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[ChTitle] Alkynedicobalt complexes in carbohydrates: Synthetic applications

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Comentado [RE1]: OPTIONAL – Current position/degrees

Abstract:

The complexation of alkynes to form dicobalt hexacarbonyl derivatives facilitates the formation, under acid catalysis, of highly stabilized propargylic cations whose reaction with nucleophiles to form propargylic compounds, currently known as the Nicholas reaction, has found ample use in organic synthesis. This transformation has shown to be particularly useful when applied to carbohydrate derivatives. In this chapter, we provide a brief overview on this subject pioneered by early contributions from Isobe's research group. Thus, carbohydrate-derived dicobalt hexacarbonyl complexes have been used in the epimerization of *C*-alkynyl glycosides, pyranose ring-opening nucleophile trapping reactions, pyranose ring-opening ring-recyclization leading to medium-sized oxacycles, glycosylation strategies, *C*-glycosylation and pyranose to carbocycle transformations among others. Finally, contributions from our research group focusing on the synthetic applications of Ferrier-Nicholas cations are also presented.

Comentado [RE2]: REQUIRED – a short summary of the chapter's contents

Key Words:

Comentado [RE3]: REQUIRED – a list of 5-10 keywords pertinent to the chapter's content

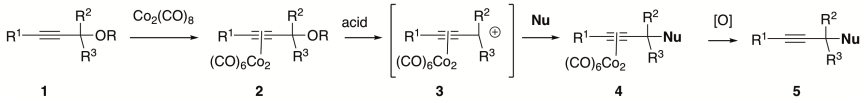
Alkynedicobalt, dicobalt hexacarbonyl, Nicholas reaction, Ferrier rearrangement, carbohydrates, glycosylation, anomerization, synthesis, Ferrier-Nicholas cations.

[Chapter Starts Here]

[H1 Title]**Introduction**

The complexation of an alkyne to dicobalt hexacarbonyl, $Co_2(CO)_6$, as in compound **2** (Scheme 1), facilitates the (acid-mediated) access to cobalt-stabilized carbocations, e.g. **3** (Scheme 1), which upon treatment with a given nucleophile, i.e. **Nu** (Scheme 1) provides access to differently substituted propargyl systems, e.g. **4** (Scheme 1). This transformation, first discovered by Nicholas and Pettit[1,2] and currently known as the Nicholas reaction,[3] is based on the enhanced stability of carbonium ions α- to an organometallic substituent, which was at the origin of the efficient and regiospecific transformation **3** → **4** (Scheme 1). The Nicholas reaction is compatible with a variety of carbon and heteroatom nucleophiles, thus providing access to a broad range of propargylic derivatives, **5**. Additionally, the overall transformation **1** → **5** (Scheme 1), benefits from: *i)* the ready availability of the starting propargyl alcohols by nucleophilic addition of organometallic alkynyl reagents to aldehydes or ketones, *ii)* the easy formation of dicobalt hexacarbonyl complexed propargyl derivatives **2**, by reaction of the corresponding alkyne **1**, with dicobalt octacarbonyl, *iii)* the use of the cobalt cluster-containing derivatives, e.g. **4** (Scheme 1), in subsequent transformations, such as the Pauson-Kand reaction,[4] or *iv)* the

easy regeneration of the original alkyne bond by a number of existing methods for cobalt decomplexation.



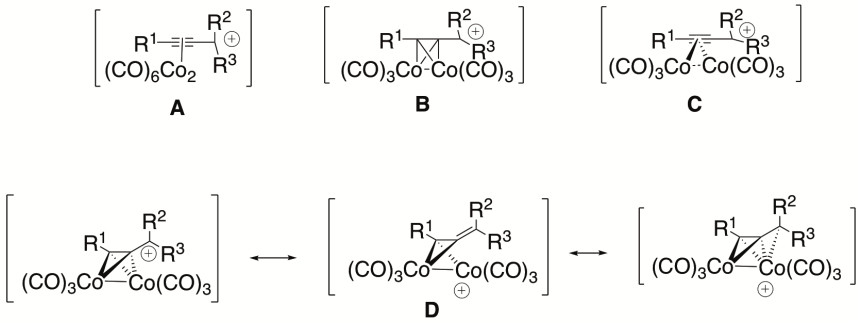
*** Insert Scheme 1 ***

Caption: Scheme 1. The Nicholas reaction

Owing to the above-mentioned virtues, the Nicholas reaction has found ample use in organic chemistry. In this Chapter we intend to provide a brief overview on synthetic transformations mediated by cobalt complexed propargylic derivatives in carbohydrate substrates, including recent contributions by our research group.

At this point, a special mention to the pioneering contributions of Isobe's group to this chemistry is pertinent.[5] Accordingly, studies from Isobe's laboratories have ranged from anomeric equilibration of cobalt complexed *C*-propargylic glycosides, to complex organic synthesis employing carbohydrate-derived dicobalt hexacarbonyl complexes as the starting materials, *vide infra*.

An inspection of literature references dealing with the use of dicobalt hexacarbonyl-stabilized propargylic cations in synthesis will show, at least, four different types of representations (Figure 1). Thus, even though drawings as **D** (Figure 1) might provide a more "realistic" picture, by highlighting the bent nature of the dicobalt hexacarbonyl compounds, for the sake of simplicity we have opted for drawings type **A** to represent dicobalt hexacarbonyl derivatives throughout the Chapter.



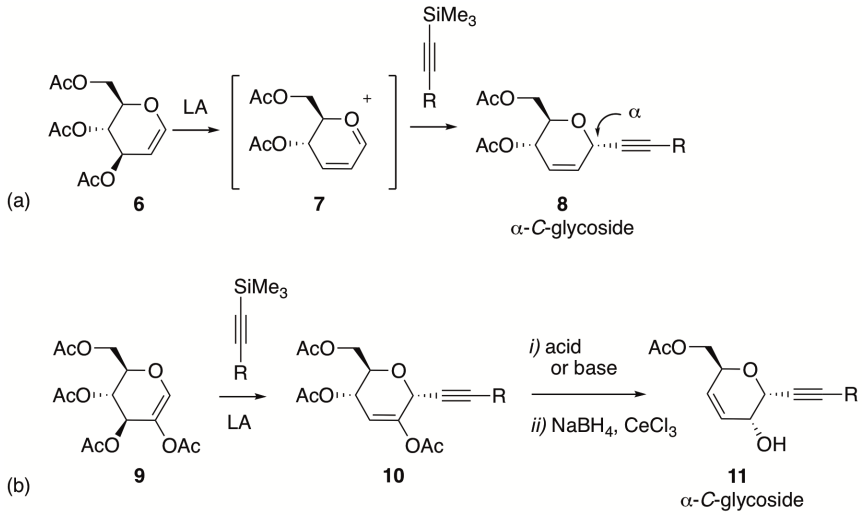
*** Insert Figure 1 ***

Caption: Figure 1. Common representation of dicobalt hexacarbonyl-stabilized propargylic cations used in the literature.

[H1 Title] **Dicobalt hexacarbonyl mediated anomerization of *C*-alkynyl glycosides**

Isobe and coworkers reported a general methodology for the introduction of different acetylenic moieties onto the anomeric position of pyranoses with the resultant *C*-glycosides having complete α-orientation (Scheme 2).[6] For instance, Ferrier-type alkynylation of tri-*O*-acetyl-D-glucal **6**, with silylacetylenes in a Lewis acid-catalyzed process, allowed the stereoselective introduction of alkynyl groups in almost quantitative yields leading to α-*C*-alkynyl glycosides **8** (Scheme 2a).[7] The reaction proceeds through formation of an allylic oxocarbenium cation **7**, which reacts selectively at the anomeric center with the appropriate silylacetylene. The anomeric effect of the ring oxygen and the conformation of the pyranose ring favor the α-attack of the incoming group, and the reaction was shown to be completely selective leading to pseudoaxial α-*C*-glycosides **8** (Scheme 2a).

Similarly, α-*C*-glycosylation of 2-acetoxy-D-glucal **9**, produced unstable α-*C*-glycosidic compounds **10**, which were easily converted to allylic alcohols **11** (Scheme 2b).

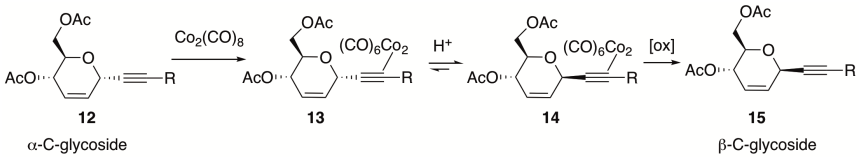


*** Insert Scheme 2***

Caption: Scheme 2. *C*-alkynylation of glycals developed by Isobe and coworkers.

In the early 1990s, contributions from Isobe's laboratories also showed that the α-*C*-alkynyl groups could be "anomerized" to the corresponding β-isomers by means of their corresponding dicobalt hexacarbonyl complexes. The overall process for α→β conversion, including cobalt complexation **12** → **13**, acid epimerization **13** → **14**, and oxidative decomplexation **14** → **15**, is illustrated in Scheme 3.[8] After the equilibration reaction, the cobalt complexes can be oxidatively decobaltated with a variety of reagents such as iodine,[9] amine N-oxides,[3] cerium(IV) ammonium nitrate (CAN),[10] ferric nitrate,[1a] tetrabutylammonium fluoride (TBAF) etc,[11] to unveil the alkyne moiety. Among these oxidants, iodine has shown to react efficiently, in short times, to restore the original triple bond in almost quantitative yield. Isobe and Hosokawa, also found reductive conditions for the cobalt decomplexation by the use of tributyltin hydride or triethylsilane.[12] The

original acetylene derivatives are then selectively transformed into the corresponding cis-olefin or cis-vinylsilanes.



*** Insert Scheme 3***

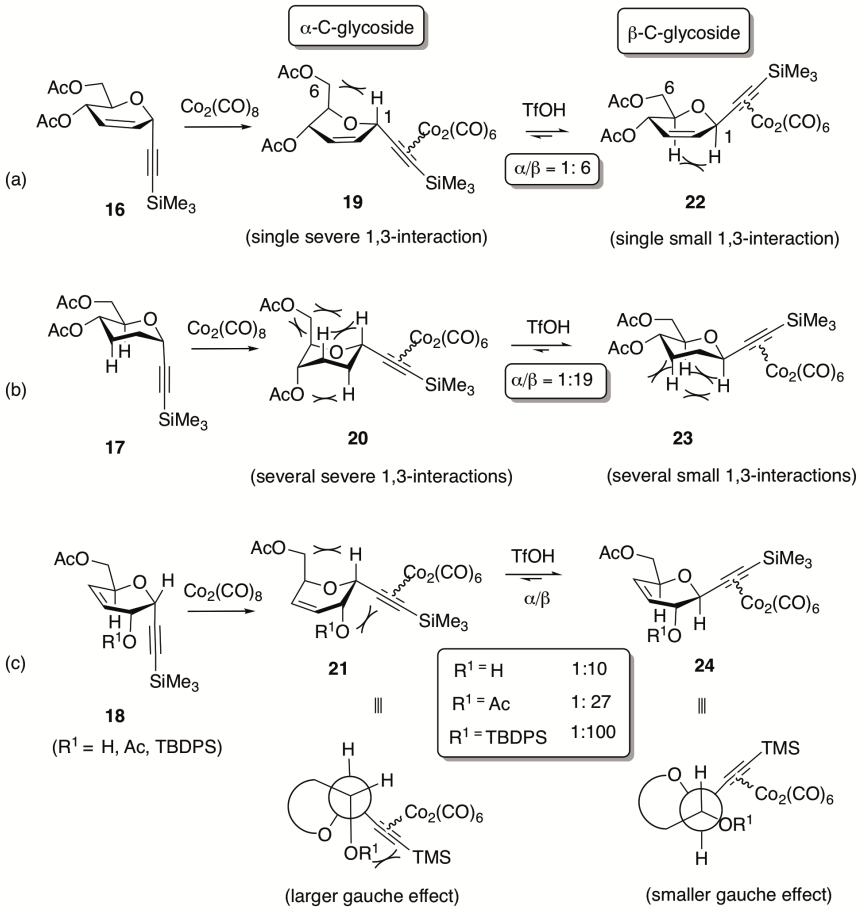
Caption: Scheme 3. Isobe´s anomerization of *C*-alkynyl sugars through cobalt complexes.

The crucial acid-catalyzed (α→β) equilibration features a propargylic anomeric oxocarbenium ion stabilized by the cobalt complex, which initiates an opening and closing of the tetrahydropyran ring leading to an equilibrium in which the thermodynamically more stable equatorial isomer will predominate. The ratio of the observed equilibration ranges from moderate to excellent, and the *C*-glycoside (α,β) ratio is controlled by the relative stability of both anomers.

Some illustrative examples are depicted in Scheme 4. In the preferred pyranose conformation of the alkynyl α-*C*-glycosides, the silylacetylene moiety is usually located in an α-axial orientation, e.g. **16** (Scheme 4a). However, after formation the corresponding dicobalt hexacarbonyl complexes, e.g. **19** (Scheme 4a), the conformation of the pyranose ring usually changes so that the dicobalt hexacarbonyl alkynyl substituent will adopt an α-equatorial orientation (see also: **17** → **20**, **18** → **21**, Scheme 4). Then, in the acid-mediated (α→β) epimerization, the driving force in the formation of the β-isomer in preference to the α-isomer could be explained on the basis of the minimization of 1,3-diaxial steric

interactions in the lowest energy conformation of the pyranose ring.[13] More recently, an exhaustive and plausible rationale for the C1-dicobalt hexacarbonyl alkynyl group epimerization has been advanced.[14]

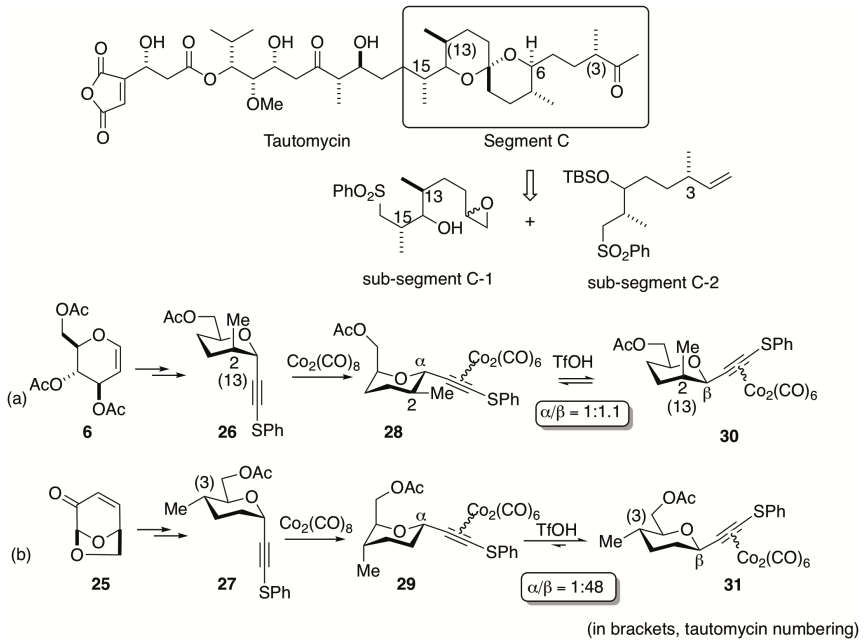
Accordingly, in the case of 2,3-dehydro pyranose systems, such as **19**, the ratio of ($\alpha \rightarrow \beta$) equilibration is rather moderate (1:6) accounting for the stability-difference due to the disfavored interaction between the axial anomeric proton H-1 and C-6 (Scheme 4a). In the corresponding saturated ring system, i.e. **20**, the equilibration provides the β-isomer **23** in a much higher ratio (α/β = 1:19), owing to the three pairs of severe 1,3-diaxial interactions existing in **20** (Scheme 4b). On the other hand, with pyranose systems containing a double bond between C-3 and C-4, such as **21**, it was observed that the α/β ratios increase in accordance to the size of the OH-2-substituent (Scheme 4c). Thus, considering that 1,3-interactions are virtually the same, the effect of the bigger C-2 substituents are then explained in the bases of an additional larger gauche effect between the C-2 substituent and the bulky cobalt-acetylene residue (Scheme 4c).



*** Insert Scheme 4***

Caption: Scheme 4. Anomerization of cobalt complexes in unsaturated (**16**, **18**) and dideoxy (**17**) pyranose derivatives.

The synthesis of "segment C" of the antibiotic *tautomycin* exemplified the application of this methodology to the preparation of natural products.[15] Thus, Isobe's group retrosynthetic analysis of the spiranic segment C of *tautomycin*, led to two sub-segments C-1 and C-2, which were prepared by application of the epimerization protocol to phenylthioalkynyl pyranoses **26** and **27**, readily available from tri-*O*-acetyl-D-glucal **6** and levoglucosenone **25**, respectively (Scheme 5).[16] Thus, complex-formation and epimerization of α-C-glycoside **28**, afforded a 1:1.1 mixture of α- and β- anomers **28** and **30**, respectively. This epimerization was found to be difficult and not very efficient because of the presence of a β-C2 axial methyl group in the pyranose ring. However, after separation of both anomers, and three additional equilibrations of the recovered α-isomer **28**, the β-anomer **30** could finally be obtained in 65% yield (Scheme 5a). Conversely, the equilibration of α-*C*-glycoside **29** was strongly shifted to its β-*C*-glycoside isomer **31**, because two substituents (methyl and acetoxymethyl) prefer to adopt an equatorial disposition (Scheme 5b).

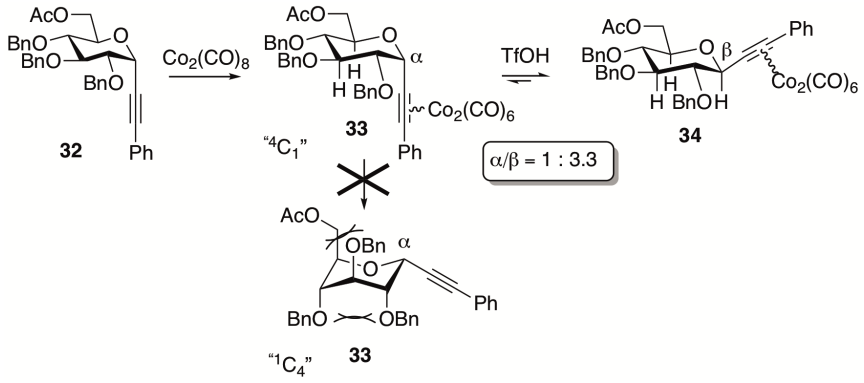


*** Insert Scheme 5***

Caption: Scheme 5. Anomerization of cobalt complexes **28** and **29** in route to the synthesis of segment C of *Tautomycin*.

Désiré and Veyrières, applied the anomerization conditions described by Isobe to "fully oxygenated" α-*C*-alkynyl glucopyranoside **32** (Scheme 6).[17] In this substrate, unlike in previous examples by Isobe's group, the cobaltation step (**32**→**33**) did not cause a conformational change [$^4C_1 \rightarrow {}^1C_4$] in the ensuing pyranoside **33**, which after complexation still exhibited a slightly distorted $^4C_1$ chair conformation with the bulky complexed-alkyne in an axial orientation (the alternate $^1C_4$ conformer would have imposed

two severe 1,3-diaxial interactions, Scheme 6). Addition of triflic acid to **33**, then brought an equilibrium with a low 1:3.3 (α/β) ratio, reflecting the slightly higher thermodynamic stability of **34** when compared to **33**.

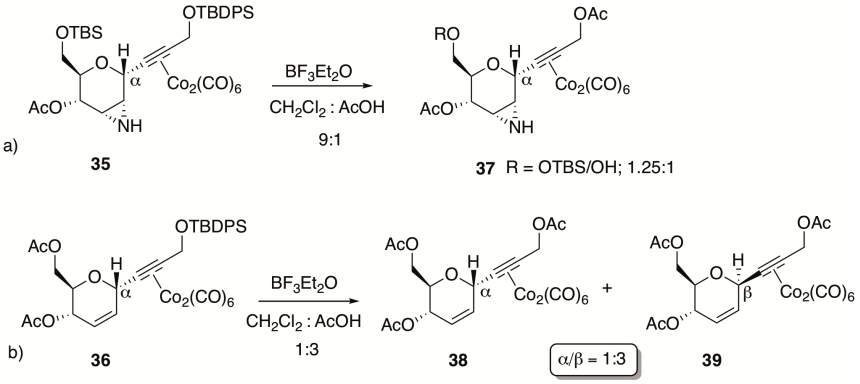


*** Insert Scheme 6 ***

Caption: Scheme 6. Equilibrium of cobalt complexes of fully substituted alkynyl α- and β-*C*-glucopyranosides **33** and **34**, respectively.

More recently, Yu and coworkers, have disclosed density functional theory (DFT) calculations to rationalize the remarkable differences observed in the attempted Nicholas epimerization of aziridinyl and allyl α-C-glycosides **35** and **36**, respectively (Scheme 7). [18] These compounds, owing to the presence of the terminal silyloxy substituent at the lateral chain, possessed two reactive sites for Nicholas-type transformations. Thus, whereas in both cases, upon activation with BF_3OEt_2 (CH_2Cl_2, AcOH), the terminal silyl group at the lateral chain was replaced by an acetate in an S_N1 Nicholas-type reaction, only the allylic glycoside **36** underwent partial (α→β) anomerization (Scheme 7b), with the α-disposition of aziridinyl derivative **37** remaining unchanged (Scheme 7a).

The observed experimental results were in agreement with the quantum calculations, which had predicted: *i)* that in the unsaturated glycoside **36**, both Nicholas substitution and Nicholas epimerization would be likely to have similar rates and to happen simultaneously; *ii)* that the β-anomer **39** would be thermodynamically preferred over the α-anomer **39** by 1 Kcal/mol, value in accordance with the experimentally observed (α/β) rate (1:3); and *iii)* that the barriers for the anomerization and substitution reactions of the azidirinyl derivative **35** would differ by 6 Kcal/mol, so that the latter process will definitely be the preferred reaction pathway. The annulated aziridine ring enhances the rigidity of the glycoside backbone, which in turn slows down the epimerization reaction.



*** Insert Scheme 7 ***

Caption: Scheme 7. Attempted epimerization of the aziridinyl and allyl α-*C*-glycosides **35** and **36**, respectively.

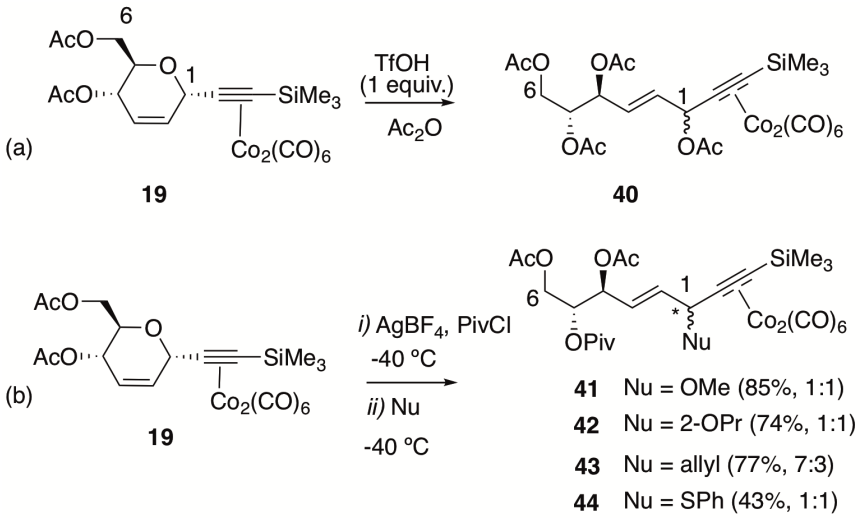
Dicobalt hexacarbonyl mediated ring-opening of *C*-alkynyl glycosides

As an extension of their studies on *C*-dicobalt hexacarbonyl alkynyl glycosides, Isobe et al, showed that the anomeric Nicholas oxocarbenium ion involved in the aforementioned

epimerization could be trapped by external nucleophiles to produce cobalt complexes of ring-opened sugar derivatives, e.g. **40**–**44** (Scheme 8).

Thus, treatment of $\Delta^{2,3}$-unsaturated-C-dicobalt hexacarbonyl alkynyl glycoside **19**, with TfOH in the presence of Ac_2O provided open-chain derivative **40**, in good yield. The product was, however, isolated as the most stable *E* olefin (Scheme 8a). The observed *Z* $\rightarrow$ *E* isomerization of the initial double bond demonstrated that, in this type of systems, not only the cobalt moiety but also the π-electrons of the double bond take part in the stabilization of the intermediate allylic cation.[19]

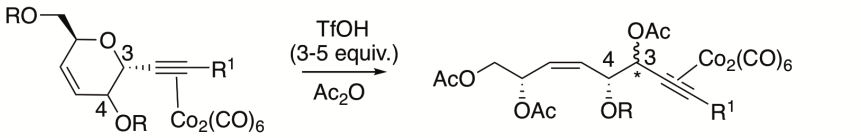
Furthermore, when the ring opening reaction was conducted using pivaloyl tetrafluoroborate,[20] a variety of nucleophiles could be used to trap the ring-opened electrophilic intermediate cation to generate differently substituted building blocks, i.e. **41**–**44**. In general, (*Z* $\rightarrow$ *E*) isomerization of the double bond was always observed in the final products, which were obtained as 1:1 diastereomeric mixtures at the new stereogenic center (C1, carbohydrate numbering, Scheme 8). However, as an exception, reaction with allyl silane as the nucleophile proved to be stereoselective furnishing a 7:3 diastereomeric mixture, **73** (Scheme 8b). All these linear cobalt complexes could be uneventfully demetallated in good yields by the use of iodine.



*** Insert Scheme 8 ***

Caption: Scheme 8. Ring opening-nucleophile trapping reactions of $\Delta_{2,3}$-unsaturated-α-*C*-dicobalt hexacarbonyl alkynyl glycosides **19**.

Additional studies by Isobe's group showed that cobalt complexes arising from $\Delta_{3,4}$-unsaturated-systems, i.e **21** and **45** (Scheme 9) required stronger reaction conditions (longer reaction times and additional amount of acid) since they do not have π-electrons to further stabilize the intermediate Nicholas cation. All products (**46**–**48**) were obtained as diastereomeric mixtures at C-3 (open-chain compound numbering) although good selectivity could be observed when a bulky susbstituent (*i. e*. TBDPS ether) was present at C-2 of the sugar ring (C-4, open-chain compound numbering). In these cases, the reaction proceeds to provide 3,4-*syn* diols as the major isomers. The authors provided a rationalization for this stereoselectivity using arguments similar to those initially proposed by Schreiber and coworkers.[21]



21a R = Ac, R^1 = $SiMe_3$

21b R = TBDPS, R^1 = $SiMe_3$

45 R = TBDPS, R^1 = H

46 R = Ac, R^1 = $SiMe_3$ (54%, 53:47)

47 R = TBDPS, R^1 = $SiMe_3$ (84%, 94:6)

48 R = TBDPS, R^1 = H (71%, 88:12)

*** Insert Scheme 9 ***

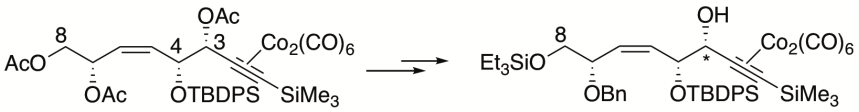
Caption: Scheme 9. Ring opening reaction of $\Delta_{3,4}$-unsaturated-α-*C*-dicobalt hexacarbonyl alkynyl glycosides.

Dicobalt hexacarbonyl mediated formation of ether rings from sugar acetylenes

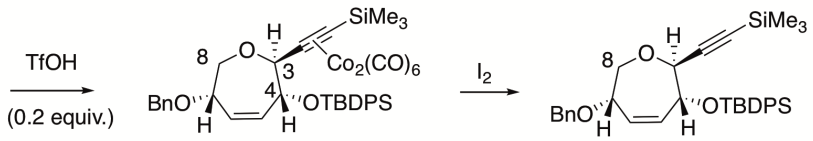
Isobe and coworkers, then drove their attention to the application of the intramolecular Nicholas cyclization as a method for the conversion of *C*-dicobalt hexacarbonyl alkynyl glycosides into medium-sized rings.

In this context, oxepane ring formation from six-membered sugar precursors is usually impractical due to thermodynamic constraints.[22] However, Isobe´s group found that Nicholas-type recyclization of the aforementioned open-chain derivatives could be used to prepare seven-membered oxepane derivatives (Scheme 10).[23] In this context, initial studies showed that open-chain Nicholas alcohol **49** (readily obtained from $\Delta_{3,4}$-unsaturated-derivative **21b**, Scheme 9, via acetyl derivative **47** Scheme 10) underwent triflic acid mediated cyclization leading to oxepene **50**, as a single isomer (Scheme 10). Apparently this highly selective cyclization is thermodynamically controlled since the two bulky substituents, cobalt acetylene moiety at *C-3* and TBDPS ether function at *C-4*, prefer to adopt a *trans* relationship to minimize steric strain. Decomplexation using oxidative

conditions then originated oxepene **51**, a useful synthetic precursor for subunits of marine *trans*-fused polyether toxins.[24]



47 **49**



50 **51**

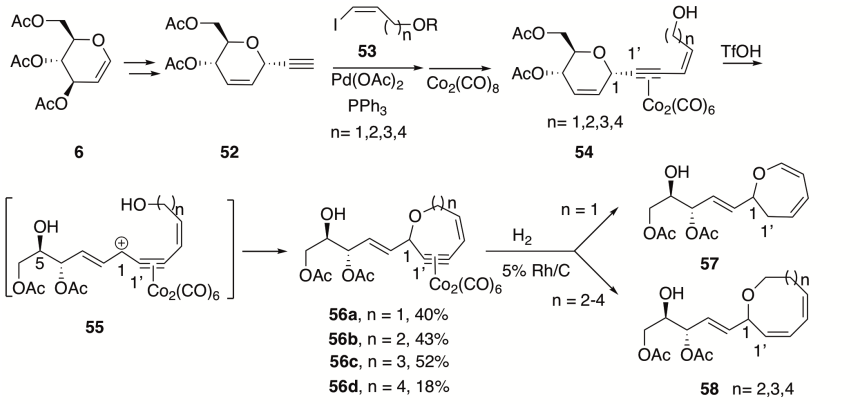
*** Insert Scheme 10 ***

Caption: Scheme 10. Application of an intramolecular Nicholas cyclization in the preparation of synthetically useful oxepanes.

Having realized that open-chain *trans*-olefin derivatives resulting from the ring-opening of $\Delta_{2,3}$-unsaturated-C-alkynyl glycosides, e.g. **55** (Scheme 11), would preclude a spontaneous ring-forming reaction, Isobe et al, introduced an alternative ring-recyclization strategy to medium size 7, 8, 9 and 10-membered rings by positioning the nucleophilic hydroxyl group at the, otherwise, terminal site of the acetylene (Scheme 11).[25] In order to induce the Nicholas cyclization, the precursors **54** were prepared by *C*-glycosidation of tri-*O*-acetyl-D-glucal **6**, with trimethylsilylacetylene followed by palladium catalyzed ene-yne coupling reaction with the appropriate vinyl iodide, **53** (Scheme 11). Then, cobalt complexation and acid treatment of the *C*-dicobalt hexacarbonyl allylic glycosides **54**, generated the intermediate Nicholas cations **55**, by a process in which an initially formed (C-1) *cis* allylic cation, isomerized to the more stable *trans* allylic cation. Under these premises,

recyclization (onto C5-OH) to regenerate the original pyranose ring will no longer be possible, and cyclization occurs onto the terminal hydroxyl group to afford **56**. This protocol was then successfully applied to the formation of cyclic ethers of various sizes, including seven, eight, nine and ten-membered rings.[26]

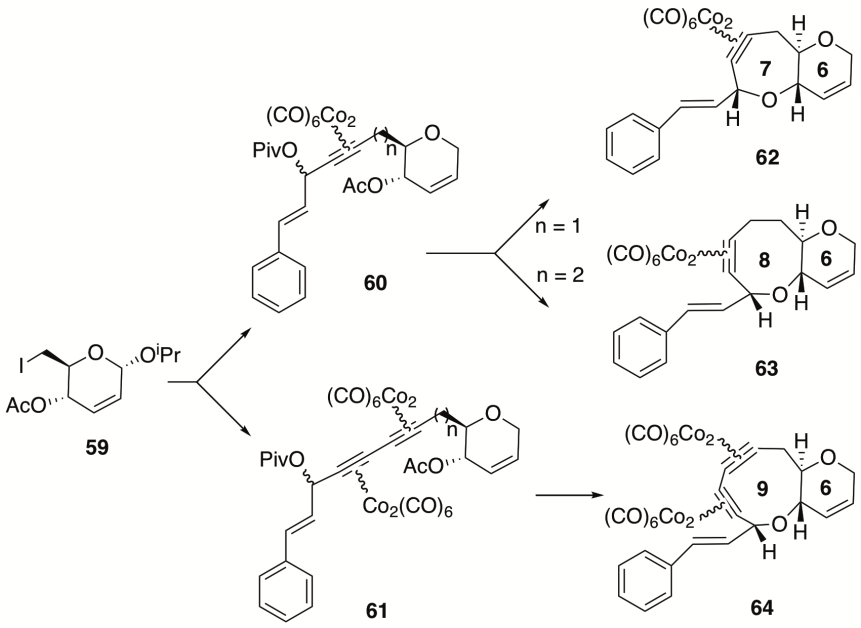
The resulting cyclic compounds, i.e. **56** (Scheme 11), with the dicobalt hexacarbonyl complex located inside the ring system, were found to be inert to the usual oxidative decomplexation conditions, probably due to the high ring-strain imposed by an internal acetylenic moiety in the desired ene-yne cyclic ethers. However, application of high H_2 pressure, in the presence of Rh-C, proved to be effective for the synthesis of the decomplexed dienes **57** and **58** (Scheme 11). Accordingly, the carbon atoms corresponding to the original acetylenes ended up as olefinic carbons in the eight, nine and ten-membered derivatives **58**. However, a double bond transposition was observed in the case of the seven-membered system, **57**.



*** Insert Scheme 11***

Caption: Scheme 11. Medium ether ring formation via dicobalthexacarbonyl complexes.

The synthesis of *ciguatoxin* and *gambiertoxin* by Isobe and coworkers, which makes use of most of the ring-opening and ring-closing methodologies described by his group, provides a remarkable example of the full potential of dicobalt hexacarbonyl alkynyl derivatives in synthesis.[27] In this context, Isobe *et al* have reviewed their efforts in the synthesis of *ciguatoxin* by application of Nicholas-related processes,[28] and readers are referred to this manuscript for a detailed account. Some selected examples are, however, outlined in Scheme 12.[29] Trans-alkenes containing a six membered ring alcohol on a dicobalt hexacarbonyl alkyne tether, as in **60** (Scheme 12), were cyclized to give 7-6 and 8-6 bicycles, **62** and **63**, respectively, with predominant or exclusive formation of the *syn* stereoisomer. Likewise, derivative **61** comprising a tether with two complexed alkynes could be cyclized to give 9-6 bycicle **64**.

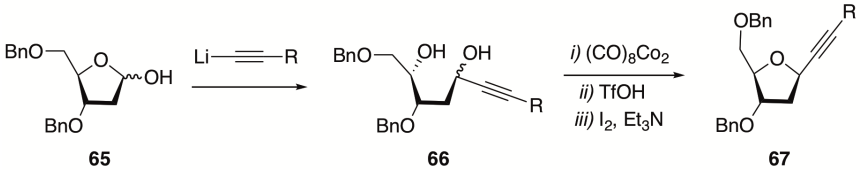


*** Insert Scheme 12***

Caption: Scheme 12. Fused bicyclic ether formation via dicobalthexacarbonyl complexes.

In 2003, Takase *et al*. developed a concise method for the synthesis of various alkynyl *C*-2-deoxy-D-ribofuranosides, by use of an intramolecular Nicholas cyclization. These derivatives had been identified as useful building blocks for oligonucleotide synthesis and in antisense DNA strategies.[30]

The approach, depicted in Scheme 13, involved a sequence of *i)* complexation, *ii)* 5-membered ring-formation, and *iii)* decomplexation, which could be conducted in a one-pot operation. The cobalt-mediated cyclization was shown to be reversible, then leading to the thermodynamically more stable β-isomers.



65 **66** **67**

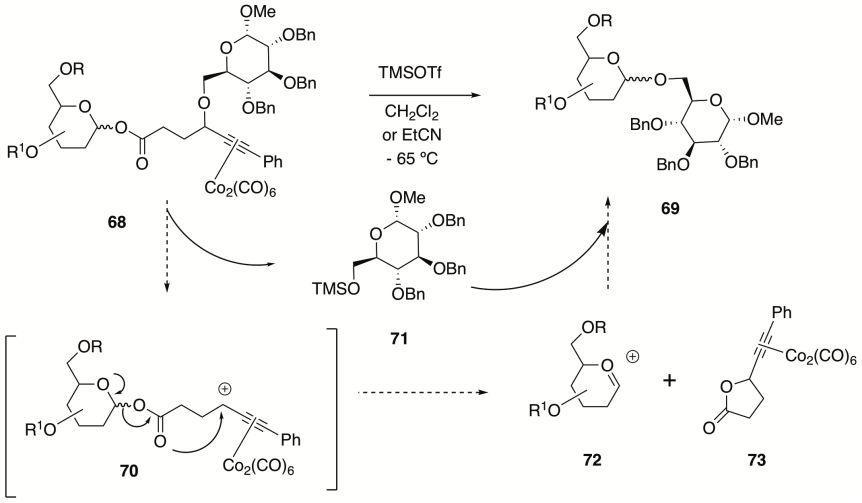
*** Insert Scheme 13***

Caption: Scheme 13. Stereoselective synthesis of alkynyl-*C*-2-Deoxy-β-D-ribofuranosides via intramolecular Nicholas reaction.

[H1 Title] **Glycosylations based on alkyne dicobalt hexacarbonyl complexes**

In 1997, Mukai et al, developed an intramolecular glycosylation method for the transformation **68** → **69**, shown in Scheme 14.[31] The designed reaction pathway involved acid-mediated release of the propargylic glycosyl-acceptor partner **71**, to generate a Nicholas cation **70**, which evolved by liberating a non-nucleophilic lactone **73**, and a glycosyl cation **72** that could intercept the aforementioned glycosyl acceptor **71**, to give

disaccharides **69**. The intramolecular nature of the process was proven via a cross-over experiment, and the observed disaccharide yields ranged from moderate to low (77–37%). The authors studied anomeric mixtures of D-gluco- D-galacto- and D-manno-pyranosides as glycosyl donors, and excellent stereoselection could be observed in the case of 2-*O*-benzoyl gluco- and manno-derivatives.

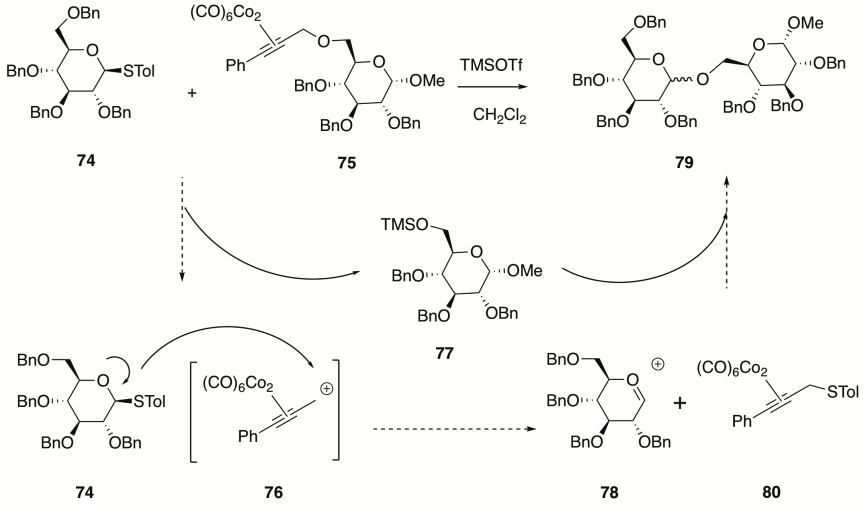


*** Insert Scheme 14 ***

Caption: Intramolecular aglycon delivery glycosylation mediated by an alkyne dicobalt hexacarbonyl complex.

Very recently, Li and co-workers have reported on the use of cobalt hexacarbonyl propargyl cations for the activation of thioglycosides in intermolecular glycosylation protocols.[32] The glycosylation process is outlined in Scheme 15, and involves the use of a cobalt hexacarbonyl propargyl derivative, e.g. **75**, functioning as the glycosyl acceptor and a thioglycoside donor, e.g. **74**. As a result of their studies, a plausible reaction pathway

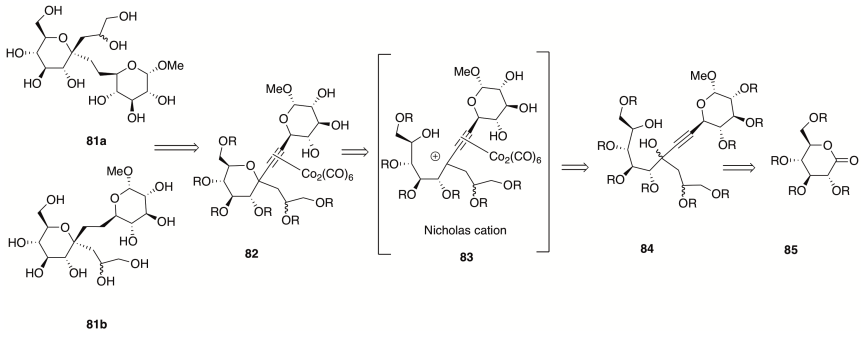
was advanced. Thus, interaction of the $Co_2(CO)_6$ propargylated acceptor with TMSOTf (0.1 equiv.) produced the Nicholas cation **76**, liberating a carbohydrate residue that could be silylated to produce **77**, as an activated glycosyl acceptor. The reaction process could then continue with the nucleophilic addition of the anomeric sulfur atom on **74**, to Nicholas cation **76**, causing the cleavage of the C-S bond and resulting in the generation of glycosyl cation **78**, which could be trapped by **77** to provide disaccharide **79**, as well as $Co_2(CO)_6$-propargyl *p*-methylphenyl sulfide **80** (Scheme 15). The scope of the method, also studied by the authors, proved to be very broad and the glycosylation could be applied to acceptors with primary and secondary hydroxyl groups, providing disaccharides in moderate to good yields (69–85%).



*** Insert Scheme 15 ***

Caption: Scheme 15. $Co_2(CO)_6$-propargyl cation mediated intermolecular glycosylation of thioglycosides.

Nicholas type cations were also used by Schmidt's group in the preparation of *C*-disaccharides of ketoses.[33] Thus, they had identified *C*-ketosides **81** (Scheme 16), as potential candidates for glycosyl-transferase inhibitor precursors. Their retrosynthetic analysis visualized the formation of the desired *C*-ketosides, by cyclization of a Nicholas cation **83** to *C*-ketoside **82**, as the key step (Scheme 16). It is noteworthy that a related acid-triggered- cyclization on decobaltated **84** had proven to be unsuccessful. Subsequent synthetic manipulations of the dicobalt hexacarbonyl cluster **82**, would then ultimately lead to **81**. Access to the alkynyl precursor **83**, was imagined via the complex structure **84**, accessible by sequential addition of allylmagnesium bromide and a pyranose-derived lithium acetylide to a gluconolactone derivative, **85**.

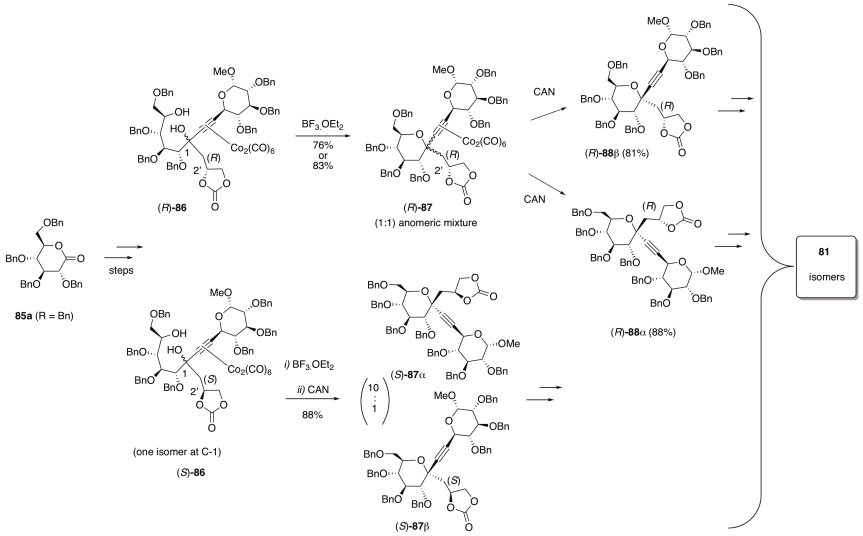


*** Insert Scheme 16***

Caption: Scheme 16. Retrosynthesis of ketose *C*-disaccharides by Nicholas cyclization.

The key steps of Schmidt's synthesis are highlighted in Scheme 17. Thus, 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5 lactone **85a** (R=Bn), was transformed into isomeric 2'-(*S*) and 2'-(*R*) Co_2-$(CO)_6$-alkynyl derivatives, (*S*)-**86** and (*R*)-**86**, respectively (Scheme 17). Additionally, (*S*)-**86** and (*R*)-**86** were composed of two isomeric C-1 derivatives. The Nicholas type cyclization was next studied in most of these isomeric derivatives.

Accordingly, Nicholas-type cyclization of each of the two isomeric C-1 carbinols (*R*)-**86** was carried out separately to provide, in each case, a 1:1 anomeric mixture of (*R*)-**87** ketosides (76% and 83% yield), which after separation of the anomers, and decobaltation with ceric ammonium nitrate (CAN), provided (*R*)-**88**α and (*R*)-**88**β, in 88% and 81% yield, respectively. On the other hand, a single C-1 isomer of cobaltated (*S*)-**86** was cyclized and demetalated (CAN), to yield a 10:1 mixture of α- and β- anomeric derivatives (*R*)-**87**α and (*R*)-**87**β, respectively. Further processing of these derivatives led to all possible isomers of **81**.

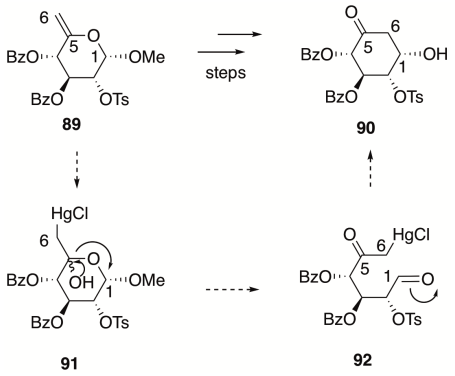


*** Insert Scheme 17 ***

Caption: Scheme 17. Schmidt's synthesis of *C*-ketosides by Nicholas-type cyclization.

[H1 Title] **Dicobalt hexacarbonyl-mediated Ferrier(II)-type carbocyclizations from pyranose derivatives.**

Several methods for the transformation of dicobalt hexacarbonyl derived pyranoses into cyclohexanone derivatives have been described by several research groups. These transformations displayed certain resemblance to the so-called Ferrier (II) carbocyclization or Ferrier (II) rearrangement. The Ferrier (II) carbocyclization process **89** → **90**, depicted in Scheme 18 was reported by R. J. Ferrier in 1979.[34,35] The transformation involved regiospecific hydroxymercuration of the vinyl ether moiety to an unstable hemiacetal, i.e. **89** → **91**, which evolves to a 1,5-dicarbonyl intermediate **92**, that might experience an aldol-like cyclization to give cyclohexanone **90** (Scheme 18).



*** Insert Scheme 18 ***

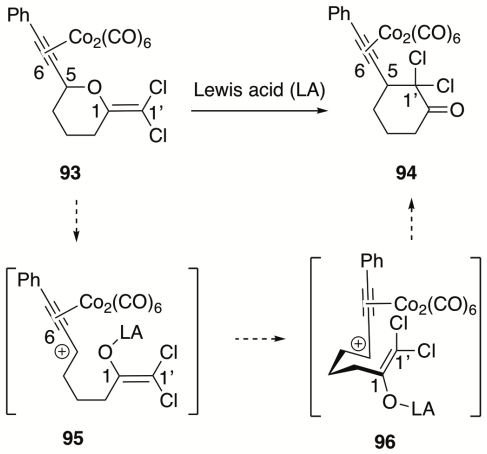
Caption: Scheme 18. Ferrier (II) rearrangement or Ferrier carbocyclization.

A report by Harrity and co-workers in 2002,[36] was the first to illustrate the value of dicobalt hexacarbonyl clusters in the Ferrier-related construction of cyclohexanones, e.g. **93** → **94** (Scheme 19). Thus, the hexacarbonyl dicobalt moiety at C-5 in enyne **93** facilitated the scission of the propargylic C-5-O bond by stabilization of the intermediate reactive carbocationic species **95**, which experienced a completely regioselective addition to the enolate moiety at C-1 to yield cyclohexanone **94**, most likely through a chair-like

transition state, e.g. **96**.[37] Although initial studies were performed in racemic series, in their work with enantiomerically enriched compounds, Harrity and co-workers were able to establish that minimal racemization occurred at the stereogenic centre during the rearrangement process.[38]

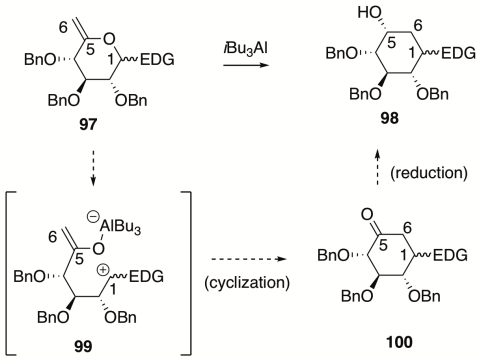
*** Insert Scheme 19***

Caption: Scheme 19. Harrity's dicobalt hexacarbonyl mediated cyclohexanone formation.



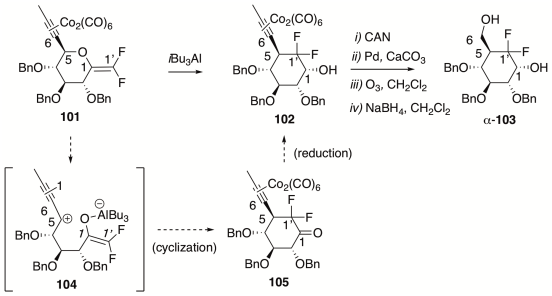
On the other hand, as a continuation of their interest in sugar-to-carbocycle transformations, e.g. **97** → **98** (Scheme 20),[39] Sinaÿ and co-workers reported on the carbocyclic ring closure of thio-, seleno-, and *C*-aryl hex-5-enopyranosides mediated by triisobutylaluminum (TIBAL).[40] In their studies, they acknowledged the key role of an electron-donating group (EDG) by stabilizing their proposed key (C-1)-carbocationic intermediate **99**, in its cyclization process to ketone **100**, the latter subsequently reduced (TIBAL) to the corresponding alcohol **98** (Scheme 20). In this context, Sollogoub, Sinaÿ and co-workers recognized the potential of the dicobalt hexacarbonyl cluster as an EDG in their general strategy for the preparation of carbocycles from carbohydrate derivatives. As

a result, they reported a concise method for the stereocontrolled synthesis of gem-difluorocarba-α- and β-D-glucopyranoses **103**, based on a Nicholas-type cyclization **101** → **105**, followed by synthetic manipulations (Schemes 21, 22).[41] Accordingly, synthesis of the α-isomer (α-**103**) was carried out by TIBAL-mediated Nicholas cyclization **101** → **102**, followed by synthetic manipulations (CAN, partial hydrogenation, ozonolysis, and reduction) on the alkynyl dicobalt hexacarbonyl group for the installation the C6-OH group (Scheme 21). In this process, the stereoselective reduction of the C-1 carbonyl group in ketone intermediate **105**, to yield the C-1 axial hydroxyl group in α-**102**, was explained by the authors via intramolecular hydride-delivery from the isobutyl group of TIBAL on the less-hindered β-face of the molecule. On the contrary, the Ferrier(II)-Nicholas rearrangement of **101**, mediated by Cl_3TiO*i*Pr led to cyclohexanone **105** that, after quenching of the Lewis acid with THF, could be reduced under steric control by super hydride (Et_3BHLi) to yield equatorial alcohol **106**, precursor of β-**103** via a synthetic sequence related to the one mentioned above (Scheme 22).



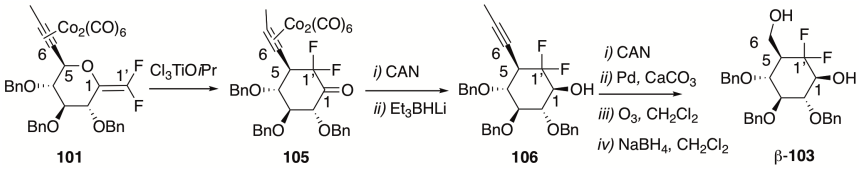
*** Insert Scheme 20 ***

Caption: Scheme 20. Sinaÿ's TIBAL mediated sugar-to-carbocycle transformation.



*** Insert Scheme 21 ***

Caption: Scheme 21. Sinaÿ and Sollogoub's TIBAL mediated synthesis of 5a-difluoro-α-D-carbaglucopyranose.

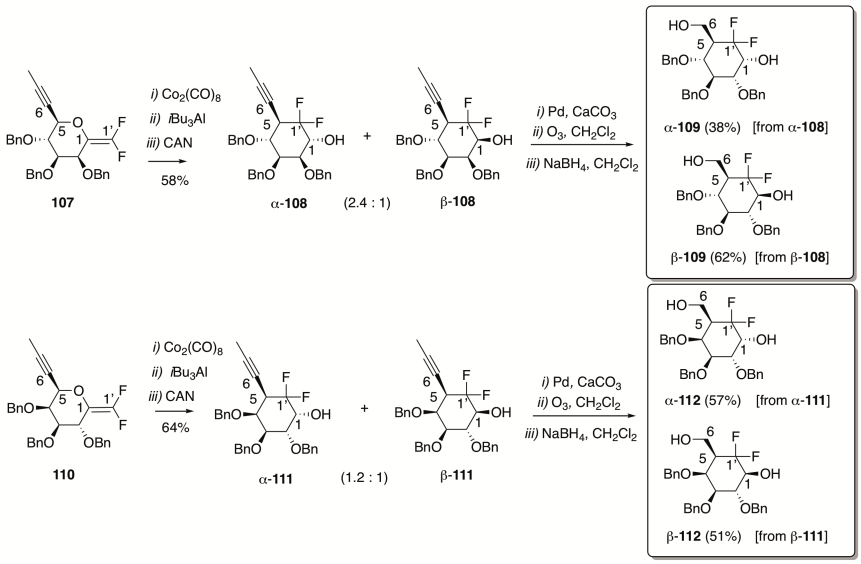


*** Insert Scheme 22 ***

Caption: Scheme 22. TIBAL mediated synthesis of 5a-difluoro-β-D-carbaglucopyranose.

By application of the aforementioned protocol, Sollogoub and co-workers were able to synthesize 5a-difluoro α- and β-carbamanno- (**109**) and 5a-difluoro α- and β-carbagalacto-pyranoses (**112**), from alkynyl derivatives **107** and **110**, respectively, readily available from the parent monosaccharides (Scheme 23).[42] As above, the cobalt cluster in **107** and **110**, played a dual role in the process: as the electron-donating-function stabilizing the propargyl cation, and as a precursor of the CH_2OH group in the desired carbasugars. Unlike their previous example with the D-gluco-derivative [**101** → α-**103**] (Scheme 22), the reduction

of the intermediate (C-1) ketones in the manno- and galacto- series proved not to be completely stereoselective, leading to α,β- anomeric mixtures **108** and **111**, respectively (Scheme 23).



*** Insert Scheme 23 ***

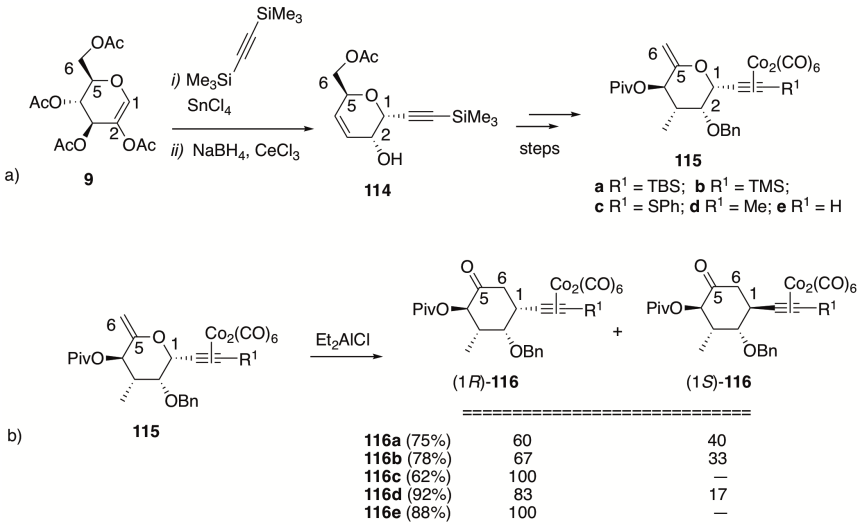
Caption: Scheme 23. TIBAL mediated synthesis of 5a-difluoro-α,β-D-carbamanno- and 5a-difluoro-α,β-D-carbagalacto- pyranoses, **109** and **112**, respectively.

In a subsequent related work, Sardinha, Rauter and Sollogoub, reported on the synthesis of the 5a-fluoro analogue of (+)-MK7607 (**113**) (Figure 2), a naturally occurring pseudo-carbasugar with herbicidal activity, from α-**112**.[43]

*** Insert Figure 2 ***

Caption: Figure 2. (+)-MK7607 and its 5a-fluoro analogue, **113**

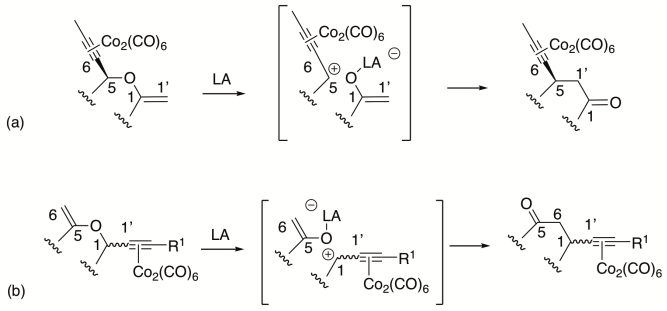
More recently, Chang and Isobe have reported on an additional diastereoselective dicobalt hexacarbonyl-assisted Nicholas-type cyclization to alkynyl cyclohexanones.[44] Their approach, highlighted in Scheme 24, was largely based in chemistry previously developed by Isobe´s group. Thus, a completely stereoselective α-*C*-alkynylation on 2-acetoxy-D-glucal triacetate (**9**) led to **114**, which was then transformed into **115a-e**, a series of compounds differing on the substituent at the acetylenic terminal position (Scheme 24a). Cobalt-assisted Ferrier(II)-type cyclization of **115** was successfully mediated by diethylaluminum chloride (Et_2AlCl),[45] to give cyclohexanones **116** (Scheme 24b). Their results showed that smaller substituents at the alkyne terminal position (R^1), as in **115c**, **115e**, resulted in higher stereoselectivities in the cyclization leading to **116** (Scheme 24b).



*** Insert Scheme 24 ***

Caption: Scheme 24. Nicholas-Ferrier(II) type carbocyclization by Isobe's group.

In summary, contributions from the Sollogoub's and the Isobe's laboratories have served to illustrate the efficiency of the alkynyl dicobalt hexacarbonyl species in the Ferrier(II) carbocyclization, as depicted in Scheme 25. Thus, whereas in Sollogoub's approach the alkynyl cobalt cluster was placed at C-5 (Scheme 25a), in Isobe's protocol the dicobalt hexacarbonyl substituent was located at C-1 (Scheme 25b), and in each case the propargyl cation, stabilized by the dicobalt hexacarbonyl cluster, played a key role in the cyclization.



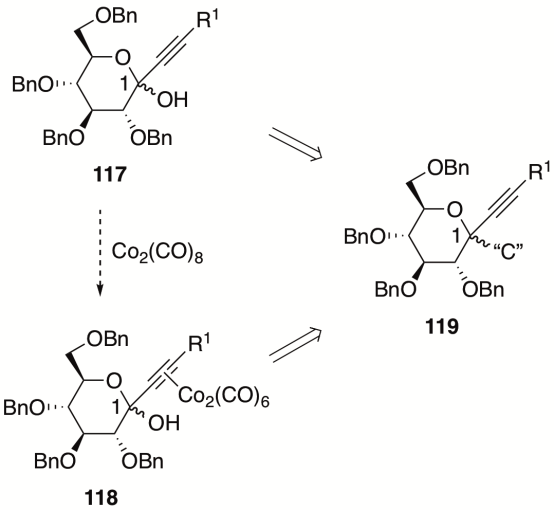
*** Insert Scheme 25 ***

Caption: Scheme 25. Approaches to Nicholas-Ferrier(II)-type carbocyclization by Sollogoub's (a) and Isobe's (b) group.

[H1 Title] **Pyranosidic dicobalt hexacarbonyl propargyl oxocarbenium ions versus oxocarbenium ions. Some remarkable features.**

Some early examples from our laboratories also served to illustrate the idiosyncrasy of anomeric (C-1) dicobalt hexacarbonyl propargyl cations, compared to the parent alkynyl cations. Thus, as part of a synthetic program we required appreciable amount of bis-*C*,*C*-pyranosides, one of the C1-substituents being an alkynyl group, e.g. **119** (Scheme

26).[46,47] A straightforward retrosynthetic analysis to bis-*C*(alkynyl),*C*-pyranosides **119**, depicted in Scheme 26, showed two possibilities based on the *C*-glycosylation of either *C*-alkynyl pyranoses **117** or their dicobalt hexacarbonyl derivatives **118**. At the outset of this work, only one example of the transformation of a *C*-vinyl ketose into a bis-*C*,*C*-pyranoside, had been described.[48]



*** Insert Scheme 26

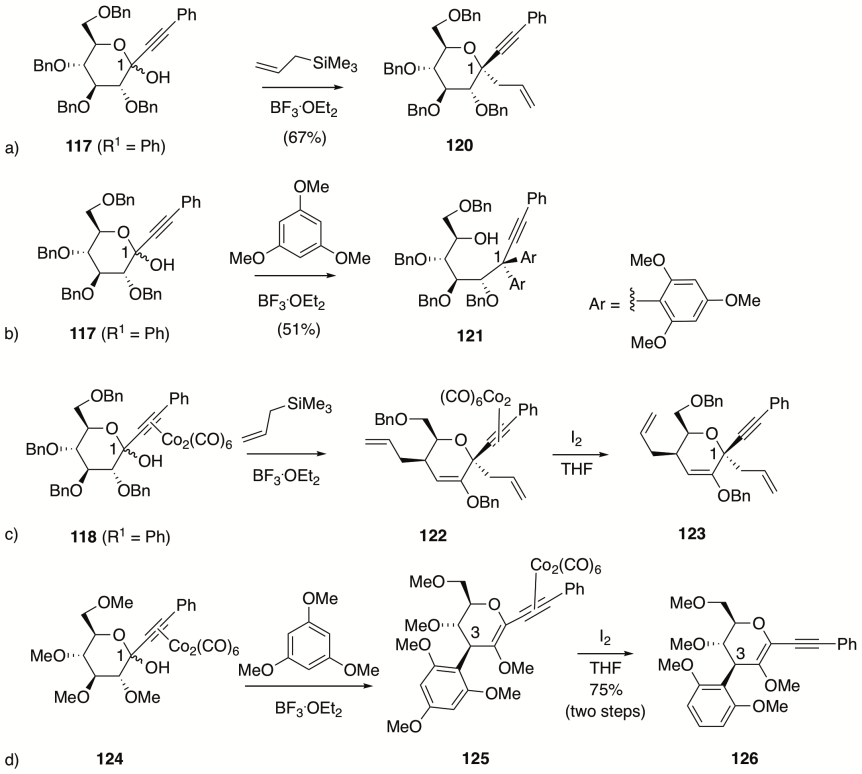
Caption: Scheme 26. Retrosynthetic analysis of bis-*C*(alkynyl),*C*-pyranosides from *C*-alkynyl derivatives.

Some representative examples of our studies are displayed in Scheme 27. Thus, the *C*-allylation (allyltrimethylsilane) of "cobalt-free" *C*-alkynyl ketose **117** ($BF_3.OEt_2$) took place smoothly to give bis-*C*,*C*-glycoside **120**, as a sole stereoisomer, in 67% yield (Scheme 27a). On the other hand, a related reaction of **117** in the presence of 1,3,5-trimethoxy

benzene as nucleophile, provided open-chain bis-arylated derivative **121** (51% yield, Scheme 27b).

Conversely, the reactions of dicobalt hexacarbonyl analogues **118** and **124** with allyltrimethyl silane and 1,3,5-trimethoxy benzene, respectively, took place to give entirely different compounds (Scheme 27c,d).[49] Thus, allylation of dicobalt hexacarbonyl derivative **118** (allyl trimethylsilane, $BF_3.OEt_2$) furnished unsaturated, C1,C4-bis-allylated derivative **122**, which after uneventful iodine-mediated decobaltation provided **123**. The incorporation of the second allyl unit had taken place at C-4 with complete stereoselectivity (Scheme 27c). Reaction of **124** with 1,3,5-trimethoxy benzene (BF_3OEt_2) provided *C3*-branched *C*-glycal **125**, that was decobaltated (I_2, THF) to provide **126** (Scheme 27d). Unlike the previous case, only one aryl residue had been incorporated, this time at C-3 with complete stereoselectivity (Scheme 27d).

From the results in Scheme 27, it became clear that the dicobalt hexacarbonyl cluster in *C*-alkynyl ketoses **118** and **124**, exerted a drastic effect on the chemical behavior of the intermediate anomeric oxocarbenium ions, when compared to "cobalt free" analogue **117** (compare Scheme 27a and Scheme 27c; and Scheme 27b and Scheme 27d).



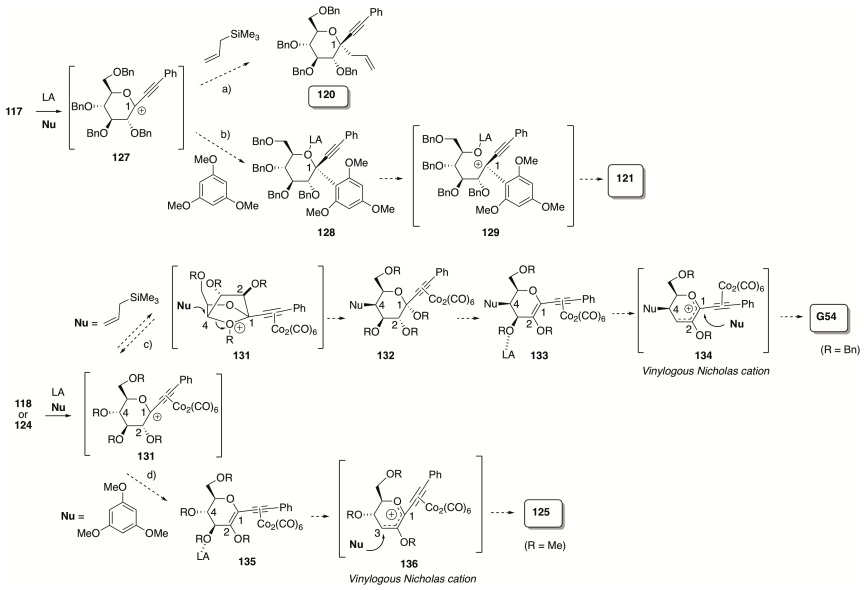
*** Insert Scheme 27 ***

Caption: Scheme 27. Lewis-acid mediated reactions of *C*-alkynyl and *C*-dicobalt hexacarbonyl alkynyl pyranoses with allyl trimethylsilane and 1,3,5-trimethoxybenzene.

Our proposed reaction pathways for the above transformations are depicted in Scheme 28a,b. Thus, the formation of compounds **120** and **121** from **117**, could be explained by alkylation or (Friedel-Crafts) arylation of an intermediate *C*-alkynyl oxocarbenium ion **127** leading to bis-*C*,*C*-glycosides **120** (Scheme 28a) or **128** (Scheme 28b), respectively. The former could be isolated as the final reaction product, whereas the highly reactive bis-*C*,*C*-glycoside intermediate **128**, underwent further acid-catalyzed ring opening to generate a

highly stabilized (benzylic, propargylic) C-1 oxocarbenium ion **129**, able to capture a second nucleophile unit, leading to **121** (Scheme 28b). On the other hand, Nicholas-oxocarbenium ion **130**, arising from Lewis acid activation of dicobalt hexacarbonyl derivatives **118** or **124**, displayed alternate reaction patterns. Thus, the formation of bis-allylated derivative **122** was explained by stereoselective nucleophilic ring opening of the bicyclic dioxolanyl ion **131** (in equilibrium with **130**), to provide a postulated *C4*-allyl derivative **132**, followed by elimination to *C*-glycal **133** (Scheme 28c).[1b, 50] The latter behaved as a Ferrier (I)-type substrate, *vide infra*, leading to vinylogous Nicholas cation **134**,[51,52] able to capture a second allyl nucleophile at C-1 to lead, after decobaltation, to allyl bis-*C,C*-glycoside **122** (Scheme 28c). A direct elimination process from oxocarbenium Nicholas cation **130** to a postulated glycal **135**, might have been at the origin of the formation of the *C3*-branched glycal **125**, via arylation at C-3 of the vinylogous Nicholas cation **136** (Scheme 28d).

From these results, it became of interest to us the chemical behavior of the postulated vinylogous Nicholas cations **134** and **136** (Scheme 28c,d), and under these premises we initiated a study on the synthesis and reactivity of the *C*-dicobalt hexacarbonyl alkynyl glycals, e.g. **133**, **135**, as precursors of the aforementioned vinylogous pyranosidic Nicholas cations.



*** Insert Scheme 28 ***

Caption: Scheme 28. Proposed reaction pathways in the transformations of *C*-alkynyl (**117**) and *C*-dicobalt hexacarbonyl alkynyl (**118**, **124**) pyranoses.

[H1 Title] **Dicobalt hexacarbonyl alkynyl derivatives as precursors of pyranosidic Ferrier-Nicholas cations. Synthesis and transformations**

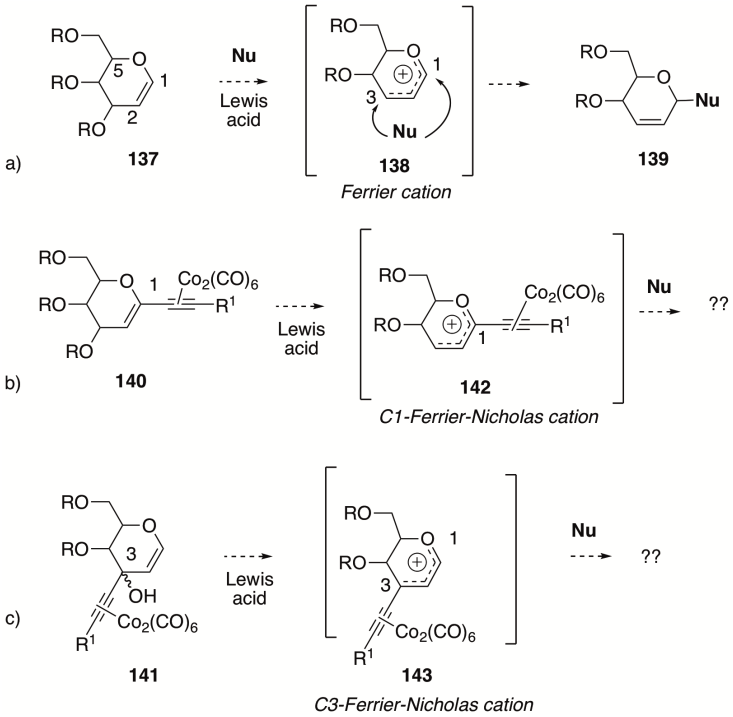
[H2 Title] **Ferrier rearrangement or Ferrier (I) reaction. Ferrier-Nicholas cations.**

Comentado [RE4]: Main text. H1 refers to main section heading; H2 refers to sub-section heading.

The transformation of glycals (1,5-anhydrohex-1-enitols, e.g. **137**, Scheme 29a) into 2,3-unsaturated glycosyl derivatives, e.g. **139**, reported by Ferrier in 1962, is currently known as Ferrier rearrangement.[53,54,55] In this transformation, allylic oxocarbenium ions, e.g. **138**, are currently accepted as the reaction intermediates. In comparison with "normal" glycosyl oxocarbenium ions, Ferrier cations **138**, are stabilized by the absence of the electron-withdrawing C2-substituent and by additional allylic conjugation.

As previously mentioned, we had postulated the existence of *C*-dicobalt hexacarbonyl glycals **133** and **135** as reaction intermediates and precursors of vinylogous Nicholas cations **134** and **136** (Scheme 28), respectively, which we had previously termed Ferrier-Nicholas cations.[49] In this context, we became interested in the study of Ferrier-Nicholas cations **142** and **143** that, as we visualized, could arise from dicobalt hexacarbonyl substrates **140** and **141**, respectively (Scheme 29b,c).

We had reasoned that "Ferrier-Nicholas" cations, e.g. **142**, **143**, would enjoy additional Nicholas-type stabilization when compared to Ferrier cations, and that the presence of the *C1*- or *C3*-substituent, would result in regioselective transformations.



*** Insert Scheme 29 ***

Caption: Scheme 29. Ferrier rearrangement, Ferrier cations (a), and Ferrier-Nicholas cations (b,c).

[H2 Title] ***C1*-Ferrier-Nicholas cations.**

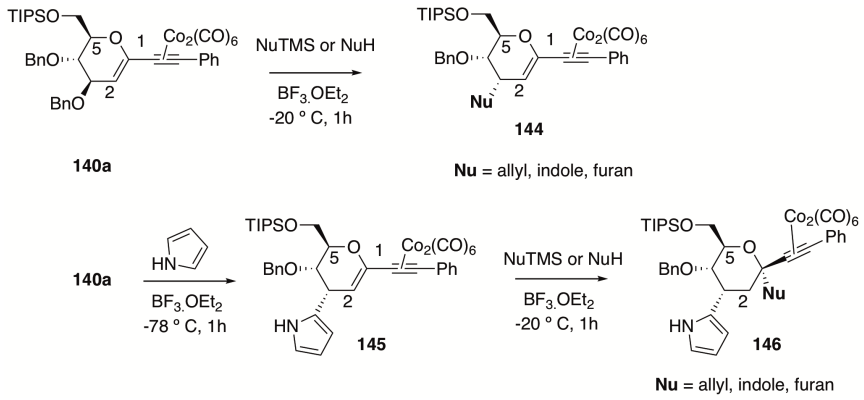
Comentado [RE5]: Main text. H1 refers to main section heading; H2 refers to sub-section heading.

Regarding the study of C1-Ferrier-Nicholas cations, we initially synthesized derivatives **140**, with a dicobalt hexacarbonyl alkynyl group at C1 as their potential precursors. Thus, compounds **140** (Figure 2), differing on the C6-substituent, were efficiently prepared from tri-*O*-acetyl D-glucal **6**, in five- or six-step synthetic sequences.[56,57]

*** Insert Figure 3 ***

Caption: Figure 3. *C1*-dicobalt hexacarbonyl alkynyl glycals **140a–d**.

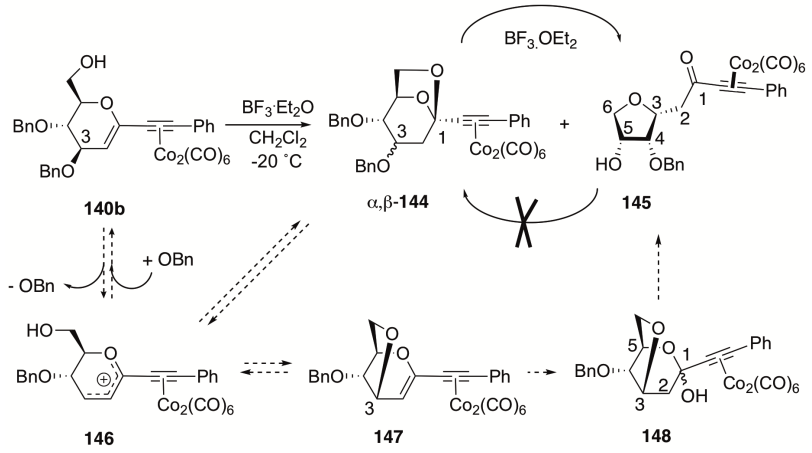
The chemical behavior of these derivatives, upon treatment with BF_3OEt_2, proved to be highly dependent on the nature of the substituent at C6. Thus, 6-*O*-triisopropylsilyl glycal **140a** reacted with a series of nucleophiles, e.g. furan, allyl trimethylsilane, indole, in the presence of BF_3OEt_2, at -20 ºC, to give α-*C3*-branched glycals **144** in fairly good yield (Scheme 30). Remarkably, the reaction of **140a** with pyrrole, which took place at -78 ºC, provided access to α-*3C*-pyrrolyl glycal **145**, whose highly nucleophilic glycal double bond proved to be able to react with a second nucleophile unit in a two-step electrophilic addition process (A_nE),[58] leading to bis-*C*,*C*-glycosides **146**, in moderate yields (Scheme 29).



*** Insert Scheme 30***

Caption: Scheme 30. Reactivity studies on 6-*O*-triisopropyl *C*-glycal, **140a**.

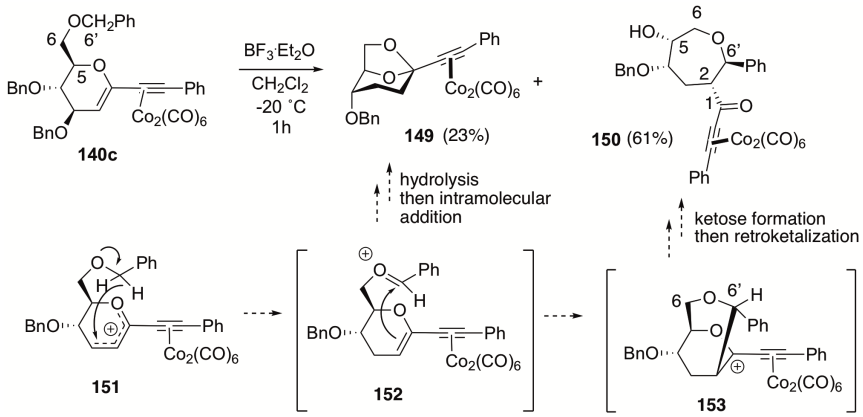
6-Hydroxy *C*-glycal **140b**, on the other hand, underwent acid-catalyzed cyclization to a mixture of epimeric 3-OBn-1,6-anhydro derivatives **147** and branched tetrahydrofuran derivative, **148** (Scheme 31). Our rationale for the observed transformation, involved the reversible formation of Ferrier-Nicholas cation **149**, which will be at the origin of the observed C3-epimeric mixture in **147**. Alternatively, an intramolecular, two-step electrophilic cyclization process (Ad_E), of the *C-6* hydroxyl group onto the glycal double bond would have led to the formation of the 1,6-anhydro derivative, **147**. On the other hand, regioisomeric intramolecular (C3) Ferrier-type reaction would produce **150**, which could undergo acid catalyzed hydration to hemiketal **151**, whose retroketalization will irreversibly produce branched tetrahydrofuran **148**, as a sole isomer. Along this line, **147** could be transformed to **148** under the same reaction conditions, whereas the opposite did not occur.



*** Insert Scheme 31 ***

Caption: Scheme 31. Reactivity studies on 6-hydroxy *C*-glycal **140b**.

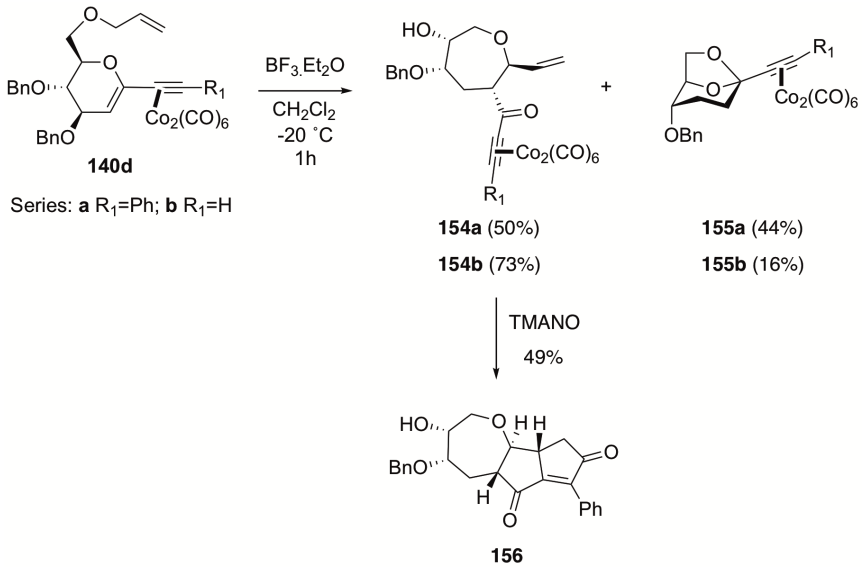
Reaction of 6-OBn derivative **140c**, in the presence of BF_3OEt_2, also proved to be a remarkable process, providing a mixture of 1,6-anhydro derivative **152** and oxepane **153** (Scheme 32). The proposed reaction pathway invoked a 1,6-hydride transfer from the 6-O-benzylic group onto an intermediate Ferrier-Nicholas cation **154**,[59] to generate a benzylic oxocarbenium ion and regenerate the glycal double bond in **155**. The latter is the key intermediate in the formation of **152** and **153**. Thus, hydrolysis of the oxocarbenium ion followed by addition to the glycal double bond produced **152**, whereas an alternate path involving cyclization through attack of the glycal double bond to the oxocarbenium ion produced, stereoselectively, bicyclic Nicholas cation **156**, which would evolve to oxepane **153** by water addition, to form an intermediate ketose, followed by pyranose ring-opening.



*** Insert Scheme 32 ***

Caption: Scheme 32. Reactivity studies on 6-*O*-benzyl *C*-glycal **140c**.

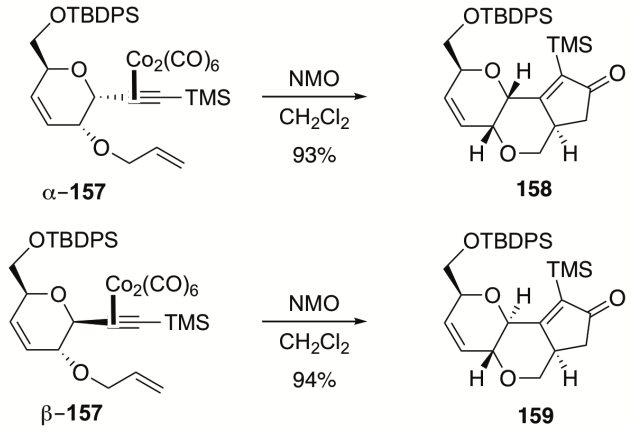
Finally, 6-*O*-allyl derivative **140d** displayed, upon treatment with BF_3OEt_2, a behavior similar to that of its 6-OBn analogue **140c**, furnishing a mixture of oxepane and 1,6-anhydro sugar derivatives, **157** and **158**, respectively (Scheme 33). It is noteworthy, that replacement of the terminal alkynyl phenyl group by H, resulted in an improved yield of oxepane over the 1,6-anhydro derivative (compare **157a/158a** versus **157b/158b**). This tendency had also been observed in the cyclization of 6-OBn derivatives.[56] Oxepanes **157**, were of special interest to us because they could be used as test substrates for the Pauson-Khand cyclization reaction.[3,60] Indeed, trimethylamine *N*-oxide (TMANO) treatment of **157a** provided tricyclic derivative **159** in 49% yield (Scheme 33).



*** Insert Scheme 33 ***

Caption: Scheme 33. Reactivity studies on 6-*O*-benzyl *C*-glycal **140d**, and Pauson-Khand reaction.

In this context, it is relevant to mention that the first Pauson-Khand reaction on carbohydrate derivatives had been reported by Isobe and Takai in 1999 (Scheme 34).[61] They studied the Pauson-Khand reaction of *C2*-allyl ethers of *C*-glycosidic α- and β-dicobalt hexacarbonyl alkynyl derivatives **160**, to give access to tricyclic derivatives **161** and **162**. The reactions were mediated by *N*-methyl morpholine *N*-oxide.



*** Insert Scheme 34 ***

Caption: Scheme 34. First Pauson-Khand cyclization on carbohydrate derivatives.

[H2 Title] **C3-Ferrier-Nicholas cations.**

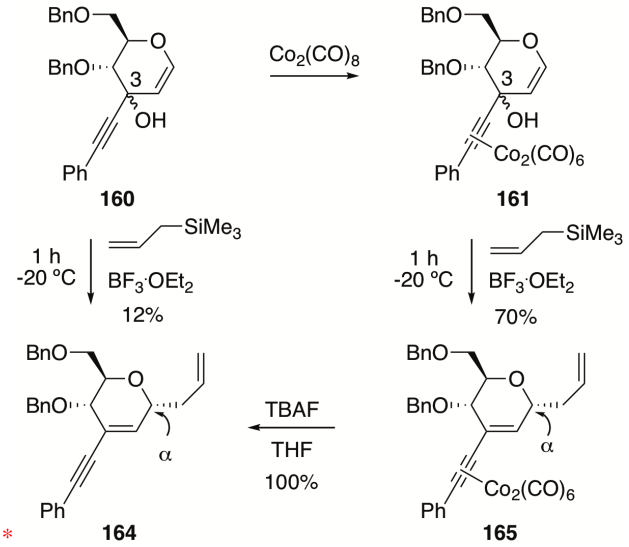
Comentado [RE6]: Main text. H1 refers to main section heading; H2 refers to sub-section heading.

As starting material for the studies on *C3*-alkynyl glycals and their dicobalt hexacarbonyl derivatives, the C3-alkyne **163**, available in a four-step sequence from tri-*O*-acetyl-D-glucal, **6**, and its cobalt complexed counterpart **164**, were used (Scheme 35).[62] Glycosylation reactions of MeOH with **163** and **164** took place at -20 ºC (BF_3OEt_2, CH_2Cl_2) to give methyl glycosides **165** and **166** respectively. Even though the glycosylation of the dicobalt hexacarbonyl derivative **164** gave better yields (87%) than that of the *3C*-alkynyl glycal **165** (63%), the main difference was the observed anomeric selectivity. Thus, whereas **163** produced a 6:1 (α/β) mixture of anomers (**165**), in keeping with literature precedents, glycosylation of *3C*-dicobalt hexacarbonyl glycal **164** furnished a 1:3 (α/β) mixture of methyl glycosides (**166**). The dependency of the anomeric selectivity on the presence of the cobalt cluster could be established when **165** [6:1 (α/β) anomeric mixture]

was treated with $Co_2(CO)_8$ followed by BF_3OEt_2 to yield **166** as a 1:3 (α/β) mixture of methyl glycosides (Scheme 35).

** Insert Scheme 35 ***

Caption: Scheme 35. Glycosylation of methanol with 3C-alkynyl and 3C-dicobalt hexacarbonyl glycals **163** and **164**, respectively.



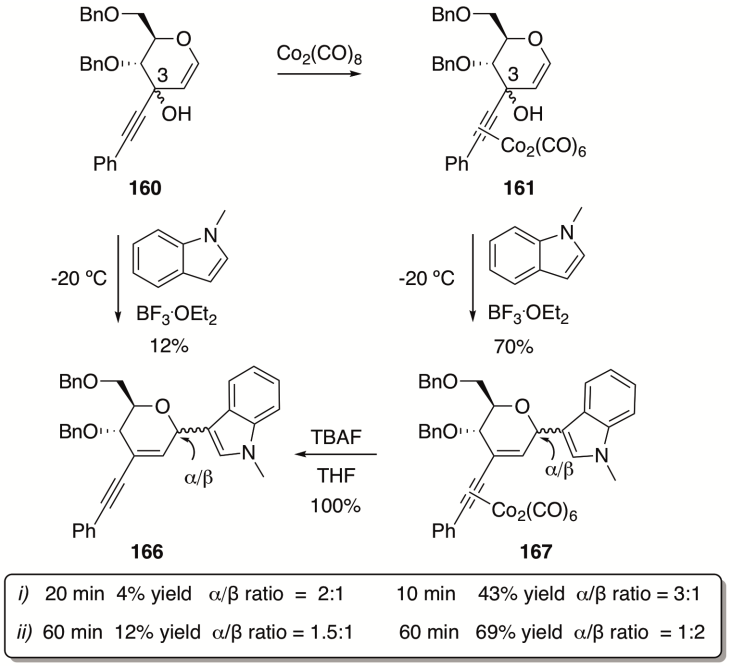
*

** Insert Scheme 36 ***

Caption: Scheme 36. Glycosylation of allytrimethylsilane with 3C-alkynyl and 3C-dicobalt hexacarbonyl glycals **163** and **164**, respectively.

The role of the cobalt complex in the reactivity of alkynyl derivative **164** coud be established when a less reactive glycosyl acceptor, allyltrimethyl silane, was employed (Scheme 36). Thus, *C*-glycosylation of allyltrimethyl silane with "decobaltated" alkynylglycal **163** produced allyl α-*C*-glycoside **167** in a scarce 12% yield, whereas *C*-

allylation of **164** produced allyl α-*C*-glycoside **168** in 70% yield (two steps, from **163**). Decobaltation of **168** was uneventfully accomplished by treatment with tetrabutyl ammonium fluoride (TBAF).

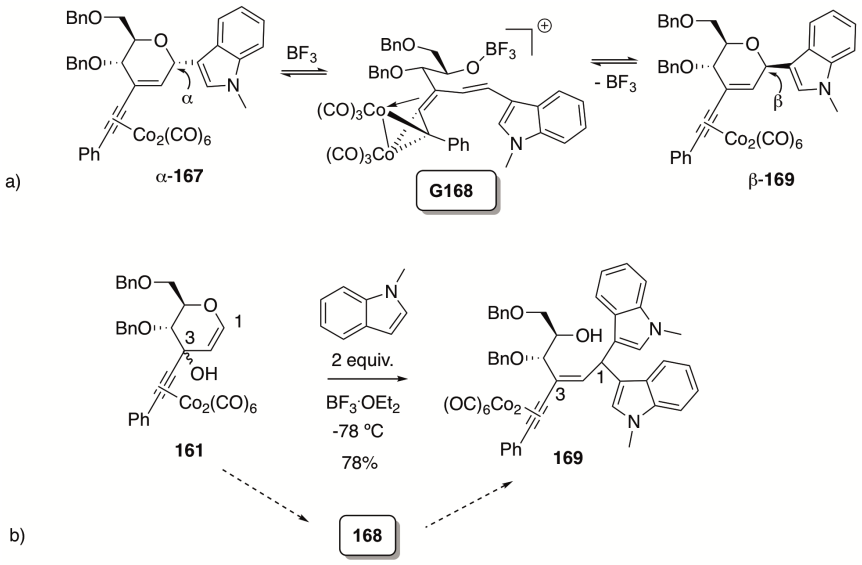


*** Scheme 37 ***

Caption: Scheme 37. Glycosylation of *N*-methyl indole with *3C*-alkynyl and *3C*-dicobalt hexacarbonyl glycals **163** and **164**, respectively. Effect of the reaction time.

The glycosylation of *N*-methyl indole with glycals **163** and **164** leading to *C*-indolyl derivatives **169** and **170**, was also studied using different reaction times (Scheme 37). From these experiments at least two conclusions could be drawn: first, the Nicholas activation was critical to obtain synthetically useful yields of heteroaryl *C*-indolyl derivatives **170** (compare 4% yield versus 43% yield, entry *i*, and 12% versus 69% yield, entry *ii*, Scheme

37), and second, longer reaction times favored the formation of β-glycosides over α-glycosides (compare α/β selectivities in entries *i* and *ii*, Scheme 37).



*** Scheme 38 ***

Caption: Scheme 38. Proposed rationale for the "α/β" equilibration in *C*-indolyl glycosides. Existence of an open-chain allylic Nicholas cation intermediate **171** (a), and synthesis of bis-indolyl open-chain derivatives **172** (b).

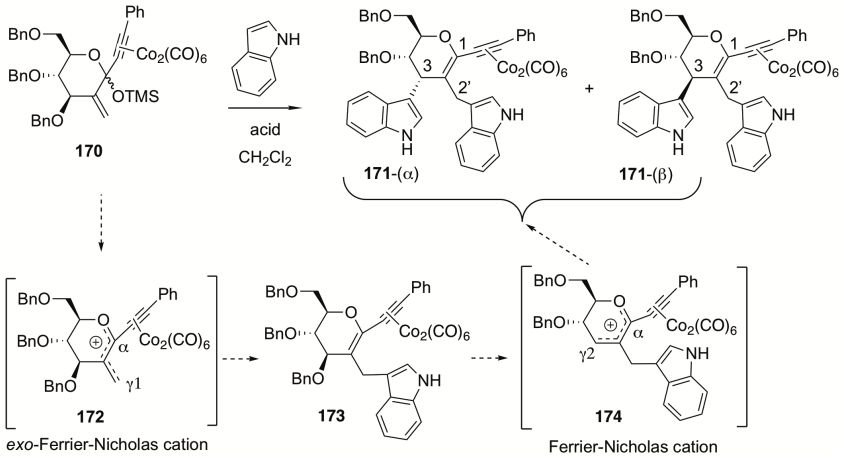
The results in Scheme 37 (variation of the α/β anomeric ratio in *C*-indolyl derivative **170** with the reaction time) seemed to indicate the existence of an equilibrium in favor of the thermodynamically more stable β-anomers, more pronounced in the doubly activated *C*-indolyl derivative β-**170**. The α→β equilibration, in these derivatives, was explained by the authors by invoking the intermediacy of an open-chain vinylogous Nicholas cation, i.e. **171** (Scheme 38a). Along this line, the observed reaction of **164** with two equivalents of

N-methyl indole to yield open-chain, bis-indolyl, derivative **172**, could be explained by reaction of open-chain Nicholas cation **171**, with a second indole molecule (Scheme 38b).

[H2 Title] **Ferrier-Nicholas systems based on 1-*C*-alkynyl-2-deoxy-2-*C*-methylene pyranosides**.

Comentado [RE7]: Main text. H1 refers to main section heading; H2 refers to sub-section heading.

A recent report has identified 2-*C*-methylene dicobalt hexacarbonyl ketoses, e.g. **173**, as precursors of C2',C3-bis functionalized glycals *C*-glycals, e.g. **172** (Scheme 39).[40] Thus, *C*-dicobalt hexacarbonyl ketose **173**, readily obtained from tri-*O*-acetyl D-glucal, **6**, reacted with heteroaryl nucleophiles in the presence of Lewis acids (BF_3OEt_2, $InBr_3$) to give bis-functionalized *C*-glycals. The proposed reaction pathway, exemplified in Scheme 39 with indole as the nucleophile, involved the sequential formation of two different Ferrier-Nicholas, vinylogous cations, i.e. **175** and **177**. Each (vinylogous) cation possessed two reactive sites (α, γ), and in each case reacted at the distal γ– position, rather than at the anomeric (α–) site, to yield the bis-functionalized species **172**. The reactions took place with moderate yields affording α-C3 derivatives as the sole isomer when BF_3OEt_2 was used as catalyst, or as major isomers when $InBr_3$ was used as promotor.



*** Scheme 39***

Caption: Scheme 39. Reaction of 1-*C*-dicobalt hexacarbonyl alkynyl-2-deoxy-2-*C*-methylene pyranosides with indole.

The reaction was also extended to the use of pyrrole, *N*-methyl indole, or thiophenol as nucleophiles, with similar results.

[H1 Title]**Conclusions**

In summary, we have illustrated the rich chemistry associated to carbohydrate-derived dicobalt hexacarbonyl compounds. In fact, the incorporation of dicobalt hexacarbonyl clusters to carbohydrate derivatives has enabled the development of variety of novel synthetically useful transformations. In most of these processes the anomeric position of the carbohydrate plays an active role. For example, the incorporation of a cobalt cluster at the anomeric position facilitates the α →β equilibration of *C*-alkynyl glycosides, the

Ferrier(II)-Nicholas carbocyclization leading to cyclohexanones and carbasugar analogues, and the formation of *C*-ketosides.

additional stabilization of the anomeric oxocarbenium ion provided by the cobalt cluster, was employed by Isobe's group to facilitate the $\alpha \rightarrow \beta$ equilibration of *C*-alkynyl glycosides, that has been used to facilitate the anomeric equilibration of C-alkynyl pyranoses, the

has proven especially useful in enabling facilitating inducing carbohydrate transformations

The success in the application applying remarkable synthetic usefulness of these derivatives arises for the Contributions in this area have

enhanced stability of carbonium ions α- to an organometallic substituent,

This chemistry takes advantage of the stabilization of propargylic cations provided by the dicobalt hexacarbonyl cluster

is extensive, diverse, and interesting. DK is easily produced from an

inexpensive and readily accessible feedstock providing a highly valuable synthetic intermediate for a wide range of pharmaceuticals, various polymer intermediates, agrichemicals, and dyestuffs. In addition, DK chemistry yet

promises abundant opportunity for future innovation.

Heterocyclizations that encompass DK frequently start with acetoacetylation

of a substrate and subsequent intramolecular condensation

reaction. Generally, the initial acetoacetylation is irreversible, whereas the

ring closing is regularly an equilibrium process. As discussed in this chapter,

the kinds of ring system that are constructed often can be anticipated on the

basis of the initial position of acetoacetylation, whereas the exact substitution pattern of the final heterocycle is a function of the reaction conditions used, because equilibrium control is also involved during the ring-closing process. When a substrate used for a heterocyclization is initially acetoacetylated on carbon, the construction of a six-membered ring system containing one heteroatom is usually anticipated.

[H1 Title]**Acknowledgements**

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Comentado [RE8]: Reference style based on editor preference.

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