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Synthesis of Glycals and Oligosaccharides of Deoxysugars via Catalytic *Endo*-Selective Alkynol Cycloisomerization

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Introduction

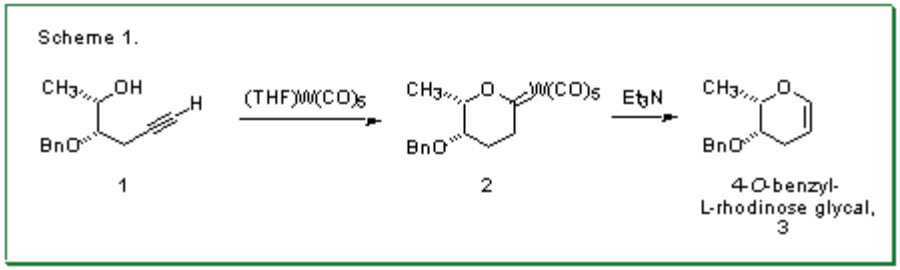
The research enterprise in our laboratory is based on the premise that many conceptually simple chemical transformations can be envisioned which have not yet been reduced to practice. This account presents the discovery and current state of optimization of a new reaction which was recently discovered in our laboratories, namely the tungsten carbonyl-catalyzed *endo*-selective cycloisomerization of alkynyl alcohols to dihydropyrans, and applications to the stereoselective synthesis of disaccharide substructures of digitoxin, landomycin, and mithramycin natural products.

Results and Discussion

1. Stoichiometric alkynyl alcohol *endo*-selective cyclizations to dihydropyrans

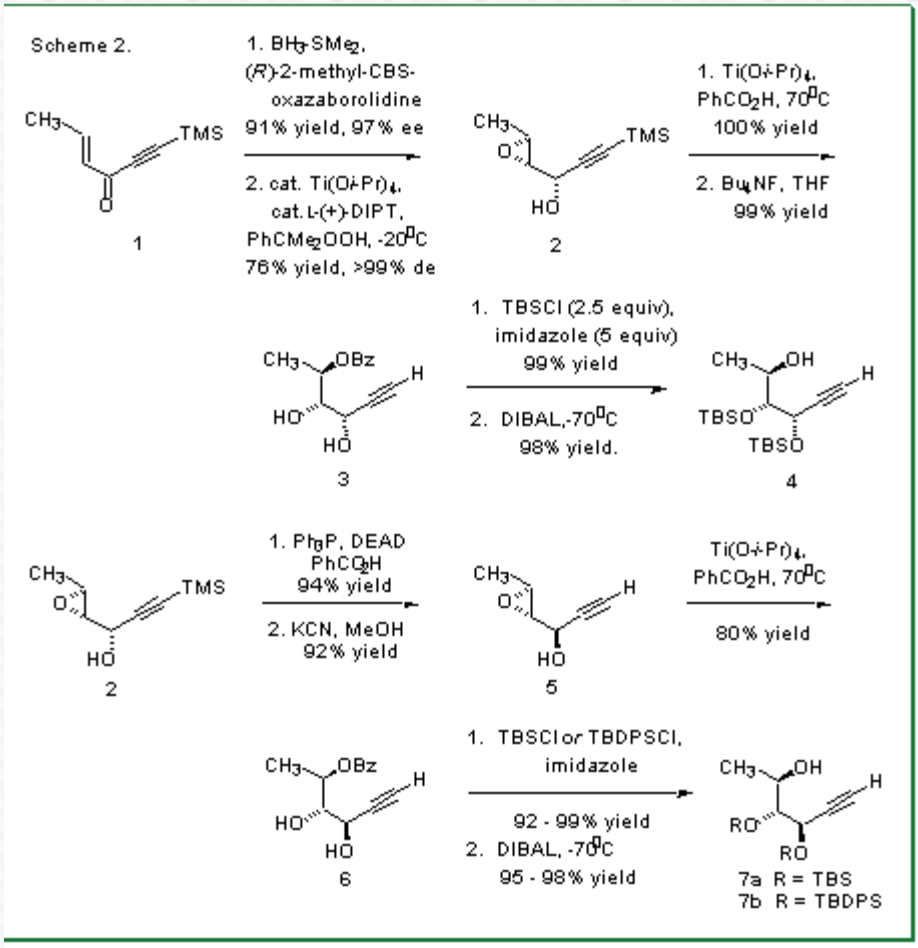
In late 1992 we discovered that simple homopropargylic alcohols underwent efficient cycloisomerization to five-membered ring (dihydrofuran) products upon reaction with catalytic $(Et_3N)Mo(CO)_5$.[1] Over the next few years we optimized this reaction for the preparation of variously substituted dihydrofurans, and successfully applied this novel transformation to short syntheses of the biologically active nucleoside compounds d4T, cordycepin, and puromycin aminonucleoside. [2] However, with only one exception [3] the molybdenum-catalyzed process was not generally effective for formation of six-membered ring products from the corresponding acyclic alkynyl alcohols. In mid-1995 we observed that six-membered ring (dihydropyran) products could be formed via a *stoichiometric, tungsten*-promoted two-step process. [4] The reaction sequence required one to three equivalents of $W(CO)_6$, isolation of the stoichiometric tungsten oxacarbene, and conversion of this oxacarbene intermediate to the endocyclic enol ether by reaction with a tertiary amine base. The yields for this process rarely exceeded 50%, with the modest overall yield of 32% reported for the two-step conversion of alkynyl alcohol **1** to the moderately functionalized dihydropyran **3** as a representative example [5] (Scheme 1). Pure samples of tungsten oxacarbene intermediates such as **2** could be converted into the corresponding enol ether in nearly quantitative yield, indicating that the first step to form the stoichiometric oxacarbene **2** was the problematic transformation in this synthesis. Our initial attempts to combine base-promoted enol ether formation with the tungsten-promoted alkynyl alcohol

cyclization as a single-step cycloisomerization transformation were unsuccessful, as the isolated reagent $(Et_3N)W(CO)_5$ was reported to be inert to simple alkynyl alcohol substrates. [6]



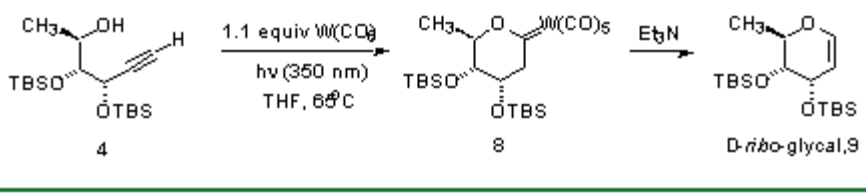
2. Discovery of the tungsten-catalyzed cycloisomerization at Emory University

We commenced further explorations in this area with studies of more highly functionalized substrates **4** and **7a-b** in early 1999. These substrates were each prepared from a common intermediate epoxyalkynol **2**, which was synthesized from enynone **1** [7] by a sequence of enantioselective ketone reduction [8] and alkene epoxidation [9] transformations (scheme 2). On larger scales, compound **2** could also be prepared by Sharpless kinetic resolution [9] of the racemic enynol obtained from $NaBH_4$ / $CeCl_3$-reduction of **1**. Regioselective titanium-promoted addition of benzoic acid [10] afforded the alkynyl diol **3**, which was converted to the alkynyl alcohol substrate **4** by a straightforward manipulation of alcohol protective groups. The epimeric substrates **7a-b** could be very easily prepared beginning with Mitsunobu inversion [11] of the epoxyalkynol **2** and subsequent cyanide-catalyzed removal [12] of benzoyl and silyl-alkyne groups to provide epoxyalkynol **5**, followed by straightforward elaboration of functional groups via alkynyl diol intermediate **6**.



Stoichiometric tungsten-promoted cyclization [3-5] of **4** afforded the tungsten oxacarbene **8**, but the reaction was extremely slow and some starting material **4** was still present after 48 h at room temperature. The tungsten oxacarbene **8** could be observed by ^{1}H NMR analysis of an aliquot, but was usually not isolated and instead the THF solution of unpurified oxacarbene **8** was directly treated with Et_3N to provide glycal **9**. We subsequently discovered that the cyclization reaction of **4** to **8** could be pushed to completion by heating the reaction mixture to the reflux point of THF (ca. 65^{o}C). Even better results were obtained when we photolyzed $W(CO)_6$ *in the presence of the alkynyl alcohol substrate* **4** with heating, and the isolated yields of glycal **9** produced by this stoichiometric procedure were consistently in the 40 - 45% range, with the first step to tungsten oxacarbene **8** judged as the low-yielding operation (Scheme 3).

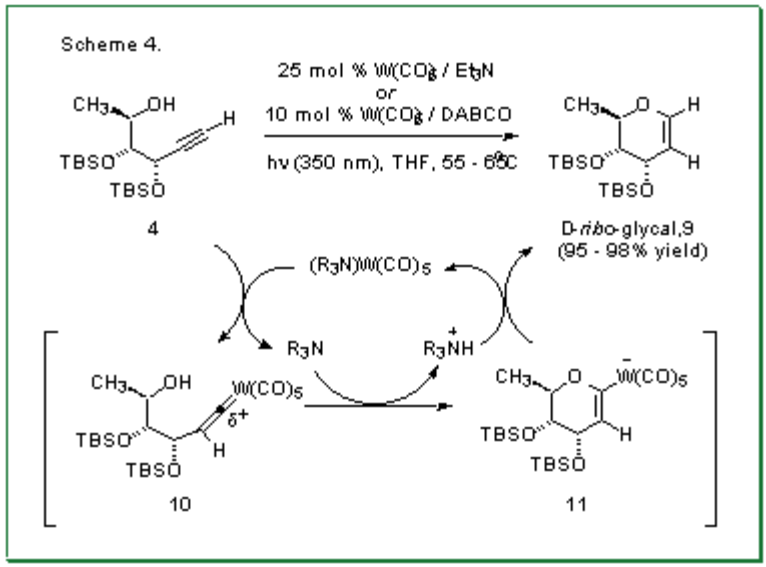
Scheme 3.



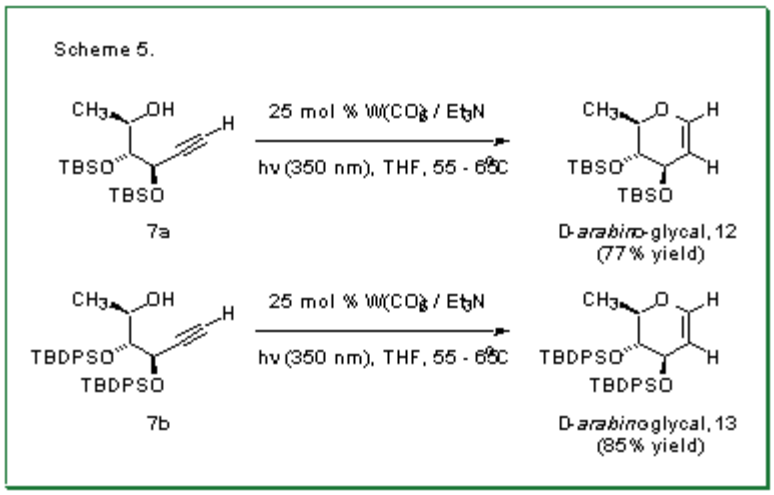
As the alkynyl alcohol substrate **4** and tungsten oxacarbene **8** were observed to be compatible with 350 nm irradiation, we reexplored the idea of a single-step conversion of compound **4** to cycloisomeric product glycal **9** by irradiating $W(CO)_6$ and substrate **4** *in the presence of triethylamine*, and were gratified to find that near-quantitative isolated yields of the glycal product **9** were obtained with only 25 mol% of tungsten hexacarbonyl (scheme 4). [13] Control experiments have demonstrated that continuous irradiation is required in order to effectively regenerate the $(Et_3N)W(CO)_5$ species which is attributed to be the active catalyst for this cycloisomerization transformation.

This catalytic protocol is perfectly suitable for small scale operations, but on larger scales (> 1 mmol) we observe that the observed glycal product is accompanied by partial recovery of starting alkynyl alcohol substrate. We have subsequently explored the use of other tertiary amine coreagents, and sublimed 1,4-diazabicyclo[2.2.2]octane (DABCO) is currently the base of choice of the cycloisomerization transformation. [14] In reworking the catalytic loading in the presence of excess DABCO, we have observed that as little as 10 mol% of $W(CO)_6$ is sufficient for high-yield cycloisomerization of **4** to **9** within 6 h provided the reaction temperature is maintained above 50^{o}C while under continuous irradiation at 350 nm. $W(CO)_6$ loadings below 10 mol% require significantly longer reaction times and/or result in incomplete conversion of alkynyl alcohol substrate.

The mechanism of the catalytic cycloisomerization transformation probably involves the intermediacy of the tungsten vinylidene **10**, followed by intramolecular nucleophilic addition of the hydroxyl group to provide the carbene anion **11** and protonation to afford the product dihydropyran **9**. Note that this mechanism does not require the neutral oxacarbene **8** (scheme 3) as a catalytic intermediate when the reaction is conducted under basic conditions.



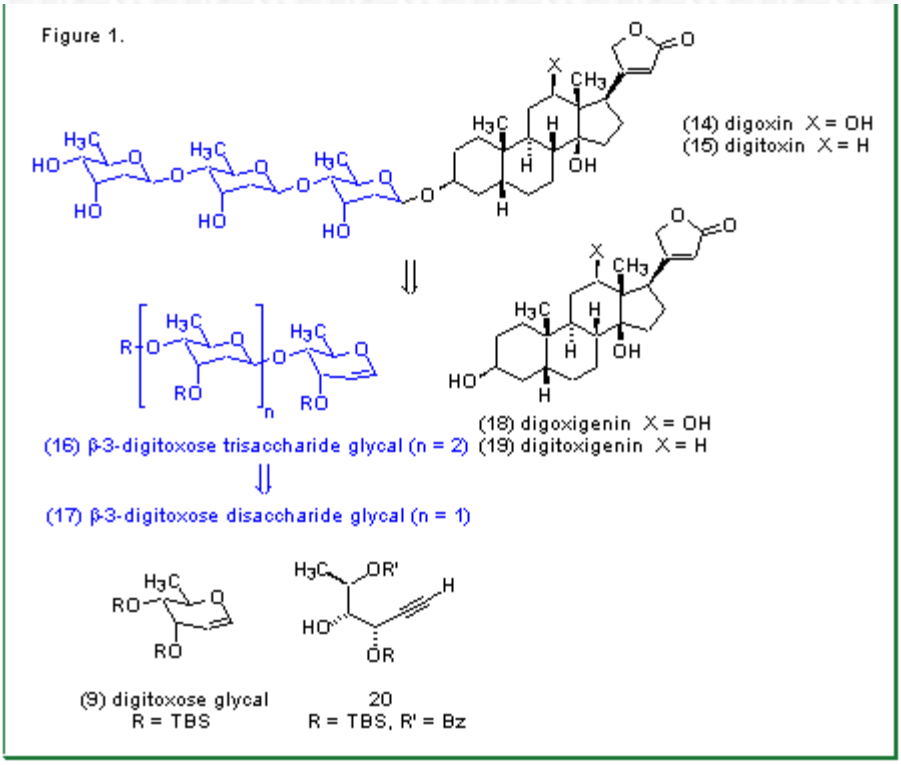
The cycloisomerization reaction has proven to be broadly general for a variety of alkynyl alcohol substrates. All stereoisomers of **4** also undergo cycloisomerization to produce the corresponding glycals in good yield. [13] For example, alkynyl alcohol **7a** is converted into D-*arabino* glycal **12** under identical reaction conditions (Scheme 5). Note also that the phenyl substituents of the TBDPS groups of **7b** are also compatible with the continuous irradiation required for catalytic cycloisomerization to give **13**.



3. Stereoselective glycosylation of D-*ribo* glycal 9 and preparation of digitoxose disaccharide glycal 17

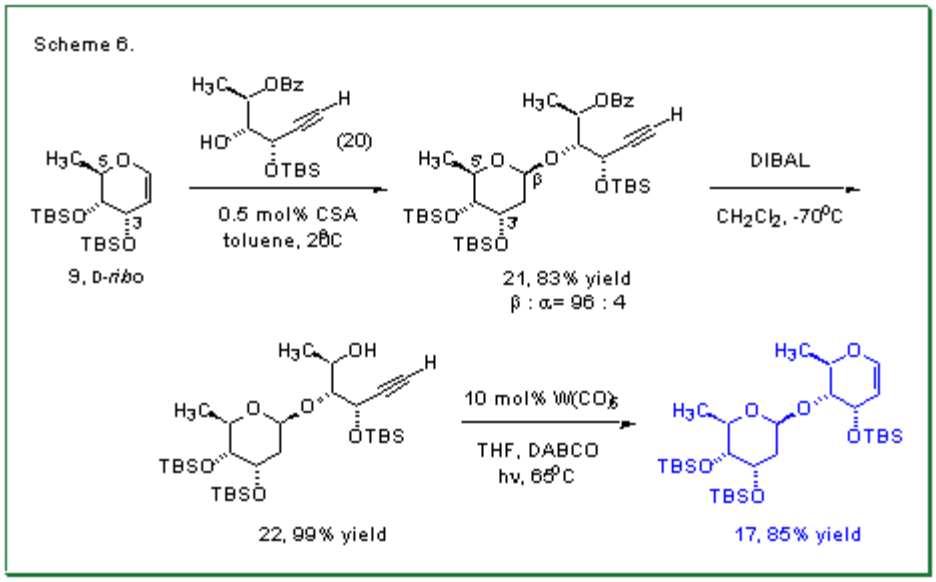
Extracts from the leaves of *Digitalis* (foxglove) plants have long been used for treating congestive heart failure and controlling cardiac arrhythmia, and the most widely used pure cardiotonic natural products are the cardenolide trisaccharides digoxin (**14**) and digitoxin (**15**, Figure 1). [15] Unfortunately the therapeutic dose [0.5 - 2.0 ng / mL for digoxin] is dangerously near the toxic dose [> 2.5 ng / mL]. Although bioavailability and pharmacokinetics are affected by the presence and type of carbohydrate substructures, structure-activity relationships of the oligosaccharide region have not been studied as extensively as modifications of the steroidal aglycone. b-Glucoside derivatives exhibit a higher therapeutic index upon intravenous adminstration in mice, [16] but the ability of these analogs to cross the blood-brain barrier make them unsuitable for use in humans. [17] Wiesner reported the first and only chemical synthesis of the all b-2,6-dideoxy-*ribo*-hexose (D-digitoxose) trisaccharide of digitoxin. [18] Our retrosynthetic analysis for a synthesis of digoxin and digitoxin involved glycosylation of the trisaccharide glycal **16** (n = 2) with the cardenolide steroid aglycones **18** - **19**. This oligosaccharide would be prepared via a sequence of

glycosylation of glycal **9** with alkynyl alcohol **20**, removal of protective group R', and cycloisomerization to give disaccharide glycal **17** (n = 1), followed by iterative application of this sequence to provide trisaccharide glycal **16** (n = 2).



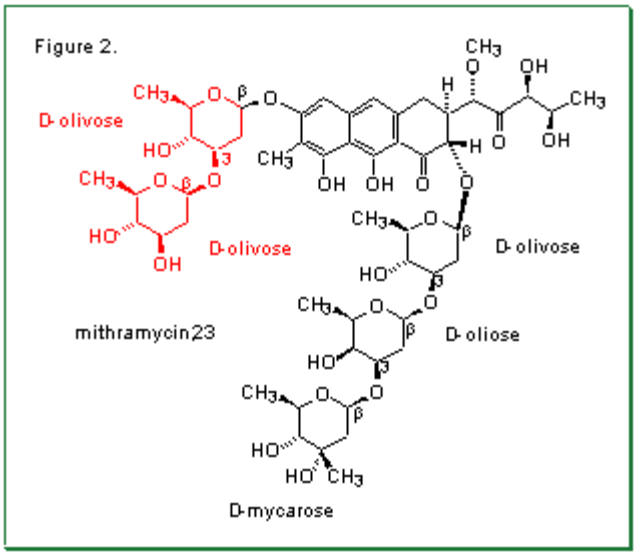
The acyclic alkynyl alcohol **20** (R' = Bz and R = TBS) was prepared in 83% isolated yield, by reaction of the alkynyl diol **3** with one equivalent of TBSCl, so that reaction occurred selectively at the less hindered propargylic alcohol. Glycosylation of the *ribo*-glycal **10** with the alkynyl alcohol **20** as the glycosyl acceptor was first explored under *p*-toluenesulfonic acid catalysis, affording a 70 : 30 ratio of b : a anomers favoring glycoside **21**. We then observed that stereoselectivity could be enhanced by reducing the acid-strength of the sulfonic acid catalyst, so that camphorsulfonic acid (CSA)-catalyzed glycosylation afforded b-glycoside **21** with much higher anomeric selectivity (83% isolated yield, Scheme 6). The stereochemistry of the major glycoside product is consistent with alcohol addition *anti* to the C3-substituent, as previously predicted by Franck. [19] Note that the glycal **9** exhibits a *cis*-relationship of the two silyloxy substituents at C3 and C4, and so that the major glycoside product was formed *trans* to the silyloxy substituents. The methyl substituent at C5 apparently has only a minor slightly nonreinforcing effect on the glycosylation stereoselectivity under optimized conditions.

The benzoate protective group of **21** was cleanly removed by DIBAL reduction, and the resulting glycosylated alkynyl alcohol **22** underwent $W(CO)_6$-catalyzed cycloisomerization to provide disaccharide glycal **17** in 85% optimized yield. Surprisingly, some of the mass balance appears to be the five-membered ring exocyclic enol ether (ca. 10% isolated yield). These results were obtained by the use of DABCO rather than Et_3N as the basic component, as well as the use of 10% $W(CO)_6$. The synthesis of trisaccharide glycal **16** (n = 2) and its glycosylation with digitoxigenin **19** has been accomplished, and will be reported separately. [20]



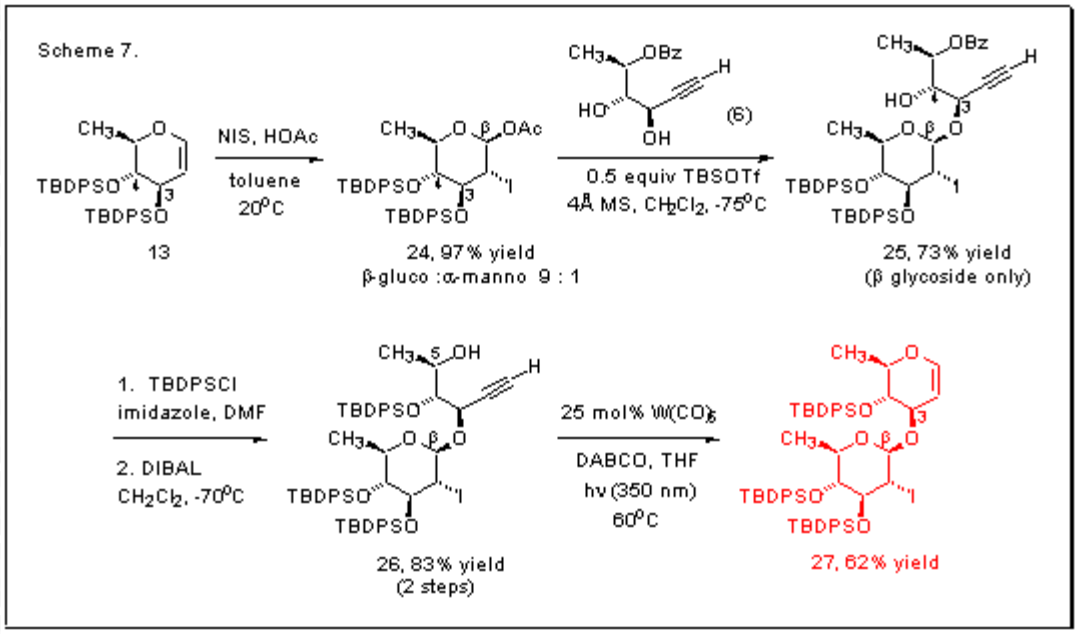
4. Glycosylations of the D-*arabino* glycal 13 and synthesis of D-*olivose*-D-*olivose* disaccharide substructures of mithramycin and landomycin

Mithramycin (**23**, Figure 2) [21] is a structurally complex antitumor antibiotic natural products which contains several 2,6-dideoxycarbohydrate components. Mithramycin has been used clinically for the treatment of cancer even though the correct chemical structure of the oligosaccharide sectors was only recently determined. The anticancer activity of this compound is probably due in part to the presence and constitution of the oligosaccharide sectors, in particular providing preferential selectivity for interaction with the DNA of cancer cells rather than the genetic material of healthy cells.

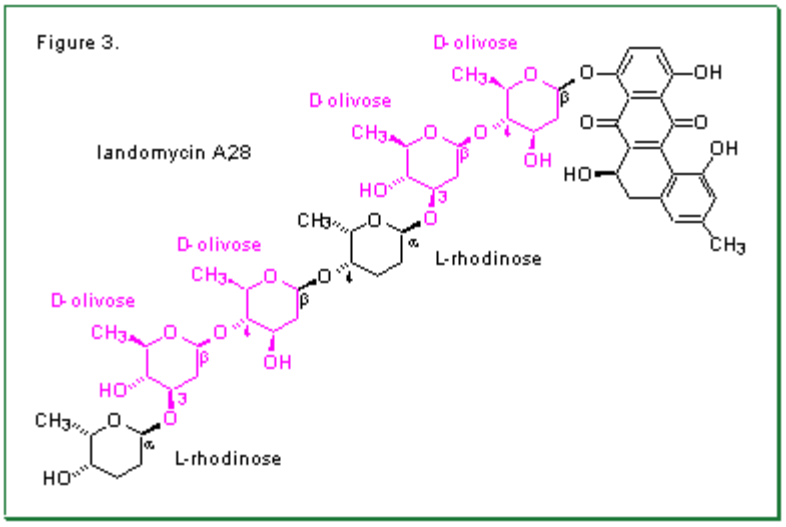


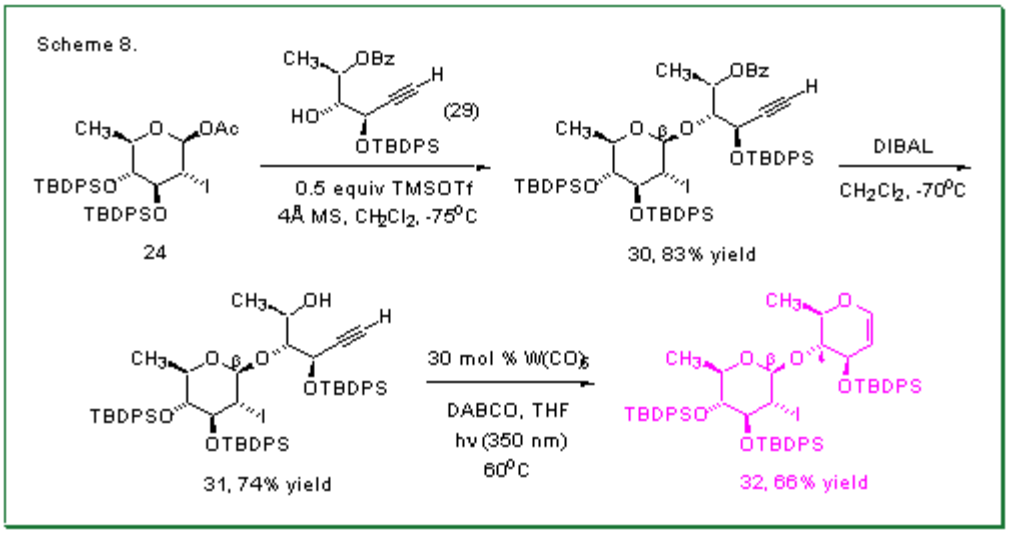
For the disaccharide and trisaccharide regions of mithramycin, each of the interglycosidic connections are b-anomers connected to the 3-oxygen of the adjacent sugar component. We sought to explore whether the D-olivose-D-olivose linkage in mithramycin could be prepared utilizing our iterative cycloisomerization - glycosylation strategy for oligosaccharide synthesis. [5] We have already reported that acid-catalyzed glycosylations of the D-*arabino*-diastereomer **12** proceed with poor anomeric selectivity favoring the a-glycoside rather than the desired b-glycoside. [13] Roush has also disclosed that the reaction of **12** with *N*-iodosuccinimide (NIS) and acetic acid results in a nearly equal mixture of diastereomeric iodoacetates. [22] However, formation of iodoacetate **24** could be accomplished with good selectivity provided that the C3

and C4 oxygen substituents were substituted with sterically bulky protective groups such as *tert*-butyldiphenylsilyl (TBDPS) ethers, so that reaction from a $^5H_4$ conformation was preferred (scheme 7). [13] This compound **24** underwent TBSOTf-catalyzed reaction [23] with the alkynyl diol **6** (prepared as shown in scheme 2) with completely regioselective and stereoselective glycosylation of the less hindered propargylic alcohol to provide a single glycoside **25**. Silylation of the free hydroxyl group in glycoside **25** and reductive debenzoylation gave the alkynyl alcohol substrate **26**, which afforded the 3-*O*-linked disaccharide glycal **27** upon W(CO)$_6$-catalyzed cycloisomerization. In this case, the cycloisomerization reaction proceeded much better when DABCO was used instead of triethylamine. Note that disaccharide glycal **27** correlates with the D-olivose-*O*-3-D-olivose disaccharide of mithramycin, **23** (figure 2).



In the antitumor antibiotic landomycin A (**28**, figure 3), [24] the two D-olivose sugars are connected by a 4-linkage, thus the regioisomeric glycoside is required in order to obtain the corresponding disaccharide glycal. Installation of a single *tert*-butyldiphenylsilyl protective group from alkynyl diol **6** did not exhibit the same level of regioselectivity observed in the previously described glycosylation, but the required compound **29** could be obtained as the major silyl ether product in 56% isolated yield. The glycosylation of iodoacetate **24** and the hindered secondary alcohol of **29** was efficiently accomplished when the more reactive TMSOTf was used as the glycosylation catalyst, affording **30** as a single isomer (scheme 8). Reductive removal of the benzoate ester and cycloisomerization of alkynyl alcohol **31** provided the disaccharide glycal **32**, corresponding to the D-olivose-*O*-4-D-olivose disaccharide of landomycin, **28** (figure 3).





Conclusions

These results demonstrate the efficacy of the W(CO)6-catalyzed *endo*-selective alkynyl alcohol cycloisomerization reaction in the synthesis of functionally and stereochemically complex organic compounds, exemplified by the effective construction of the disaccharide glycals **17**, **27**, and **32** (schemes 6 - 8) corresponding respectively to substructures of the digoxin, mithramycin, and landomycin families of natural products. Notable features of the catalytic cycloisomerization reaction include compatibility with sensitive functional groups, including glycoside linkages, silyl ethers, and iodide substituents.

Acknowledgments

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