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Application of an Enyne Metathesis/Diels–Alder Cycloaddition Sequence: A New Versatile Approach to the Syntheses of *C*-Aryl Glycosides and Spiro-*C*-Aryl Glycosides

Ayyagari V. Subrahmanyam, Kalanidhi Palanichamy, and Krishna P. Kaliappan*[a]

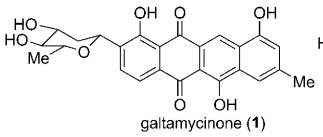
Dedicated to Professor G. K. Trivedi on the occasion of his 70th birthday

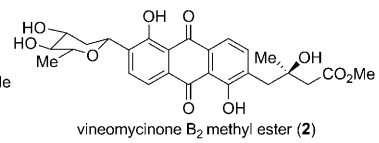
Abstract: An efficient approach for the synthesis of a variety of *C*-aryl and spiro-*C*-aryl glycosides is described. This diversity-oriented strategy employed here relies on a sequential enyne metathesis to generate the 1,3-diene moiety and Diels–Alder reaction with different dienophiles followed by aromatisation. Whereas cross-enyne metathesis with ethylene gas is used to install the 1,3-diene moiety at the anomeric centre for the synthesis of *C*-aryl glycosides, an intramolecular enyne metathesis on the sugar enyne is performed to generate the 1,3-diene moiety for the synthesis of spiro-*C*-aryl glycosides. Efforts to extend this strategy to the synthesis of the core structure of natural *C*-aryl glycoside gilvocarcin are also described. A combination of both *C*-aryl and spiro-*C*-aryl glycosides in the same moiety to combine the features thereof has also been accomplished. A tandem enyne metathesis/Diels–Alder reaction/aromatisation has also been attempted to directly access the *C*-aryl glycosides in one pot albeit in low yield.

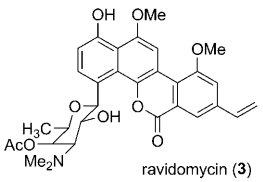
Keywords: alkynes · cycloaddition · dienes · glycosides · metathesis

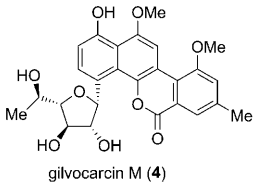
Introduction

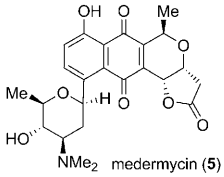
The *C*-glycosides, one of the important classes of glycosides, differ structurally from the usual *O*-glycosides and *N*-glycosides in containing a C–C bond attached to the anomeric carbon atom. If the carbohydrate is attached to an aromatic moiety through a C–C bond at the anomeric centre, then these compounds are referred to as *C*-aryl glycosides.[1,2] Owing to this change in their connectivity, these compounds are known to be quite stable towards enzymatic and acidic hydrolysis,[2] and hence their appearance in a large and diverse array of natural and synthetic products endowed with a broad spectrum of biological activities. It is also believed that they bind to DNA to form stable complexes and may have interesting biological properties. Some representative members of this class of natural products are galtamycinone (**1**),[3] vineomycinone B_2 methyl ester (**2**),[4] ravidomycin

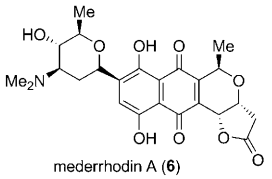

galtamycinone (**1**)

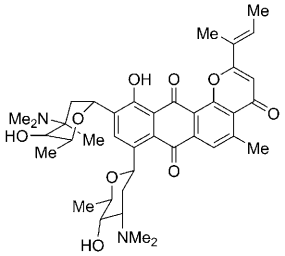

vineomycinone B_2 methyl ester (**2**)

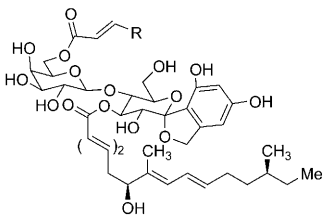

ravidomycin (**3**)


gilvocarcin M (**4**)


medermycin (**5**)


mederrhodin A (**6**)


kidamycin (**7**)


papulacandines (**8**)

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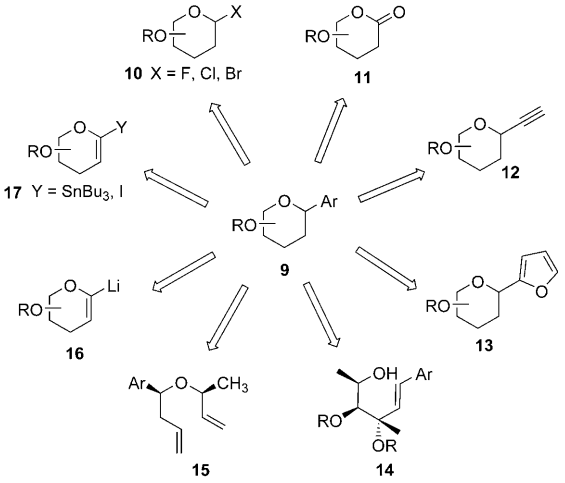
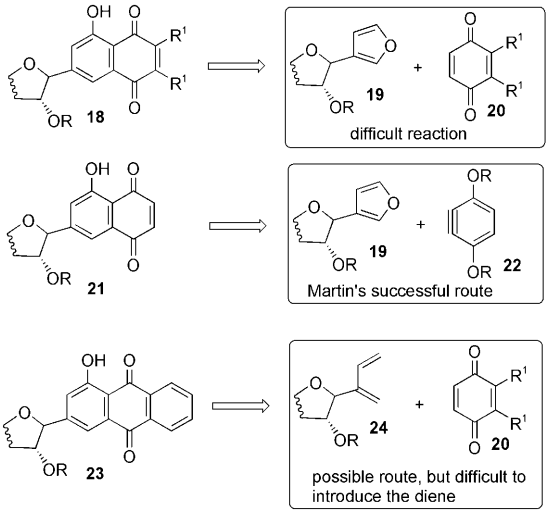
(**3**),[5] gilvocarcin M (**4**),[6] medermycin (**5**), mederrhodin A (**6**), and kidamycin (**7**).[7] Apart from *C*-aryl glycosides, the area of spirocyclic *C*-aryl glycoside has also been explored to some extent and a few methods have been developed for their synthesis as part of some natural products, such as papulacandines (**8**)[8] containing a spiro-*C*-aryl glycoside framework, which are found to be active against *Pneumocystis carinii pneumonia*, the common opportunistic infection in AIDS patients. Most of the methodologies for the synthesis of *C*-aryl glycosides involve nucleophilic, electrophilic, and radical reactions at the anomeric centre, as well as metathesis and intramolecular etherification (Scheme 1).[9–13] However, the limitation is that these methods require stereoselective generation of the anomeric centre. Apart from these methods, transition-metal-catalysed reactions[14] are also known for the synthesis of *C*-aryl glycosides though most of the cases are accompanied by β-elimination products.[13] Moreover, most of the *C*-aryl glycoside natural products have been found to possess a quinone moiety as a subunit and it could perhaps be speculated that the presence of the quinone moiety in these natural products may also be responsible for their significant biological activity.



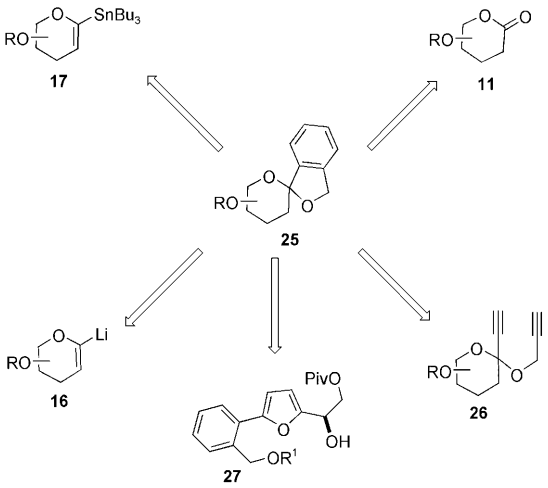
Scheme 1. Some of the existing methods available for the synthesis of *C*-aryl glycosides. Ar = aryl.

Only a few of the above-mentioned methods would allow access to *C*-aryl glycosides with quinone as an integral subunit. In this regard, Martin and co-workers have expertly utilised benzyne precursors as quinone equivalents in their synthesis of *C*-aryl glycosides by furan–benzyne cycloaddition.[15] Nevertheless, given the availability of quinones from commercial sources and also in view of their synthetic utility, it would be appreciable if practical routes that utilise Diels—Alder-like key reactions with quinones followed by aromatisation to install the napthaquinone functionality of *C*-aryl glycosides could be developed. However, this route has seldom been explored, presumably due to 1) difficulties associated with the introduction of a suitable diene moiety at the anomeric carbon atom and 2) the drastic conditions required for the cycloaddition between furan and quinones (Scheme 2).[16]



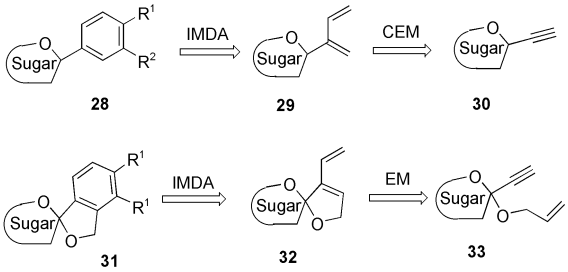
Scheme 2. Difficulties encountered in the Diels–Alder approach.

Likewise, albeit several strategies have been developed for the synthesis of *C*-aryl glycosides, there are only a few methods known for the synthesis of spiro-*C*-aryl glycosides due to difficulties associated with the generation of a spiro system at the anomeric carbon atom (Scheme 3).[17] Among these methods, addition of a lithiated aromatic precursor to a sugar-derived lactone is commonly used.[18] However, it is surprising that the cycloaddition strategy, which has been effectively utilised in the case of *C*-aryl glycosides, has not yet been studied extensively in the area of spiro-*C*-aryl glycosides except a few isolated reports.[19]

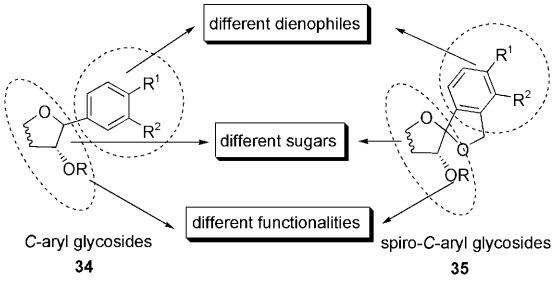


Scheme 3. Some of the existing methods available for the synthesis of spiro-C-aryl glycosides. Piv = pivaloyl.

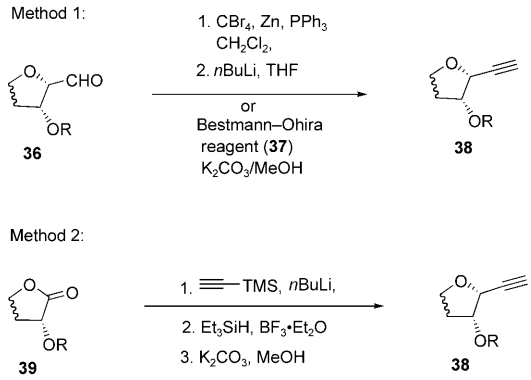
We have previously communicated our initial results on a conceptually new approach to *C*-aryl glycosides[20] that relies on sequential ethylene cross-enyne metathesis[21,22] (for the generation of an 1,3-diene at the anomeric carbon atom)/Diels–Alder (with quinones and dimethylacetylene dicarboxylate (DMAD))/aromatisation reactions.[23] Our method complements most of the existing ones in that it offers a direct access to *C*-aryl glycosides containing the quinone moiety. Herein, we wish to disclose a comprehensive account on our endeavours for the synthesis of spiro *C*-aryl glycosides through a sequential intramolecular enyne metathesis/Diels–Alder/aromatisation reaction strategy and also our further studies on *C*-aryl glycosides (Scheme 4). Furthermore, the diversity for the synthesis of a variety of *C*-aryl glycosides and spiro-*C*-aryl glycosides could be accomplished by 1) dienes derived from different carbohydrate precursors, 2) a variety of dienophiles in the Diels–Alder reaction, and 3) functionalising the free hydroxyl groups attached to the sugar unit, as shown in Scheme 5. With this aspiration for the development of a general route for the synthesis of *C*-aryl glycosides, we designed and synthesised a series of *C*-alkynyl glycosides from the respective sugars by following one of the two easily adaptable routes (Scheme 6). The first method depends mainly on the conversion of aldehyde **36** attached to the anomeric centre into the alkyne **38** by using either the Corey–Fuchs protocol[24] or Bestmann–Ohira reagent (dimethyl-1-diazo-2-oxopropyl phosphonate) **37**.[25] The second approach utilises addition of lithium (trimethylsilyl)acetylide to the sugar lactone **39** followed by treatment with triethylsilane in the presence of $BF_3{\cdot}OEt_2$.[26]



Scheme 4. Retrosynthesis for *C*-aryl glycosides and spiro-*C*-aryl glycosides. IMDA = intermolecular Diels–Alder reaction, CEM = cross-enyne metathesis, EM = (intramolecular) enyne metathesis.

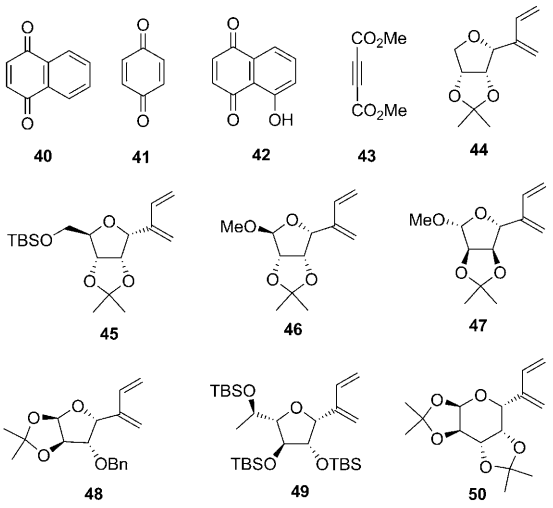


Scheme 5. Diversity-oriented approach for the synthesis of *C*-aryl and spiro-*C*-aryl glycosides.



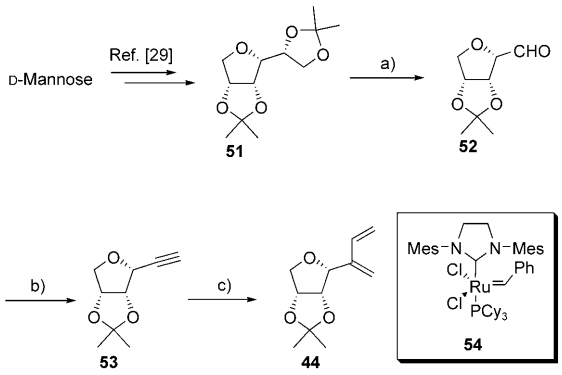
Scheme 6. Methods for the synthesis of *C*-alkynyl glycosides. TMS = trimethylsilyl.

To test the premise, we designed a set of dienes that could be synthesised from the corresponding sugar alkynes by using cross-enyne metathesis. Later, these dienes could be used in the Diels–Alder reaction with 1,4-naphthaquinone (**40**), 1,4-benzoquinone (**41**), 5-hydroxy-1,4-naphthaquinone (**42**), and DMAD (**43**) as dienophiles for the synthesis of respective *C*-aryl glycosides.

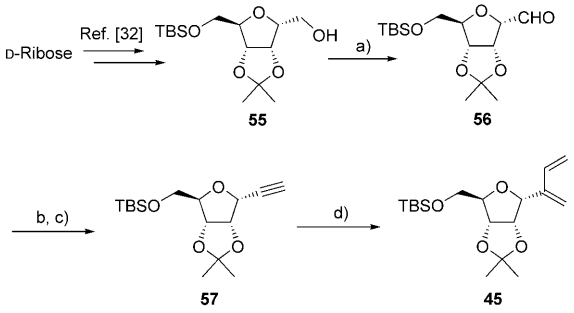


Results and Discussion

Synthesis of *C*-aryl glycosides: Towards the synthesis of diene **44** (Scheme 7), selective deprotection of acetonide **51** and then silica-supported $NaIO_4$-assisted oxidative cleavage of the corresponding diol was carried out to afford the aldehyde **52**. Treatment of this aldehyde with Bestmann–Ohira reagent **37**[25] in the presence of K_2CO_3/MeOH afforded the corresponding *C*-alkynyl glycoside **53** in 51% yield. With the alkyne **53** in hand, we initially attempted the cross-enyne metathesis by using 3 mol% of Grubbs second-gener-



Scheme 7. Synthesis of diene **44**: a) 1) 60% AcOH, RT, 8 h, 82%; 2) Silica supp. $NaIO_4$, CH_2Cl_2, 0°C to RT, 2 h, 75%; b) Bestmann–Ohira reagent, K_2CO_3, MeOH, 0°C to RT, 12 h, 51%; c) 54 (5 mol%), toluene, 80°C, 12 h, 82%. Cy = cyclohexyl, Mes = mesityl.

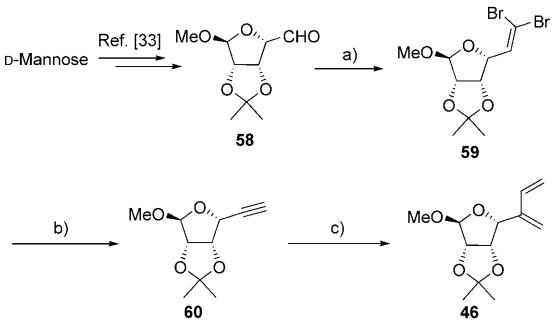


Scheme 8. Synthesis of diene **45**: a) IBX, CH_3CN, 80°C, 92%; b) CBr_4, PPh_3, Zn, CH_2Cl_2, RT, 12 h, 88%; c) *n*BuLi, THF, 0°C to RT, 2 h , 82%; d) **54** (5 mol%), toluene, 80°C, 12 h, 98%. IBX = 2-iodoxybenzoic acid, TBS = *tert*-butyldimethylsilyl.

ation catalyst **54**[27] under an ethylene atmosphere, and also using Hoveyda's phosphine-free catalyst.[28] Disappointingly, both the conditions provided the diene in poor yield along with recovered starting material. However, when 5 mol% of catalyst **54** was used for the intermolecular cross-enyne metathesis, the yield was significantly improved to afford the diene **44** in 82% yield. After successfully synthesising the diene **44**, we then turned our attention to the intermolecular Diels–Alder reaction with **40** for installing the required aromatic moiety. The reaction proceeded very well, and on the basis of our earlier experiences,[30] we decided to treat the cycloaddition product immediately with triethylamine and silica gel for air oxidative aromatisation without further purification. As anticipated, this protocol worked well and allowed us to directly isolate the respective aromatised/oxidised cycloadduct **71** in 42% yield. This sequence was then repeated with 1,4-benzoquinone (**41**) and 5-hydroxy-1,4-naphthaquinone (**42**) to give the corresponding *C*-aryl glycosides in good overall yield (Table 1). The above sequence was successfully extended to simple trisubstituted *C*-aryl glycoside **74** by using **43** as a dienophile. In this case, the subsequent aromatisation reaction was carried out under standard MnO_2 conditions to give the *C*-aryl glycoside **74** in 83% yield.[31] We also attempted a sequential tandem metathesis/cycloaddition/aromatisation reaction on *C*-alkynyl glycoside **53** to give the *C*-aryl glycoside directly in one pot. Though it was a single-pot reaction to directly provide the required C-aryl glycoside, yields were lower (30–35%) than the combined yield (more than 50%) for the two individual steps (intermolecular enyne metathesis and cycloaddition/aromatisation).

To extend the scope of our strategy, we synthesised diene **45** (Scheme 8) from D-ribose. Aldehyde **56** available from alcohol **55** was converted into the corresponding *C*-alkynyl glycoside **57** in moderate yield by using standard Corey–Fuchs protocol[24] followed by cross-enyne metathesis with ethylene by using Grubbs second-generation catalyst **54** to afford the diene **45** in good yield. The diene **45** was treated individually with quinones **40**, **41**, **42**, and DMAD (**43**) followed by oxidative aromatisation to afford the respective *C*-aryl glycosides in good yield (Table 1).

Later, the diene **46** was synthesised from D-mannose as depicted in Scheme 9. The aldehyde **58** was treated with CBr_4 and PPh_3 followed by treatment with *n*BuLi to afford



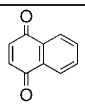
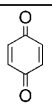
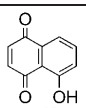
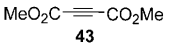
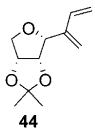
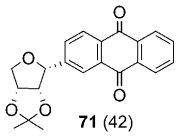
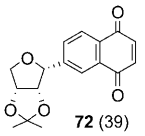
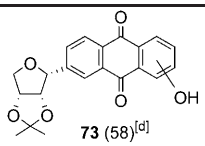
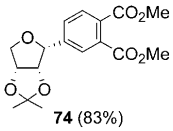
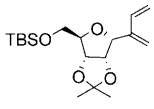
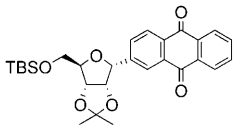
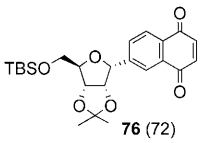
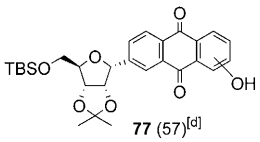
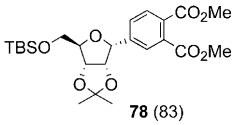
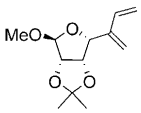
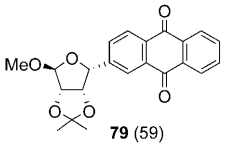
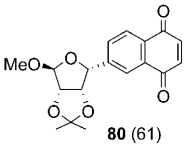
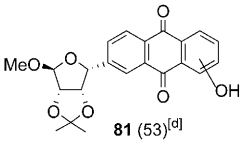
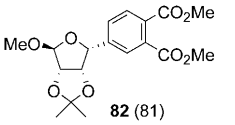
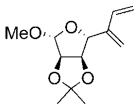
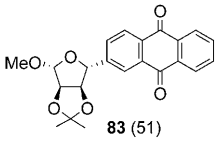
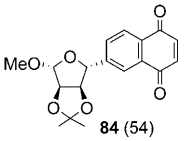
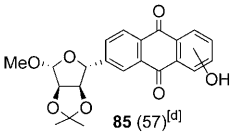
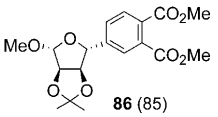
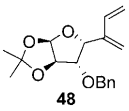
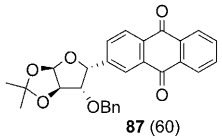
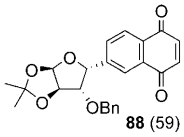
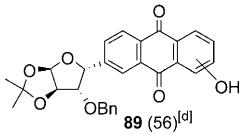
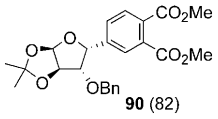
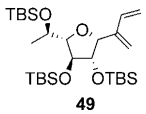
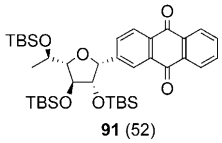
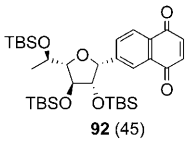
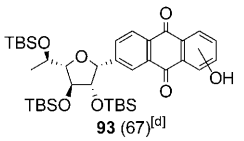
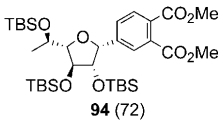
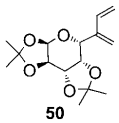
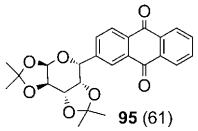
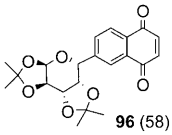
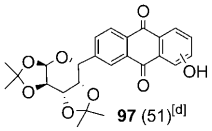
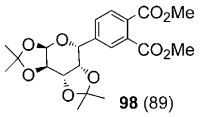
Scheme 9. Synthesis of diene **46**: a) CBr_4, PPh_3, Zn, CH_2Cl_2, RT, 12 h, 96%; b) *n*BuLi, THF, 0°C to RT, 2 h, 91%; c) **54** (5 mol%), toluene, 80°C, 12 h, 89%.

alkyne **60** in good yield. The alkyne **60** upon sequential enyne metathesis followed by Diels–Alder reactions (**40**–**43**) and aromatisation gave the third set of *C*-aryl glycosides in good yield (Table 1).

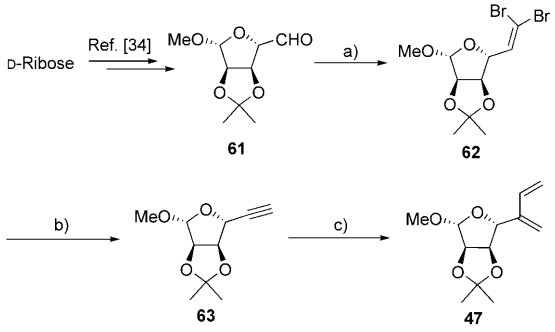
The synthesis of diene **47** began with the Corey–Fuchs reaction[24] on the aldehyde **61** to afford the required *C*-alkynyl glycoside **63**. After converting the *C*-alkynyl glycoside into a *C*-diene glycoside by using Grubbs second-generation catalyst **54**, quinones **40**, **41**, **42**, and DMAD were screened as to their effectiveness as dienophiles in the Diels–Alder reaction and subsequent aromatisation to afford the respective *C*-aryl glycosides (Scheme 10, Table 1).

In the synthesis of diene **48**, the aldehyde **64** was converted into the corresponding C-alkyne glycoside **66** by using Corey–Fuchs protocol.[24] In this connection, the aldehyde **64** was reacted with CBr_4 and PPh_3 in the presence of zinc powder to yield the corresponding dibromoalkene **65**, which on treatment with *n*BuLi afforded the alkyne **66** in 74% yield (Scheme 11). In this event, the Diels–Alder reaction of

Table 1. Synthesis of *C*-aryl glycosides.[a,b,c,e]

1,3-Diene/dienophile	 **40**	 **41**	 **42**	 **43**
 **44**	 **71** (42)	 **72** (39)	 **73** (58)[d]	 **74** (83%)
 **45**	 **75** (62)	 **76** (72)	 **77** (57)[d]	 **78** (83)
 **46**	 **79** (59)	 **80** (61)	 **81** (53)[d]	 **82** (81)
 **47**	 **83** (51)	 **84** (54)	 **85** (57)[d]	 **86** (85)
 **48**	 **87** (60)	 **88** (59)	 **89** (56)[d]	 **90** (82)
 **49**	 **91** (52)	 **92** (45)	 **93** (67)[d]	 **94** (72)
 **50**	 **95** (61)	 **96** (58)	 **97** (51)[d]	 **98** (89)

[a] The dienes were synthesised from the respective *C*-alkynyl glycosides by using Grubbs second-generation catalyst (5 mol%) under an ethylene atmosphere in toluene at 80°C. [b] All the Diels–Alder reactions were carried out in toluene at 80°C followed by aromatisation with basic (Et_3N) silica in $CHCl_3$ at RT. [c] Overall yield for 2 steps. [d] A mixture of inseparable regioisomers was obtained. [e] Yields are given in parentheses.

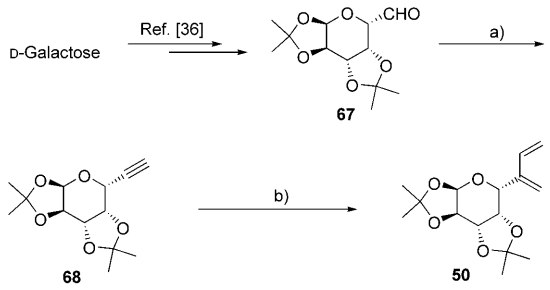


Scheme 10. Synthesis of diene **47**: a) CBr_4, PPh_3, Zn, CH_2Cl_2, RT, 12 h, 89%; b) *n*BuLi, THF, 0°C to RT, 2 h, 86%; c) **54** (5 mol%), toluene, 80°C, 12 h, 98%.

Scheme 11. Synthesis of diene **48**: a) CBr_4, PPh_3, Zn, CH_2Cl_2, RT, 12 h, 96%; b) *n*BuLi, THF, 0°C to RT, 2 h, 74%; c) **54** (5 mol%), toluene, 80°C, 12 h, 89%.

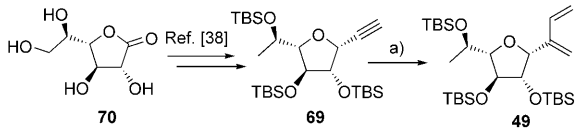
the diene **48** proceeded smoothly with **40–43**, and the respective aromatisation reactions led to the corresponding *C*-aryl glycosides in good yields (Table 1).

Synthesis of pyranose-based *C*-aryl glycosides: To extend the scope of this strategy, we intended to have some pyranose-based C-aryl glycosides. Toward this end, we prepared the known galactose aldehyde **67** from galactose in a few steps.[36] Then, aldehyde **67** was treated with Ohira–Bestmann reagent **37**[25] in the presence of K_2CO_3/MeOH to afford the *C*-alkynyl glycoside **68** in 68% yield. The alkyne **68** upon cross-enyne metathesis with Grubbs second-generation catalyst **54** afforded the diene **50**, which was then treated with **40–43** followed by aromatisation to give a set of pyranose-based *C*-aryl glycosides in good yield (Scheme 12, Table 1).



Scheme 12. Synthesis of diene **50**: a) Dimethyl-1-diazo-2-oxopropylphosphonate (**37**), K_2CO_3, MeOH, RT, 12 h, 68%; b) **54** (5 mol%), toluene, 80°C, 12 h, 98%.

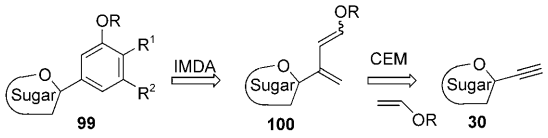
Synthesis of gilvocarcin analogues: With these promising results in the synthesis of *C*-aryl glycosides, and owing to our current interest in developing some natural and unnatural products,[37] we decided to utilise our strategy for the synthesis of natural *C*-aryl glycosides and their analogues. To this end, first we targeted the synthesis of the core structure of gilvocarcin (**4**), a biologically active natural product, by using this same strategy. In this regard, we prepared the *C*-alkynyl glycoside **69** by using the more economical albeit longer procedure of Zard and co-workers[38] by starting from D-galactono-1,4-lactone (**70**) (Scheme 13). Cross-enyne



Scheme 13. Synthesis of diene **49**: a) **54** (5 mol%), toluene, 80°C, 12 h, 79%.

metathesis of alkyne **69** with 5 mol% of Grubbs second-generation catalyst **54** under an ethylene atmosphere led to the formation of the corresponding 1,3-diene **49** in 79% yield. This was then subjected to our sequential Diels–Alder reaction/aromatisation sequence with benzoquinone to afford the aromatised product **92**, which structurally resembles the gilvocarcin skeleton. This sequence was then repeated with **40**, **42**, and **43** to give the corresponding *C*-aryl glycosides in good overall yield (Table 1).

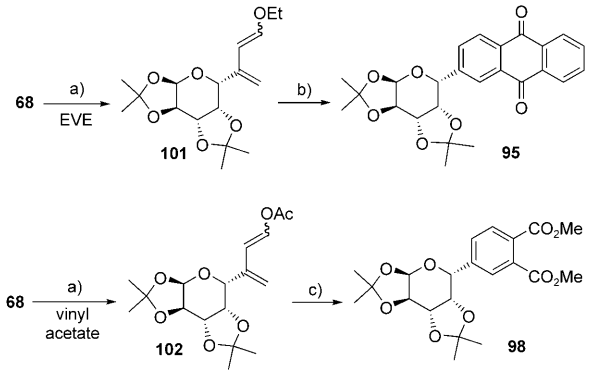
***C*-Aryl glycosides with a hydroxyl group on the aromatic ring**: Though this methodology allows access to the synthesis of a range of diverse *C*-aryl glycosides, this method as such would not be the appropriate one for the synthesis of *C*-aryl glycosides, such as gilvocarcin, with a hydroxyl group on the aromatic ring that needs to be introduced during the Diels–Alder reaction/aromatisation. To circumvent this problem, we planned to modify our strategy as shown in Scheme 14.



Scheme 14. Retrosynthetic strategy for hydroxyl-substituted *C*-aryl glycosides.

From a retrosynthetic perspective, we envisaged that the *C*-aryl glycoside **99** could be obtained from the diene **100** by using our strategy, which, in turn, could be generated by cross-enyne metathesis between the corresponding *C*-alkynyl glycosides **30** and either vinyl acetate or ethyl vinyl ether in place of simple ethylene.[39]

Accordingly, the modified approach commenced with a cross-enyne metathesis reaction of C-alkynyl glycoside **68** with ethyl vinyl ether in the presence of Grubbs second-generation catalyst **54** (5 mol%) to afford the diene **101** as a separable mixture of *cis* and *trans* isomers in 71% yield (Scheme 15). Unfortunately, when we subjected the diene **101** to the Diels–Alder reaction with 1,4-naphthaquinone **40** in toluene, and subsequent treatment with Et_3N and silica

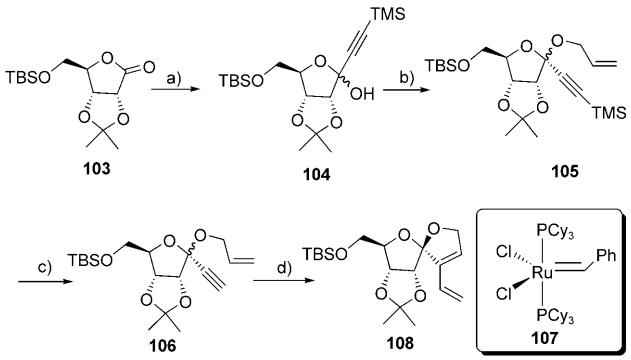


Scheme 15. Attempted strategy to synthesise hydroxyl-substituted *C*-aryl glycosides: a) Grubbs second-generation catalyst (5 mol%), toluene, reflux, 2 h, 71% (**101**), 43% (**102**); b) 1,4-naphthaquinone, toluene, 100°C, 12 h, then Et_3N, silica gel, $CHCl_3$, 58%; c) DMAD, toluene, 100°C, 12 h, 72%. EVE = ethyl vinyl ether.

gel for 2 h, only the *C*-aryl glycoside **95** that lacks the required hydroxyl group on the aromatic ring, was obtained in 62% yield. A similar result obtained from diene **101** and **43** providing **98** without a hydroxyl group on the aromatic ring, which suggests that the ethoxyl group undergoes facile elimination by the driving force of aromatisation during the reaction conditions. When ethyl vinyl ether was replaced by vinyl acetate, again similar results were observed for the whole sequence and thus depicting that this may be a shortcoming of this strategy.

Synthesis of spiro-*C*-aryl glycosides: After synthesising a library of *C*-aryl glycosides by using sequential intermolecular cross-enyne metathesis/Diels–Alder/aromatisation reactions, next we turned our attention to the development of a general relevant route to access a variety of spiro-*C*-aryl glycosides. As emphasised in the Introduction, synthesis of spiro-*C*-aryl glycosides has not been explored as much as *C*-aryl glycosides, primarily due to the difficulty in constructing the spiro-*C*-aryl moiety at the anomeric centre. However, a few groups have made significant contributions by developing efficient routes to both *C*-aryl and spiro-*C*-aryl glycosides. According to our retrosynthetic strategy as outlined in Scheme 4, we envisaged that the installation of the spiro-*C*-aryl moiety at the anomeric carbon atom could be achieved by a sequential intramolecular enyne metathesis/Diels–Alder/aromatisation reaction. To analyse our argument, we prepared a series of enynes from the corresponding sugar lactones by the addition of lithiated-ethynyltrimethylsilane followed by acid-catalysed *O*-allyl glycosidation.

Synthesis of diene 108 from D-ribose: In this manner, we synthesised diene **108** from D-ribose as depicted in Scheme 16. Addition of 2-(trimethylsilyl)ethynyllithium to

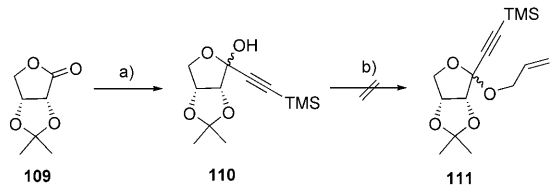


Scheme 16. Synthesis of diene **108**: a) TMS-acetylene, *n*BuLi, THF, −78°C, 40 min., 93%; b) allylalcohol, montmorillonite (K-10), 4 Å MS powder, CH_2Cl_2, RT, 8 h, 72%; c) K_2CO_3, MeOH, 4 h, 98%; d) **107** (10 mol%), toluene, 80°C, 12 h, 72%.

the TBS-protected D-ribonolactone **103**[40] followed by O-glycosidation with allyl alcohol in the presence of montmorillonite K-10 and 4 Å MS and subsequent alkaline desilylation afforded an inseparable mixture of enynes **106** with high β-selectivity. The stereochemistry at the anomeric centre was assigned based on a precedent report described by Yamamoto's group.[19d] With the ribose-derived enyne **106** in hand, an initial screening of reaction conditions for intramolecular enyne metathesis by using 10 mol% Grubbs first-generation catalyst **107** under an ethylene atmosphere in toluene at 80°C for 12 h was carried out to give the spiro-*C*-1,3-diene **108** in 72% yield as a single β- isomer.

To probe the viability of our strategy, we decided to investigate the Diels–Alder reaction of this diene with 1,4-naphthaquinone (**40**) followed by aromatisation based on our earlier experience in the synthesis of *C*-aryl glycosides for installing the required aromatic moiety. Thus, treatment of diene **108** with **40** in toluene at 80°C for 12 h gave the cycloadduct in good yield. The crude cycloadduct was directly treated with Et_3N and silica without further purification to deliver the first spiro-*C*-aryl glycoside **128** in 60% yield. Surprisingly, when we repeated this sequence with 5-hydroxy-1,4-naphthaquinone (**42**) followed by aromatisation, a well-separable pair of regioisomers **129** and **130** (1:1) were obtained in 63% yield unlike in other cases. Finally, by using DMAD (**43**), the corresponding spiro-*C*-aryl glycoside **131** was obtained in good yield (Table 2).

At this stage we realised that this strategy would be one of the most efficient entries for the synthesis of spiro-*C*-aryl glycosides. After having been successful in applying our strategy to the synthesis of spiro-*C*-aryl glycosides, we decided to check out if we could extend our methodology to other sugar-related enynes. To this end, we synthesised the known lactol intermediate **110**[41a] by starting from D-mannose-derived lactone **109** (Scheme 17).



Scheme 17. Attempts to synthesise enyne **111**: a) TMS-acetylene, *n*BuLi, THF, −78°C, 40 min; b) allylalcohol, montmorillonite (K-10), 4 Å MS powder, CH_2Cl_2, RT, 8 h.

Unfortunately, all our attempts to perform *O*-allylglycosidation by using montmorillonite K-10 and allyl alcohol failed to provide the desired product. Similar results were observed in the case of other lactol intermediates (**112**[41b], **113**, and **114**). In light of these rather unsatisfactory results, we were looking for an alternative approach for the glycosi-

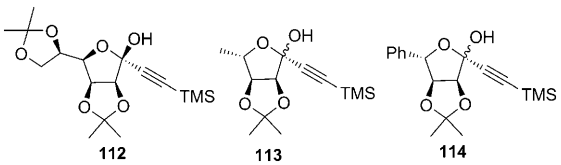
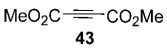
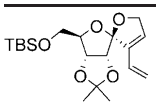
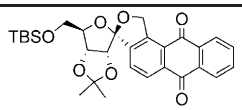
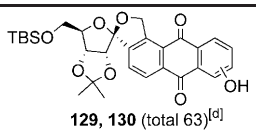
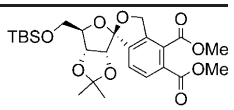
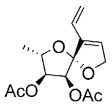
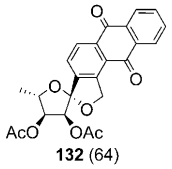
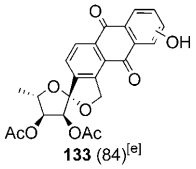
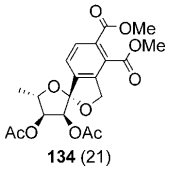
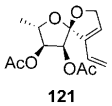
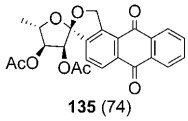
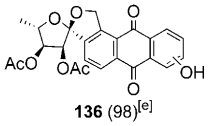
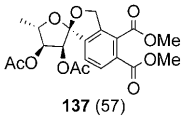
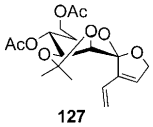
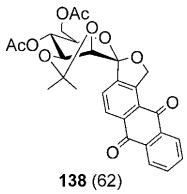
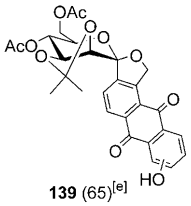
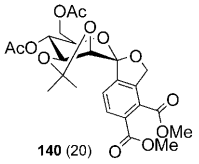


Table 2. Synthesis of spiro-*C*-aryl glycosides.[a,b,c,f]

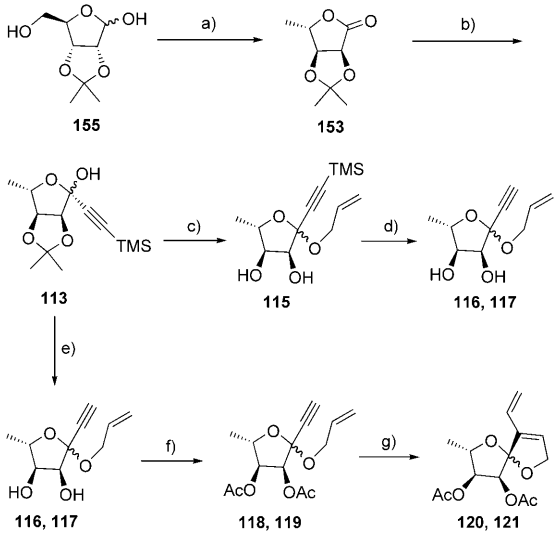
1,3-Diene/dienophile	 **40**	 **42**	 **43**
 **108**	 **128** (60)	 **129, 130** (total 63)[d]	 **131** (58)
 **120**	 **132** (64)	 **133** (84)[e]	 **134** (21)
 **121**	 **135** (74)	 **136** (98)[e]	 **137** (57)
 **127**	 **138** (62)	 **139** (65)[e]	 **140** (20)

[a] The dienes were synthesised from the respective enynes by using Grubbs first-generation catalyst (10 mol%) under an ethylene atmosphere in toluene at 80°C. [b] All the Diels–Alder reactions were carried out in toluene at 80°C followed by aromatisation with basic (Et_3N) silica in $CHCl_3$ at RT. [c] Overall yield for 2 steps. [d] Regioisomers were obtained in an 1:1 ratio, and were separated by column chromatography. [e] A mixture of inseparable regioisomers was obtained. [f] Yields are given in parentheses.

dation with allyl alcohol. We anticipated that the glycosidation reaction might be fertile under acidic conditions.

Synthesis of enynes from D-ribose: To investigate the glycosidation reaction under acidic conditions, we planned to synthesise lactol **113**. To this end, methyl Grignard addition to D-ribose monoacetonide followed by oxidative diol cleavage and then PCC oxidation provided lactone **153**, which upon treatment with lithiated trimethylsilylacetylene furnished lactols **113** as an inseparable mixture in 66% yield (Scheme 18). After screening several acid-catalysed conditions (CSA, *p*-toluene sulfonic acid (*p*-TSA), 60% AcOH and HCl), TfOH proved to be the most efficient for the glycosidation with allyl alcohol, delivering the allylated product **115** in good yield, with concomitant cleavage of the acetonide group. The mixture of anomers **116** and **117** (2:3) were separated by using column chromatography only after desilylation of allylated diol **115** under standard conditions. Interestingly, when the acid-catalysed glycosidation reaction of **113** was quenched with an excess of NH_4OH, we were pleased to see the required products **116** and **117** in the same ratio in 71% yield; this sequence involved three reactions (O-allylation, deprotection of the acetonoide, and desilylation) in a single pot.

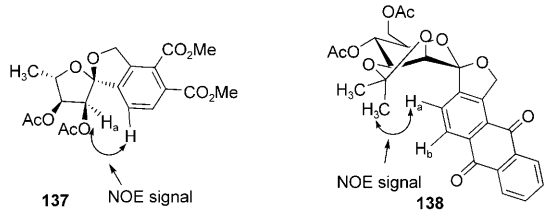
After synthesising the enynes **116** and **117**, our next task was to execute the enyne metathesis to give the correspond-



Scheme 18. Synthesis of dienes **120** and **121**: a) 1) MeMgI, Et_2O; 2) $NaIO_4$, H_2O, 79% (2 steps); 3) PCC, NaOAc, 4 Å MS powder, 73%; b) TMS-acetylene, *n*BuLi, THF, −78°C, 2 h, 66%; c) allyl alcohol, TfOH, 12 h, RT, 77%; d) K_2CO_3, MeOH, 2 h, RT, 91% (d.r. = 2:3); e) allylalcohol, TfOH, 12 h, then NH_4OH, RT, 12 h, 71% (d.r. = 2:3); f) pyridine, Ac_2O, RT, 12 h, **118** (82%), **119** (79%); g) **107** (10 mol%), toluene, 80°C, 12 h, **120** (80%), **121** (96%). d.r. = diastereomeric ratio, PCC = pyridinium chlorochromate.

ing diene for the Diels–Alder reaction. To avoid any interference of the −OH groups during the enyne-metathesis process, both the diols **116** and **117** were converted to their acetates **118** and **119** in excellent yield. To determine the stereochemistry at the anomeric centre, we undertook some spectroscopic studies of anomers **118** and **119**. The NOE spectra of both the isomers did not provide any significant information regarding the stereochemistry at the anomeric centre. Hence, both the enynes **118** and **119** were separately subjected to enyne metathesis with Grubbs first-generation catalyst to provide the corresponding dienes **120** and **121** in good yield. With these dienes **120** and **121** in hand, the Diels–Alder/aromatisation sequence was attempted with **40**, **42**, and **43** to give the respective spiro-*C*-aryl glycosides in good overall yield (Table 2).

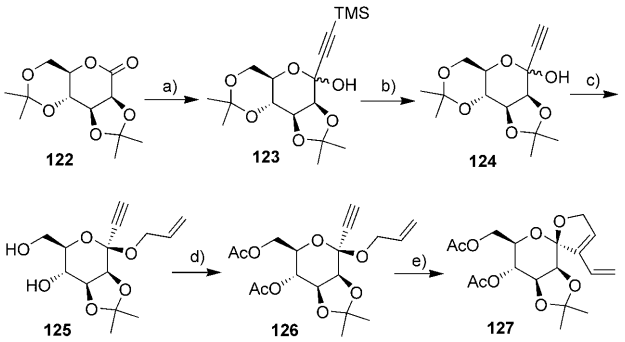
The synthesis of a wide range of spiro-*C*-aryl glycosides provided an opportunity to conclude the configuration at the anomeric centre by means of NOE spectroscopic studies (Scheme 19). Though the NOE spectra of enynes **118** and



Scheme 19. NOESY analysis of spiro-*C*-aryl glycosides **137** and **138**.

119 were inconclusive, a strong NOE between Ar−H and C−H α to the anomeric carbon atom was discernible in the NOE spectrum of spiro-*C*-aryl glycoside **137**. Assignment of this configuration is further supported by a trend of upfield chemical shift for protons in proximity to the aromatic ring. For example, when the spiroketal oxygen atom is β-oriented, the C−H α to the anomeric carbon atom is shifted approximately $\delta = 0.8$–1.0 ppm upfield relative to the other anomer containing the spiroketal oxygen atom as α-oriented. These shifts in chemical shift may be due to the anisotropic effect of the aromatic ring around the proton of interest. Similar results were obtained when we performed NOE experiments on glycosides **135** and **136**.

Synthesis of an enyne from D-mannose: Encouraged by these promising results in the synthesis of furanose-type spiro-*C*-aryl glycosides, we intended to synthesise a few pyranose-type analogues (Scheme 20). We chose lactone **122** as a viable starting material, which can be prepared from D-mannose in two steps (see the Supporting Information). Addition of 2-(trimethylsilyl)ethynyllithium to the lactone **122** afforded an inseparable anomeric mixture **123** in good yield. After desilylation under standard conditions, the alkyne **124** was obtained in 79% yield. Our attempts to effect the O-glycosidation reaction with allyl alcohol failed in the presence of montmorillonite K-10 and 4 Å MS. Further, when

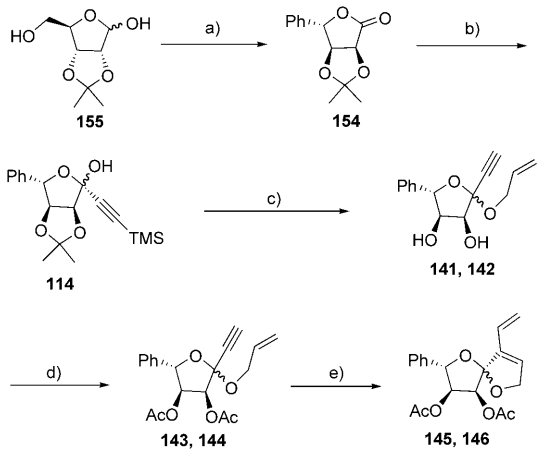


Scheme 20. Synthesis of diene **127**: a) TMS-acetylene, *n*BuLi, THF, −78 °C, 2 h, quant.; b) TBAF, THF, 2 h, RT, 79%; c) allylalcohol, CSA, CH_2Cl_2, 12 h, RT, 61%; d) pyridine, Ac_2O, RT, 12 h, 73%; e) **107** (10 mol%), toluene, 80 °C, 12 h, 75%. CSA = camphorsulfonic acid, TBAF = tetrabutylammonium fluoride.

we carried out this transformation by using TfOH in the presence of allyl alcohol, as done in the earlier cases, only the allylated tetraol was obtained in poor yield. A series of attempts to effect the glycosidation reaction of this lactol with allyl alcohol in the presence of several acids (60% AcOH, trifluoroacetic acid, *p*TSA, etc.) were not rewarding.

Ultimately, this trouble was overcome when CSA was used to afford the diol **125** in 61% yield as a single isomer. The diol **125** under standard conditions was converted into its acetate **126** in 73% yield. Intramolecular enyne metathesis of **126** by using 10 mol% Grubbs first-generation catalyst **107** under an ethylene atmosphere in toluene at 80 °C for 12 h provided the spiro-*C*-1,3-diene **127** in 75% yield as a single β-isomer. With a straightforward formula for the synthesis of spiro-*C*-aryl glycosides in hand, we explored that sequence on **126** to afford another set of spiro-*C*-aryl glycosides (Table 2). The stereochemistry at the anomeric carbon atom was established by two-dimensional NMR spectroscopic analysis of **138**. A cross-peak between one of the acetonide methyl protons and an aromatic proton was observed in the 2D-NOESY spectrum, which confirms the β-orientation of the ketal oxygen at the anomeric centre (Scheme 19).

Synthesis of dienes 145 and 146 from D-ribose: After accomplishing the synthesis of a variety of *C*-aryl glycosides and spiro-*C*-aryl glycosides, we projected to extend the scope of this strategy to synthesise hybrids of *C*-aryl and spiro-*C*-aryl glycoside scaffolds (Scheme 21). Our proposal was to combine the attractive attributes and features of the privileged *C*-aryl and spiro *C*-aryl glycosides to prepare a diverse pure library of hybrids of *C*-aryl and spiro-*C*-aryl glycoside scaffolds. At the outset, the lactol intermediate **114** was of interest as an appropriate starting material for the synthesis of a range of hybrid *C*-aryl and spiro-*C*-aryl glycoside scaffolds. The synthetic sequence commenced with the addition of a phenyl Grignard to D-ribose monoacetonide followed by oxidative diol cleavage and then PCC oxidation to provide lactone **154**. Addition of lithium trimethylsilyl acetylide to lac-



Scheme 21. Synthesis of dienes **145** and **146**: a) 1) PhMgI, Et_2O; 2) $NaIO_4$, H_2O, 80% (2 steps); 3) PCC, NaOAc, 4 Å MS powder, 76%; b) TMS-acetylene, *n*BuLi, THF, −78°C, 2 h, 93%; c) allylalcohol, TfOH, 12 h, NH_4OH, RT, 12 h, 80% (d.r. = 2:3); d) pyridine, Ac_2O, RT, 12 h, **143** (72%), **144** (63%); e) **107** (10 mol%), toluene, 80°C, 12 h, **145** (89%), **146** (94%).

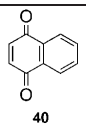
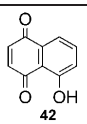
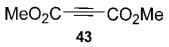
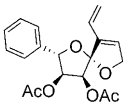
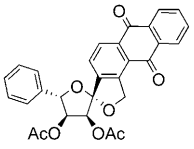
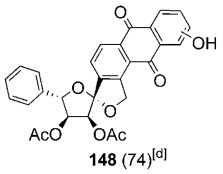
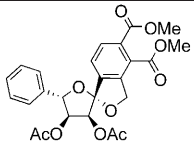
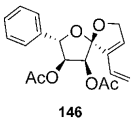
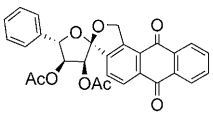
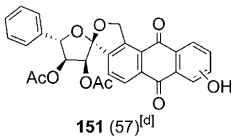
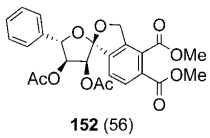
tone **154** afforded hemiketal **114**, which upon exposure to allyl alcohol in the presence of catalytic amount of TfOH followed by quenching the reaction mixture with an excess of aqueous NH_4OH furnished the required enyne–diols **141** and **142** (2:3) in good yield. Both the enyne–diols **141** and **142** were protected under standard conditions as their acetates **143** and **144** in 72 and 63% yields, respectively. Later, we applied our strategy on the enynes **143** and **144** individually. Gratifyingly, good results were obtained when enynes were treated with Grubbs first-generation catalyst **107**, affording dienes **145** and **146**. Subsequently, these dienes were subjected to the Diels–Alder reaction with quinones and DMAD, and finally aromatisation to obtain various combinations of *C*-aryl and spiro-*C*-aryl glycoside scaffolds in good to moderate yields (Table 3). At this stage, we confirmed the configuration at the anomeric centre by performing NOE spectroscopic experiments on compound **152** (Scheme 22).

Conclusion

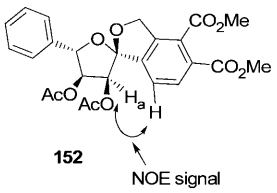
We have described efficient strategies for the synthesis of *C*-aryl glycosides and spiro-*C*-aryl glycosides. During this course, seven different *C*-alkynyl glycosides for the synthesis of respective *C*-aryl glycosides and six sugar-derived enynes for the corresponding spiro-*C*-aryl glycosides were investigated. Furthermore, in the case of spiro-*C*-aryl glycosides we were able to identify the configuration at the anomeric centre by using 2D-NMR spectroscopic experiments. The strategy used for the synthesis of spiro-*C*-aryl glycosides permits stretched out possibilities for the construction of a combination of *C*-aryl and spiro-*C*-aryl glycoside scaffolds. Finally, our conclusion clearly points out our efforts to construct the core structure of gilvocarcin and introduce the diversity on the aromatic moiety by cross-enyne metathesis of *C*-alkynyl glycosides with vinyl acetate (or ethyl vinyl ether) followed by a Diels–Alder reaction with quinones (or DMAD) and aromatisation.

The advantageous scope of this methodology should be easily extendable to the synthesis of a much greater variety of *C*-aryl glycosides and spiro-*C*-aryl glycosides by using appropriate sugar-derived alkynes, sugar-derived enynes, and dienophiles, thereby increasing the opportunities for diversity generation. This strategy to *C*-aryl glycosides and spiro-*C*-aryl glycosides should pave the way for the construction of several quinone-related *C*-aryl and spiro-*C*-aryl glycosides.

Table 3. Synthesis of a combination of *C*-aryl and spiro-*C*-aryl glycoside scaffolds.[a,b,c,e]

1,3-Diene/dienophile	 40	 42	 43
 145	 **147** (61)	 **148** (74)[d]	 **149** (91)
 146	 **150** (59)	 **151** (57)[d]	 **152** (56)

[a] The dienes were synthesised from the respective enynes by using Grubbs first-generation catalyst (10 mol%) under an ethylene atmosphere in toluene at 80°C. [b] All the Diels–Alder reactions were carried out in toluene at 80°C followed by aromatisation with basic (Et_3N) silica in $CHCl_3$ at RT. [c] Overall yield for 2 steps. [d] A mixture of inseparable regioisomers was obtained. [e] Yields are given in parentheses.



Scheme 22. NOESY analysis of spiro-*C*-aryl glycoside **152**.

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