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A tandem enyne/ring closing metathesis approach to the synthesis of novel angularly fused dioxa-triquinanes

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Abstract—Triquinanes and their oxygenated congeners, oxa- and dioxa-triquinanes, exhibit versatile biological activities in conjunction with synthetically challenging molecular architecture. Owing to these properties, several new strategies have been developed to accomplish the synthesis of these sesquiterpenes. Among the new strategies, cascade radical cyclization strategy has been broadly explored and well studied. Herein, we report our efforts in detail for the synthesis of dioxa-triquinanes using a domino enyne/RCM strategy as the key step. Carbohydrate based synthesis not only allows the use of inexpensive and optically pure starting materials, but also the furanose derivatives, which already possess one of the requisite dihydro-furan moieties in the desired dioxa-triquinane. The other two five-membered rings were constructed simultaneously by the cascade enyne/RCM reaction using the Grubbs' second-generation catalyst. During the course of our synthesis it was observed that the acetonide protection hinders the RCM reaction, after the initial enyne metathesis reaction. The reaction underwent smoothly under argon atmosphere, whilst use of ethylene atmosphere was found to hinder the formation of the tandem enyne/RCM product. The effect of substitution on the key reaction is described here.

1. Introduction

Sesquiterpenoids can be considered as important biochemical intermediates and natural products. This has driven the development of several new methodologies and strategies developed over the last four decades. Polyquinanes,[1] an important class of natural products belonging to the sesquiterpenoid family, consist of three or more fused five-membered ring systems. Amongst the polyquinanes, the triquinane framework natural products are most versatile and abundant in nature. The triquinane natural products consist of three five-membered rings fused together and depending on the fusion pattern they can be broadly classified into three types: propellanes, linear, and angular triquinanes.[1g] They are usually isolated either from plants or marine sources and occasionally show microbial origin (Fig. 1).

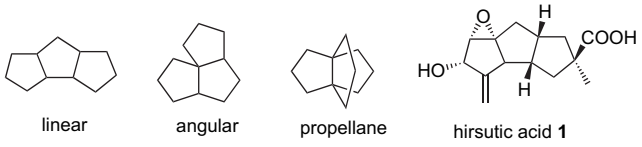

Figure 1.

Hirsuitic acid-C_1 **1** was the first polyquinane natural product isolated[2] from Basidomycetes *Stereum hirsutum* and since then synthetic chemists have been engaged in the synthesis of this novel family of sesquiterpenes. The promising biological activities have led efforts to prepare triquinane framework, which can be considered an emerging area of natural product synthesis. As a consequence, several strategies,[3] especially cascade radical methods,[4] transannulation reactions,[5] alkene–arene photocycloaddition reactions,[6] have been employed to meet the challenges posed by this family of compounds. Despite the wealth of literature available for the isolation of carbocyclic triquinanes, there are only scattered reports on the isolation[7,8] or syntheses[9] of these structurally novel siblings oxa- and dioxa-triquinanes (Fig. 2).

The oxa- and dioxa-triquinanes bear one and two dihydrofuran moieties, respectively, either in linear or angular fashion. In 1989, Kouno reported the first isolation of anislactone A (**2**) and B (**3**) from *Illicium anisatum*.[10] These anislactone-type sesquiterpenes consist of two consecutive

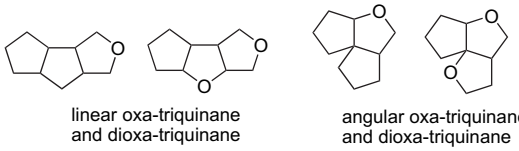

Figure 2.

Keywords: Triquinanes; Dioxa-triquinanes; Grubbs' catalyst; Tandem enyne/RCM; Carbohydrates.
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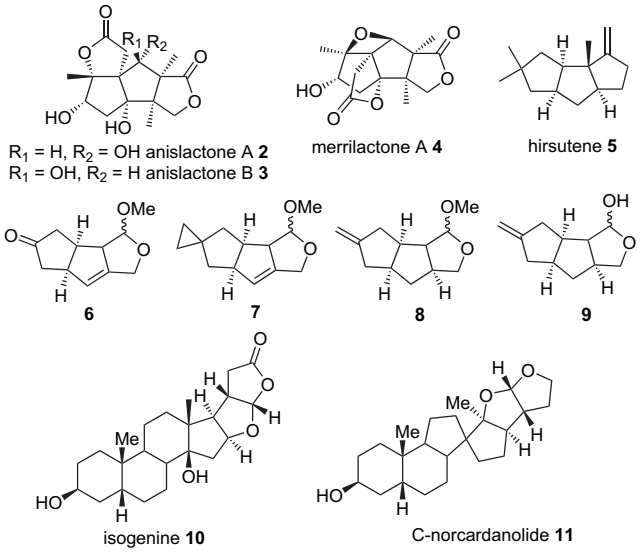


Figure 3.

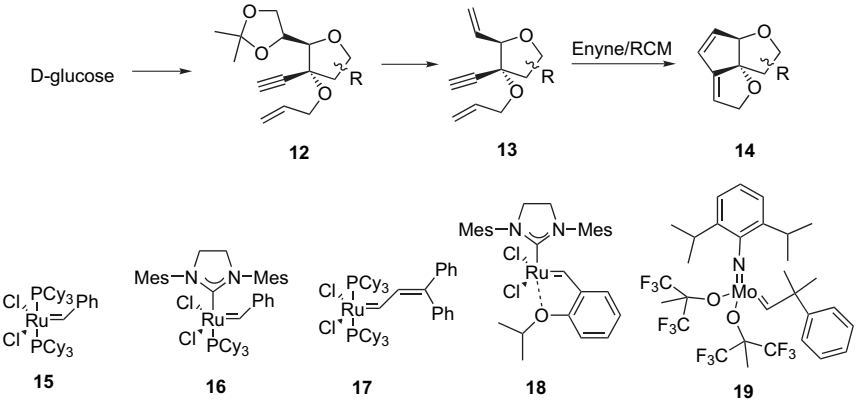
five-membered ring frameworks fused with two γ-lactones. Merrilactone A (**4**), another interesting sesquiterpene lactone, was recently isolated from *Illicium merrillianum*.[11] It was shown that merrilactone A (**4**) significantly promotes neurite growth in primary cultures of fetal rat cortical neurons at very low concentration (0.1–10 μmol). These promising biological activities can be attributed to the oxygenated pentacyclic architecture making them attractive synthetic targets.[12] Furthermore, there are a couple of steroid based hybrid natural products isogenine **10**[7] and C-norcardanolide **11**[8] possessing dioxa-triquinane subunits (Fig. 3). Moreover, interestingly some of the reported syntheses of carbocyclic triquinanes proceed via oxa-triquinanes. For example, Fukumoto's synthesis of hirsutene **5** involved oxa-triquinanes **6**, **7**, **8**, and **9** as key intermediates and fortuitously when these intermediates were subjected to biological activity testing, all these exhibited potent in vitro cytotoxic activity against murine leukemia cells and KB human epidermoid carcinoma cells.[13] From these examples, one may speculate that the oxygen in these natural and unnatural products could be important for biological activity. Thus the design and synthesis of natural and unnatural oxa- and dioxa-triquinanes become a promising area for organic synthesis. Most of the approaches employed for the construction of triquinane framework elegantly explored cascade radical cyclization methods.[4] Herein, we report our alternate approach involving a domino enyne/RCM strategy to dioxa-triquinanes.

2. Results and discussion

As a part of our Chiron approach program,[14] we developed interest in the preparation of oxa- and dioxa-triquinanes. This paper details a carbohydrate based enantiospecific route to angularly fused dioxa-triquinanes using a tandem enyne/RCM reaction.[15]

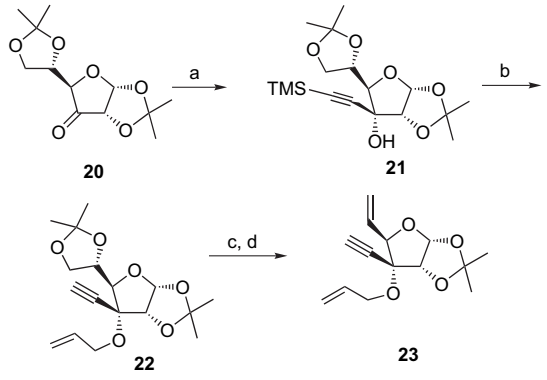
In view of developing a strategy for the synthesis of dioxa-triquinanes, it was necessary to consider some of the following points: sugar templates have been useful starting materials and they have been elegantly transformed[16] into triquinanes, oxa-triquinanes, and dioxa-triquinanes. Also cascade reactions[17] provide easy and rapid access to the polycyclic systems. The structural complexity associated with the promising biological activity has necessitated the development of new approaches for the synthesis of dioxa-triquinanes. But to date, most of the synthetic strategies elegantly utilized cascade radical cyclization methods.[4] However, to the best of our knowledge until our initial report, a tandem metathetic strategy had not been employed to construct these triquinanes. With the advent of air stable ruthenium catalysts and Schrock's molybdenum catalysts,[18] the last decade has witnessed a huge exploitation of enyne[19] and ring closing metathesis[20] (RCM) in organic synthesis and we describe here our results in detail about our successful cascade metathetic strategy[21,22] to synthesize dioxa-triquinanes.[15]

From a synthetic perspective, we envisaged that the enyne **12** could be easily prepared from a sugar template and in a couple of steps it could be transformed into the dienyne **13**, a precursor for the key tandem enyne/ring closing metathesis reaction leading to the desired dioxa-triquinane **14** using Grubbs' first generation catalyst **15** and second-generation catalyst **16** (Scheme 1). We envisaged that this new tandem metathetic strategy, if successful, would allow rapid access to a range of such dioxa-triquinanes from different sugar templates.



Scheme 1. Retrosynthesis for desired dioxa-triquinanes.

Our route to the synthesis of dioxa-triquinane commenced from the readily available ketone **20**[23] (Scheme 2), which possesses one oxaquinane unit. Treatment of the ketone **20**, with lithium trimethylsilylacetylide, generated in situ from trimethylsilylacetylene and ^{n}BuLi, afforded the alcohol **21** in high yield. The stereochemical outcome of this Grignard addition reaction is well established in the literature, which takes place from the β-face[24] to give a tertiary alcohol **21** with the required stereochemistry at C-3. This stereochemistry is important from the point of view of the key tandem metathetic reaction. Subsequent protection of the tertiary alcohol **21** as allyl ether on treatment with sodium hydride and allyl bromide in THF resulted in only 30% yield. Use of ^{n}BuLi in THF/HMPA worked well on a small scale (0.1 g). However, while on scaling up (1.0 g), this reaction failed to give **22** in consistent yield and so an alternate method was sought. Sodium hydride and allyl bromide in DMF not only achieved the protection of the tertiary alcohol **21**, but also simultaneously removed the trimethylsilyl group to generate the enyne **22** in good yield. At this stage, our next task was to install the other alkene moiety required for the tandem reaction. This was successfully achieved through selectively deprotecting the more labile acetonide group of enyne **22** under mild acidic conditions. The resultant vicinal diol, without purification, was then converted into the desired dienyne **23** in a single step following Garregg's protocol.[25]



Scheme 2. Reagents and conditions: (a) TMS–acetylene, ^{n}BuLi, THF, 0 °C, rt, 80%; (b) NaH, allyl bromide, DMF, 2 h, 78%; (c) 60% AcOH, rt, 18 h; (d) PPh_3, I_2, imidazole, toluene, reflux, 5 h, 85% (for two steps).

With the dienyne **23** in hand, we were set for the key tandem enyne/RCM reaction using the Grubbs' catalysts. However, as shown in Table 1, all efforts to obtain **25** did not succeed at this stage. The use of catalyst **15** in refluxing CH_2Cl_2 afforded only the enyne metathesis product **24** (entry 1). The use of more reactive catalyst **16** improved the yield of enyne product **24** but still could not provide the required tandem enyne/RCM product **25**. Unfortunately, alteration of solvent from refluxing CH_2Cl_2 to toluene at 80 °C also did not alter the outcome. Substituting ethylene[26] for argon atmosphere gave the intermediate enyne product, although the yield was slightly improved (see Table 1). Speculating that the activity of the catalyst would have reduced due to longer reaction time, we subjected the isolated triene **24** to RCM reaction conditions independently with catalysts **15** and **16** and unfortunately, all attempts to access the diene **25** were thwarted.

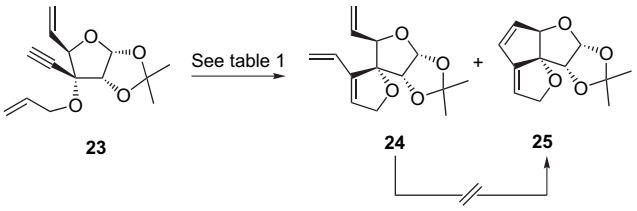


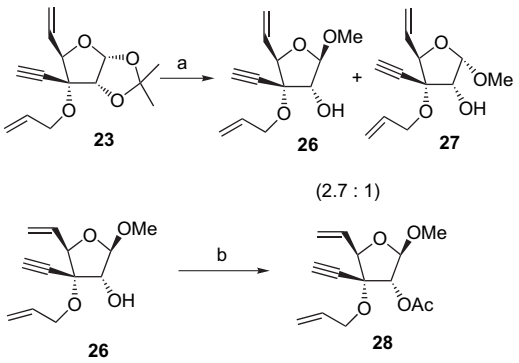
Table 1. Effect of solvent and catalyst on tandem enyne/RCM

	Catalyst	Conditions	Yield of **24**[a] (%)
1	**15** (10 mol %)	CH_2Cl_2, reflux, 36 h (argon)	65
2	**16** (5 mol %)	CH_2Cl_2, reflux, 12 h (argon)	73
3	**16** (5 mol %)	Toluene, 80 °C, 12 h (argon)	75
4	**16** (5 mol %)	CH_2Cl_2, reflux, 12 h (ethylene)	78

[a] Product **25** didn't form under these reaction conditions.

At this stage, the failure of the RCM reaction after initial enyne metathesis reaction led us to study the acetonide protection. We envisaged that the acetonide protection in the enyne product **24** would not force the two double bonds to come closer for the RCM reacton.[15,27] So we decided to remove the acetonide group of **23**, anticipating a relief in the ring strain, which in turn could probably bring the two double bonds closer after the initial enyne metathesis reaction.

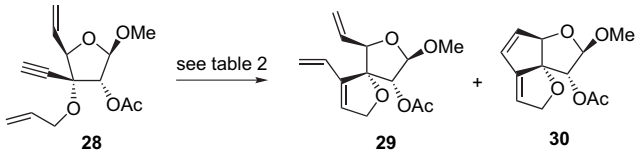
To probe the feasibility of this hypothesis, the dienyne **23** was first treated with concd HCl in methanol at room temperature to afford a readily separable anomeric mixture of hydroxy dienynes **26** and **27** in the ratio 2.7:1 with a global yield of 89% (Scheme 3). To avoid any complicated interference of OH group during the tandem metathetic process, the major anomer **26**, under standard conditions, was converted to its acetate **28** in excellent yield. It was found that the stereochemistry reported at the anomeric center for the acetate in our preliminary communication[15] was actually the opposite diastereomer, which was supported by X-ray crystallography.



Scheme 3. Reagents and conditions: (a) concd HCl, MeOH, rt, 36 h, 89% (3:11); (b) Ac_2O, Py, DMAP, rt, 8 h, 90%.

With the precursor **28** in hand, the next important task was to check the feasibility of the key tandem enyne/RCM reaction (see Table 2). To begin with, we first attempted the reaction in refluxing CH_2Cl_2 using catalyst **15** under argon atmosphere. To our surprise, the normally facile enyne metathesis

did not work under these conditions (entry 1). When this reaction was carried out under ethylene atmosphere, only a trace of the enyne product **29** was obtained, with the remainder being the starting material. When the more reactive catalyst **16** was employed in CH_2Cl_2 under argon atmosphere at room temperature, though the enyne product **29** was the major product (54%), for the first time the tandem metathesis product **30** (36%) was produced. Encouraged by this result, we attempted this reaction under reflux conditions keeping the other parameters identical. The dienyne acetate **28** underwent a smooth tandem enyne metathesis/RCM to afford a mixture of **29** and **30** in approximately a 1:2 ratio with a combined yield of more than 95% (entry 4). The yield of the tandem enyne/RCM product **30** was found to be almost unaffected when the solvent was changed from refluxing CH_2Cl_2 to toluene at 80 °C (entry 5). This shows that the solvent do not make much difference in the overall distribution of the products. When the tandem enyne/RCM metathesis of dienyne acetate **28** was carried out under ethylene atmosphere using catalyst **16** in either solvent, the major product obtained was the enyne metathesis **29** with only traces of product **30** formed (entries 6 and 7).



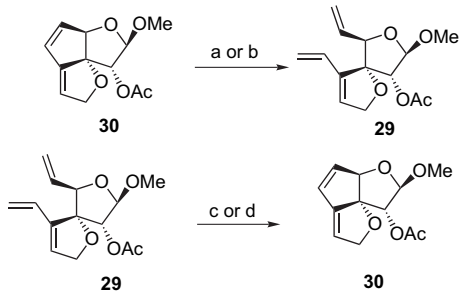
28 **29** **30**

Table 2. Effect of solvent and catalyst on tandem enyne/RCM

	Catalyst	Conditions	Products ratio (%) [**29**:**30**]	
1	**15** (10 mol %)	CH_2Cl_2, reflux, 36 h (argon)	No reaction	
2	**15** (10 mol %)	CH_2Cl_2, reflux, 36 h (ethylene)	08	00
3	**16** (5 mol %)	CH_2Cl_2, rt, 48 h (argon)	54	36
4	**16** (5 mol %)	CH_2Cl_2, reflux, 36 h (argon)	*36*	*60*
5	**16** (5 mol %)	Toluene, 80 °C, 36 h (argon)	*35*	*59*
6	**16** (5 mol %)	CH_2Cl_2, reflux, 36 h (ethylene)	61	13
7	**16** (5 mol %)	Toluene, 80 °C, 36 h (ethylene)	73	05

As shown in Table 2, ethylene atmosphere did not assist in driving the equilibrium in favor of the tandem metathesis product. Presumably, it could be due to the reversibility of the reaction or ring-opening metathetic (ROM) reaction. To support this assumption, the tandem metathesis product **30** was treated with catalyst **16** under ethylene atmosphere in refluxing CH_2Cl_2 and we observed that the reaction reverts back to give the product **29** in 40% (74% based on recovery of starting material) yield. The same reaction was found to be sluggish when the first generation catalyst **15** was used (Scheme 4).

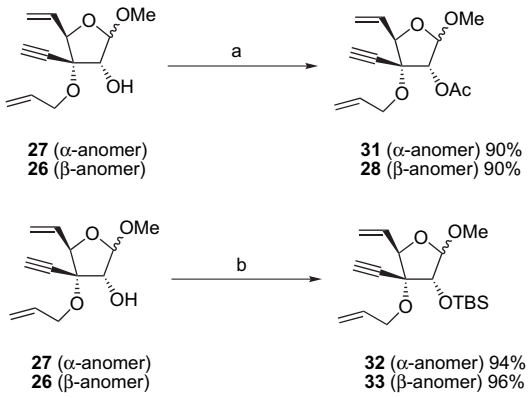
We also reasoned that during the tandem metathetic reaction, the catalyst appeared to become deactivated over time and so, we decided to isolate the enyne metathesis product **29** and subjected it to the RCM reaction conditions. As anticipated, the reaction proceeded well with catalyst **16**, though the starting material was not completely consumed. The reaction was too slow when catalyst **15** was employed.



30 **29** **29** **30**

Scheme 4. Reagents and conditions: (a) **16** (5 mol %), ethylene, CH_2Cl_2, reflux, 24 h, 40% (74% BRSM); (b) **15** (10 mol %), ethylene, CH_2Cl_2, reflux, 24 h, 19% (68% BRSM); (c) **16** (5 mol %), argon, CH_2Cl_2, reflux, 24 h, 38%; (d) **15** (10 mol %), argon, CH_2Cl_2, reflux, 24 h, 9%.

From Table 2, it is clear that use of catalyst **16** (5 mol %) in refluxing CH_2Cl_2 under argon atmosphere gives a good yield from the tandem enyne/RCM reaction. Thus we decided to study the effect of substitution at *C*-2 on the key cascade enyne/RCM reaction by employing the above standard parameters. Both the anomeric alcohols **26** (major/β-anomer) and **27** (minor/α-anomer) were protected as their acetates and TBS ethers, following the standard protocols in excellent yields (Scheme 5).



27 (α-anomer)
26 (β-anomer)

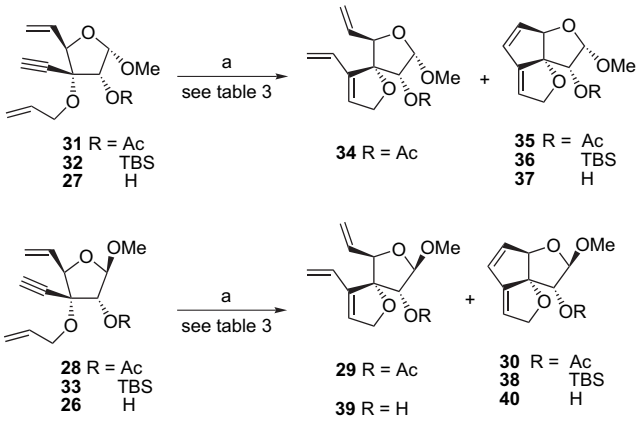
31 (α-anomer) 90%
28 (β-anomer) 90%

27 (α-anomer)
26 (β-anomer)

32 (α-anomer) 94%
33 (β-anomer) 96%

Scheme 5. Reagents and conditions: (a) Ac_2O, Py, DMAP, rt, 8 h; (b) TBSCl, imidazole, DMAP (cat.), 50 °C, 24 h.

With the anomeric substrates in hand, we evaluated the feasibility of the tandem reaction (Scheme 6 and Table 3). The tandem enyne/RCM reaction of the acetate **31** with the standard reaction conditions gave the diene **35** as the major product (56%) along the enyne product **34** (40%). The combined yield was excellent (96%) and the ratio of the tandem enyne/RCM **35** product to the interrupted product **34** was almost 3:2, which was comparable to that of the other anomeric acetate **30** (entries 1 and 2). In the case of the TBS ether **32** (α-anomer) only the tandem enyne/RCM product **36** was isolated in 76% yield (entry 3). As expected, similar results were found for TBS ether **33** (β-anomer) giving **38** in 68% yield (entry 4). After these interesting results, we employed the same reaction parameters on the dienyne alcohols **27** and **26**. The dienyne alcohol **27** (α-anomer) gave diene **37** in 58% yield after refluxing for 48 h (entry 5). In this case there was no interrupted product observed. For the major



Scheme 6. Reagents and conditions: (a) **16** (5 mol %), argon, CH_2Cl_2, reflux.

Table 3. Effect of substitution on tandem enyne/RCM

Entry	Substrate	Product ratio (%)	
		Enyne product	Tandem product
1	**31**	40	58
2	**28**	36	60
3	**32**	Not isolated	76
4	**33**	Not isolated	68
5	**27**	Not isolated	56
6	**26**	63	18

anomeric alcohol **26**, the enyne product **39** was found to be the major isolated product (63%) with a small amount of the required tandem enyne product **40** formed (entry 6). Thus the two-anomeric alcohols were found to exhibit a noticeable difference in reactivity in the key tandem enyne/RCM reaction.

The dioxa-triquinanes **36** and **37** derived from the α-anomer (minor anomer) were found to be colorless crystalline solids. The structures were confirmed by single X-ray crystallography. The ORTEP drawings for compounds **36** and **37** are shown in Figure 4.

3. Conclusion

In summary, we have developed a simple and efficient enantiospecific route to angularly fused dioxa-triquinanes utilizing a tandem enyne/ring closing metathesis reaction as the key step. We also observed and indirectly proved that the presence of an acetonide group in the system hindered the ring closing metathesis after the initial enyne metathesis reaction. We also successfully demonstrated that ethylene atmosphere hinders the progress of the final ring closing metathesis process and instead, facilitates the ring opening of the triquinanes. The generality of this synthetic scheme has been demonstrated on substrates with different alcohol protecting groups. Using this pathway, it should be possible to make several such oxa-, dioxa-triquinanes and other naturally occurring triquinanes. Efforts are underway to prepare linearly fused oxa-, dioxa-triquinanes, and linear and angular triquinanes.

4. Experimental

4.1. General

Unless and otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used without further purification. Solvents used: tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane and hexanes were freshly distilled from calcium hydride. DMF was distilled over 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 an argon/UHP nitrogen atmosphere. Column chromatography was performed using silica gel (100–200 mesh, Acme) with indicated solvents. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid and heat as developing agents. Optical rotation was recorded on Jasco DIP-370 digital polarimeter. IR spectra were recorded from Thermo Nicolet Avater 320 FTIR and Nicolete Impact 400 machine. Mass spectra were obtained

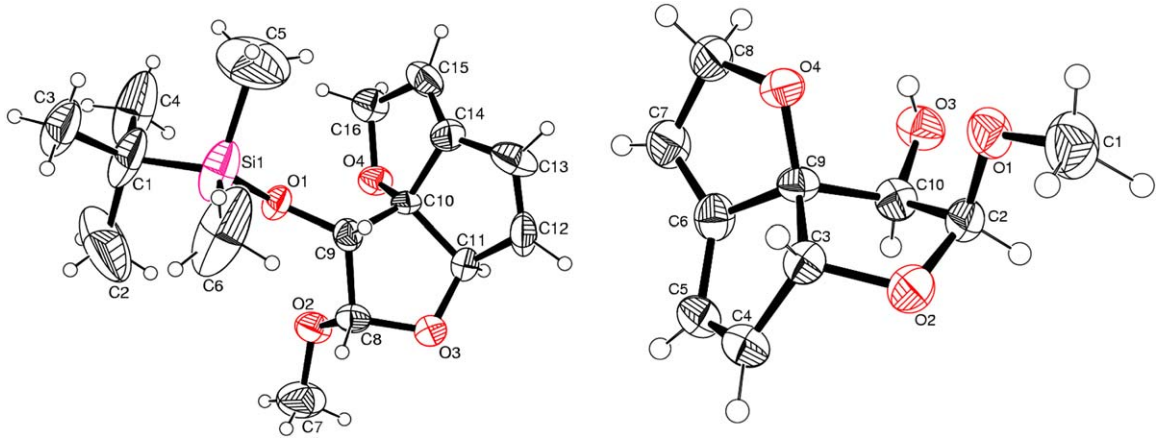


Figure 4. ORTEP diagrams for dioxa-triquinanes **36** and **37** elipsoid at 50% probability.

with Waters Micromass-Q-Tof micro™ (YA105) spectrometer. Elemental analysis was recorded on Thermo Finnigan Flash EA 1112. ^{1}H and ^{13}C NMR spectra were recorded either on Varian AS 400, Varian AS 500 or Varian ASM 300 instruments in $CDCl_3$ solutions. ^{1}H NMR data were 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).

4.1.1. 3-*C*-Trimethylsilylethynyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (21). To a solution of TMS–acetylene (1.3 ml, 9.68 mmol) in THF (15 ml) under argon atmosphere at 0 °C was added 1.6 M ^{n}BuLi in hexane (6.05 ml, 9.68 mmol). The reaction mixture was stirred at room temperature for 1 h and then a THF (20 ml) solution of the ketone **20**[23] (2.0 g, 7.75 mmol) was added dropwise at 0 °C. After 2 h at 0 °C, a saturated ammonium chloride solution (20 ml) was added and the reaction mixture was extracted with hexanes. The combined organic layer was washed with water, brine, and dried over anhydrous sodium sulfate. The organic phase was concentrated under vacuo and the residue was purified by flash column chromatography using 9:1 hexane/ethyl acetate to afford alcohol **21** (2.2 g) in 80% yield. R_f=0.59 (1:1 hexanes/ethyl acetate); mp 116–117 °C; $[\alpha]_D^{25}$ +12.66 (*c* 1.0, $CHCl_3$); IR (KBr) 3490, 2172, 1459, 1387, 1255, 1209, 1036, 858 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.20 (s, 9H), 1.38 (s, 6H), 1.46 (s, 3H), 1.59 (s, 3H), 3.02 (br s, 1H), 3.89 (d, 1H, J=7.0 Hz), 4.03 (dd, 1H, J=8.8, 5.5 Hz), 4.14 (dd, 1H, J=8.8, 6.6 Hz), 4.38–4.40 (m, 1H), 4.58 (d, 1H, J=3.7 Hz), 5.82 (d, 1H, J=3.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −0.2, 25.1, 26.7, 26.8, 26.8, 66.9, 74.8, 76.0, 81.5, 84.0, 94.4, 101.7, 104.3, 109.5, 113.8; Anal. Calcd for $C_{17}H_{28}O_6Si$: C, 57.28; H, 7.92. Found C, 57.15; H, 7.77. LRMS (EI) [M+Na]$^+$ 379.2010.

4.1.2. 3-*O*-Allyl-3-*C*-ethynyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (22). Sodium hydride (0.18 g, 4.5 mmol) was washed with 3×10 ml of dry hexane to remove the mineral oil coatings and DMF (21 ml) was added to this fine powder under argon atmosphere followed by a DMF (7 ml) solution of alcohol **21** (1.06 g, 3 mmol) dropwise at 0 °C over a period of 15 min. Then the resultant suspension was stirred at room temperature for 2 h before quenching with allyl bromide (0.57 ml, 6.6 mmol). After 2 h, the reaction was quenched with ammonium chloride solution (20 ml) and extracted with ethyl acetate. The combined organic phase was washed with excess water, brine, and dried over anhydrous sodium sulfate. The residue thus obtained after evaporation under reduced pressure was purified by silica gel column chromatography (95:5 hexanes/ethyl acetate) to afford **22** (0.8 g, 78%). R_f=0.53 (5:1 hexanes/ethyl acetate); mp 63–65 °C; $[\alpha]_D^{25}$ +44.99 (*c* 1.0, $CHCl_3$); IR (KBr) 3246, 3094, 2991, 2951, 2900, 2116, 1652, 1398, 1158, 1057, 879, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.57 (s, 3H), 2.70 (s, 1H), 4.09–4.20 (m, 4H), 4.33–4.43 (m, 2H), 4.60 (d, 1H, J=3.7 Hz), 5.16 (ddd, 1H, J=10.8, 3.3, 1.5 Hz), 5.34 (ddd, 1H, J=17.1, 3.6, 1.8 Hz), 5.81 (d, 1H, J=3.7 Hz), 5.90–6.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.4, 26.7, 26.9, 27.0, 66.1, 67.5, 74.6, 79.3, 79.4, 80.9, 81.3, 83.3, 104.3, 109.6, 113.7, 116.6, 134.4; LRMS (EI) [M+Na]$^+$ 347.1474; Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found C, 62.39; H, 7.46. HRMS (EI) calcd for $C_{17}H_{24}O_6Na$ *m/z* 347.1471, found *m/z* 347.1474.

4.1.3. 5,6-Deoxy-1,2-*O*-isopropylidene-3-*O*-allyl-3-*C*-ethynyl-α-D-*ribo*-hex-5-enofuranose (23). AcOH (10 ml, 60%) in water was added to the enyne **22** (0.6 g, 1.85 mmol) and the mixture was stirred for 18 h. Then toluene (3×20 ml) was successively added and evaporated under vacuo to remove traces of water and acetic acid. The crude diol was used in the next step without further purification.

To a refluxing solution of the crude diol (0.58 g), imidazole (0.55 g, 8.16 mmol), and triphenylphosphine (2.14 g, 8.16 mmol) in dry toluene, iodine (1.55 g, 6.13 mmol) was added portion wise through the condenser. The reaction mixture was further refluxed for 5 h and cooled to room temperature. The organic layer was washed with saturated sodium thiosulfate solution (3×10 ml), water, brine, and dried over anhydrous sodium sulfate. Removal of the solvent followed by purification by column chromatography (49:1 hexanes/ethyl acetate) yielded **23** (0.39 g) in 85% yield (for two steps). R_f=0.57 (9:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +31.30 (*c* 1.15, $CHCl_3$); IR (film) 3290, 3083, 2109, 1642, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.59 (s, 3H), 2.66 (s, 1H), 4.16 (ddt, 1H, J=7.3, 3.0, 1.5 Hz), 4.31 (ddt, 1H, J=7.0, 3.0, 1.5 Hz), 4.49 (d, J=6.6 Hz), 4.64 (d, 1H, J=3.7 Hz), 5.18 (ddd, 1H, J=10.3, 3.0, 1.5 Hz), 5.28–5.39 (m, 2H), 5.49 (ddd, 1H, J=14.3, 2.6, 1.3 Hz), 5.86 (d, 1H, J=3.7 Hz), 5.83–6.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.8, 26.8, 67.8, 78.6, 79.2, 81.7, 82.2, 82.6, 104.2, 113.6, 117.3, 120.3, 132.4, 134.4; LRMS (EI) [M+Na]$^+$ 273.1250; HRMS (EI) calcd for $C_{14}H_{18}O_4Na$ *m/z* 273.1103, found *m/z* 273.1100.

4.1.4. Methyl-5,6-deoxy-3-*O*-allyl-3-*C*-ethynyl-D-*ribo*-hex-5-enofuranosides (26 and 27). To a solution of dienyne diacetonide **23** (0.7 g, 2.8 mmol) in dry methanol (30 ml) was slowly added concd HCl (4 ml) and stirred at room temperature for 36 h. Then solid sodium bicarbonate was added to neutralize the acid and filtered. The residual solid was washed with ethyl acetate. The organic solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using 93:7 hexanes/ethyl acetate to afford a mixture of anomeric alcohols **27** (0.15 g, 24%) and **26** (0.41 g, 65%).

β-Anomer **26**: R_f=0.3 (4:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −20.59 (*c* 1.02, $CHCl_3$); IR (film) 3467, 3296, 3092, 2993, 2118, 1645, 1124, 1045, 928 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.74 (s, 1H), 3.47 (s, 3H), 4.14 (d, 1H, J=2.6 Hz), 4.23 (d, 2H, J=5.5 Hz), 4.52 (d, 1H, J=6.9 Hz), 4.89 (d, 1H, J=2.6 Hz), 5.23 (dd, 1H, J=10.2, 1.5 Hz), 5.31–5.37 (m, 2H), 5.44 (dd, 1H, J=17.1, 1.5 Hz), 5.91–6.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.3, 67.2, 78.2, 79.2, 80.4, 80.6, 84.3, 109.0, 117.9, 118.9, 133.8, 134.9; HRMS (EI) calcd for $C_{12}H_{16}O_4Na$ *m/z* 247.0946, found *m/z* 247.0935.

α-Anomer **27**: R_f=0.24 (4:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +147.27 (*c* 1.10, $CHCl_3$); IR (film) 3353, 3296, 3092, 2105, 1650, 1144, 1030, 933 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.66 (s, 1H), 3.50 (s, 3H), 4.24–4.29 (m, 3H),

4.47 (d, 1H, J=7.3 Hz), 5.04 (d, 1H, J=4.8 Hz), 5.15–5.20 (m, 1H), 5.30–5.45 (m, 3H), 5.89–6.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.9, 67.4, 77.6, 78.0, 79.9, 80.3, 83.6, 101.9, 116.9, 119.1, 134.1, 134.4; HRMS (EI) calcd for $C_{12}H_{16}O_4Na$ m/z 247.0946, found m/z 247.0943.

4.2. General procedure for methyl-5,6-deoxy-3-*O*-allyl-3-*C*-ethynyl-D-*ribo*-hex-5-enofuranosides (28 and 31)

Acetic anhydride (3 ml) and a catalytic amount of DMAP were added to alcohol **26** or **27** (0.24 g, 1.07 mmol) in pyridine (3 ml) at room temperature. After 8 h at room temperature, toluene (10 ml×3) was successively added and removed under reduced pressure. The crude residue was chromatographically purified using 95:5 hexanes/ethyl acetate as eluent. The acetate **28** or **31** was obtained as colorless oil.

Compound **28**: R_f=0.59 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −23.58 (c 1.06, $CHCl_3$); IR (film) 3310, 2258, 1743, 1641, 1231, 919 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 2.74 (s, 1H), 3.45 (s, 3H), 3.98 (ddt, 1H, J=7.2, 3.0, 1.5 Hz), 4.25 (ddt, 1H, J=6.6, 3.0, 1.5 Hz), 4.46 (d, 1H, J=6.9 Hz), 4.93 (d, 1H, J=1.5 Hz), 5.14 (ddd, 1H, J=10.8, 3.0, 1.5 Hz), 5.27 (ddd, 1H, J=17.7, 3.6, 1.8 Hz), 5.32 (d, 1H, J=1.5 Hz), 5.36 (ddd, 1H, J=10.2, 2.4, 1.5 Hz), 5.46 (ddd, 1H, J=17.1, 2.4, 1.5 Hz), 5.80–5.91 (m, 1H), 6.00–6.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9, 56.0, 67.9, 78.0, 78.7, 79.4, 79.7, 85.1, 107.3, 116.8, 119.5, 134.2, 169.4; HRMS (EI) calcd for $C_{14}H_{18}O_5Na$ m/z 289.1052, found m/z 289.1053 .

Compound **31**: R_f=0.53 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +139.86 (c 1.43, $CHCl_3$); IR (film) 3272, 2109, 1753, 1653, 1239, 1050, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 3H), 2.70 (s, 1H), 3.47 (s, 3H), 4.01 (ddt, 1H, J=7.0, 2.9, 1.5 Hz), 4.26 (ddt, 1H, J=7.0, 2.9, 1.5 Hz), 4.53 (d, 1H, J=6.9 Hz), 5.15 (ddd, 1H, J=10.2, 2.9, 1.5 Hz), 5.23–5.31 (m, 2H), 5.34 (d, 1H, J=4.4 Hz), 5.39 (ddd, 1H, J=10.2, 1.5, 0.7 Hz), 5.47 (dt, 1H, J=17.5, 1.8 Hz), 5.82–6.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.7, 56.6, 67.9, 75.2, 78.8, 79.1, 80.0, 83.1, 102.1, 116.9, 120.1, 133.2, 134.1, 169.9; HRMS (EI) calcd for $C_{14}H_{18}O_5Na$ m/z 289.1052, found m/z 289.1055.

4.3. General procedure for methyl-5,6-deoxy-3-*O*-allyl-3-*C*-ethynyl-2-*O*-tertiary butyl dimethyl silyl-D-*ribo*-hex-5-enofuranosides (32 and 33)

To a solution of alcohols **26** or **27** (0.2 g, 0.89 mmol) in DMF (1.3 ml) was added imidazole (0.182 g, 2.67 mmol), DMAP (cat.) and TBSCl (0.161 g, 1.07 mmol) and the reaction mixture was stirred for 24 h at 40–50 °C. The solution was then diluted with diethyl ether and washed with water and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by column chromatography using 97:3 hexanes/ethyl acetate as eluent to afford the TBS ethers **33** or **32** in excellent yields.

Compound **32**: Yield=94%; R_f=0.53 (4:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +134.71 (c 1.03, $CHCl_3$); IR (film) 3297, 3240, 2245, 1649, 1254, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.93 (s, 9H), 2.66 (s, 1H), 3.46 (s, 3H), 4.22–4.27 (m, 3H), 4.54 (d, 1H, J=6.9 Hz), 4.96 (d, 1H, J=3.9 Hz), 5.11 (ddd, 1H, J=10.6, 3.3, 1.5 Hz), 5.23–5.34 (m, 2H), 5.42 (dt, 1H, J=17.2, 1.8 Hz), 5.86–6.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.7, −4.5, 18.5, 25.9, 56.0, 67.6, 77.7, 78.9, 80.5, 81.1, 83.9, 103.5, 116.2, 118.9, 134.6, 135.1; HRMS (EI) calcd for $C_{18}H_{30}O_4Na$ m/z 361.1811, found m/z 361.1829.

Compound **33**: Yield=96%; R_f=0.47 (4:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +27.94 (c 1.02, $CHCl_3$); IR (film) 3290, 3240, 2240, 1652, 1263, 1088 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 2.65 (s, 1H), 3.48 (s, 3H), 4.12 (d, 1H, J=3.7 Hz), 4.29 (ddd, 2H, J=6.9, 2.9, 1.5 Hz), 4.51 (dt, 1H, J=6.2, 1.2 Hz), 4.84 (d, 1H, J=3.7 Hz), 5.14 (ddd, 1H, J=10.2, 2.7, 1.2 Hz), 5.26–5.33 (m, 2H), 5.46 (dt, 1H, J=17.2, 1.8 Hz), 5.87–6.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.7, 18.1, 25.8, 56.7, 67.7, 78.1, 79.5, 80.6, 82.0, 85.3, 109.0, 116.2, 118.0, 135.1, 135.4; HRMS (EI) calcd for $C_{18}H_{30}O_4Na$ m/z 361.1811, found m/z 361.1821.

4.4. General procedure for tandem enyne/RCM reaction

A 1 mmol portion of dienyne was dissolved in 325 ml of dry dichloromethane under argon/ethylene atmosphere and the solution was degassed. To this was added a dichloromethane solution of Grubbs' catalyst (10 mol % of **15** or 5 mol % of **16**). The reaction mixture was refluxed for 12–48 h as mentioned Tables 1–3. The reaction mixture was cooled to room temperature and DMSO (50 equiv to catalyst) was added and stirred for 6 h. Evaporation of the solvent and purification by column chromatography yielded the corresponding product(s).

4.4.1. Enyne products. *Compound* **24**: Yield=78%; R_f=0.23 (9:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −27.18 (c 1.03, $CHCl_3$); IR (film) 3085, 2987, 2934, 2854, 1643, 1382, 1374, 1088, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.65 (s, 3H), 4.34 (d, 1H, J=3.7 Hz), 4.64–4.7 (m, 3H), 5.22 (d, 2H, J=10.6 Hz,), 5.42 (d, 1H, J=17.2 Hz), 5.58 (dd, 1H, J=17.4, 0.9 Hz), 5.69–5.78 (m, 1H), 5.81 (d, 1H, J=3.7 Hz), 6.08–6.19 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.3, 26.8, 75.0, 81.5, 82.4, 96.3, 103.8, 112.8, 118.7, 119.0, 124.9, 127.7, 132.2, 138.4; HRMS (EI) calcd for $C_{14}H_{18}O_4Na$ m/z 273.1103, found m/z 273.1100.

Compound **29**: Yield=36%; R_f=0.48 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −60.82 (c 1.15, $CHCl_3$); IR (film) 3085, 2926, 2851, 1745, 1234, 1071, 1017 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.13 (s, 3H), 3.55 (s, 3H), 4.32 (d, 1H, J=6.9 Hz), 4.45 (ddd, 1H, J=13.8, 1.8, 0.9 Hz), 4.58 (ddd, 1H, J=13.8, 1.8, 1.2 Hz), 4.97 (d, 1H, J=3.9 Hz), 5.02 (d, 1H, J=3.9 Hz), 5.19–5.24 (m, 2H), 5.37 (ddd, 1H, J=17.1, 3.0, 1.5 Hz), 5.62 (dd, 1H, J=18.0, 0.6 Hz), 5.83 (ddd, 1H, J=17.4, 10.5, 6.9 Hz), 6.01 (br s, 1H), 6.35 (ddd, 1H, J=18.0, 11.4, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7, 57.0, 74.8, 79.0, 85.1, 93.2, 107.1, 117.7, 118.7, 125.1, 128.3, 133.1, 138.7, 169.9; LRMS (EI) [M+Na]$^+$ 289.1233; HRMS (EI) calcd for $C_{14}H_{18}O_5Na$ m/z 289.1052, found m/z 289.1064.

Compound **34**: Yield=40%; R_f=0.39 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +87.42 (c 1.15, $CHCl_3$); IR (film) 3087,

2926, 2851, 1748, 1234, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.15 (s, 3H), 3.47 (s, 3H), 4.62–4.69 (m, 3H), 5.04 (d, 1H, J=4.8 Hz), 5.19–5.26 (m, 3H), 5.35 (dt, 1H, J=17.2, 1.6 Hz), 5.44 (d, 1H, J=18.0 Hz), 5.85–5.94 (m, 1H), 6.03 (br s, 1H), 6.35 (dd, 1H, J=18.0, 11.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7, 55.4, 74.6, 74.7, 84.4, 93.1, 100.8, 117.9, 118.2, 126.9, 128.4, 133.1, 138.8, 170.5; HRMS (EI) calcd for $C_{14}H_{18}O_5Na$ *m/z* 289.1052, found *m/z* 289.1061.

Compound **39**: Yield=63%; R_f=0.43 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −14.99 (*c* 3.00, $CHCl_3$); IR (film) 3434, 2925, 2855, 1454, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.98 (d, 1H, J=7.2 Hz), 3.56 (s, 3H), 3.97 (dd, 1H, J=6.0, 4.39 Hz) 4.39 (d, 1H, J=8 Hz), 4.70 (s, 2H), 4.79 (d, 1H, J=4.4 Hz), 5.216 (t, 2H, J=10.6 Hz), 5.37 (d, 1H, J=17.6 Hz), 5.58 (d, 1H, J=18.0 Hz), 5.81–5.89 (m, 1H), 6.04 (br s, 1H), 6.26 (dd, 1H, J=17.6, 11.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 57.1, 74.5, 85.2, 94.8, 110.1, 118.1, 124.9, 128.1, 133.9, 138.5; HRMS (EI) calcd for $C_{12}H_{16}O_4Na$ *m/z* 247.0946, found *m/z* 247.0949.

4.4.2. Tandem enyne/RCM products. *Compound* **30**: Yield=60%; R_f=0.32 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −109.31 (*c* 1.15, $CHCl_3$); IR (film) 3079, 2933, 1742, 1377, 1242, 1110, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 3.37 (s, 3H), 4.80 (dd, 1H, J=13.5, 2.6 Hz), 4.90 (dd, 1H, J=13.5, 0.7 Hz), 5.03 (br s, 1H), 5.11–5.15 (m, 2H), 5.62 (dd, J=2.1, 1.8 Hz), 6.11 (dd, 1H, J=6.6, 1.5 Hz), 6.31 (dd, 1H, J=6.6, 0.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 55.2, 81.2, 83.0, 87.4, 102.8, 109.8, 115.4, 126.4, 141.4, 146.3, 170.2; LRMS (EI) $[M+Na]^+$ 261.2724; HRMS (EI) calcd for $C_{12}H_{14}O_5Na$ *m/z* 261.0739, found *m/z* 261.0734.

Compound **35**: Yield=58%; R_f=0.13 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ +55.22 (*c* 2.30, $CHCl_3$); IR (film) 3079, 2933, 1742, 1377, 1242, 1110, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 3H), 3.45 (s, 3H), 4.84 (d, 1H, J=2.4 Hz), 4.88 (d, 1H, J=4.0 Hz), 5.03 (br s, 1H), 5.10 (d, 1H, J=4.4 Hz), 5.21 (d, 1H, J=13.5 Hz), 5.71 (dd, 1H, J=2.2, 1.8 Hz), 6.16 (d, 1H, J=5.9 Hz), 6.27 (d, 1H, J=6.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.9, 55.5, 77.4, 82.8, 85.1, 100.5, 103.0, 116.6, 125.9, 140.7, 145.6, 170.7; HRMS (EI) calcd for $C_{12}H_{14}O_5Na$ *m/z* 261.0739, found *m/z* 261.0745.

Compound **36**: Yield=76%; R_f=0.39 (2:1 hexanes/ethyl acetate); mp 96–98 °C; $[\alpha]_D^{25}$ −4.90 (*c* 1.02, $CHCl_3$); IR (in $CHCl_3$) 2951, 2926, 1653, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 3.46 (s, 3H), 4.02 (d, 1H, J=4.4 Hz), 4.74 (d, 1H, J=4.4 Hz),4.80 (d, 1H, J=4.4 Hz), 4.97 (s, 1H), 5.24 (d, 1H, J=13.2 Hz), 5.71 (t, 1H, J=1.8 Hz), 6.14 (d, 1H, J=5.9 Hz), 6.25 (d, 1H, J=5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.9, −4.8, 18.3, 25.8, 55.3, 77.1, 82.6, 85.0, 100.9, 105.1, 116.3, 125.7, 140.9, 146.3; HRMS (EI) calcd for *m/z* $C_{16}H_{26}O_4Na$ 333.1498, found *m/z* 333.1484.

Compound **38**: Yield=68%; R_f=0.29 (2:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −131.02 (*c* 1.02, $CHCl_3$); IR (in $CHCl_3$) 2953, 2926, 1653, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 3.48 (s, 3H), 4.03 (d, 1H, J=6.0 Hz), 4.86 (dd, 1H, J=13.4, 2.4 Hz), 4.90 (s, 1H), 4.95 (d, 1H, J=6.0 Hz), 5.18 (d, 1H, J=13.4 Hz), 5.62 (br s, 1H), 6.22 (AB q, 2H, J=11.6, 6.0 Hz), 6.25 (d, 1H, J=5.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, 18.2, 25.8, 57.1, 80.4, 82.8, 85.6, 102.7, 111.4, 115.0, 125.6, 142.7, 146.5; HRMS (EI) calcd for $C_{16}H_{26}O_4Na$ *m/z* 333.1498, found *m/z* 333.1507.

Compound **37**: Yield=56%; R_f=0.30 (1:1 hexanes/ethyl acetate); mp 112–114 °C; $[\alpha]_D^{25}$ +62.14 (*c* 1.03, $CHCl_3$); IR (in $CHCl_3$) 3447, 3019, 1657, 1217, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.99 (d, 1H, J=12.3 Hz), 3.49 (s, 3H), 4.07 (dd, 1H, J=12.3, 4.5 Hz), 4.82–4.91 (m, 2H), 5.00 (s, 1H), 5.24 (d, 1H, J=13.2 Hz), 5.68 (dd, 1H, J=2.1, 1.8 Hz), 6.12 (d, 1H, J=5.7 Hz), 6.27 (d, 1H, J=5.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.7, 76.7, 83.3, 85.3, 101.1, 104.5, 115.8, 125.9, 140.6, 145.6; HRMS (EI) calcd for $C_{10}H_{12}O_4Na$ *m/z* 219.0633, found *m/z* 219.0639.

Compound **40**: Yield=18%; R_f=0.33 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ −207.69 (*c* 1.04, $CHCl_3$); IR (in $CHCl_3$) 3443, 3033, 1656, 1115, 1021 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.38 (s, 3H), 4.04 (dd, 1H, J=6.8, 2.2 Hz), 4.90 (dd, 2H, J=13.2, 2.4 Hz), 4.94 (d, 1H, J=2.2 Hz), 5.02 (s, 1H), 5.12 (d, 1H, J=13.6 Hz), 5.58 (s, 1H), 6.15 (d, 1H, J=5.8 Hz), 6.26 (d, 1H, J=5.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.5, 80.8, 82.7, 86.4, 102.9, 112.4, 113.7, 125.7, 142.8, 147.1; HRMS (EI) calcd for $C_{10}H_{12}O_4Na$ *m/z* 219.0633, found *m/z* 219.0638.

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