Synthesis of Aplyolide A, Ichthyotoxic Macrolide Isolated from the Skin of the Marine Mollusk *Aplysia depilans*

Aldo Spinella,* Tonino Caruso, Marco Martino, Carmine Sessa

Dipartimento di Chimica, Università di Salerno, Via S. Allende, 84081 Baronissi (Salerno), Italy
Fax +39(89)965296; E-mail: spinella@unisa.it

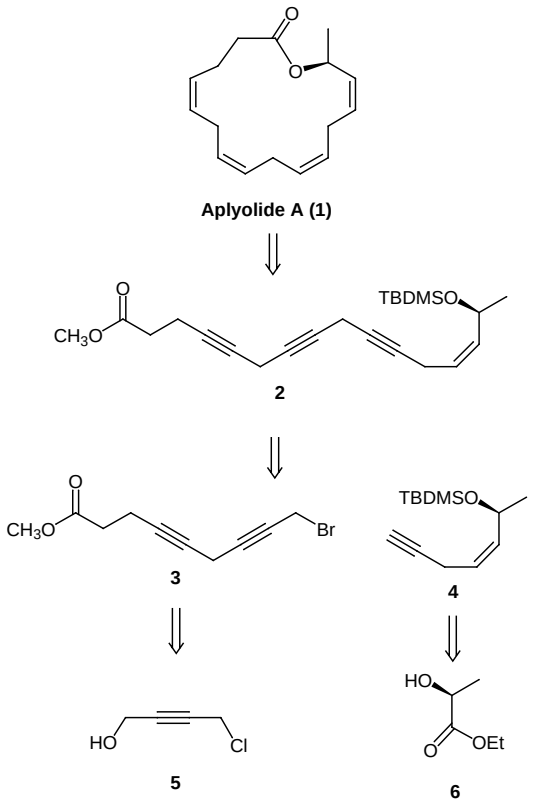
Received 14 September 2001

Dedicated to the memory of Professor G. Sodano

Abstract: A convergent pathway is described for the synthesis of (*S*)-aplyolide A (**1**) using ethyl (*S*)-lactate as chiral source. Key steps of the synthesis are two couplings between copper(I) alkynides and propargylic halides for the formation of skipped diyne systems and were performed with an improved procedure based on the use of cesium carbonate as base for alkynide preparation.

Key word: aplyolide A, natural product, macrocycles, total synthesis, alkynes

Aplyolide A (**1**) belongs to a group of lactonized hydroxy fatty acids recently isolated from the skin of the marine mollusk *Aplysia depilans*.[1] These compounds are strongly suspected to play a role as allomones in the chemical defense[2] of these mollusks because of both their ichthyotoxicity and their exclusive location on the external part of the animal skin. Aplyolides should also possess other biological activities which might be of useful application in medicine owing their structural similarities with other bioactive compounds.[3] However, these potential bioactivities are still undetected because the paucity of material obtained from the natural source has precluded further investigation. We therefore have recently been engaged with the development of a synthetic process which would make these compounds readily available for biological evaluation. Reported herein is a convergent and stereocontrolled synthesis of (*S*)-aplyolide A (**1**).



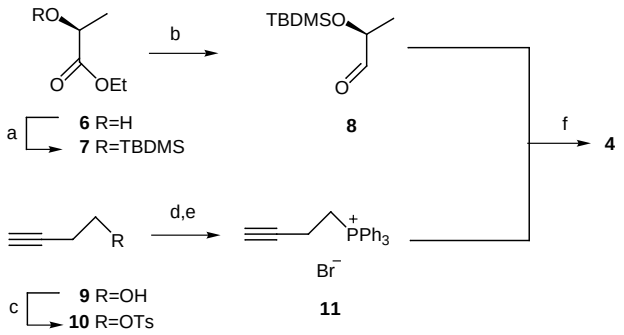
Scheme 1

Retrosynthetic analysis for **1** (Scheme 1) revealed that the enetriyne **2** could be a good precursor for the *Z*,*Z*,*Z*,*Z* skipped tetraene moiety of the hydroxy tetraunsaturated acid obtained after opening of the lactone. Further disconnection of **2** gives two fragments **3** and **4** whose disconnections lead to easily available starting materials. In fact, **4** can be prepared from cheap chiral template ethyl (*S*)-lactate (**6**) while **3** can be obtained by coupling an alkyne with a propargylic halide such as chlorobutynol (**5**).[4a] Central to the approach is the formation of skipped diynes by coupling of propargylic halides and alkynes. In this frame, a bifunctional compound such as **5** is particularly useful[4b] because, in the first coupling, it leads to a product which, after functional group transformation of the hydroxy group, can provide the needed propargylic halide **3** for the second coupling required in order to obtain **2**.

(*S*)-(*tert*-Butyldimethylsilyloxy)-2-hepten-6-yne (**4**) was synthesized by Wittig reaction of aldehyde **8** with phosphonium salt **11** as outlined in Scheme 2. The first step was the protection of the ethyl (*S*)-lactate (**6**) with the *t*-butyl-dimethylchlorosilane (TBDMS-Cl) to give 2-(*tert*-butyl-dimethyl-silyloxy)-propionic acid ethyl ester **7**.[5] Reduction of **7** with diisobutylaluminium hydride (DIBALH) in dichloromethane at –78 °C gave the aldehyde **8** in 88% yield [$[\alpha]^{22}_D$ –6.30 (c = 12.5, 95% ethanol); lit.[6] $[\alpha]^{21}_D$ –6.13 (c = 1, 95% ethanol)]. But-3-ynyl-triphenyl-phosphonium bromide (**11**)[7] was prepared starting from 3-butynol (**9**) in three steps: conversion into the corresponding tosylate **10** which was subjected to reaction with NaBr in order to obtain a bromide whose reaction with PPh_3 afforded **11** (62%, three steps yield). With the two required reagents in hand, the Wittig reaction was car-

Synlett 2001, No. 12, 30 11 2001. Article Identifier:
1437-2096,E;2001,0,12,1971,1973,ftx,en;G15201ST.pdf.

ISSN 0936-5214



Scheme 2 (a) TBDMS-Cl, imidazole, CH_2Cl_2, (100%). (b) DIBALH, CH_2Cl_2, –78 °C, (88%). (c) p-TsCl, pyridine, CH_2Cl_2, 0 °C, (100%). (d) NaBr, CH_3CN. (e) PPh_3, CH_3CN, 60 °C, (62% overall from **9**). (f) **11**, *n*-BuLi, THF, 0 °C, then addn. **8** in THF, then 60 °C, 2 h (80%).

ried out affording the required *Z* alkene **4**[8] as the sole product in 80% yield.

The following crucial steps of the planned synthesis were two coupling reactions between a terminal alkyne and a propargylic halide for the preparation of **2**. In fact, **13** (Scheme 3) was planned to derive from coupling of **12** and **5** while a second similar coupling was envisioned for the formation of **2** by reaction of **4** and the propargylic bromide **3**[9] obtained from **13**. It is well known that these coupling reactions are generally complicated by some side reactions when a Group I alkynide is used, while copper(I) alkynides proved to give better results and several methods have been proposed using preformed or in situ generated copper(I) alkynides.[10] Furthermore, in our case the reaction must be performed under conditions highly tolerant of a sensitive group such as the ester functionality. Initially, we used the methodology described by Jeffery and co-workers[11] in which a carbonate is used to produce the alkynide under phase transfer conditions but an unsatisfactory result was obtained for the coupling of the alkyne **12** with chlorobutynol (**5**) (46% yield). Therefore we turned to the procedure proposed by Lapitskaya et al.[12] in which K_2CO_3 is used as base and NaI is added in order to convert the propargylic halide into the more reactive iodide in the reaction mixture. However, the yields obtained were quite acceptable (Table; entries 1 and 2) only for the first coupling so a further improvement was needed to make also the second coupling fully satisfactory.

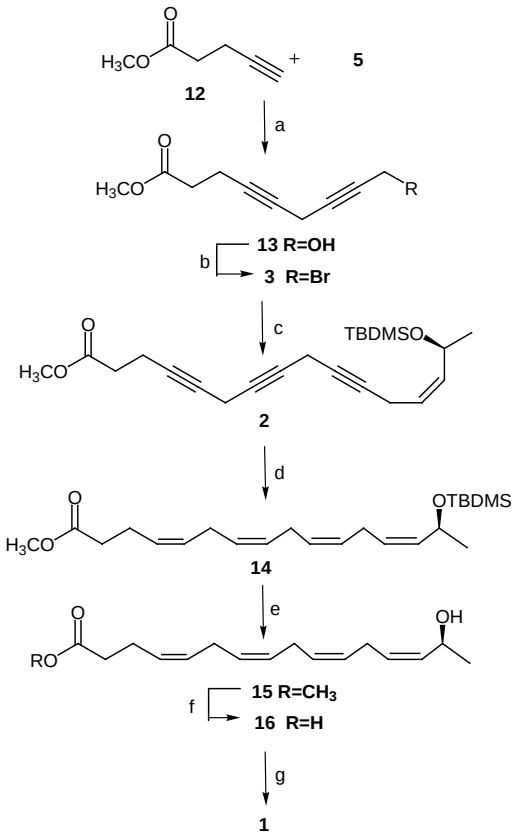
We focused our attention on the kind of carbonate used as base. In fact, it is well known that among the alkali metal cations present in carbonates cesium plays a prominent role in solving synthetic problems.[13] Many reactions in which a carbonate is used as base, take advantage of a "cesium effect" mainly due to the higher solubility in organic solvent[14] and appropriate basicity of this carbonate. Experimental results showed the improvement that we expected making these reactions fully applicable to our multistep synthesis devoted to the construction of the skipped polyyne (Table; entries 3 and 4).

Table Skipped Diyne Formation by Coupling Reactions between Copper(I) Alkynides and Propargylic Halides

Entry	Alkyne	Propargyl halide	Carbonate	Yield (%)
1	**12**	**5**	K_2CO_3	85
2	**4**	**3**	K_2CO_3	42
3	**12**	**5**	Cs_2CO_3	95
4	**4**	**3**	Cs_2CO_3	68

Finally, compound **2**[15] upon careful semi-hydrogenation over Lindlar catalyst[16] gave the corresponding all *cis* tetraene **14**[17] (Scheme 3). After removal of the *t*-butyl-dimethylsilyl group with pyridine *p*-toluenesulfonate (PPTS),[18] the hydroxy ester **15** obtained was subjected to hydrolysis with LiOH[19] affording the hydroxyacid **16**. Finally, macrolactonization according to Yamaguchi's procedure[20] gave aplyolide A (**1**) in 71% yield (Scheme 3).[21]

The $[\alpha]^{25}_D$ value (–58.5; c = 0.2, $CHCl_3$) and the other spectral data (^1H NMR, ^{13}C NMR, IR and MS) of synthetic **1** were in agreement with those of the natural product.[1]



Scheme 3 (a) Cs_2CO_3, NaI, CuI, DMF, 20 h (95%). (b) CBr_4, PPh_3, CH_2Cl_2, 0 °C (90%). (c) **4**, Cs_2CO_3, NaI, CuI, DMF, 20 h (68%). (d) 1 Atm H_2, Pd–$CaCO_3$, (Lindlar), EtOH (54%). (e) PPTS, EtOH 95% (100%). (f) LiOH, DME–H_2O, (100%). (g) 2,4,6-trichlorobenzoyl chloride, Et_3N; 4-DMAP, toluene, reflux (71%).

In conclusion, the stereo and enantioselective total synthesis of aplyolide A (**1**) has been described which confirms the *S* stereochemistry of the natural product.[22] The starting material, used as chiral source, is the relatively unexpensive ethyl (*S*)-lactate. The synthesis is convergent and requires only 10 steps from either **9** or **6**. A particularly valuable feature of the synthesis was the development and the use of an improved methodology of coupling between Cu(I) alkynide and propargylic halides. An investigation on the biological activity of aplyolide A is now in progress and the results will be given in due course.

Acknowledgement

We gratefully acknowledge Prof. G. Sodano for his review of the manuscript. This research was assisted financially by the MURST (PRIN "Chimica dei Composti Organici di Interesse Biologico").

References

(1) Spinella, A.; Zubia, E.; Martinez, E.; Ortea, J.; Cimino, G. *J. Org. Chem.* **1997**, *62*, 5471.
(2) Faulkner, D. J. *Chemical Defenses of Marine Molluscs*, In *Ecological Roles of Marines Natural Products*; Paul, V. J., Ed.; Cornell University Press: Ithaca, **1992**, 119.
(3) Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807.
(4) (a) Chlorobutynol was prepared by hydroxymethylation of propargyl chloride using a procedure according to: Schaap, A.; Brandsma, L.; Arens, J. L. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1200. (b) Durand, S.; Parrain, J. L.; Santelli, M. *Synthesis* **1998**, 1015.
(5) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Syntheses*; VCH: Weinheim, **1997**, Chap. 1, 1.
(6) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180.
(7) Dharanipragada, R.; Fodor, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 545.
(8) Compound **4**: $[\alpha]^{22}_D$ = +22.8 (c = 1.7, $CHCl_3$); FTIR (cm^{-1}): 3313, 1086. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50 (1 H, ddt, *J* = 10.9 Hz, *J* = 7.6 Hz, *J* = 1.6 Hz), 5.33 (1 H, dt, *J* = 10.9 Hz, *J* = 7 Hz), 4.59 (1 H, dq, *J* = 7.6 Hz, *J* = 6.3 Hz), 2.96 (2 H, ddd, *J* = 7 Hz, *J* = 2.8 Hz, *J* = 1.6 Hz), 1.98 (1 H, t, *J* = 2.8 Hz), 1.20 (3 H, d, *J* = 6.3 Hz), 0.88 (9 H, s), 0.06 (3 H, s), 0.05 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1 (d), 121.7 (d), 82.1 (s), 68.4 (d), 64.8 (d), 25.8 (q, 3 C), 24.4 (q), 18.1 (s), 17.1 (t), –4.6 (q), –4.8 (q). MS (EI): *m/z* (%) = 224(2), 223(4), 183(38), 167(11), 131(42), 93(27), 75(100), 57(49). Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found: C, 69.63; H, 10.97.
(9) Compound **3**: FTIR (cm^{-1}): 1735. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (2 H, t, *J* = 2.1 Hz), 3.70 (3 H, s), 3.19 (2 H, t, *J* = 2.1 Hz), 2.50–2.48 (4 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (s), 81.5 (s), 79.1 (s), 75.3 (s), 73.7 (s), 51.6 (q), 33.1 (t), 14.6 (t), 14.4 (t), 9.9 (t). MS (EI): *m/z* (%) = 244 (5.6), 242 (5.4), 229 (42), 227 (39), 213 (40), 211 (40), 185 (38), 183 (37), 171 (57), 169 (56), 163(100). Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56. Found: C, 49.47; H, 4.74.
(10) (a) Brandsma, L. *Preparative Acetylene Chemistry*, 2nd ed.; Elsevier: Amsterdam, **1998**. (b) Furber, M. In *Comprehensive Organic Functional Group Transformations*, Vol. 1; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Pergamon: London, **1995**, Chap. 1.21, 1000.
(11) Jeffery, T.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron Lett.* **1992**, *33*, 5757.
(12) Pivnistky, K. K.; Lapitskaya, M. A.; Vasijeva, L. L. *Synthesis* **1993**, 65.
(13) Flessner, T.; Doye, S. *J. Prakt. Chem.* **1999**, *341*, 186.
(14) Cella, J. A.; Bacon, S. W. *J. Org. Chem.* **1984**, *49*, 1122.
(15) Compound **2**: $[\alpha]^{22}_D$ = +12.0 (c = 1.17, $CHCl_3$); FTIR (cm^{-1}): 1734. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47 (1 H, bdd, *J* = 10.9, 7.5 Hz), 5.32 (1 H, dt, *J* = 10.9, 7.0 Hz), 4.58 (1 H, dq, *J* = 7.5, 6.2 Hz), 3.70 (3 H, s), 3.11 (4 H, m), 2.92 (2 H, bd, *J* = 7.0 Hz), 2.50 (4 H, m), 1.19 (3 H, d, *J* = 6.2 Hz), 0.91 (9 H, s), 0.05 (3 H, s), 0.04 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (s), 136.7 (d), 122.3 (d), 78.6 (s), 78.4 (s), 74.7 (s, 2C), 74.6 (s), 74.0 (s), 64.9 (d), 51.7 (q), 33.3 (t), 25.8 (q, 3 C), 24.5 (q), 18.1 (s), 17.4 (t), 14.7 (t), 9.7 (t, 2 C), –5.0 (q), –5.2 (q). MS (EI) *m/z* (%) = 386 (3.8), 329 (5), 255 (4), 226 (9.5), 159 (67), 131 (83), 115 (100). Anal. Calcd for $C_{23}H_{34}O_3Si$: C, 71.46; H, 8.86. Found: C, 71.34; H, 8.68.
(16) Huang, W.; Pulaski, S. P.; Meinwald, J. *J. Org. Chem.* **1983**, *48*, 2270.
(17) Compound **14**: $[\alpha]^{22}_D$ = +23.0 (c = 1.3, $CHCl_3$); FTIR (cm^{-1}): 1740. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43–5.34 (7 H, m), 5.26 (1 H, m), 4.63 (1 H, dq, *J* = 6.3, 7.2 Hz), 3.67 (3 H, s), 2.82 (6 H, m), 2.38 (4 H, m), 1.19 (3 H, d, *J* = 6.3Hz), 0.87 (9 H, s), 0.05 (3 H, s), 0.04 (3 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5 (s), 135.7 (d), 129.3 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.9 (d, 2 C), 125.8 (d), 65.1 (d), 51.6 (q), 34.0 (t), 25.9 (t), 25.8 (q, 3C), 25.6 (t), 25.5 (t), 24.8 (q), 22.8 (t), 18.2 (s), –4.5 (q), –4.7 (q). EIMS (EI): *m/z* (%) = 392(9)359(19), 335(100), 303(91), 261(15), 239(51), 206(58), 185(24), 131(72), 75(25), 57(19). Anal. Calcd for $C_{23}H_{40}O_3Si$: C, 70.35; H, 10.27. Found: C, 70.18; H, 10.47.
(18) Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19.
(19) Yeola, S. N.; Saleh, S. A.; Brash, A. R.; Prakash, C.; Taber, D. F.; Blair, I. A. *J. Org. Chem.* **1996**, *61*, 838.
(20) Yamaguchi, M.; Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(21) Macrolactonization procedure: 2,4,6-Trichlorobenzoyl chloride (0.28 mmol) was added to a mixture of **16** (0.28 mmol) and triethylamine (0.32 mmol) in dry THF (2.8 mL). The mixture was stirred for 3 h at r.t. After removal by filtration of triethylamine hydrochloride, the filtrate was diluted with dry toluene (140 mL) and added dropwise to a refluxing solution of 4-(dimethylamino)pyridine (DMAP) (1.68 mmol) in toluene (28 mL) over a period of 2 h. After refluxing for 12 h, the solution was cooled, diluted with ether, then washed successively with 3 N HCl, water, sat. aq $NaHCO_3$ solution and water, dried (Na_2SO_4), filtered and concentrated. Flash chromatography on silica gel (Et_2O/petroleum ether 2:98) provided **1** (49 mg, 71%).
(22) Vidar, T. V.; Stenstrom, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1407. During the submission of this manuscript we learned of a recent independent synthesis of aplyolide A which also confirms the stereo-chemistry of the natural product. However, a commercial chiral template by far more expensive than ethyl (*S*)-lactate was used in this synthesis.