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First total synthesis of neurotrophic diacetylene tetrol (−)-petrosiol D

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ABSTRACT

The first total synthesis of the natural product (−)-petrosiol D has been achieved in a linear fashion. Sharpless asymmetric epoxidation, base induced elimination reaction for the formation of chiral propargyl alcohol and Cadiot–Chodkiewicz coupling reaction are the key steps utilized for the synthesis.

Dialkyne compounds with hydroxyl functionality display a wide spectrum of structural diversities and a broad array of biological properties.[1] Recent investigations by Ojika et al., towards identification of small molecules displaying NGF-like properties lead to the isolation of five novel diyne polyols namely petrosiols A–E (Fig. 1) from the extract library of marine organism (Okinawan marine sponge) using PC12 cells.[2] Interestingly, all of these compounds (petrosiols A–D) induced neurite outgrowth in approximately 40% of PC12 cells and also displayed a dose-dependent inhibitory effect on PDF-induced DNA synthesis with an IC_{50} value of 0.73, 0.71, 0.72 and 0.69 μM, respectively.[2,3] The absolute structure of petrosiols A–E was elucidated based on spectroscopic analyses. The impressive biological property of these novel diacetylene tetrols has attracted us to take up the total synthesis of these natural products for their availability towards further biological screening.

Recently, we have accomplished the total synthesis of similar first known diyne tetrols namely oploxynes A and B (Fig. 1) and found that these compounds display cytotoxicity towards neuroblastoma and prostate cancer cell lines.[4] Our own interest in identification of small molecules for CNS activity while working towards the total synthesis of potent natural product paecilomycin A has resulted in identification of analogues with new scaffold towards neurotrophic property.[5] In continuation of our efforts towards the total synthesis of biologically active natural products[6] with an emphasis for CNS related therapeutics,[5] we herein report

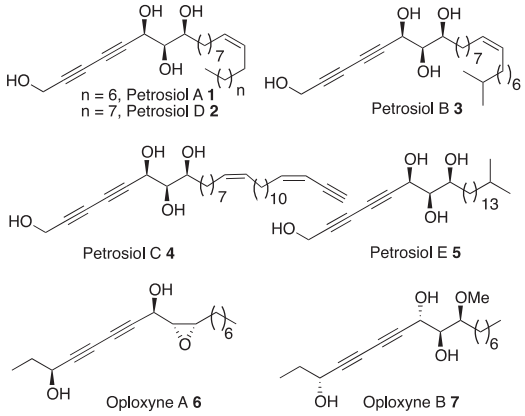

Figure 1. Structures of petrosiols A–E **1**–**5** and oploxyne A and B **6** and **7**.

the first total synthesis of natural product petrosiol D starting from the readily available (+)-diethyl L-tartrate.

Retrosynthetically, we envisaged the target compound **2** to be synthesized by Cadiot–Chodkiewicz coupling of PMB protected bromo propargyl alcohol **8** with free terminal alkyne **9** (Scheme 1). Compound **9** can be synthesized from the corresponding chiral epoxy alcohol **10** after its conversion to chiral epoxy chloride followed by a base induced elimination reaction. The chiral epoxide can be obtained from allyl alcohol **11** which in turn can be synthesized in three steps from alcohol **13**. Compound **13** can be synthesized through a Wittig reaction of the aldehyde obtained from alcohol **14** which in turn could be prepared from **15** in one

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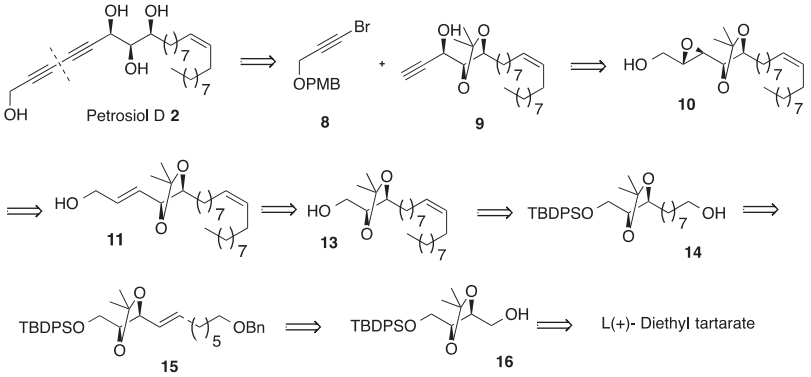
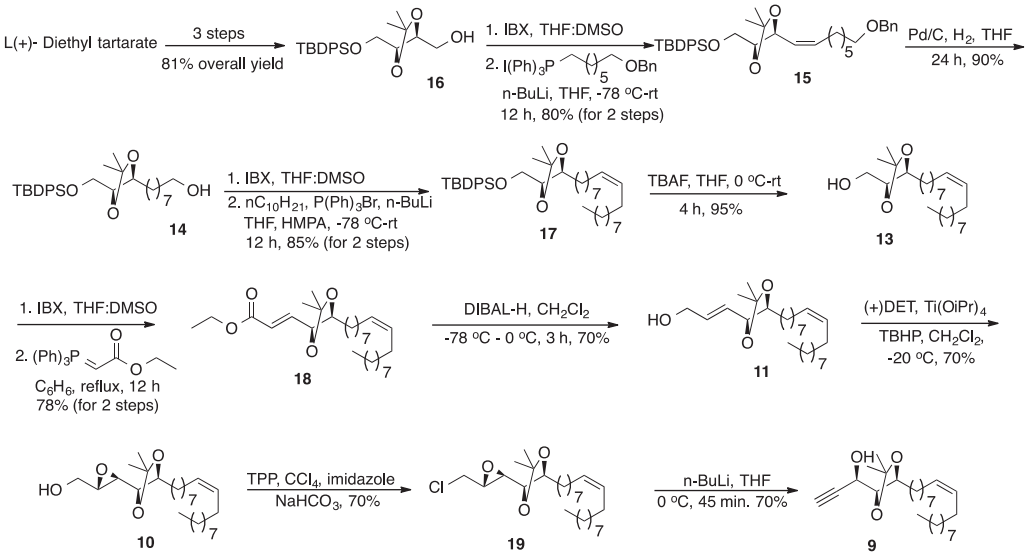
step by hydrogenation reaction. Compound **15** can be easily synthesized from **16** via an oxidation followed by the Wittig reaction. Alcohol **16** in turn was easily accessible from commercially available raw material (+)-diethyl L-tartrate in three steps.

Although petrosiol A and D have similar structure with the only difference in carbon chain length, we initially focused on the synthesis of petrosiol D as the raw materials required were readily available in our laboratory. Accordingly, the synthesis began with the readily available alcohol **16** synthesized from L-(+)-diethyl tartrate in three steps with an overall yield of 81% following well known literature procedures.[7] The alcohol was oxidized using IBX and then subjected to a Wittig reaction with 7-benzyloxy-1-heptyl-triphenylphosphonium iodide in the presence of *n*-BuLi to yield the corresponding olefin **15**. Since we had to reduce the double bond, we proceeded further with **15** by exposing it to Pd/C to result in one pot olefin reduction and debenzylation providing alcohol **14**. Alcohol **14** was oxidized to aldehyde and subjected to Wittig reaction with *n*-decyltriphenylphosphoniumbromide in the presence of *n*-BuLi to give *cis*-Wittig product **17** exclusively in 75% yield. Compound **17** was exposed to TBAF to desilylate the silyl ether and the resulted alcohol **13** was oxidized with IBX[8] to furnish the aldehyde which was further subjected to 2C-Wittig reaction with (carbethoxymethylene)triphenylphosphorane to yield α,β-unsaturated ester **18**. Chemoselective reduction of ester functionality with DIBAL-H provided allyl alcohol **11** that was subjected to sharpless asymmetric epoxidation[9] reaction to yield **10** in 80% yield. The chiral epoxy alcohol **10** was then treated with triphenylphosphine (TPP) and imidazole in CCl_4 to yield the corresponding epoxy chloride **19**.[10] Treatment of the chiral epoxy chloride with excess *n*-BuLi (6 equiv)[11] provided the chiral propargyl alcohol **9** (Scheme 2), the key alkyne fragment with all the chiral centres fixed for the total synthesis of petrosiol D.

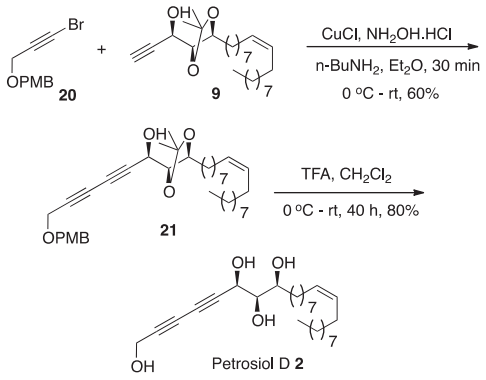
Our initial attempts to directly couple the key fragment **9** with propargyl alcohol or hydroxyl protected propargyl alcohol under Cadiot–Chodkiewicz conditions ended up in the undesired dimer by-product along with the recovery of **9**. With these unsuccessful results, we proceeded for coupling reaction of compound **9** with brominated propargyl alcohol **20**. Accordingly, propargyl alcohol was protected as the corresponding PMB ether and then treated with NBS in the presence of $AgNO_3$ to yield the brominated product **20** following earlier known procedures.[4] With the two fragments **20** and **9** in hand, we proceeded for the coupling reaction of **9** with **20** under Cadiot–Chodkiewicz coupling[12] conditions to yield the precursor **21** for petrosiol D. Finally, the protecting groups in **21** (isopropylidene moiety and PMB moiety) were unmasked using trifluoroacetic acid (TFA) to yield the target natural product petrosiol D (Scheme 3). The geometry of the olefin moiety Z configuration was conformed based on the coupling constant value of one of the olefinic protons (J = 10.7 Hz).[13] The ^{1}H NMR and ^{13}C NMR were is good agreement with that of the reported natural product.[14] The optical rotation was found to be $[\alpha]_D^{25} = -3.67$ (*c* 0.3, MeOH), lit.[2] $[\alpha]_D^{29} = -4.4$ (*c* 0.18, MeOH).



Scheme 1. Retrosynthesis for petrosiol D **2**.



Scheme 2. Synthesis of alkyne **9**.



Scheme 3. Total synthesis of petrosiol D.

In conclusion, a facile total synthesis of petrosiol D starting from commercially available (+)-diethyl L-tartrate has been achieved. The natural product was synthesized with an overall yield of 5.3% in 14 steps in linear approach starting from alcohol **16** and 17 steps with 4.2% from (+)-diethyl L-tartrate using base induced elimination reaction of chiral epoxy halides to get chiral propargyl alcohol and late stage Cadiot–Chodkiewicz coupling reaction as the key steps. Synthesis of other petrosiols is currently under progress in our laboratory.

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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.2013.09.058.

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13. The coupling constant was calculated after performing proton decoupling studies. See Supplementary data.
14. *Spectroscopic data for selected products* ***9***: $[\alpha]_D^{25}$ = −4.67 (*c* 0.6, $CHCl_3$). IR [NEAT]: 3448, 2925, 2854, 1733, 1461, 1375, 1248, 1167, 1054, 722, 658 cm^{-1}. ^{1}HNMR (300 MHz, $CDCl_3$): δ 5.40–5.32 (m, 2H), 4.33 (dd, *J* = 4.3, 1.7 Hz, 1H), 4.00–3.93 (m, 1H), 3.75 (dd, *J* = 7.5, 4.9 Hz, 1H), 2.52 (d, *J* = 2.1 Hz, 1H), 2.08–1.95 (m, 4H), 1.72–1.51 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.38–1.20 (m, 24H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.9, 129.7, 109.4, 83.2, 81.6, 77.5, 74.3, 62.6, 33.6, 32.6, 31.9, 29.7(2C), 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.9, 27.5, 27.2, 27.0, 25.9, 22.7, 14.1 ppm. MS (ESI): *m*/*z* 430 $[M+Na]^+$. *Compound* ***21*** $[\alpha]_D^{25}$ = −2.00 (*c* 0.25, $CHCl_3$). IR [NEAT]: 3447, 2925, 2854, 1741, 1612, 1513, 1461, 1374, 1249, 821, 770, 512 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.24 (m, 2H), 6.91–6.86 (m, 2H), 5.39–5.32 (m, 2H), 4.52 (s, 2H), 4.41 (d, *J* = 3.4 Hz, 1H), 4.20 (s, 2H), 3.99–3.89 (m, 1H), 3.81 (s, 3H), 3.75 (dd, *J* = 7.7, 4.5 Hz, 1H), 2.05–1.93 (m, 4H), 1.73–1.50 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.40–1.20 (m, 24H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm. MS(ESI): *m*/*z* 604 $[M+Na]^+$. *Compound* ***2***: $[\alpha]_D^{25}$ = −3.67 (*c* 0.3, MeOH), lit $[\alpha]_D^{29}$ = −4.40 (*c* 0.18, MeOH). IR [NEAT]: 3382, 2924, 2583, 1734, 1508, 1460, 1246, 1117, 1034, 771, 696, 540 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.32–5.26 (m, 2H), 4.48 (d, *J* = 5.9 Hz, 1H), 4.27 (s, 2H), 3.75–3.71 (m, 1H), 3.47 (dd, *J* = 6.6 Hz, 1H), 2.08–1.80 (m, 4H), 1.60–1.07 (m, 26H), 0.81 (t, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.0, 129.8, 78.1, 77.2, 75.7, 71.3, 70.5, 69.5, 64.9, 51.4, 34.2, 32.6, 31.9, 29.7–28.9(9C), 27.2, 25.6, 22.7, 14.1 ppm. MS(ESI): *m*/*z* 439 $[M+NH_4]^+$. HRMS(ESI) *m*/*z* calculated for $C_{26}H_{44}O_4Na$ 443.31318, found 443.31297.