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First total synthesis of natural aplyolides C and E, ichthyotoxic macrolides isolated from the skin of the marine mollusc *Aplysia depilans*†

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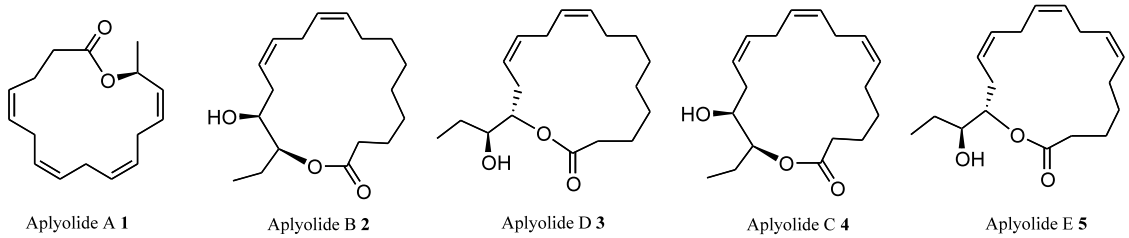
Abstract—A convergent pathway is described for the synthesis of the marine macrolides aplyolides C **4** and E **5**. The key fragment **8** was prepared stereoselectively by Sharpless asymmetric dihydroxylation of eneyne **13**.

Many macrocyclic compounds derived from natural sources contain a lactone moiety in their structure. These compounds have been the object of many studies as a result of their remarkable biological properties. Typical sources of macrolides are terrestrial organisms but recently several members of this family have been isolated from marine invertebrates.[1,2] *Aplysia depilans* is an opisthobranch mollusc scarcely predated despite its significant size and its slow motion. Early studies on the defensive strategy of this mollusc showed that some compounds of dietary origin are stored in particular glands and ejected when the marine organism is molested.[3] However, recently an investigation on secondary metabolites contained on the skin of *A. depilans* has allowed the detection of some macrolides, aplyolides A–E **1**–**5**, whose ichthyotoxic activity together with the particular location indicates that they play a defensive role.[4]

In order to evaluate their pharmacological and biological activities, synthetic efforts have recently allowed preparation of adequate quantities of some of these compounds. In particular, synthetic approaches have been developed for the preparation of aplyolide A **1**[5,6] and for aplyolides B **2** and D **3**.[7] Herein, we disclose a synthetic strategy for the first enantioselective preparation of aplyolides C **4**, and E **5**.

Aplyolides **4** and **5** are macrolides containing three unconjugated double bonds and differ from each other by the size of the macrocycle, being, respectively, a 17- and 16-membered lactone. (15*S*,16*S*)-15,16-Dihydroxy-octadecyl-(6*Z*,9*Z*,12*Z*)-trienoic acid **6** is the common *seco*-acid precursor of both macrolactones **4** and **5**. Consequently, retrosynthetic analysis of **6** offers a general synthetic strategy suitable for the preparation of both **4** and **5**. A convergent route towards triyne **7**, which was envisaged as precursor of triene **6**, was devised through a simple disconnection of the two bonds, as illustrated in Scheme 1.

We envisaged the introduction of the 15*S*,16*S* stereochemistry by Sharpless asymmetric dihydroxylation (AD) of an appropriate eneyne. The assembly of the fragments **8**, **9**, **10** was planned by using an improved methodology for the coupling of copper acetylide and propargylic halides.



Aplyolide A **1** Aplyolide B **2** Aplyolide D **3** Aplyolide C **4** Aplyolide E **5**

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† Dedicated to the memory of Professor G. Sodano.

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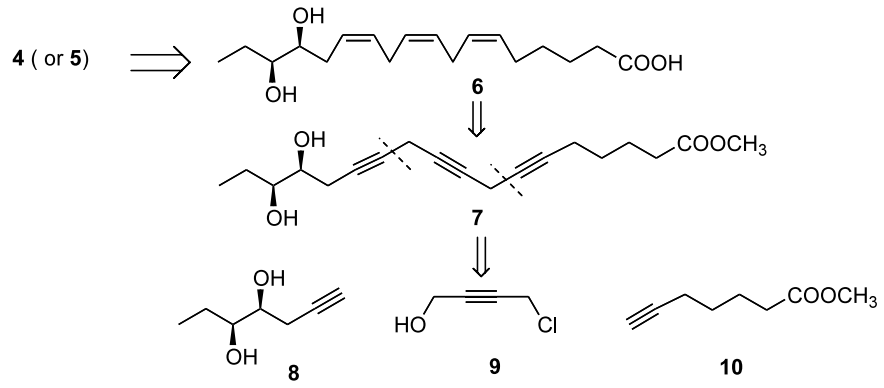


Scheme 1. Retrosynthetic analysis of **4** and **5**.

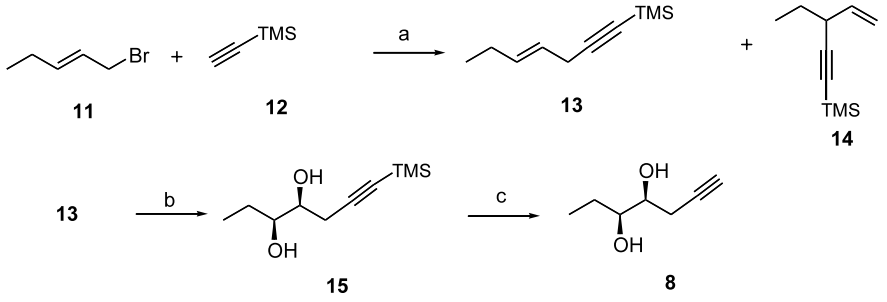
The synthesis began with the coupling of *trans*-1-bromo-2-pentene **11** and trimethylsilylacetylene **12**, which was conducted using a procedure recently improved during the synthesis of aplyolides B and D.[7] This reaction gave eneyne **13** (60% yield) together with the isomeric compound **14**. Sharpless enantioselective dihydroxylation,[8] using commercial AD-mix-α reagent, provided the expected diol **15** in excellent yield (95%) and good enantiomeric excess (85%).[9,10]

Finally, compound **8**[11] was prepared, in 99% yield, by removal of the silyl group using TBAF (Scheme 2). The planned synthetic scheme required, at this point, two consecutive coupling reactions between a propargylic halide and an acetylide. Recently, this reaction has been the subject of several investigations and an improved methodology involving copper acetylide, generated with Cs_2CO_3 in the presence of CuI, was recently proposed during our synthesis of aplyolide A **1**.[6] We applied this methodology to our synthesis of aplyolides C and E (Scheme 3) obtaining **16**[12] by coupling of **9** and **10** in 90% yield. Primary alcohol **16** was then converted into bromide **17** by treatment with CBr_4 and Ph_3P (90% yield).

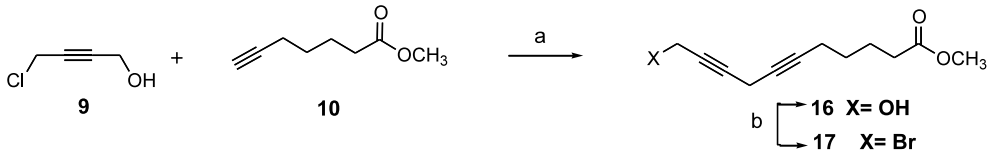
The coupling of propargyl bromide **17** and the copper acetylide derived from **8**, in the presence of CuI and Cs_2CO_3, gave an 88% yield of compound **7**. Triene **6** was obtained by partial hydrogenation[13,14] ($Pd/BaSO_4$, quinoline, 90% yield) of **7**, followed by alkaline hydrolysis using LiOH (Scheme 4).

Finally, aplyolides C **4** and E **5** were obtained in a 1.7:1 ratio in 80% yield, by macrolactonization of dihydroxy acid **6** using the Yamaguchi methodology.[15] Purification of the obtained mixture (silica gel, Et_2O–petroleum ether, 9:1) allowed the isolation of aplyolide C **4** and E **5** whose spectroscopic data (^1H, ^{13}C NMR, IR and MS) were in complete agreement with those of the natural products. The values of $[\alpha]_D$ measured for synthetic aplyolides C and E were in accordance to those reported for the natural products confirming the absolute stereochemistry assigned.[16]

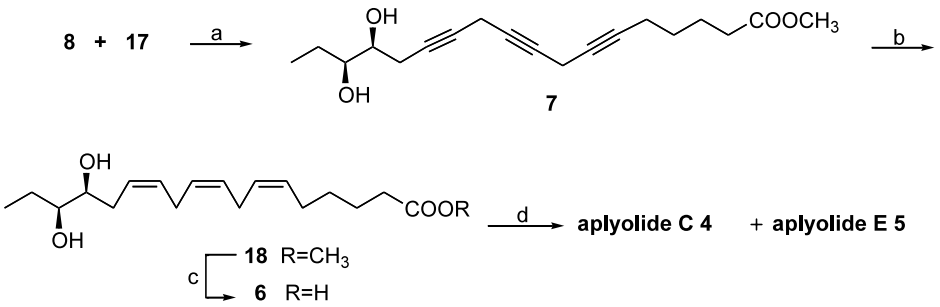
In conclusion, we have accomplished the first total synthesis of potent ichthyotoxic macrolides aplyolides C **4** and E **5**. The convergent approach uses a Sharpless asymmetric dihydroxylation and an efficient methodology for coupling alkynes with propargylic halides in key steps.



Scheme 2. *Reagents and conditions*: (a) Cs_2CO_3, CuI, NaI, DMF, 20 h, 60% of **13** and 30% of **14**; (b) AD-mix-α, *t*-BuOH–H_2O (1:1), $CH_3SO_2NH_2$, 0°C, 5 h, 95%, e.e. 85%; (c) TBAF, THF dry, 30 min, 99%.



Scheme 3. *Reagents and conditions*: (a) Cs_2CO_3, CuI, NaI, DMF, 20 h, 90%; (b) CBr_4, PPh_3 dry, CH_2Cl_2 dry, 0°C, 1 h, 90%.



Scheme 4. *Reagents and conditions*: (a) Cs_2CO_3, CuI, NaI, DMF, 20 h, 88%; (b) H_2, $Pd/BaSO_4$, quinoline, MeOH, 1 h, 90%; (c) LiOH (3N), 1,2-DME, 30 min, 99%; (d) 2,4,6-TBCl, THF dry, 3 h; 4-DMAP, toluene dry, 20 h, 50% of **4** and 30% of **5**.

An investigation into the biological activity of these aplyolides is now in progress and the results will be given in due course.

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9. The enantiomeric excess was calculated by analysis of the proton NMR spectra of the Mosher esters obtained by exposing diol **15** to (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride.
10. It is noteworthy that, in the presence of methanesulfonamide, the AD reaction was also conducted on the mixture of two eneynes **13** and **14** without any interference of compound **14**, which was recovered unchanged at the end of the reaction.
11. Compound **8**: $[\alpha]_D^{15}=-1.3$ (*c* 5.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.65 (1H, ddd, $J=6.5$ Hz, $J=5.6$ Hz, $J=4.2$ Hz); 3.54 (1H, ddd, $J=8.2$ Hz, $J=4.7$ Hz, $J=4.2$ Hz); 2.50 (1H, ddd, $J=17.0$ Hz, $J=5.6$ Hz, $J=2.7$ Hz); 2.46 (1H, ddd, $J=17.0$ Hz, $J=6.5$ Hz, $J=2.7$ Hz); 2.06 (1H, t, $J=2.7$ Hz), 1.55 (2H, m); 1.0 (3H, t, $J=7.5$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.7 (s); 74.3 (d); 71.7 (d); 70.6 (d); 26.3 (t); 23.9 (t); 9.9 (q). Anal. calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found C, 65.43; H, 9.63%.
12. **Compound 16**: ^1H NMR (400 MHz, $CDCl_3$) δ 4.26 (2H, t, $J=2.1$ Hz); 3.67 (3H, s); 3.17 (2H, tt, $J=2.1$ Hz, $J=2.4$ Hz); 2.34 (2H, t, $J=7.5$ Hz); 2.19 (2H, tt, $J=7.5$ Hz, $J=2.4$ Hz); 1.75 (2H, m); 1.56 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (s); 80.2 (s); 78.8 (s); 78.5 (s); 73.9 (s); 51.5 (q); 50.8 (t); 33.4 (t); 27.8 (t); 23.9 (t); 18.2 (t); 9.6 (t). MS *m/z*: 208, 147, 131, 115, 91, 77.
13. **Compound 18**: $[\alpha]_D^{24}=-6.9$ (*c* 2.4, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 5.56 (1H, bdt, $J=10.7$ Hz, $J=6.4$ Hz); 5.46 (1H, m); 5.42–5.32 (4H, m); 3.66 (3H, s); 3.50 (1H, m); 3.39 (1H, m); 2.85 (1H, m); 2.80 (2H, m); 2.33 (2H, m); 2.31 (2H, t, $J=7.4$ Hz); 2.06 (2H, bdt, $J=7.5$ Hz, $J=5.6$ Hz) 1.63 (2H, m); 1.57 (1H, m); 1.49 (1H, bdq, $J=15.1$ Hz, $J=7.4$ Hz); 0.99 (3H, t, $J=7.4$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2 (s); 130.6 (d); 129.5 (d); 128.3 (d); 127.9 (d); 127.6 (d); 125.4 (d); 74.9 (d); 73.3 (d); 51.4 (q); 33.8 (t); 31.6 (t); 28.9 (t); 26.7 (t); 23.3 (t); 25.6 (t); 25.5 (t); 24.4 (t); 9.9 (q). EIMS *m/z*: 324, 235, 147, 119, 105, 91, 79.
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16. Values of $[\alpha]_D$ for synthetic aplyolides C ($[\alpha]_D^{25}=-22.8$; *c* 0.7; $CHCl_3$) and E ($[\alpha]_D^{25}=+39.4$; *c* 0.3; $CHCl_3$) were in accordance with those reported for the natural products (lit.[4] **4**, $[\alpha]_D^{25}=-26.7$; $c=0.7$; $CHCl_3$ and **5** $[\alpha]_D^{25}=+46.3$; $c=0.3$; $CHCl_3$).