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C-Glycosides to fused polycyclic ethers

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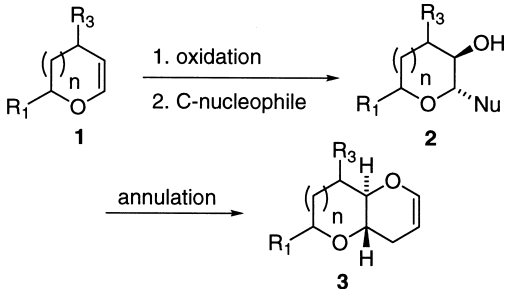
Abstract—This manuscript describes the synthesis of fused polycyclic ethers from the coupling of *C*-glycoside forming reactions with ring closing metathesis and acid mediated annulation reactions.

1. Introduction

The high degree of structural regularity present in the marine ladder toxins (cf. hemibrevetoxin B and gambierol) (Fig. 1) has influenced many,[1–6] including us,[7] to believe that an iterative approach to their synthesis might be ideal. With this in mind, over the last several years we have focused our attention on the development of an iterative strategy to these agents that couples the formation of *C*-glycosides from cyclic enol ethers with acid or metathesis based cyclizations (Scheme 1).

From our perspective it was clear that the *C*-glycoside chemistry (i.e. **1**→**2**) was critical to the success of this venture as it would not only incorporate many of the requisite atoms but it would also result in the generation of the ring junction stereocenters. Out of a desire to develop a flexible *C*-glycoside strategy that would also address these issues, we decided to concentrate on an enol ether oxidation, nucleophilic addition sequence.[8,9] Outlined herein is a full report of our efforts targeting the formation of *C*-glycosides in model systems and their use in the synthesis of fused polycyclic ethers.



Scheme 1.

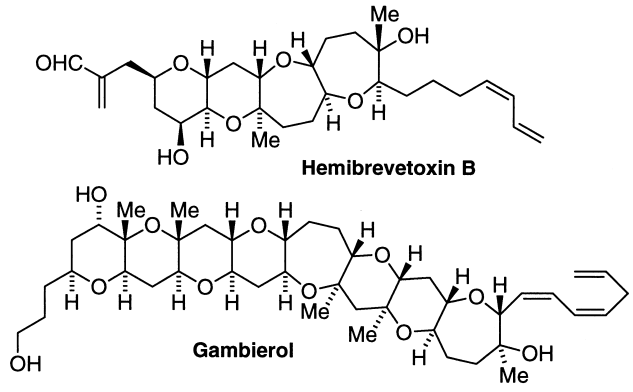


Figure 1.

2. Results and discussion

2.1. 1,2-Anhydrosugars in the synthesis of β-*C*-glycosides

Since there were a number of questions concerning the proposal outlined in Scheme 1, we decided to initially examine the formation of *C*-glycosides and bicyclic enol ethers from glucal anhydride **5** as a model substrate. Not only had Danishefsky utilized **5** in the synthesis of oligosaccharides[10,11] but Kishi and Czernecki had independently demonstrated that this and related epoxides were effective substrates for the synthesis of methyl, phenyl, and allyl-β-*C*-glucosides.[12] As illustrated in Tables 1 and 2, we have expanded upon these studies by exploring the scope of the reactions of nucleophiles with **5**.[7a,b,13]

Following the formation of **5** using Danishefky's conditions and dimethyl dioxirane,[11,14] we examined its conversion into β-*C*-glycosides (Table 1). We found that careful attention to the counterion on the nucleophile and the temperature used during the addition were essential for successful β-addition.[15] For example, while acetal Grignard

Keywords: *C*-glycosides; polycyclic ethers; annulation reactions.

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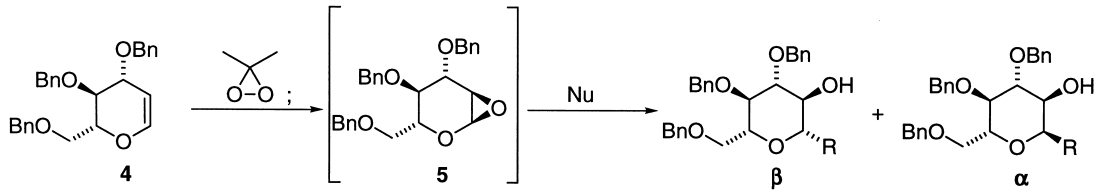
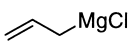
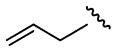
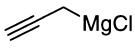
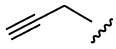
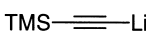
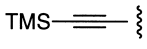
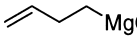
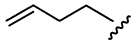
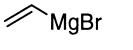
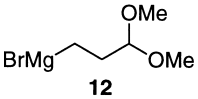
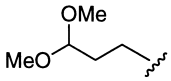
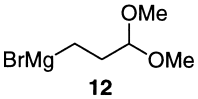
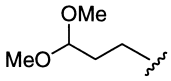
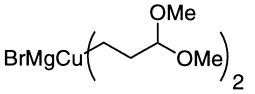
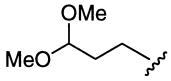
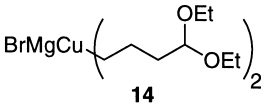
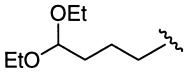
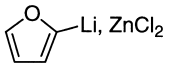
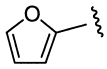
Table 1.



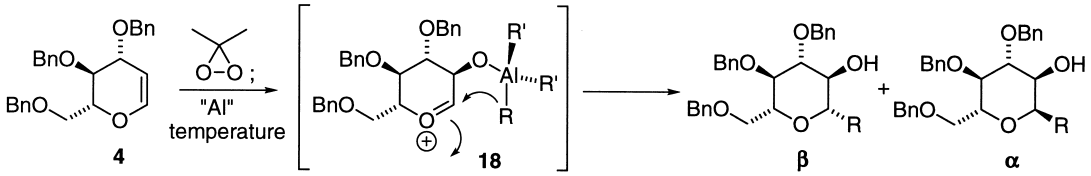
Entry	Nu	Temperature	R	Product	β/α	Yield (%)
1	Me_2CuLi	0°C	Me	**6**	1:0	82
2		0°C		**7**	1:0	82
3		0°C		**8**	1:0	78
4		0°C		**9**	0:1	80
5		−60→0°C		**10**	1:1	80
6		−0°C		**11**	1:1	–[a]
7		−40°C		**11**	1:0	57
8		−0°C		**13**	1:1	51
9		−40°C		**13**	1.7:1	29
10		−30°C		**13**	6:1	74
11		−0°C		**15**	5:1	65
12	PhMgCl	−60°C		**16**	1:1	78
13	Ph_2CuLi	0°C		**16**	1:0	84
14		−60°C→rt		**17**	1:0	78

[a] Yield was not obtained after the crude ^1H NMR spectrum indicated a 1:1 α/β mixture.

12[16] gave 1:1 mixtures of α- and β-*C*-glycosides **13**, the corresponding cuprate gave a 6:1 mixture of products favoring the β-isomer (entries 8–10). Similar results were observed with phenyl magnesium chloride and lithium diphenyl cuprate; phenyl magnesium chloride gave a 1:1 mixture of α- and β-*C*-glycosides while lithium diphenyl cuprate gave exclusively β-*C*-glycoside **16** (entries 12 and 13). With respect to temperature, addition of vinyl magnesium bromide at 0°C resulted in the formation of a 1:1 mixture of α- and β-*C*-glycosides **11** (entry 6). By simply lowering the temperature of the addition to −40°C we were able to isolate a 57% yield of β-vinyl glycoside **11** (entry 7). We propose that the temperature and counterion dependence of these coupling reactions are related to the presence of oxocarbenium ions. At higher temperatures and with some nucleophiles, oxocarbenium ion formation occurs; apparently the addition of most nucleophiles to the oxocarbenium ion from **5** is not selective. Particularly noteworthy is that these coupling reactions are efficient and flexible; both the oxidation and nucleophilic additions are carried out in the same flask. This allows one to avoid the isolation and handling of potentially labile glycosides having anomeric leaving groups.

A number of other nucleophiles also coupled with **5** to give exclusively or predominantly β-*C*-glycosides. 2-Furyl lithium in the presence of $ZnCl_2$ (entry 14),[17] propenyl magnesium chloride (entry 2),[7,8] propargyl magnesium chloride (entry 3), lithium dimethyl cuprate (entry 1), and diethyl acetal cuprate **14**[18] (entry 11) all underwent stereoselective coupling with **5** to give **17**, **7**, **8**, **6**, and **15**, respectively. These reactions have proven to be somewhat dependent upon the substrate used. For example, in contrast to the nucleophiles mentioned earlier, we have been unable to selectively generate β-*C*-glycosides from the coupling of butenyl and ethynyl nucleophiles with **5**. Thus far, these

Table 2.



Entry	'Al'	Al (equiv.)	Temperature	R	Product	β/α	Yield (%)
1	$AlMe_3$	3	−95°C	Me	**6**	0:1	82
2	Me_2Al—≡—TMS **19**	3	−95°C	—≡—TMS	**9**	0:1	80
3	Me_2Al **20**	3	−65°C		**11**	0:1	24[a]
4	Me_2Al **20**	3	−65°C→rt		**11**	0:1	40[b]
5	$Al(\sim)_3$	3	−65°C→rt		**11**	0:1	59[c]
6	$Al(\sim)_3$	6	−65°C→rt		**11**	0:1	76[d]
7	$AlPh_3$	6	−65°C→rt		**16**	0:1	79
8	$Al(O)_3$	6	−65°C→rt		**17**	0:1	85
9	$Al(\sim)_3$	6	0°C		**7**	1:2.3	73

[a] Major products were methyl glycoside **6** (40%) and anomeric chloride and/or diol from hydrolysis of the epoxide or anomeric chloride upon workup.
[b] Major by-product was methyl glycoside **6** (44%).
[c] Major by-product was glycosidic dimer resulting from alkoxy transfer.
[d] Inverse addition, see text.

have given either 1:1 mixtures of α- and β-*C*-glycosides (butenyl, entry 5) or exclusively α-*C*-glucoside (ethynyl, entry 4).[19]

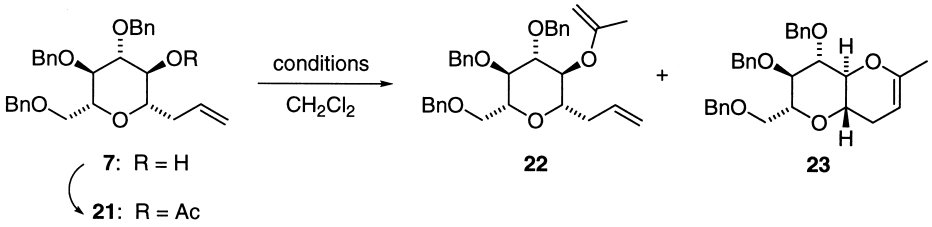
2.2. 1,2-Anhydrosugars in the synthesis of α-*C*-glycosides

Having established that a number of carbon nucleophiles are capable of coupling with **5** to provide β-*C*-glycosides, we directed our attention to the formation of the corresponding α-*C*-glycosides. It occurred to us that aluminum or boron nucleophiles might add to **5** in a *syn* fashion through the directed transfer of the nucleophile to an oxocarbenium ion intermediate. Not only would the success of these experiments enable us to tackle the synthesis of *cis*-fused polycyclic ethers as are present in a number of interesting natural products (e.g. the halichondrins[20]) but they would also provide us with unprecedented flexibility in the synthesis of *C*-glycosides. That is, if successful these experiments would enable us to convert a single glycosyl donor (glycal anhydride) into a variety α- or β-*C*-glycosides by simply changing the counterion on the carbon nucleophile.[21]

With these goals in mind we examined the reaction of Me_3Al with **5** and were pleased to find that they coupled to provide α-*C*-glucoside **6** (Table 2, entry 1).[22] To our delight, we were also able to couple other aluminum nucleophiles with **5**. TMS–acetylene was transferred to **5** from dimethyl aluminum acetylene **19**[23] at −95°C in high yield (entry 2). Competitive methyl transfer was not observed at this temperature. In contrast to this result, methyl transfer was competitive with vinyl transfer from dimethylvinyl aluminum **20** at the temperatures required for the reaction to occur (entries 3 and 4). These problems were circumvented by turning to trivinyl aluminum and by using an inverse mode of addition (addition of epoxide to excess trivinyl aluminum, entries 5 and 6). By using conditions optimized for the transfer of vinyl, we were able to also couple phenyl and furyl aluminum reagents with **5** to give α-*C*-glycosides **16** and **17**.[17] In contrast to the other reagents, the transfer of allyl from triallyl aluminum was problematic. When epoxide **5** was exposed to triallyl aluminum we isolated a 73% yield of an α,β-mixture favoring α-*C*-glucoside **7**.

It was our belief that β-*C*-allyl glucoside **7** from the triallyl aluminum reaction was the result of an intermolecular transfer of allyl from aluminum to the epoxide and that this was a consequence of our inability to purify triallylaluminum. In an effort to circumvent this problem we turned to triallylborane (Eq. (1)). Not insignificant to the choice of this reagent was the knowledge that triallylborane can be purified.[24] To our delight, exposure of **5** to triallylborane

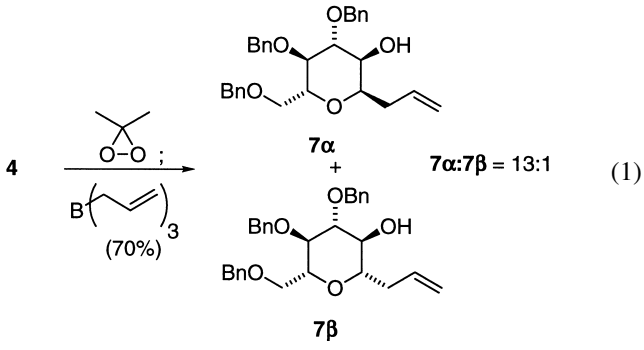
Table 3.



Entry	$TiCl_4$[a]	Zn[a]	$PbCl_2$[a]	CH_2Br_2[a]	**21** (M)	CH_2Cl_2/THF/TMEDA	Time (h)	**22**	**23**
1	4	9	0.045	2.2	0.098	1:3.5:0.6	3.0	0	0
2	16	36	0.18	8.8	0.020	1:6:0.3	0.5	65	15
3	6	13	0.72	6	0.006	16:1:1	0.5	30	50

[a] Amounts refer to equivalents relative to **21**.

resulted in a 70% yield of **7** as a 13:1 mixture of α- and β-*C*-glycosides.



(1)

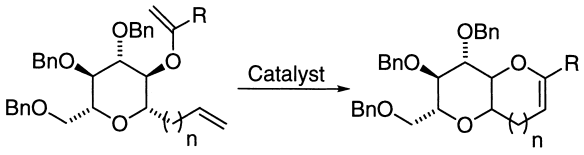
2.3. Ring closing metathesis to bicyclic enol ethers

Having overcome the challenges associated with the synthesis of *C*-glycosides, we were prepared to examine the annulation chemistry. As mentioned previously, we were interested in carrying out the transformation of *C*-glycoside **2** into cyclic enol ether **3** through the use of either ring closing metathesis (RCM) chemistry[7a,c,d,25,26] or acid mediated cyclizations and elimination reactions.[7b–d,27,28]

We initially targeted RCM reactions of the enol ethers from β-allylglycoside **7** and β-homoallylglycoside **10**.[29] Following the conversion of **7** into the corresponding acetate **21**, we examined acyclic enol ether formation using Takai's reduced Ti protocol (Table 3).[30] Interestingly, the use of 4 equiv. of the reduced Ti reagent resulted in the complete recovery of starting material (entry 1). From the notion that the oxygen atoms present in **21** might have been interfering with the ability of the Ti alkylidene reagent to react with the ester, we increased the amount of reagent four-fold. This change led, not only to the formation of the desired acyclic enol ether **22** in 65% yield, but also to the formation of cyclic enol ether **23** in 15% yield (entry 2). We subsequently found that by decreasing the concentration of **21** and increasing the relative amount of $PbCl_2$ that we could increase the cyclic enol ether to acyclic enol ether ratio (entry 3).[31] Thus far however, we have been unable to find conditions to drive the reaction completely to cyclic enol ether **23**.

It was not completely surprising that the use of Takai's reagent resulted in the formation of **23**; first Grubbs[32] and subsequently Nicolaou[33] had independently reported that other reduced Ti reagents (i.e. the Tebbe and Petasis reagents) gave cyclized material when exposed to olefins having pendant esters. Nicolaou's results were of particular interest to us as they involved the formation of fused polycyclic enol ethers and were shown to result from an enol ether–olefin RCM sequence. In contrast, cyclized products from the use of the Takai reagent appear to result from olefin metathesis, carbonyl olefination reactions as all attempts to convert acyclic enol ether **22** into cyclic enol ether **23** using our revised Takai protocol have failed.[34] We currently believe that the Takai reagent competitively reacts with either the olefin or the ester. If the initial coupling occurs at the olefin, a metathesis reaction provides the corresponding titanium alkylidene; a subsequent carbonyl olefination provides cyclic enol ether. On the other hand, reaction with the ester results in formation of the acyclic enol ether.

Table 4.



Entry	n	R	Starting material	Catalyst	Product	Yield (%)
1	1	Me	**22**	**32**	**23**	87
2	1	Me	**22**	**33**	**23**	85
3	1	Me	**22**	**34**	**23**	–[a]
4	1	H	**28**	**32**	**29**	85
5	2	Me	**26**	**33**	**31**	78

[a] Resulted in the recovery of starting material.

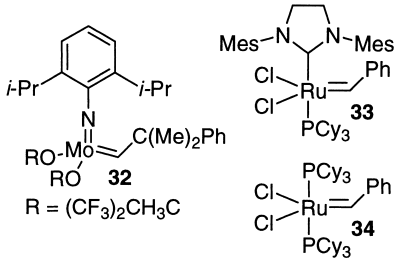
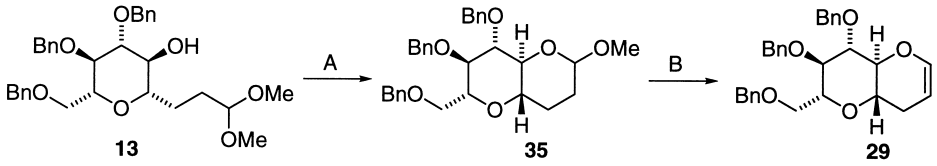
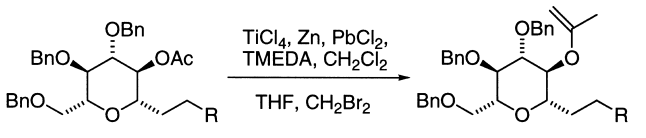


Table 5.



Entry	A	Yield (%)	B	Yield (%)
1	TMSOTf, CH_2Cl_2, −65°C	56	TMSOTf, NEt_3, CH_2Cl_2, 40°C, 14 h	50
2	TMSOTf, CH_2Cl_2, −65°C	56	PPTS, pyridine, PhCl, 60→140°C, 6 h	91

Interestingly, when the homoallyl glycoside **24** was exposed to the Takai reagent we observed no products resulting from cyclization and instead isolated enol ether **26** in yields that varied from 50–76% (Eq. (2)). In an effort to demonstrate that the capricious nature of this reaction was due to the presence of the pendant olefin, we subjected TIPS ether **25**[35] to the enol ether forming conditions. This resulted in the formation of enol ether **27** in a reproducible 78% yield.



24: R = $CHCH_2$
25: R = CH_2OTIPS
26: R = $CHCH_2$, yield = 50-76%
27: R = CH_2OTIPS, yield = 78%

(2)

That the Takai protocol provided a mixture of cyclic and acyclic enol ethers in the reaction with **21** was of little consequence as the mixture could be converted into cyclic enol ether **23** by subjecting the mixture to Schrock's molybdenum alkylidene catalyst **32**[36] or to the second generation Grubbs' Ru alkylidene catalyst **33** (Table 4, entries 1–3).[37] As depicted, we were also able to convert α-unsubstituted acyclic enol ether **28**[7a] into the corresponding α-unsubstituted dihydropyran **29** using **32** (entry 4). Alkylidene **33** also catalyzed the formation of oxepene **31** from enol ether **26** in 78% yield. This result nicely illustrates the versatility of **33**; we[38] and others[26b] have had difficulty using alkylidene **32** to catalyze enol ether–olefin RCM to form cyclic enol ethers larger than dihydropyrans having synthetically useful substitution about the cyclic enol ether.

2.4. Acid mediated cyclizations and eliminations to bicyclic enol ethers

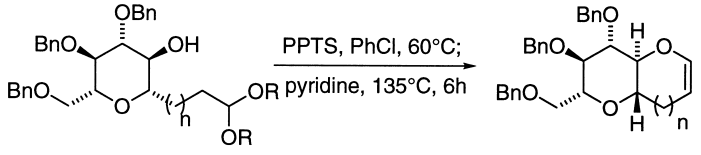
We have also investigated a complementary approach to cyclic enol ethers that employs acid mediated cyclizations and eliminations (Table 5).[7b–d] Our initial experiments examined the stepwise conversion of **13** into **29**. When **13** was exposed to TMSOTf we were able to isolate mixed acetal **35** in 56% yield.[39] In a subsequent reaction, we found that we could convert the acetal to the enol ether by subjecting **35** to either TMSOTf and NEt_3[40] or PPTS and pyridine.[27]

Bicyclic enol ether **29** could be formed more efficiently if both the acetal formation and the elimination reaction were carried out in a single flask (Table 6). Optimized conditions involved heating hydroxy acetal **13** to 60°C in the presence of PPTS; following the complete decomposition of starting material by TLC, pyridine was added to the reaction flask and the reaction was heated to 135°C. This protocol resulted in the formation of bicyclic dihydropyran **29** in 91% yield. Not surprisingly, this reaction was also amenable to the formation of rings larger than dihydropyrans. For example, when **15** was subjected to PPTS, pyridine, and heat we isolated bicyclic oxepene **36** in 72% yield.

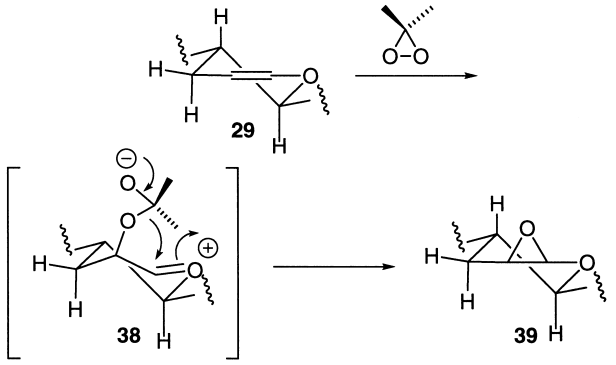
2.5. *C*-Glycosides from bicyclic enol ethers

Having established the synthesis of bicyclic enol ethers and therefore the completion of one iterative cycle, we decided to further test our strategy by carrying out a second iteration using **29**. While it was not clear to us what the selectivity in the epoxidation of **29** would be, we were hopeful that dioxirane would add to the same face as the C5 hydrogen (Eq. (3)). If this hypothesis proved accurate and we were subsequently able to add *C*-nucleophiles to the resulting

Table 6.

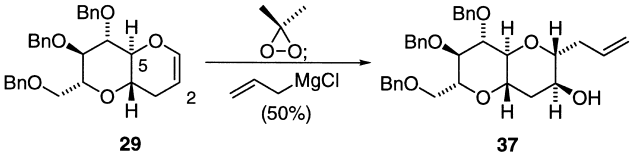


Entry	n	Starting material	R	Product	Yield (%)
1	1	**13**	Me	**29**	91
2	2	**15**	Et	**36**	72



Scheme 2.

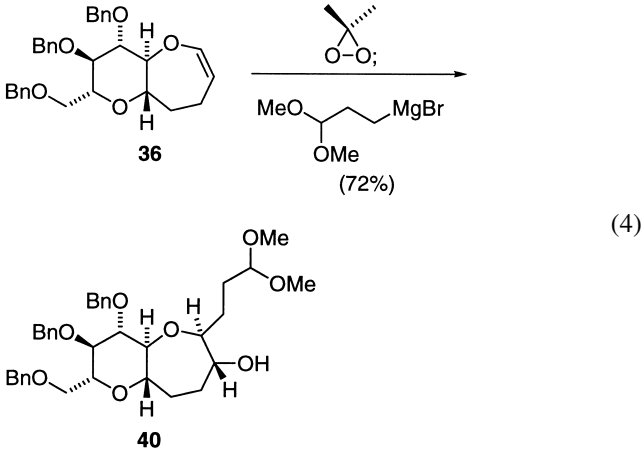
epoxide, we would have a direct access to the *trans–syn–trans* relative stereochemistry of the marine ladder toxins. However, when **29** was exposed to dimethyl dioxirane followed by propenyl magnesium chloride at −60°C we isolated *trans–anti–trans* glycoside **37** in relatively low yield.[41]



(3)

The selectivity in the epoxidation of **29** can be rationalized if one assumes an asynchronous bond forming event where bond formation at the β-carbon of the enol ether is faster than bond formation at the α-carbon (Scheme 2). With this, attack from the upper face proceeds through a 'pseudo-chair' transition state (i.e. **38**) to give **39**.

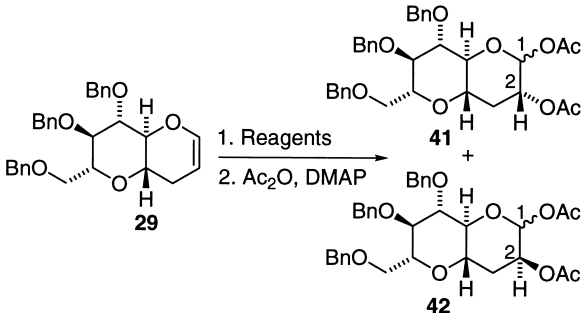
Interestingly, the epoxidation and C–C bond forming chemistry on bicyclic oxepene **36** resulted in the formation of *trans–syn–trans* isomer **40** in 72% yield (Eq. (4)). Presently, the reasons for the discrepancy between the *C*-glycoside forming reaction of **29** and **36** are not clear.



(4)

In an effort to generate the *trans–syn–trans* isomer from bicycle **29** as required by the marine ladder toxin architecture, we investigated other enol ether oxidation protocols.[42]

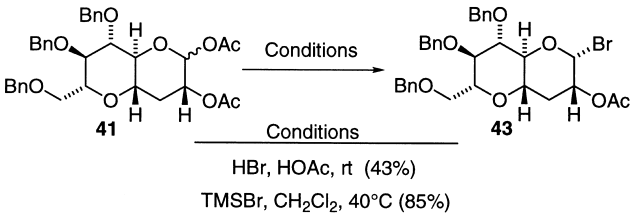
Table 7.



Entry	Reagents	41/42	Yield (%)
1	AD mix-α	12:1	88
2	AD mix-β	3:1	88
3	$K_2OsO_4{\cdot}H_2O$ (cat), $KFe(CN)_6$, K_2CO_3	4:1	77

Of particular relevance to our work was a report from the Nicolaou laboratories that described the use of OsO_4 to overcome an undesired stereochemical outcome in the hydroboration of a cyclic enol ether.[33a] Gratifyingly, OsO_4 approached **29** from the opposite face of the enol ether when compared with dimethyl dioxirane. That is, treatment of **29** with OsO_4 provided a 4:1 mixture of C2 diastereomers (Table 7, entry 3). In an attempt to optimize the **41/42** ratio, **29** was exposed to the Sharpless asymmetric dihydroxylation (AD) protocol.[43] Interestingly, both AD mix-α and AD mix-β gave the *trans–syn* isomer **41** as the major product.[44] As had also been observed by Nicolaou, AD mix-α gave the highest selectivity for the formation of the desired diol **41** (entry 1).

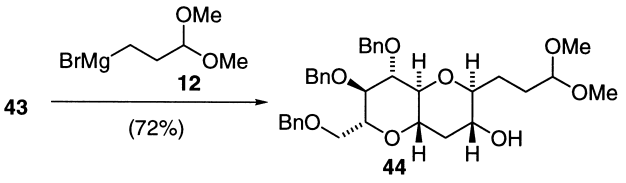
Having overcome the oxidation of **29**, the next challenge that we faced was the conversion of **41** into the corresponding *C*-glycoside. From the various possibilities, we decided to examine the displacement of an anomeric bromide (e.g. **43**) with a carbon nucleophile.[45] Towards this end, we set out to generate the anomeric bromide from **41** (Eq. (5)). Because of relatively low yields using HOAc, HBr to generate **43** from **41**, we investigated other means of carrying out this transformation. We were pleased to find that we could isolate bromide **43** in 85% yield as a single diastereomer by exposing **41** to TMSBr and CH_2Cl_2 at reflux.[46]



(5)

With bromide **43** in hand, we studied its conversion into the corresponding *C*-glycoside (Eq. (6)). The displacement of the bromide in **43** using acetal Grignard **12** provided *trans–syn–trans* diastereomer **44** in 72% yield. An added benefit to the use of **12** was that the C2 acetate had also been removed in the course of the reaction. Thus, we were now

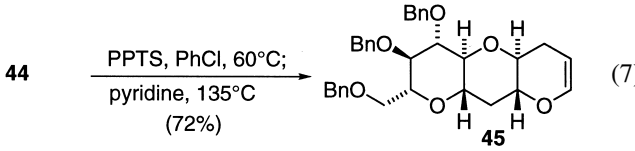
positioned to convert **44** into the correponding tricycle (vide infra).



(6)

2.6. Acid mediated cyclizations to tricylic enol ethers

By simply subjecting bicyclic *C*-glycoside **44** to PPTS, pyridine and heat, we were able to efficiently convert it into tricyclic enol ether **45**.



(7)

3. Conclusion

To conclude, we have developed a relatively efficient and flexible approach to fused polycyclic ethers that couples the synthesis of *C*-glycosides with enol ether–olefin RCM reactions and/or acid mediated cyclizations. We are continuing to optimize these approaches in model systems and to apply them in the synthesis of members of the marine ladder toxin family of natural products.

4. Experimental

4.1. General

NMR spectra were recorded on either a Bruker EM-600, Bruker EM-500, Bruker AM-250, or a Varian 300 spectrometer. Chemical shifts were reported in δ, parts per million (ppm), relative to chloroform (δ=7.24 ppm) as an internal standard. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Optical rotation was recorded on a JASCO P-1020 spectrometer. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Arizona on a Jeol HX-110A and are reported as percent relative intensity to the molecular base peak. IR spectra were recorded on a Nicolet Impact 410. Ether and THF were distilled from sodium/benzophenone. CH_2Cl_2, $CHCl_3$, hexanes, benzene, toluene, TMEDA, $(i\text{-Pr})_2NEt$, Et_3N, and Et_2NH were distilled from CaH_2. All other reagents were used without purification. Unless otherwise stated, all reactions were run under an atmosphere of argon in flame-dried glassware. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20 mmHg) with a Büchi Rotavapor. Characterization data for compounds **6**–**15**, **21**–**23**, **28**, **29**, **36**, and **37** have been reported elsewhere.[7,10]

4.2. Representative procedure for the epoxidation and the subsequent addition of *C*-nucleophiles to 5

4.2.1. (2β,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-6-benzyloxymethyl-2-methyl-tetrahydro-pyran-3-ol 6. To a solution of tri-*O*-benzyl-D-glucal (0.05 g, 0.12 mmol) and CH_2Cl_2 at 0°C was added dimethyldioxirane (1.8 mL of a 0.1 M solution in acetone, 0.18 mmol) dropwise. After stirring for 10 min, the reaction mixture was concentrated. The resulting white solid was taken up in THF (1.5 mL) and cooled to 0°C. To this solution was added Me_2CuLi (2.2 mL of a 0.27 M solution in THF, 0.60 mmol; prepared from the addition of MeLi (1.8 mL of a 1.2 M solution in hexanes, 2.1 mmol) to a slurry of CuI (0.20 g, 1.0 mmol) and THF (3.9 mL) at 0°C). The reaction was allowed to warm to rt over 1 h and was then quenched with sat. NH_4Cl (aq., 2 mL). After stirring for 0.5 h, the mixture was extracted with ether (5×5 mL). The extracts were washed with brine (1×5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) afforded 44 mg (82%) of *C*-glycoside **6** as a white solid. mp 66–68°C; $[\alpha]_D^{29}$=+42.51 (*c*=1.70, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 7.37–7.26 (m, 13H), 7.19–7.17 (m, 2H), 4.96 (d, *J*=11.6 Hz, 1H), 4.79 (d, *J*=10.8 Hz, 1H), 4.73 (d, *J*=11.6 Hz, 1H), 4.63 (d, *J*=12.2 Hz, 1H), 4.56 (d, *J*=10.3 Hz, 1H), 4.55 (d, *J*=12.2 Hz, 1H), 3.73–3.66 (m, 2H), 3.62 (dd, *J*=9.4, 9.4 Hz, 1H), 3.48–3.43 (m, 2H), 3.33–3.28 (m, 1H), 3.23 (dd, *J*=9.0, 9.0 Hz, 1H), 2.10 (s, 1H), 1.31 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.1, 138.0, 128.7, 128.4, 128.4, 128.0, 127.8, 127.7, 86.7, 78.9, 78.6, 75.6, 75.5, 75.1, 74.8, 73.5, 69.1, 18.0; IR (neat) 3454, 1109 cm^{-1}; MS (FAB^+) 449, HRMS calcd for $C_{28}H_{33}O_5$ (MH^+) 449.2328, found 449.2332.

4.2.2. (2β,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-6-benzyloxymethyl-2-(prop-2-ynyl)-tetrahydro-pyran-3-ol 8. To a solution of anhydride **5** (0.36 mmol) and CH_2Cl_2 (4.5 mL) at 0°C was added propargylmagnesium chloride (0.75 mL of a 1.2 M solution in THF, 0.90 mmol). After stirring for 10 min, the reaction was quenched with sat, aq. NH_4Cl (5 mL). The mixture was extracted with ether (5×5 mL), washed with brine (1×20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (5:1 hexanes: ethyl acetate) to afford 132 mg (78%) of alcohol **8** as a colorless oil. $[\alpha]_D^{29}$=+35.4 (*c*=0.640, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.42–7.24 (m, 13H), 7.22–7.21 (m, 2H), 4.98 (d, *J*=11.5 Hz, 1H), 4.83 (d, *J*=11.1 Hz, 1H), 4.78 (d, *J*=11.7 Hz, 1H), 4.70 (d, *J*=12.2 Hz, 1H), 4.62 (d, *J*=10.8 Hz, 1H), 4.61 (d, *J*=12.1 Hz, 1H), 3.78–3.49 (m, 6H), 3.48–3.43 (m, 1H), 2.72 (dddd, *J*=16.7, 3.2, 3.2, 1.0 Hz, 1H), 2.58 (ddd, *J*=17.2, 5.8, 2.7 Hz, 1H), 2.38 (br s, 1H), 2.04 (dd, *J*=2.6, 2.6 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.7, 138.4, 138.2, 128.8, 128.6, 128.5, 128.1, 128.0, 128.0, 127.7, 86.6, 80.7, 79.5, 78.4, 77.8, 77.3, 77.1, 75.4, 75.0, 73.6, 73.1, 70.4, 68.9, 22.2; IR (CCl_4) 3571, 3310, 2864, 1448, 1100 cm^{-1}; MS (FAB^+) 473 (MH^+), HRMS calcd for $C_{30}H_{32}O_5$ (MH^+) 473.2328, found 473.2329.

4.2.3. (2β,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-6-benzyloxymethyl-2-vinyl-tetrahydro-pyran-3-ol 11. To a solution of anhydride **5** (0.24 mmol) and CH_2Cl_2 at −60°C was added vinylmagnesium bromide (0.48 mL of a 2.0 M

solution in THF, 0.96 mmol). After stirring for 10 min, the reaction was quenched with sat, aq. NH_4Cl (2 mL). The mixture was extracted with ether (5×5 mL), washed with brine (1×5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) gave 69 mg (57%) of vinyl-*C*-glycoside **11** as a colorless oil. $[\alpha]_D^{29}$=+22.0 (*c*=0.415, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33–7.24 (m, 13H), 7.14–7.13 (m, 2H), 5.76 (ddd, *J*=17.3, 10.2, 7.2 Hz, 1H), 5.27 (d, *J*=17.2 Hz, 1H), 5.19 (d, *J*=10.8 Hz, 1H), 4.90 (dd, *J*=9.3, 9.3 Hz, 1H), 4.79 (d, *J*=11.0 Hz, 1H), 4.77 (d, *J*=10.0 Hz, 1H), 4.66 (d, *J*=11.5 Hz, 1H), 4.60 (d, *J*=12.2 Hz, 1H), 4.53 (d, *J*=10.9 Hz, 2H), 3.74–3.64 (m, 5H), 3.48 (ddd, *J*=7.3, 3.9, 2.2 Hz, 1H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 138.4, 138.1, 138.0, 134.4, 128.4, 128.4, 128.0, 127.8, 127.7, 127.7, 127.6, 119.1, 84.2, 79.9, 79.0, 78.1, 75.1, 73.5, 73.2, 68.8, 21.0; IR (CCl_4) 2858, 1758, 1375, 1233, 1110 cm^{-1}; MS (FAB^+) 503 (MH^+), 501, 91 *m/z*, HRMS calcd for $C_{31}H_{35}O_6$ (MH^+) 503.2434, found 503.2439.

4.2.4. (2β,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-6-benzyloxymethyl-2-phenyl-tetrahydro-pyran-3-ol 16. To a solution of anhydride **5** (0.12 mmol), and ether (2.0 mL) at 0°C was added Ph_2CuLi (1.3 mL of a 0.23 M solution in ether, 0.30 mmol; prepared from the addition of PhLi (0.33 mL of a 1.8 M solution in hexanes, 0.6 mmol) to CuI (0.057 g, 0.30 mmol) in ether (1 mL) at 0°C). After stirring for 10 min, the reaction was quenched with sat, aq. NH_4Cl (2 mL). After an additional 0.5 h, the mixture was extracted with ether (5×5 mL), washed with brine (1×5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) afforded 52 mg (84%) of phenyl-*C*-glycoside **16** as a colorless oil. $[\alpha]_D^{29}$=+22.7 (*c*=1.35, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.27 (m, 20H), 4.98 (d, *J*=11.4 Hz, 1H), 4.92 (d, *J*=10.6 Hz, 1H), 4.91 (d, *J*=11.4 Hz, 1H), 4.70 (d, *J*=10.6 Hz, 1H), 4.69 (d, *J*=12.2 Hz, 1H), 4.60 (d, *J*=12.2 Hz, 1H), 4.20 (d, *J*=9.2 Hz, 1H), 3.85–3.80 (m, 3H), 3.73 (dd, *J*=8.8, 8.8 Hz, 1H), 3.67–3.64 (m, 2H), 1.92 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 138.5, 138.3, 138.2, 128.5, 128.5, 128.4, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 127.5, 127.4, 86.4, 82.1, 79.5, 78.1, 75.8, 75.3, 75.0, 73.5, 69.1; IR (neat) 3446, 1092 cm^{-1}; MS (FAB^+) 511, HRMS calcd for $C_{33}H_{35}O_5$ (MH^+), 511.2484, found 511.2495.

4.2.5. (2β,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-6-benzyloxymethyl-2-(furan-2-yl)-tetrahydro-pyran-3-ol 17. To a solution of anhydride **5** (0.12 mmol) and ether (2.0 mL) at −60°C was added $ZnCl_2$ (0.018 g, 0.13 mmol) followed by 2-lithiofuran (1.0 mL of a 0.6 M solution in ether, 0.6 mmol). After warming to rt over 2 h, the reaction was quenched with 0.5 M HCl (aq., 2 mL). After stirring for 0.5 h, the mixture was extracted with ether (5×5 mL), washed with brine (1×5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) afforded 47 mg (78%) of furyl *C*-glycoside **17** as a colorless oil. $[\alpha]_D^{29}$=+21.6 (*c*=1.40, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.25 (m, 16H), 7.23–7.17 (m, 1H), 6.42–6.35 (m, 1H), 4.93 (d, *J*=11.5 Hz, 1H), 4.85 (d, *J*=11.5 Hz, 1H), 4.84 (d, *J*=10.7 Hz, 1H), 4.59 (d, *J*=12.2 Hz, 1H), 4.58 (d, *J*=9.0 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 4.26 (d, *J*=9.8 Hz, 1H), 3.95 (dd, *J*=9.5, 9.5 Hz, 1H), 3.75 (dd, *J*=11.0, 2.2 Hz, 1H), 3.74–3.71 (m, 1H), 3.71 (dd, *J*=9.3 Hz, 1H), 3.62 (dd, *J*=8.9 Hz, 1H), 3.59 (partially obscured ddd, *J*=9.3, 4.0, 2.3 Hz, 1H), 2.02 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 142.9, 138.6, 138.1, 138.0, 128.6, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.6, 110.4, 109.6, 86.4, 79.4, 77.9, 75.3, 75.0, 73.5, 72.7, 68.9; IR (neat) 3472, 1109 cm^{-1}; MS (FAB^+) 501, HRMS calcd for $C_{31}H_{33}O_6$ (MH^+) 501.2277, found 501.2289.

4.2.6. (2β,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-6-benzyloxymethyl-2-(4,4′-diethyloxybutyl)-tetrahydro-pyran-3-ol 15. To a solution of anhydride **5** (0.48 mmol) and THF (5 mL) at 0°C was added a solution of cuprate **14** (prepared from 1-bromo-4,4-diethoxybutane (0.54 mL, 2.4 mmol), Mg (0.12 g, 4.8 mmol), CuI (0.23 g, 1.2 mmol), and THF (10 mL)). After 15 min, the reaction was quenched with aq. NH_4Cl (sat., 15 mL), extracted with ether (3×20 mL), washed with brine (2×50 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (2:1 hexanes/ethyl acetate) afforded 0.18 g (65%) of alcohol **15** as a colorless oil. The alcohol was characterized as the corresponding acetate.

To a solution of alcohol **15** (0.040 g, 0.069 mmol) and CH_2Cl_2 (3.0 mL) was added *i*-Pr_2NEt (0.096 mL, 0.41 mmol), Ac_2O (0.039 mL, 0.41 mmol), and DMAP (ca. 0.005 g). After stirring for 1 h, the reaction mixture was quenched with sat. $NaHCO_3$ (aq., 5 mL). Following extraction with CH_2Cl_2 (3×10 mL), the extracts were washed with brine (1×10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) gave 38 mg (89%) of acetate **15b** as a colorless oil. Acetate of **15b**: $[\alpha]_D^{29}$=+5.6 (*c*=0.50, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (m, 13H), 7.20–7.18 (m, 2H), 4.89 (dd, *J*=9.3, 9.3 Hz, 1H), 4.82 (d, *J*=11.5 Hz, 1H), 4.79 (d, *J*=10.8 Hz, 1H), 4.67 (d, *J*=11.4 Hz, 1H), 4.63 (d, *J*=12.2 Hz, 1H), 4.57 (d, *J*=10.8 Hz, 1H), 4.56 (d, *J*=12.2 Hz, 1H), 4.46 (t, *J*=5.4 Hz, 1H), 3.74 (dd, *J*=11.0, 2.0 Hz, 1H), 3.71–3.59 (m, 5H), 3.48 (m, 2H), 3.42 (ddd, *J*=9.3, 4.3, 2.0 Hz, 1H), 3.26 (ddd, *J*=9.6, 5.7, 5.7 Hz, 1H), 1.94 (s, 3H), 1.62 (m, 3H), 1.49 (m, 2H), 1.41 (m, 1H), 1.19 (ddd, *J*=7.1, 7.1, 2.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 138.4, 138.3, 138.1, 128.4, 128.4, 128.3, 128.0, 127.7, 127.7, 127.6, 127.5, 102.9, 84.7, 79.2, 78.5, 77.8, 75.1, 74.9, 74.1, 73.5, 69.0, 31.1, 60.8, 33.5, 31.3, 20.9, 20.7, 15.3, 15.3; IR (CCl_4) 2864, 1758, 1548, 1227, 1091 cm^{-1}; MS (FAB^+) for **15b** 577 (MH^+), 91 *m/z*, HRMS for **15b** calcd for $C_{35}H_{45}O_7$ (MH^+) 577.3165, found 577.3150.

4.2.7. (2*R*,3*S*,4*R*,5*S*,6*S*)-3,4-Dibenzyloxy-2-benzyloxymethyl-6-methyl-3,4,4a,8,9,9a-hexahydro-2*H*-1,5-dioxabenzocycloheptene 31. A solution of acetate **21** (0.92 g, 1.8 mmol) and THF (57 mL) at 0°C was treated with BH_3 (1.9 mL of a 1.0 M solution in THF, 1.9 mmol). After 2 h, NaOH (1.83 mL of a 3 M solution (aq.), 5.5 mmol) and H_2O_2 (0.37 mL of a 30% solution (aq.), 3.9 mmol) were added to the reaction mixture sequentially. After warming to rt, H_2O (20 mL) was added to the reaction mixture. The aqueous phase was extracted with ether (3×20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 0.70 g (73%) of the alcohol

from **21** as a white solid. Mp 52–54°C; $[\alpha]_D^{24}$=6.9 (*c*=0.41, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.22, (m, 13H, PhH), 7.19–7.12 (m, 2H, PhH), 4.88 (dd, *J*=15.0, 7.5 Hz, 1H), 4.78 (dd, *J*=15.0, 10.0 Hz, 2H), 4.67 (d, *J*=10.0 Hz, 1H), 4.62–4.48 (m, 3H,), 3.75–3.59 (m, 4H), 3.45–3.35 (m, 1H), 3.35–3.28 (m, 1H), 2.65–2.50 (m, 2H), 1.95 (s, 3H), 1.78–1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 170.1, 138.7, 187.6, 138.5, 128.9, 128.5, 84.7, 75.1, 78.3, 77.6, 77.3, 77.0, 75.3, 75.1, 69.0, 39.6, 24.2, 21.1; IR (CH_2Cl_2) 3429, 3048, 2988, 1265 cm^{-1}; MS (FAB$^+$) 533.3, (MH^+), 185.1, 93.2 *m/z*, HRMS calcd for $C_{32}H_{38}O_7$ (MH^+) 535.2696, found 535.2719. Analysis calcd for $C_{32}H_{38}O_7$: C, 71.89; H, 7.16. Found: C, 71.97; H, 7.41.

To a solution of the alcohol from the hydroboration (0.115 g, 0.220 mmol) and CH_2Cl_2 (1 mL) was added *i*-Pr_2NEt (0.15 mL, 0.86 mmol), TIPSCl (0.092 mL, 0.43 mmol), and DMAP (ca. 0.005 g). The reaction mixture was allowed to warm to rt and was quenched with H_2O (10 mL) after 5 h. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) afforded 104 mg (69%) of TIPS ether **25** as a colorless oil. $[\alpha]_D^{24}$=4.1 (*c*=2.0, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.21 (m, 13H), 7.19–7.12 (m, 2H, PhH), 4.88 (t, *J*=7.5 Hz, 1H), 4.78 (t, *J*=10.0 Hz, 2H), 4.67 (d, *J*=10.0 Hz, 1H), 4.62–4.43 (m, 3H), 3.77–3.55 (m, 4H), 3.43–3.33 (m, 1H), 3.33–3.20 (m, 1H), 1.90 (s, 3H), 1.84–1.71 (m, 2H), 1.70–1.51 (m, 2H), 1.50–1.33 (m, 2H), 1.12–0.90 (m, 21H); ^{13}C NMR (125 MHz) δ 169.8, 138.7, 138.5, 138.3, 128.3, 127.9, 127.7, 84.8, 79.3, 78.6, 78.0, 77.6, 77.3, 77.0, 75.3, 75.1, 74.2, 73.6, 69.2, 63.2, 63.1, 28.8, 28.0, 21.0, 18.8, 18.2, 17.8, 17.2, 13.6, 12.7, 12.2; IR (CH_2Cl_2) 3049, 2296, 1750, 1430 cm^{-1}; MS (FAB$^+$) 691.43 (MH^+), 307.1, 154.0, *m/z*, HRMS calcd for $C_{41}H_{59}O_7Si$ (MH^+) 691.4030, found 691.4056.

4.2.8. (2β,3*S*,4*R*,5*S*,6*R*)-4,5-Bis-benzyloxy-6-benzyloxymethyl-2-(3-butenyl)-tetrahydro-pyran-3-acetate 24. To a solution of $(COCl)_2$ (0.45 mL, 5.2 mmol) and CH_2Cl_2 at −60°C was added DMSO (0.772 mL, 10.9 mmol) dropwise. To this solution was added a solution of the alcohol from the hydroboration, oxidation of **21** (1.05 g, 2.0 mmol) and CH_2Cl_2 dropwise via cannula. After 0.5 h, NEt_3 (3.8 mL, 31.3 mmol) was added and the mixture was allowed to warm to rt. The reaction mixture was quenched with sat. NH_4Cl (aq., 20 mL), extracted with CH_2Cl_2 (3×20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 0.98 g (94%) of the corresponding aldehyde as a colorless oil. $[\alpha]_D^{24}$=3.8° (*c*=0.65, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.50–7.22 (m, 13H), 7.19–7.12 (m, 2H), 4.88 (dd, *J*=15.0, 7.5 Hz, 1H), 4.78 (dd, *J*=15.0, 10.0 Hz, 2H), 4.67 (d, *J*=10.0 Hz, 1H), 4.62–4.48 (m, 3H), 3.75–3.59 (m, 4H), 3.45–3.35 (m, 1H), 3.35–3.28 (m, 1H), 2.65–2.50 (m, 2H), 1.95 (s, 3H), 1.78–1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 170.1, 138.7, 138.6, 138.5, 133.5, 128.9, 128.5, 84.7, 75.1, 78.3, 77.6, 77.3, 77.0, 75.3, 75.1, 69.0, 39.6, 24.2, 21.1; IR (CH_2Cl_2) 3048, 2858, 1750, 1447 cm^{-1}; MS (FAB$^+$) 533.25 (MH^+), 181.1, 91.2 *m/z*, HRMS calcd for $C_{32}H_{37}O_7$ (MH^+) 533.2461, found 533.2536.

To a slurry of CH_3PPh_3Br (0.13 g, 0.36 mmol) and THF (2 mL) at 0°C was added BuLi (0.19 mL of a 1.6 M solution in THF, 0.30 mmol) dropwise. The resulting orange solution was allowed to warm to rt. After 4 h, the solution was cooled to 0°C and a solution of the aldehyde from above (0.0190 g, 0.036 mmol) and THF (1 mL) was added via cannula. After 0.25 h, the reaction was quenched with sat. NH_4Cl (aq., 10 mL), extracted with CH_2Cl_2 (3×10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 102 mg (79%) of the alkene as a white solid. Mp 38–39°C; $[\alpha]_D^{29}$=11.7 (*c*=0.70, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.23 (m, 13H, PhH), 7.22–7.16 (m, 2H, PhH), 5.79 (ddt, *J*=17.1, 10.3, 6.8 Hz, 1H), 5.01 (d, *J*=10.0 Hz, 1H), 4.95 (d, *J*=5.0 Hz, 1H), 4.89 (t, *J*=3.0 Hz, 1H), 4.80 (dd, *J*=15.0, 10.0 Hz, 2H), 4.70–4.52 (m, 4H), 3.79–3.59 (m, 4H), 3.48–3.39 (m, 1H), 3.32–3.24 (m, 1H), 2.33–2.23 (m, 1H), 2.16–2.06 (m, 1H), 1.95 (s, 3H), 1.61–1.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 138.5, 138.3, 138.1, 128.6, 128.1, 127.8, 115.1, 85.0, 79.4, 78.8, 77.6, 77.3, 77.0, 75.3, 75.1, 74.2, 73.7, 69.2, 30.9, 29.3, 21.2; IR (CH_2Cl_2) 3048, 1733, 1413, 1265 cm^{-1}; MS (FAB$^+$) 531.28 (MH^+), 441.2, 185.1 *m/z*, HRMS calcd for $C_{33}H_{38}O_6$ (MH^+): 531.2747, found 531.2779.

To a yellow solution of $TiCl_4$ (0.35 mL, 1.1 mmol) and CH_2Cl_2 (9 mL) at 0°C was added THF (0.20 mL, 6.4 mmol) and then TMEDA (0.96 mL, 6.4 mmol) dropwise. After stirring for 10 min, Zn (0.16 g, 2.4 mmol) and $PbCl_2$ (0.035 g, 0.057 mmol) were added. The color of the reaction mixture changed from brown to green to blue to greenish blue after 20 min A solution of the acetate **24** (0.030 g, 0.057 mmol), CH_2Br_2 (0.075 mL, 1.1 mmol), and CH_2Cl_2 (1.5 mL) were transferred to the reaction mixture. The resulting slurry was heated to 65°C for 4.5 h. After cooling to 0°C, the reaction was stirred with K_2CO_3 (sat., 0.25 mL) for 0.5 h. Following vacuum filtration, the resulting solution was further filtered through a plug of neutral alumina (NEt_3/Et_2O, 3:100). Concentration provided 19 mg (63%) of enol ether **26** as a yellow oil. Enol ether **26** was immediately subjected to the subsequent RCM protocol.

To a solution of enol ether **26** (0.019 g, 0.036 mmol) and benzene (4.3 mL) at rt was added Ru catalyst **33** (0.0073 g, 0.0088 mmol). After stirring at rt for 4 h, the reaction mixture was concentrated. Flash chromatography (20:1, hexanes/ethyl acetate) gave 16 mg (78%) of bicycle **31** as a colorless oil. $[\alpha]_D^{24}$=−25.7 (*c*=0.110, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.43 (d, *J*=7.5 Hz, 2H), 7.29 (d, *J*=7.5 Hz, 2H), 7.25 (d, *J*=7.5 Hz, 2H, PhH), 7.22–7.05 (m, 8H, PhH), 5.13 (d, *J*=10 Hz, 1H), 4.95 (d, *J*=10 Hz, 1H), 4.85 (d, *J*=10 Hz, 1H), 4.68 (t, *J*=5 Hz, 1H), 4.61 (d, *J*=12.5 Hz, 1H), 4.43 (d, *J*=10.0 Hz, 1H), 4.38 (d, *J*=10.0 Hz, 1H), 3.74–3.65 (m, 4H), 3.59–3.51 (m, 1H), 3.49–3.41 (m, 1H), 3.30–3.23, (m, 1H), 2.08–2.01 (m, 1H), 1.95–1.80 (m, 1H), 1.72–1.68 (s, 3H), 1.57–1.48 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 157.1, 140.3, 139.7, 139.3, 128.0, 108.7, 86.0, 84.8, 80.2, 79.8, 78.8, 76.0, 75.2, 74.1, 70.1, 33.0, 21.5, 21.2; IR (CH_2Cl_2) 3039, 2918, 1681, 1508 cm^{-1}; MS (FAB$^+$) 501.26 (MH^+), 185.1, 93.2 *m/z*, HRMS calcd for $C_{32}H_{37}O_5$ (MH^+) 501.2641, found 501.2642.

4.2.9. Preparation of [3-(4,5-bis-benzyloxy-6-benzyloxymethyl-3-isopropenyloxy-tetrahydro-pyran-2-yl)-propoxy-[triisopropylsilane] 27. 27 was synthesized using the protocol used for the synthesis of **26** and $TiCl_4$ (0.32 mL, 1.0 mmol), CH_2Cl_2 (7.7 mL), THF (0.17 mL, 1.0 mmol), TMEDA (0.87 mL, 5.8 mmol), Zn (0.14 g, 2.2 mmol), $PbCl_2$ (0.032 g, 0.12 mmol), acetate **25** (0.036 g, 0.052 mmol), CH_2Br_2 (0.068 mL, 1.0 mmol), and CH_2Cl_2 (1.4 mL) gave 29 mg (81%) of enol ether **27** as a colorless oil. $[\alpha]_D^{24}=-24.5$ (c=0.530, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.40 (d, J=7.5 Hz, 2H), 7.30 (d, J=7.5 Hz, 2H), 7.25 (d, J=7.5 Hz, 2H), 7.20–7.16 (m, 7H), 7.10 (t, J=7.5 Hz, 2H), 4.91 (d, J=11.0 Hz, 1H), 4.72 (d, J=10.5 Hz, 1H), 4.62 (d, J=11.0 Hz, 1H), 4.48 (d, J=12.3 Hz, 1H), 4.42 (d, J=12.3 Hz, 1H), 4.30 (br s, 1H), 4.08 (t, J=9.0 Hz, 1H), 4.02 (br s, 1H), 3.78–3.62 (m, 4H), 3.42–3.40 (m, 1H), 3.34–3.31 (m, 1H), 2.03–1.94 (m, 2H), 1.78 (s, 3H), 1.65–1.57 (m, 1H), 1.52–1.43 (m, 1H), 1.38–0.98 (m, 23H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.5, 139.9, 139.8, 139.5, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 87.1, 84.6, 80.1, 79.9, 79.7, 79.7, 78.9, 75.6, 75.4, 74.0, 70.1, 64.1, 63.9, 30.5, 30.0, 29.2, 21.8, 19.3, 18.7, 18.4, 17.9, 14.2, 13.4, 12.8; IR (CH_2Cl_2) 3049, 2919, 1663, 1456 cm^{-1}; MS (FAB$^+$) 690 (MH$^+$), 632, 91 m/z, HRMS calcd for $C_{42}H_{61}O_6Si$ (MH$^+$) 689.4237, found 689.4238.

4.2.10. (4*S*,5*R*,6*S*,7*S*,8*R*)-1,2-Anhydro-6,7,9-tribenzyloxypyrano-[4,5]-pyran 36. To a solution of alcohol **15** (0.025 g, 0.043 mmol) and chlorobenzene (2 mL) at 0°C was added PPTS (0.066 g, 0.264 mmol). The solution was heated to 60°C until all of the starting material was consumed (TLC). After cooling, pyridine (0.009 mL, 0.11 mmol) was added and the resulting mixture was heated to 135°C for 4 h. The reaction was quenched with NaOH (1 M, 2 mL), extracted with ether (3×3 mL), washed with brine (2×15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) afforded 15 mg (72%) of bicyclic enol ether **36** as a colorless oil. $[\alpha]_D^{30}=-7.76$ (c=0.795, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.24 (m, 13H), 7.15–7.13 (m, 2H), 6.35 (dd, J=6.3, 1.5 Hz, 1H), 4.98 (dd, J=11.7, 6.2 Hz, 1H), 4.96 (d, J=11.1 Hz, 1H), 4.83 (d, J=10.8 Hz, 1H), 4.79 (d, J=11.2 Hz, 1H), 4.58 (d, J=12.3 Hz, 1H), 4.53 (d, J=12.7 Hz, 1H), 4.50 (d, J=10.8 Hz, 1H), 3.71 (dd, J=11.0, 1.6 Hz, 1H), 3.67 (d, J=8.8 Hz, 1H), 3.62 (dd, J=10.8, 4.9 Hz, 1H), 3.57–3.51 (m, 2H), 3.47 (ddd, J=9.9, 4.8, 1.5 Hz, 1H), 3.43–3.41 (m, 1H), 2.43–2.13 (m, 2H), 2.07–1.99 (m, 1H), 1.63–1.58 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 147.4, 139.1, 138.3, 138.2, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 112.7, 85.2, 84.6, 79.5, 78.9, 77.9, 75.5, 75.0, 73.5, 69.4, 67.3, 65.9, 32.4, 20.6; IR (CCl_4) 1647, 1449, 1208, 1073 cm^{-1}; MS (FAB$^+$) 487 (MH$^+$), 91 m/z, HRMS calcd for $C_{31}H_{35}O_5$ (MH$^+$) 487.2484, found 487.2488.

4.2.11. (1*S*,2*R*,5*S*,6*R*,7*S*,8*S*,9*R*)-2-Hydroxy-1-(3,3-dimethoxypropyl)-7,8,10-tribenzyloxypyrano-[5,6]-oxapane 40β and (1*R*,2*S*,5*S*,6*R*,7*S*,8*S*,9*R*)-2-hydroxy-1-(3,3-dimethoxypropyl)-7,8,10-tribenzyloxypyrano-[5,6]-oxepane 40α. The anhydride from **36** was prepared according to the procedure used for the preparation of **5** using enol ether **36** (0.088 g, 0.18 mmol) and dimethyldioxirane (2.7 mL of a 0.1 M solution, 0.27 mmol). A solution of the anhydride and THF (5.4 mL) at 0°C was treated with a solution of acetal Grignard **12** (1.12 mL of a 0.48 M solution in THF, 0.54 mmol). After stirring for 0.33 h, the reaction was quenched with aq. NH_4Cl (sat., 10 mL). The mixture was extracted with ether (3×10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (5:1 hexanes/ethyl acetate) afforded 73 mg (67%) of alcohol **40** as a 10:1 β/α mixture. The alcohols were characterized as the corresponding acetates.

The mixture of alcohols from above (0.024 g, 0.040 mmol) were treated with i-Pr_2NEt (0.06 mL, 0.32 mmol), Ac_2O (0.024 mL, 0.24 mmol), and DMAP (ca. 0.005 g). After stirring for 1 h, the reaction mixture was quenched with aq. $NaHCO_3$ (sat., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), washed with brine (1×10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10:1 hexanes/ethyl acetate) provided 19 mg (73%) of acetate **40**β along with 2 mg (8%) of acetate **40**α Acetate of **40**β: $[\alpha]_D^{29}=-8.25$ (c=0.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.24 (m, 13H), 7.11–7.10 (m, 2H), 4.91–4.89 (m, 2H), 4.78 (d, J=10.9 Hz, 2H), 4.58 (d, J=12.3 Hz, 1H), 4.52 (d, J=12.3 Hz, 1H), 4.48 (d, J=10.8 Hz, 1H), 4.29 (t, J=5.5 Hz, 1H), 3.69 (dd, J=10.6, 1.3 Hz, 1H), 3.63–3.60 (m, 2H), 3.56–3.50 (m, 2H), 3.45–3.42 (m, 1H), 3.37 (dd, J=8.9, 8.9 Hz, 1H), 3.21 (s, 6H), 3.17 (part. obs. dd, J=9.7, 4.4 Hz, 1H), 2.06 (s, 3H), 1.95–1.90 (m, 2H), 1.85–1.72 (m, 3H), 1.67–1.52 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 138.7, 138.2, 138.1, 128.4, 128.4, 128.4, 127.9, 127.9, 127.7, 127.6, 127.6, 104.3, 85.8, 83.9, 83.1, 79.0, 78.1, 76.6, 75.7, 75.1, 73.5, 69.2, 52.9, 52.6, 29.8, 28.8, 26.7, 23.9, 21.4; IR (CCl_4) 2944, 1740, 1245, 1073 cm^{-1}; MS (FAB$^+$) 647 (MH$^+$), 618, 91 m/z, HRMS calcd for $C_{38}H_{47}O_9$ (MH$^+$) 647.3220, found 647.3203. Acetate of **40**α: $[\alpha]_D^{28}=+0.63$ (c=0.39, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.24 (m, 13H), 7.20–7.00 (m, 2H), 4.91 (d, J=11.8 Hz, 1H), 4.88 (d, J=11.8 Hz, 2H), 4.68 (d, J=10.6 Hz, 1H), 4.67 (part. obs. m, 1H), 4.59 (d, J=12.3 Hz, 1H), 4.52 (d, J=12.3 Hz, 1H), 4.46 (d, J=10.6 Hz, 1H), 4.04 (t, J=5.4 Hz, 1H), 3.67 (dd, J=10.6, 1.6 Hz, 1H), 3.64–3.59 (m, 2H), 3.54 (dd, J=9.4, 9.4 Hz, 1H), 3.41 (ddd, J=9.7, 4.2, 1.7 Hz, 1H), 3.31 (dd, J=9.1, 9.1 Hz, 1H), 3.25–3.20 (m, 1H), 3.12 (s, 3H), 3.03 (s, 3H), 2.17 (ddd, J=13.7, 5.9, 5.9 Hz, 1H), 2.01 (s, 3H), 1.83 (ddd, J=11.8, 11.8, 11.8 Hz, 1H), 1.76–1.47 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 138.9, 138.1, 137.9, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.6, 127.1, 126.8, 104.1, 85.3, 79.3, 78.6, 78.5, 77.5, 76.1, 75.4, 75.0, 73.5, 68.9, 52.9, 52.2, 30.9, 29.1, 27.5, 26.9, 21.3; IR (CCl_4) 2938, 1740, 1233, 1079 cm^{-1}; MS (FAB$^+$) 647 (MH$^+$), 618, 91 m/z, HRMS calcd for $C_{38}H_{47}O_9$ (MH$^+$) 647.3220, found 647.3203.

4.2.12. (2*R*,4*S*,5*R*,6*S*,7*S*,8*R*)-1,2-Diacetoxy-6,7,9-tribenzyloxypyrano-[4,5]-pyran 41. A mixture of AD mix-α (0.40 g), NH_2SO_2Me (0.041 g, 0.43 mmol), t-BuOH (0.65 mL), and H_2O (0.65 mL) was stirred at rt for 0.25 h before a solution of bicyclic enol ether **29** (0.068 g, 0.14 mmol) and THF (0.65 mL) was added. After 20 h, the reaction was quenched with sat. Na_2SO_4 (aq., 3 mL). The mixture was extracted with ether (3×3 mL), washed

with brine (10 mL), dried ($MgSO_4$), and concentrated. The resulting diols were immediately acetylated using Ac_2O (0.048 mL, 0.5 mmol), *i*-Pr_2NEt (0.10 mL, 0.58 mmol), and DMAP (ca. 0.005 g). Following workup, flash chromatography afforded 65 and 9.6 mg (12:1 mixture, 88%) of acetates **41** and **42** respectively. **41** (white solid): mp 93–96°C; $[\alpha]_D^{29}$=11.3 (*c*=1.56, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.35–7.25 (m, 13H), 7.14–7.04 (m, 2H), 6.22 (d, *J*=3.4 Hz, 1H), 5.66 (d, *J*=8.3 Hz, 1H), 4.98–4.81 (m, 3H), 4.69–4.43 (m, 4H), 3.72–3.42 (m, 6H), 3.43 (ddd, *J*=10.4, 10.4, 6.4 Hz, 1H), 2.56 (ddd, *J*=11.4, 4.5, 4.5 Hz, 1H), 2.29 (ddd, *J*=11.4, 4.5, 4.5 Hz, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.99 (ddd, *J*=11.8, 11.8, 11.8 Hz, 1H), 1.70 (ddd, *J*=11.7, 11.7, 11.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 169.5, 169.2, 169.1, 138.4, 138.4, 138.1, 138.0, 137.9, 137.9, 128.3, 128.3, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 93.6, 88.2, 83.3, 83.1, 80.5, 79.5, 79.4, 77.4, 77.1, 75.2, 75.1, 75.0, 74.8, 73.5, 73.4, 72.8, 72.8, 72.4, 68.8, 68.8, 68.2, 67.3, 33.6, 29.6, 21.0, 20.9, 20.8; IR (CCl_4) 1750, 1746, 1554, 1208, 1073 cm^{-1}; MS (FAB^+) 591 (MH^+), 589, 531, 441, 451, 91 *m/z*, HRMS calcd for $C_{34}H_{39}O_9$ (MH^+) 591.2594, found 591.2606.

4.2.13. (2*R*,4*S*,5*R*,6*S*,7*S*,8*R*)-2-Acetoxy-1-bromo-6,7,9-tribenzyloxypyrano-[4,5]-pyran 43. To a solution of diacetate **41** (0.018 g, 0.030 mmol) and CH_2Cl_2 (0.5 mL) at rt was added TMSBr (0.12 mL, 1.1 mmol), dropwise. The resulting solution was heated to reflux for 18 h and then concentrated. Flash chromatography afforded 16 mg (85%) of bromide **43** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (m, 13H), 7.12–7.10 (m, 2H), 6.65 (d, *J*=3.5 Hz, 1H), 4.86 (d, *J*=11.2 Hz, 1H), 4.82 (d, *J*=10.8 Hz, 1H), 4.70 (ddd, *J*=11.8, 4.2, 4.2 Hz, 1H), 4.65 (d, *J*=11.1 Hz, 1H), 4.58 (d, *J*=12.2 Hz, 1H), 4.51 (d *J*=12.2 Hz, 1H), 4.47 (d, *J*=10.5 Hz, 1H), 3.88, (dd, *J*=9.4, 9.4 Hz, 1H), 3.70–3.60 (m, 4H), 3.48 (m, 1H), 3.28 (ddd, *J*=10.6, 10.6, 4.3 Hz, 1H), 2.20 (ddd, *J*=11.7, 4.6, 4.6 Hz, 1H), 2.12 (ddd, *J*=11.6, 11.6, 11.6 Hz, 1H), 2.11–2.09 (m, 1H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 138.4, 138.0, 137.9, 128.4, 128.3, 128.0, 128.0, 127.9, 127.7, 127.7, 127.6, 89.0, 82.7, 79.6, 77.5, 76.8, 75.3, 74.7, 73.5, 72.2, 68.9, 68.7, 30.1, 20.9; IR (CCl_4)1752, 1554, 1227, 1098 cm^{-1}; MS (FAB^+) 611 (MH^+), 609, 441, 91 *m/z*, HRMS calcd for $C_{32}H_{35}O_7Br$ (MH^+), 609.1488, found 609.1505.

4.2.14. (2*R*,4*S*,5*R*,6*S*,7*S*,8*R*)-2-Hydroxy-1-(3,3-dimethoxypropyl)-6,7,9-tribenzyl-oxypyrano-[4,5]-pyran 44. To a solution of bromo acetate **43** (0.019 g, 0.031 mmol) and THF (2 mL) at −50°C was added Grignard **12** (0.65 mL of a 0.48 M solution, 0.31 mmol) dropwise. After warming to 0°C the reaction was quenched with NH_4Cl(sat., 2 mL), extracted with ether (3×3 mL), washed with brine (2×10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (2:1, hexanes/ethyl acetate) afforded 13 mg (72%) of alcohol **44** as a colorless oil.

For characterization purposes **44** was converted into the corresponding acetate using **44** (0.13 g, 0.022 mmol), CH_2Cl_2 (1 mL), *i*-Pr_2NEt (0.032 mL, 0.18 mmol), Ac_2O (0.015 mL, 0.13 mmol), and DMAP (ca. 0.005 g) to provide the acetate of **44** as a colorless oil. $[\alpha]_D^{29}$=−8.47 (*c*=0.220, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.24 (m, 13H), 7.12–7.11 (m, 2H), 4.95 (d, *J*=11.1 Hz, 1H), 4.83 (d, *J*=10.7 Hz, 1H), 4.73 (d, *J*=11.1 Hz, 1H), 4.68 (ddd, *J*=5.7, 5.7, 2.1 Hz, 1H), 4.59 (d, *J*=12.3 Hz, 1H), 4.51 (d, *J*=13.1 Hz, 1H), 4.59–4.52 (m, 2H), 4.49 (d, *J*=12.4 Hz, 1H), 4.47 (d, *J*=10.9 Hz, 1H), 4.35 (t, *J*=5.5 Hz, 1H), 3.69 (dd, *J*=10.7, 1.5 Hz, 1H), 3.64 (dd, *J*=10.8, 4.3 Hz, 1H), 3.61–3.56 (m, 2H), 3.46 (m, 1H), 3.32 (ddd, *J*=9.4, 9.4, 2.0 Hz, 1H), 3.27 (s, 3H), 3.25 (s, 3H), 3.21–3.14 (m, 2H), 2.52–2.49 (m, 1H), 2.04 (s, 3H), 1.91–1.86 (m, 1H), 1.72–1.62 (m, 2H), 1.55 (ddd, *J*=11.1, 11.1, 11.1 Hz, 1H), 1.43–1.39 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.9, 138.6, 138.2, 138.1, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 104.2, 84.0, 82.4, 79.4, 78.8, 77.5, 75.2, 75.1, 73.5, 73.4, 70.6, 69.0, 52.9, 52.4, 35.1, 28.4, 26.7, 21.1; IR (CCl_4) 1740, 1456, 1245, 1098 cm^{-1}; MS (FAB^+) 633 ($M-H^+$), 91 *m/z*, HRMS calcd for $C_{37}H_{45}O_9$ ($M-H^+$) 633.3064, found 633.3077.

4.2.15. (2*R*,4*S*,5*R*,6*S*,7*S*,8*R*)-1,2-Dianhydro-9,10,12-tribenzyloxy-[4,5]-pyrano-[7,8]-pyran 45. According to the procedure for the preparation of **29**, acetal **43** (0.025 g, 0.038 mmol) was treated with PPTS (0.058 g, 0.23 mmol), pyridine (0.0083 mL, 0.099 mmol), and PhCl (1.1 mL) to afford 15 mg (72%) of tricyclic enol ether **45** as a colorless oil. $[\alpha]_D^{29}$=+52.1 (*c*=0.575, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.38–7.24 (m, 13H), 7.15–7.08 (m, 2H), 6.30 (d, *J*=6.0 Hz, 1H), 4.94 (d, *J*=11.3 Hz, 1H), 4.84 (d, *J*=10.7 Hz, 1H), 4.75 (d, *J*=13.1 Hz, 1H), 4.46 (d, *J*=5.7, 5.7, 2.1 Hz, 1H), 3.73–3.25 (m, 8H), 3.19 (dd, *J*=9.3, 4.0 Hz, 1H), 2.51 (ddd, *J*=11.5, 3.9, 3.9, 1H), 2.30 (ddd, *J*=16.6, 5.1, 5.1 Hz, 1H), 2.10–1.99 (m, 1H), 1.67 (ddd, *J*=11.1, 11.1, 11.1 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.9, 138.2, 138.0, 128.4, 128.0, 127.9, 127.7, 127.5, 98.6, 84.0, 82.3, 79.4, 77.6, 75.2, 75.0, 74.6, 73.9, 73.5, 73.3, 69.0, 34.9, 26.8; IR (CCl_4) 1647, 1449, 1239, 1067 cm^{-1}; MS (FAB^+) 529 (MH^+), 527, 91 *m/z*, HRMS calcd for $C_{33}H_{35}O_6$ (MH^+) 527.2434, found 527.2450.

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