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A hybrid approach to new molecular scaffolds*

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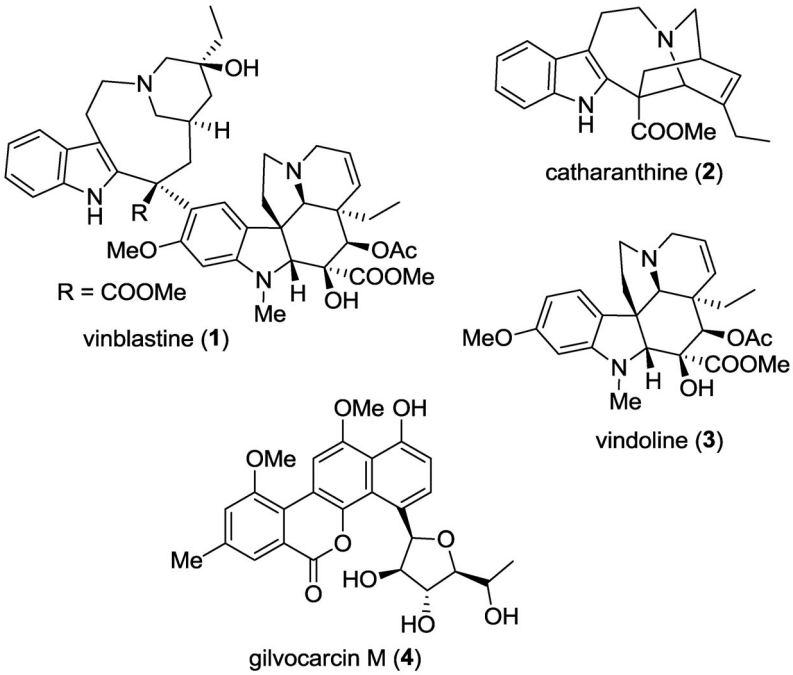
Abstract: Our various efforts toward the synthesis of a set of novel sugar hybrid scaffolds of several biologically active natural products such as taxol, steroids, β-lactams, and otteliones are presented. We have shown the application of the hybrid approach to design and rapidly generate a library of novel natural product-like compounds, which may have interesting biological features, using metathesis and/or cycloaddition reactions as key steps.

Keywords: hybrid natural products; natural product synthesis; new molecular scaffolds; olefin metathesis; organic synthesis; stereocontrolled synthesis; tandem reactions.

INTRODUCTION

Nature has long been the rich source of leads in drug discovery, and most of today's drugs are either derived from Nature or synthetic derivatives thereof. Furthermore, most drugs of yesterday's origin are no longer active primarily due to multidrug resistance (MDR), such as antibiotic, neoplastic, and anti-



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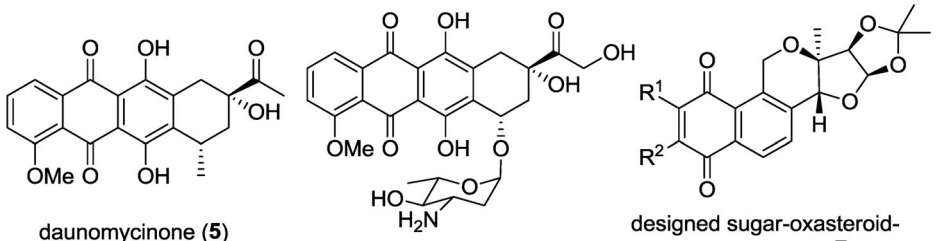
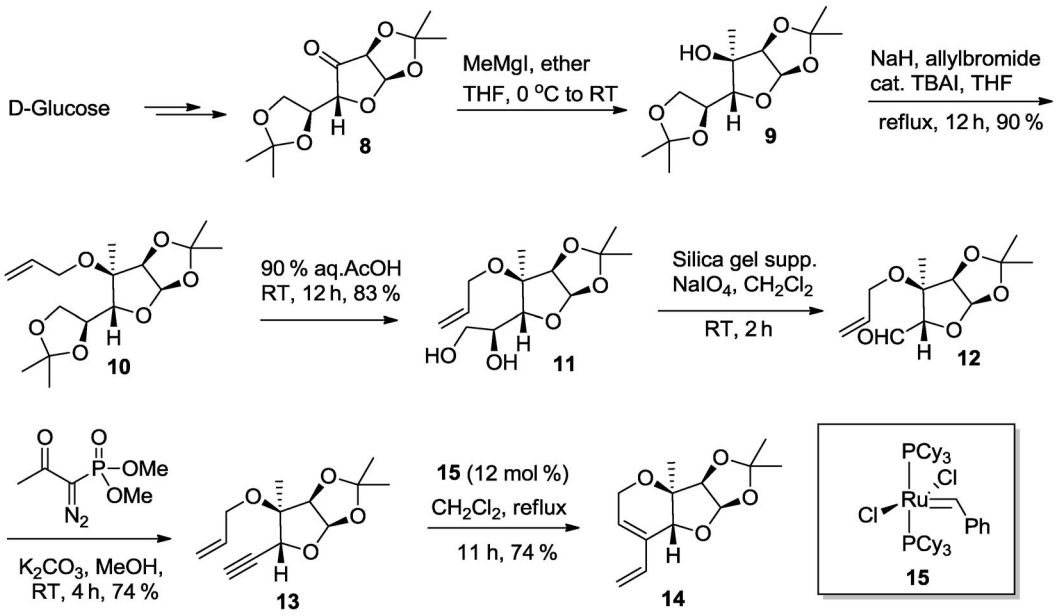
fungal resistance. In order to address this issue, great strides have been made to identify novel compounds with improved medicinal properties. Among the various methods known for the rapid synthesis of a library with a diverse array of compounds, the hybrid approach [1] has become the more preferred method as it combines the structural features of different classes of compounds to provide compounds with improved or unprecedented biological activities [2] in a short span. Nature has ingeniously produced several hybrid molecules through mixed biosynthetic pathways. For example, vinblastine **1** is a natural dimeric indole alkaloid consisting of two different classes of natural alkaloids catharanthine **2** and vindoline **3**. Whereas catharanthine **2** and vindoline **3** show weak cytotoxicity, vinblastine **1** exhibits high cytotoxicity towards cancer cells. Similarly, (–)-gilvocarcin M **4**, a hybrid of a carbohydrate and a tetracycline, shows antitumor and antibiotic activities. Inspired by Nature's ingenuity, synthetic chemists have also designed and synthesized a library of natural and unnatural hybrid compounds with different modes of biological functions [3]. In this regard, we also developed interest in the design and synthesis of a suite of novel hybrid compounds of several natural products, and herein we present a brief overview of our various approaches for the synthesis of our designed hybrids.

SYNTHESIS OF SUGAR-OXASTEROID-QUINONE HYBRIDS

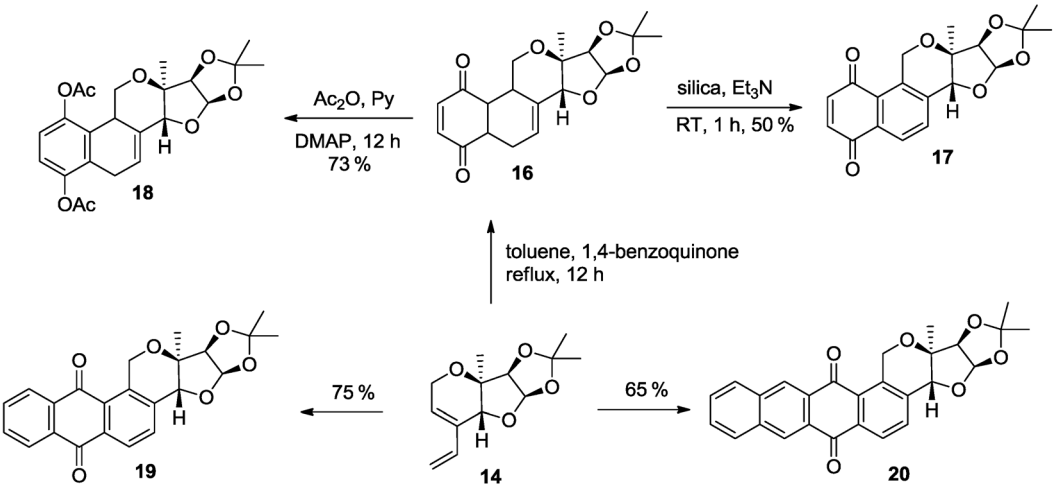
Steroids represent an important class of natural products owing to their high ability to penetrate cells and bind to membrane receptors, and consequently several strategies [4] have been developed for the synthesis of this class of natural products. On the other hand, the antineoplastic activity of anthracycline antibiotics such as daunomycinone **5** and doxorubicin **6** that has rendered their application in the treatment of cancer [5] has sparked the attention of synthetic chemists to report several strategies for the synthesis of simpler analogues of these natural products [6]. In view of the biological importance of these two classes of natural products, we have designed a novel class of sugar-oxasteroid-quinone hybrids **7** by combining the structural features of steroid and quinone with a sugar unit [7]. Our strategy for the synthesis of these hybrid molecules relies on a sequential enyne metathesis of an enyne, followed by Diels–Alder reaction [8] of the resulting 1,3-diene with a variety of 1,4-quinones to afford a range of hybrid scaffolds. Thus, our synthetic strategy commenced with the construction of the 1,3-diene. To this end, the ketone **8** was subjected to addition of methyl Grignard to provide tertiary alcohol **9**, which was protected as its allyl ether to yield olefin **10** in good yield (Scheme 1). Selective cleavage of the more exposed acetonide group under acidic conditions was followed by oxidative cleavage of the resulting diol to give aldehyde **12**. Homologation of aldehyde **12** with Bestmann–Ohira reagent afforded the required enyne **13**, which underwent an intramolecular enyne metathesis uneventfully, as anticipated, in the presence of Grubbs first-generation catalyst **15** to furnish the diene **14** in good yield.



The attempted intermolecular Diels–Alder reaction of diene **14** with 1,4-benzoquinone proceeded smoothly, affording cycloadduct **16**. However, attempts to purify the cycloadduct by silica gel column chromatography led to a mixture of compounds containing the desired sugar-oxasteroid-quinone hybrid **17** along with other unidentified products (Scheme 2). Hence, we planned to treat the crude cycloadduct



Scheme 1 Synthesis of sugar-derived 1,3-diene.

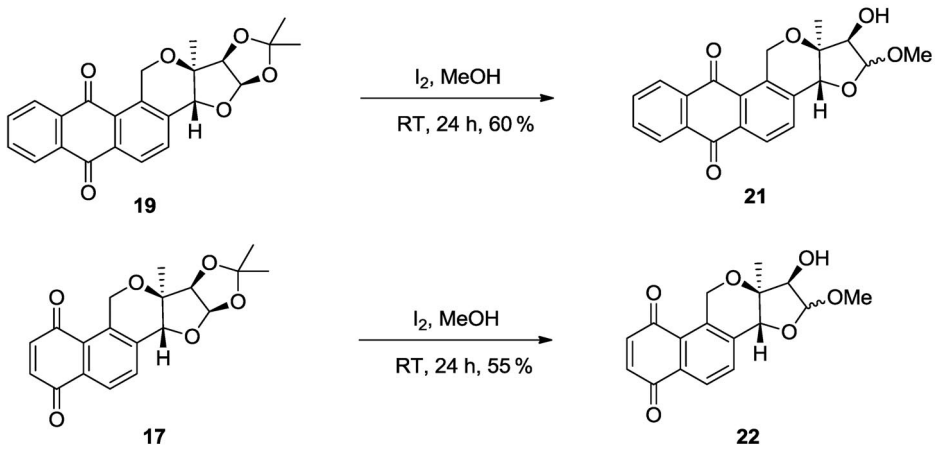


Scheme 2 Synthesis of sugar-oxasteroid-quinone hybrids.

with triethylamine and silica gel prior to purification. Thus, as anticipated, execution of the proposed protocol worked well, providing the desired sugar-oxasteroid-quinone hybrid **17** in moderate yield.

In a similar manner, hybrids **19** and **20** were also synthesized through Diels–Alder reaction of diene **14** with 1,4-naphthoquinone and 1,4-anthraquinone, respectively. On the other hand, treatment of the crude cycloadduct **16** with acetic anhydride and pyridine afforded diacetylated hybrid **18** in good yield.

The synthesized hybrids **19** and **17** were treated with iodine in the presence of methanol to afford derivatives **21** and **22**, respectively (Scheme 3). These derivatives were tested for biological activity against various cancer cell lines. Whilst compound **21** showed no appreciable activity against any cancer cell line, interestingly, derivative **22** exhibited moderate to good activity against a set of cancer cell



Scheme 3 Derivatization of the sugar-quinone hybrids.

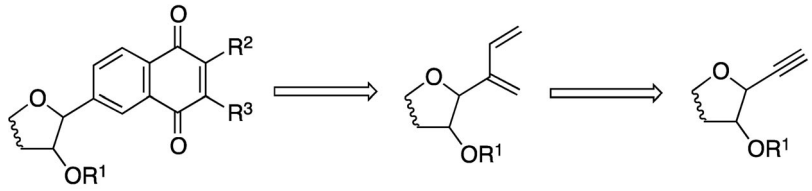
lines (Table 1). Inspired by the significant biological activity of this representative compound, a library of hybrid compounds of this class has been synthesized, and their biological evaluation against various cancer cell lines is underway.

Table 1 In vitro studies of compound **22** against various cancer cell lines.

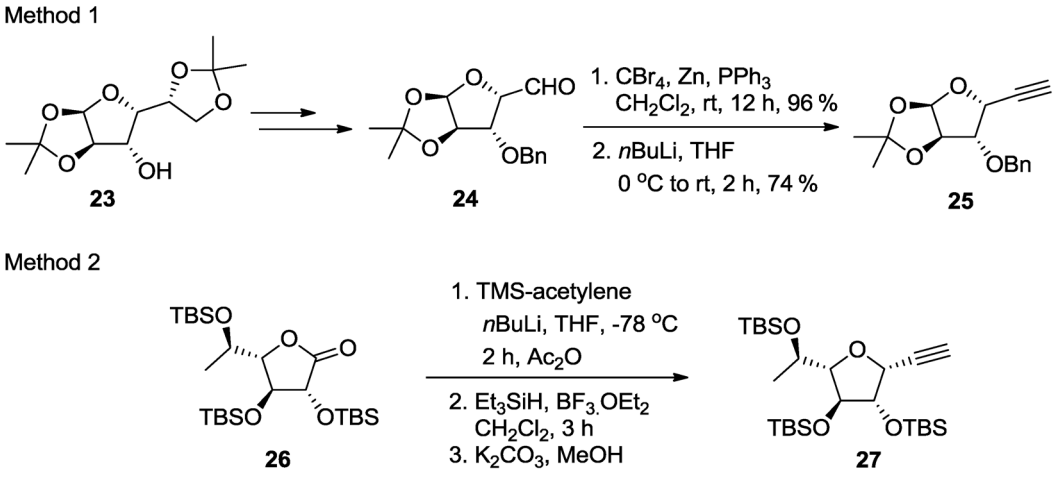
Cancer cell lines	IC_{50} (μM)
Pancreas	2.64
Oral	2.75
Colon	4.37
Breast	4.38
Leukemia	7.38
Ovary	8.63

SYNTHESIS OF *C*-ARYL GLYCOSIDES

The *C*-aryl glycosides constitute an important class of glycosides wherein the sugar unit is directly attached to an aromatic moiety at the anomeric position through a C–C bond instead of the usual C–O bond. The subtle change in the connectivity has dramatically increased the stability of *C*-aryl glycosides towards both enzymatic and acidic hydrolysis compared to the conventional *O*-glycosides [9]. In view of the importance of *C*-aryl glycosides, and considering them as a hybrid of sugar and aromatics, we developed curiosity in devising an elegant approach for the synthesis of *C*-aryl glycosides [10]. As shown in Scheme 4, we envisioned that the *C*-aryl glycoside skeleton could be constructed through a Diels–Alder reaction of a diene with various quinones. Of further interest is an enyne metathesis of an alkyne as a means to introduce the required diene at the anomeric position. We preferred two different methods for the introduction of acetylene group at the anomeric center (Scheme 5). In the first method, aldehyde **23** was converted into alkyne **25** through Corey–Fuchs olefination followed by treatment with *n*-BuLi. The second method involves addition of lithium (trimethylsilyl)acetylide to lactone **26** followed by reductive deoxygenation and removal of the trimethylsilyl (TMS) group.

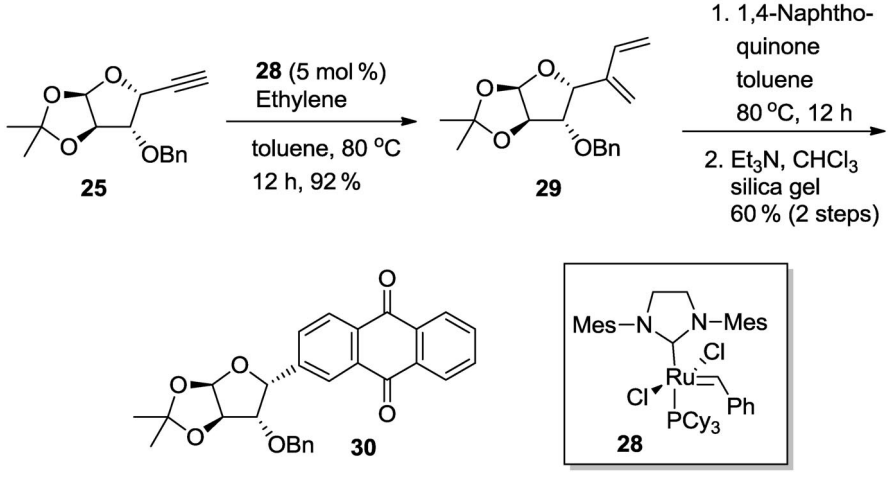


Scheme 4 Retrosynthetic plan for the synthesis of *C*-aryl glycosides.



Scheme 5 Synthesis of alkynyl glycosides.

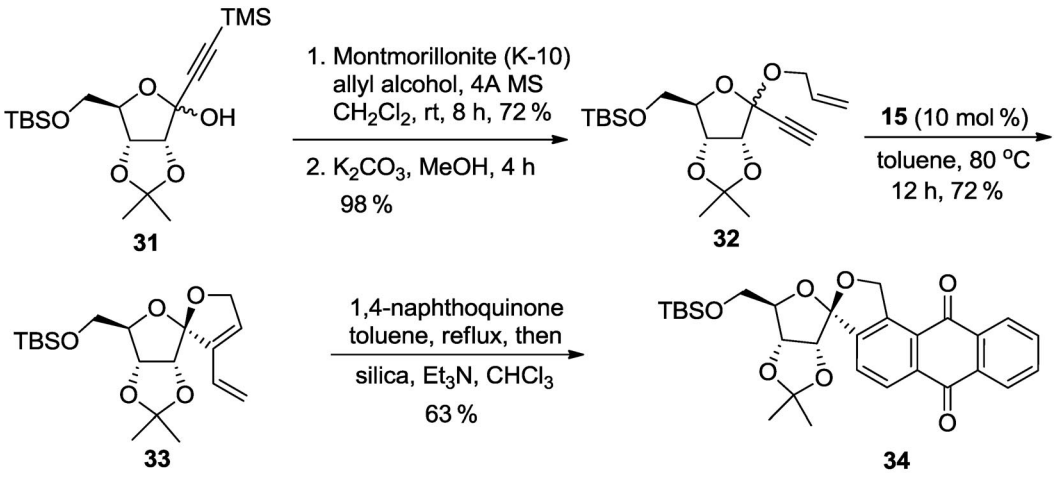
Thus, after having synthesized the alkynyl glycosides following the above two protocols, we next examined the enyne metathesis to introduce the diene required for the Diels–Alder reaction. Pleasingly, the endeavored enyne metathesis of alkyne **25** in the presence of Grubbs second-generation catalyst **28** afforded the requisite diene **29** in excellent yield (Scheme 6). The Diels–Alder reaction of diene **29** with 1,4-naphthoquinone followed by oxidative aromatization furnished the *C*-aryl glycoside **30** in good



Scheme 6 Synthesis of *C*-aryl glycosides.

yield. In a similar manner, a variety of dienes were prepared and treated with different quinones to give a range of *C*-aryl glycosides.

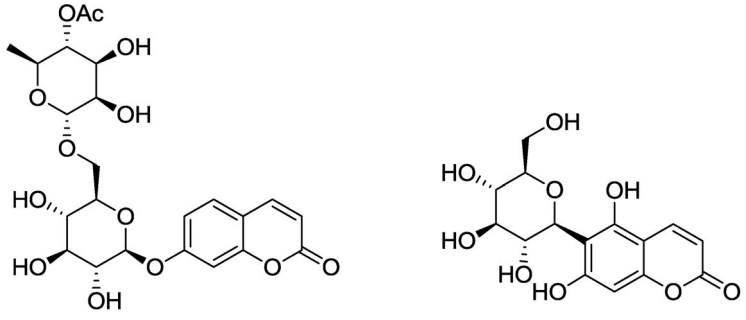
We have also developed an elegant strategy for the synthesis of an array of spiro-*C*-aryl glycosides (Scheme 7). Alkylation of hemiketal **31** with allyl alcohol followed by removal of silyl group afforded enyne **32**, which underwent an intramolecular enyne metathesis in the presence of Grubbs first-generation catalyst **15** to provide diene **33** in good yield. The key Diels–Alder reaction of diene **33** with 1,4-naphthoquinone, and subsequent oxidative aromatization provided spiro-*C*-aryl glycoside **34** in good yield. Following the similar protocol, a library of spiro-*C*-aryl glycosides was synthesized from a variety of dienes and quinones.



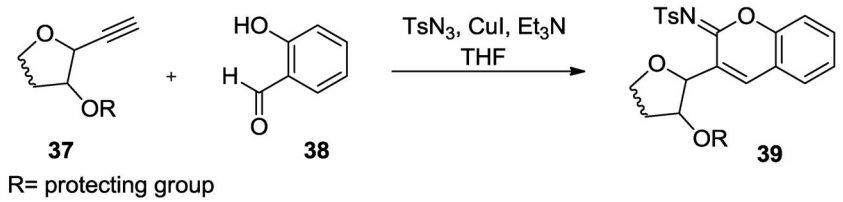
Scheme 7 Synthesis of spiro-*C*-aryl glycosides.

SYNTHESIS OF 3-*C*-LINKED GLYCOSYL IMINOCOUMARINS

Glycosides having a sugar unit attached to a coumarin pharmacophore constitute a novel class of glycosides, named coumarin glycosides [11]. Although *O*-glycosyl coumarins [12] are naturally abundant, the existence of *C*-glycosyl coumarin is rare in Nature, occurring only in dauroside D **36** [13]. Coumarin glycosides display a wide range of biological activities, such as anti-inflammatory, anticoagulant, anticancer, and antibacterial activities [14]. On the other hand, iminocoumarins find their uses as inhibitors of protein tyrosine kinase in cancer research [15]. Hence, the biological importance of coumarin inspired us to design glycosyl iminocoumarins where a carbohydrate unit is attached to an



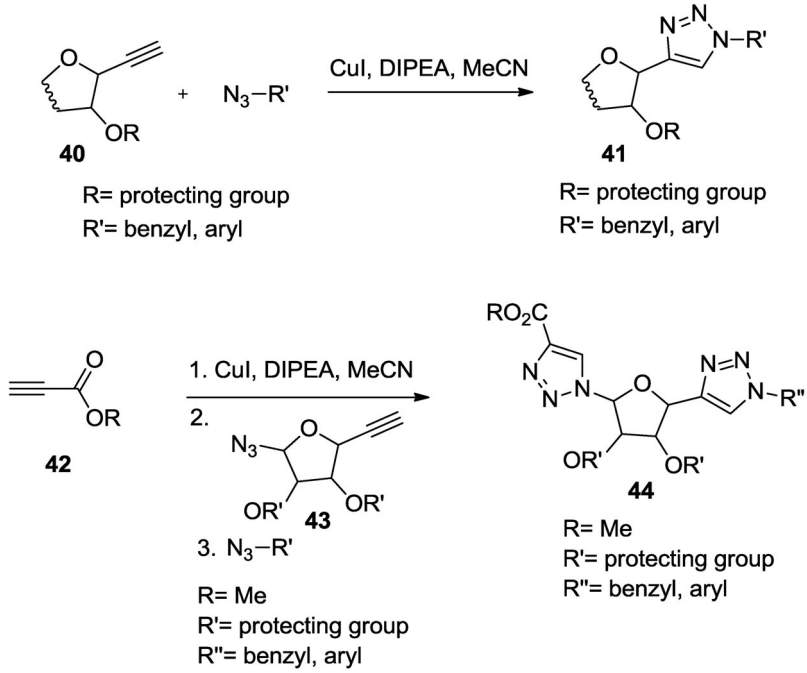
iminocoumarin unit, aiming to synthesize a new class of glycosides with interesting biological profile. Wang and co-workers successfully extended a Cu(I)-catalyzed multicomponent reaction of alkyne and sulfonyl azide, originally developed by Chang and co-workers, for the synthesis of iminocoumarins [16]. In continuation of our interest in exploring the application of sugar-derived alkynes, we wanted to use a similar Cu(I)-catalyzed reaction of sugar-derived alkynes **37** with tosyl azide and 2-hydroxy benzaldehyde **38** to provide *C*-glycosyl iminocoumarins **39**, which might also serve as precursors of coumarin 3-*C*-glycosides (Scheme 8) [17]. Thus, after screening various solvents and bases, it was concluded that Et_3N and tetrahydrofuran (THF) were the most optimal base and solvent, respectively, and using the same conditions we have eventually synthesized a variety of 3-*C*-glycosyl iminocoumarins.



Scheme 8 Synthesis of 3-*C*-linked glycosyl iminocoumarins.

SYNTHESIS OF BISTRIAZOLES

1,4-Disubstituted-1,2,3-triazoles constitute an important class of medicinally active compounds that find a range of applications, such as anti-allergic, antibacterial, and anti-HIV agents [18]. Furthermore, 1,4-disubstituted-1,2,3-triazoles are also widely used in herbicides, fungicides, and dyes [19]. Considering the biological significance of 1,4-disubstituted-1,2,3-triazoles and continuing our interest

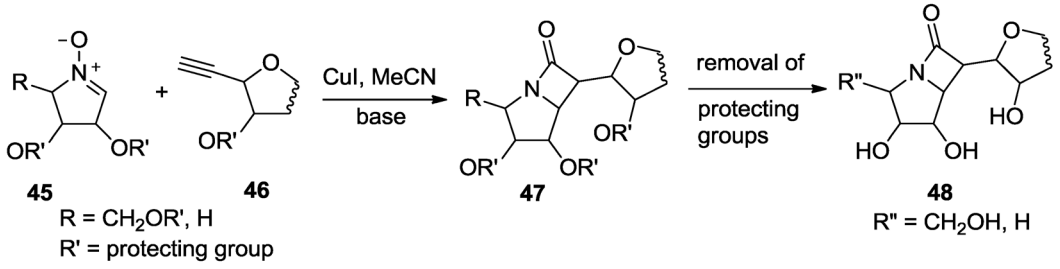


Scheme 9 Synthesis of bistriazoles using "click" approach.

in the application of sugar-derived alkynes, we developed a strategy [20] involving the formation of multiple triazole rings in one pot utilizing the "click" [21] reaction. Thereby, it allows us to design another class of *C*-aryl glycosides **41**. Pleasingly, utilizing the Cu(I)-catalyzed "click" reaction between a sugar-derived alkyne and an azide, we have synthesized a wide array of *C*-aryl glycosides **41**. Further, a variety of bistriazoles **44** are synthesized by a tandem "click-click" approach using sugar-derived azido-alkyne, methyl propiolate, and a variety of azides (Scheme 9).

SYNTHESIS OF SUGAR-β-LACTAM-AZASUGAR HYBRIDS

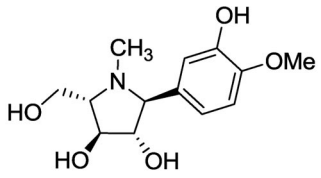
The β-lactam antibiotics [22], such as penicillins, cephalosporins, carbapenems, and monobactams, have been successfully used as first-level antibiotics. However, due to the emerging antibiotic resistance of bacteria, these antibiotics are no longer active. Hence, there has been an urgent need for the design and synthesis of new molecular scaffolds that are structurally similar to the existing antibiotics but with additional features. Besides their antibiotic activity, β-lactams have also served as important synthetic intermediates in organic synthesis [23]. In view of the biological importance of β-lactams, and in continuation of our interest in exploring the chemistry of nitrones [24], we have developed a simple strategy for the synthesis of sugar-β-lactam-azasugar hybrids **48** by combining the structural features of azasugar, β-lactam, and a sugar unit [25]. In our search for various methods to link the sugar and the azasugar through a β-lactam unit, the comparatively less explored Kinugasa reaction [26] that involves a Cu(I)-mediated 1,3-dipolar cycloaddition of a nitrone with an alkyne and subsequent protonation, seemed to us the appropriate method for the synthesis of the designed β-lactam hybrids. Thus, we investigated the Kinugasa reaction of sugar-derived nitrone **45** with sugar-derived alkyne **46** in the presence of CuI with different bases in acetonitrile to optimize the reaction conditions. Eventually, dicyclohexylamine proved to be the appropriate base providing the desired Kinugasa product **47** in good yield along with trace to little amount of the alkyne-dimerized product. Following this optimized protocol, a variety of sugar-β-lactam-azasugar hybrids **48** were synthesized through Kinugasa reaction of a range of sugar-derived cyclic nitrones with different sugar-derived alkynes followed by removal of the protecting groups (Scheme 10).



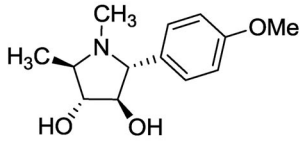
Scheme 10 Synthesis of sugar-β-lactam-azasugar hybrids.

SYNTHESIS OF AZA-*C*-ARYL GLYCOSIDES

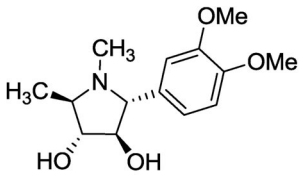
Our continued interest in the synthesis of glycosides also led to the development of a two-step strategy for the synthesis of aza-*C*-aryl glycosides, which were designed as hybrids of azasugar and aromatic scaffolds [27]. In view of the biological importance of polyhydroxylated pyrrolidine natural products **49–53** [28], we envisaged that the aza-*C*-aryl glycoside framework could be derived from the corresponding isoxazoline through N–O bond cleavage, and the isoxazoline could, in turn, be obtained through 1,3-dipolar cycloaddition of a sugar-derived cyclic nitrone with a benzyne. Thus, treatment of *o*-(trimethylsilyl)aryl triflate **55** with CsF generated in situ the desired benzyne, which subsequently



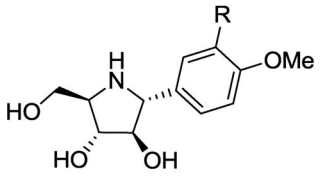
(-)-codonopsinol (**49**)



(-)-codonopsinine (**50**)

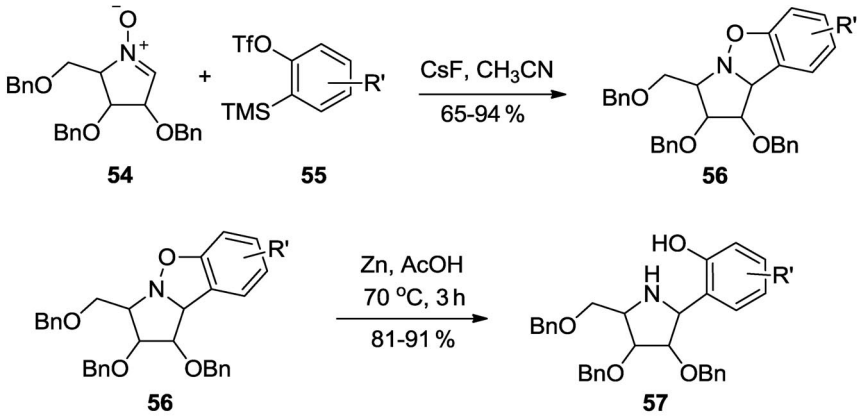


(-)-codonopsine (**51**)



radicamine A, R = OH (**52**)
radicamine B, R = H (**53**)

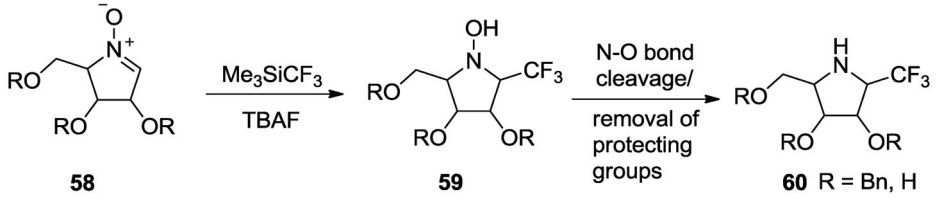
underwent 1,3-dipolar cycloaddition with nitrone **54** in the same pot providing isoxazoline **56** in good yield. Cleavage of the N–O bond was achieved by reduction with Zn and AcOH at elevated temperature to furnish the required aza-*C*-aryl glycoside **57** in excellent yield (Scheme 11). In a similar manner, a variety of aza-*C*-aryl glycosides were synthesized to show the diversity, from different substituted sugar-derived nitrones and benzyne precursors.



Scheme 11 Synthesis of aza-*C*-aryl glycosides.

SYNTHESIS OF TRIFLUOROMETHYL ANALOGUES OF POLYHYDROXY PYRROLIDINES

Amines bearing a trifluoromethyl group at the α-position constitute an important class of biologically active compounds [29]. The strong electron-withdrawing nature and large hydrophobic domain of the trifluoromethyl group can significantly influence the basicity and solubility of amines modifying the bioavailability and stability of target drugs. As part of our studies on the sugar-derived cyclic nitrones [24] and fluorinated compounds, we developed interest to synthesize chiral trifluoro-methylated pyrrolidine hybrid molecules **60** (Scheme 12). Trifluoromethyl group was introduced by treating the sugar-derived nitrone **58** with (trifluoromethyl) trimethylsilane (Ruppert–Prakash's reagent) [30]. The result-

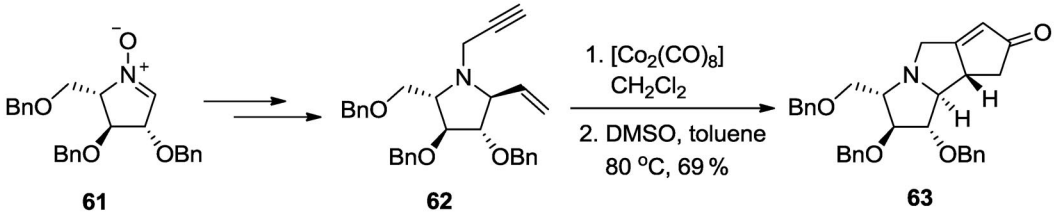


Scheme 12 Synthesis of trifluoromethylated polyhydroxylated pyrrolidines.

ant hydroxylamine **59** upon N–O bond cleavage [24] and global deprotection yielded trifluoromethylated polyhydroxylated pyrrolidine **60** (Scheme 12). For diversity, we performed the same series of reactions on various sugar-derived cyclic nitrones to afford a set of trifluoromethylated polyhydroxylated pyrrolidine analogs.

SYNTHESIS OF LINEAR 4-AZATRIQUINANES

Being impressed by the promising biological activities of the hetero-analogues of triquinanes, namely, azatriquinanes [31], and oxatriquinanes [32] and also with continuation of our work on sugar-derived nitrones, we became interested in developing a simple approach to the synthesis of a set of linear azatriquinanes using Pauson–Khand reaction [33] as the key step. The synthesis of enyne **62** involved the addition of vinyl magnesium bromide to the sugar-derived cyclic nitrone **61**, cleavage of the N–O bond in the resultant hydroxyl amine followed by *N*-propargylation (Scheme 13).



Scheme 13 Synthesis of linear 4-azatriquinanes.

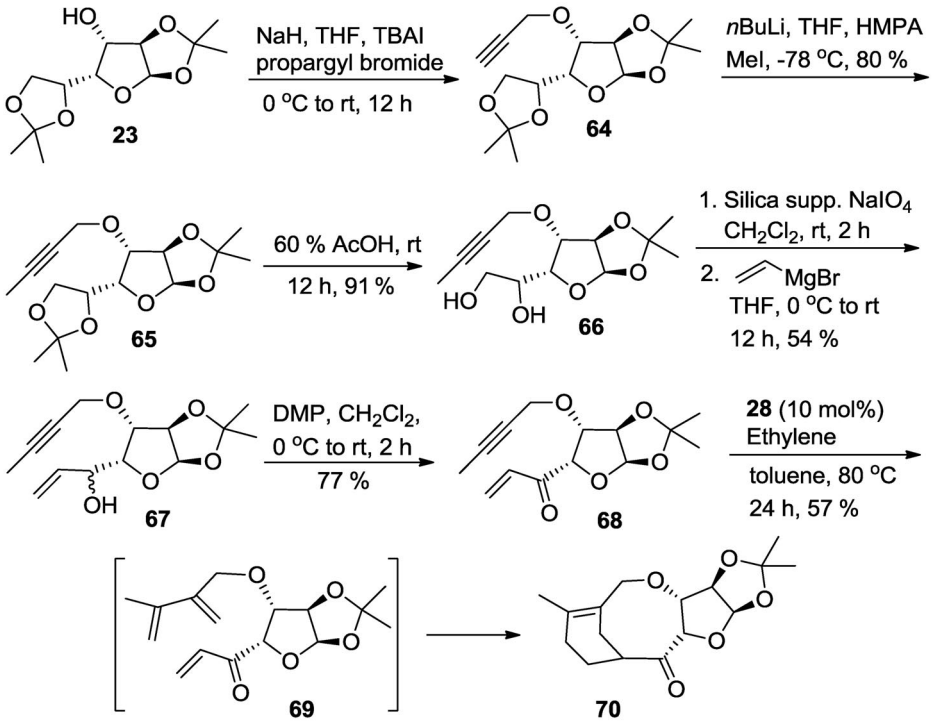
Pleasingly, treatment of enyne **62** with $[Co_2(CO)_8]$ and subsequent treatment with dimethyl sulfoxide (DMSO) led to exclusive formation of a single diastereoisomer **63** in good yield (Scheme 13). By using similar reaction sequence, a set of linear azatriquinanes were prepared starting from different sugar-derived cyclic nitrones, in good to excellent yields [34].

SYNTHESIS OF TAXA-OXA-SUGAR HYBRID

Taxol (paclitaxel), isolated in 1967 from the bark of *Taxus brevifolia* by Wall and Wani, was reported to combat cancer cells by a novel mechanism [35a]. Taxol has been shown to inhibit cell division of cancer cells and hence leads to cell death by arresting or disturbing the polymerization/depolymerization dynamics of microtubules through binding [35b]. The outstanding biological profile of taxol has extensively inspired the synthetic community, and consequently several groups have reported their attempts toward the synthesis of taxol. Several hybrid molecules of taxol with other natural products have also been designed and synthesized [36]. However, most of these hybrids exhibited diminished cytotoxic activities compared to their parent molecules. In view of the biological importance of taxol, and in view of the need for developing new hybrid scaffolds of taxol, we developed interest in the syn-

thesis of taxa-oxa-sugar hybrids, which were designed by combining the structural features of taxol and sugar [37].

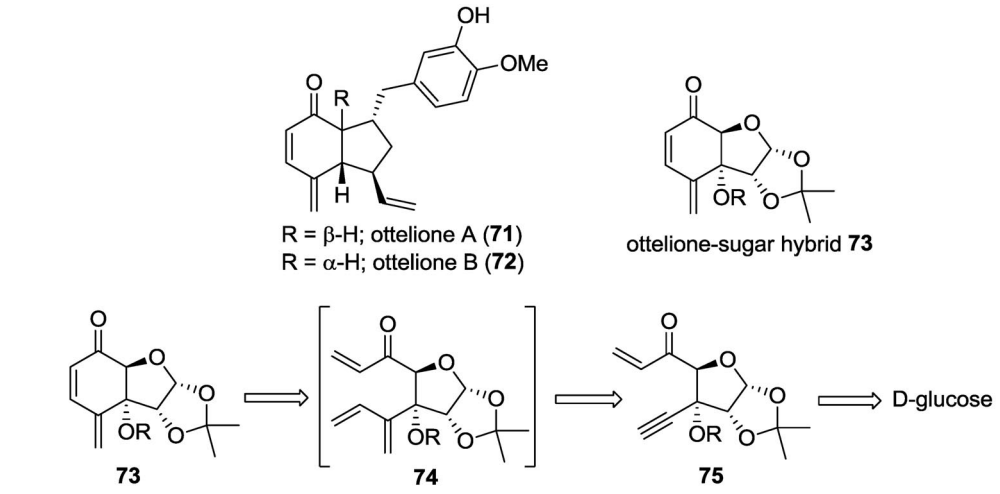
To this end, diacetone-D-glucose **23** was subjected to propargylation to afford propargyl ether **64**, which upon methylation gave alkyne **65** in good yield (Scheme 14). Cleavage of the more exposed acetonide group under mild acidic conditions provided the diol **66**, which upon oxidative cleavage and subsequent addition of vinyl magnesium bromide furnished allylic alcohol **67** as a mixture of diastereomers. Oxidation of alcohol **67** with DMP produced the required enyne **68**, which underwent a one-pot tandem cross enyne metathesis with ethylene in the presence of Grubbs second-generation catalyst **28** followed by an intramolecular Diels–Alder reaction of intermediate **69** in toluene at elevated temperature, to provide the taxa-oxa-sugar hybrid **70** in 57 % yield.



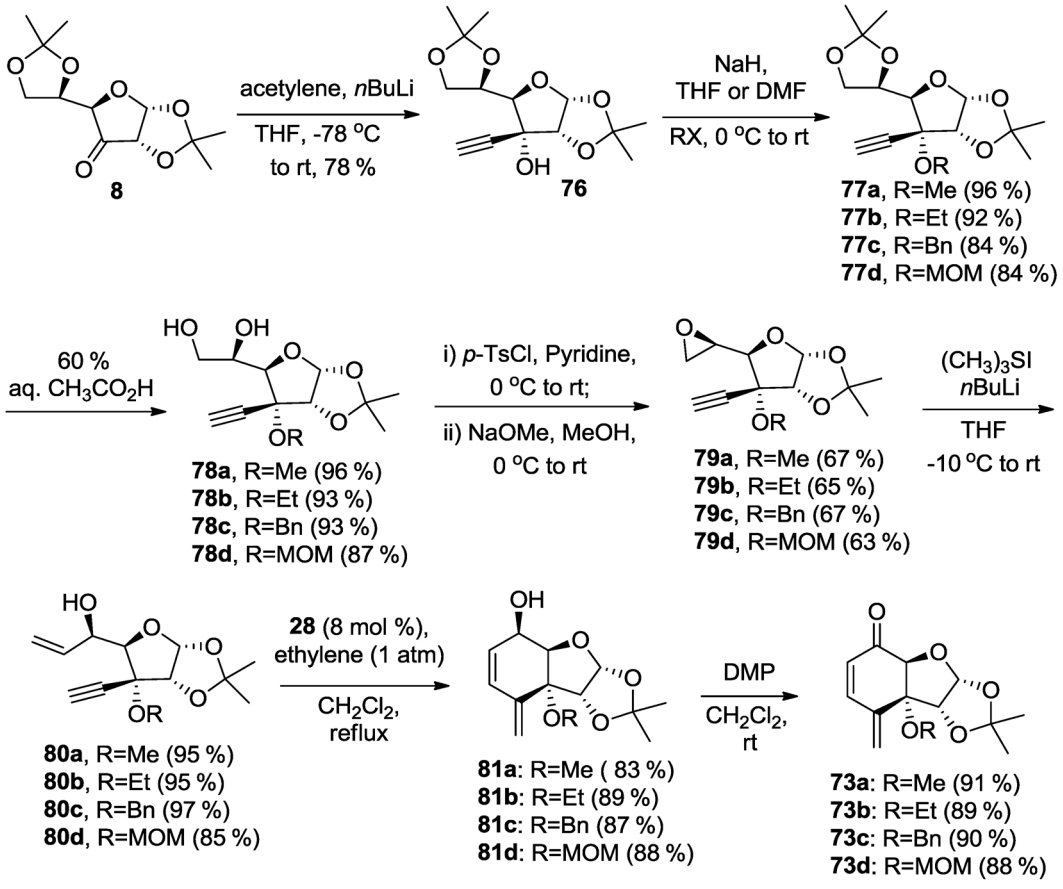
Scheme 14 Synthesis of taxa-oxa-sugar hybrid **70**.

SYNTHESIS OF OTTELIONE-SUGAR HYBRID

Otteliones **71** and **72**, isolated from the freshwater plant *Ottelia alismoides* collected in the Nile Delta [38,39], show an impressive biological activity profile, such as antitubercular activity and cytotoxicity at nM-pM levels against a panel of 60 human cancer cell lines. Loloanolides, which are structurally similar to otteliones, have been isolated [40] from the extract of aerial parts of *Camchaya loloana*, and shown to exhibit cytotoxicity against the HepG2 cell line, with GI_{50} values at a nanomolar level. It is believed that the biological activity of these molecules is attributed to the presence of a unique 4-methylene-2-cyclohexenone moiety. In view of the biological importance of otteliones, and in continuation of our interest in exploring sugar chemistry, we designed a few novel scaffolds as ottelione-sugar hybrids **73** (Scheme 15) [41]. Based on our earlier experience, we intended to utilize a tandem enyne-ring-closing metathesis (RCM) strategy to construct the labile 4-methylene-2-cyclohexenone framework **73** (Scheme 16). Thus, addition of lithium acetylide to the ketone **8** was followed by protection

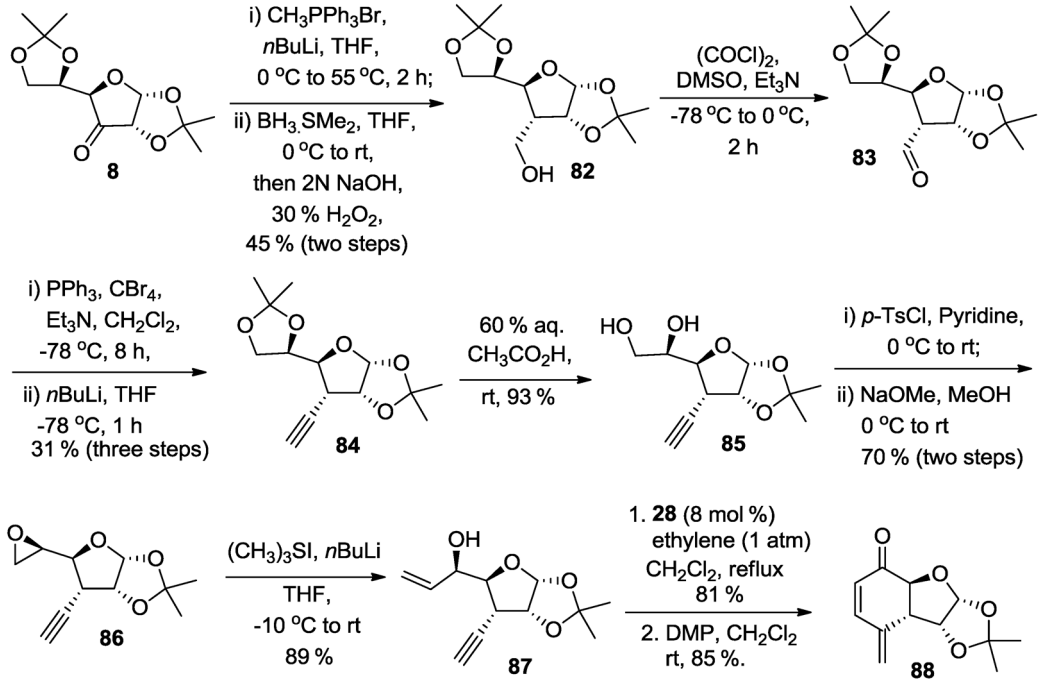


Scheme 15 Design and synthesis of ottelione-sugar hybrids.



Scheme 16 Synthesis of *cis*-fused ottelione-sugar hybrid **73**.

of the resulting alcohol **76** with various alkyl halides to afford a range of ethers **77a–d**. Selective cleavage of the more exposed acetonide of **77a** under acidic conditions provided diol **78a**, which upon monotosylation followed by treatment with NaOMe furnished epoxide **79a**. Opening of the epoxide with trimethylsulfonium ylide delivered the required enyne **80a** in excellent yield. With a sufficient quantity of enyne **80a** in hand, we then investigated the key tandem enyne/RCM sequence. Pleasingly, treatment of enyne **80a** with ethylene gas (1 atm) in the presence of Grubbs' second-generation catalyst **28** (8 mol %) in refluxing CH_2Cl_2, afforded cyclohexenol **81a** in excellent yield. Oxidation of alcohol **81a** with Dess–Martin periodinane furnished ottelione-sugar hybrid **73a** in 91 % yield. In a similar manner, hybrids **73b–d** were also synthesized to show diversity. Thereafter, we extended the scope of this strategy to synthesize the *trans*-fused hybrid **88** (Scheme 17). Towards this end, ketone **8** was subjected to Wittig reaction and then hydroboration to yield alcohol **82**, which upon oxidation under Swern conditions afforded aldehyde **83**. Homologation of aldehyde **83** through Corey–Fuchs olefination and subsequent treatment with *n*BuLi provided alkyne **84**, which was elaborated to the *trans*-fused ottelione-sugar hybrid **88** following the same sequence of reactions as discussed above.



Scheme 17 Synthesis of *trans*-fused ottelione-sugar hybrid **88**.

CONCLUSION

In summary, we have presented in this article our various efforts toward the synthesis of simpler hybrid analogues of sugar and certain biologically active natural products. We have synthesized several novel hybrid scaffolds of various natural products such as steroids, glycosides, β-lactams, taxol, and ottelione, using metathesis and/or cycloaddition reactions as key steps. Further, we have also shown the application of the hybrid approach to design and rapidly synthesize a library of novel scaffolds. Some of these hybrid compounds have already been tested for biological activity, and among them, for example, compound **22** exhibits moderate to good in vitro inhibition activities against various cancer cell

lines. Biological evaluation of other hybrid compounds and their structure–activity relationship studies are underway.

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