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Surveying approaches to the formation of carbon–carbon bonds between a pyran and an adjacent ring

Jeffrey D. Frein and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

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Abstract—We have examined several methods for the stereoselective formation of carbon–carbon bonds between contiguous rings where a stereogenic center is already present. The approaches investigated were a [1,3] oxygen to carbon rearrangement of cyclic vinyl acetals, an intermolecular enolsilane addition into an in situ generated oxocarbenium ion, an intramolecular conjugate addition of tethered alkoxy enones, and epimerization of several α-pyranyl cycloalkanones. These routes have been found to be complementary in several cases and have enabled formation of both the trans:*anti* and cis:*anti* stereoisomers in good to excellent yields and varying diastereoselectivities. We have proven C2–C2′ relative stereochemistry of 1–2 via a chemical correlation.

1. Introduction

Among the largest and most complicated non-biopolymer molecules discovered to date are maitotoxin, prymnesin and ciguatoxin, along with other members of the polyether ladder toxin family.[1] These molecules are characterized by sections of fused oxacycles connected to each other by carbon linkers. Only a handful of total syntheses have emerged to date, including Nicolaou's synthesis of brevetoxin[2] and Hirama's recent synthesis of ciguatoxin.[3] No syntheses have yet appeared of the largest members of this family, maitotoxin and prymnesin. At least a part of the reason for this is the comparative complexity of subsections of maitotoxin, compelling and challenging targets in their own right. We became interested in the problem of how to connect subsections of these molecules once they are assembled. Arguably, the most obvious bond disconnections involve the single C–C bonds that connect the fused oxacycle subsections to each other.[4] An approach to these types of bonds must address the key issue of controlling stereochemistry at both ends, a problem that is shared by various other natural product targets as well.

We chose to conduct an in-depth study of various approaches to this type of ring juncture. Prime among these was our intention to apply our recently developed stereoretentive O to C rearrangement to this problem.[5] In doing so, we hoped to take advantage of the relative facility of controlling stereochemistry in the formation of a C–O bond and induce it to rearrange to a C–C bond, having already paid the entropic price of bringing two fragments together in the formation of the 'easy' bond. The question that we needed to address was our ability to control the second stereocenter in the rearrangement (Eq. 1).[6] Second, we hoped to contrast these results with selectivities obtained in the more classical Lewis acid induced intermolecular enolsilane addition to an in situ generated oxocarbenium ion (Eq. 2). This method is comparable to the rearrangement method without having to address the issue of creating the oxocarbenium ion and enolate via an intramolecular event, although it lacks the possibility of providing the cis adduct via a stereoretentive process. Last, we wanted to exploit an intramolecular conjugate addition of an alkoxide into an α,β-unsaturated ketone (Eq. 3).

Keywords: Stereoretentive process; Lewis acid; Oxocarbenium ions; [1,3]rearrangement.
* Corresponding author. Tel.: +1 970 491 7208; fax: +1 970 491 1801; e-mail: rovis@lamar.colostate.edu

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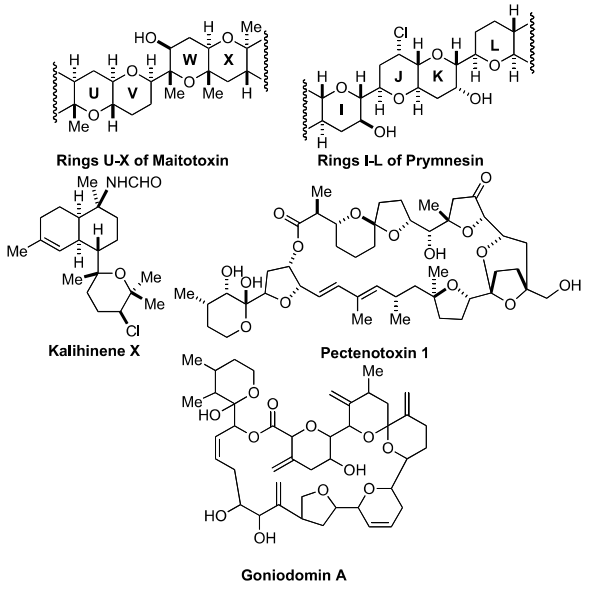
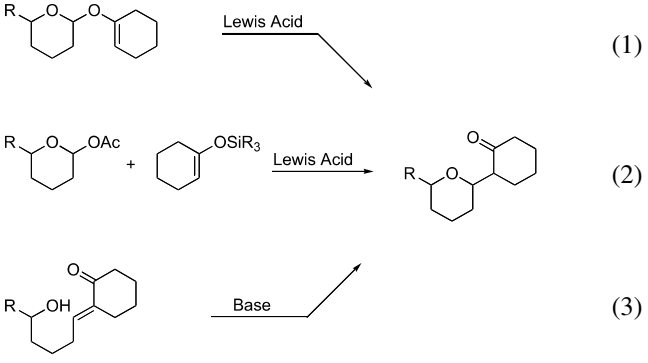




Other groups have exploited various methods for the formation of these carbon–carbon linkers.[7] Suzuki and co-workers have reported a $BF_3 \cdot OEt_2$ mediated 1,3-oxygen to carbon rearrangement of vinyl acetals resulting in pyranyl aldehydes in good yields (85–89%) and modest to good C2–C2′ diastereoselectivities (3:2–3:1).[6i] In addition, Ley and co-workers have shown a $SnCl_4$ mediated oxygen to carbon rearrangement of silyl enol ethers derived from lactols.[6e,f] This rearrangement affords exclusively the trans orientation across the pyran ring with the resultant contiguous stereocenters (C2–C2′) in poor to modest diastereoselectivities (1:1–3:1) and in good yields (79–90%).[6e,f] Also, Ley and co-workers have shown the use of the oxygen to carbon rearrangement for the formation of various mono- and bi-cyclic ethers.[6g,h]

As stated above, recently we have developed a Lewis acid-mediated highly stereoretentive [1,3] rearrangement of vinyl acetals, wherein the selectivity is controlled by tight ion pairing of the resulting oxocarbenium ion and Lewis acid coordinated enolate intermediate.[5] Should the generated ions escape the solvent cage prior to recombination, the trans product would predominate. However, if recombination occurs faster, the cis product would result. In many cases, either isomer may be prepared by simple choice of Lewis acid system—$BF_3 \cdot OEt_2$ proved to be trans selective while $Me_3Al/BF_3 \cdot OEt_2$ afforded products of stereoretention, with a crossover study providing conclusive evidence. We envisioned the chosen Lewis acid would have the ability to control the recombination of the intermediates and possibly form a single diastereomer in a highly selective manner (Fig. 1).

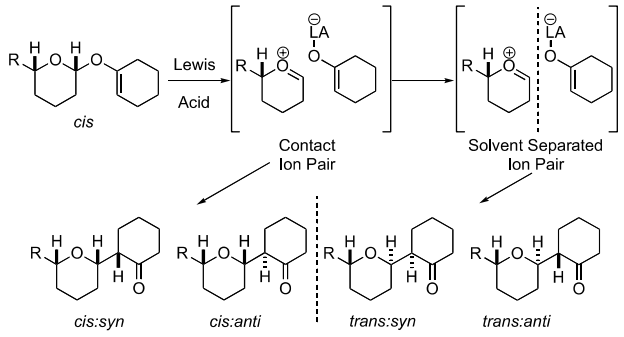


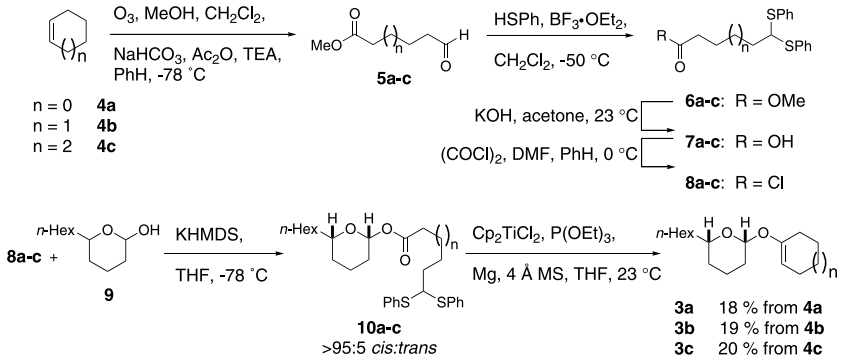
Figure 1.

2. Results and discussion

We chose to begin our investigations with simple enolates and oxocarbenium ions devoid of electronic or steric features, which might dictate selectivity in the bond forming event.[8] The requisite cyclic vinyl acetals **3a–c** were prepared by ozonolysis of the corresponding cycloalkenes **4a–c** using Schreiber's conditions.[9] The resulting aldehyde–methyl esters **5a–c** were treated with $BF_3 \cdot OEt_2$ and thiophenol to yield the thioacetal–methyl esters **6a–c**. Hydrolysis of **6a–c** and treatment with $(COCl)_2$ resulted in the acyl chloride–thioacetals **8a–c**. Using conditions reported by Ley,[6d] **8a–c** were treated with lactol **9** and KHMDS at −78 °C yielding the *cis*-tetrahydropyran esters **10a–c** in high cis:trans selectivity (>95:5). **10a–c** were cyclized via Takeda's titanocene(II)-promoted intramolecular carbonyl olefination of esters to yield the desired cyclic vinyl acetals **3a–c** (Scheme 1).[10]

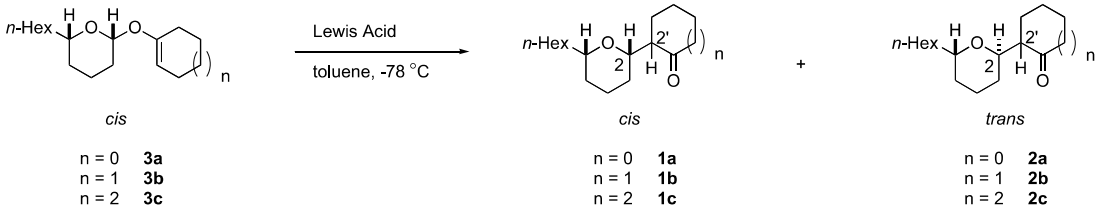
Our intitial screening of Lewis acids that would induce the rearrangement began with $BF_3 \cdot OEt_2$ (Table 1). From our previous work, we expected the strong Lewis acid would allow the complexed enolate to escape from the solvent cage prior to recombination and thus form the kinetically favored trans-isomer.[5a] Under these conditions, the rearrangements of **3a–c** resulted in extremely high trans:cis selectivities (entries 1, 5, and 9; Table 1).[11] Moreover, we were pleased that **3a** and **3b** (entries 1 and 5; Table 1) also had relatively good *anti*:*syn* selectivity for the C2–C2′ bond, (79:21 and 82:18, respectively). Unfortunately, further investigations aimed at identifying a Lewis acid capable of forming the opposite C2–C2′ stereochemistry were unsuccessful.

From our previous findings, we knew that the use of Me_3Al–$BF_3 \cdot OEt_2$ (4/1) results in a highly stereoretentive rearrangement.[5a] These conditions proved unsuccessful with the trisubstituted alkenes in this study (entries 3, 6, and 10; Table 1) which we interpret as due to the increased steric requirement of the trisubstituted alkene. However, adjustment of the acidity of the Lewis acid to Et_2AlCl provided a partial solution, potentially due to a slightly more reactive



Scheme 1.

Table 1.



Entry	*n*	Lewis acid	cis:trans[a]	cis (*anti*:*syn*)[a]	trans (*anti*:*syn*)[a]	Yield (%)[b]
1	0	$BF_3 \cdot OEt_2$	<1:>99	NA	79:21	90
2	0	$FeCl_3$	16:84	74:26	81:19	87
3	0	$Me_3Al/BF_3 \cdot OEt_2$[c]	40:60	62:38	71:29	75
4	0	Et_2AlCl	70:30	69:31	78:22	86
5	1	$BF_3 \cdot OEt_2$	4:96	>99:<1	82:18	88
6	1	$Me_3Al/BF_3 \cdot OEt_2$[c]	55:45	72:28	58:42	81
7	1	Et_2AlCl	92:8	63:37	86:14	84
8	1	Me_2AlCl	78:22	79:21	75:25	75
9	2	$BF_3 \cdot OEt_2$	2:98	52:48	52:48	92
10	2	$Me_3Al/BF_3 \cdot OEt_2$[c]	38:62	69:31	52:48	68
11	2	Et_2AlCl	72:28	58:42	57:43	90
12	2	Et_2AlCl/PPh_3[d]	89:11	55:45	52:48	88

[a] Ratios were determined by GC analysis.
[b] Isolated yield.
[c] Reaction conducted using 4 equiv Me_3Al and 1 equiv $BF_3 \cdot OEt_2$.
[d] Reaction conducted using 1.5 equiv Et_2AlCl and 1.65 equiv PPh_3.

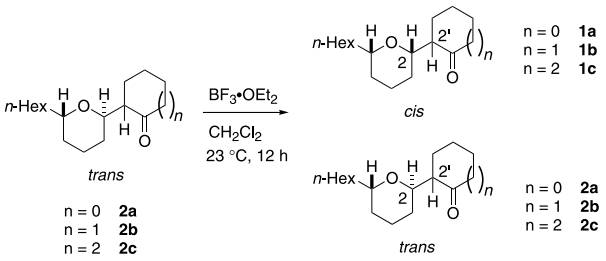
enolate intermediate. The Et_2AlCl mediated rearrangement presumably proceeds via tight ion-pairing and results in modest to good cis:trans selectivities for entries 4, 7, and 11 in Table 1 (70:30, 92:8, and 72:28, respectively).

Previous work had established that the cis-isomer is thermodynamically preferred, relative to the trans-isomer, due to reduced diaxial interactions and Ley has exploited this aspect to access the cis-isomer by epimerizing the trans-isomer with TMSOTf at 23 °C.[6c,d,12] As a result, our attention was focused on the ability to epimerize the stereocenter at the anomeric carbon (C2) in the reaction products. Treatment of the *trans*-ketone **2a–c** (products of entries 1, 3, and 5, respectively, in Table 3) with $BF_3 \cdot OEt_2$ at room temperature resulted in a highly efficient method for the epimerization to the *cis*-ketones **1a–c** (Table 2). All entries showed high cis:trans selectivity and **1a** exhibited good C2–C2′ diastereoselectivity (entry 1).

Our attention next focused on forming products **1a–c** and **2a–c** via a Lewis acid mediated intermolecular substitution reaction of an anomeric acetate (**11**) and enolsilanes (**12a–c**). The results of this substitution study, shown in Table 3, are comparable to the results from the [1,3] O to C rearrangement and the epimerization studies (Tables 1 and 2, respectively). Compound **1a** illustrates a higher selectivity for the cis isomer than in the two previous methods (entry 2; Table 3). While the C2–C2′ selectivities for the cis isomer of **1b** and **1c** (entries 4 and 6, respectively) were disappointing, the room temperature enolsilane addition afforded the α-pyranyl cyclopentanone (**1a**) with good stereoselectivity for the formation of the cis:*anti* diastereomer (entry 2). The enolsilane addition to the oxocarbenium ion derived from **11** at −78 °C yielded the α-pyranyl cycloalkanones (**2a–c**) in high trans:cis diastereoselectivities with modest C2–C2′ diastereoselectivities (entries 1, 3, and 5; Table 3).

Finally, our attention shifted to forming these bonds via an intramolecular conjugate addition. These types of reactions have been employed previously in the synthesis of substituted pyran compounds using a variety of bases including catalytic amounts of KO*t*-Bu.[13] Under these conditions (Table 4), the selectivities observed were comparable to the selectivities obtained in the previously

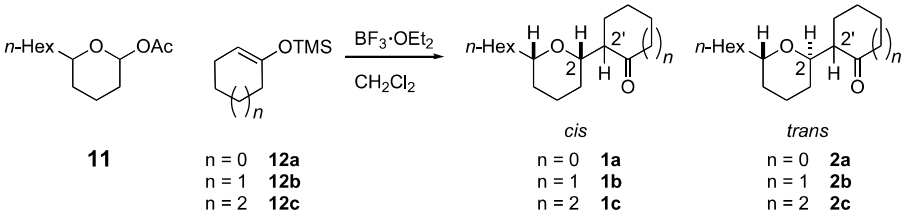
Table 2.



Entry	*n*	cis:trans[a]	cis (*anti*:*syn*)[a]	trans (*anti*:*syn*)[a]	Yield (%)[b]
1	0	93:7	80:20	92:8	98
2	1	97:3	50:50	79:21	96
3	2	99:1	50:50	50:50	97

[a] Ratios were determined by GC analysis.
[b] Isolated yield.

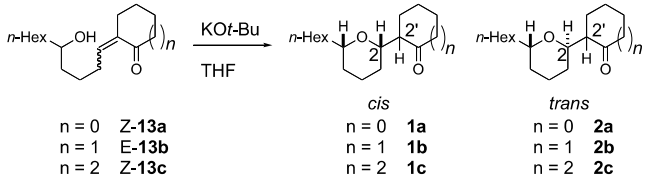
Table 3.



Entry	*n*	Temperature (°C)	Time (h)	cis:trans[a]	cis (*anti*:*syn*)[a]	trans (*anti*:*syn*)[a]	Yield (%)[b]
1	0	−78	1	4:96	64:36	64:36	90
2	0	23	12	98:2	76:24	64:36	86
3	1	−78	1	3:97	70:30	77:23	94
4	1	23	12	98:2	52:48	66:34	87
5	2	−78	1	<1:>99	37:63	57:43	92
6	2	23	12	99:1	52:48	66:34	92

[a] Ratios were determined by GC analysis.
[b] Isolated yield.

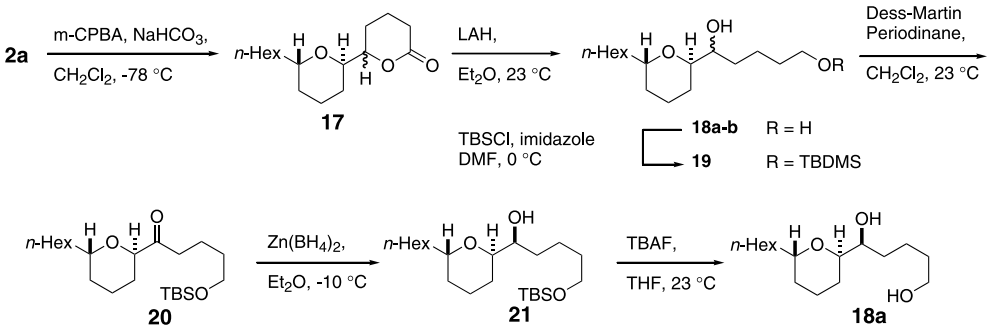
Table 4.



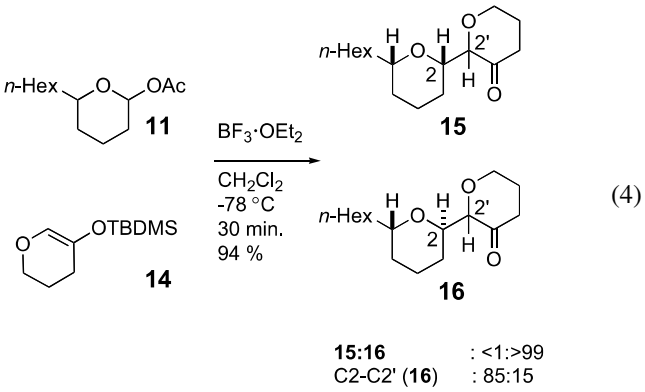
Entry[a]	*n*	Temperature (°C)	Time (min)	cis:trans[b]	cis (*anti*:*syn*)[b]	trans (*anti*:*syn*)[b]	Yield (%)[c]
1	0	−78	30	16:84	74:26	81:19	83
2	0	0	10	96:4	77:23	94:6	88
3	1	−78	30	18:82	60:40	74:26	84
4	1	0	10	98:2	55:45	60:40	86
5	2	−78	30	48:52	55:45	62:38	85
6	2	0	10	89:11	52:48	55:45	90

[a] Starting materials used as >95:5 isomerically enriched favoring the defined olefin isomer.
[b] Ratios of C2/C2′ isomers, determined by GC analysis.
[c] Isolated yield.

listed methods (Tables 1–3). Stereoselectivities in the synthesis of the cis isomer were good to excellent in all the systems that were explored (entries 2, 4, and 6; Table 4). In addition, the C2–C2′ selectivities were poor to modest for systems **1a–c** (entries 2, 4, and 6, respectively). The selectivity towards the trans isomers (**2a–c**) were modest at best for all three substrates and the C2–C2′ selectivities were poor to good (entries 1, 3, and 5; Table 4). In all entries, the yields of the conjugate addition products were good (84–90%).



Scheme 2.



(4)

With these results in hand, we wanted to apply this technique to a system containing a heteroatom in both ring segments. Therefore, enolsilane **14** was prepared according to methods reported by Gallagher and co-workers.[14b] When acetal **11** and enolsilane **14** were treated with $BF_3 \cdot OEt_2$ at −78 °C, the trans-isomers **15** (Eq. 4) were the only observed diastereomers.[15] A control experiment was performed in order to determine whether the more bulky silyl group (TBS / TMS) caused a significant change in the diastereoselectivity observed for the all carbon system (**1b** and **2b**); no significant change in diastereoselectivity was observed at either −78 or 23 °C.[16]

Determination of C2–C2′ stereochemistry was not trivial due to our inability to separate the C2–C2′ diastereomers formed from the reaction products. As a result, we resorted to a chemical correlation to prove stereochemistry (Scheme 2). First, a Baeyer–Villiger oxidation of ketone **2a** affords the lactone **17**. The reduction of **17** with LAH yielded the two diastereomeric diols **18a** and **18b** (3:1), separable by column chromatography on silica gel. The major isomer **18a** was then mono-protected with TBDMSCl and oxidized with Dess–Martin periodinane yielding the ketone **20**. Chelate controlled reduction of **20** with $Zn(BH_4)_2$ resulted in a single diastereomer, **21**.[17] $Zn(BH_4)_2$ delivers the hydride in a manner, which leaves a *syn* relationship between C2 and C2′ (Fig. 2). Following the deprotection of **21** with TBAF and a comparison of spectroscopic data, it was established that the major isomer was that shown as **18a**, corresponding to the rearrangement product *anti* **2a**. This route was also performed on substrates **1a** and **2b**. The assignment of stereochemistry in **1b–c** and **2c** was based on analogies derived from predictable GC retention times of the product diastereomers. Thus, all reactions resulted in the *anti* isomer (C2–C2′) as the major product. We propose that the C2–C2′ *anti* selectivity is a result of the recombination of the oxocarbenium ion and Lewis acid complexed enolate in the lowest energy staggered conformation when the two hydrogen atoms are *anti*-periplanar (Fig. 3). cis:trans Selectivity in the rearrangement is a result of the recombination from either a contact (cis) or solvent separated (trans) ion pair. The cis:trans selectivity in the intermolecular oxocarbenium/enolsilane addition mirror this model (Fig. 3). The epimerization studies reflect thermodynamic (cis) stability.

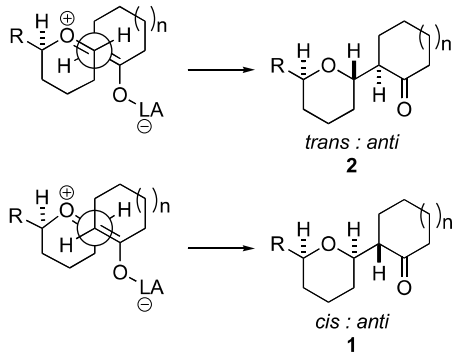


Figure 3.

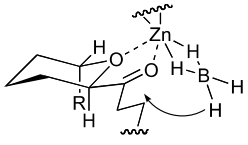
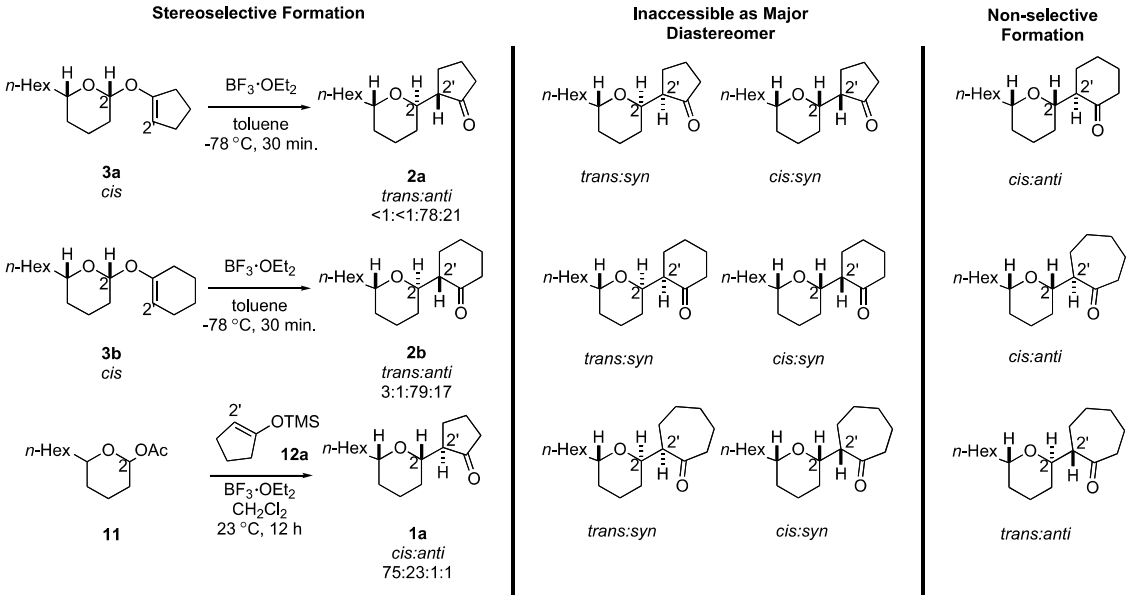


Figure 2.

3. Conclusions

In summary, we have investigated the formation of carbon–carbon bonds between adjacent rings via a stereoretentive rearrangement of cyclic vinyl acetals, an intermolecular addition of an enolsilane into an oxocarbenium ion, and an intramolecular conjugate addition of an ω-hydroxy-α,β-unsaturated ketones. Furthermore, we have shown that the product ratios obtained from the epimerization studies (Table 2) are indeed at their equilibrium positions, as justified by the similar results shown in Tables 3 and 4. The [1,3] oxygen to carbon rearrangement proved the best route for synthesizing the trans:*anti* diastereomer for substrates **2a**



[a]Ratios represented as: (*cis:anti*):(*cis:syn*):(*trans:anti*):(*trans:syn*).

Figure 4.

and **2b** in 70% yield for each of the desired diastereomers (Fig. 4). The enolsilane addition into an in situ generated oxocarbenium ion afforded the cis:*anti* diastereomer in 65% yield for substrate **1a** (Fig. 4). The synthesis of substrates **1b**, **1c**, and **2c** proceeded in a non-selective manner and unfortunately, the synthesis of the C2–C2′ *syn* diastereomers in all cases proved to be stereoselectively inaccessible by these approaches. The most promising result that we have identified is the selective assembly of bis-pyrans such as **16**, of particular relevance to key subsections of the polyether ladder toxins. Efforts at elaborating these substrates to probe the behavior of fully functionalized substrates are ongoing.

4. Experimental

4.1. General

4.1.1. General procedure for the synthesis of cyclic vinyl acetals. A 500 mL, three necked, round bottomed flask with a glass tube to admit ozone, a calcium chloride drying tube, and a glass stopper is charged with 5.109 g (75.0 mmol) of cyclopentene **4a**, 250 mL of CH_2Cl_2, 50 mL of MeOH, and 2.0 g of anhydrous $NaHCO_3$. After the apparatus is cooled to ca. −78 °C, ozone is bubbled through the solution as it is stirred (flow rate =4.0 lpm; 50 V). Ozone addition is stopped when the solution turns blue. Argon is passed through until the blue color is discharged and then the cold bath is removed. The solution is filtered into a 1-L, round-bottomed flask and 80 mL of benzene is added. The volume is reduced to approximately 50 mL by rotary evaporation. After dilution with 225 mL of CH_2Cl_2 the flask is cooled to 0 °C and 16 mL (113 mmol) of TEA and 21.24 mL (225 mmol) of Ac_2O are added via syringe, and the solution is stirred under an argon atmosphere at 0 °C for 15 min. The ice bath is removed and stirring is continued for 4 h. The solution is washed with 150 mL portions of aq 0.1 N HCl, 10% aq NaOH, and H_2O. The organic layer is dried over $MgSO_4$, filtered, and concentrated to provide 9.85 g (89%) of aldehyde–methyl ester **5a** as colorless oil.

A 250 mL round bottomed flask was charged with 1.68 g (12.9 mmol) of **5a** and 40 mL of CH_2Cl_2 then cooled to −50 °C. Next, 2.91 g (26.45 mmol) of PhSH and 4.58 g (32.25 mmol) of $BF_3\cdot OEt_2$ were added successively. The mixture was stirred at −50 °C for 30 min, then poured into a little ice-water and extracted with CH_2Cl_2. The organic layer was washed successively with 30 mL portions of 7% aq KOH, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield 4.22 g (98%) of thioacetal–methyl ester **6a** as a yellow oil.

A 50 mL round bottomed flask was charged with thioacetal–methyl ester **6a** (4.22 g, 12.69 mmol), 3.56 g (63.46 mmol) of KOH, and 40 mL of acetone. The mixture was stirred overnight and then acidified with concd HCl to pH 4. The reaction mixture was extracted with EtOAc (3×50 mL) and washed with 100 mL H_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield a black oil. The crude product was purified by standard acid/base workup to yield 3.6 g (89%) of thioacetal-acid **7a**.

A 25 mL round bottomed flask was charged with 1.0 g (3.14 mmol) of thioacetal-acid **7a**, five drops of dry DMF, and 10.0 mL of benzene, then cooled to 0 °C and 1.24 g (9.73 mmol) of $(COCl)_2$ was added dropwise. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. Excess reagents and solvent were removed by rotary evaporation and the residue was twice treated with 10 mL of benzene and concentrated by rotary evaporation. Reaction yielded 1.04 g (98%) of thioacetal–acyl chloride **8a** as a yellow oil.

To a stirred solution of lactol **9** (0.547 g, 2.94 mmol) in 10 mL THF at −78 °C was added a solution of KHMDS in toluene (0.5 M, 5.94 mL, 2.97 mmol) dropwise, and the reaction mixture was warmed to 0 °C over 5 min before

cooling to −78 °C. A solution of thioacetal–acyl chloride **8a** (1.04 g, 3.09 mmol) in 5 mL THF was added dropwise, and the reaction mixture was stirred for 2 h at −78 °C before quenching with satd aq NH_4Cl (20 mL). Next, distilled water (20 mL) was added and the aqueous layer was extracted with Et_2O (3×25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. Purification by flash column chromatography, eluting with 15% EtOAc in hexanes with 1% TEA, provided 1.10 g (76%) of ester **10a** as a yellow oil in >95:5 cis:trans diastereoselectivity.

Finely powdered 4 Å MS (400 mg), Mg turnings (120 mg, 4.94 mmol), and Cp_2TiCl_2 (1.03 g, 4.12 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure (2–3 mmHg). During this procedure care was taken not to sublime Cp_2TiCl_2. After cooling, THF (5 mL) and $P(OEt)_3$ (1.37 g, 8.24 mmol) were added successively with stirring at room temperature under argon. Within 15 min, the reaction mixture turned dark green and then dark brown with slight evolution of heat. After 3 h, the ester **10a** (0.5 g, 1.03 mmol) in 10 mL THF was added to the reaction mixture dropwise over 20 min. After stirring for 3 h, the reaction was quenched by addition of aq 1 M NaOH (20 mL) and then the insoluble materials were filtered off through Celite and washed with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with aq 1 M NaOH, stirred with deactivated charcoal, and dried over $MgSO_4$. The slurry was then filtered and concentrated. The residue was purified by flash column chromatography, eluting with 25% EtOAc in hexanes containing 1% TEA, to afford 138 mg (32%) of cyclic vinyl acetal **3a** as a colorless oil.

4.1.2. General procedure for rearrangement of cyclic vinyl ethers. To a flame dried 5 mL round bottomed flask was added 5.0 mg (0.019 mmol) of cyclic vinyl ether **3b** and 1.0 mL of toluene. The reaction mixture was cooled to −78 °C and $BF_3\cdot OEt_2$ (2.7 μL, 0.021 mmol) was added dropwise. The reaction was allowed to stir until **3b** was completely consumed as seen by TLC, then quenched with 2 mL of satd aq Na_2CO_3 and separated layers. The aqueous layer was extracted with EtOAc (3×3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 4.4 mg (88%) of a 2:98 (cis:trans) mixture of ketones **1b** and **2b**.

4.1.3. General procedure for the epimerization of *trans*-ketone (2) to *cis*-ketone (1). To a flame dried 5 mL round bottomed flask containing 100 mg (0.438 mmol) of ketone **2b** and 5.0 mL of CH_2Cl_2 was added dropwise at room temperature 124 mg (0.876 mmol) of $BF_3\cdot OEt_2$. The mixture was stirred for 12 h and quenched with 7.0 mL of satd aq Na_2CO_3. The layers were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield 96 mg (96%) of a 98:2 (cis:trans) mixture of ketones **1b** and **2b**.

4.1.4. General procedure for the intermolecular enolsilane addition reaction. To a flame dried 5 mL round bottomed flask was added 22.8 mg (0.10 mmol) of lactol **11**, 25.5 mg (0.15 mmol) of silyl enol ether **12b**, and 1.0 mL of CH_2Cl_2. The reaction was then cooled to −78 °C and 19 μL (0.15 mmol) of $BF_3\cdot OEt_2$ was added dropwise. After 1 h at −78 °C, the reaction was quenched by the addition of 1.0 mL satd aq Na_2CO_3 and extracted with Et_2O (3×10 mL). The organics were combined and washed with H_2O, then satd aq $NaHCO_3$. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to yield 21.2 mg (94%) of 3:97 (cis:trans) mixture of ketones **1b** and **2b**.

4.1.5. General procedure for the conjugate addition. To a flame dried 5 mL round bottomed flask was added 10.0 mg (0.036 mmol) of hydroxy-ketone **13a** and 0.5 mL of THF. The reaction was cooled to 0 °C and 1.0 mg (0.0072 mmol) of KO*t*Bu was added. After 10 min, the reaction was quenched with 0.5 mL of satd aq NH_4Cl and extracted with Et_2O (3×10 mL). The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated to afford 8.8 mg (88%) of 96:4 (cis:trans) mixture of ketones **1a** and **2b**.

4.1.6. Determination of C2–C2′ stereochemistry. A 25 mL round bottomed flask was charged with 370 mg (1.63 mmol) of ketone **2a**, 3.3 mL of aq 0.5 M $NaHCO_3$ (1.63 mmol), and 6.0 mL of CH_2Cl_2. *m*-CPBA (564 mg, 3.27 mmol, purity 77% max) was added portionwise at room temperature and the reaction was allowed to stir overnight. The reaction was quenched by addition of 15% aq Na_2SO_3 (5 mL) and stirred at room temperature for 1 h. The layers were separated and the organic layer was washed with 5 mL portions of H_2O, 5% aq $NaHCO_3$, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 255 mg (55%) of lactone **17**.

To a 125 mL round bottomed flask charged with 255 mg (0.908 mmol) of lactone **17** and 30.0 mL of Et_2O was added portionwise 111 mg (2.937 mmol) of LAH. The reaction was stirred for 12 h, then cooled to 0 °C and added to the reaction flask 0.111 mL of H_2O, 0.111 mL of 15% aq NaOH, and 0.333 mL of H_2O (Fieser workup).[18] The reaction was allowed to stir until the gray solution turned clear. The precipitate was filtered off and the filtered solution was then concentrated to afford a crude oil. The crude oil was purified by flash column chromatography using 90% EtOAc in hexanes as eluant to yield 146 mg (56%) of diol **18a** and 50.6 mg (19%) of diol **18b**.

A 25 mL round bottomed flask was charged with 40 mg (0.140 mmol) of diol **18a** and 2.0 mL of dry DMF. The reaction was cooled to 0 °C and then successively added 11.4 mg (0.168 mmol) of imidazole and 21.9 mg (0.145 mmol) of TBDMSCl. After 15 min, the reaction was diluted with 5.0 mL of Et_2O and 5.0 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 50 mg (89%) of alcohol **19**.

A 5 mL round bottomed flask was charged with 50 mg (0.125 mmol) of alcohol **19**, trace amount of $NaHCO_3$, 84.4 mg (0.200 mmol) of Dess–Martin periodinane, and 1.0 mL of DCM and stirred for 12 h at room temperature.

The reaction mixture was diluted with 2.0 mL satd aq $NaHCO_3$ and 2.0 mL of satd aq $Na_2S_2O_3$, then extracted with Et_2O (3×5 mL). The combined organics were washed with 5 mL portions of H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 48 mg (96%) of ketone **20**.

To a stirred solution of 20.0 mg (0.0502 mmol) of ketone **20** in ether (1.0 mL) was added dropwise a 0.14 M solution of $Zn(BH_4)_2$[19] in ether at −10 °C, and the mixture was stirred at the same temperature for 0.5 h. After quenching with satd aq NH_4Cl (2.0 mL), the resulting mixture was dried over $MgSO_4$, filtered through a pad of Celite, and concentrated to yield 19 mg (94%) of alcohol **21**.

A 5 mL round bottomed flask was charged with 20 mg (0.050 mmol) of alcohol **21**, a solution of TBAF in THF (1.0 M, 0.10 mmol, 0.1 mL), and 0.5 mL of THF. The reaction was allowed to stir at room temperature for 12 h, then quenched with 1.0 mL satd aq $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic layers were washed with 10.0 mL brine, and dried over $MgSO_4$. The slurry was filtered and concentrated to afford 14.0 mg (97%) of diol **18a**.

4.2. Compound characterization

4.2.1. α-Pyranyl-cycloalkonones (1a–c, 2a–c).

4.2.1.1. (2′*S,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclopentanone (1a).** Following the general procedure afforded **1a**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.429 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (2H, d, J=11.3 Hz), 3.56 (1H, ddd, J=10.9, 3.4, 1.9 Hz), 3.19 (2H, m), 0.95–2.33 (46H, m), 0.84 (3H, t, J=7.0 Hz), 0.84 (3H, t, J=9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.0, 219.9, 78.5, 78.2, 77.9, 76.8, 53.8, 53.3, 39.6, 39.5, 36.6, 32.0, 31.6, 31.5, 29.9, 29.5, 29.4, 27.7, 26.4, 25.6, 25.5, 24.4, 23.8, 22.8, 21.3, 21.2, 14.3; IR (NaCl, neat) 2931, 2857, 1738 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_2$, 253.2168. Found 253.2177.

4.2.1.2. (2′*R,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclopentanone (2a).** Following the general procedure afforded **2a**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.365 (15% EtOAc/hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78–3.94 (2H, m), 3.56–3.67 (1H, m), 1.10–2.38 (47H, m), 0.82–0.94 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.1, 219.4, 73.3, 72.4, 69.9, 69.6, 52.8, 51.9, 39.5, 32.7, 32.2, 31.1, 29.7, 29.0, 28.9, 27.7, 26.4, 26.3, 26.0, 25.3, 23.0, 21.2, 21.0, 19.0, 14.5; IR (NaCl, neat) 2931, 2857, 1738 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_2$, 253.2168. Found 253.2177.

4.2.1.3. (2′*S,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclohexanone (1b).** Following the general procedure afforded **1b**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.429 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (1H, ddd, J=11.2, 6.2, 1.5 Hz); 3.51 (1H, ddd, J=10.2, 9.0, 1.3 Hz), 3.22 (2H, m), 2.20–2.49 (6H, m), 0.95–2.40 (44H, m), 0.80–0.90 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 212.1, 78.5, 78.3, 76.5, 76.0, 56.7, 56.1, 42.9, 42.0, 36.8, 36.6, 32.1, 31.7, 30.5, 30.0, 29.5, 29.4, 29.2, 28.5, 28.2, 28.0, 25.8, 25.6, 24.4, 24.0, 23.8, 22.8, 14.3; IR (NaCl, neat) 2931, 2858, 1711 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{31}O_2$, 267.2324. Found 267.2331.

4.2.1.4. (2′*R,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclohexanone (2b).** Following the general procedure afforded **2b**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.341 (15% EtOAc/hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (1H, ddd, J=10.6, 8.1, 3.3 Hz), 3.92 (1H, ddd, J=9.9, 5.9, 4.0 Hz), 3.69 (1H, m), 3.51 (1H, m), 2.53–2.66 (2H, m), 2.37–2.49 (1H, m), 2.20–2.32 (4H, m), 2.07–2.20 (1H, m), 1.45–2.00 (20H, m), 1.13–1.40 (22H, m), 0.77–0.88 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 212.1, 72.4, 71.8, 69.1, 69.0, 54.2, 53.0, 42.9, 41.5, 33.8, 32.8, 30.4, 30.2, 29.8, 29.7, 29.7, 29.4, 28.9, 27.3, 26.1, 24.4, 23.3, 23.0, 19.0, 18.8, 14.4; IR (NaCl, neat) 2931, 2858, 1710 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{31}O_2$, 267.2324. Found 267.2331.

4.2.1.5. (2′*S,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cycloheptanone (1c).** Following the general procedure afforded **1c**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.455 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (1H, ddd, J=12.7, 6.1, 1.6 Hz), 3.18 (1H, m), 2.30–2.62 (3H, m), 2.16–2.19 (1H, m), 1.00–1.98 (23H, m), 0.85 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 215.4, 79.3, 79.0, 78.3, 58.5, 58.4, 44.4, 44.4, 36.7, 36.5, 32.1, 31.9, 31.7, 30.0, 29.7, 29.6, 29.5, 28.8, 28.5, 28.1, 27.4, 26.2, 25.7, 25.6, 25.4, 24.9, 23.9, 22.8, 14.3; IR (NaCl, neat) 2930, 2856, 1702 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2486.

4.2.1.6. (2′*R,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cycloheptanone (2c).** Following the general procedure afforded **2c**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.417 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (2H, ddd, J=15.0, 6.7, 2.6 Hz), 3.72 (1H, m), 3.61 (1H, m), 2.68–2.81 (2H, m), 2.20–2.65 (7H, m), 2.06–2.18 (1H, m), 1.12–1.98 (44H, m), 0.80–0.92 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.8, 214.5, 72.4, 72.2, 72.0, 71.4, 56.5, 55.5, 44.1, 42.2, 33.1, 32.9, 32.2, 32.2, 30.3, 30.1, 29.9, 29.7, 29.6, 28.8, 27.7, 27.6, 26.9, 26.0, 25.0, 24.7, 23.0, 19.1, 18.8, 14.5; IR (NaCl, neat) 2930, 2856, 1702 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2486.

4.2.2. Cyclic vinyl acetals (3a–c).

4.2.2.1. (2*R,6*S**)-2-(Cyclopent-1-enyloxy)-6-hexyl-tetrahydro-pyran (3a).** Following the general procedure afforded **3a** as a yellow oil: R_f=0.309 (25% EtOAc/hex with 1% TEA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (1H, d, J=9.4 Hz), 3.89 (1H, m), 3.37 (1H, m), 1.06–1.88 (22H, m), 0.84 (3H, t, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.4, 92.1, 69.0, 36.4, 36.2, 33.1, 32.0, 31.3, 30.6, 30.0, 29.6, 25.6, 22.8, 22.3, 17.7, 14.3; IR (NaCl, neat) 2932, 2858 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_2$, 253.2168. Found 253.2176.

4.2.2.2. (2*R,6*S**)-2-(Cyclohex-1-enyloxy)-6-hexyl-tetrahydro-pyran (3b).** Following the general procedure afforded **3b** as a yellow oil: R_f=0.283 (25% EtOAc/hex with 1% TEA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (1H, d, J=9.2 Hz), 3.89 (1H, m), 3.37 (1H, m), 1.05–1.89 (24H, m), 0.84 (3H, t, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ

96.7, 92.1, 69.0, 36.4, 36.2, 33.1, 32.0, 31.3, 30.6, 30.0, 29.5, 25.7, 25.6, 22.8, 22.3, 17.7, 14.3; IR (NaCl, neat) 2932, 2858 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{31}O_2$, 267.2324. Found 267.2329.

4.2.2.3. (2*R,6*S**)-2-(Cyclohept-1-enyloxy)-6-hexyl-tetrahydro-pyran (3c).** Following the general procedure afforded **3c** as a yellow oil: R_f=0.278 (25% EtOAc/hex with 1% TEA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (1H, m), 3.88 (1H, m), 3.37 (1H, m), 1.05–1.89 (26H, m), 0.84 (3H, t, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.4, 92.1, 69.0, 36.4, 36.2, 33.1, 32.0, 31.4, 30.6, 30.0, 29.6, 29.5, 25.7, 25.6, 22.8, 22.3, 17.7, 14.3; IR (NaCl, neat) 2931, 2858 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2489.

4.2.3. Hydroxy ketones (13a–c).

4.2.3.1. 2-(5-Hydroxy-undecylidene)-cyclopentanone (13a). Compound **13a** was prepared from the Horner–Wadsworth–Emmons reaction of undecanoic δ-lactol and diethyl 2-oxocyclohexylphosphonate and was isolated as the *Z* isomer as a yellow oil: R_f=0.138 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.5 (1H, dddd, J=2.8, 2.8, 7.5, 10.2 Hz), 3.55 (1H, m), 2.54 (2H, t, J=7.0 Hz), 2.29 (2H, t, J=7.7 Hz), 2.13 (2H, q, J=7.0 Hz), 1.90 (2H, quint., J=7.7 Hz), 1.19–1.67 (15H, m), 0.84 (3H, t, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 137.7, 136.1, 71.9, 38.8, 37.8, 37.2, 32.0, 29.8, 29.5, 26.9, 25.8, 24.7, 22.8, 20.0, 14.3; IR (NaCl, neat) 3430, 2929, 2857, 1718, 1647 cm^{-1}; HRMS (EI+) Calcd for $C_{16}H_{28}O_2$, 252.2089. Found 252.2084.

4.2.3.2. 2-(5-Hydroxy-undecylidene)-cyclohexanone (13b). Compound **13b** was prepared via the ring opening of **1b** with Me_2BBr and Et_3N and was isolated as the *E* isomer as a yellow oil:[20] R_f=0.142; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, t, J=4.3 Hz), 3.55 (1H, m), 2.39 (2H, m), 2.32 (2H, m), 2.15 (2H, m), 1.94 (2H, m), 1.25–1.65 (15H, m), 0.86 (3H, t, J=5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 145.3, 140.0, 72.1, 38.8, 37.7, 37.4, 32.0, 29.7, 29.6, 28.9, 26.2, 25.8, 25.6, 23.4, 22.8, 14.3; IR (NaCl, neat) 3431, 2928, 2856, 1666 cm^{-1}; HRMS (EI+) calcd for $C_{17}H_{30}O_2$, 266.2246. Found 266.2248.

4.2.3.3. 2-(5-Hydroxy-undecylidene)-cycloheptanone (13c). Compound **13c** was prepared from the Horner–Wadsworth–Emmons reaction of undecanoic δ-lactol and diethyl 2-oxocycloheptylphosphonate and was isolated as the *Z* isomer as a yellow oil: R_f=0.150 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (1H, t, J=7.46 Hz), 3.55 (1H, m), 2.56 (2H, m), 2.39 (2H, m), 2.13 (2H, m), 1.20–1.76 (21H, m), 0.85 (3H, t, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 140.9, 139.0, 71.9, 43.5, 37.7, 37.3, 32.0, 31.6, 30.0, 29.5, 28.1, 27.3, 25.8, 25.4, 25.1, 22.8, 14.3; IR (NaCl, neat) 3433, 2927, 2855, 1686, 1616 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2482.

4.2.4. Bipyranyl ketone (16).

4.2.4.1. (2′*R,6′*S**)-6′-Hexylhexahydro-2*H*, 2′*H*-2,2′-bipyran-3(4*H*)-one (16).** Following the general procedure afforded **16** as a yellow oil: R_f=0.175 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (1H, ddd, J=11.7, 5.5, 5.5 Hz, major), 4.09 (1H, m, minor), 4.01 (1H, m, major), 3.91 (d, 1H, J=3.6 Hz, minor), 3.78–3.85 (2H, m), 3.70 (1H, d, J=3.2 Hz, major), 3.62 (1H, ddd, J=11.6, 8.1, 5.1 Hz, major), 2.50–2.64 (1H, m), 2.35–2.46 (1H, m), 2.02–2.27 (1H, m), 1.86–2.00 (1H, m), 1.52–1.80 (7H, m), 1.38–1.50 (1H, m), 1.06–1.38 (13H, m), 0.84 (3H, t, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 208.1, 85.1, 85.0, 73.3, 73.1, 69.6, 69.1, 64.4, 64.8, 37.9, 37.2, 31.8, 30.9, 30.4, 29.2, 29.1, 28.2, 28.4, 26.9, 25.9, 25.6, 25.5, 25.2, 23.8, 22.6, 18.6, 18.2, 14.1; IR (NaCl, neat) 2930, 2857, 1723 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_3$, 269.2117. Found 269.2113.

4.2.5. Determination of C2–C2′ stereochemistry (17–21).

4.2.5.1. (2′*R,6′*S**)-6′-Hexyl-octahydro-[2,2′]-bipyranyl-6-one (17).** Following the general procedure **17** was isolated as a yellow oil: R_f=0.179 (25% EtOAc/hex) major isomer, R_f=0.120 (25% EtOAc/hex) minor isomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (1.5H, ddd, J=3.5, 8.0, 11.11 Hz), 4.19–4.25 (1.25H, m), 3.87 (1H, m), 3.55–3.67 (4H, m), 2.50–2.61 (2.75H, m), 2.36–2.48 (2.75H, m), 1.18–2.11 (60H, m), 0.85 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.6, 82.8, 80.6, 73.2, 72.8, 72.4, 70.7, 32.9, 32.0, 31.0, 30.0, 29.9, 29.7, 29.5, 28.7, 26.4, 26.1, 26.0, 24.6, 23.8, 22.8, 18.7, 18.6, 18.4, 14.3; IR (NaCl, neat) 2931, 2857, 1736, 1241, 1049 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_3$, 269.2117. Found 269.2113.

4.2.5.2. 1-(*S)-(6-(*S**)-Hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentane-1,5-diol (18a).** Following the general procedure **18a** was isolated as a clear oil: R_f=0.242 (90% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (1H, m), 3.55–3.64 (3H, m), 3.42 (1H, dddd, J=4.1, 4.1, 8.8, 13.3 Hz), 2.25 (1H, s), 1.82 (1H, s), 1.18–1.79 (22H, m), 0.85 (3H, t, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 73.0, 72.4, 62.9, 32.8, 32.0, 31.9, 31.2, 29.5, 29.1, 26.2, 24.9, 22.8, 22.3, 18.3, 14.3; IR (NaCl, neat) 3344, 2930, 2858, 1077, 1037 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{33}O_3$, 273.2430. Found 273.2427.

4.2.5.3. 1-(*R)-(6-(*S**)-Hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentane-1,5-diol (18b).** Following the general procedure **18b** was isolated as a clear oil: R_f=0.328 (90% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (1H, ddd, J=4.3, 4.3, 8.8 Hz), 3.61 (2H, t, J=6.0 Hz), 3.54 (1H, ddd, J=2.5, 8.4, 10.3 Hz), 3.34 (1H, ddd, J=2.7, 7.8, 10.7 Hz), 2.77 (1H, s), 1.83 (1H, s), 1.18–1.75 (22H, m), 0.84 (3H, t, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.7, 72.4, 72.0, 62.9, 32.9, 32.6, 32.4, 32.0, 29.5, 29.4, 26.7, 26.0, 22.8, 21.9, 18.6, 14.3; IR (NaCl, neat) 3402, 2932, 2858, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{33}O_3$, 273.2430. Found 273.2441.

4.2.5.4. 5-(*t*-Butyl-dimethyl-silanyloxy)-1-(*S)-(6-(*S**)-hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentan-1-ol (19).** Following the general procedure **19** was isolated as a clear oil: R_f=0.424 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (1H, m), 3.54–3.62 (3H, m), 3.42 (1H, ddd, J=4.3, 4.3, 8.8 Hz), 2.01 (1H, d, J=3.9 Hz), 1.18–1.79 (22H, m), 0.86 (9H, s), 0.85 (3H, t, J=7.2 Hz), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 72.4, 63.4, 33.0, 32.2, 32.0, 31.3, 29.5, 29.1, 26.2, 24.8, 22.8, 22.4, 18.4, 18.3, 14.3, −5.1; IR (NaCl, Neat) 3434, 2930, 2857, 1100,

1040 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{47}O_3Si$, 387.3294. Found 387.3296.

4.2.5.5. 5-(*t*-Butyl-dimethyl-silanyloxy)-1-(6-(*S)-hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentan-1-one (20).** Following the general procedure **20** was isolated as a clear oil: R_f=0.282 (10% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (1H, dd, J=4.3, 4.3 Hz), 3.58 (2H, t, J=6.4 Hz), 3.42 (1H, m), 2.59 (1H, ddd, J=1.8, 1.8, 6.2 Hz), 2.53 (1H, ddd, J=1.8, 1.8, 6.2 Hz), 1.92 (1H, m), 1.20–1.67 (19H, m), 0.86 (9H, s), 0.85 (3H, t, J=6.0 Hz), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 78.5, 74.4, 63.1, 38.4, 35.3, 32.6, 32.0, 30.7, 29.6, 26.2, 25.8, 25.2, 22.8, 20.2, 19.7, 18.5, 14.3, −5.1; IR (NaCl, neat) 2930, 2857, 1717, 1101 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{45}O_3Si$, 385.3138. Found 385.3128.

4.2.5.6. 5-(*t*-Butyl-dimethyl-silanyloxy)-1-(*S)-(6-(*S**)-hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentan-1-ol (21).** Following the general procedure **19** was isolated as a clear oil: R_f=0.424 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (1H, m), 3.54–3.62 (3H, m), 3.42 (1H, ddd, J=4.3, 4.3, 8.8 Hz), 2.01 (1H, d, J=3.9 Hz), 1.18–1.79 (22H, m), 0.86 (9H, s), 0.85 (3H, t, J=7.2 Hz), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 72.4, 63.4, 33.0, 32.2, 32.0, 31.3, 29.5, 29.1, 26.2, 24.8, 22.8, 22.4, 18.4, 18.3, 14.3, −5.1; IR (NaCl, Neat) 3434, 2930, 2857, 1100, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{47}O_3Si$, 387.3294. Found 387.3296.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.042

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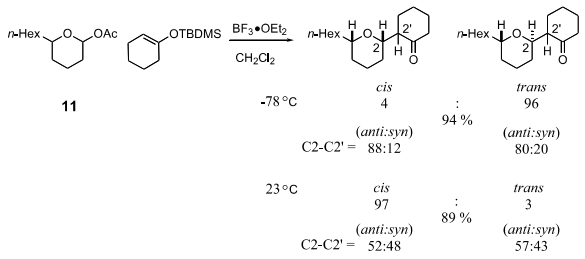
15. At 23 °C, this reaction also provided trans-isomer as the major adduct (<1:>99; cis:trans). Efforts to epimerize trans to cis have so far met with failure. cis C2–C2′ diastereoselectivity deteriorated to 75:25 (*anti*:*syn*) at 23 °C.
16. The resultant diastereomers obtained are comparable with entries 3 and 4 in Table 3.



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