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Synthesis of Plakortethers F and G

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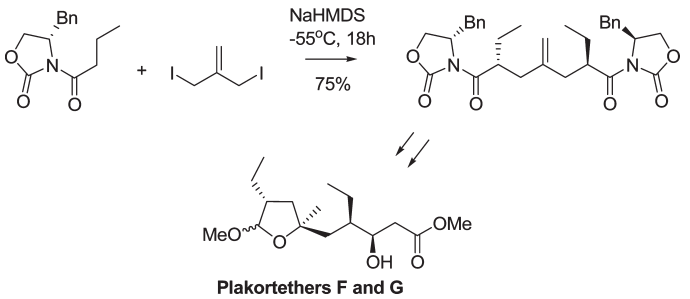

Plakortethers F and G

Synthesis of plakortethers F and G has been performed by taking advantage of the symmetry in the structure. The structures of the prepared compounds have been confirmed by COSY, 1D NOE, and chemical transformation studies. The synthetic plakortether F was found to match the natural product by all physical data. The synthetic plakortether G exhibited several disagreements in ^{13}C NMR data with the reported values. However, on the basis of an extremely close match in appearance of its ^{1}H NMR spectrum to the obtained ^{1}H NMR spectrum of the natural product, as well as matching optical rotations, the two compounds are believed to be identical.

Introduction

Sponges of the genus *Plakortis* have served as the source of a number of related natural products. These natural products have exhibited several interesting types of biological activity, such as antimalarial,[1] antibacterial,[2] and antitumor.[3] Structurally, these are poliketides (often butyrate derived) that have been known to contain cyclic peroxide and lactone functionalities, as well as, in some cases, an all-carbon bicyclic framework, evidently resulting from biosynthetic intramolecular Diels−Alder reaction.[4] These compounds enjoyed significant attention as targets for total synthesis.[5]

Recently, a set of unusual secondary metabolites of plakortin[1] have been isolated from *Plakortis simplex* and have shown a selective cytotoxic activity against the RAW 264-6 cell line.[6] These new compounds, named plakortethers A−G, possessed the parent plakortin carbon skeleton but featured additional functionality, most notably an unusual highly substituted tetrahydrofuran fragment. Later, a related alkaloid simplakidine A was isolated from the same source, additionally containing a pyridine ring (Figure 1).[7] While generally tetrahydrofurans are very commonly encountered in natural products, tetrahydrofurans with this density of substitution (2,2,4,5-tetrasubstituted) are much more rare.

No synthesis of plakortethers A−G has been reported to date. The following report describes a preparation of the proposed structures of plakortethers F and G by taking advantage of the symmetry in the structure.

Results and Discussion

Our approach to plakortethers F and G (**1a** and **1b**, Scheme 1) stemmed from the recognition of the partial

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(2) Fattorusso, E.; Parapini, S.; Campagnuolo, C.; Basilico, N.; Taglialatela-Scafati, O.; Taramelli, D. *J. Antimicrob. Chemother.* **2002**, *50*, 883.
(3) Pettit, G. R.; Nogawa, T.; Knight, J. C.; Doubek, D. L.; Hooper, J. N. A. *J. Nat. Prod.* **2004**, *67*, 1611.
(4) Huang, X.; Soest, R. V.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2004**, *6*, 75.
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(6) Campagnuolo, C.; Fattorusso, E.; Taglialatela-Scafati, O.; Ianaro, A.; Pisano, B. *Eur. J. Org. Chem.* **2002**, 61.
(7) Campagnuolo, C.; Fattorusso, C.; Fattorusso, E.; Ianaro, A.; Pisano, B.; Taglialatela-Scafati, O. *Org. Lett.* **2003**, *5*, 673.

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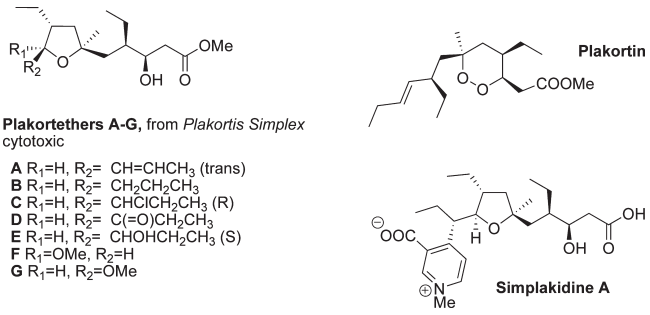


Plakortethers A-G, from *Plakortis Simplex* cytotoxic

A R_1=H, R_2= CH=CHCH$_3$ (trans)
B R_1=H, R_2= $CH_2CH_2CH_3$
C R_1=H, R_2= $CHClCH_2CH_3$ (R)
D R_1=H, R_2= $C(=O)CH_2CH_3$
E R_1=H, R_2= $CHOHCH_2CH_3$ (S)
F R_1=OMe, R_2=H
G R_1=H, R_2=OMe

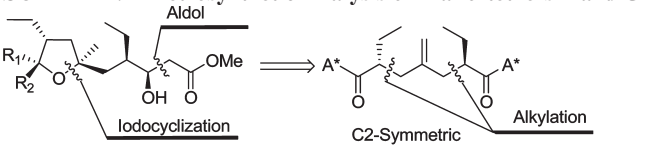
FIGURE 1. Plakortethers and related compounds.

symmetry in the structures of these compounds. The disconnection of the 3-hydroxyester via acetate aldol and the tetrahydrofuran ring via iodocyclization leads to a completely C_2-symmetric intermediate that can be assembled via a bis-alkylation of a conveniently allylic dihalide by a chiral auxiliary modified butyrate (Scheme 1).

The synthesis was initiated via a bis-alkylation of 3-iodo-2-(iodomethyl)prop-1-ene, **3** (X = I), obtained from the commercial 3-chloro-2-(chloromethyl)prop-1-ene,[8] by the enolate of oxazalidinone **2** (Table 1). In the initial experiments, low yields and poor reproducibility were observed, producing only small amounts, if at all, of the desired bis-alkylated product, **4**, either with lithium or sodium enolates. Isolation of the monoalkylated product **5**, along with the unsubstituted 4-benzyloxazolidin-2-one, **6**, suggested a competitive decomposition of the enolate, possibly by the ketene pathway.[9] Maintaining a low temperature (at or below −50 °C) throughout the course of the reaction resolved this problem (Table 1, entry 4). Isolation of small amounts of unsubstituted 4-benzyloxazolidin-2-one, **6**, indicated that the enolate decomposition was still taking place, although apparently at a slow enough rate to permit the target alkylation to happen. Under optimized conditions, the bis-alkylation product was cleanly obtained in 75% yield with no detectable amount of undesired diastereomers.

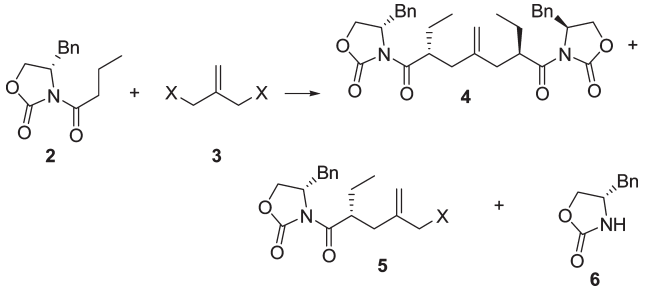
The resulting C_2-symmetric intermediate **4** was subjected to iodolactonization using the standard conditions (I_2−$NaHCO_3$−H_2O−CH_3CN).[10] Slow formation of iodolactones **8a**,**b** was observed, along with several unidentified byproducts. It was found that the use of I_2 in THF−H_2O, followed by treatment with silica gel, provided a cleaner reaction and superior yields. Under the latter conditions the initial product that formed appeared to be acyclic iodohydrin **7**.[11] It could be observed in the crude reaction mixture, but would very easily cyclize to lactones **8a**,**b**, particularly in the course of flash chromatography. Thus, it was converted to the iodolactones by treatment with silica gel, and the iodolactones were isolated. Under both conditions, iodolactones **8a** and **8b** formed as a separable mixture of diastereomers in an approximately 1.5:1 ratio (Scheme 2).

SCHEME 1. Retrosynthetic Analysis of Plakortethers F and G



1a R_1=OMe, R_2=H
1b R_1=H, R_2=OMe

TABLE 1. Optimization of the Alkylation Step



			yield (%)		
entry	X	conditions[a]	**4**	**5**	**6**
1	Br	NaHMDS, THF −78 → −25 °C, 8 h[b]	3	ND[c]	10
2	I	NaHMDS, THF −78 → −25 °C, 8−16 h[b]	0−2	50−60	10−15
3	I	LDA, THF −78 → −25 °C, 8 h[b]	0	20	6
4	I	NaHMDS, THF −55 °C, 16 h	75	0	5

[a]In all cases, the reaction was carried out by addition of **3** to 2.5 equiv of the enolate of **2** in THF. [b]After addition of **3** to the enolate at −78 °C, the mixture was gradually (over ∼1.5 h) warmed to −25 °C and kept at −25 °C for the remainder of the reaction time. [c]Not determined. The monoalkylated product appeared to form in substantial quantities but could not be separated from unreacted **2** and characterized.

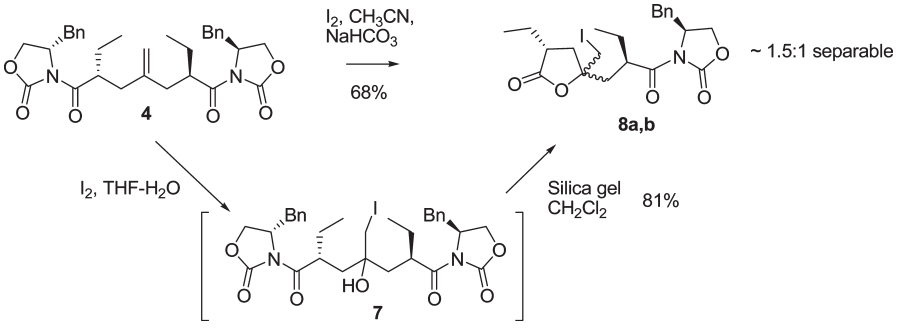
The major diastereomer **8a** was hydrogenolyzed and then reduced by sodium borohydride to provide the alcohol, which was assigned configuration **10b** on the basis of the observed NOE correlation (Scheme 3).

Despite our hopes, the influence of the chiral auxiliary did not bring the diastereoselectivity of iodocyclization to a useful level. The possibility to improve the diastereoselectivity via the change of the chiral auxiliary was briefly explored but was not pursued any further due to a poor availability of the chiral auxiliaries that are potentially effective for this transformation.[12] Instead, we decided to exploit the symmetry of the structure. Since both diastereomers of the alcohol (**10a** and **10b**, Scheme 4) could be utilized, thanks to their nearly symmetric nature, the diastereoselectivity control was not necessary, as long as the diastereomers could be separated.

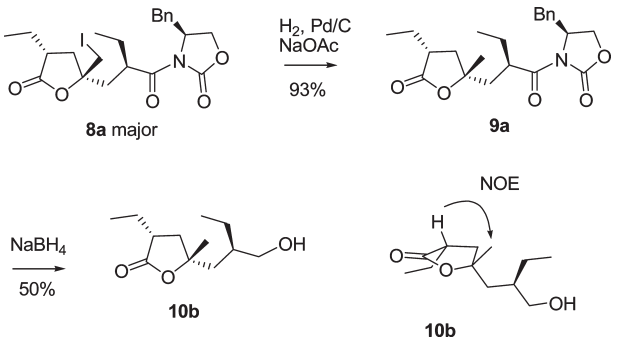
Thus, starting with **4**, the chiral auxiliaries were removed by peroxide-assisted hydrolysis,[13] producing diacid **11** that readily and cleanly cyclized upon treatment with trifluoroacetic acid at room temperature for 8 h. The resulting diastereomeric lactonic acids **12a** and **12b** were obtained as a mixture with the same ratio of approximately 1.5:1. This ease of the cyclization of the diacid is notable, since, in

(8) Purchased from Acros Organics, product code 277070050.
(9) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(10) Silva, F. M. D.; Junior, J. J.; Mattos, M. C. D. *Curr. Org. Synth.* **2005**, *2*, 393.
(11) Curiously, the opposite trend was observed in iodocyclization of amides: basic conditions tended to produce iodohydrins, while acidic produce lactones: Maligres, P. E.; Weissman, S. A.; Upadhyay, V.; Cianciosi, S. J.; Reamer, R. A.; Purick, R. M.; Sager, J.; Rossen, K.; Eng, K. K.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1996**, *52*, 3327.
(12) Moon, H.; Eisenberg, S. W. E.; Wilson, M. E.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1994**, *59*, 6504.
(13) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

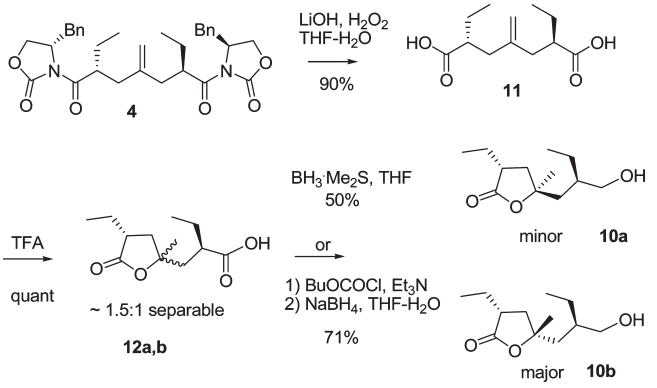
SCHEME 2. Idocyclization of 4



SCHEME 3. Determination of Stereoselectivity in the Iodocyclization

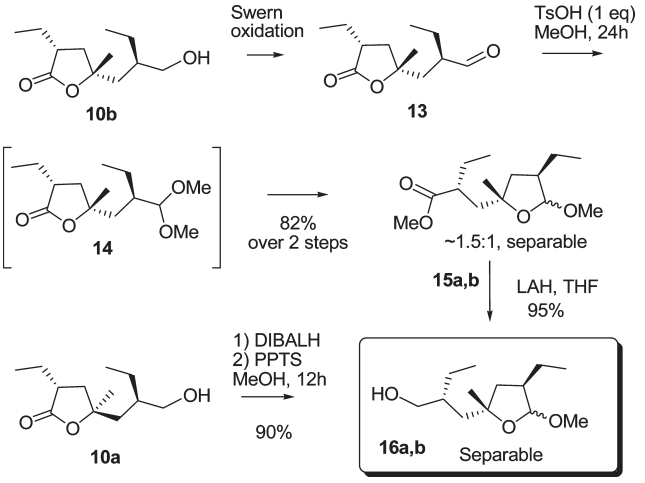


SCHEME 4. Simplification of the Sequence



comparison, **4** was inert to trifluoroacetic acid or $HClO_4$ in $THF-H_2O$, probably due to added steric hindrance from the presence of the two auxiliaries. Separation of the diastereomers of the lactonic acids was possible by flash chromatography via a careful choice of chromatographic system (2-propanol−hexanes proved effective). It was later found that separation of alcohols **10a** and **10b**, obtained after the reduction, was more convenient. The reduction could be performed using borane−dimethyl sulfide complex in THF,[14] although noticeable overreduction was observed. Superior results were obtained using the method that

SCHEME 5. Preparation of the Key Intermediates 16a and 16b



involves formation of the mixed anhydride followed by its reduction with sodium borohydride.[15]

Comparison of the NMR data confirmed that the observed major diastereomer was equivalent to **10b**, indicating that the stereoselectivity of the cyclization was the same as in the iodocyclization. Both alcohol **10a** and its diastereomer **10b** were then independently converted to the desired key intermediates **16a** and **16b** (Scheme 5).

The major diastereomer of the alcohol **10b** was oxidized to the aldehyde and treated with *p*-toluenesulfonic acid in methanol. Initially formed dimethyl acetal **14**, which could be observed in the reaction mixture and isolated from the reaction mixture at incomplete conversions, upon longer exposure to the reaction conditions was converted to cyclic acetals **15a**,**b**, apparently via an opening of the lactone and a subsequent closing of the cyclic acetal ring. The acetal was formed as an approximately 1.5:1 mixture of diastereomers at the acetal center, corresponding to the configuration of plakortethers F (**15a**) and G (**15b**), respectively. The mixture was separable. The separation, however, was found to be more convenient at the next step. Lithium aluminum hydride reduction of **15a**,**b** provided alcohols **16a** and **16b**.

The minor diastereomer of the alcohol **10a**, in turn, was converted to the same key intermediates **16a** and **16b** by a sequence of a reduction with DIBALH and treatment with *p*-toluenesulfonic acid in methanol (**16a** and **16b** were

(14) Examples of the reduction of carboxylic acids in presense of a butyrolactone in BH_3 in THF: (a) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273–2273. (b) Fuji, K.; Node, M.; Terada, S.; Murata, M.; Nagasawa, H.; Taga, T.; Machida, K. *J. Am. Chem. Soc.* **1985**, *107*, 6404. (c) Janssen, A. J. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 5513.

(15) An example of the reduction of a carboxylic acid in presense of a butyrolactone: Burke, S. D.; Shankaran, K.; Helber, M. J. *Tetrahedron Lett.* **1991**, *32*, 4655.

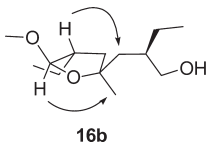


FIGURE 2. NOE confirmation of the stereochemistry of **16b**.

obtained as a 1:1 mixture in this case). 1D NOE study showed that the more polar isomer **16b** had the configuration corresponding to plakortether G while also confirming the expected configuration around the acetal ring (Figure 2).

After separation, diastereomers **16a** and **16b** were independently converted to target **1a** and **1b**. Swern oxidation of alcohol **16a** provided the aldehyde, which was unstable and had to be immediately used (storage for 8 h at −15 °C resulted in significant decomposition of the material). It was subjected to samarium(II) iodide mediated Reformatsky reaction using bromoacetylated Evans oxazalidinone[16] to provide aldol adduct **17a** as the major diastereomer (formation of small amounts of the minor diastereomer was also observed, but it could be separated by flash chromatography).

Hydrogen peroxide assisted hydrolysis, followed by a careful acidification (decreasing pH below 3 tended to lead to transformations of the acetal moiety) provided the free carboxylic acid, which was immediately converted to methyl ester using the trimethylsilyldiazomethane method (Scheme 6).[17] Compound **1a**, thus obtained, was a satisfactory match to the natural plakortether F by ^{1}H, ^{13}C, and HRMS data as well as by the value and sign of specific rotation.

The same sequence of aldol condensation, peroxide-assisted hydrolysis and methylation, performed on alcohol **16b** provided **1b** (Scheme 7). In this case, however, while the sign and value of specific rotation matched, the NMR data showed significant deviations from those reported for plakortether G. While a good match was observed in ^{1}H NMR chemical shifts, certain disagreements in the coupling constants were seen. The *J* values for the acetal hydrogen (H9, numbering as shown in Table 2) noticeably differed, as did the coupling constants for the proton in the CH_2 on the acetal ring (H7b). The latter discrepancy appears to indicate a typo in the original report, as no common *J* value is listed between the reportedly interacting protons H7a and H7b. The most significant differences, however, were observed in the ^{13}C chemical shifts. The signal for the acetal carbon (C9) was displaced by 5.6 ppm in ^{13}C NMR, the alcohol carbon (C3) by 1.9 ppm, acetal methoxy (C15) by 2.6 ppm, C7 by 2.1 ppm, and C10 by 2.6 ppm. Smaller differences are observed for other carbons (Table 2).

To confirm the structure of the prepared compound, additional NMR studies were performed. COSY confirmed the ^{1}H NMR peak assignments, coinciding with the assignments in the original report. Observed NOE correlations confirmed the proposed configuration of the acetal center in both **1a** and **1b**, as well as the relative configuration of substituents around the acetal ring in **1b** (Figure 3).

Furthermore, treatment of both **1a** and **1b** with pyridinium tosylate in chloroform at 45 °C produced the same

SCHEME 6. Completion of the Synthesis of 1a

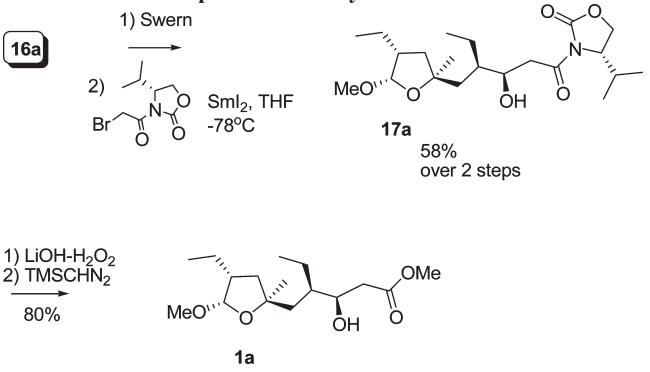
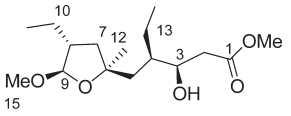
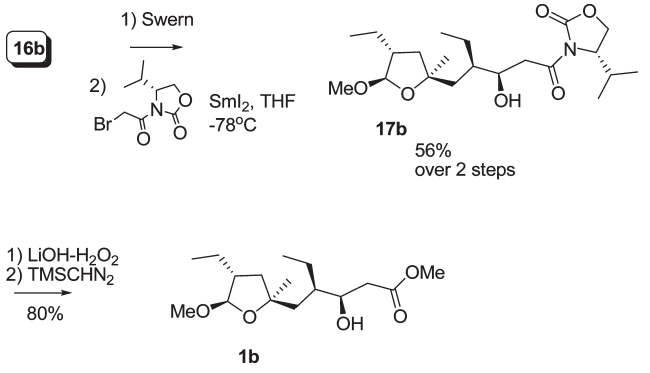


TABLE 2. Differences in the NMR Data for 1b



entry	signal	reported	obsd
1	H9	4.65 (d, *J* = 3.2 Hz)	4.66 (d, *J* = 5 Hz)
2	H7b	1.48 (dd, *J* = 1.5, 2 Hz)	1.49 (dd, *J* = 12, 10 Hz)
3	C1	173.6	173.9
4	C2	37.6	38.1
5	C3	71.4	69.5
6	C4	42.2	41.5
7	C5	42.1	41.3
8	C6	83.8	84.5
9	C7	43.6	45.7
10	C9	107.1	112.7
11	C10	21.9	24.5
12	C12	26.9	26.8
13	C13	27.1	26.0
14	C15	54.8	57.4

SCHEME 7. Completion of the Synthesis of 1b



bicyclic acetal, **18**, confirming the identical configuration of both compounds with the exception of the acetal center (Scheme 8).

NOE correlations, obtained in **18**, were also consistent with the assigned stereochemistry (Figure 4).

To clarify the matter, we have contacted the authors of the original paper. Dr. Taglialatela-Scafati graciously provided us with a copy of the ^{1}H NMR spectrum of the natural plakortether G (included in the Supporting Information) as well as a confirmation that the reported odd *J* values are a

(16) Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702.
(17) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475.

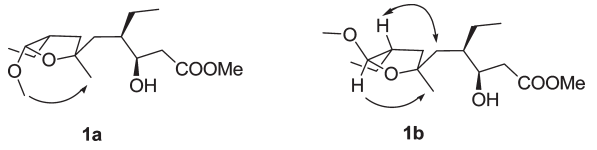
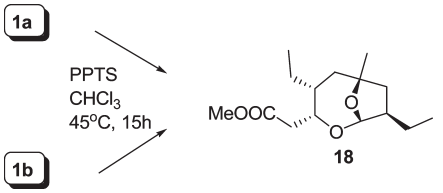


FIGURE 3. NOE correlations in the synthetic **1a** and **1b**.

SCHEME 8. Conversion of 1a and 1b to Rigid Bicycle 18



recording error, with the actual J values matching our findings. A nearly photographic match in the appearance of the key regions of the spectra leads us to believe the two compounds are identical. The nature of the differences in the ^{13}C NMR data, however, is still unclear.

Conclusion

Thus, synthesis of plakortethers F and G was achieved by taking advantage of the symmetry of the structure. The structure of the obtained compounds was confirmed by the COSY and 1D NOE NMR data, as well as by chemical transformations. The synthetic plakortether F matched the natural counterpart by ^1H, ^{13}C NMR, and optical rotation data. The synthetic plakortether G exhibited several inexplicable differences in ^{13}C NMR data with the reported values, but it is also believed to match the natural counterpart on the basis of optical rotation, ^1H NMR data, and the identical appearance of the ^1H NMR spectrum. Further synthetic studies to confirm the structure of plakortethers are being performed and will be reported in due course.

Experimental Section

Preparation of 3-Iodo-2-(iodomethyl)prop-1-ene. To the solution of 3-chloro-2-(chloromethyl)prop-1-ene (3 g, 24 mmol, purchased from Acros Organics) in acetone (50 mL) was added sodium iodide (10.8 g, 72 mmol), and the reaction mixture was refluxed for 10 h. Then, the reaction mixture was cooled and vapped almost to dryness, and the residue was treated with hexanes (70 mL) and water (70 mL). After shaking and separation of layers, the organic layer was washed with saturated Na_2SO_3 (10 mL) and brine, dried, and carefully concentrated. The product was obtained as a white solid, 7.01 g (95%).

Preparation of (4*S*,4′*S*)-3,3′-((2*R*,6*R*)-1,7-Dioxo-2,6-diethyl-4-methylene-1,7-heptanediyl)bis(4-benzyl)-2-oxazolidinone (4) by Alkylation. Butyryl oxazalidinone **2** (1.2 g, 4.86 mmol) was dissolved in THF (7 mL) and cooled to −55 °C (using a recirculative cooler). A solution of sodium hexamethyldisilazide (2.5 mL, 2 M in THF, purchased from Acros Organics, 5 mmol) was added dropwise. After the miture was stirred for 40 min at −55 °C, a solution of 3-iodo-2-(iodomethyl)prop-1-ene (598 mg, 1.95 mmol, prepared as described above, immediately before use dissolved in hexanes, filtered through basic Al_2O_3, and evaporated) in THF (3 mL) was added. The reaction mixture was stirred at −55 °C for 16 h and then quenched with saturated NH_4Cl. After being warmed to rt, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate

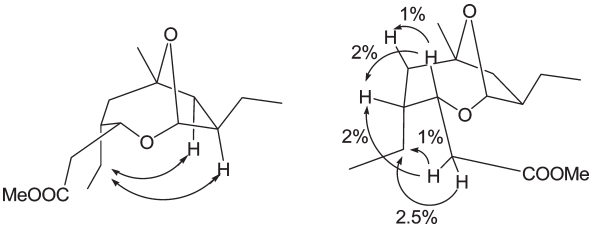


FIGURE 4. NOE correlations in **18**.

(3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Chromatography (EtOAc/hexanes, 0:1 to 3:7) provided 797 mg (75%) of bis-oxazalidinone **4** as a pale yellow oil.

(4*S*,4′*S*)-3,3′-((2*R*,6*R*)-1,7-Dioxo-2,6-diethyl-4-methylene-1,7-heptanediyl)bis(4-benzyl)-2-oxazolidinone (4): pale yellow oil; R_f 0.6 (3:7 EtOAc/hexanes); $[\alpha]^{20}_D$ = +33 (0.147, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.18−7.35 (m, 10H), 4.87 (s, 2H), 4.66−4.73 (m, 2H), 4.06−4.19 (m, 6H), 3.33 (dd, J = 13, 3 Hz, 2H), 2.69 (dd, J = 13, 10.5 Hz, 2H), 2.60 (dd, J = 14.5, 8 Hz, 2H), 2.27 (dd, J = 14, 6 Hz, 2H), 1.68−1.79 (m, 2H), 1.57−1.66 (m, 2H), 0.94 (t, J = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.4 (C), 153.4 (C), 144.6 (C), 135.8 (C), 129.6 (CH), 129.0 (CH), 127.3 (CH), 113.5 (CH2), 66.0 (CH2), 55.7 (CH), 42.3 (CH), 38.7 (CH2), 38.1 (CH2), 25.5 (CH2), 11.8 (CH3); HRMS (ESI) calcd for $C_{32}H_{38}N_2O_6Na$ [M+Na] 569.2622, found 569.2625.

Also isolated during the initial experimentation, at incomplete conversion:

(*S*)-3-((*R*)-2-Ethyl-4-(iodomethyl)pent-4-enoyl)-4-benzyloxazolidin-2-one (5): pale yellow oil, darkens on standing; R_f 0.35 (1:4 EtOAc/hexanes); $[\alpha]^{20}_D$ = +24 (0.183, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.32−7.36 (m, 2H), 7.29 (d, J = 7 Hz, 1H), 7.22 (d, J = 7 Hz, 2H), 5.31 (s, 1H), 5.00 (s, 1H), 4.66−4.73 (m, 1H), 4.13−4.20 (m, 2H), 4.03−4.09 (m, 2H), 3.99 (d, J = 9.5 Hz, 1H), 3.27 (dd, J = 13, 3 Hz, 1H), 2.64−2.72 (m, 2H), 2.52 (dd, J = 14.5, 5.5 Hz, 1H), 1.70−1.79 (m, 1H), 1.56−1.66 (m, 1H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 176.0 (C), 153.4 (C), 144.5 (C), 135.4 (C), 129.6 (CH), 129.1 (CH), 127.5 (CH), 115.9 (CH2), 66.1 (CH2), 55.7 (CH), 42.4 (CH), 38.2 (CH2), 36.7 (CH2), 25.8 (CH2), 11.7 (CH3), 10.5 (CH2); HRMS (ESI) calcd for $C_{18}H_{23}NO_3I$ $[M+H]^+$ 428.0717, found 428.0715.

Iodocyclization of (4*S*,4′*S*)-3,3′-((2*R*,6*R*)-1,7-Dioxo-2,6-diethyl-4-methylene-1,7-heptanediyl)bis(4-benzyl)-2-oxazolidinone (4). To the solution of bis-oxazalidinone **4** (50 mg, 0.092 mmol) in THF (0.5 mL) and water (0.1 mL) was added iodine (116 mg, 0.46 mmol). The mixture was stirred at rt for 36 h while being monitored by TLC. Upon disappearance of the starting material, the solution was diluted with EtOAc (20 mL) and washed with saturated solution of Na_2SO_3 (20 mL). The organic layer was washed with brine, dried, and concentrated. The crude iodohydrin was dissolved in methylene chloride (5 mL) and stirred with silica gel (200 mg) for 10 h. The reaction mixture was filtered, the silica gel was washed with ethyl acetate (2 × 30 mL), and the combined organic washings were concentrated. Chromatography (EtOAc/hexanes, 0:1 to 3:7) afforded the two diastereomers of the product, **8a** (23 mg, 49%) and **8b** (15 mg, 32%).

(*S*)-3-((*R*)-2-(((2*S*,4*R*)-4-Ethyltetrahydro-2-(iodomethyl)-5-oxofuran-2-yl)methyl)butanoyl)-4-benzyloxazolidin-2-one (8a): pale yellow oil; R_f 0.5 (1:4 EtOAc/hexanes); $[\alpha]^{20}_D$ = +22 (0.027, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.25−7.36 (m, 5H), 4.60−4.68 (m, 1H), 4.06−4.23 (m, 3H), 3.59 (dd, J = 13.5, 3 Hz, 1H), 3.34 (s, 2H), 2.89 (dd, J = 13.5, 11.5 Hz, 1H), 2.66−2.74 (m, 1H), 2.63 (dd, J = 14.5, 11 Hz, 1H), 2.53 (dd, J = 13, 9.5 Hz, 1H), 1.95−2.07 (m, 3H), 1.69−1.76 (m, 1H), 1.52−1.65 (m, 2H, overlapped with water peak), 1.03 (t, J = 7.5 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.6 (C), 176.3 (C), 153.7

(C), 136.7 (C), 129.6 (CH), 129.0 (CH), 127.1 (CH), 82.7 (C), 66.2 (CH2), 56.4 (CH), 42.0 (CH2), 41.8 (CH), 38.7 (CH), 37.3 (CH2), 35.8 (CH2), 27.4 (CH2), 23.8 (CH2), 12.7 (CH2), 12.4 (CH3), 11.5 (CH3); HRMS (ESI) calcd for $C_{22}H_{29}NO_5I$ [M + H] 514.1085, found 514.1092.

(*S*)-3-((*R*)-2-(((2*R*,4*R*)-4-Ethyltetrahydro-2-(iodomethyl)-5-oxofuran-2-yl)methyl)butanoyl)-4-benzyloxazolidin-2-one (8b): pale yellow oil; R_f 0.45 (1:4 EtOAc/hexanes); $[\alpha]^{20}_D$ = +33 (0.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29−7.34 (m, 2H), 7.21−7.28 (m, 3H), 4.60−4.67 (m, 1H), 4.17 (dd, J = 9, 2.5 Hz, 1H), 4.14 (d, J = 7 Hz, 1H), 4.02−4.11 (m, 1H), 3.71(d, J = 10.5 Hz, 1H), 3.56 (dd, J = 13.5, 3 Hz, 1H), 3.39 (dd, J = 10.5, 1.5 Hz, 1H), 2.72−2.81 (m, 2H), 2.57 (dd, J = 14, 11.5 Hz, 1H), 2.33 (dd, J = 13, 9 Hz, 1H), 2.19 (dd, J = 15, 1.5 Hz, 1H), 1.87−1.95 (m, 1H), 1.84 (dd, J = 13, 12 Hz, 1H), 1.64−1.74 (m, 1H), 1.47−1.57 (m, 2H), 0.99 (m, J = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.1 (C), 176.1 (C), 153.7 (C), 136.4 (C), 129.7 (CH), 129.0 (CH), 127.1 (CH), 83.0 (C), 66.3 (CH2), 56.1 (CH), 41.7 (CH), 40.4 (CH2), 39.0 (CH), 37.7 (CH2), 37.5 (CH2), 27.5 (CH2), 23.5 (CH2), 12.7 (CH2), 11.8 (CH3), 11.7 (CH3); HRMS (ESI) calcd for $C_{22}H_{29}NO_5I$ [M+H] 514.1085, found 514.1082.

Hydrogenolysis of (*S*)-3-((*R*)-2-(((2*S*,4*R*)-4-Ethyltetrahydro-2-(iodomethyl)-5-oxofuran-2-yl)methyl)butanoyl)-4-benzyloxazolidin-2-one (8a). Iodide **8a** (10 mg, 0.026 mmol) was dissolved in methanol (0.5 mL), sodium acetate (10 mg, 0.12 mmol) and Pd/C (3 mg) were added, and the reaction mixture was stirred under an atmosphere of hydrogen (hydrogen balloon) for 20 h. After filtration through Celite, the solvent was removed, and the residue was treated with water (10 mL) and ethyl acetate (20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Chromatography (EtOAc/hexanes, 0:1 to 3:7) provided **9a** as pale yellow oil: 7 mg (93%).

(*S*)-3-((*R*)-2-(((2*S*,4*R*)-4-Ethyltetrahydro-2-methyl-5-oxofuran-2-yl)methyl)butanoyl)-4-benzyloxazolidin-2-one (9a): pale yellow oil; R_f 0.6 (1:4 EtOAc/hexanes); $[\alpha]^{20}_D$ = +10 (0.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.35 (m, 4H), 7.23−7.27 (m, 1H), 4.61−4.66 (m, 1H), 4.13−4.20 (m, 2H), 4.15 (dd, J = 9, 2.5 Hz), 4.10 (ddd, J = 9, 7.5, 1 Hz, 1H), 3.58 (dd, J = 13.5, 3 Hz, 1H), 2.89 (dd, J = 13.5, 11 Hz, 1H), 2.55−2.66 (m, 2H), 2.58 (dd, J = 14.5, 11 Hz), 2.03−2.11 (m, 2H), 1.93−2.03 (m, 1H), 1.68−1.75 (m, 2H), 1.50−1.62 (m, 2H, overlapped with water peak), 1.38 (s, 3H), 1.01 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.4 (C), 177.0 (C), 153.8 (C), 136.8 (C), 129.8 (CH), 129.0 (CH), 127.1 (CH), 83.1 (C), 66.3 (CH2), 56.5 (CH), 43.5 (CH2), 41.9 (CH), 38.7 (CH), 38.0 (CH2), 37.4 (CH2), 27.5 (CH2), 27.0 (CH3), 23.4 (CH2), 12.5 (CH3), 11.6 (CH3); HRMS (ESI) calcd for $C_{22}H_{29}NO_5Na$ [M + Na] 410.1937, found 410.1938.

Borohydride Reduction of (*S*)-3-((*R*)-2-(((2*S*,4*R*)-4-Ethyltetrahydro-2-methyl-5-oxofuran-2-yl)methyl)butanoyl)-4-benzyloxazolidin-2-one (9a). Compound **9a** (7 mg, 0.018 mmol) was dissolved in THF (0.3 mL), and water (0.2 mL) was added followed by sodium borohydride (5 mg, 0.131 mmol). After the mixture was stirred for 3 h, saturated NH_4Cl (5 mL) was added, and the reaction mixture was extracted with ethyl acetate (3×10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Chromatography (EtOAc/hexanes, 0:1 to 1:1) afforded alcohol **10b** (2 mg, 50%).

Hydrolysis of (4*S*,4′*S*)-3,3′-((2*R*,6*R*)-1,7-Dioxo-2,6-diethyl-4-methylene-1,7-heptanediyl)bis(4-benzyl)-2-oxazolidinone (4). To the solution of bis-oxazalidinone **4** (520 mg, 0.95 mmol) in THF (8 mL) at 0 °C was added sequentially H_2O (4 mL), 30% H_2O_2 (1 mL), and $LiOH\cdot H_2O$ (160 mg, 3.8 mmol). The reaction mixture was stirred for 1.5 h at 0 °C (care should be taken to keep the temperature low, as warming of the mixture appears to degrade the yield), and then solid Na_2SO_3 (1.5 g) was added in several portions (quick addition may cause excessive bubbling and foaming). The resulting mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The methylene chloride layer was concentrated to recover the auxiliary. To the aqueous layer a saturated solution of NaH_2PO_4 was added (15 mL), followed by acidification by 1 N HCl to pH of a 2−3 and extraction with EtOAc (3× 30 mL). The organic layer was dried and concentrated. The resulting diacid was used without further purification. 195 mg (90%).

+(2*R*,6*R*)-2,6-Diethyl-4-methyleneheptanedioic acid (11): white crystals; mp 93−94 °C; R_f 0.3 (1:9 2-propanol/hexanes); $[\alpha]^{20}_D$ = −5 (0.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.12 (br s, 2H), 4.82 (s, 2H), 2.58−2.65 (m, 2H), 2.41 (dd, J = 15, 11 Hz, 2H), 2.04 (dd, J = 15, 3.5, 2H), 1.62−1.73 (m, 2H), 1.51−1.61 (m, 2H), 0.99 (t, J = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 182.6 (C), 144.0 (C), 112.9 (CH2), 45.6 (CH), 38.1 (CH2), 25.6 (CH2), 11.8 (CH3); HRMS (ESI) calcd for $C_{12}H_{19}O_4$ $[M - H]^-$ 227.1288, found 227.1293.

Acidic Cyclization of (2*R*,6*R*)-2,6-Diethyl-4-methyleneheptanedioic acid (11). Diacid **11** (150 mg, 0.65 mmol) was dissolved in TFA (1 mL) and stirred overnight at rt. Removal of TFA in vacuo (followed by dilution with $CHCl_3$ and repeated concentration) afforded the diastereomeric mixture of acid lactones that was used without further purification. For analytical purposes, the diastereomers were separated using flash chromatography (hexanes/2-propanol 4:1).

(*R*)-2-(((2*R*,4*R*)-4-Ethyltetrahydro-2-methyl-5-oxofuran-2-yl)-methyl)butanoic acid (12a): pale yellow oil; R_f 0.4 (3:7 2-propanol/hexanes); $[\alpha]^{20}_D$ = +21 (0.048, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.7 (br s, 1H), 2.65−2.73 (m, 1H), 2.36−2.44 (m, 1H), 2.20−2.28 (m, 2H), 1.81−1.90 (m, 1H), 1.60−1.68 (m, 2H), 1.46−1.56 (m, 2H), 1.32−1.42 (m, 4H), 1.40 (s), 0.92 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.4 (C), 178.4 (C), 83.3 (C), 42.7 (CH), 41.8 (CH), 41.6 (CH2), 40.0 (CH2), 27.1 (CH2), 27.0 (CH3), 24.0 (CH2), 11.7 (CH3), 11.6 (CH3); HRMS (ESI) calcd for $C_{12}H_{19}O_4$ [M − H] 227.1283, found 227.1290.

(*R*)-2-(((2*S*,4*R*)-4-Ethyltetrahydro-2-methyl-5-oxofuran-2-yl)-methyl)butanoic acid (12b): pale yellow oil; R_f 0.4 (3:7 2-propanol/hexanes); $[\alpha]^{20}_D$ = −27 (0.097, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.06 (br s, 1H), 2.64−2.73 (m, 1H), 2.47−2.54 (m, 1H), 2.24 (dd, J = 14.5, 10 Hz, 1H), 2.17 (dd, J = 12.5, 9 Hz, 1H), 1.85−1.95 (m, 1H), 1.63−1.83 (m, 3H), 1.55−1.63 (m, 1H), 1.44−1.52 (m, 1H), 1.35 (s, 3H), 0.96 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 181.7 (C), 178.4 (C), 83.6 (C), 43.4 (CH2), 42.8 (CH), 41.6 (CH), 39.0 (CH2), 26.9 (CH2), 25.0 (CH3), 23.6 (CH2), 11.7 (CH3), 11.5 (CH3); HRMS (ESI) calcd for $C_{12}H_{19}O_4$ [M − H] 227.1283, found 227.1288.

Mixed Anhydride/Borohydride Reduction of (3*R*)-3-Ethyldihydro-5-((*R*)-2-(hydroxymethyl)butyl)-5-methylfuran-2(3*H*)-one (12a,b). The crude mixture of acids **12a** and **12b** (152 mg) was dissolved in THF (5 mL) at 0 °C, and Et_3N (100 μL, 0.79 mmol) was added followed by dropwise addition of *n*-butyl chloroformate (107 mg, 0.79 mmol). After 30 min at rt, a solution of $NaBH_4$ in water (150 mg in 3 mL) was added, and the mixture stirred at 0 °C for 5 h. The mixture was diluted with water (20 mL), and extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Chromatography (hexanes/isopropanol 93:7) qafforded **10a** (40 mg, 29%) and **10b** (58 mg, 42%).

(3*R*,5*R*)-3-Ethyldihydro-5-((*R*)-2-(hydroxymethyl)butyl)-5-methylfuran-2(3*H*)-one (10a): pale yellow oil; R_f 0.5 (1:4 2-propanol/hexanes); $[\alpha]^{20}_D$ = −7.7 (0.039, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.59 (dd, J = 10.5, 5 Hz, 1H), 3.52 (dd, J = 10.5, 5 Hz, 1H), 2.69 (ddd, J = 9.5, 9.5, 4.5 Hz, 1H), 2.28 (dd, J = 12.5, 9.5 Hz, 1H), 2.15 (br s, 1H), 1.86−1.94 (m, 1H), 1.78 (dd, J = 14.5, 7 Hz, 1H), 1.72 (dd, J = 12.5, 10.5 Hz, 1H), 1.57−1.63 (m, 1H), 1.45−1.53 (m, 3H), 1.44 (s, 3H), 1.25−1.34 (m, 1H), 0.96 (t, J = 7.5 Hz, 3H), 0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR

($CDCl_3$, 125 MHz): δ 178.9 (C), 84.8 (C), 65.2 (CH2), 42.1 (CH), 41.5 (CH2), 41.0 (CH2), 38.4 (CH), 26.9 (CH3), 25.6 (CH2), 24.2 (CH2), 11.9 (CH3), 11.5 (CH3); HRMS (ESI) calcd for $C_{12}H_{22}O_3Na$ [M + Na] 237.1461, found 237.1456.

(3*R*,5*S*)-3-Ethyldihydro-5-((*R*)-2-(hydroxymethyl)butyl)-5-methylfuran-2(3*H*)-one (10b): pale yellow oil; R_f 0.45 (1:4 2-propanol/hexanes); $[\alpha]^{20}_D = -6.8$ (0.118, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.51 (dd, J = 10.5, 5.5 Hz, 1H), 3.47 (dd, J = 10.5, 5.5 Hz, 1H), 2.61−2.68 (m, 1H), 2.45 (br s, 1H), 2.13 (dd, J = 12.5, 9 Hz, 1H), 1.83−1.91 (m, 1H), 1.72−1.83 (m, 2H), 1.50−1.58 (m, 2H), 1.38−1.48 (m, 3H), 1.33 (s, 3H), 0.93 (t, J = 7.5 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.7 (C), 84.6 (C), 65.5 (CH2), 42.4 (CH2), 41.6 (CH), 39.5 (CH2), 38.2 (CH), 26.0, 25.1, 23.8, 11.9 (CH3), 11.3 (CH3); HRMS (ESI) calcd for $C_{12}H_{22}O_3Na$ [M + Na] 237.1461, found 237.1454.

Preparation of (*R*)-Methyl 2-(((2*R*,4*R*)-4-Ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)butanoate (15a,b) from (3*R*,5*S*)-3-Ethyldihydro-5-((*R*)-2-(hydroxymethyl)butyl)-5-methylfuran-2(3*H*)-one (10b). DMSO (77 μL, 85 mg, 1.1 mmol) was added to the solution of oxalyl chloride (48 μL, 70 mg, 0.55 mmol) in CH_2Cl_2 (2 mL) at −78 °C. After being stirred for 10 min, a solution of alcohol **10b** (108 mg, 0.5 mmol) in CH_2Cl_2 (3 mL) was added and stirred for additional 30 min at −78 °C. Et_3N (348 μL, 252 mg, 2.5 mmol) was added, and the solution was allowed to gradually warm to 0 °C over 30 min. After 5 min at 0 °C (and when the slurry stopped getting thicker), 1 N HCl (20 mL) was added. The solution was diluted with CH_2Cl_2, and layers were separated. The organic layer was washed with satd $NaHCO_3$ (30 mL) and brine, dried over Na_2SO_4, and concentrated. The crude aldehyde (100 mg) was dissolved in methanol (1 mL) and *p*-toluenesulfonic acid (80 mg, 0.47 mmol) was added. The solution was kept at rt for 24 h. Upon completion, the reaction mixture was neutralized with saturated $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 30). The organic layer was dried over Na_2SO_4 and concentrated. The resulting crude diastereomeric mixture was directly used in the following step. For purposes of analysis, the esters were separated using flash chromatography (hexanes/ether, 0:1 to 4:1), providing **15a** (66 mg, 51%) and **15b** (41 mg, 31%).

(*R*)-Methyl 2-(((2*S*,4*R*,5*S*)-4-ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)butanoate (15a): pale yellow oil; R_f 0.6 (1:4 ether/hexanes); $[\alpha]^{20}_D = +50$ (0.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.60 (d, J = 4.5 Hz, 1H), 3.66 (s, 3H), 3.27 (s, 3H), 2.39−2.46 (m, 1H), 2.07−2.15 (m, 1H), 2.04 (dd, J = 14, 10.5 Hz, 1H), 1.80 (dd, J = 12.5, 8 Hz, 1H), 1.41−1.62 (m, 5H), 1.32−1.39 (m, 1H), 1.29 (s, 3H), 0.89 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5 (C), 105.7 (CH), 82.9 (C), 54.4 (CH3), 51.5 (CH3), 46.4 (CH), 44.4 (CH2), 43.3 (CH), 41.8 (CH2), 28.9 (CH3), 27.6 (CH2), 21.7 (CH2), 13.1 (CH3), 11.9 (CH3); HRMS (ESI) calcd for $C_{14}H_{26}O_4Na$ [M+Na] 281.1723, found 281.1721.

(*R*)-Methyl 2-(((2*S*,4*R*,5*R*)-4-ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)butanoate (15b): pale yellow oil; R_f 0.5 (1:4 ether/hexanes); $[\alpha]^{20}_D = -55$ (0.107, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.63 (d, J = 2.2 Hz, 1H), 3.69 (s, 3H), 3.34 (s, 3H), 2.37−2.44 (m, 1H), 2.15 (dd, J = 14, 9.5 Hz, 1H), 2.03−2.11 (m, 2H), 1.61−1.69 (m, 2H, overlapped with water peak), 1.46−1.59 (m, 2H), 1.37−1.44 (m, 1H), 1.28−1.37 (m, 1H), 1.25 (s, 3H) 0.92 (t, J = 7 Hz, 3H), 0.89 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.3 (C), 111.1 (CH), 84.1 (C), 55.6 (CH3), 51.6 (CH3), 48.1 (CH), 45.1 (CH2), 44.0 (CH), 42.4 (CH2), 27.8 (CH2), 27.6 (CH3), 26.3 (CH2), 12.8 (CH3), 12.0 (CH3); HRMS (ESI) calcd for $C_{14}H_{26}O_4Na$ [M + Na] 281.1723, found 281.1715.

Reduction of (*R*)-Methyl 2-(((2*R*,4*R*)-4-Ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)butanoate (15a,b). Compound **15a** (105 mg, 0.41 mmol) was dissolved in THF (1.5 mL) and LAH (31 mg, 0.81 mmol) was added. The reaction mixture was stirred at rt overnight. Water (30 μL) was added with vigorous stirring. After 10 min, 15% NaOH (30 μL) was added, and then, after 15 min, water again (30 μL). The resulting mixture was stirred until the color of the suspended solids changed to white or pale gray and a readily sedimenting precipitate formed. The mixture was filtered through a pad of Celite, washed with EtOAc (2 × 10 mL), and concentrated. Chromatography (ether/hexanes 1:4) provided pure **16a** (89 mg, 95%).

(*R*)-2-(((2*R*,4*R*,5*S*)-4-Ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)butan-1-ol (16a): pale yellow oil; R_f 0.45 (3:7 ether/hexanes); $[\alpha]^{20}_D = +69.3$ (0.075, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.78 (d, J = 4.5 Hz, 1H), 4.10 (br s, 1H), 3.65 (d, J = 10.5 Hz, 1H), 3.35 (d, J = 10.5 Hz, 1H), 3.31 (s, 3H), 2.09−2.19 (m, 1H), 1.87 (dd, J = 12, 8 Hz, 1H), 1.64−1.77 (m, 2H), 1.47−1.64 (m, 3H, overlapped with water peak), 1.28−1.45 (m, 5H), 1.38 (s), 1.13−1.24 (m, 1H), 0.91 (t, J = 7.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 105.8 (CH), 84.2 (C), 67.6 (CH2), 54.6 (CH3), 47.0 (CH2), 46.3 (CH), 44.0 (CH2), 39.3 (CH), 28.0 (CH3), 26.9 (CH2), 21.7 (CH2), 13.0 (CH3), 11.9 (CH3); HRMS (ESI) calcd for $C_{13}H_{26}O_3Na$ [M+Na] 253.1774, found 253.1768.

Similarly, by a reduction of **15b**, or a mixture of **15a** and **15b**, with a following separation, compound **16b** was obtained.

(*R*)-2-(((2*R*,4*R*,5*R*)-4-Ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)butan-1-ol (16b): pale yellow oil; R_f 0.4 (3:7 ether/hexanes); $[\alpha]^{20}_D = +12.5$ (0.016, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.67 (d, J = 4 Hz, 1H), 3.95 (br s, 1H), 3.73 (d, J = 10.5 Hz, 1H), 3.44 (d, J = 4.5 Hz, 1H), 3.42 (s, 3H), 2.15−2.24 (m, 1H), 2.04 (dd, J = 12.5, 8 Hz, 1H), 1.76 (dd, J = 14, 10.5 Hz, 1H), 1.64−1.73 (m, 1H, overlapped with water peak), 1.45−1.62 (m, 3H), 1.28−1.42 (m, 5H), 1.33 (s), 1.14−1.24 (m, 1H), 0.93 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H); ^{1}H NMR (C_6D_6, 500 MHz) δ 4.49 (d, J = 4 Hz, 1H), 3.96 (d, J = 10 Hz, 1H), 3.60−3.77 (m, 2H), 3.64 (dd, J = 11, 6 Hz), 3.25 (s, 3H), 2.06−2.15 (m, 1H), 1.80 (dd, J = 14, 10 Hz, 1H), 1.73 (dd, J = 12.5, 8 Hz, 1H), 1.63−1.72 (m, 1H), 1.23−1.44 (m, 6H), 1.25 (s), 1.06−1.23 (m, 3H), 0.87 (t, J = 7.5 Hz, 3H), 0.77 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 112.3 (CH), 84.8 (C), 66.1 (CH2), 56.7 (CH3), 47.8 (CH), 45.7 (CH2), 45.5 (CH2), 39.3 (CH), 26.8 (CH3), 26.6 (CH2), 26.1 (CH2), 12.8 (CH3), 12.0 (CH3); HRMS (ESI) calcd for $C_{13}H_{26}O_3Na$ [M+ Na] 253.1774, found 253.1782.

Preparation of (*R*)-2-(((4*R*,5*R*)-4-Ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)butan-1-ol (16a,b) from (3*R*,5*R*)-3-Ethyldihydro-5-((*R*)-2-(hydroxymethyl)butyl)-5-methylfuran-2(3*H*)-one (10a). In a wide test tube equipped with a septum, submerged in an acetone−dry ice bath, to a solution of alcohol **10a** (43 mg, 0.2 mmol) at −78 °C in CH_2Cl_2 (0.5 mL) was added DIBALH (0.5 mL 1 M solution in hexanes, 0.5 mmol), letting each drop descend on the cooled side of the test tube. Upon completion of the addition, the mixture was stirred for 2 h at −78 °C. MeOH (1 mL) was added, followed by a saturated Rochelle salt (sodium potassium tartrate) solution (5 mL), and the mixture was allowed to warm to rt. After 1 h of vigorous stirring, two clear layers formed. The aqueous layer was washed with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude lactol was dissolved in MeOH (2 mL), and pyridinium *p*-toluenesulfonate (25 mg, 0.1 mmol) was added. The mixture was stirred at rt overnight. Saturated $NaHCO_3$ (1 mL) was added and the mixture concentrated. Water (10 mL) and ethyl acetate (20 mL) were added, the mixture was shaken, and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The diastereomeric mixture was separated by flash chromatography (ether/hexanes 1:4) to yield 21 mg of **16a** (46%) and 20 mg of **16b** (44%).

Preparation of (*S*)-3-((3*R*,4*R*)-4-(((2*R*,4*R*,5*S*)-4-Ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)-3-hydroxyhexanoyl)-4-isopropyloxazolidin-2-one (17a). DMSO (18 mg, 0.23 mmol) was

added to the solution of oxalyl chloride (6 μL, 0.11 mmol) in CH_2Cl_2 (0.4 mL) at −78 °C. After being stirred for 10 min, a solution of alcohol **13a** (15 mg, 0.065 mmol) in CH_2Cl_2 (0.6 mL) was added and the mixture stirred for 30 min at −78 °C. Et_3N (75 μL, 0.54 mmol) was added, and the solution was allowed to gradually warm to 0 °C over 30 min. After 5 min at 0 °C (and when the slurry stopped getting thicker), saturated NH_4Cl (5 mL) was added. The solution was diluted with CH_2Cl_2 (15 mL) and extracted with water (20 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was dissolved in hexanes, filtered through a pad of cotton, and immediately used. Storing of the aldehyde even at low temperatures and short times was found to result results in significant decomposition. To the crude aldehyde was added (*S*)-3-(2-bromoacetyl)-4-isopropyloxazolidin-2-one (115 mg, 0.46 mmol), along with anhydrous THF (1 mL). This mixture was canulated to a cooled to −78 °C solution of samarium(II) iodide (10 mL of 0.1 M solution, 1 mmol, purchased from Aldrich), washing twice with more THF (2×0.5 mL). After being stirred for 40 min, the reaction mixture was quenched with pH 7 phosphate buffer (5 mL) at −78 °C. After warming, the mixture was diluted with ethyl acetate (30 mL) and water (10 mL). The layers were separated, and the organic layer was washed with saturated Na_2SO_3 (10 mL) and brine, dried over Na_2SO_4, and concentrated. Chromatography (EtOAc/hexanes 0:1 to 3:7) provided 15 mg (58%) of the aldol product **17a**.

(*S*)-3-((3*R*,4*R*)-4-(((2*R*,4*R*,5*S*)-4-Ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)-3-hydroxyhexanoyl)-4-isopropyloxazolidin-2-one (17a): white needles; mp 95−96 °C; R_f 0.3 (3:7 EtOAc/hexanes); $[\alpha]^{20}_D = +74$ (0.027, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.82 (d, *J* = 4.4 Hz, 1H), 4.65 (d, *J* = 8 Hz, 1H), 4.48−4.52 (m, 1H), 4.28 (br t, *J* = 8.5 Hz, 1H), 4.19−4.25 (m, 2H), 3.30 (s, 3H), 3.26 (dd, *J* = 14.5, 10 Hz, 1H), 2.78 (dd, *J* = 14.5, 2 Hz, 1H), 2.36−2.43 (m, 1H), 2.15−2.23 (m, 1H), 1.90−1.97 (m, 1H), 1.89 (dd, *J* = 11.5, 7.5 Hz, 1H), 1.79 (dd, *J* = 14.5, 9 Hz, 1H), 1.68 (br t, *J* = 12 Hz, 1H), 1.49−1.57 (m, 1H), 1.32−1.46 (m, 6H), 1.37 (s), 1.14−1.21 (m, 1H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.88−0.94 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8 (C), 154.5 (C), 105.9 (CH), 84.0 (C), 71.0 (CH), 63.5 (CH2), 58.7 (CH), 54.6 (CH3), 46.3 (CH), 43.8 (CH2), 42.21 (CH), 42.2 (CH2), 38.3 (CH2), 28.7 (CH), 28.0 (CH3), 26.7 (CH2), 21.7 (CH2), 18.2 (CH3), 14.9 (CH3), 13.0 (CH3), 12.6 (CH); HRMS (ESI) calcd for $C_{21}H_{37}NO_6Na$ $(M + Na)^+$ 422.2513, found 422.2503.

Using the same procedure, (*S*)-3-((3*R*,4*R*)-4-(((2*R*,4*R*,5*R*)-4-ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)-3-hydroxyhexanoyl)-4-isopropyloxazolidin-2-one (**17b**) was prepared from (*R*)-2-(((2*R*,4*R*,5*R*)-4-ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)butan-1-ol (**15b**) in 56% yield. A second chromatography (ether) was necessary in this case.

(*S*)-3-((3*R*,4*R*)-4-(((2*R*,4*R*,5*R*)-4-Ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)-3-hydroxyhexanoyl)-4-isopropyloxazolidin-2-one (17b): pale yellow oil; R_f 0.3 (3:7 EtOAc/hexanes); $[\alpha]^{20}_D = +23$ (0.06, $CHCl_3$); ^{1}H ($CDCl_3$, 500 MHz) δ 4.64 (d, *J* = 4.4 Hz, 1H), 4.45−4.55 (m, 2H), 4.27 (br t, *J* = 8.5 Hz, 1H), 4.21 (dd, *J* = 9, 3 Hz, 1H), 3.70 (d, *J* = 6.5 Hz, 1H), 3.43 (s, 3H), 3.13 (dd, *J* = 15.5, 10 Hz, 1H), 3.02 (dd, *J* = 15.5, 2.5 Hz, 1H), 2.35−2.43 (m, 1H), 2.17−2.25 (m, 1H), 2.05 (dd, *J* = 12, 8 Hz, 1H), 1.91 (dd, *J* = 14.5, 9 Hz, 1H), 1.73−1.79 (m, 1H), 1.53−1.62 (m, 1H, overlapped with water peak), 1.33−1.53 (m, 4H), 1.31 (s, 3H), 1.20−1.29 (m, 1H), 0.88−0.96 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.5 (C), 154.4 (C), 112.6 (CH), 84.6 (C), 68.9 (CH), 63.6 (CH2), 58.6 (CH), 57.2 (CH3), 47.6 (CH), 45.6 (CH2), 41.8 (CH), 41.1 (CH2), 39.7 (CH2), 28.7 (CH), 26.9 (CH3), 26.0 (CH2), 23.9 (CH2), 18.2 (CH3), 14.9 (CH3), 12.8 (CH3), 12.5 (CH3); HRMS (ESI) calcd for $C_{21}H_{37}NO_6Na$ $(M + Na)^+$ 422.2513, found 422.2514.

Preparation of (3*R*,4*R*)-methyl 4-(((2*R*,4*R*,5*S*)-4-ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)-3-hydroxyhexanoate (1a). To the solution of **17a** (10 mg, 0.02 mmol) in THF (1 mL) at 0 °C were added sequentially H_2O (0.5 mL), 30% H_2O_2 (0.125 mL), and $LiOH \cdot H_2O$ (2 mg, 0.048 mmol). The reaction mixture was stirred for 1.5 h at 0 °C, and then solid Na_2SO_3 (0.2 g) was added in several portions (quick addition may cause excessive bubbling and foaming). The resulting mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (2×10 mL). The methylene chloride layer was concentrated to recover the auxiliary. To the aqueous layer saturated buffer with pH 3 ($NaH_2PO_4-H_3PO_4$ in H_2O, 20 mL) was added, and the water layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried and concentrated. The resulting crude acid was dissolved in methanol (0.1 mL) and benzene (0.3 mL), and the solution of $TMSCHN_2$ (50 μL, 1 M solution, 0.05 mmol) was added. The mixture was stirred at rt for 30 min and concentrated. Chromatography (EtOAc/hexanes 0:1 to 1:1) provided **1a**, 6 mg (80%).

(3*R*,4*R*)-Methyl 4-(((2*R*,4*R*,5*S*)-4-ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)-3-hydroxyhexanoate (1a): pale yellow oil; R_f 0.45 (3:7 EtOAc/hexanes); $[\alpha]^{20}_D = +39$ (0.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.79 (d, *J* = 4.4 Hz, 1H), 4.39 (d, *J* = 7.5 Hz, 1H), 4.15−4.21 (m, 1H), 3.72 (s, 3H), 3.31 (s, 3H), 2.36−2.39 (m, 2H), 2.08−2.16 (m, 1H), 1.86−1.91 (m, 2H), 1.88 (dd, *J* = 11.5, 8 Hz), 1.65−1.74 (m, 2H), 1.50−1.56 (m, 1H, overlapped with water peak), 1.29−1.44 (m, 6H), 1.37 (s), 1.32 (dd, *J* = 14.5, 3.5 Hz), 1.15−1.22 (m, 1H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.5 (C), 105.8 (CH), 84.1 (C), 70.6 (CH), 54.6 (CH3), 51.9 (CH3), 46.6 (CH), 43.7 (CH2), 42.1 (CH2), 41.7 (CH), 37.9 (CH2), 28.1 (CH3), 26.5 (CH2), 21.7 (CH2), 13.0 (CH3), 12.5 (CH3); HRMS (ESI) calcd for $C_{16}H_{30}O_5Na$ $(M + Na)^+$ 325.1985, found 325.1977.

Using the same procedure, (3*R*,4*R*)-methyl 4-(((2*R*,4*R*,5*R*)-4-ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)methyl)-3-hydroxyhexanoate (**1b**) was prepared from (*S*)-3-((3*R*,4*R*)-4-(((2*R*,4*R*,5*R*)-4-ethyltetrahydro-5-methoxy-2-methylfuran-2-yl)-methyl)-3-hydroxyhexanoyl)-4-isopropyloxazolidin-2-one (**17b**) in 80% yield: pale yellow oil; R_f 0.45 (3:7 EtOAc/hexanes); $[\alpha]^{20}_D = -14$ (0.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.66 (d, *J* = 5 Hz, 1H), 4.35−4.41 (m, 1H), 3.97 (d, *J* = 7 Hz, 1H), 3.70 (s, 3H), 3.44 (s, 3H), 2.62 (dd, *J* = 15, 10 Hz, 1H), 2.37 (dd, *J* = 15, 3.5 Hz, 1H), 2.16−2.24 (m, 1H), 2.05 (dd, *J* = 12.5, 7.5 Hz, 1H), 1.86 (dd, *J* = 14.5, 9.5 Hz, 1H), 1.74−1.80 (m, 1H), 1.54−1.61 (m, 1H, overlapped with water peak), 1.49 (dd, *J* = 12, 10 Hz, 1H), 1.34−1.42 (m, 3H), 1.32 (s, 3H), 1.17−1.23 (m, 1H), 0.93 (t, *J* = 7.5, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{1}H NMR (C_6D_6, 500 MHz) δ 4.72−4.78 (m, 1H), 4.47 (d, *J* = 4.7 Hz, 1H), 4.00 (d, *J* = 7 Hz, 1H), 3.40 (s, 3H), 3.34 (s, 3H), 2.76 (dd, *J* = 15, 10 Hz, 1H), 2.33 (dd, *J* = 15, 3.5 Hz, 1H), 2.05−2.12 (m, 1H), 1.86 (dd, *J* = 14.5, 9.5 Hz, 1H), 1.72−1.79 (m, 1H), 1.68 (dd, *J* = 12, 7.5 Hz, 1H), 1.30−1.38 (m, 2H), 1.25 (s, 3H), 1.15−1.24 (m, 3H), 1.07−1.15 (m, 1H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.77 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6 (C), 112.7 (CH), 84.5 (C), 69.5 (CH), 57.4 (CH3), 51.8 (CH3), 47.7 (CH), 45.7 (CH2), 41.5 (CH), 41.3 (CH2), 38.1 (CH2), 26.8 (CH3), 26.0 (CH2), 24.5 (CH2), 12.8 (CH3), 12.5 (CH3); HRMS (ESI) calcd for $C_{16}H_{30}O_5Na$ $(M+Na)^+$ 325.1985, found 325.1969.

Preparation of Methyl 2-((1*S*,3*R*,4*R*,6*R*,8*R*)-4,8-Diethyl-6-methyl-2,9-dioxabicyclo[4.2.1]nonan-3-yl)acetate (18). 1a or **1b** (4 mg, 0.013 mmol) was dissolved in chloroform (0.5 mL), pyridinium *p*-toluenesulfonate (3.3 mg, 0.013 mmol) was added, and the reaction mixture was kept at 45 °C for 15 h (in the rotavap bath. Initially, the reaction was carried out directly in the NMR tube, monitoring by periodic ^{1}H NMR spectra. Gradual emergence of the product peaks was observed, along with decay of the starting material peaks, with a small degree of equilibration of **1a** to **1b**, or vice versa). Upon completion, the reaction mixture was diluted with methylene chloride (5 mL), washed with satd $NaHCO_3$ (5 mL) and brine, dried over Na_2SO_4, and concentrated. Chromatography (EtOAc/hexanes, 0:1 to 3:7) afforded pure **18** (3 mg, 84%).

Methyl 2-((1*S*,3*R*,4*R*,6*R*,8*R*)-4,8-diethyl-6-methyl-2,9-dioxabicyclo[4.2.1]nonan-3-yl)acetate (18): pale yellow oil; R_f 0.25 (1:9 EtOAc/hexanes); $[\alpha]^{20}_D = +25$ (0.02, $CHCl_3$); ^{1}H NMR (C_6D_6, 500 MHz) δ 5.25 (s, 1H), 4.97 (ddd, J = 9.5, 4.5, 1 Hz, 1H), 3.37 (s, 3H), 2.76 (dd, J = 15.5, 9.5 Hz, 1H), 2.19 (dd, J = 15.5, 4.5 Hz, 1H), 1.97−2.08 (m, 2H), 1.49−1.55 (m, 2H), 1.42−1.49 (m, 2H), 1.36−1.41 (m, 1H), 1.24−1.32 (m, 4H), 1.25 (s), 1.00−1.09 (m, 2H), 0.79 (t, J = 7.5 Hz, 3H), 0.72 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.6 (C), 104.9 (CH), 87.0 (C), 69.3 (CH), 51.8 (CH3), 51.4 (CH), 44.4 (CH), 40.5 (CH2), 39.3 (CH), 39.1 (CH2), 32.1 (CH3), 26.9 (CH2), 19.3 (CH2), 13.1 (CH3), 12.5 (CH3); HRMS (ESI) calcd for $C_{15}H_{27}O_4$ $(M+H)^+$ 271.1904, found 271.1908.

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Supporting Information Available: Copies of ^{1}H, ^{13}C, COSY and 1D NOE difference spectra. This material is available free of charge via the Internet at http://pubs.acs.org.