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Synthesis of a Novel Taxa-Oxa-Sugar Hybrid Core Structure by Tandem Cross-Enyne Metathesis/IMDA

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This paper describes our design and efforts in synthesizing new scaffolds with taxol-eleutherobin hybrid core structures and a taxol-sugar hybrid. The synthesis of taxol-eleutherobin hybrids involved the synthesis of the A-ring fragment from carvone and the C-ring fragment from either D-mannose or D-glucose. The Shapiro reaction was used as the key reaction to couple the A- and C-ring fragments of these hybrid structures. Unfortunately, another key reaction (RCM) failed to form the B-ring and essentially the core unit. However, a tandem enyne cross-metathesis/intramolecular Diels–Alder strategy was utilized for the synthesis of a taxa-oxa-sugar hybrid.

Introduction

Nature has been and still continues to be the prime source of most pharmaceutical leads in the form of biologically active natural products. It is also the main inspirational leader for an organic chemist synthetically to mimic such natural products with their varied complex molecular architectures and also to access new chemical entities such as natural product analogues for understanding key biological events. Moreover, as the number of drug-resistant diseases continues to increase, it becomes necessary to use combinations of two or more drugs to cure particular diseases. Medicinal chemists are therefore on constant lookout for new drugs that could be used individually to cure various diseases.

Although there may be several ways to make new molecules, one interesting way would be to couple the active components of two or more natural products by making hybrid structures.[1,2] By definition, hybrid systems are constructs formed from different molecular entities, natural or unnatural, to generate functional molecules in which the characteristics of various components are modulated. From a synthetic point of view, based on this hybrid concept and also mimicking nature, one can design and synthesize new types of molecules possessing the structural features of two (or more) different classes of known natural/unnatural products with interesting biological activities. The idea of generating novel molecular entities by combination of two or more different classes of compounds is appealing because this approach may provide numerous possibilities for molecular design, and a diverse array of these has been referred to in the literature as "hybrid molecules" or new types of molecules. During the past two decades the design of such entities has been receiving increasing attention and these "conjugates" or "chimeras" or even "mermaids" and a large number of molecular hybrids have been designed and synthesized.[3] Our laboratory is involved in the synthesis of biologically active natural products and their hybrid systems.[4] This line of interest motivated us to design and to synthesize new types of hybrid structures that might have potential anti-cancer activities. This paper details our design and efforts in synthesizing new taxa-sugar, taxa-oxa-sugar, and taxol-eleutherobin hybrid structures.

Background and Significance

Taxol® (paclitaxel, **1**, Figure 1) was isolated in 1967 from the bark of *Taxus brevifolia* by Wall and Wani.[5a] Horwitz[5b] reported a completely new mechanism of action for taxol. According to this new mechanism, it promotes the assembly of the proteins α- and β-tubulin into microtubules, which in vitro disturbs the polymerization/depolymerization dynamics of microtubules by binding with the microtubules, making them extremely stable. This inhibits their cell division, resulting in cell death.[5b] The outstanding biological profile of **1** attracted many synthetic groups, but only six were able to complete its total synthesis.[5c] The mid- to late 1990s witnessed the discoveries of four natural products – epothilones A and B (**2**),[6] eleutherobin[7] (**3**, Figure 1) and discodermolide[8] – that showed anti-cancer activities comparable to those of **1**. Although structurally dissimilar from **1**, these compounds each displayed a paclitaxel-like mechanism of action. Eleutherobin (**3**) was isolated by Fenical and co-workers from a marine soft coral found in the Indian Ocean.[9] It is a member of the eunicellanes, a class of ma-

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rine diterpenes, and is closely related to sarcodictyins[10] and valdivones.[11] Two groups succeeded in the total synthesis of eleutherobin,[12] whereas several groups pursued strategies for the core structure and its formal synthesis.[13]

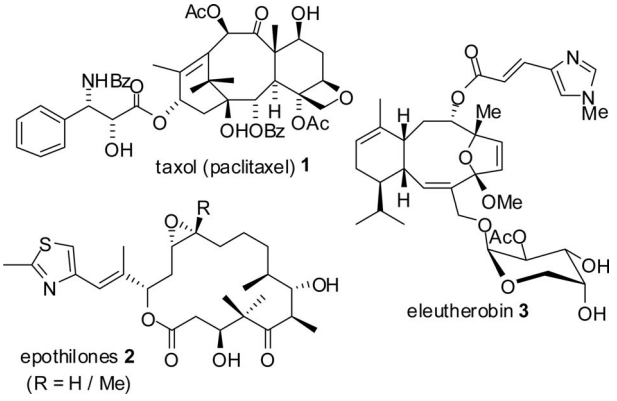


Figure 1. Structures of taxol, eleutherobin, and epothiolones.

In view of the biological significance of taxol and eleutherobin, we developed an interest in their syntheses[14,15] and furthermore became engrossed in designing a new class of hybrid molecules of these two natural products. To the best of our knowledge there is so far no report of any taxol-eleutherobin hybrid structure, though there are other reports in which new hybrid molecules of taxol and other natural products have been synthesized and studied. Danishefsky and co-workers were probably the first to report a cholesterol-baccatin hybrid,[16] primarily synthesized to check the feasibility of the key "Heck reaction" in the total synthesis of taxol. Ojima's[17] and Kingston's[18] groups have synthesized and evaluated taxol-epothilone hybrids, which provided evidence in support of a common pharmacophore for these two drugs, which share the same tubulin-binding mechanism of action. Hybrid structures of taxol with porphyrins,[19] calicheamicin,[20] steroids,[21] daunorubicin,[22] epipodophyllotoxin,[23] thiocolchicine,[24] chloroambucil,[25] camptothecin,[26] etc. have also been reported in the literature. The syntheses of these hybrid structures involved elegant synthetic strategies, including modern metathesis approaches. The non-taxane components in these hybrid structures exhibit significant biological activities and various concepts for utilization of multiple anti-tumor activity mechanisms have been proposed. Most of these hybrids, however, show diminished cytotoxic activities in relation to their parent structures, probably due to decreased affinities of targets resulting from their increased steric bulks. Moreover, many of these reported taxol hybrids involve the construction of a complex skeleton as in taxol.

Design of the Hybrid Systems

Prior to attempts to design taxol-eleutherobin hybrids, the available structure/activity relationship (SAR) studies of these two natural products were considered in depth. SAR studies of eleutherobin and sarcodictyins by Nicolaou's group had found[27] that the side chain is crucial for biological activity (Figure 2). Both nitrogen atoms in the side chain are essential for the activity, but substitutions on the dihydrofuran ring are tolerated well. Esters are preferred over alcohols and amides and even other substitutions are also tolerated. Another report[28] also suggests that a double bond in the side chain is vital for tubulin binding in the eleuthesides.

On taxol, SAR studies[5c] have been carried out fairly thoroughly. It is generally believed that the A-ring side chain in taxol at C-13 is essential for its biological activity. It is also reported, however, that substituents on the C-2 benzoyloxy group have significant effects on the biological activity of taxol. Taxol analogues possessing bulky substituents at the *para* position, for example, are inactive,[29] whereas those with the same substituents at the *meta* position are more active.[30] Kingston and Horwitz disclosed the surprising observation that 2-*m*-azidobaccatin III, a taxol analogue lacking the C-13 side chain but with the *m*-azido group at the C-2 position, possesses all of the biological activities of taxol.[31] At the same time, however, the *p*-azido substitution product did not show any biological activity. This highlights the significance of the *m*-azidobenzoyl side chain for the new hybrid structures. A common pharmacophore that unites taxol, epothilones, eleutherobin, and discodermolide has also been proposed.[32] However, our current strategies relating to tubulin-binding hybrid agents re-

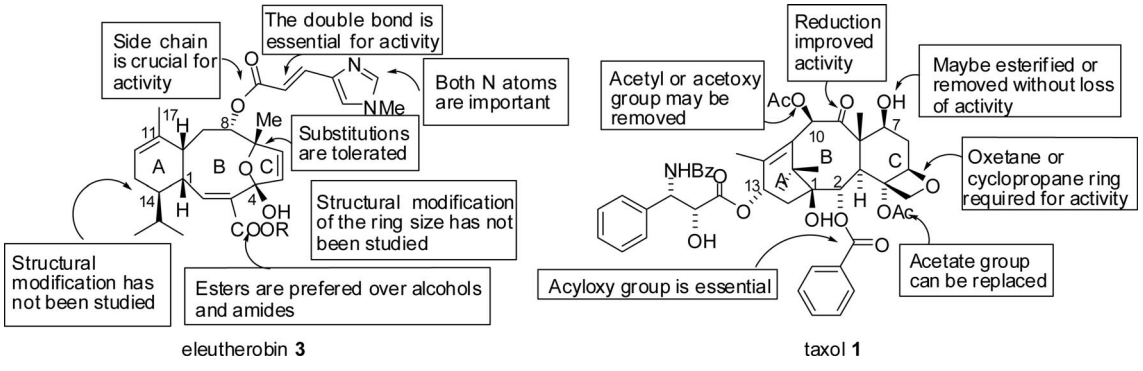
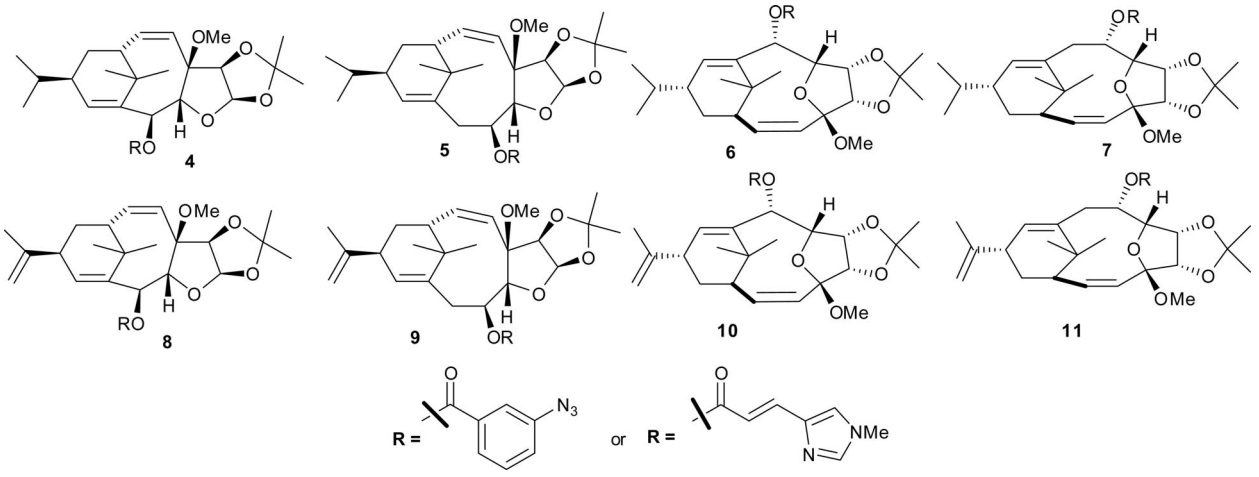


Figure 2. Representation of SAR studies for eleutherobin and taxol.



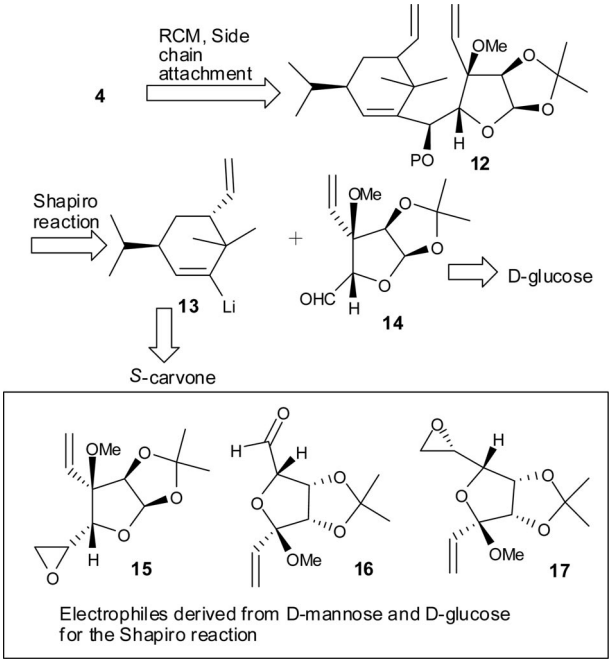
Scheme 1. Designed taxa-sugar and taxol-eleutherobin hybrid structures.

volve around epothilones and taxol. In view of the above requirement, we decided that hybrid systems of taxol and eleutherobin might provide more information relating to the mechanism of binding of taxol-eleutherobin to tubulin.

We thus set out to design, to synthesize, and to evaluate new, simple hybrid structures of taxol and eleutherobin (**4** to **11**, Scheme 1). These molecules were designed for the following reasons. Like eleutherobin, the proposed hybrid structures each have a rigid A-ring with a *cis*-AB and *cis*-BC fused skeleton. Although there is no double bond present in the C-ring, it is substituted with an additional ring. The compounds each have a common 1,5-disubstituted cyclohexene A-ring with a *gem*-dimethyl group, as is typical of a taxol A-ring. Compounds **4** to **7** also each have an additional isopropyl group reminiscent of eleutherobin. Each possesses a 13- to 15-membered fused ring system so that it can retain either the taxol or the eleutherobin backbone. The complex C- and D-ring system of taxol has been replaced by a simple tetrahydrofuran ring so that it can have the effect of eleutherobin as well as epothilones. The size of the B-ring varies from eight to nine members, it having been kept in mind that taxol has an eight-membered B-ring and eleutherobin has a nine-membered B-ring. The side chain would be either *m*-azidobenzoyl or methyl uraconic acid, as required for taxol and eleutherobin, respectively. All the molecules are designed to represent simple hybrid structures of taxol and eleutherobin with all the special features and active sites of both taxol and eleutherobin.

Retrosynthetic Analysis

An illustrative retrosynthetic analysis of the hybrid structure **4** is shown in Scheme 2. The strategy involves the construction of the B-ring of the hybrid system through a ruthenium-carbene-catalyzed ring-closing metathesis (RCM)[33] reaction and the attachment of different side chains. The RCM precursor **12** should be obtainable through a Shapiro reaction between the vinyllithium species **13** and the aldehyde **14**, followed by subsequent protection of the hydroxy group. The vinyllithium species **13** should be derivable from dihydrocarvone to constitute the A-ring system whereas the C-ring aldehyde **14** should be accessible from diacetone D-glucose. The synthesis of other hybrid structures should be achievable by changing the electrophiles in the Shapiro reaction. The epoxide **15**, derived from D-glucose, should be utilizable to synthesize the hybrid systems **5** and **9**. The epoxide **15** and the D-mannose-derived aldehyde **16** should be exploitable in the Shapiro reaction to form the AC-ring adducts of the hybrid structures **6**/**10**, and **7**/**11**, respectively.



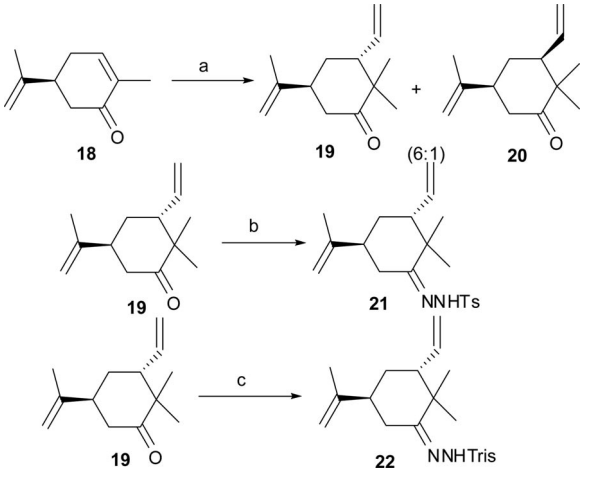
Scheme 2. An illustrative retrosynthesis for the hybrid structure **4** and structures of all electrophiles required for the Shapiro reaction.

Results and Discussion

Synthesis of the A-Ring Fragment

Initially, our focus was to synthesize the hybrids **8**–**11**, starting from (*S*)-carvone. Our synthesis, as outlined in

Scheme 3, commenced with the 1,4 addition of a vinylcopper reagent to (*S*)-carvone (**18**), followed by quenching of the enolate with iodomethane in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU) to afford the ketones **19** and **20** in a combined yield of 92%. GC analysis of the crude product showed that **19** and **20** were present in a ratio of ca. 6:1. It had previously been reported[34] that the addition of a nucleophile to (*S*)-carvone occurs preferentially from the pseudoaxial position, thus leading to a *trans* 1,3-disubstituted ketone. The ketone **19**, obtained as the major product, was further converted into its tosylhydrazone derivative **21** in good yield.[35] The ketone **19** was also treated with trisyl hydrazide ($TrisNHNH_2$) in THF in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*TsA) to provide the trisylhydrazone **22** in 62% yield.[36]

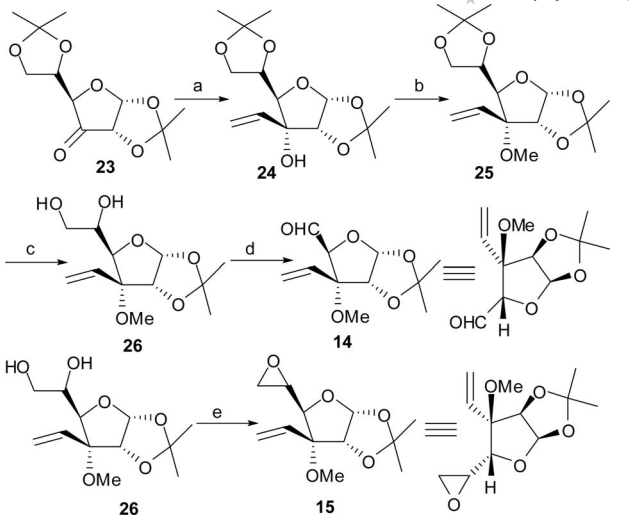


Scheme 3. *Reagents and conditions*: a) vinylmagnesium bromide, CuI, THF, –78 °C, DMPU, MeI, 92%; b) *p*$TsNHNH_2$, absolute EtOH, concd. HCl (cat.), 6 h, room temp., 80%; c) $TrisNHNH_2$, THF, *p*TsA (cat.), 24 h, room temp., 62%.

Synthesis of the C-Ring Fragments

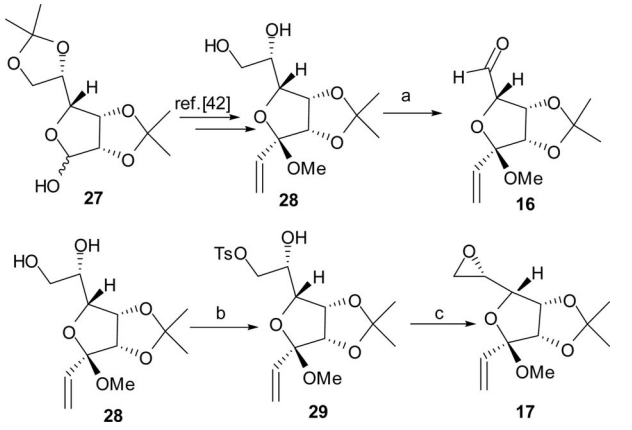
The synthesis of the C-rings in hybrids **5**, **6**, **9**, and **10** started from the D-glucose-derived ketone **23** (Scheme 4).[37] Stereoselective addition[37,38] of vinylmagnesium bromide to a THF solution of ketone **23** afforded the tertiary alcohol **24**. The crude alcohol **24** was then transformed into its methyl ether **25** in 60% yield over two steps.[39] The more labile acetonide protection in the methyl ether **25** was removed with aqueous acetic acid (60%). The resulting diol **26** was oxidatively cleaved with silica-supported sodium periodate[40] in dry CH_2Cl_2 to afford the aldehyde **14**. Because the aldehyde **14** was unstable, it was freshly prepared and used immediately, without purification, for the Shapiro reaction.

The synthesis of hybrid **9** would require the epoxide **15** (Scheme 4) as an electrophile for the Shapiro reaction, so the required epoxide **15** was synthesized by treatment of the diol **26** with triphenylphosphane (TPP), diisopropyl azodicarboxylate (DIAD), and molecular sieves (4 Å) in toluene at 80 °C.[41]



Scheme 4. *Reagents and conditions*: a) vinylmagnesium bromide, THF, 0 °C, 42 h; b) NaH, THF, 0 °C, MeI, 60% (two steps); c) aq. AcOH (60%), 24 h, room temp., 68%; d) silica-supported $NaIO_4$, CH_2Cl_2, 1.5 h, room temp.; e) TPP, DIAD, molecular sieves (4 Å), toluene, 80 °C, 76%.

The synthesis of the C-ring fragments for the hybrids **10** and **11** started from mannose diacetonide (**27**, Scheme 5). The diol **28** was synthesized by the protocol developed in our laboratory[42] and was then easily converted into the aldehyde **16** by the protocol used for compound **14**. Like the aldehyde **14**, the aldehyde **16** was freshly prepared and used immediately for the Shapiro reaction.



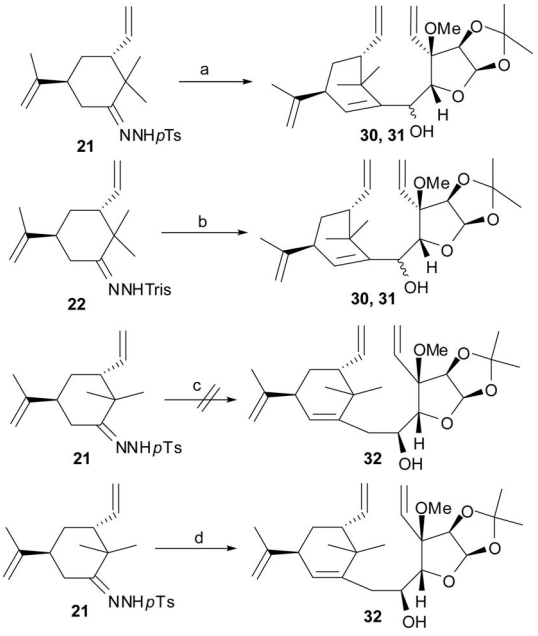
Scheme 5. *Reagents and conditions*: a) silica-supported $NaIO_4$, CH_2Cl_2, 1 h, room temp.; b) *p*TsCl, py., 0 °C to RT, 12 h, 88%; c) NaOMe, 0 °C to RT, 2 h, 75%.

Finally, the epoxide **17** (Scheme 5) was synthesized from the diol **28** in a couple of steps. The primary hydroxy group of the diol **28** was selectively tosylated (*p*TsCl in pyridine) to afford **29** (88%), and this was subsequently transformed into the epoxide **17** on treatment with sodium ethoxide.

Coupling of A- and C-Rings by Shapiro Reaction

After the successful syntheses of the key intermediates for the Shapiro reactions, the next key task was to couple

the A- and C-ring fragments of the hybrids. To start with, we first attempted a Shapiro reaction between the tosylhydrazone **21** and the aldehyde **14** (Scheme 6). The tosylhydrazone **21** was treated with *n*BuLi (3.3 equiv.) in THF to generate the vinyllithium species,[35] which was quenched with the aldehyde **14** to give a mixture of the separable epimeric alcohols **30** and **31** in almost 1:1 ratio (32% combined yield). The yield of the Shapiro reaction was improved substantially (60%) by using the trisylhydrazone **22** instead of **21** (Scheme 6).

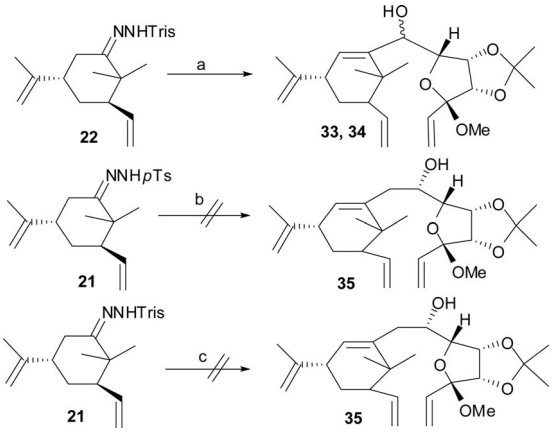


Scheme 6. *Reagents and conditions*: a) *n*BuLi (3.3 equiv.), THF, –78 °C, 30 min, then room temp. 12 min, **14** added at –78 °C, 32%; b) *n*BuLi (2.2 equiv.), THF, –78 °C, 30 min, then 0 °C 5 min, **14** added at –78 °C, 60%; c) *n*BuLi (3.3 equiv.), THF, –78 °C, 30 min, then room temp. 15 min, BF_3·OEt_2 and **15** added at –78 °C: d) *n*BuLi (3.3 equiv.), THF, –78 °C, 30 min, then room temp. 15 min, CuBr·SMe_2 in THF and **15** added at –78 °C.

The synthesis of a hybrid of type **10** required the coupling of hydrazone **21** and epoxide **15** (Scheme 6). Unfortunately, quenching of the vinyllithium species generated in the Shapiro reaction with the epoxide **15** in the presence of a Lewis acid such as BF_3·OEt_2 failed to produce the required product **32**. However, on transmetallation with the CuBr·SMe_2 complex it was possible to open the epoxide ring of **15** to give the alcohol **32** in 30% yield.

The trisylhydrazone **22** was treated with *n*BuLi (2.2 equiv.) in THF at low temperature and the aldehyde **16** in THF was added to this reaction mixture to afford the alcohols **33** and **34** in 46% yield, but these were found to be inseparable by column chromatography (Scheme 7).

For the synthesis of the hybrid structure of type **7**, the vinylcopper species generated by treatment of the tosylhydrazone **21** with *n*BuLi and transmetallation with the CuBr·SMe_2 complex could not open the epoxide **17** to form the product **35** (Scheme 7). The use of trisylhydrazone **22** in the Shapiro reaction, and use of catalytic and equimolar amounts of BF_3·OEt_2 also did not afford the desired product **35**.

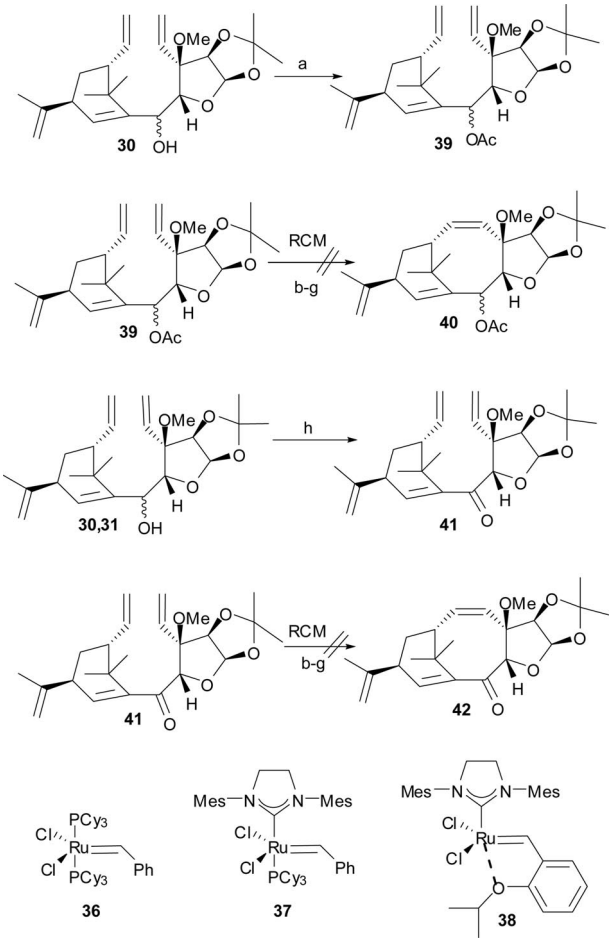


Scheme 7. *Reagents and conditions*: a) *n*BuLi (2.2 equiv.), THF, –78 °C, 30 min, then 0 °C 5 min, **16** added at –78 °C, 46%; b) *n*BuLi (3.3 equiv.), THF, –78 °C, 30 min, then room temp. 15 min, BF_3·OEt_2 and **17** added at –78 °C; c) *n*BuLi (2.2 equiv.), THF, –78 °C, 30 min, then 0 °C, 5 min, CuBr·SMe_2 in THF and **18** added at –78 °C.

Attempted RCM to Make the B-Ring

The next important phase in the synthesis of hybrid molecules involved the key RCM of the available Shapiro reaction products. If successful, RCM would provide the B-rings of the hybrids and attachment of the side chains at C-2 would furnish the desired hybrid systems.

For the synthesis of hybrid molecules of type **8**, the polar –OH functional group in one of the Shapiro reaction products was protected as its acetate **39** (Scheme 8), in order to avoid any undesired interference in the RCM reaction. Attempted RCM in the presence of the first-generation Grubbs catalyst **36** (10 mol-%) at high dilution (0.003 M) in CH_2Cl_2 at reflux, as well as under a variety of other conditions, often led to the recovery of the starting material. Because the substrate contains many oxygen functionalities it was presumed that the active ruthenium carbene complex might be becoming chelated at these oxygen centers, making it unavailable for the reaction. Ti(O*i*Pr)$_4$ is known to prevent such chelation of the active ruthenium carbene with oxygen functionalities, thus making it available for RCM (Scheme 8),[43] so Ti(O*i*Pr)$_4$ (10 mol-%) was added prior to the catalyst **37** either in CH_2Cl_2 or in toluene, both at reflux, and yet the results remain the same. Even the use of three equivalents of Ti(O*i*Pr)$_4$ with respect to the substrate did not change the course of the reaction.[44] Attempts to carry out RCM in the presence either of the second-generation Grubbs catalyst **37** or of the phosphane-free and more functional-group-tolerant Hoveyda–Grubbs catalyst **38** also did not succeed in furnishing the product **40**.

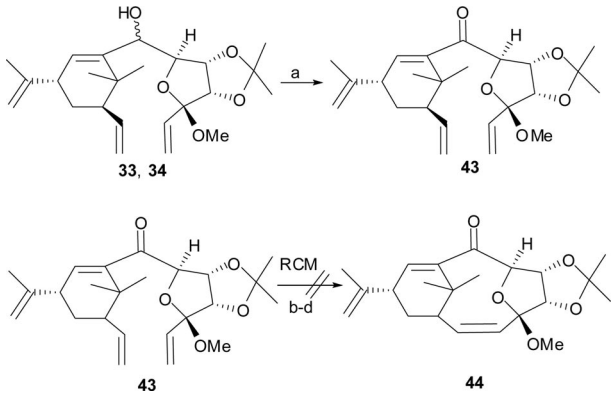


Scheme 8. *Reagents and conditions*: a) Ac_2O, Py, DMAP (cat.), 90%; b) **36** (10 mol-%), CH_2Cl_2, reflux, 12 h; c) **36** (10 mol-%), $Ti(OiPr)_4$ (10 mol-%) CH_2Cl_2, reflux, 12 h; d) **36** (10 mol-%), $Ti(OiPr)_4$ (10 mol-%), toluene, 80 °C, 12 h; e) **37** (5 mol-%), CH_2Cl_2, reflux, 24 h; f) **37** (5 mol-%), CH_2Cl_2, reflux, 24 h; g) **38** (3 mol-%), CH_2Cl_2, reflux, 24 h; h) oxalyl chloride, DMSO, CH_2Cl_2, –78 °C, TEA, 75%.

After the failure of attempted RCM with the acetate **39**, we switched over to the allylic alcohols **30** and **31** (Scheme 8), transforming them into the enone **41** under Swern conditions[45] and studying their reactivity towards RCM. Attempted RCM of the enone **41** in the presence of the Grubbs catalyst **37** (10 mol-%) and $Ti(OiPr)_4$ (10 mol-%) in CH_2Cl_2 at reflux or in toluene at 80 °C failed to give the product **42**. Independent attempts to perform RCM in the presence variously of catalyst **36** (10 mol-%) with $[Ti(OiPr)_4]$ (3 equiv.) as an additive, of the Grubbs catalyst **37** (5 mol-%), and of the Hoveyda–Grubbs catalyst **38** (1 mol-%) in CH_2Cl_2 at reflux also failed.

Attempted RCM of the allylic alcohols **30** and **31** under conditions similar to those used with the acetate **39** and the enone **41** also did not succeed.

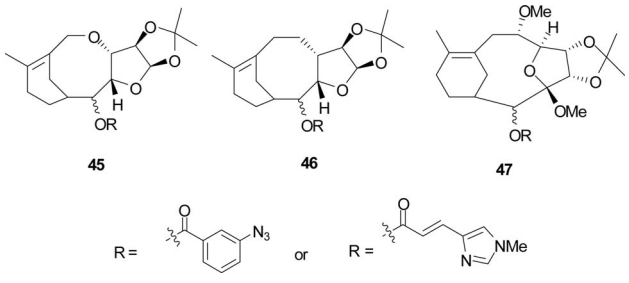
In parallel, for the other set of hybrid structures, the mixture of allylic alcohols **33** and **34** (Scheme 9) was oxidized to the corresponding ketone **43** with Dess–Martin periodinane[46] (DMP) in CH_2Cl_2 in 67% yield. Unfortunately though, attempts to perform the key metathesis reaction of enone **43** in the presence either of the second-generation Grubbs catalyst **37** (5 mol-%) or of the Hoveyda–Grubbs catalyst **38** (1 mol-%) failed to produce the required cyclized products. Similar failures were experienced for the mixture of alcohols **33** and **34** under various conditions.



Scheme 9. *Reagents and conditions*: a) DMP, CH_2Cl_2, room temp., 8 h, 67%; b) **36** (10 mol-%), $Ti(OiPr)_4$ (10 mol-%), CH_2Cl_2, reflux, 12 h; c) **37** (5 mol-%), CH_2Cl_2, reflux, 24 h; d) **38** (1 mol-%), CH_2Cl_2, reflux, 24 h.

The attempts to construct eight- and nine-membered rings in the hybrid systems by means of the key RCM reaction were thus unsuccessful. Construction of medium-sized rings by RCM is a difficult task, but there are reports of syntheses of seven- to nine-membered rings by RCM, including a few from our laboratory.[15] Probably the high steric congestion in the RCM precursors is presenting additional complication for the construction of these medium-sized rings. So far our attempts have revolved around the use of RCM precursors with different functional groups at the junctions of their A- and C-rings. It is evident from these failures that new structural changes to minimize the steric congestion in the RCM precursors are essential. Efforts in this direction are underway.

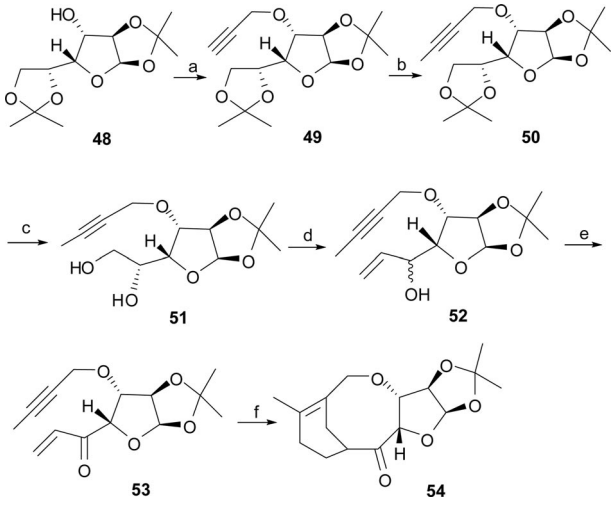
However, we have also been engaged in exploring an alternative strategy to synthesize some new taxol hybrids. From our previous experience in enyne metathesis[4] and the Diels–Alder reaction,[14] a domino enyne metathesis/intramolecular Diels–Alder (IMDA) reaction[47–49] has been considered as a plausible strategy to synthesize interesting hybrid molecules of this type. We designed a few hybrid molecules such as the taxa-oxa-sugar **45**, the taxa-sugar hybrids **46**, and the taxa-eleutherobin hybrid **47** (Scheme 10)



Scheme 10. Designed taxa-oxa-sugar, taxa-sugar, and taxaol-eleutherobin hybrid structures.

and set out to construct their A-rings by domino enyne metathesis.

This new synthetic route began with alkylation of diacetone-D-glucose (**48**) with propargyl bromide to furnish the propargyl ether **50** in good yield (Scheme 11). The alkyne **49** was subsequently methylated by treatment with *n*BuLi and iodomethane to afford the required product **50**. The more labile acetonide in **50** was selectively removed under mild acidic conditions to give the diol **51**, which was further oxidatively cleaved with silica-gel-supported $NaIO_4$ to afford an aldehyde. This was then treated with vinylmagnesium bromide, leading to a mixture of allyl alcohols **52** in 1:2 ratio, and these were further oxidized to **53** with DMP.



Scheme 11. *Reagents and conditions*: a) NaH, DMF, propargyl bromide, 0 °C to room temp., 12 h, 95%; b) *n*BuLi, MeI, THF, HMPA, –78 °C to room temp., 3 h, 80%; c) aq. AcOH (60%), room temp., 12 h, 91%. d) i) silica-supp. $NaIO_4$, CH_2Cl_2, room temp., 2 h, ii) vinylmagnesium bromide, THF, 0 °C to room temp., 12 h, 54% (for 2 steps); e) DMP, CH_2Cl_2, room temp., 12 h, 77%; f) **37** (10 mol-%), toluene, 80 °C, 12 h, 57%.

The tandem enyne/cross-metathesis/IMDA reaction of compound **53** under ethylene (1 atm) in the presence of the second-generation Grubbs catalyst **37** in toluene at 80 °C gave the core structure of the taxa-oxa-sugar hybrid **54** in 57% yield. The alternative strategy has thus been successfully used to synthesize the core structure **54** and currently our laboratory is engaged in attaching the side chain and extending the protocol to synthesize other hybrid structures.

Conclusions

In conclusion, we have designed a new class of taxa-oxa-sugar, taxa-sugar, and taxol-eleutherobin hybrid systems that might be synthesizable from various sugars. The C-ring fragments were successfully synthesized from D-glucose and D-mannose. The A- and C-ring fragments of the hybrid systems were coupled through Shapiro reactions. Unfortunately, however, all attempts to carry out the key RCM reactions with the Shapiro reaction products and their derivatives failed. The failure of the RCM could be attributed to the high steric congestion in the RCM precursors, which would be disadvantageous to the formation of the thermodynamically less favored eight- and nine-membered rings. However, we have successfully synthesized the core structure of a taxa-oxa-sugar hybrid by utilizing tandem enyne cross-metathesis/IMDA as a key step. Efforts in elaborating this successful domino approach for the synthesis of various taxa-sugar hybrids and in evaluating their biological activities are underway.

Experimental Section

General: Unless otherwise noted, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and hexanes were freshly distilled from calcium hydride. DMF was distilled from calcium hydride and stored over molecular sieves (4 Å). Solvents for routine isolation of products and chromatography were reagent grade and glass-distilled. Reaction flasks were dried in an oven at 100 °C for 12 h before use. Air- and moisture-sensitive reactions were performed under argon/UHP nitrogen. Column chromatography was performed with silica gel (100–200 mesh, Acme) and indicated solvents. All reactions were monitored by thin-layer chromatography carried out on E. Merck silica plates (0.25 mm, 60F-254) with UV light as visualizing agent and ethanolic phosphomolybdic acid (7%) and heat as developing agents. Optical rotations were recorded with a Jasco DIP-370 digital polarimeter. IR spectra were recorded with a Thermo Nicolet Avatar 320 FT-IR and a Nicolete Impact 400 machine. Mass spectra were obtained with a Waters Micromass-Q-Tof micro™ (YA105) spectrometer. Elemental analysis was recorded with a Thermo Finnigan Flash EA 1112 instrument. ^1H and ^{13}C NMR spectra were recorded with Varian AS 400, Varian AS 500, or Varian ASM 300 instruments in $CDCl_3$ solutions. ^1H NMR spectroscopic data are reported in the order of chemical shift (δ in ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constant (J) in Hertz [Hz].

(3*S*,5*S*)-5-Isopropenyl-2,2-dimethyl-3-vinylcyclohexanone (19 and 20): Vinylmagnesium bromide solution (67.2 mL, 67.2 mmol) was added under argon at –50 °C to a suspension of CuI (2.56 g, 13.44 mmol) in THF (45 mL) and the mixture was stirred for 30 min. A solution of (*S*)-carvone (**18**, 5.23 mL, 33.6 mmol) in THF (20 mL) was added dropwise at –78 °C. After 1 h the reaction mixture was allowed to warm to room temp. and stirred for 2 h. It was then cooled to –78 °C and DMPU (16.25 mL, 134.4 mmol) was added, followed by methyl iodide (20.91 mL, 336 mmol). The flask was then allowed to warm to room temp., and the mixture was stirred for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (4 × 50 mL). The combined organic layer was washed with saturated sodium thiosulfate solution, water, and brine, and dried with anhydrous sodium sulfate. Solvent was evaporated at low pressure. The crude product was subjected to column purification by eluting with hexanes to afford the isomeric ketones **19** and **20** along with some mixture of the two with a global yield of 92% as colorless oils.

GC analysis: R_t for **19** = 1.145 min R_t for **20** = 0.975 min (in 10% carbowax column, oven temp. 150 °C, injection port temp. 200 °C, detector temp. 200 °C, flow rate 30 mL min^{-1}).

Data for 19: R_f = 0.71 (hexanes/ethyl acetate 9.5:0.5). $[\alpha]_D^{25}$ = –15.19 (c = 1.58, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.00 (s, 3 H), 1.18 (s, 3 H), 1.73 (s, 3 H), 1.80–1.87 (m, 1 H), 2.00–2.07 (m, 1 H), 2.36–2.41 (m, 2 H), 2.46–2.51 (m, 2 H), 4.72 (d, J = 0.6 Hz, 1 H), 4.82 (d, J = 0.6 Hz, 1 H), 5.02–5.06 (m, 2 H), 5.72–5.78 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.2, 21.8, 24.9, 31.6, 40.8, 42.0, 47.4, 49.8, 110.9, 116.4, 138.2, 147.1, 215.6 ppm. IR (film): $\tilde{\nu}$ = 3091, 2973, 2940, 2888, 1716, 1644, 1137 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{21}O$ $[M + H]^+$ 193.1592; found 193.1598.

Data for 20: R_f = 0.74 (9.5:0.5 hexanes/ethyl acetate). $[\alpha]_D^{25}$ = –11.38 (c = 2.46, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ = 0.97 (s, 3 H), 1.30 (s, 3 H), 1.73 (s, 3 H), 2.17 (m, 3 H), 2.42–2.49 (m, 2 H), 2.70–2.76 (m, 1 H), 4.75 (s, 1 H), 4.78 (s, 1 H), 4.99–5.07 (m, 2 H), 5.58–5.71 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 21.4, 22.0, 25.1, 31.7, 41.0, 42.1, 47.5, 49.9, 110.8, 116.3, 138.1, 147.0, 215.3 ppm. IR (film): $\tilde{\nu}$ = 3072, 2986, 2933, 2888, 1716, 1637, 1466, 1394 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{21}O$ $[M + H]^+$ 193.1592; found 193.1587.

Synthesis of the Tosylhydrazone 21: *p*-Tolylsulfonyl hydrazide (0.59 g, 3.172 mmol) and a drop of concd. HCl were added to a solution of the ketone **19** (0.47 g, 2.44 mmol) in absolute ethanol (3 mL), and the mixture was stirred at 40 °C for 20 min. This solution was then allowed to warm to room temp. and stirred for 6 h. The solvent was evaporated and the crude mass was recrystallized from hexanes to afford white crystals of **20** (0.706 g, 80%). R_f = 0.42 (hexanes/ethyl acetate 4:1); m.p. 84–86 °C. $[\alpha]_D^{25}$ = +50.39 (c = 1.27, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.10 (s, 3 H), 1.57–1.65 (m, 2 H), 1.68 (s, 3 H), 1.8–1.95 (m, 2 H), 2.01–2.38 (m, 2 H), 2.43 (s, 3 H), 4.60 (s, 1 H), 4.72 (s, 1 H), 4.88–5.07 (m, 2 H), 5.42–5.54 (m, 1 H), 7.31 (d, J = 8.1 Hz, 2 H), 7.85 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 21.1, 21.7, 24.3, 26.8, 27.1, 32.6, 39.5, 41.4, 50.3, 110.2, 115.8, 128.3, 129.3, 135.2, 138.9, 143.9, 147.5, 165.2 ppm. IR (in CH_2Cl_2): $\tilde{\nu}$ = 3218, 3072, 1699, 1644, 1598, 1167 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{29}N_2O_2S$ $[M + H]^+$ 361.1950; found 361.1965.

Synthesis of the Trisylhydrazone (22): A catalytic amount of *p*-toluenesulfonic acid was added to the mixture of ketone **19** (0.5 g, 2.6 mmol) and 2,4,6-triisopropylbenzenesulfonyl hydrazide (1.0 g, 3.38 mmol) in dry THF at room temp. After 24 h, the solvent was evaporated under reduced pressure and the white solid product **22** (0.76 g, 62%) was obtained after column chromatographic purification on basic alumina with hexanes/ethyl acetate (8:2) as eluent. R_f = 0.32 (hexanes/ethyl acetate 9.5:0.5); m.p. 108–110 °C. $[\alpha]_D^{25}$ = +40.39 (c = 1.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.82 (s, 3 H), 1.05 (s, 3 H), 1.23–1.27 (m, 18 H), 1.67 (s, 3 H), 2.08–2.19 (m, 2 H), 2.28–2.44 (m, 3 H), 2.84–2.93 (m, 1 H), 4.10–4.18 (m, 3 H), 4.67 (s, 1 H), 4.76 (s, 1 H), 4.90 (dd, J = 17.2, 10.0 Hz, 2 H), 5.46–5.55 (m, 1 H), 7.16 (s, 2 H) ppm. ^{13}C NMR (75 MHz): δ = 20.9, 23.6, 24.4, 24.9, 25.0, 26.9, 30.0, 32.6, 34.3, 39.5, 41.2, 50.2, 110.4, 115.8, 123.5, 131.4, 139.0, 147.4, 151.2, 153.2, 162.6 ppm. IR (KBr): $\tilde{\nu}$ = 3224, 2962, 2929, 2872, 1639, 1458, 1380 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{45}N_2O_2S$ $[M + H]^+$ 473.3202; found 473.3208.

3-*O*-Methyl-1,2:5,6-di-*O*-isopropylidene-3-*C*-vinyl-α-D-allofuranose (25): The ketone **23**[37] (6.5 g, 25.19 mmol) was dehydrated by azeotropic distillation with dry toluene. Dry THF (80 mL) was added to this ketone and the mixture was cooled to 0 °C. A solution of vinylmagnesium bromide (1 M, 37.8 mL, 37.8 mmol) was added dropwise and the mixture was stirred at room temp. for 42 h. The reaction mixture was cooled to 0 °C and quenched with saturated ammonium chloride and the residue was extracted with ethyl acetate (3 × 40 mL). The combined organic extracts were washed with brine solution and dried with anhydrous sodium sulfate. The organic extract was concentrated by evaporation of solvent at reduced pressure to obtain crude **24** used for the following step.

Sodium hydride (2.9 g, 72.64 mmol) was washed with dry hexanes (3 × 10 mL) and suspended in dry THF (20 mL) under argon at 0 °C. A solution of the crude alcohol **24** (5.2 g, 18.16 mmol) in THF (80 mL) was added dropwise and the reaction mixture was left to stir at room temp. for 1 h. Methyl iodide (5.65 mL, 90.8 mmol) was added dropwise. TBAI (a catalytic amount) was added and the reaction mixture was stirred for 12 h at room temp. Methanol (6 mL) was slowly added, followed by addition of water (10 mL). The aqueous layer was extracted with ethyl acetate (4 × 50 mL). The combined extracts were washed with brine, dried with anhydrous sodium sulfate, and filtered. Concentration of the filtrate followed by column chromatography (hexanes/ethyl acetate 9:1) afforded the methyl ether **25** (3.98 g, 60% for two steps). R_f = 0.39 (hexanes/ethyl acetate 4:1). $[\alpha]_D^{25}$ = +54.17 (c = 2.40, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 3 H), 1.37 (s, 3 H), 1.43 (s, 3 H), 1.61 (s, 3 H), 3.39 (s, 3 H), 3.87–3.99 (m, 2 H), 4.06–4.17 (m, 2 H), 4.56 (d, J = 3.7 Hz, 1 H), 5.26 (d, J = 17.9 Hz, 1 H), 5.49 (d, J = 11.4 Hz, 1 H), 5.75 (d, J = 3.7 Hz, 1 H), 5.78 (dd, J = 17.9, 11.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz): δ = 25.4, 26.6, 27.1, 53.2, 66.8, 73.8, 81.3, 82.3, 85.3, 104.1, 109.2, 112.9, 118.9, 135.1 ppm. IR (film): $\tilde{\nu}$ = 2987, 2939, 2834, 1635, 1457, 1377, 1218, 1164, 1077, 1030 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{24}NaO_6$ $[M + Na]^+$ 323.1471; found 323.1481. $C_{15}H_{24}O_6$: calcd. C 59.98, H 8.05; found C 60.46, H 8.04.

3-*O*-Methyl-1,2-*O*-isopropylidene-3-*C*-vinyl-α-D-allofuranose (26): The methyl ether **25** (3.45 g, 11.48 mmol) was dissolved in aqueous acetic acid (60%, 40 mL) and the solution was stirred at room temp. for 24 h. The acetic acid and water were removed by repeated co-evaporation in vacuo with toluene. The yellow syrup was purified by column chromatography (hexanes/ethyl acetate 3:2) to give the diol **26** (2 g, 68%). R_f = 0.16 (hexanes/ethyl acetate 2:1). $[\alpha]_D^{25}$ = +56.76 (c = 1.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 3 H), 1.62 (s, 3 H), 2.57 (br. s, 2 H), 3.44 (s, 3 H), 3.62–3.77 (m, 3 H), 4.06 (d, J = 7.3 Hz, 1 H), 4.57 (d, J = 3.7 Hz, 1 H), 5.33 (d, J = 18.3 Hz, 1 H), 5.55 (d, J = 11 Hz, 1 H), 5.78 (d, J = 3.7 Hz, 1 H), 5.83 (dd, J = 18.3, 11 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 26.5, 26.8, 53.5, 64.2, 70.2, 79.4, 80.6, 86.1, 104.2, 113.2, 119.0, 133.8 ppm. IR (film): $\tilde{\nu}$ = 3464, 3090, 2988, 2939, 1640, 1457, 1425, 1378, 1219, 1096, 1025 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{20}NaO_6$ $[M + Na]^+$ 283.1158; found 283.1169. $C_{12}H_{20}O_6$ (260.29): calcd. C 55.37, H 7.74; found C 55.84, H 7.91.

Epoxide 15: DIAD (0.28 mL, 1.44 mmol) was slowly added at room temp. to a mixture of the diol **26** (0.34 g, 1.31 mmol), triphenylphosphane (0.376 g, 1.44 mmol), and molecular sieves (4 Å) in toluene (15 mL), and the mixture was then heated to 80 °C for 8 h. It was then allowed to cool to room temp., quenched with water (10 mL), extracted with ethyl acetate (3 × 15 mL), washed with brine, dried with anhydrous sodium sulfate, and concentrated. Column chromatographic purification (hexanes/ethyl acetate 9.2:0.8) gave the epoxide **15** (0.24 g, 76%). R_f = 0.48 (hexanes/ethyl acetate 2:1). $[\alpha]_D^{25}$ = +35.45 (c = 1.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.59 (s, 3 H), 2.74–2.80 (m, 2 H), 3.01–3.04 (m, 1 H), 3.42 (s, 3 H), 3.94 (d, J = 6.0 Hz, 1 H), 4.55 (d, J = 3.6 Hz, 1 H), 5.38 (d, J = 18.0 Hz, 1 H), 5.54 (d, J = 11.2 Hz, 1 H), 5.78 (d, J = 3.6 Hz, 1 H), 5.83 (dd, J = 18.0, 11.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 26.5, 27.0, 45.3, 49.4, 53.4, 81.0, 81.5, 85.8, 104.4, 113.2, 119.3, 134.2 ppm. IR (film): $\tilde{\nu}$ = 1648, 1463, 1259, 1213, 1113, 1034 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{18}NaO_5$ $[M + Na]^+$ 265.1052; found 265.1044.

Tosylate 29: *p*TsCl (0.33 g, 1.75 mmol) was added portionwise to a solution of the diol **28**[42] (0.38 g, 1.46 mmol) in dry pyridine (3 mL), and the mixture was stirred for 2 h at 0 °C and then for 12 h at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried with anhydrous sodium sulfate and evaporated under reduced pressure to give a residue that was purified by silica gel chromatography (hexanes/ethyl acetate 4:1) to afford **29** (0.54 g, 88%) as a colorless oil. R_f = 0.6 (hexanes/ethyl acetate 3:2). $[\alpha]_D^{25}$ = +60.4 (*c* = 0.48, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (s, 3 H), 1.40 (s, 3 H), 2.45 (s, 3 H), 3.09 (s, 3 H), 3.81 (dd, *J* = 8.4, 3.9 Hz, 1 H), 4.23–4.11 (m, 3 H), 4.35 (dd, *J* = 10.5, 2.7 Hz, 1 H), 4.45 (d, *J* = 6.0 Hz, 1 H), 4.85 (dd, *J* = 5.7, 3.9 Hz, 1 H), 5.42–5.41 (m, 2 H), 5.66 (dd, *J* = 7.8, 6.3 Hz, 1 H), 7.35 (dd, *J* = 8.4, 1.5 Hz, 2 H), 7.83 (dd, *J* = 6.6, 1.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 24.7, 25.9, 49.0, 68.1, 71.8, 76.6, 86.3, 108.0, 113.0, 119.9, 128.1, 129.9, 131.9, 132.9, 145.0 ppm. IR (film): $\tilde{\nu}$ = 3486, 3104, 2940, 1657 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{26}NaO_8S$ [M + Na]$^+$ 437.1246; found 437.1231.

Epoxide 17: A solution of NaOMe (0.13 g, 2.41 mmol) in methanol (2 mL) was added at 0 °C to a stirred solution of **29** (0.5 g, 1.2 mmol) in dry methanol (20 mL), and the mixture was stirred for 1 h at 0 °C and then for 2 h at room temp. The reaction mixture was quenched with water (25 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, concentrated in vacuo, and purified by silica gel chromatography (hexanes/ethyl acetate 9:1) to afford the epoxide **17** (0.22 g, 75%) as a colorless oil. R_f = 0.8 (hexanes/ethyl acetate 3:2). $[\alpha]_D^{25}$ = +64.4 (*c* = 1.64, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.46 (s, 3 H), 2.81 (dd, *J* = 5.2, 2.9 Hz, 1 H), 2.95–2.92 (m, 1 H), 3.13 (s, 3 H), 3.35–3.32 (m, 1 H), 3.57 (dd, *J* = 6.0, 4.0 Hz, 1 H), 4.49 (d, *J* = 5.6 Hz, 1 H), 4.89 (dd, *J* = 6.0, 3.6 Hz, 1 H), 5.49 (m, 2 H), 5.73 (dd, *J* = 17.6, 10.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8, 26.1, 46.2, 48.9, 79.3, 80.7, 86.5, 108.1, 113.0, 119.9, 132.2 ppm. IR (film): $\tilde{\nu}$ = 3065, 2923, 1663, 1104 cm^{-1}. LRMS (ESI): *m*/*z* = 265.0534 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{12}H_{18}NaO_5$ [M + Na]$^+$ 265.1062; found 265.1052.

General Procedures for the Shapiro Reactions: Silica-supported $NaIO_4$[40] was added portionwise to a stirred solution of diol **26** or **28**[42] (0.42 g, 1.61 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred vigorously for 1–1.5 h and filtered, and the residue was washed with CH_2Cl_2 (2 × 20 mL). The combined CH_2Cl_2 extracts were concentrated and the resultant pale yellow syrup (0.41 g) was used immediately for the next step.

Method with the Tosylhydrazone as Starting Material: *n*BuLi in hexane (1.6 M solution, 3.5 mL, 5.58 mmol) was slowly added at –78 °C to a solution of the tosylhydrazone **21** (0.667 g, 1.69 mmol) in THF (0.6 mL). The deep red solution was stirred at –78 °C for 30 min and then allowed to warm to room temp. After 12 min of stirring at room temp (until all the nitrogen bubbling had ceased), the reaction mixture was cooled to –78 °C and a solution of aldehyde **14** (previously dried by azeotropic distillation with toluene) in THF (1 mL) was added dropwise. The reaction mixture was allowed to stir at room temperature for 2 h and was then quenched with saturated ammonium chloride solution at 0 °C, extracted with ethyl acetate (3 × 20 mL), and dried with anhydrous sodium sulfate. The crude product was purified by column chromatography (hexanes/ethyl acetate 9.5:0.5) to afford the epimeric alcohols **30** (0.08 g) and **31** (0.09 g) as colorless oils in 32% combined yield.

Method with the Trisylhydrazone as Starting Material: *n*BuLi (1.6 M solution in hexane, 2.3 mL, 3.72 mmol) was added dropwise at –78 °C to a solution of the trisylhydrazone **22** (0.8 g, 1.69 mmol) in THF (0.6 mL). After stirring for 30 min at –78 °C, the reaction mixture was stirred at 0 °C for 5 min and cooled to –78 °C, the aldehyde **14** or **16** was added slowly, and the mixture was stirred for 1 h. The reaction mixture was allowed to stir at room temp. for 2 h and then quenched with saturated ammonium chloride and extracted with ethyl acetate (3 × 20 mL), washed with brine, dried with anhydrous sodium sulfate, and concentrated. Column chromatographic purification gave the epimeric alcohols **30** (0.16 g) and **31** (0.17 g) in a combined yield of 60% or the epimeric mixture of alcohols **43** and **34** (0.25 g, 46%).

Data for Alcohol 30: R_f = 0.59 (hexanes/ethyl acetate 2:1). $[\alpha]_D^{25}$ = +11.36 (*c* = 0.44, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (s, 3 H), 1.11 (s, 3 H), 1.37 (s, 3 H), 1.61 (s, 3 H), 1.63–1.73 (m, 2 H),1.74 (s, 3 H), 2.06–2.11 (m, 1 H), 2.36 (d, *J* = 2.8 Hz, 1 H), 2.80 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.44 (s, 3 H), 4.15–4.16 (m, 2 H), 4.56 (d, *J* = 3.6 Hz, 1 H), 4.69 (s, 1 H), 4.79 (s, 1 H), 4.97–5.02 (m, 2 H), 5.33 (d, *J* = 18.0 Hz, 1 H), 5.58 (d, *J* = 11.2 Hz, 1 H), 5.72 (d, *J* = 3.6 Hz, 1 H), 5.77 (d, *J* = 4.4 Hz, 1 H), 5.81–5.91 (m, 2 H, 2 × C*H*=) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 22.8, 26.7, 27.1, 27.4, 29.2, 36.6, 40.8, 47.5, 53.6, 68.5, 80.9, 81.5, 86.7, 103.9, 111.5, 112.9, 115.0, 118.9, 126.9, 134.2, 141.0, 145.7, 148.1 ppm. IR (film): $\tilde{\nu}$ = 3522, 3075, 1640, 1376, 1219, 1112 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{36}NaO_5$ [M + Na]$^+$ 427.2460; found 427.2454.

Data for Alcohol 31: R_f = 0.46 (hexanes/ethyl acetate 2:1). $[\alpha]_D^{25}$ = +16.99 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (s, 3 H), 1.06 (s, 3 H), 1.39 (s, 3 H), 1.50 (s, 3 H), 1.60–1.72 (m, 2 H), 1.73 (s, 3 H), 2.05–2.11 (m, 1 H), 2.27 (d, *J* = 7.6 Hz, 1 H), 3.35 (s, 3 H), 4.21 (d, *J* = 0.8 Hz, 1 H), 4.33 (d, *J* = 7.6 Hz, 1 H), 4.60 (d, *J* = 3.2 Hz, 1 H), 4.70 (s, 1 H), 4.79 (s, 1 H), 4.97–5.02 (m, 2 H), 5.28 (d, *J* = 12.0 Hz, 1 H), 5.48 (d, *J* = 11.2 Hz, 1 H), 5.81–5.98 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 23.0, 26.8, 27.1, 27.3, 29.1, 36.6, 40.8, 47.3, 53.0, 65.5, 80.1, 84.0, 84.8, 104.0, 111.6, 113.0, 115.2, 117.7, 126.7, 135.6, 140.6, 147.0, 148.2 ppm. IR (film): $\tilde{\nu}$ = 3499, 3084, 1640, 1379, 1219, 1112 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{36}NaO_5$ [M + Na]$^+$ 427.2460; found 427.2474.

Compound 32: *n*BuLi in hexane (1.6 M, 2.06 mL, 3.3 mmol) was added dropwise to a solution of the tosylhydrazone **21** (0.36 g, 1 mmol) in THF (3 mL). The deep red solution was stirred at –78 °C for 30 min and was then allowed to warm slowly to room temp. After 12 min of stirring at room temp., the reaction mixture was cooled to –78 °C and $CuBr{\cdot}SMe_2$ in THF (3 mL) was added. After 15 min the epoxide **15** (0.17 g, 0.7 mmol) was added and the mixture was allowed to warm to room temp, stirred at room temp. for 8 h, quenched with saturated ammonium chloride solution, extracted with ethyl acetate, and dried with sodium sulfate. The crude product obtained after concentration was purified by column chromatography (hexanes/ethyl acetate 9:1) to afford the alcohol **32** (0.088 g, 30%). R_f = 0.31 (hexanes/ethyl acetate 4:1). $[\alpha]_D^{25}$ = +19.99 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 1.00 (s, 3 H), 1.38 (s, 3 H), 1.63 (s, 3 H), 1.65–1.73 (m, 2 H), 1.73 (s, 3 H), 2.01–2.11 (m, 2 H), 2.32 (s, 1 H), 2.55 (dd, *J* = 15.2, 1.2 Hz, 1 H), 2.77–2.79 (m, 1 H), 3.42 (s, 3 H), 3.79–3.90 (m, 2 H), 4.59 (d, *J* = 3.2 Hz, 1 H), 4.68 (d, *J* = 0.8 Hz, 1 H), 4.78 (d, *J* = 0.8 Hz, 1 H), 5.00–5.01 (m, 2 H), 5.30 (d, *J* = 18 Hz, 1 H), 5.43 (d, *J* = 4 Hz, 1 H), 5.52 (d, *J* = 11.2 Hz, 1 H), 5.75–5.94 (m, 3 H) ppm. IR (film): $\tilde{\nu}$ = 3431, 3286, 1657, 1462, 1379, 1106 cm^{-1}. LRMS (ESI): *m*/*z* = 441.2486 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{25}H_{38}NaO_5$ [M + Na]$^+$ 441.2617; found 441.2613.

Synthesis of the Acetate 39: Acetic anhydride (0.5 mL) and a catalytic amount of DMAP were added to the alcohol **30** (0.07 g,

0.17 mmol) in pyridine (0.75 mL) at room temp. After the system had been kept for 8 h at room temp., toluene (10 mL × 3) was repeatedly added and then removed under reduced pressure. The crude residue was chromatographically purified with hexanes/ethyl acetate 95:5 as eluent. The acetate **39** was obtained (0.07 g, 90%) as a colorless oil. R_f = 0.53 (hexanes/ethyl acetate 4:1). $[\alpha]_D^{25}$ = +32.49 (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 3 H), 1.00 (s, 3 H), 1.29 (s, 3 H), 1.54 (s, 3 H), 1.56–1.63 (m, 2 H), 1.64 (s, 3 H), 1.94 (s, 3 H), 1.96–2.01 (m, 1 H), 2.76 (dd, J = 10.0, 6.8 Hz, 1 H), 3.27 (s, 3 H), 4.19 (d, J = 9.6 Hz, 1 H), 4.50 (d, J = 3.2 Hz, 1 H), 4.59 (s, 1 H), 4.68 (s, 1 H), 4.88–4.94 (m, 2 H), 5.06 (d, J = 18 Hz, 1 H), 5.42 (d, J = 9.2 Hz, 1 H), 5.45 (d, J = 11.6 Hz, 1 H), 5.61 (d, J = 3.6 Hz, 1 H), 5.71 (d, J = 4.0 Hz, 1 H), 5.77 (ddd, J = 19.6, 10.0, 9.2 Hz, 1 H); 5.90 (dd, J = 18.4, 11.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 21.8, 22.5, 26.8, 27.1, 27.4, 28.6, 36.7, 41.0, 47.2, 53.2, 67.1, 81.0, 82.9, 85.1, 103.8, 112.2, 112.8, 115.6, 116.6, 128.9, 134.4, 140.3, 142.4, 147.7, 169.6 ppm. IR (film): $\tilde{\nu}$ = 2962, 2931, 1740, 1657, 1374, 1240, 1097 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{38}NaO_6$ $[M + Na]^+$ 469.2566; found 469.2556.

Compound 41: DMSO (0.025 mL, 0.47 mmol) in CH_2Cl_2 (0.1 mL) was added at –78 °C to a solution of oxalyl chloride (0.019 mL, 0.218 mmol) in dry CH_2Cl_2 (0.5 mL), and the mixture was stirred for 15 min. The solution of the mixture of alcohols **30** and **31** (0.08 g, 0.19 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise, the mixture was stirred for 35 min, and then triethylamine (0.14 mL, 0.98 mmol) was added. After 30 min of stirring the reaction mixture was allowed to attain room temp. and further stirred for 2 h. The reaction mixture was quenched with water (1 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine and dried with sodium sulfate and concentrated. Column chromatographic purification (9.5:0.5) gave the enone **41** (0.06 g, 75%). R_f = 0.59 (hexanes/ethyl acetate 2:1). $[\alpha]_D^{25}$ = +14.99 (c = 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11 (s, 3 H), 1.14 (s, 3 H), 1.39 (s, 3 H), 1.62 (s, 3 H), 1.70–1.78 (m, 2 H), 1.81 (s, 3 H), 2.05–2.10 (m, 1 H), 2.95–2.99 (m, 1 H), 3.35 (s, 3 H), 4.58 (d, J = 3.7 Hz, 1 H), 4.86 (s, 1 H), 4.91 (s, 1 H), 4.99–5.05 (m, 2 H), 5.20 (d, J = 17.1 Hz, 1 H), 5.34 (s, 1 H), 5.40 (d, J = 11 Hz, 1 H), 5.57 (d, J = 17.1, 11 Hz, 1 H), 5.76–5.85 (m, 1 H), 5.95 (d, J = 3.7 Hz, 1 H), 6.93 (d, J = 3.7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 22.5, 26.5, 26.7, 27.2, 28.2, 36.5, 42.1, 47.6, 53.0, 81.4, 82.3, 86.4, 104.0, 113.0, 113.1, 115.9, 118.9, 133.3, 139.7, 144.7, 146.2, 146.6, 194.7 ppm. IR (film): $\tilde{\nu}$ = 3076, 1681, 1641, 1456, 1378, 1113, 1044 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{34}NaO_5$ $[M + Na]^+$ 425.2304; found 425.2293.

Synthesis of the Enone 43: A solution of a mixture of allylic alcohols **33** and **34** (0.06 g, 0.15 mmol) in CH_2Cl_2 (3 mL) was added at room temp. to a suspension of DMP (0.251 g, 0.60 mmol) in CH_2Cl_2 (10 mL), the mixture was stirred for 8 h at room temp., and then a solution of sodium thiosulfate and sodium hydrogen carbonate (5 mL) was added. After the solution had become clear, it was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The crude product was purified by column chromatography (hexanes/ethyl acetate 9.4:0.6) to afford the enone **43** (0.04 g, 67%) as a colorless oil. R_f = 0.59 (hexanes/ethyl acetate 4:1). $[\alpha]_D^{25}$ = –30.49 (c = 2.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (s, 3 H), 1.19 (s, 3 H), 1.23 (s, 3 H), 1.35 (s, 3 H), 1.61–1.81 (m, 2 H), 1.83 (s, 3 H), 2.10–2.18 (m, 1 H), 2.91–2.95 (m, 1 H), 3.17 (s, 3 H), 4.45 (d, J = 5.7 Hz, 1 H), 4.76 (s, 1 H), 4.93 (s, 1 H), 4.99 (d, J = 4.5 Hz, 1 H), 5.05–5.12 (m, 3 H), 5.51 (dd, J = 10.8, 2.1 Hz, 1 H), 5.66 (dd, J = 17.7, 2.1 Hz, 1 H), 5.77–5.87 (m, 2 H), 6.59 (d, J = 3.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 22.6, 25.0, 25.2, 26.0, 27.7, 29.8, 36.8, 41.6, 46.0, 49.4, 81.7, 82.0, 86.2, 107.8, 113.1, 113.4, 116.0, 120.6, 132.0, 139.5, 146.6, 147.1, 193.7 ppm. IR (film): $\tilde{\nu}$ = 3075, 1678, 1641, 1377, 1219, 1113, 1032 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{34}NaO_5$ $[M + Na]^+$ 425.2304; found 425.2321.

6-(But-2-ynyloxy)-5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,2-*d*][1,3]dioxole (50): A solution of the alcohol **48** (6.5 g, 25 mmol) in DMF (20 mL) was added dropwise at 0 °C to a suspension of sodium hybrid (3.6 g, 75 mmol, 60% dispersion in mineral oil) in dry DMF (20 mL) and the mixture was stirred for 30 min. Propargyl bromide (5.2 mL, 62.5 mmol) was added to this mixture, which was stirred at 0 °C for 1 h and then at room temperature for 12 h. It was then quenched with saturated ammonium chloride solution (30 mL). The mixture was extracted with ethyl acetate (3 × 50 mL), and the organic layer was dried with anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified by silica gel column chromatography (hexanes/ethyl acetate 4:1) to give **49** (7.12 g, 95%) as a colorless oil.

*n*BuLi (1.6 M solution in hexane, 19.3 mL, 31 mmol) was added at –78 °C over a period of 10 min to a solution of the alkyne **49** (7.12 g, 23.8 mmol) in THF (100 mL). The reaction mixture was stirred at –78 °C for 45 min, followed by addition of HMPA (4.2 mL, 24.5 mmol) and methyl iodide (2.9 mL, 47.7 mmol). After the mixture had been stirred for 1 h at –78 °C and for 2 h at room temp., saturated ammonium chloride solution (30 mL) was added and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was concentrated in vacuo and the residue was purified by flash column chromatography with hexanes/ethyl acetate 4:1 to afford **50** (6 g, 80%) as a pale yellow syrup. R_f = 0.53 (hexanes/ethyl acetate 2:1) $[\alpha]_D^{25}$ = –42.57 (c = 0.14, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.35 (s, 3 H), 1.43 (s, 3 H), 1.50 (s, 3 H), 1.86 (t, J = 2.4 Hz, 3 H), 4.01–3.98 (m, 1 H), 4.11–4.07 (m, 2 H), 4.16–4.13 (m, 1 H), 4.26 –4.22 (m, 2 H), 4.31–4.28 (m, 1 H), 4.61 (d, J = 3.6 Hz, 1 H), 5.87 (d, J = 3.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.7, 108.8, 105.1, 82.8, 82.7, 81.0, 80.9, 74.5, 72.5, 67.0, 58.5, 26.7, 26.7, 26.1, 25.3, 3.5 ppm. IR (film): $\tilde{\nu}$ = 2986, 2937, 2227, 1644, 1455, 1374, 1255, 1164, 1075, 850 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{24}NaO_6$ $[M + Na]^+$ 335.1471; found 335.1462.

1-[6-(But-2-ynyloxy)-2,2-dimethyltetrahydrofuro[3,2-*d*][1,3]dioxol-5-yl]ethane-1,2-diol (51): AcOH in water (60%, 90 mL) was added to the alkyne **50** (6 g, 19.2 mmol) and the mixture was stirred for 12 h at room temp. Toluene (3 × 20 mL) was then repeatedly added and the solvents were evaporated in vacuo to remove traces of water and acetic acid. The crude diol was purified by flash column chromatography with hexanes/ethyl acetate 1:4 to afford the diol **51** (4.8 g, 91%) as a pale yellow syrup. R_f = 0.18 (hexanes/ethyl acetate 1:4). $[\alpha]_D^{25}$ = –48.57 (c = 0.28, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.50 (s, 3 H), 1.86 (t, J = 2.8 Hz, 3 H), 3.75–3.71 (m, 1 H), 3.87–3.84 (m, 1 H), 4.11 (br. s, 1 H), 4.19–4.16 (m, 2 H), 4.24 (d, J = 3.6 Hz, 1 H), 4.29 (t, J = 2.4 Hz, 1 H), 4.56 (d, J = 4.0 Hz, 1 H), 5.92 (d, J = 3.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.7, 105.2, 83.7, 82.0, 80.9, 79.7, 74.4, 69.1, 64.1, 57.9, 26.6, 26.1, 3.4 ppm. IR (film): $\tilde{\nu}$ = 3436, 2985, 2937, 2241, 1645, 1455, 1376, 1256, 1164, 1076, 887 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{20}NaO_6$ $[M + Na]^+$ 295.1158; found 295.1148.

1-[6-(But-2-ynyloxy)-2,2-dimethyltetrahydrofuro[3,2-*d*][1,3]dioxol-5-yl]prop-2-en-1-ol (52): Silica-supported $NaIO_4$[40] (96 g) was added portionwise to the diol **51** (4.8 g, 16.76 mmol) in CH_2Cl_2 (500 mL) at room temp. After 1 h, the reaction mixture was filtered and the residue was washed with CH_2Cl_2 (2 × 25 mL). The filtrate was concentrated in vacuo. The crude aldehyde was used in the next step

without further purification. Vinylmagnesium bromide (13.73 mL, 13.73 mmol) was added dropwise to a stirred solution of the aldehyde (1.65 g, 6.86 mmol) in dry THF (40 mL), which was stirred for 1 h at 0 °C under argon, and then for 12 h at room temperature. The reaction mixture was quenched with saturated ammonium chloride solution (30 mL), extracted with ethyl acetate (3 × 50 mL), washed with brine, and dried with anhydrous sodium sulfate. The resulting mixture was concentrated in vacuo and purified by silica gel column chromatography (hexanes/ethyl acetate 2:1) to afford the two diastereomeric alcohols **52** in 1:1 ratio as a colorless oil in 54% yield. R_f = 0.46, 0.4 (hexanes/ethyl acetate 1:2). $[\alpha]_D^{25}$ = –50.21 (c = 0.47, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 3 H), 1.49 (s, 3 H), 1.86 (t, J = 2.8 Hz, 3 H), 2.62 (br. s, 1 H), 4.35–4.03 (m, 3 H), 4.51–4.47 (m, 1 H), 4.62 (d, J = 4.8 Hz, 1 H), 5.25 (dt, J = 2.0, 4.0 Hz, 1 H), 5.48 (dt, J = 2.0, 4.0 Hz, 1 H), 6.00–5.88 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.5, 117.0, 111.9, 105.0, 83.6, 83.2, 82.2, 81.2, 74.1, 70.9, 57.7, 26.8, 26.3, 3.5 ppm. IR (film): $\tilde{\nu}$ = 3500, 2987, 2933, 2224, 1645, 1454, 1375, 1259, 1217, 1165, 1139, 1076, 1025, 853 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{20}NaO_5$ $[M + Na]^+$ 291.1208; found 291.1200.

Compound 54: DMP (5.62 g, 13.27 mmol) was added at 0 °C in one portion to a solution of **52** (1.45 g, 6.03 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred for 2 h at room temp. It was then quenched with saturated aqueous $NaHCO_3$ (4 mL, containing 0.5 g of $Na_2S_2O_3$), and the crude enone was isolated by extraction with CH_2Cl_2 (2 × 20 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified on silica gel with hexanes/ethyl acetate (4:1) to yield **53** (1.1 g, 77%) as a colorless oil. A solution of **53** (0.5 g, 1.87 mmol) in toluene (50 mL) was purged with ethylene for 20 min, a solution of the Grubbs catalyst **37** (0.159 g, 0.187 mmol) in toluene (2 mL) was added, and the mixture was then heated at 80 °C for 24 h. DMSO (0.1 mL) was then added to the reaction mixture, which was stirred for 12 h at room temp. The solvent was evaporated and the crude product was purified by column chromatography (hexanes/ethyl acetate 6:1) to afford **54** (0.32 g, 57%) as a white solid. R_f = 0.78 (hexanes/ethyl acetate 1:1). $[\alpha]_D^{25}$ = –45.71 (c = 0.28, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.48 (s, 3 H), 1.63 (s, 3 H), 1.79–1.70 (m, 2 H), 2.17–2.02 (m, 3 H), 3.01–2.93 (m, 2 H), 3.86 (dd, J = 2.4, 1.2 Hz, 1 H), 4.11 (s, 2 H), 4.45 (d, J = 2.8 Hz, 1 H), 4.56 (dd, J = 3.6, 1.2 Hz, 1 H), 6.06 (d, J = 4.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.2, 136.8, 128.3, 112.5, 104.6, 84.6, 84.5, 83.4, 68.3, 45.3, 28.4, 26.9, 26.5, 24.4, 22.5, 18.3 ppm. IR (film): $\tilde{\nu}$ = 2985, 2934, 1701, 1455, 1383, 1375, 1259, 1216, 1163, 1100, 1020, 869 cm^{-1}.HRMS (ESI): calcd. for $C_{16}H_{22}NaO_5$ $[M + Na]^+$ 317.1365; found 317.1364.

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