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Stereoselective Total Synthesis of (+)-Oploxyne A, (−)-Oploxyne B, and Their C-10 Epimers and Structure Revision of Natural Oploxyne B

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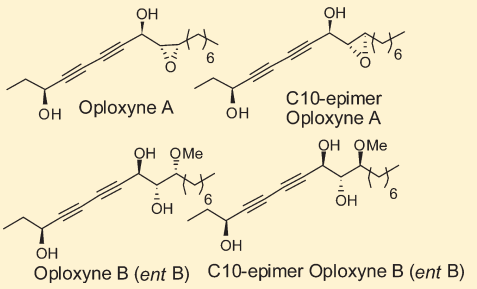
Supporting Information

ABSTRACT: The first total synthesis of recently isolated diacetylene alcohols oploxyne A, oploxyne B, and their C-10 epimers was accomplished. The structure of natural oploxyne B has been revised. The key steps involved are base-induced double elimination of a carbohydrate-derived β-alkoxy chloride to generate the chiral acetylenic alcohol and Cadiot−Chodkiewicz cross-coupling reaction. The target compounds displayed potent cytotoxicity against neuroblastoma and prostate cancer cell lines.



INTRODUCTION

Polyacetylene containing molecules attract significant attention due to their impressive biological properties such as antitumor, antiinflammatory, antimicrobial, antiviral, cytotoxic, and phytotoxic activities.[1] For example, the diacetylene panaxydol **1** (Figure 1) displayed antiproliferative effects against malignant cells[2] and panaxytriol **2**, obtained from Red ginseng, was found to show inhibitory activity against MK-1 cells with IC_{50} 8.5 ng/mL and suppress the growth of B16 melanoma cells in mice.[3] Recently, investigations on the inhibitors for the formation of NO and prostaglandin E_2 (PGE_2) in lipopolysaccharide (LPS)-induced murine macrophage RAW 267.7 cells resulted in isolation of two new diynes oploxynes A and B from the CH_2Cl_2 extract of the stem of *Oplopanax elatus*.[4] The structures of oploxyne A **3** and oploxyne B **4** were established based on NMR spectroscopy through chiral derivatization. Oploxyne A was found to display inhibition of NO and PGE_2 production with an IC_{50} of 1.90 ± 0.28 and 3.08 ± 0.37 mg/mL. In continuation to our program toward the development of new protocols and their applications in the total synthesis of biologically potent natural products,[5] we herein describe the first total synthesis of oploxyne A, oploxyne B, and their C-10 epimers **5** and **6**, wherein a strategy that allows facile access to all four molecules (**3**−**6**) has been employed. These target compounds when screened against cancer cell lines were found to display potent cytotoxicity.

We initially focused on the total synthesis of oploxynes A and B and also accomplished the total synthesis of their C-10 epimers. Retrosynthetically, oploxyne A and oploxyne B were envisaged to be obtained in a convergent fashion wherein two fragments **10** and **11** are coupled together by Cadiot−Chodkiewicz cross-coupling to give the key intermediate **9**. The intermediate **9** can be easily maneuvered to synthesize the final targets involving two steps: tosylation to obtain **7**, one-pot PMB cleavage, acetonide deprotection, and epoxide formation to yield the target oploxyne A or methylation of **9** to obtain methyl ether **8** followed by PMB and acetonide deprotection to yield oploxyne B **4**. While the fragment **10** can be obtained from readily available sugar D-mannitol, the other key fragment **11** could be obtained from D-ribose (Scheme 1).

RESULTS AND DISCUSSION

Our synthesis of fragment **10** is delineated in Scheme 2, which departs from the prior work at the readily available secondary alcohol **12** obtained from D-mannitol.[6] PMB protection of compound **12** yielded the corresponding PMB ether **13**, which was treated with 1 M HCl to obtain the diol **14**. The diol **14** upon treatment with $NaIO_4$ yielded the corresponding aldehyde,[7] which was converted to alkyne **16** by employing Ohira−Bestmann reagent **15**.[8] The free terminal acetylene was converted to the key intermediate bromo alkyne **10** by using NBS and catalytic silver nitrate in 98% yield (Scheme 2).

For the synthesis of fragment **11**, we started with the mixture of esters **18** and **19** synthesized from D-ribose following the known procedures.[9] The mixture of esters **18** and **19** was reduced to a mixture of aldehydes **20** and **21** and subjected to a Wittig reaction with *n*-pentyltriphenylphosphonium bromide in the presence of $NaNH_2$ to afford diastereomers **22** and **23** in 68.5:31.5 ratio (diastereomers **22**, **23** were in turn a mixture of

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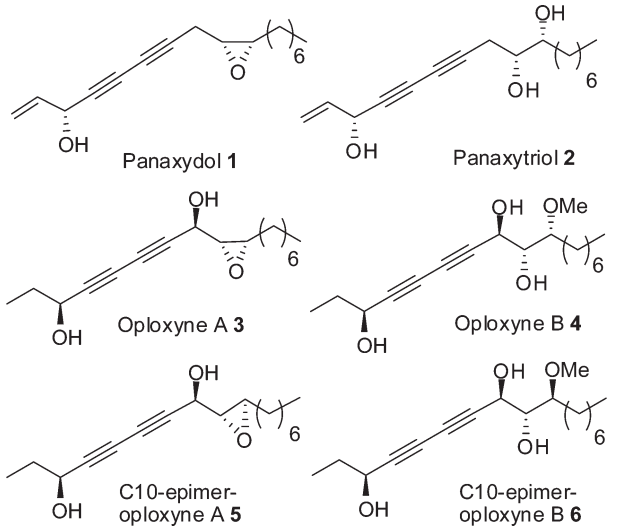
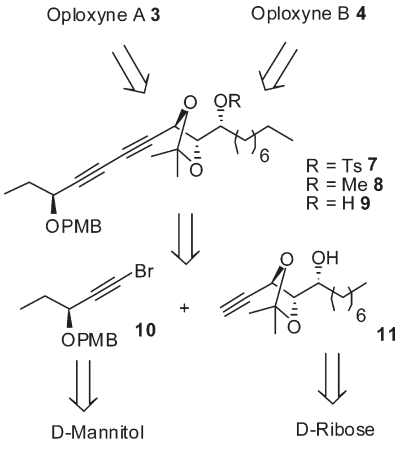
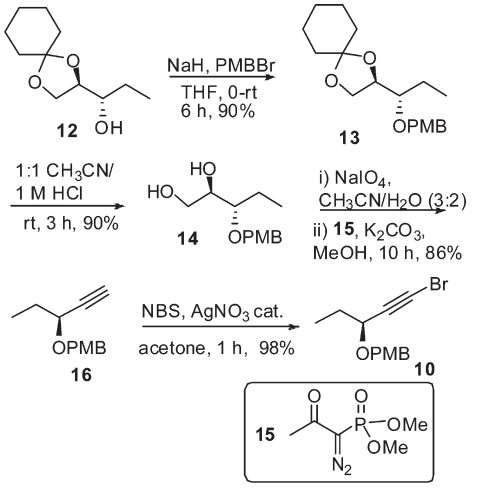


Figure 1. Diacetylene hydroxyl compounds.

Scheme 1. Retrosynthesis



Scheme 2. Synthesis of Fragment 10



geometrical isomers (*E*,*Z* mixture as observed from ^{1}H NMR spectroscopy)). The major compound **22** can be utilized for the synthesis of oploxynes A and B, whereas the minor isomer **23** can be used for the synthesis of C-10 epimers of oploxynes A and B. Reduction of **22** with Pd/C afforded **24**, which was thoroughly characterized by 2D NMR studies for the *anti* relation of C2 and C5 protons (for NOESY correlations see the Supporting Information). The free hydroxyl group in **24** was converted to chloride **25** in the presence of TPP and cat. imidazole at reflux in CCl_4. Compound **25**, a β-alkoxy chloride, was subjected to our protocol of base-induced elimination reaction to provide the chiral propargylic alcohol.[5a,b] Thus, compound **25** when treated with $LiNH_2$ in NH_3 afforded the chiral acetylenic alcohol **11** (Scheme 3). Compound **11** was cross-coupled with alkynyl bromide **10** under Cadiot−Chodkiewicz conditions to yield diyne **9**.[10] Tosylation of **9** with *p*-toluenesulfonyl chloride afforded tosylate **7**, which was converted to the target molecule oploxyne A **3** upon exposure to TFA followed by base (*N*,*N*′-diisopropylethylamine)-induced epoxide formation.[11]

Synthesis of oploxyne B started with methylation of **9** to yield **8**, albeit low yields resulted either with methyl iodide and NaH (35%) or Meerwein's salt in the presence of proton sponge (36%).[12] For the scheme to be amenable for large-scale synthesis, we also proceeded alternatively for product **8** starting from **11** by *O*-methylation with NaH and methyl iodide followed by coupling with **10** (Scheme 4) in good yields. Compound **26** was cross-coupled with alkynyl bromide **10** under Cadiot−Chodkiewicz conditions to yield the precursor intermediate **8** for the synthesis of oploxyne B. One-pot PMB and acetonide deprotection was achieved by exposing **8** to TFA for 36 h to yield oploxyne B **4**. Thus the total syntheses of oploxynes A and B were accomplished. The spectroscopic data of the synthesized compounds oploxyne A **3** (Table 1) and oploxyne B **4** (Table 2) were found to be identical with those of the isolated natural products. However, surprisingly in the case of oploxyne B, the optical rotation for the synthetic product was found to be with opposite sign, i.e., $[\alpha]_D$ −12.0 (*c* 0.28, MeOH) instead of $[\alpha]_D$ +11.7 (*c* 0.06, MeOH) as reported for natural material. Upon comparison of the 2D NOESY spectrum of the acetonide product[4] from isolated compound and our synthetic product **8a**, similar NOE correlations were observed as noticed previously[4] (see Figure 2). As both the synthetic compound and isolated product (from the previous paper) displayed similar NOE correlations, it presents stronger evidence for the possibility of the synthetic and isolated oploxyne B to be the enantiomers. Having all the experimental evidence (for oploxyne A and a similar strategy applied for synthesis of oploxyne B), we came to the conclusion that Yang et al. have misassigned the structure of oploxyne B formulated as **4** after its isolation and characterization through Mosher's ester ^{1}H NMR spectroscopic experiments. We herein revise the structural configuration of natural oploxyne B as compound **4a** (*ent*-**4**).

After completion of the total synthesis of (+)-oploxyne A and (−)-oploxyne B, we proceeded further with the minor isomer **23** for the synthesis of their C-10 epimers. Accordingly, compound **23** was subjected to a similar sequence of reactions such as reduction of olefin to yield **27**, chlorination of alcohol to yield chloride **28**, and then base-induced elimination to afford acetylenic alcohol **29** (Scheme 5).

Alcohol **29** can be utilized directly for the synthesis of C-10 epimers of (+)-oploxyne A and (−)-oploxyne B. Compound **29** on cross-coupling with **10** provided **30**, which on treatment with tosyl chloride in the presence of diisopropylethylamine and DMAP provided **31**. Compound **31** on exposure to TFA followed by treatment with diisopropylethylamine provided

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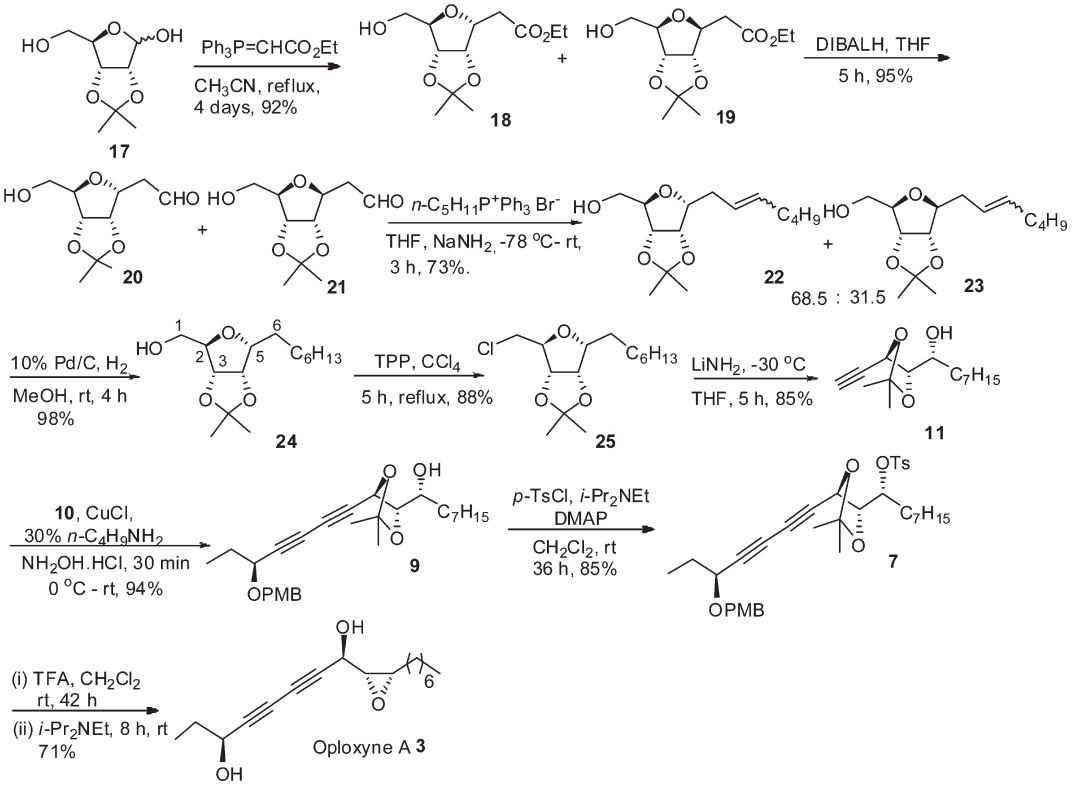
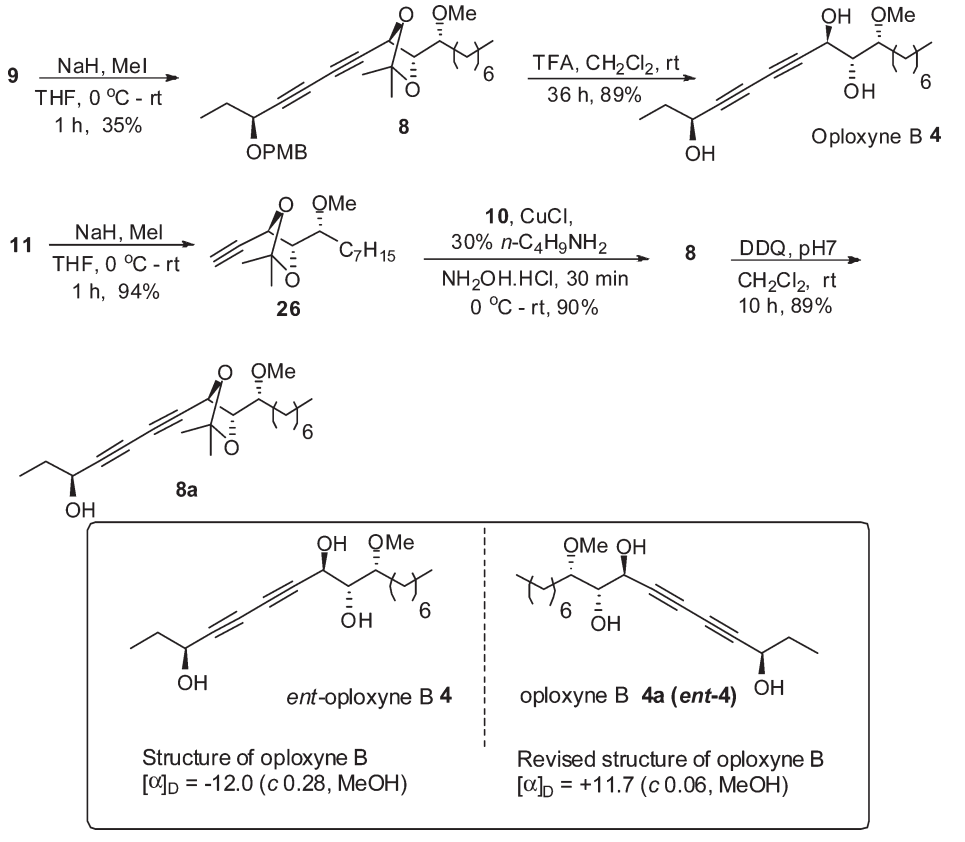
Scheme 3. Synthesis of (+)-Oploxyne A



Scheme 4. Synthesis of Oploxyne B



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5 (Scheme 5). Similarly, for the synthesis of **6**, we proceeded with methylation of the free secondary hydroxyl group in compound **30**. Since the yield for methylation was low, compound **32** was also synthesized from **29** by methylation with methyl iodide and sodium hydride followed by cross-coupling with **10** in overall 79% yield. Exposure of **32** to TFA for 36 h led to the deprotection of isopropylidene moiety and PMB ether cleavage to yield the C-10 epimer of (−)-oploxyne B **6** (Scheme 6).

Table 1. Comparison of ^{1}H and ^{13}C NMR Data for Natural, Synthetic Oploxyne A 3 and Its C-10 Epimer 5

	isolated		synthesized **3**		C-10 epimer **5**	
position	H mult [*J* (Hz)] $CDCl_3$, 500 MHz	^{13}C NMR $CDCl_3$, 125 MHz	H mult [*J* (Hz)] $CDCl_3$, 300 MHz	^{13}C NMR $CDCl_3$, 75 MHz	H mult [*J* (Hz)] $CDCl_3$, 300 Hz	^{13}C NMR $CDCl_3$, 75 MHz
1	1.03 t (7.5)	9.3 CH_3	1.02 t (7.4)	9.3	1.01 t (7.5)	9.3
2	1.76 m	30.6 CH_2	1.83−1.68	30.5	1.82−1.65	30.5
3	4.40 br dt (6.0, 6.0)	64.0 CH	4.43−4.33	64.0	4.65 d (3.0)	64.0
4		81.0 C		80.9		80.7
5		68.7 C		68.7		68.6
6		70.3 C		70.3		70.4
7		77.4 C		77.4		75.7
8	4.36 br dd (7.5, 3.5)	60.7 CH	4.43−4.33	60.7	4.38 t (6.4)	61.5
9	3.16 dd (7.5, 4.0)	58.0 CH	3.16 dd (7.4, 4.0)	58.0	3.10 td (5.6, 2.3)	56.3
10	3.07 br ddd (7.0,5.5,4.0)	58.1 CH	3.10−3.01	58.1	3.02 dd (3.4, 2.4)	59.2
11	1.64 m	27.5 CH_2	1.67−1.57	27.5	1.64−1.52	29.1
12	1.51 m	26.5 CH_2	1.57−1.43	26.5	1.52−1.38	25.8
13	1.35 m	29.4 CH_2	1.42−1.18	29.4	1.37−1.19	31.1
14	1.29 m	29.2 CH_2	1.42−1.18	29.1	1.37−1.19	29.2
15	1.29 m	31.8 CH_2	1.42−1.18	31.7	1.37−1.19	31.7
16	1.29 m	22.6 CH_2	1.42−1.18	22.6	1.37−1.19	22.6
17	0.89 t (7.0)	14.1 CH_3	0.89 t (7.0)	14.1	0.88 t (7.0)	14.0
3-OH	2.19 br d (6.0)		2.19 br s		2.10 br s	
8-OH	2.50 br d (3.5)		2.50 br s		2.50 br s	

Table 2. Comparison of ^{1}H and ^{13}C NMR Data for Natural, Synthetic Oploxyne B 4 and Its C-10 Epimer 6

	isolated		synthesized **4**		C-10 epimer **6**	
position	H mult [*J* (Hz)] $CDCl_3$, 500 MHz	^{13}C NMR $CDCl_3$, 125 MHz	H mult [*J* (Hz)] $CDCl_3$, 300 MHz	^{13}C NMR $CDCl_3$, 75 MHz	H mult [*J* (Hz)] $CDCl_3$, 500 MHz	^{13}C NMR $CDCl_3$, 75 MHz
1	1.04 t (7.5)	9.5 CH_3	1.02 t (7.8)	9.3	1.02 t (7.8)	9.3
2	1.77 m	30.8 CH_2	1.80−1.71	30.5	1.80−1.68	30.5
3	4.40 dt (6.0, 6.0)	64.3 CH	4.39 t (6.8)	64.0	4.38 t (6.9)	63.9
4		80.7 C		80.5		80.4
5		69.0 C		68.7		68.8
6		70.7 C		70.4		70.7
7		77.8 C		77.6		77.4
8	4.53 dd (9.0, 4.5)	65.7 CH	4.52 d (4.9)	65.3	4.67 d (3.9)	65.1
9	3.66 ddd (8.5, 4.5, 3.5)	73.1 CH	3.65 t (3.9)	73.2	3.73−3.68	74.4
10	3.61 ddd (7.5, 5.0, 3.5)	81.7 CH	3.61−3.55	81.3	3.35−3.29	82.1
11	1.64 m	29.4 CH_2	1.68−1.57	29.3	1.80−1.68, 1.67−1.57	29.8
12		25.2 CH_2	1.36−1.24	25.0		24.3
13	1.31 m	30.0 CH_2	1.36−1.24	29.7	1.35−1.22	29.9
14	1.31 m	29.3 CH_2	1.36−1.24	29.2	1.35−1.22	29.3
15	1.30 m	32.0 CH_2	1.36−1.24	31.7	1.35−1.22	31.8
16	1.31 m	22.9 CH_2	1.36−1.24	22.6	1.35−1.22	22.6
17	0.90 t (7.0)	14.3 CH_3	0.89 t (7.8)	14.0	0.89 t (6.9)	14.1
3-OH	1.85 d (6.0)		2.89−2.36 br s		2.54 br s	
8-OH	3.41 d (9.0)		2.89−2.36 br s		3.90−3.79	
9-OH	2.68 d (8.5)		2.89−2.36 br s		3.79−3.64	
OCH_3	3.44 s	57.5 CH_3	3.44 s	57.4	3.39 s	57.9

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Since several diacetylene containing molecules are found to display potent biological activities, and we had the new natural products in ample amounts, we were interested in investigating their cytotoxic properties. All four target molecules **3**−**6** along with other intermediate compounds such as **7**, **8**, **9**, **11**, **26**, **29**, **30**, **32**, and **33** were screened for cytotoxicity employing MTT assay against four different cancer cell lines,[13] viz., A549 (lung cancer), MCF-7 (breast), DU-145 (prostate), and SK-N-SH (neuroblastoma), using doxorubicin as a reference sample (see the Supporting Information). Interestingly, compounds **3** (IC_{50} of 7 μM) and **5** (IC_{50} of 12 μM) were found to be better than or similar to doxorubicin (IC_{50} of 9 μM) against the human neuroblastoma cell line, while compound **4** was found to be effective against the human prostate cancer cell line with an IC_{50} value of 17 μM.

CONCLUSIONS

In conclusion, the first total synthesis of diacetylene molecules (+)-oploxyne A, (−)-oploxyne B, and their C-10 epimers has been accomplished. Two compounds **3** and **5** were found to display potent activity similar to that of doxorubicin. Our total synthesis has led to the structural revision of oploxyne B. The strategy with readily available raw materials and simple experimental procedures merits its use toward scaling up of the materials for their further availability toward biological screening.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on 200, 300, or 500 MHz spectrometers at ambient temperature. The coupling constant *J* is given in Hz. The chemical shifts are reported in ppm on scale downfield from TMS as internal standard and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. FTIR spectra were recorded in $CHCl_3$. Optical rotations were measured on a digital polarimeter, using a 1 mL cell with a 1 dm path length. For low (MS) and high (HRMS) resolution, *m*/*z* ratios are reported as values in atomic mass units. Mass analysis was done in either APCI mode or EI mode. All reagents and solvents were reagent grade and were used without further purification unless specified otherwise. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. Tetrahydrofuran (THF) and diethyl ether (Et_2O), when used as solvent for reactions, were freshly distilled from sodium benzophenone ketyl radical. Column chromatography was carried out with silica gel (60−120 mesh or 100−200 mesh) packed in glass columns. All reactions were performed under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring.

(*R*)-2-[(*S*)-1-(4-Methoxybenzyloxy)propyl]-1,4-dioxaspiro[4.5]decane (13). To a well-stirred suspension of freshly activated (washed with anhydrous hexane) NaH (1.5 g, 37.5 mmol, 60% dispersion in mineral oil) in anhydrous THF (20 mL) was added a solution of

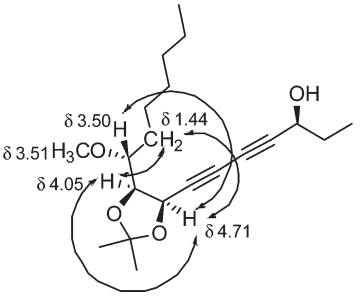
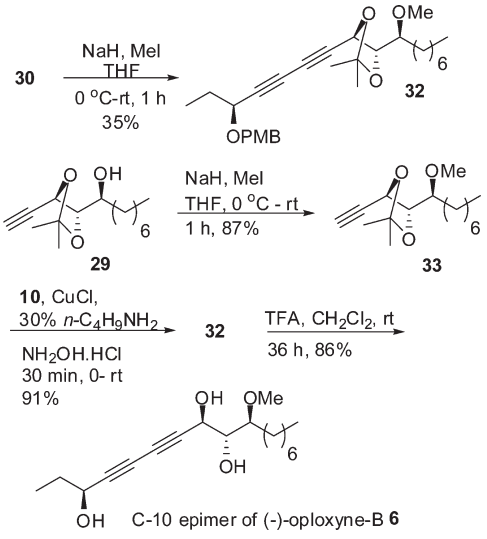
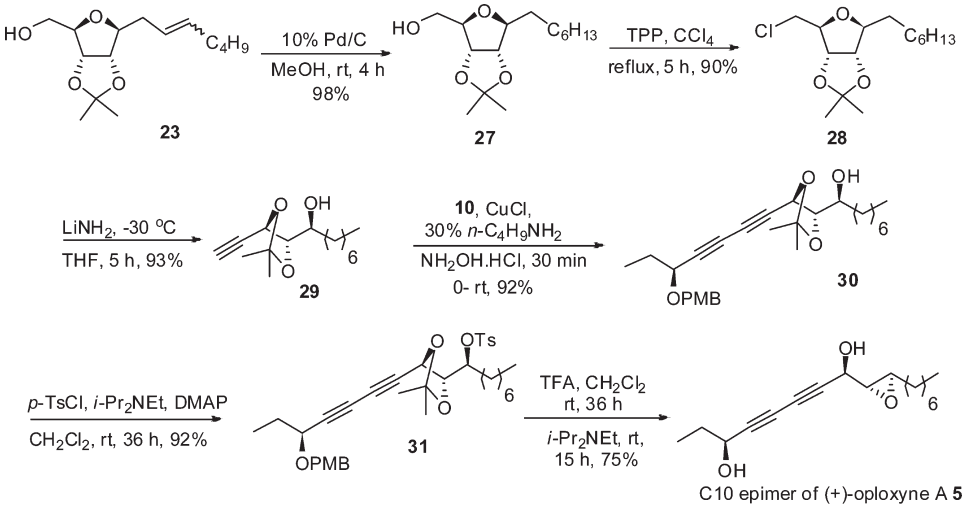


Figure 2. Key NOE correlations in the NOESY spectra of **8a** in $CDCl_3$.

Scheme 6. Synthesis of C-10 Epimer of (−)-Oploxyne B 6



Scheme 5. Synthesis of C-10 Epimer of (+)-Oploxyne A 5



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alcohol **12** (5.0 g, 25 mmol) in THF (50 mL) at 0 °C. After 30 min, *p*-methoxybenzyl bromide (5.53 g, 27.5 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched with ice pieces and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (60−120 mesh, 2% EtOAc/hexane) to afford compound **13** (7.2 g, 90% yield) as a colorless oil. $[\alpha]^{29}_D$ +16.4 (*c* 1, $CHCl_3$); IR ($CHCl_3$) 2935, 2862, 1613, 1513, 1248, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.22 (m, 2H), 6.96−6.83 (m, 2H), 4.59−4.45 (m, 2H), 4.12−3.97 (m, 1H), 3.93−3.85 (m, 1H), 3.83−3.77 (m, 4H), 3.54−3.43 (m, 1H), 1.96−1.78 (m, 1H), 1.70−1.49 (m, 9H), 1.50−1.26 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.8, 129.4, 113.7, 109.4, 79.9, 72.2, 71.4, 66.1, 55.2, 41.9, 36.3, 34.9, 25.2, 24.0, 23.8, 9.2; MS (ESI) *m*/*z* 343 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{28}NaO_4$ 343.1880, found 343.1876.

(2*R*,3*S*)-3-(4-Methoxybenzyloxy)pentane-1,2-diol 14. A solution of cyclohexylideneacetal **13** (4 g, 12.5 mmol) in 60 mL of 1:1 CH_3CN/1 M HCl was stirred at room temperature for 3 h. The reaction was quenched with solid sodium bicarbonate (until neutralization) at room temperature. The CH_3CN in the reaction mixture was removed under vacuum. Then, it was diluted with ethyl acetate (30 mL) and the aqueous layer was further extracted with ethyl acetate (3 × 60 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (60−120 mesh, 40% EtOAc/hexane) to afford the compound **14** (2.7, 90% yield). $[\alpha]^{28}_D$ +13.7 (*c* 2.7, $CHCl_3$); IR($CHCl_3$) 3372, 2964, 2936, 2878, 1612, 1514, 1248, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23−7.14 (m, 2H), 6.84−6.77 (m, 2H), 4.53−4.39 (m, 2H), 3.78−3.74 (m, 3H), 3.62 (s, 3H), 3.43−3.30 (m, 1H), 3.20 (br s, 1H), 1.72−1.46 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.4, 129.4, 113.8, 81.3, 72.4, 72.0, 63.5, 55.0, 23.0, 9.6; MS (ESI) *m*/*z* 241 $[M + H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{20}O_4Na$ 263.1254, found 263.1250.

(*S*)-1-Methoxy-4-[(pent-1-yn-3-yloxy)methyl]benzene 16. $NaIO_4$ (3.4 g, 16.2 mmol) was added to a solution of diol **14** (2.6 g, 10.8 mmol) in 60% CH_3CN/H_2O (30 mL) at 0 °C. Then the reaction was stirred at room temperature for 1 h. The reaction mixture was extracted with ethyl acetate (3 × 60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting aldehyde was dissolved in dry methanol and K_2CO_3 (4.4 g, 31.7 mmol) and to this was added Ohira−Bestmann reagent **15** (2.5 g, 13.2 mmol) at rt, then the mixture was stirred for 10 h. The reaction mixture was extracted with diethyl ether (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and the residue was purified by silica gel chromatography (60−120 mesh, 1−2% EtOAc/hexane) to afford the compound **16** (1.9 g, 86% yield) as a colorless oil. $[\alpha]^{30}_D$ −112.2 (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3306, 2926, 2956, 2853, 2129, 1613, 1514, 1248, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.15 (m, 2H), 6.87−6.75 (m, 2H), 4.67 (d, *J* = 11.3 Hz, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 3.92 (dt, *J* = 1.8, 6.4 Hz, 1H), 3.73 (s, 3H), 2.39 (d, *J* = 1.8 Hz, 1H), 1.75−1.63 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 129.9, 129.6, 113.7, 82.8, 73.7, 70.1, 69.3, 55.2, 28.7, 9.6; MS (EI) *m*/*z* 204.

(*S*)-1-[(1-Bromopent-1-yn-3-yloxy)methyl]-4-methoxybenzene (10). Compound **16** (500 mg, 2.4 mmol) was dissolved in acetone (8 mL). NBS (523 mg, 2.9 mmol) and silver nitrate (83 mg, 0.49 mmol) were added to this solution. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was cooled to 0 °C, mixed with cold water, and extracted with Et_2O (3 × 15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, then the residue was purified by silica gel chromatography (60−120 mesh, 1% EtOAc/hexane) to afford compound **10** (677 mg, 98% yield) as a yellow oil. $[\alpha]^{30}_D$ −107.5 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 2967, 2936, 2874, 2837, 2205, 1612, 1513, 1249, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.24 (m, 2H), 6.91−6.85 (m, 2H), 4.72 (d, *J* = 11.3 Hz, 1H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 1.81−1.68 (m, 2H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 129.8, 129.6, 113.8, 79.4, 70.4, 70.3, 55.2, 45.0, 28.8, 9.3.

Ethyl 2-{(3a*S*,4*R*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl}acetate (18) and Ethyl 2-{(3a*S*,4*S*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl}acetate (19). A solution of 2,3-*O*-isopropylidene-D-ribose **17** (2.0 g, 10.5 mmol) and (carbethoxymethylene)triphenylphosphorane (9.1 g, 26.3 mmol) in CH_3CN (50 mL) was refluxed for 4 days. Examination of the reaction mixture by TLC showed the absence of starting material and the formation of two products. The solvent was removed under reduced pressure, then the residue was purified by column chromatography on silica gel (100−200 mesh, 10% EtOAc/hexane) to afford compound **19** (340 mg, 12%; this material was utilized for data purpose) followed by a mixture of **19** and **20** (2.2 g, 80% yield) as a colorless oil. Analytical data of compound **19**: $[\alpha]^{29}_D$ −6.5 (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 2987, 2939, 1734, 1373, 1213, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.73 (dd, *J* = 6.8, 3.8 Hz, 1H), 4.54 (dd, *J* = 6.8, 4.3 Hz, 1H), 4.29−4.21 (m, 1H), 4.16 (q, *J* = 6.8, 11.3 Hz, 2H), 4.07 (q, *J* = 6.8, 3.8 Hz, 1H), 3.80 (dd, *J* = 12.1, 3.0 Hz, 1H), 3.65 (dd, *J* = 12.1, 3.0 Hz, 1H), 2.73 (dd, *J* = 15.8, 5.3 Hz, 1H), 2.61 (dd, *J* = 15.8, 6.0 Hz, 1H), 1.53 (s, 3H), 1.34 (s, 3H), 1.26 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 114.2, 84.6, 83.9, 81.4, 80.6, 62.5, 60.7, 37.8, 27.4, 25.3, 14.0; MS (ESI) *m*/*z* 261 $[M + H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{20}O_6Na$ 283.1157, found 283.1166.

2-{(3a*S*,4*R*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl}acetaldehyde (20) and 2-{(3a*S*,4*S*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl}acetaldehyde (21). Diisobutylaluminium hydride (21.9 mL, 30.7 mmol, 20% in hexane) was added to a mixture of esters (4.0 g, 15.3 mmol) in CH_2Cl_2 (40 mL) at −78 °C and the solution was stirred for 5 h. The reaction was quenched with aq saturated sodium-potasium tartarate (10 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure, then the residue was passed through a short pad of silica gel (60−120 mesh, 50% EtOAc/hexane) to afford the mixture of compounds **20** and **21** (3.1 g, 95% yield) which were directly used for further reaction.

{(3a*R*,4*R*,6*R*,6a*S*)-6-(Hept-2-enyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl}methanol (22) and {(3a*R*,4*R*,6*S*,6a*S*)-6-(Hept-2-enyl)-2,2-dimethyltetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl}methanol (23). A solution of *n*-pentyltriphenylphosphonium bromide (47.8 g, 115.7 mmol) in THF (200 mL) and $NaNH_2$ (4.1 g, 106.5 mmol) was refluxed for 4 h. Then the reaction was cooled to −78 °C and to this a mixture of aldehydes **20** and **21** (10 g, 46.3 mmol) in THF (60 mL) was added then the solution was stirred for 3 h at room teperature. The reaction was quenched with aq saturated ammonium chloride solution (10 mL). The aqueous layer was extracted with ethyl actate (3 × 100 mL) and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (60−120 mesh, 10% EtOAc/hexane) to afford **23** (2.9 g, 23% yield) comprised of a mixture of *E* and *Z* isomers and **22** (6.2 g, 50% yield) comprised of a mixture of *E* and *Z* isomers.

{(3a*R*,4*R*,6*R*,6a*S*)-6-Heptyl-2,2-dimethyltetrahydrofuro-[3,4-*d*][1,3]dioxol-4-yl}methanol (24). To a solution of compound **22** (3.0 g, 11.1 mmol) in methanol (30 mL) was added 10% Pd/C (100 mg) and the mixture was stirred for 4 h under hydrogen atmosphere at 55 psi pressure. After filtering the catalyst and solvent evaporation, the resulting residue was chromatographed on silica gel (60−120 mesh,

10% EtOAc/hexane) to afford compound **24** (2.96 g, 98%) as a colorless oil. $[\alpha]^{31}_{D}$ −2.5 (*c* 2, $CHCl_3$); IR ($CHCl_3$) 3450, 2929, 2856, 1638, 1210, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.66−4.55 (m, 2H), 4.11 (t, *J* = 6.2 Hz, 1H), 3.85 (ddd, *J* = 10.2, 6.8, 3.6 Hz, 1H), 3.57 (d, *J* = 6.2 Hz, 2H), 1.99 (br s, 1H), 1.70 (q, *J* = 14.5, 7.4 Hz, 2H), 1.49 (s, 3H), 1.45−1.35 (m, 2H), 1.33 (s, 3H), 1.32−1.20 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.4, 83.9, 82.3, 81.6, 80.9, 61.5, 31.8, 29.7, 29.1, 29.0, 26.3, 26.2, 25.1, 22.6, 14.1; MS (ESI) *m*/*z* 295 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{29}O_4$ 273.2060, found 273.2068.

(3a*S*,4*S*,6*R*,6a*S*)-4-(Chloromethyl)-6-heptyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole (25). To a stirred solution of compound **24** (3.0 g, 11.0 mmol) in CCl_4 (50 mL) was added TPP (4.3 g, 16.5 mmol) followed by a catalytic amount of imidazole and the resulting reaction mixture was refluxed for 4 h. The reaction mixture was then cooled to 0 °C, diluted with hexane, and filtered through Celite. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (60−120 mesh, 10% Et_2O/hexane) to afford compound **25** (2.72 g, 88% yield) as a colorless oil. $[\alpha]^{32}_{D}$ −11.6 (*c* 2.8, $CHCl_3$); IR ($CHCl_3$) 2928, 2857, 1443, 1372, 1218, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (dd, *J* = 6.0, 1.1 Hz, 1H), 4.65 (dd, *J* = 6.0, 3.8 Hz, 1H), 4.22 (t, *J* = 6.4 Hz, 1H), 3.93 (ddd, *J* = 10.4, 6.8, 3.8 Hz, 1H), 3.58−3.42 (m, 2H), 1.69 (q, *J* = 14.5, 7.2 Hz, 2H), 1.50 (s, 3H), 1.35 (s, 3H), 1.34−1.22 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.5, 83.5, 83.3, 82.0, 81.7, 43.4, 31.7, 29.6, 29.1, 29.0, 26.3, 26.1, 25.1, 22.6, 14.1; MS (ESI) *m*/*z* 279 $[M + Na - Cl]^+$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{28}ClO_3$ 291.1721, found 291.1735 and calcd 293.1697, found 293.1694.

(*R*)-1-{(4*S*,5*R*)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl}octan-1-ol (11). To a freshly distilled ammonia (20 mL) in a 100 mL two-necked round-bottomed flask fitted with a coldfinger condenser was added freshly cut lithium metal pieces (0.6 g, 86.2 mmol) at −33 °C and the resulting gray suspension was stirred for 30 min. To this reaction mixture was added chloro compound **25** (2.5 g, 8.6 mmol) in anhydrous THF (15 mL) over a period of 20 min. After being stirred at −33 °C for 5 h, the reaction was quenched by the portion wise addition of solid NH_4Cl and then ammonia was allowed to evaporate. The reaction mixture was diluted with water (30mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (60−120 mesh, 10% EtOAc/hexane) to afford compound **11** (1.86 g, 85%) as a colorless oil. $[\alpha]^{29}_{D}$ +47 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3508, 3310, 2986, 2928, 2857, 2113, 1458, 1381, 1372, 1228, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (dd, *J* = 5.7, 2.4 Hz, 1H), 4.01−3.85 (m, 2H), 2.56 (d, *J* = 2.4 Hz, 1H), 2.28 (br s, 1H), 1.57 (s, 3H), 1.55−1.40 (m, 3H), 1.37 (s, 3H), 1.36−1.18 (m, 9H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.4, 81.0, 79.5, 75.9, 71.2, 66.9, 32.7, 31.7, 29.3, 29.1, 27.4, 25.9, 25.2, 22.6, 14.0; MS (ESI) *m*/*z* 277 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{26}O_3Na$ 277.1774, found 277.1762.

(*R*)-1-{(4*S*,5*R*)-5-[(*S*)-5-(4-Methoxybenzyloxy)hepta-1,3-diynyl]-2,2-dimethyl-1,3-dioxolan-4-yl}octan-1-ol (9). Compound **9** was prepared according to the procedure described for compound **8** starting from compounds **11** (150 mg, 0.6 mmol) and **10** (183 mg, 0.65 mmol). The crude product was purified by column chromatography on silica gel (60−120 mesh, 5% EtOAc/hexane) to afford compound **9** (257 mg, 94% yield). $[\alpha]^{30}_{D}$ −40.4 (*c* 2.3, $CHCl_3$); IR ($CHCl_3$) 3467, 2926, 2854, 2230, 2142,1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.25 (m, 2H), 6.91−6.86 (m, 2H), 4.82 (d, *J* = 5.3 Hz, 1H), 4.71 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.05 (t, *J* = 6.8 Hz, 1H), 4.00−3.87 (m, 2H), 3.81 (s, 3H), 2.06 (br s, 1H), 1.83−1.68 (m, 2H), 1.58 (s, 3H), 1.56−1.39 (m, 3H), 1.38 (s, 3H), 1.37−1.22 (m, 9H), 0.99 (t, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 129.6 (2C), 113.8, 110.7, 81.5, 79.8, 74.2, 71.9, 71.3, 70.5, 69.8, 69.4, 67.6, 55.2, 32.8, 31.8, 29.3, 29.2, 28.6, 27.6, 25.9, 25.2, 22.6, 14.1, 9.6; MS (ESI) *m*/*z* 479 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{40}O_6N$ 474.2850, found 474.2860.

***R*)-1-{(4*R*,5*R*)-5-[(*S*)-5-(4-Methoxybenzyloxy)hepta-1,3-diynyl]-2,2-dimethyl-1,3-dioxolan-4-yl}octyl 4-Methylbenzenesulfonate (7).** Diisopropylethylamine (0.24 mL, 1.4 mmol) was added to a solution of compound **9** (160 mg, 0.35 mmol) in CH_2Cl_2 (8 mL) at 0 °C and the mixture was stirred for 20 min at room temperature. Then the reaction mixture was cooled to 0 °C, and to this *p*-toluenesulfonylchloride (133.8 mg, 0.7 mmol) and DMAP (51.4 mg, 0.42 mmol) were added and the reaction was stirred at room temperature for 36 h. Then the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography by eluting with 5% EtOAc/hexane to afford compound **7** (181.5, 85% yield). $[\alpha]^{30}_{D}$ −101.8 (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 2955, 2925, 2853, 2064,1639, 1513, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87−7.80 (m, 2H), 7.35−7.24 (m, 4H), 6.93−6.83 (m, 2H), 4.91−4.82 (m, 1H), 4.78−4.67 (m, 2H), 4.44 (d, *J* = 11.3, 1H), 4.11−3.99 (m, 2H), 3.81 (s, 3H), 2.43 (s, 3H), 1.87−1.72 (m, 2H), 1.72−1.65 (m, 1H), 1.64 (s, 3H), 1.57−1.40 (m, 2H), 1.29 (s, 3H), 1.28−1.17 (m, 9H), 1.02 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 144.0, 134.9, 129.6, 129.5, 129.0, 128.2, 113.8, 111.0, 82.7, 80.2, 78.8, 73.6, 72.1, 70.6, 69.8, 69.2, 67.2, 55.2, 31.7, 31.4, 29.1, 29.0, 28.6, 27.3, 25.7, 24.4, 22.6, 21.5, 14.0, 9.6; MS (ESI) *m*/*z* 628 $[M + NH_4]^+$; HRMS (ESI) *m*/*z* calcd for for $C_{35}H_{50}NO_7S$ 628.3303, found 628.3280.

(+)-Oploxyne A (3). A solution of compound **7** (70 mg, 0.11 mmol) in CH_2Cl_2 (8 mL) and trifluoroacetic acid (0.1 mL) was stirred at room temperature for 42 h. Diisopropylethylamine (0.6 mL) was introduced o basify the reaction mixture, which was then stirred for 8 h at room temperature. The solution was concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (60−120 mesh, 20% EtOAc/hexane) to afford oploxyne A **3** (22.6 mg, 71% yield) as a colorless oil. $[\alpha]^{30}_{D}$ +33.3 (*c* 0.9, $CHCl_3$), $[\alpha]^{23}_{D}$ +126.6 (*c* 0.15, MeOH), lit.[4] $[\alpha]^{25}_{D}$ +123.4 (*c* 0.4, MeOH); IR ($CHCl_3$) 3432, 2956, 2925, 2854, 2252, 2144, 1247 cm^{-1}; MS (ESI) *m*/*z* 301 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{30}NO_3$ 296.2220, found 296.2207.

(4*R*,5*S*)-4-Ethynyl-5-[(*R*)-1-methoxyoctyl]-2,2-dimethyl-1,3-dioxolane (26). To a sirred suspension of NaH (71 mg, 1.77 mmol) in anhydrous THF (3 mL) at 0 °C, was added compound **11** (0.3 g, 1.18 mmol) in anhydrous THF (5 mL) slowly with a syringe over a period of 5 min. After stirring at 0 °C for 15 min, CH_3I (0.1 mL, 1.5 mmol) was added and the mixture was further stirred at room temperature for 1 h. After quenching the reaction with ice pieces, the reaction mixture was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with brine and dried on anhydrous Na_2SO_4. After removing the solvent under reduced pressure, crude residue was purified by column chromatography on silica gel (60−120 mesh, 5% Et_2O/hexane) to afford compound **26** (0.29 g, 94%) as a colorless oil. $[\alpha]^{29}_{D}$ +37.5 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3310, 2929, 2857, 2112, 1456, 1380, 1228, 1107 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.64 (dd, *J* = 4.9, 2.0 Hz, 1H), 4.02 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.51 (s, 3H), 3.50−3.46 (m, 1H), 2.50 (d, *J* = 2.0 Hz, 1H), 1.57 (s, 3H), 1.55−1.37 (m, 4H), 1.36 (s, 3H), 1.35−1.06 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.8, 81.1, 80.5, 80.2, 75.2, 67.2, 58.7, 31.8, 30.8, 29.5, 29.1, 27.7, 26.2, 24.7, 22.6, 14.0; MS (ESI) *m*/*z* 291 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{28}O_3Na$ 291.1931, found 291.1928.

(4*R*,5*S*)-4-[(*S*)-5-(4-Methoxybenzyloxy)hepta-1,3-diynyl]-5-[(*R*)-1-methoxyoctyl]-2,2-dimethyl-1,3-dioxolane (8). CuCl (1.84 mg, 0.02 mmol) was added to a 30% *n*-$BuNH_2$ (3 mL) aqueous solution at room temperature to result in the formation of a blue solution. A few crystals of hydroxylamine hydrochloride were added to discharge the blue color. The resulting colorless solution indicated the presence of Cu(I) salt. To this solution was added alkyne **26** (250 mg, 0.93 mmol) in Et_2O (2 mL) at room temperature to result in the

formation of a yellow acetylide suspension that was immediately cooled with an ice−water mixture. To this mixture bromoalkyne **10** (210 mg, 0.7 mmol) was added at once and the ice bath was removed. More crystals of hydroxylamine hydrochloride were added throughout the reaction as necessary to prevent the solution from turning blue or green. After 30 min, additional bromoalkyne **10** (79 mg, 0.28 mmol) was added. At this point the reaction was completed according to TLC. The product was repeatedly extracted with Et_2O (4 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (60−120 mesh, 1% EtOAc/hexane) to afford compound **8** (392 mg, 90%). $[\alpha]^{30}_D$ −37.2 (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) 2928, 2856, 2228, 2143, 1612, 1513, 1463, 1249, 1228, 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.23 (m, 2H), 6.92−6.84 (m, 2H), 4.76−4.69 (m, 2H), 4.43 (d, *J* = 11.3 Hz, 1H), 4.05 (dd, *J* = 8.3, 6.2 Hz, 2H), 3.81 (s, 3H), 3.53 (s, 3H), 3.52−3.48 (m, 1H), 1.83−1.70 (m, 2H), 1.59 (s, 3H), 1.58−1.53 (m, 2H), 1.51−1.41 (m, 1H), 1.37 (s, 3H), 1.36−1.20 (m, 9H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 129.6, 113.8, 111.0 (2C), 81.6, 80.4, 79.4, 75.0, 71.2, 70.5, 69.8, 69.6, 67.8, 58.8, 55.3, 31.8, 31.1, 29.7, 29.2, 28.7, 27.8, 26.1, 24.8, 22.6, 14.1, 9.7; MS (ESI) *m*/*z* 488 $[M + NH_4]^+$; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{42}O_5Na$ 493.2929, found 493.2937.

(−)-Oploxyne B (4). Trifluoroacetic acid (0.07 mL) was added to a solution of compound **8** (60 mg, 0.13 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the mixture was stirred for 36 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (60−120 mesh, 20% EtOAc/hexane) to afford oploxyne B (**4**) (35.8 mg, 89% yield). $[\alpha]^{29}_D$ −12.0 (*c* 0.28, MeOH), lit.[4] $[\alpha]^{25}_D$ +11.7 (*c* 0.06, MeOH); IR ($CHCl_3$) 3389, 2925, 2855, 2250, 2140, 1496, 1463, 1081 cm^{-1}; MS (ESI) *m*/*z* 333 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{30}O_4Na$, 333.2036, found 333.2040.

(*S*)-7-{(4*R*,5*S*)-5-[(*R*)-1-Methoxyoctyl]-2,2-dimethyl-1,3-dioxolan-4-yl}hepta-4,6-diyn-3-ol (8a). To a solution of **8** (50 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added aqueous NaH_2PO_4/Na_2HPO_4 (pH 7), buffer (3 mL), and DDQ (97 mg, 0.42 mmol). The reaction was allowed to warm to room temperature. After 10 h at room temperature, the reaction mixture was filtered through a Celite pad, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, then the residue was purified on silica gel chromatography (60−120 mesh, 7% EtOAc/hexane) to afford the compound **8a** (33 mg, 89% yield) as a yellow oil. $[\alpha]^{33}_D$ +23 (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, *J* = 5.1 Hz, 1H), 4.42−4.36 (m, 1H), 4.05 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.51 (s, 3H), 3.50−3.44 (m, 1H), 1.93 (br s, 1H), 1.79−1.71 (m, 2H), 1.56 (s, 3H), 1.52−1.38 (m, 2H), 1.36 (s, 3H), 1.35−1.24 (m, 10H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.0, 81.6, 80.5, 80.4, 75.7, 71.0, 68.8, 67.8, 64.0, 58.8, 31.8, 31.0, 30.6, 29.7, 29.6, 29.2, 27.8, 26.1, 24.7, 22.6, 14.1, 9.3; MS (ESI) *m*/*z* 373 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{34}O_4Na$ 373.2349, found 373.2332.

{(3a*R*,4*R*,6*S*,6a*S*)-6-Heptyl-2,2-dimethyltetrahydrofuro-[3,4-*d*][1,3]dioxol-4-yl}methanol (27). Compound **27** was prepared according to the procedure described for compound **24** starting from compound **23** (2.5 g, 9.3 mmol). Purification by silica gel (60−120 mesh, 10% EtOAc/hexane) afforded compound **27** (2.4 g, 98% yield) as a colorless oil. $[\alpha]^{31}_D$ −3.6 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) 3453, 2928, 2858, 1458, 1381, 1212, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.58 (dd, *J* = 7.0, 4.5 Hz, 1H), 4.27 (dd, *J* = 7.0, 5.3 Hz, 1H), 3.94 (q, *J* = 7.9, 4.3 Hz, 1H), 3.88−3.76 (m, 2H), 3.65 (dd, *J* = 11.7, 4.0 Hz, 1H), 2.07 (br s, 1H), 1.63−1.54 (m, 2H), 1.52 (s, 3H), 1.46−1.34 (m, 2H), 1.33 (s, 3H), 1.32−1.20 (m, 8H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.6, 85.0, 84.5, 83.8, 81.3, 62,7, 33.6, 31.7, 29.4, 29.1, 27.3, 25.4, 25.36, 22.6, 14.0; MS (ESI) *m*/*z* 273 $[M + H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{28}O_4Na$ 295.1885, found 295.1876.

(3a*S*,4*S*,6*S*,6a*S*)-4-(Chloromethyl)-6-heptyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole (28). Compound **28** was prepared according to the procedure described for compound **25** starting from compound **27** (2.2 g, 8.5 mmol). Purification by silica gel chromatography (60−120 mesh, 10% Et_2O/hexane) afforded compound **28** (2.4 g, 90% yield) as a colorless oil. $[\alpha]^{32}_D$ −14.4 (*c* 2, $CHCl_3$); IR ($CHCl_3$) 2955, 2928, 2857, 1639, 1381, 1212, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (dd, *J* = 7.0, 4.1 Hz, 1H), 4.25 (dd, *J* = 7.0, 4.9 Hz, 1H), 4.05 (q, *J* = 9.4, 4.3 Hz, 1H), 3.80 (q, *J* = 11.7, 6.6 Hz, 1H), 3.64−3.50 (m, 2H), 1.63−1.51 (m, 2H), 1.49 (s, 3H), 1.44−1.35 (m, 2H), 1.30 (s, 3H), 1.30−1.23 (m, 8H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.5, 85.0, 84.7, 82.9, 82,8, 44.5, 33.7, 31.9, 29.6, 29.3, 27.5, 25.6, 25.5, 22.7, 14.2; MS (ESI) *m*/*z* 279 $[M + Na - Cl]^+$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{28}O_3Cl$ 291.1721, found 291.1736.

(*S*)-1-[(4*S*,5*R*)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl]octan-1-ol (29). Compound **29** was prepared according to the procedure described for compound **11** starting from compound **28** (2.2 g, 7.6 mmol). Purification by silica gel (60−120 mesh, 10% EtOAc/hexane) afforded compound **29** (1.8 g, 93% yield) as a colorless oil. $[\alpha]^{33}_D$ +7.5 (*c* 2, $CHCl_3$); IR ($CHCl_3$) 3450, 3310, 2986, 2926, 2857, 2112, 1636, 1458, 1371, 1228, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.81 (dd, *J* = 5.3, 2.3 Hz, 1H), 3.88−3.82 (m, 2H), 2.56 (d, *J* = 2.3 Hz, 1H), 2.14 (br s, 1H), 1.82−1.68 (m, 1H), 1.60−1−52 (m, 1H), 1.49 (s, 3H), 1.47−1.36 (m, 2H), 1.32 (s, 3H), 1.31−1.25 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.7, 80.7, 80.5, 76.0, 71.3, 68.1, 34.0, 31.9, 29.7, 29.3, 27.6, 26.0, 25.2, 22.7, 14.2; MS (ESI) *m*/*z* 255 $[M + H]^+$; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{26}O_3Na$ 277.1779, found 277.1789.

(*S*)-1-{(4*S*,5*R*)-5-[(*S*)-5-(4-Methoxybenzyloxy)hepta-1,3-diynyl]-2,2-dimethyl-1,3-dioxolan-4-yl}octan-1-ol (30). Compound **30** was prepared according to the procedure described for compound **8** starting from compounds **29** (200 mg, 0.79 mmol) and **10** (244 mg, 0.86 mmol). Purification by silica gel (60−120 mesh, 5% EtOAc/hexane) afforded compound **30** (330 mg, 92%) as a colorless oil. $[\alpha]^{29}_D$ −58.5 (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 3450, 2929, 2857, 2156, 2240, 1612, 1514, 1249, 1226, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.24 (m, 2H), 6.92−6.85 (m, 2H), 4.96 (dd, *J* = 4.7, 2.6 Hz, 1H), 4.71 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 11.3 Hz, 1H), 4.05 (t, *J* = 6.4 Hz, 1H), 3.97−3.87 (m, 2H), 3.81 (s, 3H), 1.86−1.69 (m, 4H), 1.54 (s, 3H), 1.53−1.40 (m, 1H), 1.36 (s, 3H), 1.35−1.22 (m, 9H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 129.6, 129.6, 113.8, 110.9, 81.0, 79.8, 75.0, 71.8, 71.3, 70.5, 69.8, 69.4, 68.9, 55.2, 34.2, 31.8, 29.6, 29.2, 28.6, 27.6, 25.9, 25.1, 22.6, 14.0, 9.6; MS (ESI) *m*/*z* 474 $[M + NH_4]^+$; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{40}O_5Na$ 479.2773, found 479.2771.

(*S*)-1-{(4*R*,5*R*)-5-[(*S*)-5-(4-Methoxybenzyloxy)hepta-1,3-diynyl]-2,2-dimethyl-1,3-dioxolan-4-yl}octyl 4-Methylbenzenesulfonate (31). Compound **31** was prepared according to the procedure described for compound **7** starting from compound **30** (152 mg, 0.33 mmol). Purification by silica gel column chromatography (60−120 mesh, 5% EtOAc/hexane) afforded the compound **31** (187 mg, 92% yield) as a colorless oil. $[\alpha]^{32}_D$ −32 (*c* 1.75, $CHCl_3$); IR ($CHCl_3$) 2925, 2854, 2235, 2154, 1638, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93−7.78 (m, 2H), 7.39−7.21 (m, 4H), 6.94−6.81 (m, 2H), 4.89−4.82 (m, 2H), 4.74 (d, *J* = 11.3 Hz, 1H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.33 (dd, *J* = 11.3, 6.0 Hz, 1H), 4.07 (dd, *J* = 12.8, 6.0 Hz, 1H), 3.80 (s, 3H), 2.42 (s, 3H), 1.85−1.62 (m, 4H), 1.50 (s, 3H), 1.32 (s, 3H), 1.31−1.07 (m, 10 H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 144.7, 134.0, 129.6, 129.5, 127.8, 124.6, 113.7, 110.6, 81.6, 80.0, 78.2, 73.7, 72.8, 70.4, 69.7, 69.4, 68.1, 55.2, 31.6, 30.4, 29.0, 28.6, 26.8, 25.3, 24.0, 22.6, 21.5, 14.0, 9.6; MS (ESI) *m*/*z* 633 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{50}O_7NS$ 628.3307, found 628.3278.

C-10 Epimer of (+)-Oploxyne A (5). A solution of compound **31** (90 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) and trifluoroacetic acid (0.1 mL) was stirred at room temperature for 42 h. Diisopropylethylamine (0.6 mL)

was introduced to basify the reaction mixture and the solution was stirred for 8 h at room tempeature. The solution was then concentrated under reduced pressure and the resulting residue was purified by silica gel column chromatography (60−120 mesh, 20% EtOAc/hexane) to afford oploxyne A C-10 epimer **5** (30.7 mg, 75%) as a colorless oil. $[\alpha]^{27}_{D}$ +2.0 (*c* 0.45, MeOH); IR ($CHCl_3$) 3435, 2959, 2928, 2856, 2252, 2144, 1463 cm^{-1}; MS (ESI) *m*/*z* 296 $[M + NH_4]^+$; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{30}O_3N$ 296.2220, found 296.2211.

(4*R*,5*S*)-4-[(*S*)-5-(4-Methoxybenzyloxy)hepta-1,3-diynyl]-5-((*S*)-1-methoxyoctyl)-2,2-dimethyl-1,3-dioxolane (32). Compound **32** was prepared according to the procedure described for compound **8** starting from compounds **33** (60 mg, 0.22 mmol) and **10** (69 mg, 0.24 mmol). Purification by silica gel column chromatrography (60−120 mesh, 1% EtOAc/hexane) afforded compound **32** (96 mg, 91% yield) as a colorless oil. $[\alpha]^{29}_{D}$ −66.2 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 2956, 2923, 2318, 1458, 1371, 1228, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.22 (m,2H), 6.92−6.85 (m, 2H), 4.94 (d, *J* = 6.0 Hz, 1H), 4.73 (dd, *J* = 11.3, 9.1 Hz, 1H), 4.43 (dd, *J* = 11.3, 6.8 Hz, 1H), 4.10 −3.96 (m, 2H), 3.81 (s, 3H), 3.61−3.53 (m, 1H), 3.41 (s, 3H), 1.83−1.71 (m, 2H), 1.58 (s, 3H), 1.57−1.36 (m, 3H), 1.34 (s, 3H), 1.33−1.23 (m, 9H), 0.99 (t, *J* = 6.0 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 129.7, 113.8 (2C), 110.6, 79.8, 79.0, 78.9, 75.9, 71.1, 70.5, 69.8 (2C), 69.5, 57.6, 55.3, 31.8, 31.5, 30.6, 29.7, 29.3, 28.7, 27.6, 25.9, 22.7, 14.0, 9.6; MS (ESI) *m*/*z* 470 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{42}O_5Na$ 493.2929, found 493.2928.

(4*R*,5*S*)-4-Ethynyl-5-[(*S*)-1-methoxyoctyl]-2,2-dimethyl-1,3-dioxolane (33). A similar procedure was followed as described for compound **26** starting from compound **29** (200 mg, 0.78 mmol). Purification by silica gel column chromatography (60−120 mesh, 5% Et_2O/hexane) afforded compound **33** (183 mg, 87%) as a colorless oil. $[\alpha]^{28}_{D}$ + 6.8 (*c* 0.7, $CHCl_3$); IR ($CHCl_3$) 2986, 2929, 2857,2113, 1458, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.79 (dd, *J* = 5.3, 2.3 Hz, 1H), 3.89 (dd, *J* = 5.3, 8.3 Hz, 1H), 3.59−3.52 (m, 1H), 3.35 (s, 3H), 2.46 (d, *J* = 2.3 Hz, 1H), 1.81−1.67 (m, 1H), 1.63−1.52 (m, 1H), 1.50 (s, 3H), 1.48−1.33 (m, 4H), 1.32 (s, 3H), 1.31−1.23 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.3, 81.0, 79.7, 78.5, 75.2, 68.8, 57.4, 31.8, 30.5, 29.9, 29.2, 27.5, 26.0, 23.9, 22.6, 14.0; MS (ESI) *m*/*z* 291 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{28}O_3Na$ 291.1931, found 291.1918.

C-10 Epimer (−)-Oploxyne B (6). Trifluoroacetic acid (0.07 mL) was added to a solution of compound **32** (55 mg, 0.12 mmol) in CH_2Cl_2 (10 mL) at 0 °C and the solution was stirred for 36 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (60−120 mesh, 30% EtOAc/hexane) to afford compound **6** (31.0 mg, 86% yield) as a semi solid. $[\alpha]^{30}_{D}$ +6.3 (*c* 2.2, $CHCl_3$); IR ($CHCl_3$) 3453, 2955, 2924, 2852, 2253, 2152, 2064, 1247 cm^{-1}; MS (ESI) *m*/*z* 333 $[M + Na]^+$; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{30}O_4Na$ 333.2036, found 333.2034.

■ ASSOCIATED CONTENT

Supporting Information. Biological experimental details, screening data, and ^1H NMR and ^{13}C NMR spectra of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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