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First total synthesis and structure confirmation of diacetylenic polyol (+)-oploxyne B

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ABSTRACT

The first total synthesis of the natural product (+)-oploxyne B is achieved. The synthesis has led to the confirmation of absolute stereochemistry of the natural product. The natural product displayed cytotoxic activity with IC_{50} values varying from 16 to 53 μM in four cancer cell lines tested.

Recently synthetic organic chemists have become interested in the total synthesis of polyacetylenic alcohols because of their wide spectrum of structural diversity and broad array of biological properties.[1] The polyacetylene alcohols are isolated from natural sources and include a wide variety of plant species, cultures of fungi, marine sponges, corals, etc.[2] Yang et al. have recently isolated two new diynes namely oploxyne A and oploxyne B (Fig. 1) during their investigations on the inhibitors for the formation of NO and prostaglandin E2 (PGE2) from the CH_2Cl_2 extract of the stem of *Oplopanax elatus*.[3] Though, initially the structures were established based on NMR spectroscopy through chiral derivatization, the total synthesis[4] of originally proposed structures for oploxyne A and oploxyne B from our group had reconfirmed the absolute structure of oploxyne A while revising the structure of natural oploxyne B as its enantiomer based on the outcome of the analytical data and optical rotation of the synthetic product. It was also found that the synthetic compound (−)-oploxyne B was found to be effective against neuroblastoma cell line with an IC_{50} value of 12 μM against 9 μM for reference drug doxorubicin whereas in other cell lines like lung, prostate and breast cancer the IC_{50} values were found 25, 24 ad 28 μM. The reference doxorubicin showed IC_{50} values of 11.5, 11 and 12 μM. These results have prompted us to take up the total synthesis of natural oploxyne B to enable further screening. In continuation of our programme on the total synthesis of biologically active natural products,[5] we herein report the first total synthesis of natural oploxyne B starting from the readily available (−)-diethyl D-tartrate and D(−)-ribose in a convergent fashion.

Retrosynthetically, we envisaged the target compound to be synthesized based on a convergent approach utilizing two key intermediates, terminal alkyne **4** and the brominated alkyne **5**. Accordingly, these two fragments could be coupled under Cadiot–Chodkiewicz conditions and subjected to deprotection of PMB and acetonide moieties to get the desired target molecule. The key fragment **4** can be in turn synthesized from olefin **6** by oxidative degradation followed by one step alkyne formation with Ohira–Bestmann reagent. Compound **6** can be obtained from epoxide **7** through a ring opening reaction of epoxide **7** by a Grignard reaction followed by protection of the generated secondary alcohol as the corresponding methyl ether. Epoxide **7** in turn was easily accessible from commercially available D-ribose. Simultaneously,

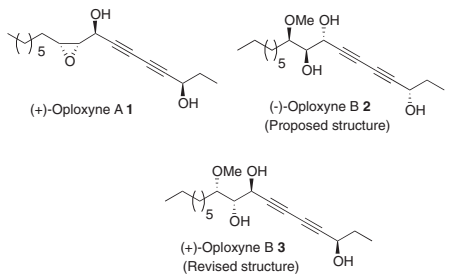

Figure 1. Structures of (+)-oploxyne A, (−)-oploxyne B and (+)-oploxyne B.

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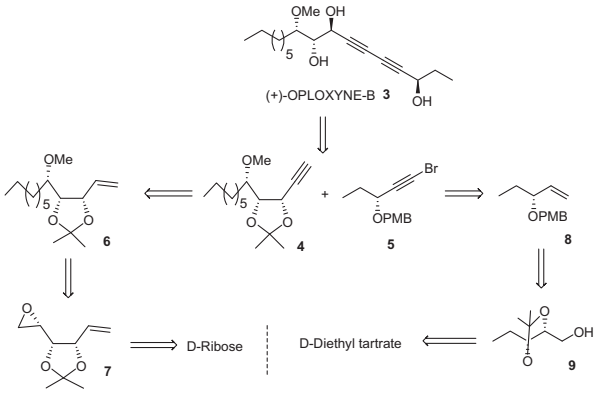
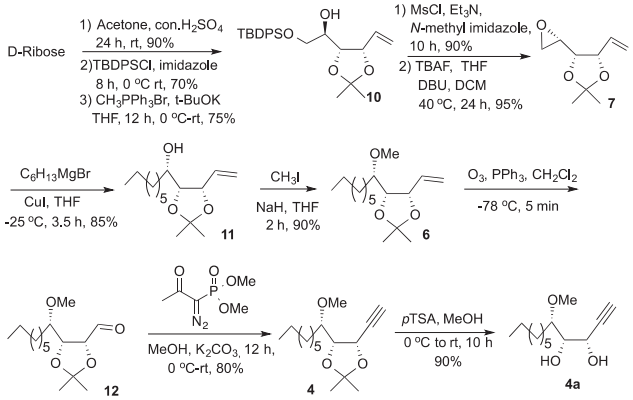


Scheme 1. Retrosynthesis for (+)-oploxyne B **3**.



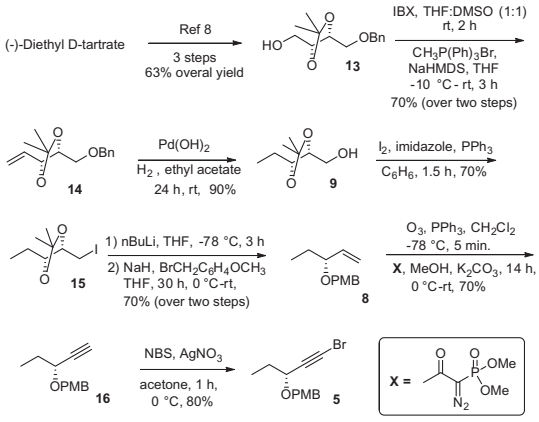
Scheme 2. Synthesis of key intermediate alkyne **4**.

the bromo alkyne **5** can be synthesized from the olefin **8** through oxidative degradation, followed by conversion of aldehyde to monosubstituted acetylene with Ohira–Bestmann reagent and further treatment with NBS in the presence of $AgNO_3$. Olefin **8** in turn was obtained from commercially available (−)-diethyl D-tartrate (Scheme 1).

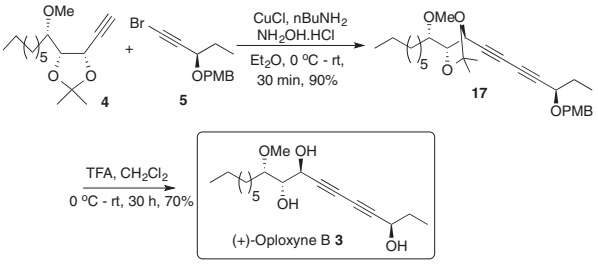
Thus, the synthesis began with D(−)-ribose which was converted to alcohol **10** in three steps (acetonide protection, TBDPS protection, followed by one carbon Wittig reaction). The free secondary alcohol in **10** was mesylated with MsCl in the presence of *N*-methyl imidazole. TBDPS deprotection with TBAF followed by DBU treatment afforded epoxide **7**.[6] Compound **7** on ring opening reaction under Grignard conditions (epoxide opening with in situ generated *n*-hexylmagnesium bromide) afforded chiral secondary alcohol **11**, which was further protected as the corresponding methyl ether **6** since this motif (–OMe) was present in the natural product. The terminal alkene was converted to alkyne through oxidative degradation, that is, ozonolysis followed by exposure of the resulting aldehyde **12** to Ohira–Bestmann reagent[7] to afford the key intermediate alkyne **4** (Scheme 2).

The other key fragment bromo alkyne **5** was synthesized starting from (−)-diethyl D-tartrate (see Scheme 3). Commercially available (−)-diethyl D-tartrate was converted to alcohol **13** by following known procedures in three steps (acetonide protection, $LiAlH_4$ mediated diester reduction and selective mono benzylation).[8] The free alcohol **13** was oxidized with 2-iodoxybenzoic acid (IBX)[9] to afford the aldehyde which was immediately treated with methyltriphenylphosphorane that was generated from methyltriphenylphosphoniumbromide and NaHMDS to get olefin **14**. One pot debenzylation and hydrogenation of the double bond was achieved with $Pd(OH)_2$ to yield the saturated alcohol **9** which upon treatment with I_2, triphenylphosphin[10] and imidazole afforded the corresponding iodide **15**. Our initial efforts to treat iodide **15** with excess base to get the chiral propargyl alcohol did not succeed and prompted us to proceed via chiral allyl alcohol. Towards this, iodide **15** was treated with *n*-BuLi to undergo elimination affording chiral allyl alcohol,[11] which was immediately protected as the corresponding PMB ether **8** with PMBBr and NaH. The olefin was subjected to ozonolysis and the resulting aldehyde was converted to alkyne **16** following Ohira–Bestmann procedure and was then brominated with NBS the in presence of $AgNO_3$ to afford the key intermediate brominated alkyne **5**.[12]

With the two intermediates in hand, the stage was set to couple them and proceed further for the total synthesis. The key reaction Cadiot–Chodkiewicz coupling[13] of alkyne **4** with brominated alkyne **5** resulted in the formation of masked oploxyne B **17** (Scheme 4). Finally, deprotection of isopropylidene and PMB moiety in **17** with TFA afforded the desired target compound oploxyne B. The spectroscopic data[14] was analysed and found to be compa-



Scheme 3. Synthesis of bromo alkyne **5**.



Scheme 4. Synthesis of natural product (+)-oploxyne B **3**.

rable with the natural product. The optical rotation of the final product was found to be $[\alpha]_D^{25}$ +12.5 (*c* 0.04, MeOH); lit.[2] $[\alpha]_D^{25}$ +11.7 (*c* 0.06, MeOH).

The natural product along with the intermediate compound **4** and its acetonide deprotected product **4a** (from Scheme 2) when evaluated for their in vitro cytotoxicity employing MTT assay[15] in four different human cancer cell lines displayed IC_{50} values varying from 16 to 53 μM (Table 1). Although the natural product (+)-oploxyne B displayed lowest IC_{50} of 16 μM in lung cancer cell line (A549) and 25 μM, 31 μM and 54 μM in neuroblastoma (SK-N-SH), prostate cancer (DU145) and breast cancer (MCF-7) respectively, the intermediate compound **4** and its acetonide deprotected product **4a** did not show any remarkable cytotoxicity.

In conclusion, a facile convergent strategy for the total synthesis of oploxyne B starting from commercially available D-ribose and (−)-diethyl D-tartrate has been achieved. The natural product was synthesized with an overall yield of 16% in 12 steps starting

Table 1
In vitro antiproliferative activity of the compounds **3**, **4** and **4a**[a]

	IC_{50} values in μM			
	A549 (lung cancer)	MCF-7 (breast cancer)	SK-N-SH (neuroblastoma)	DU-145 (prostrate cancer)
Oploxyne A[b]	NT	27 ± 1	7 ± 1	86 ± 2
(+)-Oploxyne B **3**	16.29 ± 4.67	53.78 ± 6.24	25.0 ± 4.39	31.34 ± 9.39
4	96.55 ± 12.35	>100	99.8 ± 21.7	>100
4a	No effect	No effect	No effect	No effect
Doxorubicin (Reference)	6.13 ± 0.54	15.12 ± 2.96	7.22 ± 1.16	14.19 ± 0.84

[a] Cell lines were treated with different concentrations of compounds (1 μM, 10 μM, 25 μM and 50 μM) for 48 h. (see Supplementary data). Cell viability was measured employing MTT assay. IC_{50} values are indicated as the mean ± SD of three independent measurements.
[b] The values for oploxyne A are from the previous results wherein the reference doxorubicin showed IC_{50} of 11.5, 12, 9 and 11.5 μM for MCF-7, SK-N-SH and DU-145 respectively.[4]

from D-ribose using Cadiot–Chodkiewicz coupling reaction as the key step. Also, we have confirmed the true structure of the natural product correcting the initial mis-assignment and this result is also in favour towards supporting the revised structure. The cytotoxic properties exhibited by the natural product (+)-oploxyne B were similar to those of (−)-oploxyne B and warrants detailed structure function studies for improved efficacy.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and analytical data for all the new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.020.

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14. Spectroscopic data for selected products **4**, colorless oil. $[\alpha]_D^{25}$ −48.00 (*c* 3.0, $CHCl_3$). R_f = 0.7 (10% EtOAc–Hexane). IR [neat]: 3309, 2985, 2929, 2856, 1735, 1461, 1340, 1106, 865, 497 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.65 (dd, *J* = 2.1, 5.2 Hz, 1H), 4.03 (dd, *J* = 5.3, 8.5 Hz, 1H), 3.51 (s, 3H), 3.53–3.50 (m, 1H), 2.51 (d, *J* = 2.1 Hz, 1H), 1.58 (s, 3H), 1.50–1.40 (m, 2H), 1.37 (s, 3H), 1.35–1.22 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H) ppm. ^{13} C NMR (75 MHz, $CDCl_3$): δ 110.7, 81.2, 80.6, 80.2, 75.2, 61.2, 58.6, 31.7, 30.9, 29.5, 29.1,27.7, 26.2, 24.7, 22.6, 14.0 ppm. MS(ESI): *m*/*z* 291 $[M+Na]^+$. HRMS(ESI) *m*/*z* calculated for $C_{16}H_{28}O_3Na$ 291.19307, found 293.19324. Compound **5**, yellow oil. R_f = 0.65 (5% EtOAc-Hexane). $[\alpha]_D^{25}$ +93.22 (*c* 0.3, $CHCl_3$). IR [neat]: 2983, 2933, 2877, 1632, 1458, 1238, 1032, 997, 510 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.29–7.26 (m, 2H), 6.89–6.86 (m, 2H), 4.71 (d, *J* = 11.4 Hz, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.00 (t, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 1.78–1.70 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm. ^{13} C NMR (125 MHz, $CDCl_3$): δ 159.0, 129.6, 129.4 (2C), 113.6 (2C), 79.3, 70.3, 70.1, 55.0, 45.0, 28.6, 9.5 ppm. Compound **17**, colorless oil. R_f = 0.5 (10% EtOAc-Hexane). $[\alpha]_D^{25}$ +43.20 (*c* 1.5, $CHCl_3$). IR [neat]: 2926, 2854, 2235, 1721, 1609, 1461, 1376, 1251, 1061, 863, 759, 511 cm^{-1}. (^1H NMR, 500 MHz, $CDCl_3$): δ 7.31–7.25 (m, 2H), 6.90–6.86 (m, 2H), 4.79–4.68 (m, 2H), 4.43 (d, *J* = 11.3 Hz, 1 H), 4.05 (dd, *J* = 8.5, 5.8 Hz, 2 H), 3.81 (s, 3 H), 3.53 (s, 3H), 3.52–3.49 (m, 1H), 1.82–1.72 (m, 2H), 1.59 (s, 3H), 1.58–1.41 (m, 3H), 1.38 (s, 3H), 1.35–1.24 (m, 9 H), 1.00 (t, *J* = 7.5 Hz, 3 H), 0.87 (t, *J* = 6.7 Hz, 3H) ppm. ^{13} C NMR (75 MHz, $CDCl_3$): δ 159.3, 129.6, 113.8, 111.6, 111.0, 81.5, 80.3, 79.4, 75.0, 71.2, 70.5, 69.8, 69.6, 67.8, 58.8, 55.2, 31.8, 31.0, 29.5, 29.2, 28.7, 27.8, 26.1, 24.7, 22.6, 14.1, 9.7 ppm. MS(ESI): *m*/*z* 493 $[M+Na]^+$. HRMS(ESI) *m*/*z* calculated for $C_{29}H_{42}O_5Na$ 493.29245, found 293.29388. Compound **3**, colorless oil. R_f = 0.25 (40% EtOAc-Hexane). $[\alpha]_D^{25}$ +12.5 (*c* 0.04, MeOH); lit.[1] $[\alpha]_D^{25}$ +11.7 (*c* 0.06, MeOH). IR [neat]: 3389, 2928, 2856, 1725, 1632, 1461, 1378, 1278, 1086, 1045, 969, 865, 757, 581 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.55–4.50 (m, 1H), 4.39 (t, *J* = 6.2 Hz, 1H), 3.69-3.61 (m, 1H), 3.61–3.55 (m, 1H), 3.44 (s, 3H), 3.42 (s, 1H), 2.79–2.63 (br s, 1H), 2.10–2.01 (br s, 1H), 1.80–1.71 (m, 2H), 1.68–1.57 (m, 2H), 1.37–1.23 (m, 10H), 1.02 (t, *J* = 7.3 Hz, 3H), 0.89 (t, *J* = 6.7 Hz, 3H) ppm.^{13} C NMR (75 MHz, $CDCl_3$): δ 81.4, 80.5, 77.6, 73.0, 70.5, 68.8, 65.4, 64.0, 57.4, 31.8, 30.5, 29.8, 29.2(2C), 25.0, 22.6, 14.1, 9.3 ppm. MS(ESI): *m*/*z* 333 $[M+Na]^+$. HRMS (ESI) *m*/*z* calculated for $C_{18}H_{30}O_4Na$ 333.20363, found 333.20386.
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