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Stereoselective synthesis of *syn*-2,7-disubstituted-4,5-oxepenes

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Abstract—An efficient synthesis of the title compounds as pure enantiomers is reported. The method is based on the intramolecular trapping of a carbocation generated by acid treatment of *exo*-$Co_2(CO)_6$-propargyl alcohols by a stereochemically controlled secondary hydroxy group located in a suitable chain.

An interesting and increasingly large group of marine products is a series of nonterpenoid C15-metabolites generically named lauroxanes that derive from fatty acid metabolism (acetogenins).[1] The structural diversity of this kind of molecule is very wide, but all have in common the presence of polysubstituted cyclic ethers with a defined stereochemistry in the substituents and a ring size varying from five to nine members. Among such structural diversity a particularly interesting family are those compounds having the oxepane (7-membered oxa-cyclic) ring. The common structural feature is the presence of 2,7-dialkyl-substituents with one or more halide atoms incorporated at different positions, one of which is usually located in an alkyl group in the α-carbon relative to the ring. A few representative lauroxepanes isolated from different species of red seaweeds of the genus *Laurencia* are outlined in Fig. 1.[2] Seven-membered oxacycles occur also in many other interesting natural compounds such as the marine polycyclic toxins.[1,3] The structural complexity, novelty and biological activity of these compounds have made them very attractive synthetic targets.[4]

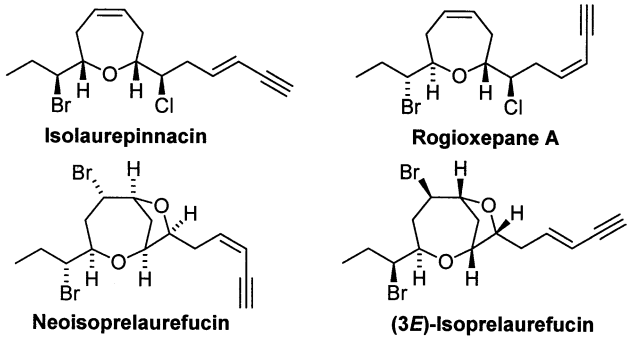
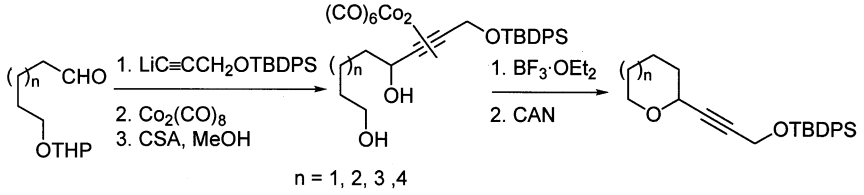


Figure 1. Representative examples of lauroxepanes.

As a part of our program directed to the synthesis of marine natural products[5] we developed a general procedure for the synthesis of cyclic ethers based on an intramolecular Nicholas reaction[6] in which a hydroxy group located in a suitable chain attacks a carbocation generated by acid treatment of *exo*-$Co_2(CO)_6$-propargyl alcohols leading to cyclic ethers with a ring size ranging from 6- to 9-membered rings (Scheme 1).[7]

Taking advantage of such a methodology we envisioned a way to synthesize 2,7-dialkyl-oxepenes, confident that with



Scheme 1.

Keywords: marine metabolites; oxepenes; Nicholas reaction.

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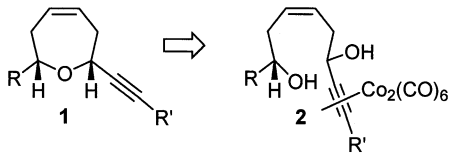
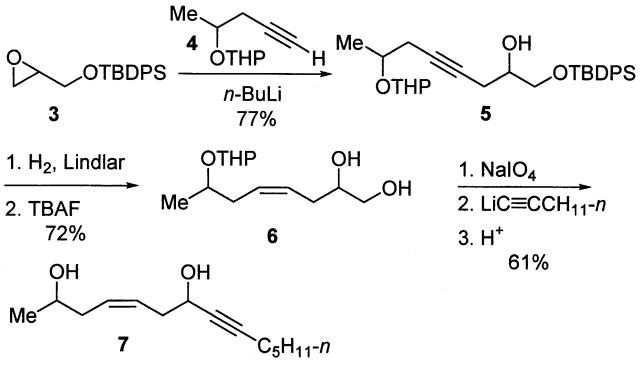
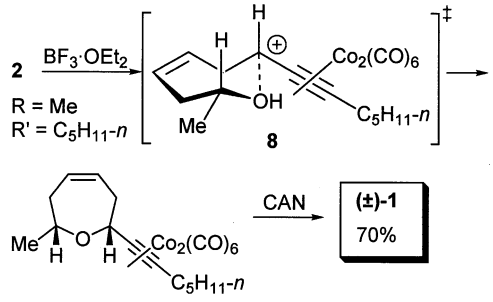


Scheme 2.



Scheme 3.



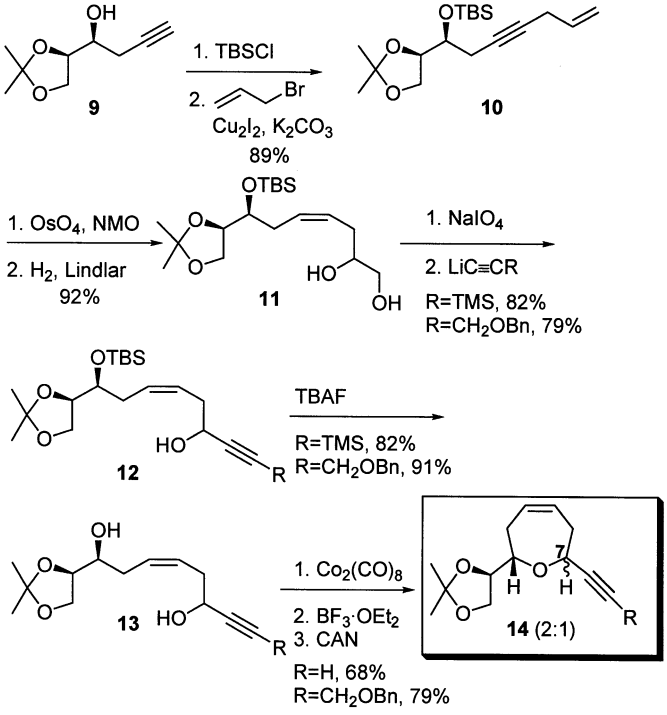
Scheme 4.

the suitable linear precursor we would be able to control the stereochemistry in the cyclization step. Outlined herein are our studies directed to the stereocontrolled synthesis of 2,7-dialkyl oxepenes by an intramolecular Nicholas reaction (Scheme 2).

In an attempt to explore the scope and limitations of our methodology we first synthesized the diastereomeric mixture of racemic diol **7** (R=Me, R′=C_5H_{11}-*n*) (Scheme 3). Racemic glycidol was protected as the TBDPS-ether **3** and treated with the lithium salt of the THP-ether **4** of commercially available 4-pentyn-2-ol yielding the diprotected triol **5**. Lindlar hydrogenation and further *O*-silyl deprotection provided stereoselectively the *Z*-diol **6**. Oxidative cleavage of the diol, treatment of the resulting crude aldehyde with the lithium acetylide of 1-heptyne and cleavage of the THPO-ether provided the diol **7**.

In order to probe our idea about the capability of the secondary nucleophilic carbinol to control the stereochemistry in the cyclization step we submitted **7** to $Co_2(CO)_8$ obtaining in almost quantitative yield the corresponding $Co_2(CO)_6$–alkyne complex **2** (R=Me, R′=C_5H_{11}-*n*). Acidic treatment followed by acetylene demetalation[8] provided exclusively the *syn*-diastereoisomer of (±)-**1**. It should be pointed out that the cyclization step is very fast (ca. 5 min) and that the stereochemical results are similar from −20°C to room temperature. We think that a possible explanation of the strong selectivity could be related to the formation of a transition state such as **8** in which the more bulky groups, the metallic complexes alkyne and the alkyl substituent at the secondary nucleophilic carbinol, occupy a pseudo-equatorial position (Scheme 4).[9]

In light of these results we decided to obtain 2,7-disubstituted-4,5-oxepenes as pure enantiomers to show that our

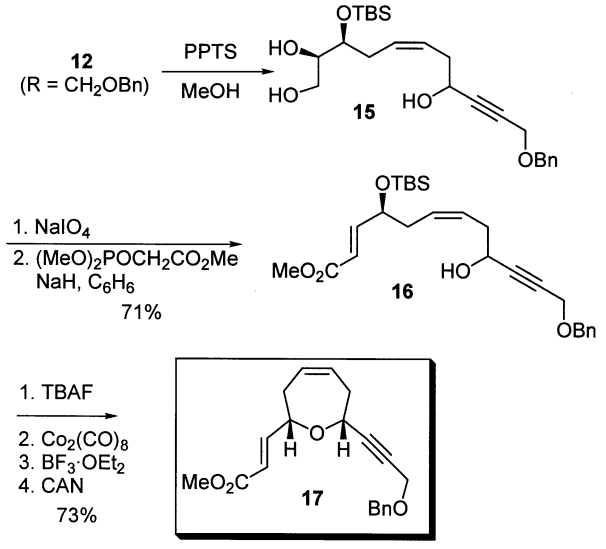


Scheme 5.

methodology can be easily applied for the synthesis of several natural compounds. We directed our attention to the known homopropargylic alcohol **9**, easily available on a multigram scale[10] from (*R*)-glyceraldehyde.[11] Protection as TBS-ether and further alkylation with allylic bromide and the assistance of Cu(I) provided the skipped enyne **10** that was submitted to dihydroxylation and further Lindlar's hydrogenation providing the diastereomeric mixture of diols **11** (Scheme 5). With these products in our hands a similar sequence to that performed before, namely oxidative cleavage, lithium acetylides addition provided **12** (R=TMS or $-CH_2OBn$) as a stereoisomer mixture at the propargylic position. Silyl-cleavage affords the diols **13** (R=H or $-CH_2OBn$). Finally, **13** was complexed and the resulting $Co_2(CO)_6$–acetylene treated with Lewis acid at $-20°C$ obtaining the corresponding cyclic ether that after demetalation yielded **14** (R=H or $-CH_2OBn$) as a mixture of epimers at C7 (2:1) regardless the nature of the acetylenic substituent.[12] Interestingly, when the reaction was performed at higher temperature the deprotection of the acetonide competes with the ring formation producing a mixture.

Although the overall results regarding the synthesis of the oxacycles were satisfactorily achieved, we worried about the role of the additional stereocenter in the linear precursor (compared with the model **7**) over the stereochemistry in the cyclization reaction.[13] In order to probe such influence we selectively deprotected the acetonide[14] yielding the diol **15** that was oxidatively cleavage to the corresponding aldehyde and further homologated to the α,β-unsaturated ester **16** (Scheme 6). Fortunately, when we followed a similar cyclization sequence of that outlined above we obtained the highly functionalized oxepene **17** as the only stereoisomer.

In summary, we have described an efficient method to obtain enantiomerically pure *syn*-2,7-disubstituted-4,5-oxepenes with enough functionalities in the lateral chains to perform the necessary conversions to some marine natural products with the 7-membered ring as the key structural feature. Synthetic studies of some of such compounds are under study and will be published in due course.



Scheme 6.

1. Experimental

1.1. Materials and methods

^1H NMR spectra were recorded at 400 and 300 MHz, ^{13}C NMR spectra were recorded at 75 MHz, and chemical shifts are reported relative to internal Me_4Si. Optical rotations were determined for solutions in chloroform. Column chromatography was performed on Merck silica gel, 60 Å and 0.2–05 mm. Compounds were visualized by use of UV light and/or 2.5% phosphomolybdic acid in ethanol with heating. All solvents were purified by standard techniques.[15] Reactions requiring anhydrous conditions were performed under nitrogen. Anhydrous magnesium sulfate was used for drying solutions.

1.1.1. Preparation of 1-methyl-3-butynyl tetrahydro-2*H*-pyran-2yl ether (4). To a stirred solution of the 4-pentyn-2-ol (10 g, 119 mmol) in dry CH_2Cl_2 (300 mL) under argon was added dihydropyran (21.7 mL, 238 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate at 0°C. The reaction was allowed to warm to rt and stirred for 6 h. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2 (2×100 mL). The combined organic phases were washed with brine (200 mL), dried and concentrated. The crude obtained was purified by flash chromatography, yielding **4** (17.5 g, 88% yield) as an oil: ^1H NMR ($CDCl_3$) δ 1.21 (d, J=6.2 Hz, 3H), 1.28 (d, J=6.3 Hz, 3H), 1.49 (m, 9H), 1.67 (m, 2H), 1.79 (m, 2H), 1.95 (ddd, J=7.4, 2.6, 2.6 Hz, 1H), 2.32 (m, 3H), 2.51 (ddd, J=16.0, 5.1, 2.7 Hz, 1H), 3.45 (m, 2H), 3.89 (m, 4H), 4.67 (m, 1H), 4.71 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.8 (q), 19.5 (t), 19.7 (t), 21.0 (q), 25.4 (t), 25.4 (t), 25.7 (t), 27.1 (t), 30.8 (t), 30.9 (t), 62.3 (t), 62.6 (t), 69.7 (s), 69.7 (s), 70.6 (d), 70.9 (d), 81.1 (d), 81.4 (d), 96.7 (d), 97.7 (d). IR ($CHCl_3$) $\bar{\nu}_{max}$ (cm^{-1}) 3308, 3010, 2946, 2853, 2360, 1126, 1030. MS *m/z* (relative intensity) 169 $(M+1)^+$ (2), 149 (100), 117 (25), 105 (11), 97 (15), 85 (21), 31 (55). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.40; H, 9.61.

1.1.2. Preparation of 1-(*tert*-butyl-diphenyl-silanyloxy)-7-(tetrahydro-2*H*-pyran-2-yloxy)-4-octyn-2-ol (5). To a stirred solution of the alkyne **4** (2.7 g, 16 mmol) dissolved in dry THF (160 mL) under argon was added *n*-butyl lithium 1.9 M in *n*-hexane (8 mL, 15.2 mmol) at $-78°C$. After the addition, the reaction was maintained with stirring for 15 min, after which time, 1 equiv. of $BF_3{\cdot}Et_2O$ (2.03 mL, 16 mmol) was added. After 5 min, *tert*-butyl-dimethyl-oxiranylmethoxy-silane (1.6 g, 8.5 mmol) in dry THF (10 mL) was added slowly. The reaction mixture was stirred for 30 min, until TLC showed complete conversion. The mixture was poured into a saturated aqueous solution of $NaHCO_3$ (100 mL) and ether (100 mL), both phases were separated and the aqueous phase was washed with ether (2×50 mL). The combined organic phases were dried, concentrated and the obtained crude was purified by flash-chromatography, to yield **5** (2.96 g, 77% yield) as an oil: ^1H NMR ($CDCl_3$) δ 1.04 (d, J=6.3 Hz, 6H), 1.09 (s, 18H), 1.17 (d, J=6.12 Hz, 3H), 1.18 (d, J=6.0 Hz, 3H), 1.27 (ddd, J=14.5, 14.5, 6.1 Hz, 4H), 1.51 (m, 12H), 1.68 (m, 4H), 1.83 (m, 4H), 2.30 (m, 4H), 2.47 (m, 8H), 2.65 (d, J=5.2 Hz, 2H), 2.78 (d, J=5.3 Hz, 2H), 3.48 (m, 4H), 3.73 (m, 8H), 3.89 (m, 12H), 4.67 (m, 2H), 4.73 (m, 2H),

7.37 (m, 24H), 7.64 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 19.2 (q), 19.3 (s), 19.7 (t), 19.8 (t), 21.1 (q), 23.6 (t), 23.8 (t), 25.5 (t), 26.1 (t), 26.9 (q), 27.0 (t), 27.5 (t), 30.9 (t), 31.1 (t), 62.6 (t), 62.7 (t), 66.5 (t), 66.5 (t), 66.5 (t), 67.9 (t), 70.5 (d), 71.1 (d), 71.2 (d), 71.3 (d), 77.3 (s), 77.4 (s), 77.4 (s), 79.3 (s), 79.3 (s), 79.7 (s), 79.8 (s), 97.0 (d), 97.6 (d), 127.8 (d), 129.8 (d), 129.8 (d), 133.1 (s), 133.2 (s), 135.6 (d). IR ($CHCl_3$) $\bar{\nu}_{max}$ (cm^{-1}) 3572, 3009, 2932, 2859, 1428, 1113, 1074; MS *m/z* (relative intensity): 423 $(M-57)^+$ (1), 379 (2), 339 (17), 295 (4), 261 (18), 241 (51), 199 (100), 163 (29), 135 (16); Anal. Calcd for $C_{29}H_{40}O_4Si$: C, 72.46; H, 8.39. Found: C, 72.22; H, 8.50.

1.1.3. Preparation of (4*Z*)-7-(tetrahydropyran-2-yloxy)-4-octen-1,2-diol (6). A mixture of **5** (4.7 g, 9.71 mmol) and Lindlar's catalyst (50 mg) in dry EtOAc (63 mL) was stirred at room temperature under a H_2 atmosphere (≈1 atm). The reaction was stirred for 2 h, after which time TLC showed the end of the reaction. The solution was filtered through a pad of Celite and the filter was washed with EtOAc. The combined organic phases were concentrated, and the crude obtained was used without purification.

To a stirred solution of the alkene in dry THF (50 mL) under argon was added *n*-tetrabutylammonium fluoride 1 M in THF (11.7 mL, 11.7 mmol) at 0°C. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was poured into H_2O (50 mL) and extracted with ether (2×30 mL). The combined organic solutions were washed with brine (50 mL) and dried. The resulting solution was concentrated and purified by column chromatography, yielding the diol **6** (1.7 g, 72% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.14 (d, *J*=6.2 Hz, 3H), 1.15 (d. *J*=6.1 Hz, 3H), 1.23 (d, *J*=6.4 Hz, 3H), 1.24 (d, *J*=6.3 Hz, 3H), 1.52 (m, 14H), 1.68 (m, 4H), 1.81 (m, 6H), 2.18 (m, 4H), 2.31 (m, 12H), 3.48 (m, 8H), 3.63 (m, 2H), 3.66 (m, 2H), 3.73 (m, 4H), 3.80 (dddd, *J*=6.2, 6.2, 6.2, 1.4 Hz, 2H), 3.88 (m, 6H), 5.66 (m, 4H), 5.54 (m, 6H), 5.64 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.0 (q), 19.0 (q), 19.7 (t), 19.8 (t), 19.9 (t), 21.3 (q), 24.6 (q), 25.3 (t), 25.4 (t), 30.9 (t), 30.9 (t), 31.0 (t), 31.0 (t), 31.3 (t), 31.4 (t), 31.5 (t), 34.2 (t), 34.5 (t), 35.1 (t), 35.3 (t), 62.7 (t), 62.8 (t), 63.0 (t), 66.0 (t), 66.3 (t), 71.0 (d), 71.4 (d), 71.6 (d), 71.7 (d), 71.8 (d), 73.3 (d), 73.7 (d), 96.0 (d), 96.6 (d), 98.4 (d), 98.7 (d), 126.8 (d), 126.4 (d), 126.5 (d), 126.7 (d), 128.9 (d), 129.2 (d), 129.4 (d), 129.9 (d). IR ($CHCl_3$) $\bar{\nu}_{max}$ (cm^{-1}) 3452, 3009, 2974, 2948, 1381, 1074, 1029, 877. MS *m/z* (relative intensity): 225 $(M-19)^+$ (1), 149 (2), 140 (1), 101 (3), 84 (100), 67 (13), 55 (13); Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.73; H, 10.21.

1.1.4. Preparation of (4*Z*)-4-tetradecen-8-yne-2,7-diol (7). To a stirred solution of the diol **6** (330 mg, 1.35 mmol) dissolved in THF/H_2O (5:1, 13.5 mL) were added $NaIO_4$ (1.16 g, 5.4 mmol) and a catalytic amount of tetra-butylammonium periodate at room temperature. After 1 h, the mixture was diluted with ether (20 mL) and washed with brine (15 mL), and the aqueous phase washed with ether (3×20 mL). The combined organic solutions were dried over $MgSO_4$, concentrated and the crude aldehyde obtained was used without purification.

To a solution of 1-heptyne (0.355 mL, 2.7 mmol) in dry THF (22 mL) under argon was added dropwise 0.9 equiv. of *n*-BuLi (1.28 mL, 2.43 mmol, 1.9 M in *n*-hexane) at −78°C. The reaction was allowed to warm to −20°C and stirred for 15 min, after which time was added the aldehyde in dry THF (5 mL) at −78°C. The reaction mixture was stirred for 1 h, after which time TLC showed complete conversion. The reaction was poured into NH_4Cl saturated aqueous solution (20 mL) and ether (20 mL) and the aqueous phase extracted with ether (2×10 mL). The combined organic solutions were dried over $MgSO_4$ and concentrated and the crude was used without purification.

The crude alcohol was dissolved in MeOH and a catalytic amount of concentrated HCl was added at 0°C. The reaction was stirred for 1 h, after which time TLC showed that the starting material had disappeared, and then Et_3N was added at 0°C until neutral pH was reached. The reaction was concentrated and purified by column chromatography, yielding the diol **7** (185 mg, 61% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.90 (dd, *J*=7.1, 7.1 Hz, 6H), 1.22 (d, *J*=6.3 Hz, 3H), 1.23 (d, *J*=6.3 Hz, 3H), 1.33 (m, 8H), 1.51 (dddd, *J*=7.1, 7.1, 7.1, 7.1 Hz, 4H), 1.61 (bs, 4H), 2.20 (ddd, *J*=7.2, 7.2, 1.9 Hz, 4H), 2.22 (m, 1H), 2.29 (m, 1H), 2.45 (m, 1H), 2.54 (m, 1H), 3.86 (m, 2H), 4.41 (m, 1H), 4.46 (m, 1H), 5.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 18.6 (t), 22.2 (t), 23.0 (q), 23.1 (q), 28.3 (t), 31.0 (t), 35.7 (t), 36.1 (t), 37.0 (t), 61.8 (d), 61.9 (d), 67.4 (d), 67.4 (d), 80.6 (s), 80.7 (s), 85.8 (s), 86.0 (s), 127.3 (d), 127.6 (d), 129.1 (d), 129.2 (d). IR ($CHCl_3$) $\bar{\nu}_{max}$ (cm^{-1}) 3456, 3008, 2975, 2933, 2896, 2360, 1390, 1046, 877; MS *m/z* (relative intensity): 191 $(M-33)^+$ (1), 169 (2), 125 (24), 106 (12), 91 (18), 82 (100), 67 (61); Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.77; H, 11.01.

1.1.5. Preparation of (2*R,7*R**)-2-hept-1-ynyl-7-methyl-3*H*,6*H*-oxepin (1) (R=Me, R′=C_5H_{11}-*n*).** To a solution of **7** (131 mg, 0.58 mmol) in dry CH_2Cl_2 (6 mL) was added $Co_2(CO)_8$ (238 mg, 0.7 mmol) at room temperature. The reaction mixture was stirred at room temperature until TLC showed complete conversion to the hexacarbonyl-dicobalt complex (ca. 1 h). The mixture was filtered through a pad of silica gel and concentrated to yield red–brown oil that was used without any purification.

To a stirred solution of the crude $Co_2(CO)_6$ complex in dry CH_2Cl_2 (6 mL) under argon was added $BF_3{\cdot}OEt_2$ (88 μL, 0.70 mmol) at room temperature. The reaction mixture was stirred for 20 min and poured into a saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was vigorously stirred for 15 min and extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated to give the $Co_2(CO)_6$ complex that was employed in the next step without further purification.

To a stirred solution of the complexed acetylene in dry acetone (6 mL) was added CAN (1.27 g, 2.32 mmol) in one portion at 0°C. The reaction mixture was stirred at 0°C until TLC showed completion of the reaction (ca. 5 min). The mixture was evaporated and the residue diluted with water (10 mL) and extracted with Et_2O (2×15 mL). The combined organic solutions were dried ($MgSO_4$), filtered and concentrated. Flash column chromatography

yielded **1** (R=Me, R′=C_5H_{11}-*n*) (83 mg, 70% overall yield) as a colourless oil: ^{1}H NMR ($CDCl_3$) δ 0.88 (dd, *J*=6.9, 6.9 Hz, 3H), 1.24 (d, *J*=6.2 Hz, 3H), 1.32 (m, 4H), 1.49 (dddd, *J*=7.1, 7.1, 7.1, 7.1 Hz, 2H), 2.15 (m, 1H), 2.19 (ddd, *J*=7.0, 7.0, 1.8 Hz, 2H), 2.31 (ddd, *J*=16.4, 10.0, 2.3 Hz, 1H), 2.42 (dddd, *J*=16.7, 6.6, 1.8, 1.8 Hz, 1H), 2.63 (m, 1H), 3.54 (m, 1H), 4.15 (dddd, *J*=10.5, 1.8, 1.8, 1.8 Hz, 1H), 5.76 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 18.8 (t), 22.2 (t), 23.1 (q), 28.3 (t), 31.1 (t), 39.1 (t), 39.3 (t), 70.4 (d), 76.6 (d), 80.2 (s), 84.5 (s), 129.1 (d), 130.3 (d). IR ($CHCl_3$) $\bar{\nu}_{max}$ (cm^{-1}) 3005, 2959, 2933, 2861, 2360, 1318, 1078, 1025. MS *m/z* (relative intensity): 205 $(M-1)^+$ (2), 173 (9), 162 (8), 123 (10), 106 (18), 97 (11), 86 (41), 82 (100); Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.32; H, 10.99.

1.1.6. Preparation of *tert*-butyl-{(1*S*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-6-hepten-3-ynyloxy}-dimethylsilane (10). To a stirred solution of the alcohol **9** (3 g, 17.6 mmol) in dry CH_2Cl_2 (88 mL) under argon were added imidazole (1.8 g, 26.4 mmol) and *tert*-butylchlorodimethylsilane (3.45 g, 22.9 mmol) at 0°C. The reaction was allowed to warm to room temperature and stirred overnight. Then it was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (2×30 mL). The combined organic phases were washed with brine (100 mL), dried, filtered and concentrated. The crude obtained was purified by flash chromatography affording the silyl ether (4.81 g, 96% yield) as an oil: $[\alpha]^{25}_D$=+26.5 (*c* 1.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.11 (s, 3H), 0.87 (s, 9H), 1.32 (s, 3H), 1.37 (s, 3H), 1.96 (t, *J*=2.7 Hz, 1H), 2.42 (m, 2H), 3.76 (dd, *J*=12.5, 6.3 Hz, 1H), 3.85 (dd, *J*=8.0, 6.3 Hz, 1H), 4.00 (dd, *J*=8.0, 6.4 Hz, 1H), 4.12 (dd, *J*=12.5, 6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.3 (q), 18.0 (s), 24.6 (t), 25.4 (q), 25.7 (q), 26.7 (q), 66.2 (t), 70.4 (d), 71.2 (d), 77.4 (d), 80.5 (s), 109.0 (s). MS *m/z* (relative intensity): 227 (1.7) $(M-{}^tBu)^+$, 169 (76), 95 (25), 75 (100), 73 (91); HRMS Calcd for $C_{11}H_{19}O_3Si$ $(M-{}^tBu)^+$ 227.11035, found 227.10922.

To a stirred solution of the alkyne (4 g, 14.1 mmol) in dry DMF (47 mL) under argon were added sequentially K_2CO_3 (2.74 g, 19.8 mmol), tetra-*n*-butylammonium bromide (590 mg, 1.83 mmol) and copper(I) iodine (134 mg, 0.7 mmol) at room temperature. After 10 min, allyl bromide (1.58 mL, 18.3 mmol) was added. The reaction mixture was stirred for 60 h. Then, it was poured into H_2O (200 mL) and extracted with ether (3×50 mL). The combined organic phases were washed with brine (100 mL), dried and concentrated. The crude obtained was purified by flash chromatography, yielding **10** (4.24 g, 93% yield): $[\alpha]^{25}_D$=+25.4 (*c* 1.93, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 1.32 (s, 3H), 1.37 (s, 3H), 2.41 (m, 2H), 2.91 (m, 2H), 3.78 (dd, *J*=10.6, 5.3 Hz, 1H), 3.86 (dd, *J*=7.0, 7.0 Hz, 1H), 4.00 (dd, *J*=7.1, 7.1 Hz, 1H), 4.13 (dd, *J*=12.3, 6.0 Hz, 1H), 5.06 (d, *J*=10.0 Hz, 1H), 5.29 (d, *J*=16.9 Hz, 1H), 5.78 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.4 (q), 18.0 (s), 23.1 (t), 25.0 (t), 25.3 (q), 25.6 (q), 26.6 (q), 66.0 (t), 71.5 (d), 77.4 (s), 77.6 (d), 78.6 (s), 108.9 (s), 115.7 (t), 133.0 (d). MS *m/z* (relative intensity): 267 (3.4) $(M-{}^tBu)^+$, 245 (14), 209 (33), 117 (31), 75 (90), 73 (100). HRMS Calcd for $C_{18}H_{32}O_3Si$ $(M)^+$ 324.21207, found 324.21320.

1.1.7. Preparation of (2*R* and 2*S*, 7*S*)-7-(*tert*-butyldimethyl-silanyloxy)-7-[(4*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-4-heptene-1,2-diol (11). To a stirred solution of 4-methylmorpholine *N*-oxide (4.34 g, 37.0 mmol) in H_2O (40 mL) at room temperature, were added OsO_4 (6 mg, 0.02 mmol) and the alkene **10** (4 g, 12.3 mmol) in THF/acetone (1:1) (80 mL). The mixture was vigorously stirred overnight. Then it was diluted with EtOAc (100 mL) and washed with a saturated solution of $NaHSO_3$ (150 mL), the aqueous phase was extracted with AcOEt (2×50 mL) and the combined organic phase was washed with H_2O (150 mL) and dried over $MgSO_4$, filtered and concentrated. Flash column chromatography yielded the corresponding diol (4.07 g, 92% yield) as a colourless oil: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.33 (s, 3H), 1.38 (s, 3H), 2.40 (m, 4H), 3.24 (br s, 2H), 3.73 (dd, *J*=10.6, 5.0 Hz, 2H), 3.85 (dd, *J*=7.9, 6.2 Hz, 2H), 4.01 (dd, *J*=7.1, 7.1 Hz, 2H), 4.09 (dd, *J*=12.4, 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.4 (q), 17.9 (s), 24.9 (t), 25.3 (q), 25.7 (q), 26.6 (q), 66.1 (t), 71.4 (d), 77.5 (d), 78.1 (s), 78.8 (s), 109.1 (s). MS *m/z* (relative intensity): 301 (1.8) $(M-{}^tBu)^+$, 187 (18), 117 (38), 75 (97), 73 (100). Anal. Calcd for $C_{18}H_{34}O_5Si$: C, 60.30; H, 9.56. Found: C, 60.36; H, 9.77.

A mixture of the diol (4 g, 11.2 mmol), Lindlar catalyst (200 mg, 5% w) and quinoline (7 μL, 0.2% w) in dry EtOAc (112 mL) was stirred at room temperature under a H_2 atmosphere (≈1 atm) for 30 min, after which time TLC showed the end of the reaction. The solution was filtered through a pad of Celite and the filter was washed with EtOAc. The combined organic phases were concentrated, and the crude obtained was purified by flash-chromatography, yielding **11** (4.02 g, quantitative) as an oil: ^{1}H NMR ($CDCl_3$) δ; ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.4 (q), 18.0 (s), 23.1 (t), 25.0 (t), 25.3 (q), 25.6 (q), 26.6 (q), 66.0 (t), 71.5 (d), 77.4 (s), 77.6 (d), 78.6 (s), 108.9 (s), 115.7 (t), 133.0 (d). MS *m/z* (relative intensity): 303 (0.23) $(M-{}^tBu)^+$, 245 (14), 187 (25), 117 (20), 75 (71), 73 (100). Anal. Calcd for $C_{18}H_{36}O_5Si$: C, 59.96; H, 10.06. Found: C, 59.99; H, 10.68.

1.1.8. Preparation of (3*R* and 3*S*, 5*Z*, 8*S*)-8-(*tert*-butyldimethyl-silanyloxy)-8-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-trimethylsilanyl-5-octen-1-yn-3-ol (12) (R=TMS). The sequence used above to obtain **7** from **6** was applied to **11** on a 3.5 g (9.7 mmol) scale, yielding **12** (R=TMS) (3.4 g, 82% overall yield) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.05 (s, 6H), 0.13 (s, 18H), 0.85 (s, 18H), 1.29 (s, 6H), 1.36 (s, 3H), 1.37 (s, 3H), 2.22 (m, 2H), 2.44 (m, 6H), 2.68 (br s, 2H), 3.76 (m, 4H), 3.94 (m, 4H), 4.32 (dd, *J*=7.0, 5.9 Hz, 1H), 4.37 (dd, *J*=5.8, 5.8 Hz, 1H), 5.64 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.2 (q), −0.2 (q), 17.9 (s), 25.3 (q), 25.7 (q), 26.7 (q), 32.4 (t), 32.5 (t), 35.6 (t), 36.0 (t), 62.0 (d), 62.1 (d), 66.7 (t), 72.4 (d), 72.5 (d), 77.6 (d), 88.8 (s), 89.1 (s), 106.4 (s), 106.8 (s), 109.0 (s), 109.1 (s), 126.1 (d), 126.3 (d), 128.2 (d), 128.3 (d). MS *m/z* (relative intensity). Anal. Calcd for $C_{22}H_{42}O_4Si_2$: C, 61.92; H, 9.92. Found: C, 61.77; H, 10.08.

1.1.9. Preparation of (1*S*,3*Z*,6*R* and 6*S*)-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-octen-7-yne-1,6-diol (13) (R=H). The TBDPS-deprotection used above to obtain **6**

was applied to **12** (R=TMS) on a 3 g (7.03 mmol) scale, yielding **13** (R=H) (1.39 g, 82% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 6H), 1.37 (s, 6H), 2.15–2.53 (m, 10H), 3.42 (bs, 4H), 3.64 (m, 2H), 3.86–4.00 (m, 6H), 4.33–4.43 (m, 2H), 5.60–5.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 25.2 (q), 26.6 (q), 31.2 (t), 34.9 (t), 35.5 (t), 61.0 (d), 61.1 (d), 65.9 (t), 71.2 (d), 71.3 (d), 72.8 (d), 73.1 (d), 78.1 (d), 78.2 (d), 84.4 (s), 84.6 (s), 109.2 (s), 126.9 (d), 127.3 (d), 128.8 (d). MS *m/z* (relative intensity); HRMS Calcd for $C_{13}H_{15}O_3$ $(M-CH_3)^+$, found.

1.1.10. Preparation of (2*S*,7*R* and 7*S*)-2-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-7-ethynyl-3*H*,6*H*-oxepine (14) (R=H). The sequence used above to obtain (±)**1** (R=Me, R′=C_5H_{11}-*n*) was applied to **13** (R=H) on a 1 g (4.2 mmol) scale, yielding **14** (R=H) as a diastereoisomeric mixture (629 mg, 68% overall yield): ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 4.5H), 1.36 (s, 4.5H), 2.23 (m, 2H), 2.42–2.62 (m, 5.5H), 3.29 (dd, *J*=8.3, 8.3 Hz, 1H), 3.86–3.94 (m, 3.5H), 4.03–4.16 (m, 2.5H), 4.73 (m, 0.5H), 5.68–5.85 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 25.2 (q), 26.6 (q), 26.8 (q), 33.1 (t), 33.6 (t), 35.6 (t), 38.4 (t), 66.2 (d), 67.6 (t), 67.8 (t), 70.2 (d), 72.2 (d), 74.3 (d), 74.6 (s), 77.5 (d), 77.6 (d), 77.7 (d), 81.8 (d), 83.1 (d), 109.3 (s), 109.4 (s), 127.2 (d), 128.5 (d), 130.1 (d), 130.8 (d). MS *m/z* (relative intensity). HRMS Calcd for CHO $(M)^+$, found.

1.1.11. Preparation of (6*Z*,4*R* and 4*S*,9*S*)-1-benzyloxy-9-(*tert*-butyl-dimethyl-silanyloxy)-9-(2,2-dimethyl-1,3-dioxolan-4-yl)-6-nonen-2-yn-4-ol (12) (R=CH_2OBn). The sequence used above to obtain **7** from **6** was applied to **11** on a 3.5 g (9.7 mmol) scale using the lithium salt of the [(2-propynyloxy)methyl]benzene, yielding **12** (R=TMS) (3.6 g, 79% overall yield) as colourless oil: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.88 (s, 9H), 1.32 (s, 3H), 1.39 (s, 3H), 2.15 (s, 1H), 2.15–2.27 (m. 1H), 2.44–2.59 (m, 3H), 3.76–3.84 (m, 2H), 3.91–4.00 (m, 2H), 4.20 (s, 2H), 4.42–4.51 (m, 1H), 4.59 (s, 2H), 5.58–5.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.2 (q), 18.0 (s), 25.3 (q), 25.8 (q), 26.7 (q), 32.4 (t), 32.5 (t), 35.6 (t), 36.0 (t), 57.4 (t), 61.8 (d), 66.7 (t), 66.8 (t), 71.5 (t), 72.4 (d), 72.5 (d), 77.6 (d), 80.3 (s), 80.7 (s), 87.2 (s), 87.6 (s), 109.1 (s), 125.9 (d), 126.2 (d), 127.8 (d), 128.0 (d), 128.4 (d), 128.6 (d), 137.4 (s). MS *m/z* (relative intensity); Anal. Calcd for $C_{27}H_{42}O_5Si$: C, 68.31; H, 8.92. Found: C, 68.32; H, 9.06.

1.1.12. Preparation of (1*S*,3*Z*,6*R* and 6*S*)-9-benzyloxy-1-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-nonen-7-yne-1,6-diol (13) (R=CH_2OBn). The TBDPS-deprotection used above to obtain **6** was applied to **12** (R=CH_2OBn) compound on a 3 g (6.3 mmol) scale, yielding **13** (R=CH_2OBn) (2.0 g, 91% yield): ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.40 (s, 3H), 2.25–2.30 (m, 2H), 2.30–2.46 (m, 1H), 2.46–2.56 (m, 1H), 3.64–3.72 (m, 1H), 3.92–4.00 (m, 4H), 4.18 (s, 2H), 4.44–4.60 (m, 1H), 4.66 (s, 2H), 5.63–5.71 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.2 (q), 26.6 (q), 26.9 (q), 30.8 (t), 31.2 (t), 35.0 (t), 35.6 (t), 56.9 (t), 57.4 (t), 61.3 (d), 61.4 (d), 65.9 (t), 71.3 (d), 71.7 (t), 78.1 (d), 78.2 (d), 80.7 (s), 80.9 (s), 87.1 (s), 87.3 (s), 109.2 (s), 127.0 (d), 127.1 (d), 127.5 (d), 127.9 (d), 128.1 (d), 128.4 (d), 128.5 (d), 128.8 (d), 129.0 (d), 129.7 (s), 134.5 (s), 137.3 (s). MS *m/z* (relative intensity); HRMS Calcd for $C_{13}H_{15}O_3$ $(M-CH_3)^+$, found.

1.1.13. Preparation of (2*R* and 2*S*,7*S*)-2-(3-benzyloxy-prop-1-ynyl)-7-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3*H*,6*H*-oxepine (14) (R=CH_2OBn). The $Co_2(CO)_6$–alkyne complex formation, acidic treatment followed by acetylene demetalation used above to obtain (± **1** (R=Me, R′=C_5H_{11}-*n*) was applied to **13** (R=CH_2OBn) on a 1 g (2.8 mmol) scale, yielding **14** (R=CH_2OBn) as a diastereoisomeric mixture (756 mg, 79% overall yield): ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.39 (s, 3H), 2.26–2.30 (m, 1H), 2.45–2.57 (2H), 2.62–2.66 (m, 1H), 3.29 (m, 1H), 3.92–3.98 (m, 2H), 4.08–4.19 (m, 1H), 4.20 (s, 2H), 4.19–4.26 (m, 1H), 4.57 (s, 2H), 5.72–5.77 (m, 1H), 5.84–5.88 (m, 1H), 7.27–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.2 (q), 26.6 (q), 26.8 (q), 33.1 (t), 33.6 (t), 35.8 (t), 38.5 (t), 57.1 (t), 57.3 (t), 60.2 (t), 66.4 (d), 67.6 (t), 67.8 (t), 70.5 (d), 71.2 (s), 71.4 (s), 74.3 (d), 77.6 (d), 77.7 (d), 80.0 (s), 81.7 (d), 82.5 (s), 84.7 (s), 85.9 (s), 109.3 (s), 109.4 (s), 127.5 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.6 (d), 130.1 (d), 130.7 (d), 137.3 (s). MS *m/z* (relative intensity); HRMS Calcd for CHO $(M)^+$, found.

1.1.14. Preparation of (2*R*,3*S*,5*Z*,8*R* and 8*S*)-11-benzyloxy-3-(*tert*-butyl-dimethyl-silanyloxy)-5-undecen-9-yne-1,2,8-triol (15). To a solution of **12** (R=CH_2OBn) (1 g, 2.25 mmol) in MeOH (5 mL) was added pyridinium *p*-toluenesulfonate (505 mg, 2.25 mmol), the reaction was stirred for 1 h, after which time was quenched with Et_3N until pH≈7 and methanol was evaporated under vacuum. The residue was purified by chromatography column giving the triol **15** (390 mg, 43% yield) and the unreacted substrate **12** (550 mg): ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.89 (s, 9H), 2.16–2.24 (m, 1H), 2.37–2.43 (m, 1H), 2.54–2.62 (m, 1H), 3.00 (bs, 3H), 3.60–3.70 (m, 2H), 3.72–3.77 (m, 2H), 4.19 (br s, 2H), 4.58 (s, 2H), 5.52–5.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −4.9 (q), −4.4 (q), 14.1 (s), 17.9 (s), 25.6 (q), 25.8 (q), 31.4 (t), 31.5 (t), 35.1 (t), 35.9 (t), 57.4 (t), 60.4 (s), 61.5 (d), 61.6 (d), 63.6 (t), 71.7 (t), 72.9 (d), 73.0 (d), 77.4 (d), 80.7 (s), 81.1 (s), 86.9 (s), 87.3 (s), 125.7 (d), 126.3 (d), 127.3 (d), 127.9 (d), 128.4 (d), 128.6 (d), 137.3 (s). MS *m/z* (relative intensity); HRMS Calcd for CHO $(M)^+$, found.

1.1.15. Preparation of methyl(2*E*,4*S*,6*Z*,9*R* and 9*S*)-12-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxy)-9-hydroxy-2,6-dodecadien-10-ynate (16). To a stirred solution of the triol **15** (300 mg, 0.74 mmol) dissolved in THF/H_2O (5:1, 7.4 mL) was added $NaIO_4$ (652 mg, 3.05 mmol) and a catalytic amount of tetra-*n*-butylammonium periodate at rt. After 1 h, the mixture was filtered through a pad of Celite and extracted with ether (2×10 mL) and washed with brine (20 mL). The resulting solution was concentrated, yielding an oil of the crude aldehyde, which was used without purification.

To a suspension of sodium hydride (43 mg, 1.07 mmol, 60% in mineral oil) in benzene (5 mL), at 0°C was added slowly trimethylphosphonoacetate (0.19 mL, 1.18 mmol) in benzene (1 mL). After complete addition the mixture was stirred for 5 min and the crude aldehyde dissolved in benzene (2 mL) was added dropwise. The reaction mixture was stirred for 30 min, after which time TLC showed complete conversion to the unsaturated ester. The reaction was quenched with saturated aqueous solution of NH_4Cl (5 mL), extracted with ether (20 mL) and washed with

water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Flash-chromatography provided α,β-unsaturated esters **16** (238 mg, 71% yield from the triol): ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.06 (bs, 6H), 0.91 (s, 9 H), 2.30–2.37 (m, 2H), 2.47 (t, *J*=6.0 Hz, 2H), 3.73 (s, 3H), 4.20 (s, 2H), 4.33–4.37 (m, 1H), 4.43–4.47 (m, 1H), 4.59 (s, 2H), 5.57–5.69 (m, 2H), 6.00 (d, *J*=15.5 Hz, 1H), 6.88–6.98 (m, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.2 (s), 25.8 (q), 35.6 (t), 35.7 (t), 35.8 (t), 51.5 (q), 57.4 (t), 61.8 (d), 71.3 (d), 71.6 (t), 80.9 (s), 87.0 (s), 119.7 (d), 126.5 (d), 126.6 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.4 (d), 137.4 (s), 150.5 (d), 167.0 (s). MS *m*/*z* (relative intensity); HRMS Calcd for CHO $(M)^+$, found.

1.1.16. Preparation of methyl(2*E*)-3-[(2*S*,7*R*)-7-(3-benzyloxy-prop-1-ynyl)-3*H*,6*H*-oxepin-2-yl]-acrylate (17). The sequence used above to obtain **14** from **12** was applied to **16** on a 220 mg (0.48 mmol) scale, yielding **17** as an oil (114 mg, 73% overall yield): $[\alpha]^{25}_D$=−13.0 (*c* 5.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.31–2.43 (m, 2H), 2.49–2.55 (1H), 2.68–2.74 (m, 1H), 3.73 (s, 3H), 4.10 (br s, 1H), 4.18 (s, 2H), 4.30 (d, *J*=7.7 Hz, 1H), 4.59 (s, 2H), 5.80 (br s, 2H), 6.13 (d, *J*=11.8 Hz, 1H), 6.89 (dd, *J*=11.7, 2.8 Hz, 1H), 7.29–7.41 (br s, 5H); ^{13}C NMR ($CDCl_3$) δ 36.6 (t), 38.6 (t), 51.5 (q), 57.3 (t), 70.3 (d), 71.6 (t), 78.7 (d), 80.3 (s), 85.8 (s), 120.4 (d), 127.8 (d), 128.4 (d), 129.2 (d), 129.3 (d), 129.6 (d), 137.4 (s), 147.5 (d), 166.9 (s). MS *m*/*z* (relative intensity); HRMS Calcd for CHO $(M)^+$, found.

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