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First total synthesis of natural aplyolides B and D, ichthyotoxic macrolides isolated from the skin of the marine mollusk *Aplysia depilans*†

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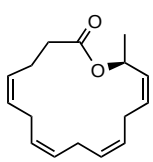
Abstract—A convergent pathway is described for the synthesis of the marine macrolides aplyolides B (**2**) and D (**3**). Stereoselective preparation of a key fragment was achieved by Sharpless asymmetric dihydroxylation of eneyne **10**.

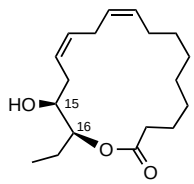
Marine organisms have been proven to be a unique source of novel and diverse bioactive compounds.[1] Aplyolides, e.g. **1**–**3**, are lactonized hydroxy fatty acids recently isolated from the skin of the marine mollusk *Aplysia depilans*, during a study on chemical aspects of the ecology of marine organisms.[2] These compounds displayed potent ichthyotoxicity and are probably involved in the defence strategy of the mollusc involving organic molecules (chemical defence).[3] However, aplyolides are intriguing synthetic targets also because of their structure related to some others bioactive lactonized fatty acids from marine source[4] and their preparation will provide enough material for an investigation of their biological activities. Recently, two synthetic routes have been reported for aplyolide A (**1**);[5,6] in this communication we present the first stereocontrolled total synthesis of natural aplyolides B (**2**) and D (**3**).

Aplyolides B (**2**) and D (**3**) are macrolides characterized by the presence of two not conjugated double bonds. They derive from the cyclization respectively at C-15 and C-16 of the same precursor, (*S*,*S*)-15,16-dihydroxy-octadeca-9(*Z*),12(*Z*)-dienoic acid (**4**). A convergent way for the synthesis of both **2** and **3** was planned starting from easily available materials. Our retrosyntetic plan is shown in Scheme 1. Dihydroxyacid **4** could be prepared by diyne **5** which should be readily obtainable by coupling the propargylic bromide **6** and methyl decinoate (**7**). Compound **6** would be available after Sharpless asymmetric dihydroxylation of an appropriate eneine precursor.

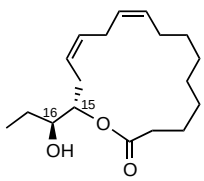
The synthesis of **6** (Scheme 2) began with a coupling reaction between *trans* 2-bromo-1-pentene (**8**) and methyl propiolate (**9**). This reaction was carried out using a recent methodology which forms in situ Cu(I) alkynide as nucleofile.[6,7] The reaction gave eneyne **10** (86% yield) together with a small amount (10%) of isomeric compound **11**. Sharpless enantioselective dihydroxylation[8] of compound **10**, using commercial AD-mix-α reagent, afforded diol **12** with good yield (95%) and satisfactory enantiomeric excess (85%).[9]



Aplyolide A (1)



Aplyolide B (2)



Aplyolide D (3)

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† Dedicated to the memory of Professor G. Sodano.

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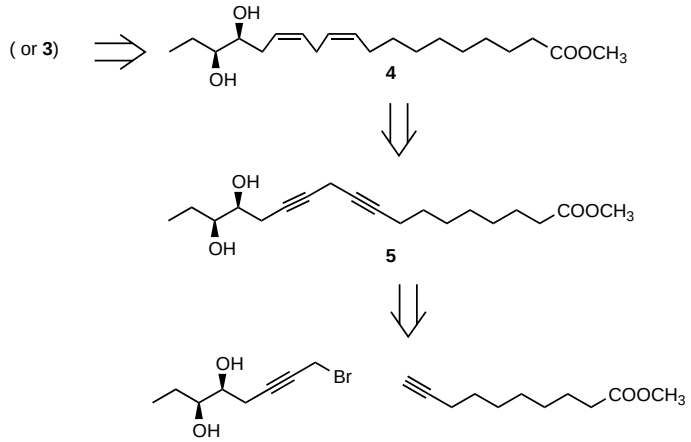
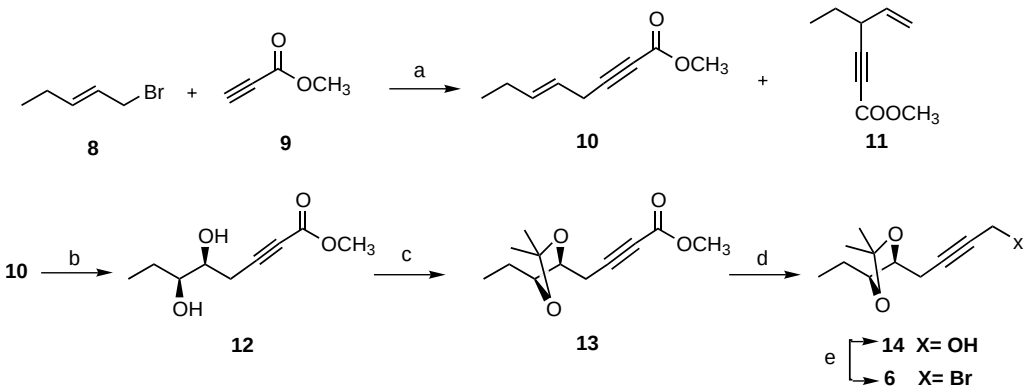


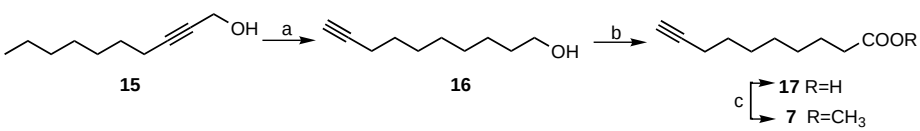
Scheme 1. Retrosynthetic analysis of **2** and **3**.



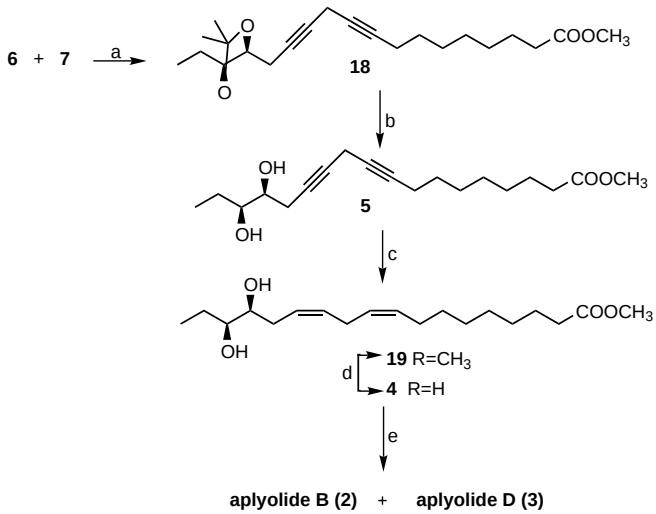
Scheme 2. *Reagents and conditions*: (a) Cs_2CO_3, CuI, NaI, DMF, 20 h, 86% of **10**; (b) AD-mix-α, *t*-BuOH–H_2O 1:1, $CH_3SO_2NH_2$, 0°C, 20 h, 95%, e.e. 85%; (c) 2,2-DMP, PPTS, 24 h, 99%; (d) DIBAL, Et_2O dry, 0°C, 3 h, 85%; (e) CBr_4, PPh_3 dry, CH_2Cl_2 dry, 0°C, 20 h, 85%.

Protection of diol **12** as an acetonide, followed by reduction of the ester functionality with diisobutylaluminium hydride (DIBAL), furnished alcohol **14** (84% two-step yield). The preparation of bromide **6** was completed by treatment of **14** with CBr_4 and Ph_3P.

The synthesis of the required coupling partner **7** is presented in Scheme 3. Preparation of methyl dec-9-ynoate (**7**) started submitting 3-decinol (**15**) to a 'zipper' reaction using NaH and 1,3-diaminopropane (DAP).[10] This reaction led to dec-9-yn-1-ol (**16**) which was oxidized with Jones reagent and esterified with MeOH under sulfuric acid catalysis. Union of alkyne **7** and propargyl bromide **6** (Scheme 4) was achieved, once again, via an improved methodology set-up during the synthesis of aplyolide A.[6] In fact, the use of Cs_2CO_3 as a base for the preparation of Cu(I) alkynide allowed the preparation of diyne **18** in 86% yield. Deprotection of **18** was performed by treatment of pyridinium *p*-toluenesulfonate (PPTS) in methanol. This allowed us to obtain **5** with a 85% yield. Final conversion to aplyolides B and D was achieved upon sequential partial hydrogenation[11] ($Pd/BaSO_4$, quinoline, 95% yield) of **5**, saponification (LiOH 3N, 1,2-DME) of the obtained ester **19** and lactonization of dihydroxyacid **4** using the Yamaguchi protocol.[12] This last step furnished a mixture of macrolides **2** and **3** in 2.5:1 ratio with a yield of 70%. Purification of the obtained mixture (silica gel, Et_2O–petroleum ether 9:1) allowed the isolation of aplyolide B (**2**) and D (**3**) whose spectroscopic data (^1H NMR, ^{13}C NMR, IR and MS) were in complete agreement with those of the natural products.[13] The value of $[\alpha]_D$ measured for synthetic aplyolides B ($[\alpha]_D^{24} = -18$; $c = 0.7$; $CHCl_3$) and D ($[\alpha]_D^{24} = +24$; $c = 0.2$; $CHCl_3$) were in accordance to those reported for the natural products (lit.[2] **2** $[\alpha]_D^{25} = -43$; $c = 0.2$; $CHCl_3$ and **3** $[\alpha]_D^{25} = +28$; $c = 0.1$; $CHCl_3$).



Scheme 3. *Reagents and conditions*: (a) NaH, 1,3-DAP, 70°C, 20 h, 95%; (b) CrO_3, CH_3COCH_3, H_2SO_4, H_2O, 1 h, 95%; (c) CH_3OH, H_2SO_4, 70°C, 20 h, 95%.



Scheme 4. *Reagents and conditions*: (a) Cs_2CO_3, CuI, NaI, DMF, 20 h, 86%; (b) PPTS, MeOH, 50°C, 10 h, 85%; (c) H_2, $Pd/BaSO_4$, quinoline, MeOH, 3 h, 95%; (d) LiOH 3N, 1,2-DME, 30 min, 99%; (e) 2,4,6-TBCl, THF dry, 3 h; 4-DMAP, toluene dry, 20 h, 50% of **2** and 20% of **3**.

In conclusion, a concise total synthesis of potent ichthyotoxic macrolides aplyolides B (**2**) and D (**3**) is presented. The approach uses a Sharpless asymmetric dihydroxylation of the eneyne **10** to give the diol **12** and an efficient methodology for coupling alkynes with propargylic halides in key steps. This is also the first confirmation of the absolute stereochemistry of aplyolides B and D.

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

Acknowledgements

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9. When we submitted to Sharpless dihydroxylation also a mixture of **10** and **11** in presence of methanesulfonamide only **10** reacted while all alkene **11** was recovered at the end of the reaction. The enantiomeric excess was calculated by analysis of the proton NMR spectra of the Mosher esters obtained exposing diol **12** to (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride.
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13. All new compounds gave satisfactory spectral and analytical data. All yields are from material purified by column chromatography.