-glucopyranoside (2.70)



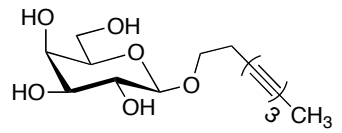
To a solution of **2.69** (82.0 mg, 0.160 mmol) in CH_3OH (5.00 mL) at rt was added 1 M $NaOCH_3$ solution (51.0 μL, 0.050 mmol) as described in the general procedure. Purification by column chromatography (CH_3OH–EtOAc, 1:20) afforded **2.70** (39.0 mg, 68%) as an oil: R_f = 0.23 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ –16.2 (*c* = 0.3, CH_3OH); IR (CH_3OH, cast) 3384 (O–H), 2888, 2215 (C≡C) cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.50–7.52 (m, 2H, Ar), 7.37–7.43 (m, 3H, Ar), 4.30 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 3.98 (dt, 1H, *J* = 9.6 Hz, *J* = 6.8 Hz, C$\underline{H}_2$CH$_2$C≡C), 3.86 (dd, 1H, $J_{6a,6b}$ = 11.6 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 3.73 (dt, 1H, *J* = 9.6 Hz, *J* = 6.8 Hz, C$\underline{H}_2$CH$_2$C≡C), 3.66 (dd, 1H, $J_{6a,6b}$ = 11.6 Hz, $J_{5,6b}$ = 5.2 Hz, H-6b), 3.34 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 8.8 Hz, H-3), 3.30–3.37 (m, 2H, H-4, H-5), 3.18 (dd, 1H, $J_{2,3}$ = 8.8 Hz, $J_{1,2}$ = 7.6 Hz, H-2), 2.71 (t, 2H, *J* = 6.8 Hz, propargyl C$\underline{H}_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 133.8 (2 × Ar), 130.8 (Ar), 129.6 (2 × Ar), 121.9 (Ar), 104.3 (C-1, $^1J_{C1,H1}$ = 158.5 Hz), 80.6 ($\underline{C}$≡C), 77.8 (C-3, C-5), 76.4 ($\underline{C}$≡C), 74.8 (C-2), 74.6 ($\underline{C}$≡C), 71.4 (C-4), 68.0 ($\underline{C}$H$_2$CH$_2$C≡C), 67.6 ($\underline{C}$≡C), 66.6 ($\underline{C}$≡C), 62.5 (C-6), 60.1 ($\underline{C}$≡C), 21.6 (propargyl $\underline{C}H_2$); HRMS (ESI) calcd. for $C_{20}H_{20}O_6Na$ $[M + Na]^+$ 379.1152, found 379.1152.

Nona-3,5,7-triyn-1-yl 2,3,5,6-tetra-*O*-acetyl-β-D-galactopyranoside (2.71)



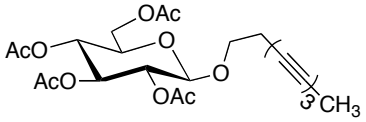
Nona-3,5,7-triyn-1-ol **2.65** (50.0 mg, 0.400 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (200 mg, 0.480 mmol) in CH_2Cl_2 (5.00 mL) in the presence of crushed activated 4 Å molecular sieves (60.0 mg) and BF_3•OEt_2 (151 μL, 1.20 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc 8:1) afforded **2.71** (70.0 mg, 38%) as an oil: R_f = 0.47 (CH_2Cl_2–EtOAc 12:1); IR (CH_2Cl_2, cast) 2941, 2222 (C≡C), 1751 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.39 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 5.20 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 5.02 (dd, 1H, $J_{2,3}$ = 10.5 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.52 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.16 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6a}$ = 6.5 Hz, H-6a), 4.12 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6b}$ = 6.5 Hz, H-6b), 3.95 (dt, 1H, J = 10.0 Hz, J = 6.5 Hz, C$\underline{H}_2$CH$_2$C≡C), 3.90 (td, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 3.65 (dt, 1H, J = 10.0 Hz, J = 6.5 Hz, C$\underline{H}_2$CH$_2$C≡C), 2.56-2.59 (m, 2H, propargyl C$\underline{H}_2$), 2.15 (s, 3H, C=OC$\underline{H}_3$), 2.08 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 1.98 (s, 3H, C=OC$\underline{H}_3$), 1.95 (s, 3H, C≡CC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 (C=O), 170.2 (C=O), 170.1 (C=O), 169.5 (C=O), 101.3 (C-1), 75.4 (C≡C), 74.9 (C≡C), 70.8 (2 ×), 68.5, 67.2, 67.0, 66.8 (C≡C), 64.8 (C≡C), 61.3, 61.2 (C≡C), 59.4 (C≡C), 20.9, 20.7, 20.6 (3 ×), 4.4 (C≡CCH$_3$); HRMS (ESI) calcd. for $C_{23}H_{26}O_{10}Na$ $[M + Na]^+$ 485.1418, found 485.1417.

Onoa-3,5,7-triyn-1-yl β-D-galactopyranoside (2.72)



To a solution of **2.71** (60.0 mg, 0.130 mmol) in CH_3OH (4.00 mL) at rt was added 1 M $NaOCH_3$ solution (40.0 μL, 0.040 mmol) as described in the general procedure. Purification by column chromatography (CH_3OH–EtOAc, 1:15) afforded **2.72** (17 mg, 44%) as an oil: R_f = 0.16 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ –7.0 (*c* = 0.3, CH_3OH); IR (CH_3OH, cast film microscope) 3395 (O–H), 2891, 2222 (C≡C) cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 4.23 (d, 1H, $J_{1,2}$ = 7.2 Hz, H-1), 3.94 (dt, 1H, *J* = 9.6 Hz, *J* = 6.8 Hz, C<u>H</u>$_2$CH$_2$C≡C), 3.80 (dd, 1H, $J_{3,4}$ = 3.2 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 3.75 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{5,6a}$ = 6.8 Hz, H-6a), 3.71 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, $J_{5,6b}$ = 5.2 Hz, H-6b), 3.70 (dt, 1H, *J* = 9.6 Hz, *J* = 6.8 Hz, C<u>H</u>$_2$CH$_2$C≡C), 3.50 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{1,2}$ = 7.2 Hz, H-2), 3.49–3.52 (m, 1H, H-5), 3.44 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 3.2 Hz, H-3), 2.64 (t, 2H, *J* = 6.8 Hz, propargyl C<u>H</u>$_2$), 1.93 (s, 3H, C≡CC<u>H</u>$_3$); ^{13}C NMR (125 MHz, CD_3OD) δ 107.6 (C-1, $^1J_{C1,H1}$ = 158.3 Hz), 79.5 (<u>C</u>≡C), 79.3 (C-5), 78.9 (<u>C</u>≡C), 77.5 (C-3), 74.9 (C-2), 72.8 (C-4), 70.8 (<u>C</u>H$_2$CH$_2$C≡C), 69.5 (<u>C</u>≡C), 67.6 (<u>C</u>≡C), 65.0 (C-6), 63.9 (<u>C</u>≡C), 62.6 (<u>C</u>≡C), 24.1 (propargyl <u>C</u>H$_2$), 6.2 (C≡C<u>C</u>H$_3$); HRMS (ESI) calcd. for $C_{15}H_{18}O_6Na$ $[M + Na]^+$ 317.0996, found 317.0995.

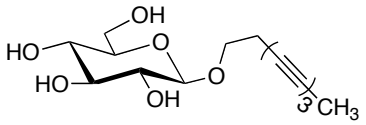
Nona-3,5,7-triyn-1-yl 2,3,5,6-tetra-*O*-acetyl-β-D-glucopyranoside (2.73)



Nona-3,5,7-triyn-1-ol **2.65** (50.0 mg, 0.400 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (200 mg, 0.500 mmol) in CH_2Cl_2 (5.00 mL) in the presence of crushed activated 4 Å molecular sieves (60.0 mg) and BF_3•OEt_2 (151 μL, 1.20 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc 8:1) afforded **2.73** (89.0 mg, 48%) as a syrup: R_f = 0.25 (hexanes–EtOAc 3:1). IR (CH_2Cl_2, cast) 2957, 2222 (C≡C), 1755 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, H-3), 5.08 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H-4), 4.99 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{1,2}$ = 8.0 Hz,

H-2), 4.56 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.27 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6a}$ = 4.8 Hz, H-6a), 4.13 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6b}$ = 2.4 Hz, H-6b), 3.94 (dt, 1H, J = 9.6 Hz, J = 6.4 Hz, C$\underline{H}_2$CH$_2$C≡C), 3.71 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{5,6b}$ = 2.4 Hz, H-5), 3.64 (dt, 1H, J = 9.6 Hz, J = 7.2 Hz, C$\underline{H}_2$CH$_2$C≡C), 2.58 (t, 2H, J = 6.4 Hz, propargyl C$\underline{H}_2$), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.08 (s, 3H, C=OC$\underline{H}_3$), 2.03 (s, 3H, C=OC$\underline{H}_3$), 2.01 (s, 3H, C=OC$\underline{H}_3$), 1.96 (s, 3H, C≡CC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C=O), 170.2 (C=O), 169.4 (C=O), 169.3 (C=O), 100.8 (C-1), 75.4 (C≡C), 74.8 (C≡C), 72.7, 71.9, 71.0, 68.4, 67.3, 66.8 (C≡C), 64.8 (C≡C), 61.8, 61.2 (C≡C), 59.3 (C≡C), 20.8, 20.7, 20.6 (3 ×), 4.4 (C≡C$\underline{C}$H$_3$); HRMS (ESI) calcd. for $C_{23}H_{26}O_{10}Na$ $[M + Na]^+$ 485.1418, found 485.1416.

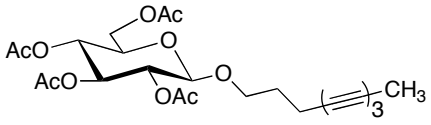
Nona-3,5,7-triyn-1-yl β-D-glucopyranoside (2.74)



To a solution of **2.73** (81.0 mg, 0.167 mmol) in CH_3OH (5.00 mL) at rt was added 1 M $NaOCH_3$ solution (54.0 μL, 0.054 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.74** (41.0 mg, 76%) as an oil: R_f = 0.22 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ –15.4 (c = 0.2, CH_3OH); IR (CH_3OH, cast film microscope) 3365 (O–H), 2912, 2222 (C≡C) cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 4.28 (d, 1H, $J_{1,2}$ = 7.8 Hz, H-1), 3.95 (dt, 1H, J = 9.6 Hz, J = 6.8 Hz, C$\underline{H}_2$CH$_2$C≡C), 3.84 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 3.71 (dt, 1H, J = 9.6 Hz, J = 6.8 Hz, C$\underline{H}_2$CH$_2$C≡C), 3.64 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 5.2 Hz, H-6b), 3.33 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 8.8 Hz, H-3), 3.26–3.27 (m, 2H, H-4, H-5), 3.16 (dd, 1H, $J_{1,2}$ = 7.8 Hz, $J_{2,3}$ = 8.8 Hz, H-2), 2.64 (t, 2H, J = 6.8 Hz, propargyl C$\underline{H}_2$), 1.93 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (125 MHz, CD_3OD) δ 104.4 (C-1, $^1J_{C1,H1}$ = 158.5 Hz), 78.0 (C-3, C-4), 77.0 (C≡C), 76.5 (C≡C), 75.0 (C≡C), 71.5 (C-2), 68.3 (C-5), 67.0 (C$\underline{H}_2$CH$_2$C≡C), 65.0 (C≡C), 62.7 (C≡C), 61.5 (C-6), 60.1

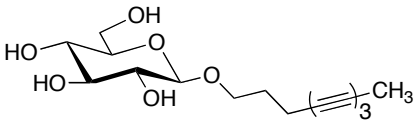
(C≡C), 21.6 (propargyl $\underline{C}H_2$), 3.8 (C≡C$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{15}H_{18}O_6Na$ $[M + Na]^+$ 317.0996, found 317.0995.

Deca-4,6,8-triyn-1-yl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (2.75)



Deca-4,6,8-triyn-1-ol **2.66** (80.0 mg, 0.550 mmol) was coupled with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose (280 mg, 0.720 mmol) in CH_2Cl_2 (7.00 mL) in the presence of crushed activated 4 Å molecular sieves (60.0 mg) and BF_3•OEt_2 (207 μL, 1.65 mmol) as described in the general procedure. Purification by column chromatography (hexanes–EtOAc 8:1) afforded **2.75** (67.0 mg, 26%) as a syrup: R_f = 0.25 (hexanes–EtOAc 3:1); IR (CH_2Cl_2, cast) 2960, 2886, 2220 (C≡C), 1755 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.6 Hz, H-3), 5.08 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.6 Hz, H-4), 4.98 (dd, 1H, $J_{2,3}$ = 9.6 Hz, $J_{1,2}$ = 8.0 Hz, H-2), 4.49 (d, 1H, $J_{1,2}$ = 8.0 Hz, H-1), 4.27 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 4.8 Hz, H-6a), 4.14 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 2.4 Hz, H-6b), 3.94 (dt, 1H, J = 9.6 Hz, J = 5.2 Hz, C$\underline{H}_2$CH$_2$CH$_2$C≡C), 3.70 (ddd, 1H, $J_{4,5}$ = 9.6 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{5,6b}$ = 2.4 Hz, H-5), 3.61 (ddd, 1H, J = 9.6 Hz, J = 8.4 Hz, J = 4.8 Hz, C$\underline{H}_2$CH$_2$CH$_2$C≡C), 2.37 (t, 2H, J = 6.8 Hz, propargyl C$\underline{H}_2$), 2.09 (s, 3H, C=OC$\underline{H}_3$), 2.06 (s, 3H, C=OC$\underline{H}_3$), 2.03 (s, 3H, C=OC$\underline{H}_3$), 2.01 (s, 3H, C=OC$\underline{H}_3$), 1.96 (s, 3H, C≡CC$\underline{H}_3$), 1.80 (m, 2H, CH$_2$C$\underline{H}_2$CH$_2$C≡C); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (C=O), 170.2 (C=O), 169.4 (C=O), 169.3 (C=O), 101.0 (C-1), 77.7 (C≡C), 75.2 (C≡C), 72.8, 71.8, 71.3, 68.4, 68.1, 66.3 (C≡C), 64.8 (C≡C), 61.9, 60.8 (C≡C), 59.5 (C≡C), 27.9 (propargyl $\underline{C}H_2$), 20.7 (C=O$\underline{C}H_3$), 20.6 (3 × C=O$\underline{C}H_3$), 15.8 (CH$_2\underline{C}$H$_2$CH$_2$C≡C), 4.4 (C≡C$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{24}H_{28}O_{10}Na$ $[M + Na]^+$ 499.1575, found 499.1576.

Deca-4,6,8-triyn-1-yl β-D-glucopyranoside (2.76)



To a solution of **2.75** (65.0 mg, 0.130 mmol) in CH_3OH (4.00 mL) at rt was added 1 M $NaOCH_3$ solution (40.0 μL, 0.040 mmol) as described in general procedure. Purification by column chromatography (CH_3OH–EtOAc, 1:20) afforded **2.76** (30.0 mg, 70%) as an oil: R_f = 0.34 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ –18.9 (*c* = 1.0, CH_3OH); IR (CH_2Cl_2 cast) 3374 (O–H), 2915, 2221 (C≡C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 4.24 (d, 1H, $J_{1,2}$ = 7.5 Hz, H-1), 3.93 (dt, 1H, *J* = 10.0 Hz, *J* = 6.0 Hz, C$\underline{H}_2$CH$_2$CH$_2$C≡C), 3.85 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.5 Hz, H-6a), 3.66 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 5.5 Hz, H-6b), 3.62 (dt, 1H, *J* = 10.0 Hz, *J* = 6.0 Hz, C$\underline{H}_2$CH$_2$CH$_2$C≡C), 3.34 (t, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H-3), 3.28 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.5 Hz, H-4), 3.25-3.27 (m, 1H, H-5), 3.15 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{1,2}$ = 7.5 Hz, H-2), 2.45 (t, 2H, *J* = 7.5 Hz, propargyl C$\underline{H}_2$), 1.93 (s, 3H, C≡CC$\underline{H}_3$), 1.79-1.85 (m, 2H, CH$_2$C$\underline{H}_2$CH$_2$C≡C); ^{13}C NMR (125 MHz, CD_3OD) δ 104.5 (C-1, $^1J_{C1,H1}$ = 159.0 Hz), 79.6 (C≡C), 78.1 (C-3), 77.9 (C-5), 76.2 (C≡C), 75.1 (C-2), 71.6 (C-4), 69.1 (CH$_2$CH$_2$CH$_2$C≡C), 66.4 (C≡C), 65.2 (C≡C), 62.8 (C-6), 61.2 (C≡C), 60.2 (C≡C), 29.6 (CH$_2$CH$_2$CH$_2$C≡C), 16.7 (propargyl CH$_2$), 3.8 (C≡CCH$_3$); HRMS (ESI) calcd. for $C_{16}H_{20}O_6Na$ $[M + Na]^+$ 331.1152, found 331.1153.

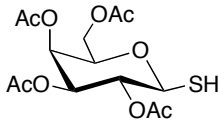
3.4 Procedure for the synthesis of polyacetylene thioglycosides

3.4.1 General procedure for synthesis of glycosyl thiols

To a solution of peracylated carbohydrate (5.60 mmol) in CH_2Cl_2 (9.50 mL) was added HBr (33% in AcOH, 26.0 mL) slowly at 0 °C. The reaction was allowed to stir for 1 h and then warmed to rt. The reaction mixture was poured into ice-water

(100 mL) and extracted with CH_2Cl_2 (4 × 15.0 mL). The organic layer was combined and washed with sat. aq. $NaHCO_3$ (25.0 mL) and then brine (25.0 mL). The organic layer was dried over $MgSO_4$ and solvent was evaporated to afford the glycosyl bromide as pale yellow syrup. This material was carried on without further purification. Thiourea (8.10 mmol) was added to a solution of the crude glycosyl bromide in acetone (20.0 mL). The reaction mixture was heated at reflux under N_2 for 30 min and the solvent was removed to afford a white salt. The white salt and K_2SO_5 (1.30 g, 6.84 mmol) were dissolved in H_2O (20.0 mL) and CH_2Cl_2 (30.0 mL). The reaction mixture was heated at reflux overnight, cooled to rt and then extracted with CH_2Cl_2 (3 × 25.0 mL). The organic layers were combined and dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by column chromatography to afford the glycosyl thiol.

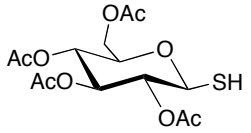
2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl thiol (2.79)



1,2,3,4,6-Penta-*O*-acetyl-β-D-galactopyranose (3.00 g, 7.70 mmol) was treated with HBr (33% in AcOH, 35.0 mL) to give 2,3,4,6-tetra-*O*-acetyl-galactosyl bromide: R_f = 0.51 (hexanes–EtOAc, 2:1). This material was treated with thiourea (0.870 g, 15.4 mmol) and then K_2SO_5 (1.45 g, 6.47 mmol) as described in the general procedure to give **2.79**[12] (2.10 g, 75% over three steps) as a white solid: Mp: 84–85 °C; R_f = 0.23 (hexanes–EtOAc 2:1); IR (CH_2Cl_2, cast) 2561 (S-H), 1747 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.44 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 5.19 (t, 1H, $J_{1,2} = J_{2,3}$ = 10.00 Hz, H-2), 5.02 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.54 (t, 1H, $J_{1,2} = J_{1,SH}$ = 10.0 Hz, H-1), 4.14 (d, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6a}$ = 6.5 Hz, H-6a), 4.13 (d, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6b}$ = 6.5 Hz, H-6b), 3.95 (td, 1H, $J_{5,6a} = J_{5,6b}$ = 6.5 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 2.37 (d, 1H, $J_{1,SH}$ = 10.0 Hz, S<u>H</u>), 2.17 (s, 3H, C=OC<u>H</u>$_3$), 2.10 (s, 3H, C=OC<u>H</u>$_3$), 2.06 (s, 3H,

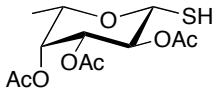
C=OC$\underline{H}_3$), 1.99 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4 ($\underline{C}$=O), 170.1 ($\underline{C}$=O), 169.9 ($\underline{C}$=O), 169.8 ($\underline{C}$=O), 79.2, 75.0, 71.6, 70.9, 67.2, 61.5, 20.8 (C=O$\underline{C}H_3$), 20.7 (2 × C=O$\underline{C}H_3$), 20.6 (C=O$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{14}H_{20}O_9NaS$ $[M + Na]^+$ 387.0720, found 387.0725.

2,3,4,6-Tetra-*O*-acetyl-β-β-D-glucopyranosyl thiol (2.80)



1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (4.50 g, 11.5 mmol) was treated with HBr (33% in AcOH, 52.0 mL) to give 2,3,4,6-tetra-*O*-acetyl-glucosyl bromide **2.77**: R_f = 0.47 (hexanes–EtOAc, 2:1). This material was treated with thiourea (1.31 g, 17.2 mmol) and then K_2SO_5 (2.67 g, 12 mmol) as described in the general procedure to give **2.80**[12] (2.84 g, 68% over three steps) as a white solid: Mp: 70–71 °C; R_f = 0.21 (hexanes–EtOAc 2:1); IR (CH_2Cl_2, cast) 2560 (S-H), 1754 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.5 Hz, H-3), 5.10 (t, 1H, $J_{3,4} = J_{4,5}$ = 9.5 Hz, H-4), 4.97 (t, 1H, $J_{1,2} = J_{2,3}$ = 10.0 Hz, H-2), 4.55 (t, 1H, $J_{1,2} = J_{1,SH}$ = 10.0 Hz, H-1), 4.24 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6a}$ = 4.5 Hz, H-6a), 4.13 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6b}$ = 2.5 Hz, H-6b), 3.72 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 4.5 Hz, $J_{5,6b}$ = 2.5 Hz, H-5), 2.31 (d, 1H, $J_{1,SH}$ = 10.0 Hz, S$\underline{H}$), 2.09 (s, 3H, C=OC$\underline{H}_3$), 2.07 (s, 3H, C=OC$\underline{H}_3$), 2.02 (s, 3H, C=OC$\underline{H}_3$), 2.00 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 ($\underline{C}$=O), 170.1 ($\underline{C}$=O), 169.6 ($\underline{C}$=O), 169.3 ($\underline{C}$=O), 78.7, 76.4, 73.6 (2 ×), 68.1, 62.0, 20.7 (2 × C=O$\underline{C}H_3$), 20.6 (C=O$\underline{C}H_3$), 20.5 (C=O$\underline{C}H_3$); HRMS (ESI) calcd. for $C_{14}H_{20}O_9NaS$ $[M + Na]^+$ 387.0720, found 387.0720.

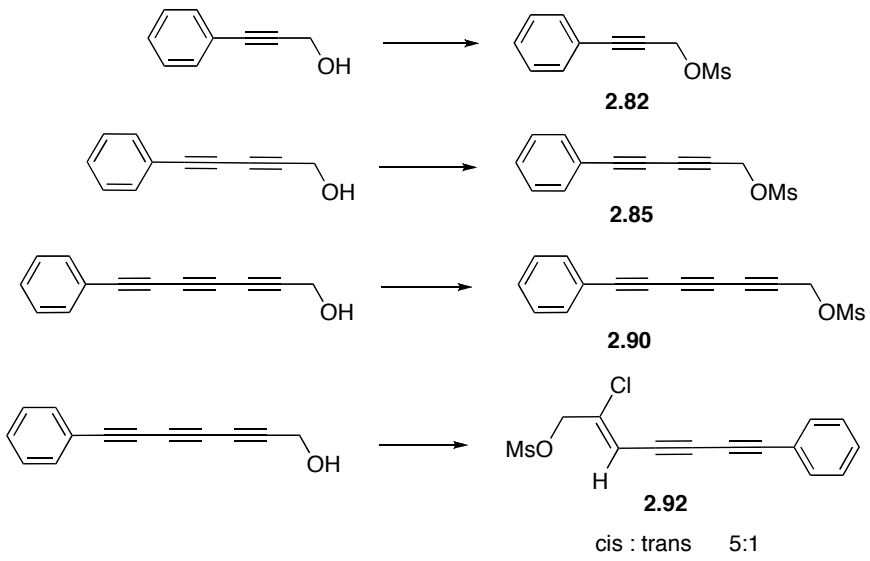
2,3,4-Tri-*O*-acetyl-β-L-fucopyranosyl thiol (2.81)



1,2,3,4-Tetra-*O*-acetyl-β-L-fucopyranose (1.30 g, 3.90 mmol) was treated with HBr (33% in AcOH, 17.6 mL) to give 2,3,4-tri-*O*-acetyl-fucosyl bromide: R_f = 0.54 (hexanes–EtOAc, 3:1). This material was treated with thiourea (0.440 g, 5.80 mmol) and then K_2SO_5 (1.30 g, 6.84 mmol) as described in the general procedure to give **2.81**[13] (0.640 g, 54% over three steps) as a syrup: R_f = 0.16 (hexanes–EtOAc 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (dd, 1H, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 0.8 Hz, H-4), 5.16 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 10.0 Hz, H-2), 5.03 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 4.51 (t, 1H, $J_{1,2}$ = $J_{1,SH}$ = 10.0 Hz, H-1), 3.84 (qd, 1H, $J_{5,6}$ = 6.4 Hz, $J_{4,5}$ = 0.8 Hz, H-5), 2.33 (d, 1H, $J_{1,SH}$ = 10.0 Hz, S<u>H</u>), 2.19 (s, 3H, C=OC<u>H</u>$_3$), 2.09 (s, 3H, C=OC<u>H</u>$_3$), 1.99 (s, 3H, C=OC<u>H</u>$_3$), 1.23 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (<u>C</u>=O), 170.0 (<u>C</u>=O), 169.9 (<u>C</u>=O), 78.8, 73.8, 72.0, 71.0, 70.4, 20.9 (C=O<u>C</u>H$_3$), 20.7 (C=O<u>C</u>H$_3$), 20.6 (C=O<u>C</u>H$_3$), 16.4 (C-6); HRMS (ESI) calcd. for $C_{12}H_{18}O_7NaS$ $[M + Na]^+$ 329.0666, found 329.0671.

3.4.2 General procedure for synthesis of polyacetylene thioglycosides

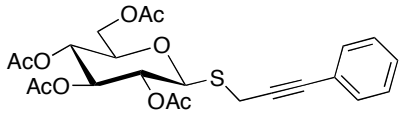
To a solution of polyyne alcohol (0.390 mmol) in CH_2Cl_2 (1.50 mL) was added Et_3N (0.070 mL, 0.780 mmol) and methanesulfonyl chloride (45.0 μL, 0.590 mmol). The reaction solution was heated to reflux for 2 h and then quenched by the addition of H_2O (3.00 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 5.00 mL), and then the organic layer was dried over $MgSO_4$. The solvent was evaporated to afford a crude mesylate as a brown liquid. 3-Phenylprop-2-ynyl methansulfonate **2.82**: R_f = 0.78 (hexanes–EtOAc 2:1); 5-phenylpenta-2,4-diynyl methansulfonate **2.85**: R_f = 0.72 (hexanes–EtOAc 3:1); 7-phenylhepta-2,4,6-triynyl methansulfonate **2.90**: R_f = 0.68 (hexanes–EtOAc 3:1); 7-phenylhepta-4,6-diyne-2-chloro-2-eneyl methansulfonate **2.92**: R_f = 0.70 (hexanes–EtOAc 3:1).



K_2CO_3 (0.400 mmol) was added to a solution of peracetylated glycosyl thiol (0.400 mmol) and the crude mesylate in acetone (6.00 mL). The reaction was stirred at rt overnight, and the solvent was evaporated before CH_2Cl_2 (10.0 mL) and H_2O (5.00 mL) were added. The organic layer was separated and washed with brine (5.00 mL) and then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography to afford the polyyne thioglycosides.

To a solution of the polyyne thioglycoside (0.300 mmol) in CH_3OH (13.0 mL) was added K_2CO_3 (41.4 mg, 0.300 mmol). After stirring for 2 h at rt, the solution was concentrated. Purification by column chromatography afforded the deprotected polyyne thioglycoside.

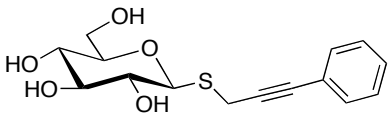
3-Phenylprop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (2.83)



To a solution of **2.80** (0.140 g, 0.362 mmol) and **2.82** (81.9 mg, 0.39 mmol) in acetone (20.0 mL) was added K_2CO_3 (0.050 g, 0.362 mmol) as described in the

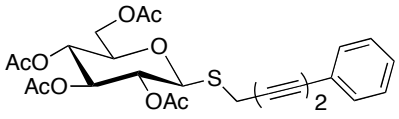
general procedure to afford **2.83** (0.210 g, 55% based on 3-phenyl-2-propyn-1-ol) as a syrup. R_f = 0.47 (CH_2Cl_2–EtOAc 15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.44 (m, 2H, Ar), 7.28–7.37 (m, 3H, Ar), 5.27 (t, 1H, $J_{2,3} = J_{3,4}$ = 9.4 Hz, H-3), 5.12 (t, 1H, $J_{2,3} = J_{1,2}$ = 9.4 Hz, H-2), 5.10 (dd, 1H, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 10.0 Hz, H-4), 4.82 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1), 4.27 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6a}$ = 4.8 Hz, H-6a), 4.14 (dd, 1H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6b}$ = 2.4 Hz, H-6b), 3.80 (d, 1H, J = 16.4 Hz, propargyl C$\underline{H}_2$), 3.74 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 4.8 Hz, $J_{5,6b}$ = 2.4 Hz, H-5), 3.55 (d, 1H, J = 16.4 Hz, propargyl C$\underline{H}_2$), 2.07 (s, 3H, C=OC$\underline{H}_3$), 2.06 (s, 3H, C=OC$\underline{H}_3$), 2.03 (s, 3H, C=OC$\underline{H}_3$), 2.02 (s, 3H, C=OC$\underline{H}_3$).

3-Phenylprop-2-ynyl 1-thio-β-D-glucopyranoside (2.84)



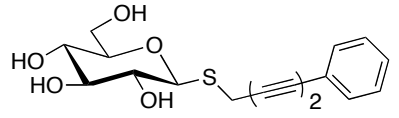
To a solution of **2.83** (88.0 mg, 0.180 mmol) in CH_3OH (14.0 mL) at rt was added K_2CO_3 (24.8 mg, 0.180 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.84** (56 mg, 98%) as a pale yellow syrup; R_f = 0.35 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ –130.7 (c = 0.2, CH_3OH); IR (CH_3OH, cast film microscope) 3377 (O–H), 2915 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.42–7.44 (m, 2H, Ar), 7.28–7.37 (m, 3H, Ar), 4.62 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 3.87 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 3.85 (d, 1H, J = 16.6 Hz, propargyl C$\underline{H}_2$), 3.66 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 5.6 Hz, H-6b), 3.63 (d, 1H, J = 16.6 Hz, propargyl C$\underline{H}_2$), 3.28–3.39 (m, 4H, H-2, H-3, H-4, H-5). ^{13}C NMR (125 MHz, CD_3OD) δ 132.6 (2 × Ar), 129.4 (Ar), 129.3 (2 × Ar), 124.5 (Ar), 86.4 ($\underline{C}$≡C), 85.8 (C-1), 83.9 (C≡$\underline{C}$), 82.2, 79.7, 74.3, 71.5, 62.9 (C-6), 18.5 (propargyl $\underline{C}H_2$); HRMS (ESI) calcd. for $C_{15}H_{18}O_5SNa$ $[M + Na]^+$ 333.0767, found 333.0766.

5-Phenylpenta-2,4-diynyl 2,3,5,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (2.86)



To a solution of **2.80** (0.140 g, 0.362 mmol) and **2.85** (91.3 mg, 0.39 mmol) in acetone (20.0 mL) was added K_2CO_3 (0.050 g, 0.362 mmol) as described in the general procedure to afford **2.86** (86.0 mg, 43% based on 5-phenyl-2,4-pentadiyn-1-ol) as a syrup. R_f = 0.34 (hexanes–EtOAc, 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.51 (m, 2H, Ar), 7.28–7.37 (m, 3H, Ar), 5.28 (t, 1H, $J_{2,3} = J_{3,4}$ = 10.0 Hz, H-3), 5.11 (t, 1H, $J_{3,4} = J_{4,5}$ = 10.0 Hz, H-4), 5.06 (t, 1H, $J_{1,2} = J_{2,3}$ = 10.0 Hz, H-2), 4.77 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.26 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6a}$ = 5.0 Hz, H-6a), 4.17 (dd, 1H, $J_{6a,6b}$ = 12.5 Hz, $J_{5,6b}$ = 2.0 Hz, H-6b), 3.76 (ddd, 1H, $J_{4,5}$ = 10.0 Hz, $J_{5,6a}$ = 5.0 Hz, $J_{5,6b}$ = 2.0 Hz, H-5), 3.74 (d, 1H, J = 17.5 Hz, propargyl C$\underline{H}_2$), 3.45 (d, 1H, J = 17.5 Hz, propargyl C$\underline{H}_2$), 2.09 (s, 3H, C=OC$\underline{H}_3$), 2.07 (s, 3H, C=OC$\underline{H}_3$), 2.02 (s, 3H, C=OC$\underline{H}_3$), 2.00 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6 (<u>C</u>=O), 170.1 (<u>C</u>=O), 169.4 (<u>C</u>=O), 169.3 (<u>C</u>=O), 132.6 (2 × Ar), 129.3 (Ar), 128.4 (2 × Ar), 121.4 (Ar), 82.2, 77.7 (<u>C</u>≡C), 77.4 (<u>C</u>≡C), 76.0, 73.8, 73.5 (<u>C</u>≡C), 69.8, 68.3 (<u>C</u>≡C), 68.2, 61.9, 20.7 (C=O<u>C</u>H$_3$), 20.6 (3 × C=O<u>C</u>H$_3$), 18.8 (propargyl <u>C</u>H$_2$).

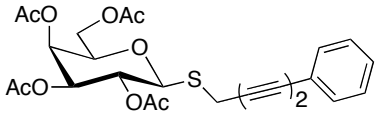
5-Phenylpenta-2,4-diynyl 1-thio-β-D-glucopyranoside (2.87)



To a solution of **2.86** (40 mg, 0.074 mmol) in CH_3OH (10.0 mL) at rt was added K_2CO_3 (10.2 mg, 0.074 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.87** (17.0 mg, 65%) as an oil: R_f =

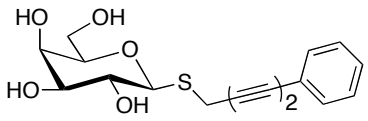
0.26 (CH_3OH–EtOAc, 1:10); ^{1}H NMR (500 MHz, CD_3OD) δ 7.47–7.49 (m, 2H, Ar), 7.32–7.40 (m, 3H, Ar), 4.58 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1), 3.88 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 2.0 Hz, H-6a), 3.82 (d, 1H, J = 17.2 Hz, propargyl C$\underline{H}_2$), 3.66 (dd, 1H, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6b}$ = 5.6 Hz, H-6b), 3.59 (d, 1H, J = 17.2 Hz, propargyl C$\underline{H}_2$), 3.25–3.39 (m, 4H, H-2, H-3, H-4, H-5). ^{13}C NMR (125 MHz, CD_3OD) δ 133.5 (Ar), 130.4 (Ar), 129.7 (Ar), 122.8 (Ar), 85.8 (C-1), 82.2, 80.5 (C≡C), 79.7, 77.5 (C≡C), 74.5 (C≡C), 74.4, 71.5, 68.0 (C≡C), 62.9, 18.4 (propargyl $\underline{C}H_2$).

5-Phenylpenta-2,4-diynyl 2,3,5,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (2.88)



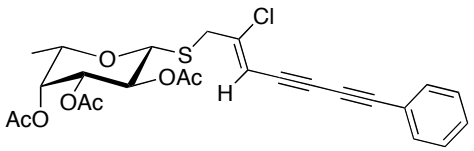
To a solution of **2.80** (0.140 g, 0.362 mmol) and **2.85** (81.9 mg, 0.35 mmol) in acetone (20.0 mL) was added K_2CO_3 (50.0 mg, 0.362 mmol) as described in the general procedure to afford **2.88** (80.0 mg, 39% based on 5-phenyl-2,4-pentadiyn-1-ol) as a white solid. Mp: 146–147 °C; R_f = 0.34 (hexanes–EtOAc, 3:1); IR (CH_2Cl_2, cast) 3059, 2968, 2245 (C≡C), 1754 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.52 (m, 2H, Ar), 7.30–7.39 (m, 3H, Ar), 5.46 (dd, 1H, $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 5.27 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 10.0 Hz, H-2), 5.12 (dd, 1H, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.5 Hz, H-3), 4.74 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.19 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6a}$ = 6.5 Hz, H-6a), 4.13 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6b}$ = 6.5 Hz, H-6b), 3.99 (td, 1H, $J_{5,6a}$ = $J_{5,6b}$ = 6.5 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 3.78 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 3.48 (d, 1H, J = 17.0 Hz, propargyl C$\underline{H}_2$), 2.17 (s, 3H, C=OC$\underline{H}_3$), 2.10 (s, 3H, C=OC$\underline{H}_3$), 2.06 (s, 3H, C=OC$\underline{H}_3$), 1.99 (s, 3H, C=OC$\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3 ($\underline{C}$=O), 170.2 ($\underline{C}$=O), 170.0 ($\underline{C}$=O), 169.7 ($\underline{C}$=O), 132.6 (2 × Ar), 129.3 (Ar), 128.4 (2 × Ar), 121.4 (Ar), 82.7, 77.8 ($\underline{C}$≡C), 77.4 ($\underline{C}$≡C), 74.7, 73.6 ($\underline{C}$≡C), 71.8, 68.2 ($\underline{C}$≡C), 67.3, 67.2, 61.4, 20.8 (C=O$\underline{C}H_3$), 20.7 (C=O$\underline{C}H_3$), 20.6 (2 × C=O$\underline{C}H_3$), 18.8 (propargyl $\underline{C}H_2$); HRMS (ESI) calcd. for $C_{25}H_{26}O_9Na$ $[M + Na]^+$ 525.1190, found 525.1189.

5-Phenylpenta-2,4-diynyl 1-thio-β-D-galactopyranoside (2.89)



To a solution of **2.88** (70.0 mg, 0.133 mmol) in CH_3OH (10.0 mL) at rt was added K_2CO_3 (18.4 mg, 0.133 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.89** (22.0 mg, 52%) as an oil: R_f = 0.29 (CH_3OH–EtOAc, 1:10); $[\alpha]_D$ –154.6 (*c* = 0.3, CH_3OH); IR (CH_3OH, cast) 3396 (O–H), 2916, 2244 (C≡C) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.45–7.47 (m, 2H, Ar), 7.32–7.40 (m, 3H, Ar), 4.54 (d, 1H, $J_{1,2}$ = 9.5 Hz, H-1), 3.90 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 1.0 Hz, H-4), 3.81 (d, 1H, *J* = 17.0 Hz, propargyl C$\underline{H}_2$), 3.78 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6a}$ = 7.0 Hz, H-6a), 3.70 (dd, 1H, $J_{6a,6b}$ = 11.5 Hz, $J_{5,6b}$ = 5.2 Hz, H-6b), 3.61 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.5 Hz, H-2), 3.59 (d, 1H, *J* = 17.0 Hz, propargyl C$\underline{H}_2$), 3.57 (ddd, 1H, $J_{5,6a}$ = 7.0 Hz, $J_{5,6b}$ = 5.2 Hz, $J_{4,5}$ = 1.0 Hz, H-5), 3.50 (dd, 1H, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 3.3 Hz, H-3); ^{13}C NMR (125 MHz, CD_3OD) δ 133.5 (Ar), 130.4 (Ar), 129.7 (Ar), 122.9 (Ar), 86.1 (C-1), 80.8 (C-5), 80.7 (C≡C), 77.5 (C≡C), 76.3 (C-3), 74.6 (C≡C), 71.4 (C-2), 70.6 (C-4), 67.9 (C≡C), 62.7 (C-6), 18.5 (propargyl $\underline{C}H_2$); HRMS (ESI) calcd. for $C_{17}H_{18}O_5SNa$ $[M + Na]^+$ 357.0767, found 357.0770.

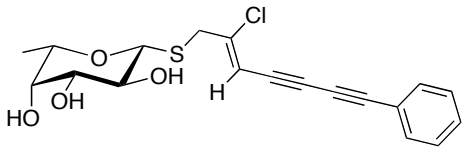
7-Phenylhepta-4,6-diyne-2-chloro-2-eneyl 2,3,4-tri-*O*-acetyl-1-thio-β-L-fucopyranoside (2.93)



To a solution of **2.80** (0.140 g, 0.362 mmol) and **2.92** (65.0 mg, 0.22 mmol) in acetone (20.0 mL) was added K_2CO_3 (50.0 mg, 0.362 mmol) as described in the general procedure to afford **2.93** (0.100 g, 90%) as a white solid: R_f = 0.32 (hexanes–EtOAc, 3:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.49–7.51 (m, 2H, Ar),

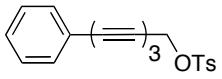
7.28–7.38 (m, 3H, Ar), 6.25 (t, 1H, J = 1.2 Hz, ClC=C<u>H</u>), 5.30 (dd, 1H, $J_{3,4}$ = 3.3 Hz, $J_{4,5}$ = 0.9 Hz, H-4), 5.26 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, H-2), 5.09 (dd, 1H, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 3.3 Hz, H-3), 4.95 (d, 1H, $J_{1,2}$ = 9.9 Hz, H-1), 4.43 (dd, 1H, J = 13.8 Hz, J = 1.2 Hz, SC<u>H</u>$_2$), 4.38 (dd, 1H, J = 13.8 Hz, J = 1.2 Hz, SC<u>H</u>$_2$), 3.88 (qd, 1H, $J_{5,6}$ = 6.3 Hz, $J_{4,5}$ = 0.9 Hz, H-5), 2.20 (s, 3H, C=OC<u>H</u>$_3$), 2.14 (s, 3H, C=OC<u>H</u>$_3$), 1.99 (s, 3H, C=OC<u>H</u>$_3$), 1.24 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (<u>C</u>=O), 170.4 (<u>C</u>=O), 169.5 (<u>C</u>=O), 144.8 (Cl<u>C</u>=CH), 132.4 (2 × Ar), 129.5 (Ar), 128.5 (2 × Ar), 121.5 (Ar), 114.7 (ClC=<u>C</u>H), 84.8 (<u>C</u>≡C), 83.7, 83.3 (<u>C</u>≡C), 77.0 (<u>C</u>≡C), 73.7 (<u>C</u>≡C), 73.6, 72.3, 70.3, 67.3, 46.8 (S<u>C</u>H$_2$), 20.8 (C=O<u>C</u>H$_3$), 20.7 (C=O<u>C</u>H$_3$), 20.6 (C=O<u>C</u>H$_3$), 16.4 (C-6).

7-phenylhepta-4,6-diyne-2-chloro-2-eneyl 1-thio-β-L-fucopyranoside (2.94)



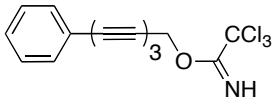
To a solution of **2.93** (68.0 mg, 0.130 mmol) in CH_3OH (10.0 mL) at rt was added K_2CO_3 (17.9 mg, 0.130 mmol) as described in the general procedure. Purification by column chromatography (EtOAc) afforded **2.94** (19.0 mg, 38%) as an oil: R_f = 0.28 (CH_3OH–EtOAc, 1:10); IR (CH_2Cl_2 cast) 3388 (O–H), 2934, 2209 (C≡C), 1595 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.51 (m, 2H, Ar), 7.33–7.42 (m, 3H, Ar), 6.48 (s, 1H, ClC=C<u>H</u>), 4.93 (d, 1H, $J_{1,2}$ = 9.4 Hz, H-1), 4.54 (dd, 1H, J = 12.8 Hz, J = 1.2 Hz, SC<u>H</u>$_2$), 4.46 (dd, 1H, J = 12.8 Hz, J = 1.2 Hz, SC<u>H</u>$_2$), 3.72 (qd, 1H, $J_{5,6}$ = 6.4 Hz, $J_{4,5}$ = 1.2 Hz, H-5), 3.67 (dd, 1H, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 1.2 Hz, H-4), 3.60 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.4 Hz, H-2), 3.51 (dd, 1H, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 3.6 Hz, H-3), 1.24 (d, 3H, $J_{5,6}$ = 6.4 Hz, H-6); ^{13}C NMR (125 MHz, CD_3OD) δ 150.5 (Cl<u>C</u>=CH), 133.4 (2 × Ar), 130.6 (Ar), 129.7 (2 × Ar), 122.9 (Ar), 110.2 (ClC=<u>C</u>H), 85.1, 85.1 (<u>C</u>≡C), 78.5 (<u>C</u>≡C), 78.0 (<u>C</u>≡C), 76.4, 76.3, 74.4 (<u>C</u>≡C), 73.1, 71.4, 46.8 (S<u>C</u>H$_2$), 17.0 (C-6); HRMS (ESI) calcd. for $C_{19}H_{19}O_4SClNa$ $[M + Na]^+$ 401.0585, found 401.0589.

Procedure for synthesis of triyne tosylate (2.95)



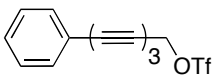
To a solution of tosyl chloride (19.1 mg, 0.100 mmol) in 0.500 mL of Et_2O was added 7-phenyl-2,4,6-heptatriyn-1-ol (**1.52**) (15.0 mg, 0.083 mmol). The reaction mixture was then cooled to –5 °C to –10 °C, powder KOH (41.5 mg, 0.741 mmol) was added while stirring. Keep stirring at –5 °C to –10 °C for 1 h. Work up was carried out by pouring the reaction mixture to 10.0 mL ice-water. Extract the mixture with Et_2O (3×15.0 mL). Combine the organic layers and dry with $MgSO_4$. Solvent was removed under vacuum to get crude **2.95** as oil.

Procedure for synthesis of triyne trichloroimidate (2.96)



To a solution of 7-phenyl-2,4,6-heptatriyn-1-ol (**1.52**) (20.0 mg, 0.110 mmol) in 1.50 mL of CH_2Cl_2 was added DBU (3.32 μL, 0.022 mmol). The reaction was stirred at rt for 30 min, then CCl_3CN (55.7 μL, 0.550 mmol) was added. The reaction was concentrated to dryness under vacuum after stirring for 2 h. Hexane (25.0 mL) was added and then the mixture was filtered through celite (1.50 g). The filtrate was concentrated under vacuum to give crude triyne trichloroimidate **2.96** as oil.

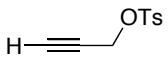
Procedure for synthesis of triyne triflate (2.97)



To a solution of 7-phenyl-2,4,6-heptatriyn-1-ol (**1.52**) (100 mg, 0.640 mmol) in 15.0 mL of CH_2Cl_2 was added DMPA (109 mg, 0.900 mmol). The reaction was cooled to –20 °C, Tf_2O (0.240 g, 83.2 mmol) was then added to the reaction.

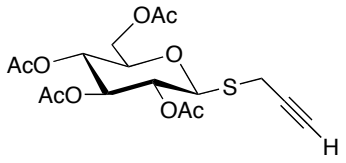
Keep stirring for 1 h, then the reaction mixture was filtered through celite (2.00 g). The filtrate was concentrated under vacuum to give crude **2.97** as oil.

Procedure for synthesis of monoyne tosylate (2.98)



To a solution of tosyl chloride (229 mg, 1.20 mmol) in 12.0 mL of Et_2O was added propargyl alcohol (56.0 mg, 1.00 mmol). The reaction mixture was then cooled to –5 °C to –10 °C, powder KOH (350 mg, 6.25 mmol) was added while stirring. Keep stirring at –5 °C to –10 °C for 1 h. Work up was carried out by pouring the reaction mixture to 25.0 mL ice-water. Extract the mixture with Et_2O (3×25.0 mL). Combine the organic layers and dry with $MgSO_4$. Solvent was removed under vacuum to get crude **2.98** as oil.

Prop-2-ynyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (2.99)



To a solution of **2.80** (380 mg, 0.982 mmol) and **2.98** (220 mg, 1.05 mmol) in acetone (21 mL) was added K_2CO_3 (120 mg, 0.870 mmol) as described in the general procedure to afford **2.99** (0.422 g, 98%) as a syrup:); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (t, 1H, $J_{2,3} = J_{3,4} = 9.4$ Hz, H-3), 5.02–5.10 (m, H-4, H-2), 4.73 (d, 1H, $J_{1,2} = 10.4$ Hz, H-1), 4.12 (dd, 1H, $J_{6a,6b} = 11.6$ Hz, $J_{5,6a} = 2.8$ Hz, H-6a), 4.22 (dd, 1H, $J_{6a,6b} = 12.5$ Hz, $J_{5,6b} = 4.8$ Hz, H-6b),4.17 (dd, 1H, $J_{6a,6b} = 12.5$ Hz, $J_{5,6b} = 2.8$ Hz, H-6b), 3.72 (m, 1H, H-5), 3.52 (d, 1H, $J = 16.4$ Hz, $J = 2.4$ Hz, propargyl C$\underline{H}_2$), 3.24 (d, 1H, $J = 16.4$ Hz, $J = 2.4$ Hz, propargyl C$\underline{H}_2$), 2.26 (t, 1H, $J = 2.4$ Hz, C≡CH), 2.07 (s, 3H, C=OC$\underline{H}_3$), 2.05 (s, 3H, C=OC$\underline{H}_3$), 2.01 (s, 3H, C=OC$\underline{H}_3$), 2.00 (s, 3H, C=OC$\underline{H}_3$).

3.5 General procedure and results for cancer cell lines test

3.5.1 Cell culture

MCF-7, HT-29, and HepG2/C3A cell lines were purchased from the American Type Culture Collection (ATCC). They were maintained in DMEM/HIGH culture media supplemented with 10% FBS and 2 mM L-glutamine. Cell cultures were grown in monolayers in a humidified atmosphere of 5% CO_2 and 95% air at 37 °C. The culture media were changed every 2–3 days. Cell cultures were passaged once a week using trypsin-EDTA (0.25%) to detach the cells from their culture flasks.

3.5.2. MTS Non-radioactive Cell Proliferation Assay

Rapidly growing cells were counted and seeded at a concentration of 1×10^4 cells/well in 100 μL total volume per well into a 96-well microtiter plate. After incubation at 37 °C for 24 h, the culture medium was removed and the cell assay media (DMEM-F12 media with 1.0 mg/mL human albumin, 5.0 mg/L human transferin, and 5.0 mg/L bovine insulin) with or without tested compounds in 100 μL total volume were added to each well containing the exponentially growing cancer cells. Culture wells (quintuplicate per sample) were incubated for 3 days at 37 °C (5% CO_2, 95% air). Then 20 μL of MTS dye solution was added to each sample well. After 2–2.5 hours of incubation at 37 °C, the absorbance of formazan was recorded at 490 nm. Cell viability was calculated as a percentage of control wells, which contained the cell assay media only. Statistical and graphical analysis information was determined using Origin Pro 7.5 software (OriginLab Corp.) and Microsoft Excel (Microsoft Corp.).

3.5.3 Results of cell lines test

Results of cancer cell lines test are summarized in table below.

Table 3.1 Results of cancer cell lines test.

Allive Cell (%) / Comp.	Target compound concentration (μM)									
	Against MCF-7 breast cancer cell lines					Against HT-29 colon cancer cell lines				
	100	50	25	12.5	10	100	50	25	12.5	10
2.21	83.9	-	-	-	-	80.5	-	-	-	-
2.23	83.9	-	-	-	-	81.4	-	-	-	-
2.25	91.0	-	-	-	-	89.5	-	-	-	-
2.27	86.6	-	-	-	-	84.3	-	-	-	-
2.29	84.2	-	-	-	-	80.2	-	-	-	-
2.31	87.0	-	-	-	-	84.8	-	-	-	-
2.33	100	-	-	-	-	98.1	-	-	-	-
2.35	97.0	-	-	-	-	94.3	-	-	-	-
2.44	81.9	-	-	-	-	79.0	-	-	-	-
2.46	81.4	-	-	-	-	78.7	-	-	-	-
2.48	76.9	-	-	-	-	76.0	-	-	-	-
2.51	82.6	-	-	-	-	81.2	-	-	-	-
2.52	84.1	-	-	-	-	81.5	-	-	-	-
2.54	5.0	7	77	77.6	-	6.4	10	69	100	-
1.61	6.0	6.2	44	69.0	-	2.6	4.1	28	71	-
2.56	5.0	3.1	3.5	6.4	83.0	2.8	4.6	11	54	-
1.60	1.5	5.2	9.8	11.0	76.0	1.4	3.8	10	59	-
2.58	60.8	-	-	-	-	58.4	-	-	-	-
2.60	66.7	-	-	-	-	64.2	-	-	-	-
2.68	62	-	-	-	-	65.1	-	-	-	-
2.70	96	-	-	-	-	92.4	-	-	-	-
2.72	100	-	-	-	-	99.1	-	-	-	-
2.74	100	-	-	-	-	98.7	-	-	-	-
2.76	91	-	-	-	-	90.5	-	-	-	-
2.84	80	-	-	-	-	81.4	-	-	-	-
2.87	72	-	-	-	-	73.2	-	-	-	-
2.89	82	-	-	-	-	81.0	-	-	-	-
2.94	2.6	6.7	27	41	-	7.8	11	20	72	-
1.52	7.5	-	24	52	72	3.8	4.6	47	-	-

3.6 General procedure for bacterial test

3.6.1. Media preparation

LB (Luria–Burtani): 1 g yeast extract, 2 g tryptone and 2 g NaCl were added to 200 mL water in a 250 mL flask. Then half of the solution was separated into two bottles, each bottle for 50 mL. The other solution in the flask was added 1.5 g Agar.

NB (Nutrient Broth): 1.6 g NB was added to 200 mL water in a 250 mL flask. Then half of the solution was separated into two bottles, each bottle for 50 mL. The other solution in the flask was added 1.5 g Agar.

MHA (Mueller–Hinton Agar): 8.4 g MHA and 6.8 g Agar were added to 400 mL water in a 1 L flask.

All the media solutions were autoclaved for 15 minus and then the three flasks were put into a 50 °C water bath for about 30 minutes. The solution was transferred to culture plates, 25 mL each plate. Culture plates were stored in refrigerator after the medium cooled down and turned solid.

3.6.2. General anti-bacterial assay

Frozen bacterial were streaked agar culture plate (*E. coli* on a LB agar culture plate and *Bacillus* on a NB agar culture plate) with sterile wooden applicator sticks and then were incubated at 37 °C for overnight. Colonies of bacterial (2–4), were dissolved into 4 mL media solution (*E. coli* in LB solution and *Bacillus* in NB solution) and then incubated at 35 °C for about 5 hours. The bacterial solution concentrations were then checked by a microplate spectrophotometer. The solution was diluted with medium solution until the UV reading is 0.1 at 640 nm. The bacterial solution was streaked over the entire agar surface evenly with a

sterile cotton swab. Paper plates (6 mm) with drug solution were loaded onto the surface of the culture plates and then incubated at 35 °C for 17 hours. The diameters of the transparent zones of inhibition on the plates were measured.

3.6.3 Result of bacterial test

Results of bacterial test are summarized in the table below. Zone diameter equal 6.0 mm means target molecule has no activity against bacterial; larger than 6.0 mm means target molecule has activity against bacterial.

Table 3.2 results of bacterial test.

Compounds	Zone diameter (mm)		Compounds	Zone diameter (mm)	
	Against *Escherichia coli.*	Against *Bacillus subtilis*		Against *Escherichia coli.*	Against *Bacillus subtilis*
Penicillin. G	6.0	27.9	**1.61**	6.0	8.1
Streptomycin	15.9	19.0	**2.56**	6.0	10.5
Tetracycline	23.5	30.8	**1.60**	6.0	9.7
2.21	6.0	6.0	**2.58**	6.0	6.0
2.23	6.0	6.0	**2.60**	6.0	6.0
2.25	6.0	6.0	**2.62**	6.0	6.0
2.27	6.0	6.0	**2.68**	6.0	6.0
2.29	6.0	6.0	**2.70**	6.0	6.0
2.31	6.0	6.0	**2.72**	6.0	6.0
2.33	6.0	6.0	**2.74**	6.0	6.0
2.35	6.0	6.0	**2.76**	6.0	6.0
2.44	6.0	6.0	**2.84**	6.0	6.0
2.46	6.0	6.0	**2.87**	6.0	6.0
2.48	6.0	6.0	**2.89**	6.0	6.0
2.51	6.0	6.0	**2.94**	6.0	6.0
2.52	6.0	6.0	**1.52**	6.0	10.4
2.54	6.0	9.4			

-means no test.

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