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Synthesis of a polyunsaturated amino ketone isolated from a Guangxi sponge of the genus *Haliclona*

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ABSTRACT

The first synthesis of (all-*Z*)-1-[(2-phenylethyl)amino]-octadeca-6,9,12,15-tetraen-3-one has been achieved in nine steps and in 13% overall yield using eicosapentaenoic acid as the starting material.

The polyunsaturated amino ketone **1** (Fig. 1) was isolated in 2010, by Xin and Guo, from a marine sponge of the genus *Haliclona* off the coast of southern China.[1] This unusual natural product has so far only been evaluated for its cytotoxic effects, but was found to be inactive at 10 μg/ml against three different tumor cell lines. No total synthesis of **1** has been reported. In connection with our interest in the synthesis and biological evaluation of polyunsaturated natural products,[2–6] herein an efficient first total synthesis of (all-*Z*)-1-[(2-phenylethyl)amino]octadeca-6,9,12,15-tetraen-3-one (**1**) is reported.

According to the retrosynthetic analysis depicted in Figure 1, we envisioned a Grignard reaction between polyunsaturated bromide **2a** and aldehyde **3** as the key step in the synthesis. We have used eicosapentaenoic acid (EPA) as a starting material for the synthesis of other polyunsaturated natural products.[2–4] The polyunsaturated bromide **2a** has been obtained from EPA through aldehyde **4** by Flock and Skattebøl.[7] Aldehyde **4** was obtained over four steps from EPA as reported by Holmeide and Skattebøl.[8] Reduction of **4** with $NaBH_4$ and subsequent treatment of the resulting alcohol **5** with triphenylphosphine and bromine in the presence of pyridine afforded bromide **2a**[7] as depicted in Scheme 1.

For the synthesis of aldehyde **3**, Michael addition of 2-phenyl ethylamine (**6**) to ethyl acrylate (**7**) in methanol afforded secondary amine **8** in high yield, essentially as reported for the corre-

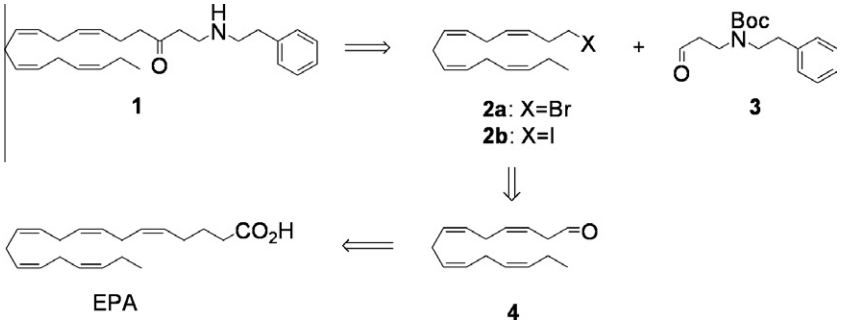

Figure 1.

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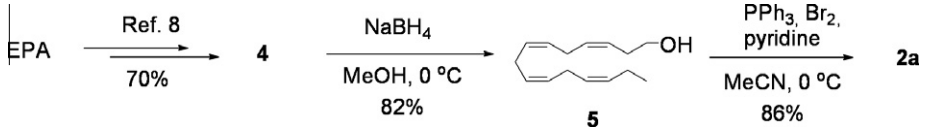
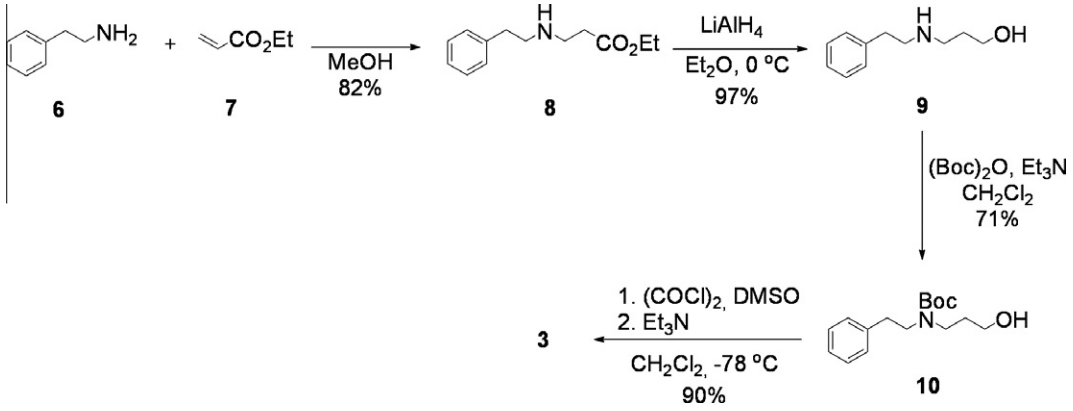


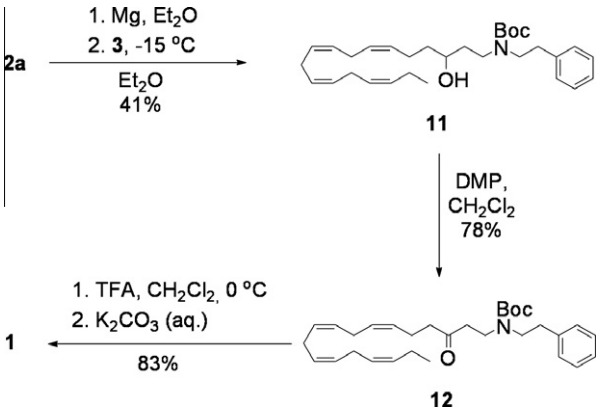
Scheme 1.



Scheme 2.

sponding methyl ester[9] (Scheme 2). An attempt to obtain amine **8** in a reductive amination reaction between 2-phenylacetaldehyde and β-alanine ethyl ester using sodium cyanoborohydride was less successful. Boc-protection of **8** followed by reduction of the resulting ester with DIBAL-H gave poor results. We, therefore, avoided the use of DIBAL-H and reduced ester **8** to alcohol **9** with lithium aluminum hydride and then protected the secondary amine in **9** as its Boc-amide. Oxidation of alcohol **10** using pyridinium chlorochromate (PCC) gave poor results, but Swern oxidation provided aldehyde **3** in a total yield of 51% over the four steps.

The Grignard reagent of bromide **2a** reacted with aldehyde **3** to give alcohol **11** in 41% yield when using one equivalent of the bromide (Scheme 3); using 1.5 equiv of the bromide increased the yield to 58%. We also tried to use the lithium compound derived from iodide **2b** prepared in 95% yield by Finkelstein reaction of bromide **2a**. The metal-halogen exchange on **2b** was performed using two equivalents of *t*-BuLi in diethyl ether.[10] However, significant isomerization of the double bonds in **11** was observed under these conditions. Alcohol **11** was oxidized with Dess–Martin periodinane (DMP) to afford ketone **12** in 78% yield. Finally, removal of the Boc-group with trifluoroacetic acid (TFA) in dichloromethane followed by aqueous basic work-up provided the polyunsaturated amino ketone **1** in 83% yield. The spectral data were in agreement with those published.[1,11]



Scheme 3.

In conclusion, the polyunsaturated amino ketone **1** was obtained in 13% yield over nine steps from EPA. The particular advantage of our method is the conservation of the all-*Z*-configuration of the methylene-interrupted double bonds. Biological evaluation of this polyunsaturated amino ketone is in progress and will be reported elsewhere.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.089.

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11. *Spectroscopic data of* **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 2H), 7.21 (m, 3H), 5.47–5.28 (m, 8H), 2.92–2.76 (m, 12H), 2.61 (t, J = 6.4 Hz, 2H), 2.48 (m, 2H), 2.39–2.29 (m, 2H), 2.15–2.03 (m, 2H), 1.60 (br s, 1H, NH), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.68 (q), 139.98 (q), 132.04 (CH), 129.04 (CH), 128.69 (2 × CH), 128.61 (CH), 128.47 (2 × CH), 128.33 (CH), 128.26 (CH), 128.06 (CH), 127.87 (CH), 127.05 (CH), 126.17 (CH), 51.39 (CH_2), 44.22 (CH_2), 43.00 (CH_2), 42.77 (CH_2), 36.43 (CH_2), 25.66 (CH_2), 25.61 (CH_2), 25.58 (CH_2), 21.58 (CH_2), 20.60 (CH_2), 14.32 (CH_3). R_f = 0.32 (CH_2Cl_2/MeOH, 90:10). IR (CH_2Cl_2); ν_{max} 3322, 3054, 3014, 2966, 2933, 1711, 1454, 1422, 1265, 896, 746, 704. MS EI m/z (rel.%) 379 (3, M^+), 289 (27), 288 (100), 134 (14), 105 (28). HRMS (EI) $C_{26}H_{37}NO$ requires 379.2875, found 379.2865.