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Novel "Protecting Group-Dependent" Alkylation−RCM Strategy to Medium-Sized Oxacycles: First Total Synthesis of (−)-Isoprelaurefucin

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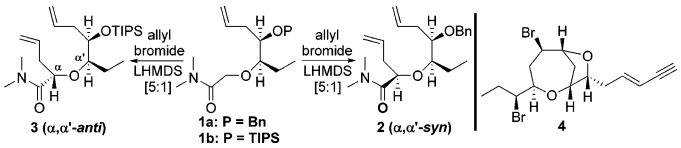

A novel "protecting group-dependent" alkylation strategy was developed for complementary diastereoselective syntheses of α,α′-*syn*- and α,α′-*anti*-bis-alkenes **2** and **3**, which represent ring-closing metathesis (RCM) substrates for medium-sized oxacycles. This principle has been applied to a stereoselective and concise total synthesis of (−)-isoprelaurefucin (**4**) in 14 steps in 12% overall yield from known epoxide **8**.

Introduction

An asymmetric alkylation−RCM strategy has been employed for construction of medium-sized oxacycles by Crimmins' group, culminating in total syntheses of a number of interesting and complex natural products.[1] In particular, the requisite α,α′-*syn*- and α,α′-*anti*-RCM substrates in their syntheses have been efficiently prepared by asymmetric alkylation reactions. In this paper, we report a novel "protecting group-dependent" alkylation to synthesize the α,α′-*syn*- and α,α′-*anti*-RCM substrates without a recourse to chiral auxiliary and its application to the first synthesis of (−)-isoprelaurefucin, a seven-membered ring ether marine natural product.

Results and Discussion

In view of the demonstrated versatility of the α-alkoxy *N*,*N*-dimethyl amide functionality in our syntheses of oxacyclic marine natural products,[2] we were intrigued by the possibility of synthesizing RCM substrates, α,α′-*syn*- and α,α′-*anti*-bis-alkenes **2** and **3**, in a stereoselective fashion by alkylation of *N*,*N*-dimethyl amide **1** without resorting to chiral auxiliary. The embedded oxygen atoms in amide **1** suggested a way to a novel protecting group-dependent alkylation strategy as summarized in Scheme 1. Thus, benzyl-protected α-alkoxy amide **1a** produced α,α′-*syn*-RCM substrate **2** in a 5:1 diastereoselectivity in 74% total yield upon successive treatment with lithium bis(trimethylsilyl)amide (LHMDS) and allyl bromide in tetrahydrofuran (THF) at −78 °C for 30 min, presumably by attack of allyl bromide from the side opposite the ethyl group at C-13 (laurencin numbering) in bidentate model **A**.[3−5] On the other hand, α-alkoxy amide **1b** protected with the triisopropylsily (TIPS) group, which is known

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(1) (a) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548−7549. (b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653−5660. (c) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029−2032. (d) Crimmins, M. T.; Emmitte, K. A. *Synthesis* **2000**, 899−903. (e) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473−5476. (f) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165−2167. (g) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533−1534. (h) Crimmins, M. T.; Stanton, M. G.; Allwein, S. P. *J. Am. Chem. Soc.* **2002**, *124*, 5958−5959. (i) Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592−7595. (j) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264−10266.

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(3) Stereochemistry of the alkylated products was firmly established by spectroscopic analysis after their conversion to the corresponding RCM products. See Supporting Information.

(4) The RCM product of α,α′-*syn*-bisalkene **2** has been previously converted to (+)-laurencin by us, thus constituting a formal synthesis of the natural product.[2c]

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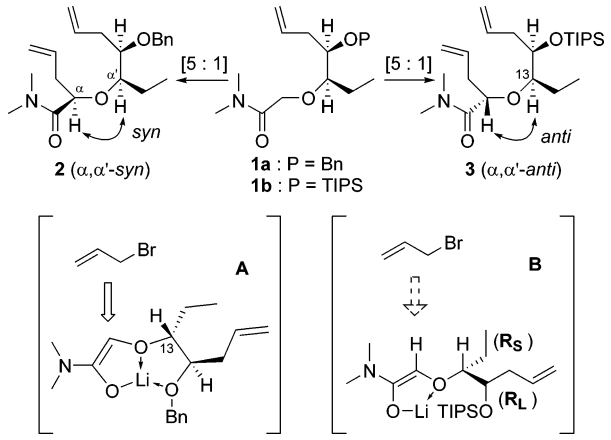
SCHEME 1. Protecting Group-Dependent Alkylation of α-Alkoxy Amide Enolates



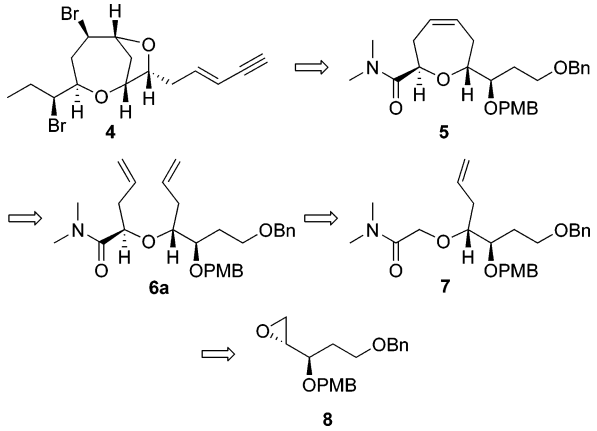
to be a poor coordinating group for steric and electronic reasons,[6] furnished α,α′-*anti*-bis-alkene **3** in a 5:1 stereoselectivity in 65% total yield under comparable conditions. This product results from attack of allyl bromide from the side of the smaller ethyl group (R_S) rather than the bulkier butenyl side chain (R_L) in the "H-eclipsed" monodentate model **B**.

To illustrate the potential of our "chelation- and substrate-controlled" alkylation strategy, we embarked on total synthesis of (−)-isoprelaurefucin (**4**), a seven-membered ring ether marine natural product with a 2,7-dioxabicyclo[4.2.1]nonane skeleton. This metabolite was isolated from the red alga *Laurencia nipponica* by Irie and co-workers in 1973.[7a] Its relative and absolute stereochemistry was established by spectroscopic methods, biogenetic considerations, and chemical correlation with known compounds.[7]

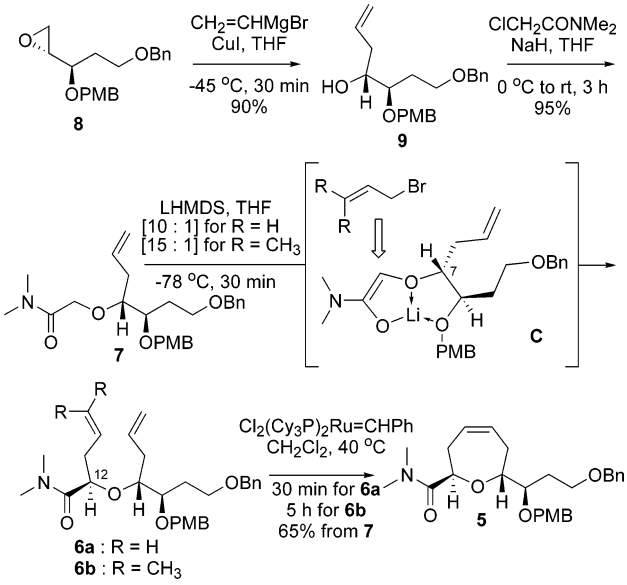
As shown in our retrosynthetic plan (Scheme 2), we were confident that **4** could be secured from α,α′-*trans*-oxepene **5** via a synthetic sequence analogous to that employed in our previous synthesis of α,α′-*cis*-(+)-neoisoprelaurefucin.[2b] We envisaged that key oxepene **5** could be constructed by RCM of α,α′-*anti*-bis-alkene **6a**, which could in turn be synthesized by pivotal chelation- and substrate-controlled alkylation of α-alkoxy amide **7**. Further analysis suggested acyclic alkylation substrate **7** should be readily available from known chiral epoxide **8**.[2b,8]

To commence the synthesis, opening of readily available oxirane **8** with vinylmagnesium bromide, followed by *O*-alkylation of the resulting alcohol **9** with 2-chloro-*N*,*N*-dimethylacetamide, yielded key alkylation substrate

SCHEME 2. Retrosynthetic Plan for (−)-Isoprelaurefucin (4)



SCHEME 3. Synthesis of Oxepene 5



7 (86% for the two steps) (Scheme 3). To our satisfaction, crucial alkylation of α-alkoxy amide **7** with allyl bromide by treatment with LHMDS in THF at −78 °C for 30 min furnished the desired α,α′-*anti*-diene **6a** with high diastereoselectivity (10:1; ^{1}H NMR analysis).[3] The improved stereoselectivity (5:1 vs 10:1) of alkylation of amide **7** compared to **1a** can be attributed to the fact that the allyl group at C-7 in bidentate model **C** is larger than the corresponding ethyl group in **A**. Furthermore, use of bulkier prenyl bromide as the electrophile improved the diastereoselectivity to 15:1. RCM of α,α′-*anti*-bis-alkene **6b** with the first-generation Grubbs' Ru catalyst[9] afforded key oxepene **5** in 65% overall yield for the two steps.

With key intermediate **5** in hand, the remaining steps of the synthesis, patterned after our previous syntheses,[2b] proceeded without incident (Scheme 4). Thus, elaboration of the C-12 side chain was accomplished via our versatile three-step sequence (62% overall): direct ketone synthesis with ethylmagnesium bromide [**5** → **10**],[2a] reduction with L-Selectride [**10** → **11**],[2a,10] and bromination by the

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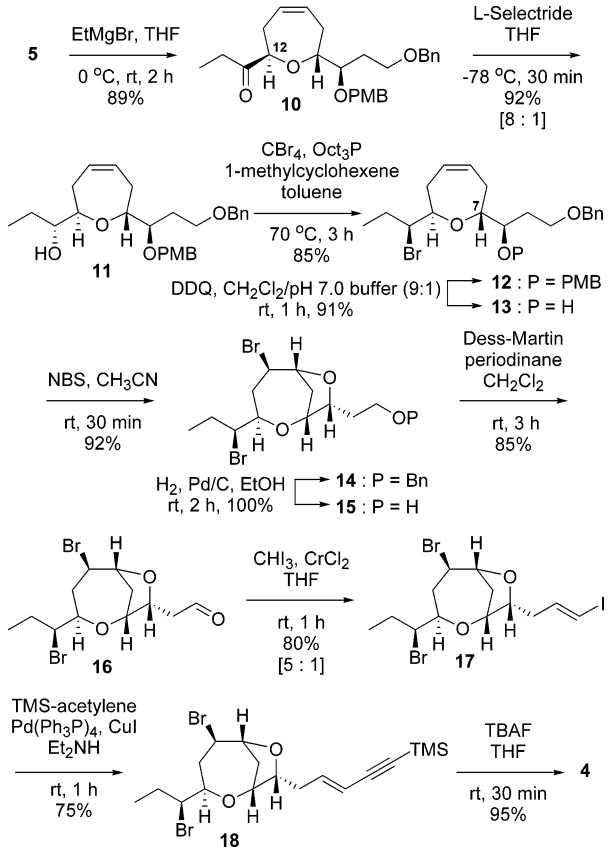
SCHEME 4. Completion of Total Synthesis of (−)-Isoprelaurefucin (4)



Hooz protocol [**11** → **12**].[10,11] We next turned our attention to construction of the 2,7-dioxabicyclo[4.2.1]nonane skeleton and the (*E*)-enyne system at C-7. Bromoetherification of *γ,δ*-unsaturated alcohol **13**, prepared by removal of the PMB protecting group of oxepene **12** with wet 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[12] furnished the desired bicyclic ether **14** in good overall yield (84% for the two steps). Deprotection of the benzyl group in compound **14** by catalytic hydrogenolysis and Dess−Martin periodinane oxidation[13] of the resulting primary alcohol **15** yielded aldehyde **16** (85% for the two steps), setting the stage for introduction of the (*E*)-enyne moiety. Using the Takai olefination protocol[14] on aldehyde **16** produced (*E*)-vinyl iodide **17** (80% total yield; *E*/*Z* = 5/1; ^{1}H NMR analysis), which was converted to the penultimate (*E*)-TMS-enyne **18** (TMS = trimethylsilyl) by a Sonogashira coupling[15] with TMS−acetylene (75%). Finally, deprotection of TMS-enyne **18** with tetrabutylammonium fluoride (TBAF) (95%) gave rise to (−)-isoprelaurefucin (**4**), whose spectral characteristics and optical rotation (syn. $[\alpha]^{25}_D = -56.18$, lit. $[\alpha]_D = -54.4$) were in agreement with those of the natural product.[7a,16]

Conclusions

In summary, we have accomplished a highly stereoselective and concise total synthesis of (−)-isoprelaurefucin (**4**) from known oxirane **8** in 14 steps and 12% overall yield, featuring a novel protecting group-dependent alkylation−RCM strategy to form oxepene **5**. The scope of this methodology and its application to the synthesis of other medium-sized oxacyclic natural products are under investigation in our laboratories.

Experimental Section

(1a*R*,2a*R*,2*R*)-2-(2a-Benzyloxy-1a-ethylpent-4-enyloxy)-pent-4-enoic Acid Dimethylamide (2). To a solution of amide **1a** (39.8 mg, 0.130 mmol) in anhydrous THF (4 mL, 0.03 M) was added dropwise LHMDS (0.19 mL, 1.0 M solution in THF, 0.190 mmol) at −78 °C. The mixture was stirred for 30 min at −78 °C, and allyl bromide (0.05 mL, 0.591 mmol) was added rapidly. After being stirred for an additional 30 min at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 5/1 to 2/1) to afford an inseparable 5/1 mixture of α,α′-*syn*-diene **2** and α,α′-*anti*-diene **2′** (by ^{1}H NMR analysis) as colorless oils (33.3 mg, 74%). For diene **2**: ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 7.26−7.34 (m, 5 H), 5.73−5.90 (m, 2 H), 5.02−5.13 (m, 4 H), 4.57 (AB, J_{AB} = 11.6, $\Delta\nu_{AB}$ = 28.7 Hz, 2 H), 4.31 (dd, *J* = 6.3, 7.8 Hz, 1 H), 3.52 (ddd, *J* = 4.3, 4.3, 8.1 Hz, 1 H), 3.33 (ddd, *J* = 4.7, 4.7, 7.3 Hz, 1 H), 3.06 (s, 3 H), 2.93 (s, 3 H), 2.39−2.49 (m, 3 H), 2.24 (ddd, *J* = 7.4, 7.4, 14.7 Hz, 1 H), 1.63−1.71 (m, 1 H), 1.41−1.47 (m, 1 H), 0.90 (dd, *J* = 7.4, 7.4 Hz, 3 H).

(1a*R*,2a*R*,2*S*)-2-(1a-Ethyl-2a-(triisopropylsilanyloxy)-pent-4-enyloxy)pent-4-enoic Acid Dimethylamide (3). To a solution of amide **1b** (65.3 mg, 0.176 mmol) in anhydrous THF (16 mL, 0.03 M) was added dropwise LHMDS (0.35 mL, 1.0 M solution in THF, 0.351 mmol) at −78 °C. The mixture was stirred for 30 min at −78 °C, and allyl bromide (0.07 mL, 0.876 mmol) was added rapidly. After being stirred for an additional 3 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether (15 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 5/1 to 2/1) to afford α,α′-*anti*-diene **3** (39.1 mg, 54%) and α,α′-*syn*-diene **3′** (8.0 mg, 11%) as colorless oils. For diene **3**: $[\alpha]^{25}_D = +20.94$ (*c* 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 5.14−5.90 (m, 2 H), 4.93−5.14 (m, 4 H), 4.22 (dd, *J* = 6.1, 7.9 Hz, 1 H), 3.94 (ddd, *J* = 3.8, 4.0, 7.8 Hz, 1 H), 3.27 (ddd, *J* = 3.4, 3.4, 9.1 Hz, 1 H), 3.11 (s, 3 H), 2.91 (s, 3 H), 2.52 (ddd, *J* = 7.0, 7.2, 14.2 Hz, 1 H), 2.40−2.46 (m, 2 H), 2.13 (ddd, *J* = 7.8, 15.1, 15.1 Hz, 1 H), 1.75 (ddddd, *J* = 2.8, 7.5, 7.5, 7.5, 15.1 Hz, 1 H), 1.43 (ddddd, *J* = 7.3, 7.3, 7.3, 7.3, 14.5 Hz, 1 H), 1.05 (s, 21 H), 0.98 (dd, *J* = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 171.7, 136.7, 133.7, 117.7, 116.2, 85.4, 80.5, 72.8, 37.6, 36.8, 36.5, 36.0, 21.6, 18.1, 12.7, 11.3; IR (neat) 2867, 997 cm^{-1}; HRMS (FAB) found 412.3245 [(M + H)$^+$; calcd for $C_{23}H_{46}NO_3Si$: 412.3247]. For diene **3′**: $[\alpha]^{25}_D = +48.78$ (*c* 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 5.89 (dddd, *J* = 7.2, 7.2, 10.0, 17.1 Hz, 1 H), 5.81 (dddd, *J* = 7.1, 7.1, 10.0, 17.1 Hz, 1 H), 5.00−5.13 (m, 4 H), 4.22 (dd, *J* =

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(16) For copies of ^{1}H and ^{13}C NMR spectra, see Supporting Information.

5.8, 8.1 Hz, 1 H), 3.97 (ddd, J = 3.7, 4.1, 7.8 Hz, 1 H), 3.24 (ddd, J = 3.6, 3.7, 8.5 Hz, 1 H), 3.12 (s, 3 H), 2.94 (s, 3 H), 2.44−2.48 (m, 3 H), 2.15 (ddd, J = 7.4, 7.4, 14.2 Hz, 1 H), 1.74 (ddddd, J = 3.5, 7.6, 7.6, 7.6, 15.2 Hz, 1 H), 1.41 (ddddd, J = 7.4, 7.4, 7.4, 7.4, 14.7 Hz, 1 H), 1.06 (s, 21 H), 0.96 (dd, J = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 136.4, 134.0, 117.8, 116.5, 84.4, 79.7, 72.1, 37.7, 36.8, 36.6, 36.1, 21.7, 18.19, 18.17, 12.7, 12.3,11.0; IR (neat) 2867, 996 cm^{-1}; HRMS (FAB) found 412.3247 [(M + H)$^+$; calcd for $C_{23}H_{46}NO_3Si$: 412.3247].

(4*R*,5*R*)-7-Benzyloxy-5-(4-methoxybenzyloxy)hept-1-en-4-ol (9). CuI (290.5 mg, 1.525 mmol) was gently heated in vacuo until the solid turned light yellow. The flask was then filled with Ar and cooled to −30 °C, followed by addition of anhydrous THF (51 mL, 0.05 M). Vinylmagnesium bromide (15.30 mL, 1.0 M in THF, 15.300 mmol) was added dropwise via syringe, and the resulting mixture was stirred for 15 min at −30 °C. Epoxide **8** (1.0023 g, 3.051 mmol) in THF (10 mL) was added dropwise, and the reation mixture was then stirred for 15 min at −30 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether (50 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 10/1) to afford allylic alcohol **9** as a colorless oil (1.0201 g, 90%): $[\alpha]^{25}_D$ = +3.63 (*c* 1.26, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.37 (m, 5 H), 7.22 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 5.80−5.88 (m, 1 H), 5.09 (d, J = 16.1 Hz, 1 H), 5.08 (d, J = 11.2, 1 H), 4.49 (AB, J_{AB} = 11.0, $\Delta\nu_{AB}$ = 44.0 Hz, 2 H), 4.49 (AB, J_{AB} = 12.1, $\Delta\nu_{AB}$ = 28.7 Hz, 2 H), 3.80 (s, 3 H), 3.57−3.62 (m, 1 H), 3.59 (dd, J = 6.0, 6.0 Hz, 2 H), 3.54 (dd, J = 5.2, 10.0 Hz, 1 H), 2.46 (d, J = 5.5 Hz, 1 H), 2.31−2.36 (m, 1 H), 2.22−2.28 (m, 1 H), 1.97 (dddd, J = 6.5, 6.5, 6.5, 14.6 Hz, 1 H), 1.86 (dddd, J = 5.7, 5.7, 5.7, 14.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 138.1, 135.1, 130.4, 129.6, 128.4, 127.73, 127.64, 117.3, 113.8, 78.2, 73.0, 72.46, 72.41, 66.4, 55.3, 38.0, 30.9; IR (neat) 3440, 1612 cm^{-1}; HRMS (FAB) found 379.1886 [(M + Na)$^+$; calcd for $C_{22}H_{28}O_4Na$: 379.1881].

(1a*R*,1*R*)-2-{1-[3-Benzyloxy-1a-(4-methoxybenzyloxy)-propyl]but-3-enyloxy}-*N,N*-dimethylacetamide (7). To a cooled (0 °C) solution of homoallylic alcohol **9** (1.0100 g, 2.719 mmol) in anhydrous THF (27 mL, 0.1 M) was added NaH (326.3 mg, 60% dispersion in mineral oil, 8.156 mmol). After the resulting mixture was stirred for 10 min at the same temperature, 2-chloro-*N,N*-dimethylacetamide (661.1 mg, 5.438 mmol) was added, and stirring was continued for 3 h at room temperature. The reaction mixture was recooled to 0 °C, quenched with H_2O, and diluted with diethyl ether (20 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (20 mL). The combined organic layers were washed with saturated aqueous NH_4Cl and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 4/1 to 2/1) to afford amide **7** as a colorless oil (1.1406 g, 95%): $[\alpha]^{25}_D$ = +27.93 (*c* 2.62, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5 H), 7.22 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.85 (dddd, J = 7.0, 7.0, 10.0, 17.1 Hz, 1 H), 5.08 (dd, J = 1.6, 17.1 Hz, 1 H), 5.04 (d, J = 10.1 Hz, 1 H), 4.48 (AB, J_{AB} = 11.1, $\Delta\nu_{AB}$ = 52.0 Hz, 2 H), 4.43 (AB, J_{AB} = 11.9, $\Delta\nu_{AB}$ = 27.7 Hz, 2 H), 4.20 (AB, J_{AB} = 13.3, $\Delta\nu_{AB}$ = 16.3 Hz, 2 H), 3.78 (s, 3 H), 3.72 (ddd, J = 3.6, 5.2, 13.7 Hz, 1 H), 3.53−3.59 (m, 3 H), 2.94 (s, 3 H), 2.89 (s, 3 H), 2.41−2.46 (m, 1 H), 2.25 (ddd, J = 7.2, 7.2, 14.5 Hz, 1 H), 1.94 (dddd, J = 3.3, 6.7, 6.7, 14.1 Hz, 1 H), 1.70 (dddd, J = 4.3, 4.8, 9.1, 14.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 159.1, 138.4, 135.2, 130.6, 129.6, 128.2, 127.6, 127.4, 116.9, 113.6, 80.6, 76.0, 72.8, 72.2, 70.0, 66.7, 55.2, 36.6, 35.2, 34.3, 30.2; IR (neat) 1648, 1248, 1099 cm^{-1}; HRMS (FAB) found 442.2593 [(M + H)$^+$; calcd for $C_{26}H_{36}NO_5$: 442.2592].

(1a*R*,1b*R*,2*R*)-2-{1a-[3-Benzyloxy-1b-(4-methoxybenzyloxy)propyl]but-3-enyloxy}pent-4-enoic Acid Dimethylamide (6a). To a solution of amide **7** (1.1010 g, 2.493 mmol) in anhydrous THF (25 mL, 0.1 M) was added dropwise LHMDS (2.99 mL, 1.0 M solution in THF, 2.990 mmol) at −78 °C. The mixture was stirred for 20 min at −78 °C, and allyl bromide (1.05 mL, 12.450 mmol) was added rapidly. After being stirred for an additional 10 min at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether (20 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 5/1 to 2/1) to afford an inseparable 10/1 mixture of α,α′-*anti*-diene **6a** and α,α′-*syn*-diene **6a′** (by ^{1}H NMR analysis) as colorless oils (1.0010 g, 84%). For diene **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.36 (m, 5 H), 7.21 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.72−5.89 (m, 2 H), 5.07−5.09 (m, 1 H), 5.00−5.04 (m, 3 H), 4.45 (AB, J_{AB} = 11.2, $\Delta\nu_{AB}$ = 46.5 Hz, 2 H), 4.43 (AB, J_{AB} = 11.9, $\Delta\nu_{AB}$ = 35.5 Hz, 2 H), 4.26 (dd, J = 7.0, 7.0 Hz, 1 H), 3.78 (s, 3 H), 3.66 (ddd, J = 3.1, 4.5, 9.1 Hz, 1 H), 3.49−3.58 (m, 3 H), 3.01 (s, 3 H), 2.89 (s, 3 H), 2.40−2.46 (m, 3 H), 2.19 (ddd, J = 7.2, 7.4, 14.6 Hz, 1 H), 1.95 (dddd, J = 2.9, 7.0, 8.3, 14.5 Hz, 1 H), 1.66 (dddd, J = 4.6, 5.1, 9.7, 19.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 159.1, 138.5, 135.5, 133.7, 130.7, 129.5, 128.3, 127.6, 127.5, 117.7, 116.6, 113.7, 79.4, 79.3, 75.7, 72.8, 72.1, 66.8, 55.2, 37.3, 36.9, 36.0, 34.4, 29.8. For diene **6a′**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.35 (m, 5 H), 7.21 (d, J = 8.6 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 5.74−5.89 (m, 2 H), 5.03−5.10 (m, 4 H), 4.45 (AB, J_{AB} = 11.3, $\Delta\nu_{AB}$ = 69.9 Hz, 2 H), 4.41 (AB, J_{AB} = 11.8, $\Delta\nu_{AB}$ = 29.7 Hz, 2 H), 3.79 (s, 3 H), 3.65 (ddd, J = 3.0, 4.1, 9.4 Hz, 1 H), 3.48−3.55 (m, 4 H), 2.98 (s, 3 H), 2.82 (s, 3 H), 2.38−2.50 (m, 3 H), 2.20 (ddd, J = 7.4, 7.7, 15.0 Hz, 1 H), 1.96 (dddd, J = 2.9, 6.3, 8.1, 14.5 Hz, 1 H), 1.66 (dddd, J = 4.7, 5.5, 10.2, 14.4 Hz, 1 H).

(1a*R*,1b*R*,2*R*)-2-{1a-[3-Benzyloxy-1b-(4-methoxybenzyloxy)propyl]but-3-enyloxy}-5-methylhex-4-enoic Acid Dimethylamide (6b). To a solution of amide **7** (200.0 mg, 0.453 mmol) in anhydrous THF (4.5 mL, 0.1 M) was added dropwise LHMDS (0.54 mL, 1.0 M solution in THF, 0.543 mmol) at −78 °C. The mixture was stirred for 20 min at −78 °C and prenyl bromide (0.23 mL, 2.250 mmol) was added rapidly. After being stirred for an additional 10 min at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 4/1 to 2/1) to afford an inseparable 15/1 mixture of diene **6b** and **6b′** (by ^{1}H NMR analysis) as colorless oils (194.3 mg, 84%). For diene **6b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5 H), 7.21 (d, J = 8.5 Hz, 2 H), 6.84 (d, J = 8.5 Hz, 2 H), 5.80−5.89 (m, 1 H), 5.00−5.10 (m, 3 H), 4.45 (AB, J_{AB} = 11.2, $\Delta\nu_{AB}$ = 65.5 Hz, 2 H), 4.44 (AB, J_{AB} = 11.9, $\Delta\nu_{AB}$ = 30.9 Hz, 2 H), 4.19 (dd, J = 7.0, 7.0 Hz, 1 H), 3.79 (s, 3 H), 3.65 (ddd, J = 3.1, 4.4, 9.4 Hz, 1 H), 3.48−3.57 (m, 3 H), 3.02 (s, 3 H), 2.90 (s, 3 H), 2.38−2.46 (m, 3 H), 2.19 (ddd, J = 7.5, 7.5, 14.8 Hz, 1 H), 1.90−1.97 (m, 1 H), 1.65−1.70 (m, 1 H), 1.66 (s, 3 H), 1.57 (s, 3 H).

(1b*R*,2*R*,7a*R*)-7a-[3-Benzyloxy-1b-(4-methoxybenzyloxy)propyl]-2,3,6,7-tetrahydrooxepine-2-carboxylic Acid Dimethylamide (5). To a solution of 10/1 mixture of α,α′-*anti*-diene **6a** and α,α′-*syn*-diene **6a′** (752.0 mg, 1.561 mmol) in dichloromethane (520 mL, 0.003M) was added $Cl_2(Cy_3P)_2$-Ru=CHPh (385.5 mg, 0.468 mmol) in one portion at room temperature. The reaction mixture was stirred at 40 °C for 30 min and then cooled to room temperature. Dimethyl sulfoxide (1.20 mL, 1.404 mmol) was added to the solution,

and it was stirred open to the air overnight and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 20/1 to 10/1) to afford a 10/1 mixture of α,α′-*trans*-oxepene **5** and α,α′-*cis*-oxepene **5′** (by ^{1}H NMR analysis) as colorless oils (608 mg, 86%). For oxepene **5**: $[\alpha]^{25}_D = -5.71$ (*c* 0.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.35 (m, 5 H), 7.19 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 5.69−5.76 (m, 2 H), 4.83 (dd, J = 2.9, 10.1 Hz, 2 H), 4.44 (AB, J_{AB} = 11.2, $\Delta\nu_{AB}$ =43.3 Hz, 2 H), 4.44 (AB, J_{AB} = 11.9, $\Delta\nu_{AB}$ = 25.4 Hz, 2 H), 4.30 (ddd, J = 1.7, 3.5, 11.0 Hz, 1 H), 3.79 (s, 3 H), 3.59 (ddd, J = 3.6, 3.6, 8.9 Hz, 1 H), 3.52−3.55 (m, 2 H), 3.06 (s, 3 H), 2.90 (s, 3 H), 2.89−2.93 (m, 1 H), 2.43−2.49 (m, 1 H), 2.25−2.29 (m, 2 H), 1.92 (dddd, J = 3.8, 7.5, 7.5, 11.2 Hz, 1 H), 1.74 (dddd, J = 5.6, 5.6, 9.2, 14.4 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 159.0, 138.4, 130.6, 129.4, 128.9, 128.2, 127.6, 127.4, 127.0, 113.5, 77.2, 74.3, 73.7, 72.7, 71.9, 70.0, 55.1, 37.1, 35.6, 30.4, 29.9, 29.7; IR (neat) 1648, 1360, 1105 cm^{-1}; HRMS (FAB) found 454.2605 [(M + H)$^+$; calcd for $C_{27}H_{36}NO_5$: 454.2593]. For oxepene **5′**: $[\alpha]^{25}_D$ = +33.30 (*c* 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.36 (m, 5 H), 7.19 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.83−5.84 (m, 2 H), 4.49 (AB, J_{AB} = 11.1, $\Delta\nu_{AB}$ = 56.1 Hz, 2 H), 4.45 (AB, J_{AB} = 11.9, $\Delta\nu_{AB}$ = 24.3 Hz, 2 H), 4.08 (dd, J = 1.4, 10.7 Hz, 2 H), 3.79 (s, 3 H), 3.64 (ddd, J = 3.0, 5.3, 9.4 Hz, 1 H), 3.58 (dd, J = 5.3, 7.4 Hz, 2 H), 3.49 (ddd, J = 5.4, 5.4, 5.5 Hz, 1 H), 2.98 (s, 3 H), 2.91 (s, 3 H), 2.72 (brdd, J = 10.9, 15.7 Hz, 1 H), 2.33−2.39 (m, 3 H), 1.97 (dddd, J = 3.0, 7.4, 7.4, 14.0 Hz, 1 H), 1.67 (dddd, J = 5.0, 5.0, 9.4, 14.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 159.1, 138.5, 130.7, 129.7, 129.44, 129.39, 129.1, 128.3, 127.61, 127.55, 127.4, 113.6, 81.2, 78.7, 77.5, 72.70, 72.59, 66.9, 55.2, 37.0, 35.8, 33.4, 31.5, 30.5; IR (neat) 1652, 1400, 1107 cm^{-1}; HRMS (FAB) found 454.2605 [(M + H)$^+$; calcd for $C_{27}H_{36}NO_5$: 454.2593].

To a solution of 15/1 mixture of diene **6b** and **6b′** (151.0 mg, 0.296 mmol) in dichloromethane (98 mL, 0.003M) was added $Cl_2(Cy_3P)_2Ru$=CHPh (72.3 mg, 0.089 mmol) in one portion at room temperature. The reaction mixture was stirred at 40 °C for 5 h and then cooled to room temperature. Dimethyl sulfoxide (0.30 mL, 0.310 mmol) was added to the solution, and it was stirred open to the air overnight and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 4/1 to 1/1) to afford a 15/1 mixture of oxepene **5** and **5′** (by ^{1}H NMR analysis) as colorless oils (112.4 mg, 84%).

(1b*R*,2a*R*,7a*R*)-1-{7a-[3-Benzyloxy-1b-(4-methoxybenzyloxy)propyl]-2,3,6,7-tetrahydrooxepin-2a-yl}propan-1-one (10). To a cooled (0 °C) solution of oxepene **5** (482.5 mg, 1.064 mmol) in anhydrous THF (21 mL, 0.05 M) was added dropwise ethylmagnesium bromide (1.16 mL, 1.0 M in THF, 1.164 mmol). The reaction mixture was gradually warmed to room temperature over 1 h and stirred for an additional 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 10/1 to 5/1) to afford ketone **10** as a colorless oil (415.3 mg, 89%): $[\alpha]^{25}_D$ = +34.69 (*c* 1.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.36 (m, 5 H), 7.20 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.66−5.74 (m, 2 H), 4.54 (dd, J = 5.2, 7.8 Hz, 1 H), 4.44−4.51 (m, 4H), 4.25 (d, J = 10.8 Hz, 1 H), 3.79 (s, 3 H), 3.64 (ddd, J = 4.0, 4.1, 8.0 Hz, 1 H), 3.58 (dd, J = 5.8, 6.8 Hz, 2 H), 2.53−2.66 (m, 3 H), 2.45−2.48 (m, 2 H),2.17 (dd, J = 5.9, 17.0 Hz, 1 H), 2.01 (dddd, J = 4.5, 7.1, 7.1, 14.1 Hz, 1 H), 1.85 (dddd, J = 5.5, 5.6, 8.5, 14.0 Hz, 1 H), 1.00 (dd, J = 7.2, 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4, 159.2, 138.4, 130.6, 129.5, 128.9, 128.3, 127.6, 127.5, 113.7, 80.9, 77.7, 76.4, 72.8, 72.2, 67.0, 55.2, 31.9, 31.2, 30.3, 29.2, 7.2; IR (neat) 1717, 1249, 1104 cm^{-1}; HRMS (FAB) found 439.2491 [(M + H)$^+$; calcd for $C_{27}H_{35}O_5$: 439.2484].

(1*R*,1b*R*,2a*R*,7a*R*)-1-{7a-[3-Benzyloxy-1b-(4-methoxybenzyloxy)propyl]-2,3,6,7-tetrahydrooxepin-2a-yl}propan-1-ol (11). To a cooled (−78 °C) solution of ketone **10** (390.0 mg, 0.889 mmol) in anhydrous THF (18 mL, 0.05 M) was added dropwise L-Selectride (1.78 mL, 1.0 M in THF, 1.783 mmol). After being stirred for 30 min at −78 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether (20 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 15/1 to 5/1) to afford a 8/1 mixture of (*R*)-alcohol **11** and (*S*)-alcohol **11′** (by ^{1}H NMR analysis) as colorless oils (361.3 mg, 92%) For alcohol **11**: $[\alpha]^{25}_D$ = +13.19 (*c* 1.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.35 (m, 5 H), 7.22 (d, J = 8.5 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 5.61−5.68 (m, 2 H), 4.50 (AB, J_{AB} = 11.4, $\Delta\nu_{AB}$ =11.4 Hz, 2 H), 4.47 (AB, J_{AB} = 11.9, $\Delta\nu_{AB}$ = 18.9 Hz, 2 H), 4.29 (ddd, J = 2.2, 5.5, 11.3 Hz, 1 H), 3.97 (ddd, J = 2.7, 4.9, 11.3 Hz, 1 H), 3.79 (s, 3 H), 3.53−3.59 (m, 3 H), 3.32 (brs, 1 H), 3.21 (brs, 1 H), 2.55−2.60 (m, 1 H), 2.36−2.42 (m, 1 H), 2.23 (ddd, J = 2.2, 5.0, 17.0 Hz, 1 H), 2.10 (d, J = 14.3 Hz, 1 H), 1.95 (dddd, J = 7.0, 11.2, 11.2, 18.4 Hz, 1 H), 1.75 (dddd, J = 5.8, 5.8, 7.3, 14.3 Hz, 1 H), 1.37−1.55 (m, 2 H), 0.92 (dd, J = 7.4, 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 138.3, 130.2, 129.5, 128.3, 127.9, 127.6, 127.5, 127.1, 113.7, 78.7, 78.0, 75.5, 74.8, 72.9, 71.9, 66.5, 55.2, 31.1. 31.0, 30.2, 26.7, 10.0; IR (neat) 3455, 1247, 1097 cm^{-1}; HRMS (FAB) found 441.2633 [(M + H)$^+$; calcd for $C_{27}H_{37}O_5$: 441.2641].

(1a*S*,1b*R*,2*R*,7*R*)-2-[3-Benzyloxy-1b-(4-methoxybenzyloxy)propyl]-7-(1a-bromopropyl)-2,3,6,7-tetrahydrooxepine (12). To a solution of alcohol **11** (293.0 mg, 0.665 mmol) in dry toluene (13 mL, 0.05 M) was added carbon tetrabromide (2.1820 g, 6.650 mmol), 1-methylcyclohexene (1.55 mL, 13.300 mmol), and trioctylphosphine (5.87 mL, technical 90%, 13.300 mmol) at room temperature. After being stirred for 20 min at room temperature, the mixture was stirred for 3 h at 70 °C. After being cooled to room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 20/1) to afford bromide **12** as a colorless oil (284.6 mg, 85%): $[\alpha]^{25}_D$ = +12.80 (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.35 (m, 5 H), 7.20 (d, J = 8.6 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.67−5.72 (m, 2 H), 4.47 (AB, J_{AB} = 11.2, $\Delta\nu_{AB}$ = 25.3 Hz, 2 H), 4.47 (AB, J_{AB} = 11.9, $\Delta\nu_{AB}$ = 15.4 Hz, 2 H), 4.24 (ddd, J = 1.1, 3.4, 10.9 Hz, 1 H), 4.15 (ddd, J = 1.6, 5.3, 10.0 Hz, 1 H), 4.01 (ddd, J = 3.6, 5.1, 9.2 Hz, 1 H), 3.78 (s, 3 H), 3.56−3.61 (m, 3 H), 2.56−2.60 (m, 1 H), 2.45−2.53 (m, 1 H), 2.37 (dd, J = 6.7, 17.5 Hz, 1 H), 2.18 (dd, J = 6.2, 17.4 Hz, 1 H), 2.00 (dddd, J = 4.5, 7.2, 7.2, 14.4 Hz, 1 H), 1.90 (ddddd, J = 3.6, 7.2, 7.2, 7.2, 14.4 Hz, 1 H), 1.73−1.80 (m, 2 H), 1.02 (dd, J = 7.2, 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.5, 130.8, 129.5, 129.2, 128.3, 127.7, 127.5, 127.3, 113.6, 78.0, 77.8, 74.8, 72.7, 72.1, 67.1, 62.9, 55.2, 30.7, 30.1, 29.9, 28.2, 12.3; IR (neat) 1173, 1098, 617 cm^{-1}; HRMS (FAB) found 503.1782 [(M + H)$^+$; calcd for $C_{27}H_{36}O_4{}^{79}Br$: 503.1797].

(1*R*,1b*S*,2a*R*,7a*R*)-3-Benzyloxy-1-[7a-(1b-bromopropyl)-2,3,6,7-tetrahydrooxepin-2a-yl]propan-1-ol (13). To a cooled (0 °C) solution of *p*-methoxybenzyl ether **12** (260.0 mg, 0.516 mmol) in 1,2-dichloroethane/pH 7.0 phosphate buffer (9/1, total 5 mL, 0.1 M) was added DDQ (117.4 mg, 0.516 mmol). After being stirred for 1 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL). The resulting dark red solution was stirred vigorously for 2 h at room temperature. The layers were separated, and the aqueous layer was extracted twice with dichloromethane (10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 10/1 to 5/1) to afford alcohol **13** as a colorless oil (180.0 mg, 91%): $[\alpha]^{25}_D = -5.93$ (*c* 1.10, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.36 (m, 5 H), 5.65−5.73 (m, 2 H), 4.53 (AB, J_{AB} = 12.0, $\Delta\nu_{AB}$ = 14.0 Hz, 2 H), 4.22 (ddd, J = 1.5, 4.6, 10.1 Hz, 1 H), 4.00−4.05 (m, 2 H), 3.65−3.74 (m, 3 H), 2.82 (d, J = 4.2 Hz, 1 H), 2.53−2.65 (m, 2 H), 2.33 (dd, J = 6.6, 17.3 Hz, 1 H), 2.22 (dd, J = 6.3, 17.5 Hz, 1 H), 1.77−1.93 (m, 4 H), 1.06 (dd, J = 7.2, 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.7, 128.4, 127.64, 127.59, 127.3, 77.9, 77.6, 73.2, 72.6, 68.1, 62.8, 33.3, 31.1, 31.0, 27.6, 12.5; IR (neat) 1540, 1211, 615 cm^{-1}; HRMS (FAB) found 383.1220 [(M + H)$^+$; calcd for $C_{19}H_{28}{}^{79}BrO_3$: 383.1220].

(1a*S*,3*R*,5*R*,8*R*)-8-(2-Benzyloxyethyl)-5-bromo-3-(1a-bromopropyl)-2,7-dioxabicyclo[4.2.1]nonane (14). To a stirred solution of alcohol **13** (151.0 mg, 0.394 mmol) in acetonitrile (8 mL, 0.05M) was added *N*-bromosuccinimide (350.6 mg, 1.970 mmol) at room temperature. After being stirred for 30 min at the same temperature, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and diluted with diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 20/1) to afford **14** as a colorless oil (167.5 mg, 92%): $[\alpha]^{25}_D$ = −43.23 (*c* 1.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27−7.36 (m, 5 H), 4.61 (d, J = 8.6 Hz, 1 H), 4.52 (s, 2 H), 4.29 (dd, J = 2.6, 3.8 Hz, 1 H), 4.19 (dd, J = 4.0. 9.3 Hz, 1 H), 4.15 (dd, J = 6.2, 10.9 Hz, 1 H), 3.97 (ddd, J = 2.3, 6.9, 6.9 Hz, 1 H), 3.84 (ddd, J = 3.7, 3.7, 10.2 Hz, 1 H), 3.61 (dd, J = 6.3, 6.3 Hz, 2 H), 2.53 (dd, J = 6.2, 15.0 Hz, 1 H), 2.41 (d, J = 14.2 Hz, 1 H), 2.28 (ddd, J = 9.5, 11.0, 15.0 Hz, 1 H), 2.19 (ddd, J = 4.4, 8.8, 13.6 Hz, 1 H), 2.01−2.10 (m, 2 H), 1.89 (ddddd, J = 3.7, 7.3, 7.3, 7.3, 14.6 Hz, 1 H), 1.76 (ddddd, J = 7.3, 7.3, 7.3, 10.2, 14.6 Hz, 1 H), 1.05 (dd, J = 7.3, 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 128.4, 127.65, 127.63, 81.5, 75.97, 75.92, 73.0, 67.5, 62.2, 50.5, 40.6, 33.5, 28.5, 27.3, 12.8; IR (neat) 1085, 796, 697, 617 cm^{-1}; HRMS (FAB) found 461.0324 [(M + H)$^+$; calcd for $C_{19}H_{27}{}^{79}Br_2O_3$: 461.0327].

(1b*S*,3a*R*,5a*R*,8a*R*)-2-[5a-Bromo-3a-(1b-bromopropyl)-2,7-dioxabicyclo[4.2.1]non-8a-yl]ethanol (15). To a stirred solution of benzyl ether **14** (120.0 mg, 0.260 mmol) in ethanol (5 mL, 0.05 M) was added 10% Pd/C (24.0 mg, 20 wt % of starting material). The solution was stirred under H_2 balloon condition for 2 h at room temperature. The reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 4/1 to 1/1) to afford alcohol **15** as a colorless oil (96.7 mg, 100%): $[\alpha]^{25}_D$ = −46.13 (*c* 0.85, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (d, J = 8.6 Hz, 1 H), 4.35 (dd, J = 2.7, 3.8 Hz, 1 H), 4.25 (dd, J = 3.8, 9.3 Hz, 1 H), 4.14 (dd, J = 6.1, 10.9 Hz, 1 H), 3.99 (ddd, J = 2.3, 5.6, 8.2 Hz, 1 H), 3.79−3.87 (m, 3 H), 2.52 (dd, J = 5.8, 15.0 Hz, 1 H), 2.43 (d, J = 14.3 Hz, 1 H), 2.30 (ddd, J = 9.6, 10.9, 15.0 Hz, 1 H), 2.20 (ddd, J = 4.4, 8.8, 13.7 Hz, 1 H), 1.97−2.06 (m, 2 H), 1.90 (ddddd, J = 3.6, 7.3, 7.3, 7.3, 14.6 Hz, 1 H), 1.79 (ddddd, J = 7.3, 7.3, 7.3, 10.1, 14.6 Hz, 1 H), 1.06 (dd, J = 7.3, 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.2, 81.8, 76.3, 76.0, 62.1, 61.0, 50.2, 40.6, 33.3, 30.9, 27.1, 12.8; IR (neat) 3398, 1289, 1137, 862, 616 cm^{-1}; HRMS (FAB) found 370.9849 [(M + H)$^+$; calcd for $C_{12}H_{21}{}^{79}Br_2O_3$: 370.9857].

(1a*S*,3*R*,5*R*,8*R*)-[5*R*-Bromo-3*R*-(1a*S*-bromopropyl)-2,7-dioxabicyclo[4.2.1]non-8*R*-yl]acetaldehyde (16). To a solution of alcohol **15** (95.4 mg, 0.256 mmol) in dry CH_2Cl_2 (5 mL, 0.05M) was added Dess−Martin periodinane (271.9 mg, 0.641 mmol) at room temperature. The reaction mixture was stirred for 3 h, diluted with *n*-hexane (10 mL), filtered through a short plug of silica gel, and concentrated in vacuo to give the crude aldehyde **16** (80.5 mg, 85%). Without further purification, the crude aldehyde **16** was carried on to the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1 H), 4.65 (d, J = 8.6 Hz, 1 H), 4.33−4.41 (m, 2 H), 4.10−4.20 (m, 2 H), 3.84 (ddd, J = 3.7, 3.7, 10.3 Hz, 1 H), 2.89−2.98 (m, 2 H), 2.52 (dd, J = 6.4, 15.2 Hz, 1 H), 2.46 (d, J = 15.2 Hz, 1 H), 2.17−2.36 (m, 2 H), 1.73−1.93 (m, 2 H), 1.07 (dd, J = 7.3, 7.3 Hz, 3 H).

(1a*S*,3*R*,3b*E*,5*R*,8*R*)-(5-Bromo-3-(1a-bromopropyl)-8-(3b-iodoallyl)-2,7-dioxabicyclo[4.2.1]nonane (17). Anhydrous $CrCl_2$ (181.9 mg, flame-dried under argon, 1.480 mmol) and freshly distilled THF (12 mL, 0.01M) were stirred for 30 min at room temperature, generating a creamy gray-green suspension. After cooling the mixture to 0 °C, a solution of iodoform (291.5 mg, 0.740 mmol) in dry THF (1 mL) and the crude aldehyde **16** (55.0 mg, 0.148 mmol) in dry THF (2 mL) was injected via a syringe. The resulting dark red reaction mixture was stirred at 0 °C to room temperature for 1 h. The reaction mixture was quenched with H_2O and diluted with diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (10 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 50/1) to afford (*E*)-vinyl iodide **17** (49.0 mg, 67%) and (*Z*)-vinyl iodide **17′** (9.8 mg, 13%). For (*E*)-vinyl iodide **17**; $[\alpha]^{25}_D$ = −49.93 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (ddd, J = 7.4, 7.4, 14.6 Hz, 1 H), 6.24 (d, J = 14.4 Hz, 1 H), 4.63 (d, J = 8.5 Hz, 1 H), 4.30 (dd, J = 2.5, 3.9 Hz, 1 H), 4.23 (dd, J = 3.8, 9.3 Hz, 1 H), 4.14 (dd, J = 6.4, 10.9 Hz, 1 H), 3.80−3.85 (m, 2 H), 2.47−2.54 (m, 3 H), 2.42 (d, J = 14.3 Hz, 1 H), 2.29 (ddd, J = 9.5, 11.0, 15.0 Hz, 1 H), 2.18 (ddd, J = 4.3, 9.3, 13.6 Hz, 1 H), 1.89 (ddddd, J = 3.6, 7.2, 7.2, 7.2, 14.5 Hz, 1 H), 1.79 (ddddd, J = 7.3, 7.3, 7.3, 10.1, 14.6 Hz, 1 H), 1.06 (dd, J = 7.3, 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 82.6, 81.9, 78.1, 76.3, 75.3, 62.1, 50.0, 40.8, 34.7, 33.3, 26.9, 12.9; IR (neat) 3739, 1648, 1538, 943 cm^{-1}; HRMS (FAB) found 492.8880 [(M + H)$^+$; calcd for $C_{13}H_{20}{}^{79}Br_2IO_2$: 492.8875]. For (*Z*)-vinyl iodide **17′**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, J = 7.5 Hz, 1 H), 6.30 (dd, J = 7.3, 14.0 Hz, 1 H), 4.64 (d, J = 8.5 Hz, 1 H), 4.30−4.33 (m, 2 H), 4.17 (dd, J = 6.0, 10.9 Hz, 1 H), 3.89−3.95 (m, 2 H), 2.68 (ddd, J = 7.3, 7.4, 14.5 Hz, 1 H), 2.46−2.56 (m, 2 H), 2.44 (d, J = 14.3 Hz, 1 H), 2.31 (ddd, J = 9.5, 11.0, 13.7 Hz, 1 H), 2.20 (ddd, J = 4.3, 8.6, 13.5 Hz, 1 H), 1.94 (ddddd, J = 3.8, 7.2, 7.2, 7.2, 14.4 Hz, 1 H), 1.80 (ddddd, J = 7.3, 7.3, 7.3, 10.1, 14.4 Hz, 1 H), 1.08 (dd, J = 7.2, 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 85.1, 82.3, 81.9, 76.2, 75.7, 62.1, 50.2, 40.5, 34.1, 33.4, 27.5, 12.9.

(1b*S*,3*E*,3a*R*,5a*R*,8a*R*)-{5-[5a-Bromo-3a-(1b-bromopropyl)-2,7-dioxabicyclo[4.2.1]non-8a-yl]pent-3-en-1-ynyl}-trimethylsilane (18). To a solution of vinyl iodide **17** (32.5 mg, 0.065 mmol) in Et_2NH (1 mL) was added $Pd(PPh_3)_4$ (7.5 mg, 0.006 mmol). The mixture was stirred at room temperature for 10 min in the dark (flask wrapped with foil). To a solution of CuI (2.5 mg, 0.013 mmol) in Et_2NH (1 mL) was added trimethylsilylacetylene (12.8 mg, 0.131 mmol). The mixture was stirred at room temperature for 10 min and then added via syringe to the solution of vinyl iodide **17**. The reaction mixture was stirred for 1 h and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 50/1) to afford (*E*)-enyne **18** (22.7 mg, 75%): $[\alpha]^{25}_D$ = −55.80 (*c* 0.61, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (ddd, J = 7.4, 7.4, 15.7 Hz, 1 H), 5.67 (d, J = 15.9 Hz, 1 H), 4.62 (d, J = 8.6 Hz, 1 H), 4.30 (dd, J = 2.4, 3.8 Hz, 1 H), 4.23 (dd, J = 4.0, 9.3 Hz, 1 H), 4.14 (dd, J = 6.2, 10.8 Hz, 1 H), 3.79−3.85 (m, 2 H), 2.50−2.57 (m, 3 H), 2.42 (d, J = 14.3 Hz, 1 H), 2.28 (ddd, J = 9.5, 10.9, 15.0 Hz, 1 H), 2.16 (ddd, J = 4.4, 9.5, 13.5 Hz, 1 H), 1.90 (ddddd, J = 3.7, 7.3, 7.3, 7.3, 14.6 Hz, 1 H), 1.78 (ddddd, J = 7.3, 7.3, 7.3, 10.1, 14.6 Hz, 1 H), 1.06 (dd, J = 7.2, 7.2 Hz, 3 H), 0.17 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 112.9, 103.4, 94.0, 83.2, 81.9, 76.3, 75.2, 62.0, 50.2, 40.2, 33.4, 31.8, 27.1, 12.9, −0.1; IR (neat) 2131, 1729, 1249, 1135 cm^{-1}; HRMS (FAB) found 463.0305 [(M + H)$^+$; calcd for $C_{18}H_{29}{}^{79}Br_2O_2Si$: 463.0304].

3-(*E*)-Isoprelaurefucin (4). To a cooled (0 °C) solution of enyne **18** (18.0 mg, 0.039 mmol) in THF (2 mL, 0.02 M) was added dropwise TBAF (0.10 mL, 1.0 M solution in THF, 0.100

mmol). After being stirred for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether (10 mL). The layers were separated, and the aqueous layer was extracted twice with diethyl ether (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; *n*-hexane/ethyl acetate, 20/1) to afford 3-(*E*)-isoprelaurefucin (**4**) as a colorless oil (14.5 mg, 95%): $[\alpha]^{25}_D = -56.18$ (*c* 0.41, $CHCl_3$) [lit. $[\alpha]_D = -54.4$]; ^1H NMR (500 MHz, $CDCl_3$) δ 6.24 (ddd, J = 7.3, 7.3, 15.9 Hz, 1 H), 5.63 (dd, J = 1.5, 15.9 Hz, 1 H), 4.63 (d, J = 8.6 Hz, 1 H), 4.30 (dd, J = 2.7, 3.5 Hz, 1 H), 4.24 (dd, J = 3.9, 9.3 Hz, 1 H), 4.15 (dd, J = 6.2, 10.9 Hz, 1 H), 3.80−3.84 (m, 2 H), 2.83 (d, J = 2.0 Hz, 1 H), 2.51−2.57 (m, 3 H), 2.42 (d, J = 14.3 Hz, 1 H), 2.29 (ddd, J = 9.7, 10.8, 15.0 Hz, 1 H), 2.17 (ddd, J = 4.4, 8.7, 14.0 Hz, 1 H), 1.91 (ddddd, J = 3.7, 7.3, 7.3, 7.3, 14.6 Hz, 1 H), 1.79 (ddddd, J = 7.3, 7.3, 7.3, 10.1, 14.6 Hz, 1 H), 1.07 (dd, J = 7.2, 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 111.7, 83.1, 81.8, 77.2, 76.8, 76.3, 75.3, 62.1, 50.1, 40.8, 33.4, 31.8, 27.0, 12.9; IR (neat) 3290, 2131, 1458, 616 cm^{-1}; HRMS (FAB) found 390.9919 [$(M + H)^+$; calcd for $C_{15}H_{21}{}^{79}Br_2O_2$: 390.9908].

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Supporting Information Available: Experimental procedures and product characterization for compounds **1a** and **1b** and copies of the ^1H and ^{13}C NMR spectra of compounds **1**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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