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First total synthesis of (−)-aplyolide A

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Abstract—The first total synthesis of (−)-aplyolide A†, (16*S*)-methyloxacyclohexadeca-(5*Z*,8*Z*,11*Z*,14*Z*)-tetraen-2-one, **1** is reported. The synthesis is based on three consecutive couplings of terminal alkynes with propargylic halides and proves the absolute configuration of the stereogenic center of the natural product.

1. Introduction

Over the past decades interest in the syntheses of fatty acids and their derivatives has increased as was pointed out in a recent review.[1] The ability of some organisms to utilize these derivatives for different purposes has been apparent for a long time. Optically active polyunsaturated fatty acids pose a special challenge in stereospecific synthesis. In a recent paper Spinella et al.[2] isolated and characterized several macrocyclic lactones from the skin of the Mediterranean sea hare *Aplysia depidans*. The compounds, which were named aplyolides, act as defensive allomones and are ichthyotoxic. They belong to a small, but growing group of hydroxy fatty acid lactones isolated from marine organisms.[3] One of the compounds, aplyolide A **1**, has four (*Z*)-skipped double bonds and a stereogenic center in the ω-2 position. Three years ago a ω-2 hydroxy polyunsaturated fatty acid derivative, volicitin, was isolated and characterized by Tumlinson et al.[4] and shown to have an interesting tritrophic interaction. We have recently set up a protocol for the synthesis of volicitin.[5] The structural similarities between volicitin and aplyolide A, and their similar biological activities made us interested in the problem of synthesizing the latter as well. Our goal was both to prove its absolute stereochemistry through synthesis and present a practical, high yielding synthesis for its large-scale production.

In our strategy towards the target molecule the four skipped double bonds are all derived from the partial reduction of the corresponding alkyne. The most obvious strategy is to make the tetrayne and reduce all four triple bonds in one operation. It was thought that this could be achieved by a procedure described in some recent papers[6] where terminal alkynes are coupled with propargylic and allylic halides including 4-chloro-2-butyn-1-ol **2**. The method is mild and appears to be compatible with most functional groups, and in particular isomerisation of the skipped polyenes and polyynes is avoided. However, although 15-acetoxy-4,7,10,13-hexadecatetraynoate (the tetrayne corresponding to **10** in Scheme 1) could be made in good yield according to this strategy, the P-2 nickel hydrogenation[7] yielded a complex, inseparable mixture with the all (*Z*)-tetraene **11** isolated in less than 60% yield and the remainder being partial (*E*)-alkenes (according to GLC and ^{1}H NMR analysis). We were not able to improve this result in favor of the all (*Z*)-alkene and have no rationale for this observation. These results are surprising in view of the high yield observed for the reduction of the triene methyl 17-acetoxy-9,12,15-triynoctadecanoate in the synthesis of volicitin.[5] Moreover, examples of both the reduction of all triple bonds in one step and sequential reduction of each triple bond in separate steps can be found in the literature.[1] The disadvantages of one over the other have not been discussed in general. However, we thought that the latter strategy would be better here, with reduction of the triple bonds in the separate fragments. Using the coupling procedure on **2** and methyl 4-pentynoate **3** yielded the skipped diyne **4**. Bromination with CBr_4 and triphenylphosphine gave the corresponding diyne in 79% yield for the two step reaction. According to both GLC and ^{1}H and ^{13}C NMR analysis (*Z*,*Z*)-6 was >95% pure with only one impurity. Based on the coupling constant observed in the ^{1}H NMR spectrum the minor product was tentatively identified as one of the two possible (*Z*,*E*)-diene isomers.[8]

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† Unfortunately the trivial name aplyolide A has previously been used for a sesterpene with a completely different structure: Crews, P.; Jimenez, C.; O'Neil-Johnson, M. *Tetrahedron* **1991**, 47, 3585.

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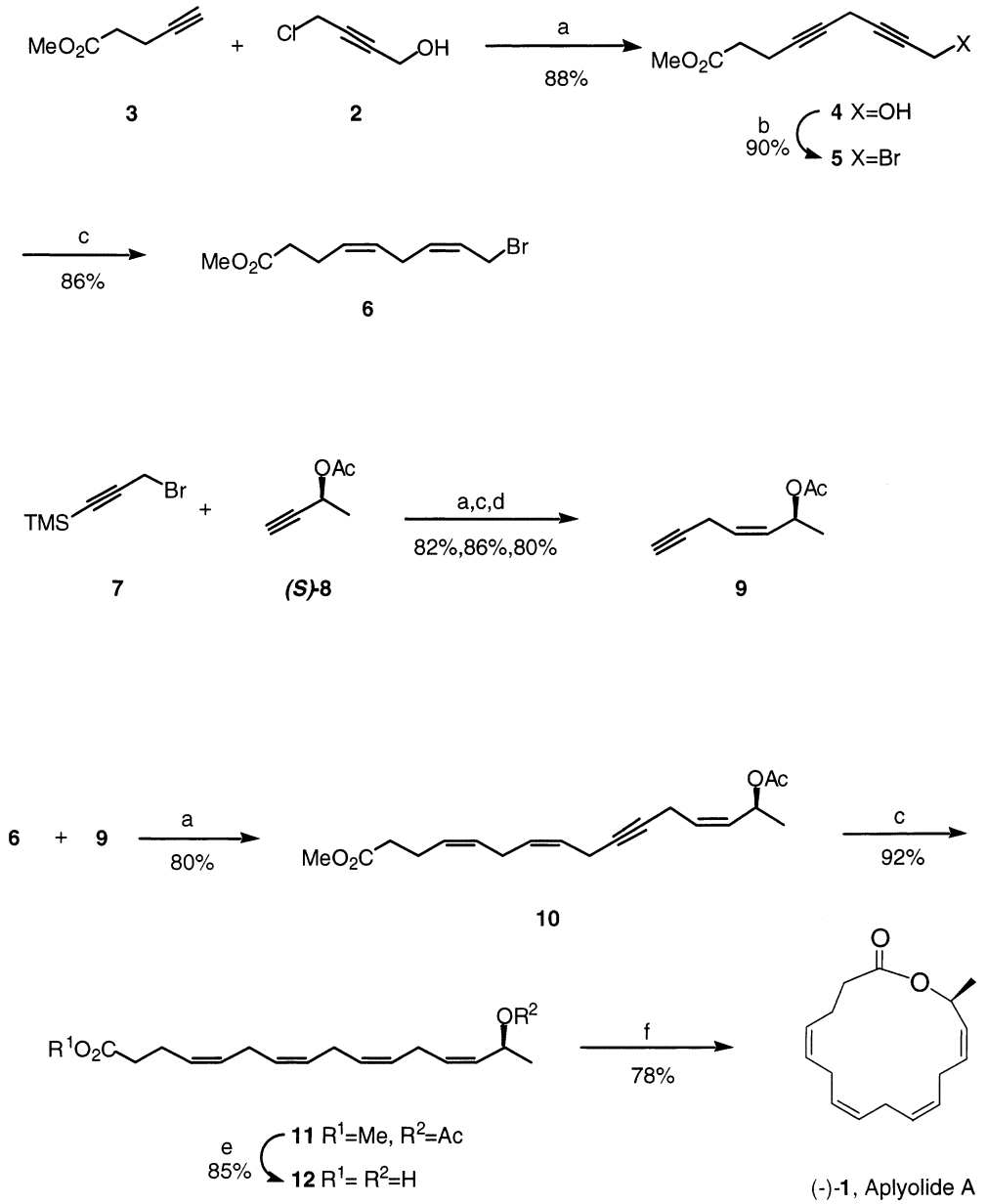

Scheme 1. (a) NaI, CuI, K_2CO_3, DMF; (b) CBr_4, Ph_3P, CH_2Cl_2; (c) P-2 Ni, H_2, EtOH; (d) Bu_4NF, DMF; (e) LiOH, MeOH, H_2O; (f) 2,2′-dipyridyl disulfide, PPh_3, toluene, Δ.

The optically active acetate **9** needed for the coupling with **6** was made by a similar route, starting with the coupling of the TMS-protected terminal alkyne **7** and the optically active, commercially available 3-butyn-2(*S*)-acetate **8**. Stereo- and regiospecific reduction of the internal alkyne followed by removal of the TMS-protecting group gave **7** in 56% yield for the three steps.

Coupling of **6** and **9**, again using the anion-alkylation procedure gave **10**. Stereo- and regiospecific reduction of the remaining triple bond was then accomplished in 92% yield using P-2 nickel hydrogenation affording the tetraene **11**. Removal of the acetate and methyl ester protecting groups by hydrolysis with lithium hydroxide in aqueous methanol afforded (15*S*)-hydroxy-(4*Z*,7*Z*,10*Z*,13*Z*)-hexadecatetraenoic acid **12**[9] with minor impurities most likely being mono-(*E*)-alkenes as indicated by the double allylic signals in the ^{13}C NMR spectrum.[10]

To facilitate the lactonization of **12** several methods were tried.[11] However, an approximate yield of 60% of the lactone was invariably obtained with a 10–15% yield of the corresponding diolide. An exception to this was the lactonization method of Corey and Nicolaou.[12] Adding **12** to a solution of 2,2′-dipyridyl disulfide and triphenylphosphine in toluene at room temperature and stirring overnight, then adding a catalytic amount of triethylamine and stirring the mixture under reflux for 5 hours, gave a 78% yield of aplyolide A with approxi-

mately 5% of the diolide impurity. The latter could be easily separated from **1** by flash chromatography. Spectroscopic data were in accord with those published.[2] The specific rotation ($[\alpha]_D^{24}$) of the product was −55.5 (*c* 0.3 $CHCl_3$) as compared to the reported $[\alpha]_D^{25}$ of −57.9 (*c* 0.4 $CHCl_3$) proving the stereochemistry as assigned by Spinella et al.[2]

2. Conclusion

In conclusion, the first synthesis of (−)-aplyolide A was achieved in ten steps with a non-optimized overall yield of 18%.

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9. Spectral and structural data were in accord with the assigned structures. Some selected spectroscopic data of key intermediates: **6-Acetoxyhept-4-en-1-yne 9** ^{1}H NMR (300 MHz): 1.42 (d, J=6.3 Hz, 3H), 2.03 (s, 3H), 2.70 (m, 2H), 1.86 (t, J=2.1 Hz, 1H), 4.90–4.92 (m, 1H), 5.64–5.70 (m, 2H); ^{13}C NMR (75 MHz): 19.51 (q), 20.21 (q), 69.97 (d), 74.07 (d), 81.12 (s), 124.22 (d), 130.71 (d), 171.91 (s); IR (film) cm^{-1}: 3328, 1726. **Methyl 15-acetoxy-hexadeca-(4*Z*,7*Z*,13*Z*)-trien-10-ynoate 10** ^{1}H NMR (300 MHz): 1.33 (d, J=6.5 Hz, 3H), 2.04 (s, 3H), 2.27-2.35 (m, 4H), 2.60-2.73 (m, 6H), 3.65 (s, 3H), 4.92 (m, 1H), 5.35-5.49 (m, 4H), 5.62–5.71 (m, 2H); ^{13}C NMR (75 MHz): 14.32 (t), 14.89 (t), 19.88 (q), 20.51 (q), 22.34 (t), 23.94 (t), 33.80 (t), 50.69 (q), 68.63 (d), 74.65 (s), 78.21 (s), 124.12 (d), 124.66 (d), 125.28 (d), 125.81 (d), 129.53 (d), 130.04 (d), 172.22 (s), 172.91 (s); IR (film): 3040, 2231, 1723, 1718 cm^{-1}. **Methyl 15-acetoxy-(4*Z*,7*Z*,10*Z*, 13*Z*)-hexadeca-4,7,10,13-tetraenoate 11** $C_{19}H_{28}O_4$, ^{1}H NMR (300 MHz): 1.28 (d, J=6.5 Hz, 3H), 1.99 (s, 3H), 2.30–2.35 (m, 4H), 2.68–2.76 (m, 4H), 2.90–2.92 (m, 2H), 3.65 (s, 3H), 5.30–5.46 (m, 8H), 5.52 (dq, J=6.5 and 7.0 Hz, 1H); ^{13}C NMR (75 MHz): 20.48 (q), 20.85 (q), 23.74 (t), 25.44 (t), 25.80 (t), 26.24 (t), 34.66 (t), 51.88 (q), 69.03 (d), 126.92 (d), 127.68 (d), 127.84 (d), 128.28 (d), 128.63 (d), 129.48 (d), 130.28 (d), 132.31 (d), 172.56 (s), 173.41 (s); IR (film): 3048, 1728, 1718, 1648 cm^{-1}. **15-hydroxy-(4*Z*,7*Z*,10*Z*,13*Z*)-hexadecatetraenoic acid 12** $C_{16}H_{24}O_3$; ^{1}H NMR: (300 MHz 1.24 (d, J=6.3 Hz, 3H), 2.35–2.38 (m, 4H), 2.60–2.65 (br s, 1H), 2.79–2.88 (m, 4H), 2.90-2.93 (m, 2H), 4.65 (dq, J=6.3 and 7.2 Hz, 1H), 5.32–5.54 (m, 8H); ^{13}C NMR (75 MHz): 22.63 (q), 23.88 (t), 25.34 (t), 25.83 (t), 26.20 (t), 34.62 (t), 63.10 (d), 126.89 (d), 127.47 (d), 127.79 (d), 128.26 (d), 128.51 (d), 129.53 (d), 130.40 (d), 132.22 (d), 178.62 (s); IR (film) cm^{-1}: 3440, 3045, 1720, 1640.
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