ORGANIC LETTERS

2009
Vol. 11, No. 3
587−588

First Total Synthesis of a Polyunsaturated Chromone Metabolite Isolated from the Brown Algae *Zonaria tournefortii*

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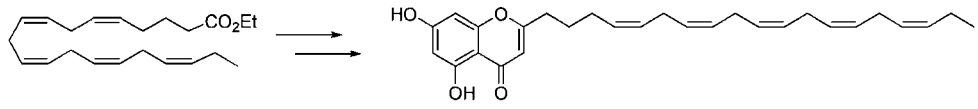
Received November 14, 2008

ABSTRACT



all-(*Z*)-5,7-Dihydroxy-2-(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-nonadecapentaenyl)chromone (**1**)

Starting from the ethyl ester of eicosapentaenoic acid, the first total synthesis of the marine natural product *all*-(*Z*)-5,7-dihydroxy-2-(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-nonadecapentaenyl)chromone has been achieved in six steps and in 14% overall yield.

Marine organisms have proven to be a rich source of biologically interesting secondary metabolites.[1,2] In 1982, Plattelli and Tringali reported the isolation and structural elucidation of *all*-(*Z*)-5,7-dihydroxy-2-(4*Z*,7*Z*,10*Z*,13*Z*,16*Z*-nonadecapentaenyl)chromone (**1**) from the pacific brown algae *Zonaria tournefortii*.[3] This natural product has also been isolated recently from two other *Zonaria* species.[4] Compound **1** contains the same number of methylene interrupted cis double bonds as those present in eicosapentaenoic acid (**2a**, EPA). To the best of our knowledge, no total synthesis or biological data of this polyunsaturated natural product have been reported. As part of our ongoing efforts on the synthesis and biological evaluation of polyunsaturated natural products,[5] we report herein a stereoselective and efficient synthesis of **1** from the ethyl ester of EPA (Figure 1).

Our total synthesis of **1** started with the preparation of aldehyde **3** in 97% yield as previously described.[6] Aldehyde **3** was transformed to the terminal alkyne **4** in a Colvin rearrangement[7] in 58% yield. Alternatively, compound **4** was obtained by using the Corey−Fuchs reaction[8] in 52% yield. To the anion of **4** at −78 °C, obtained after reaction with *n*-butyllithium, a THF solution of 2,4,6-trihydroxybenzaldehyde (**5a**) was added. Unfortunately, the desired secondary alcohol **6a** was not obtained, even after several attempts with either 3, 4, or 6 equiv of the anion of **4**. On the other hand, when a THF solution of commercially available 2,4,6-trimethoxybenzaldehyde (**5b**) was added to the anion of **4** at −78 °C, the secondary alcohol **6b** was obtained in 58% yield.

Oxidation of **6b** with activated MnO_2[9] yielded ketone **7b** in 96% yield. We envisioned that deprotection of **7b**, followed by an intramolecular Michael addition, would yield

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(7) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Chem. Commun.* **1973**, 151.
(8) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
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10.1021/ol802635a CCC: $40.75
Published on Web 12/23/2008

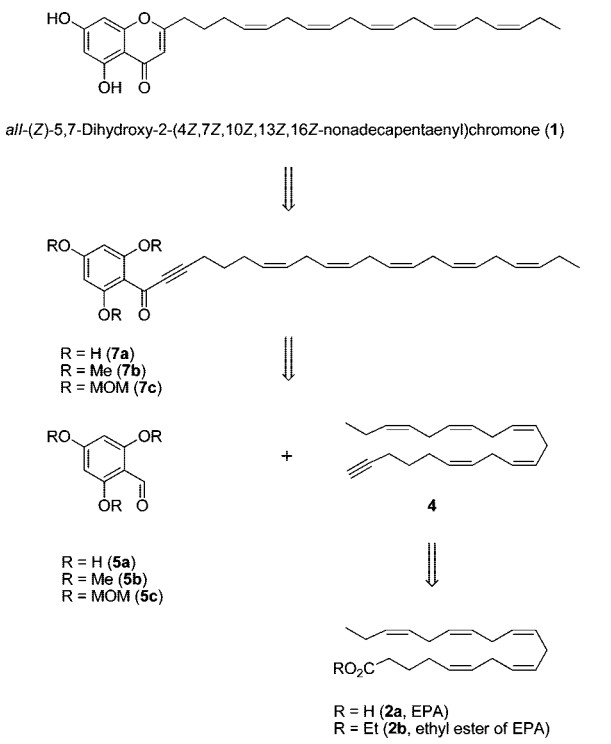

Figure 1. Chromone **1** and retrosynthetic analysis.

the natural product **1**. However, decomposition of the starting material associated with formation of polymeric material was observed with most common deprotection methods.[10] We then prepared the known 2,4,6-tris(methoxymethoxy)benzaldehyde **5c** according to a literature procedure.[11] Addition of aldehyde **5c** in THF to the anion of **4** at −78 °C yielded the secondary alcohol **6c** in 60% yield. Oxidiation of **6c** with MnO_2 yielded MOM-protected ketone **7c** in 88% yield. Mild deprotection of **7c** with HCl in EtOH at ambient temperature, followed by intramolecular Michael addition under lenient basic conditions (K_2CO_3, acetone), afforded the natural product **1** in 49% yield for the latter two steps (Scheme 1). All spectral data were in agreement with those previously reported.[3,4]

In conclusion, we have reported the first total synthesis of the naturally occurring chromone derivative **1** in six steps

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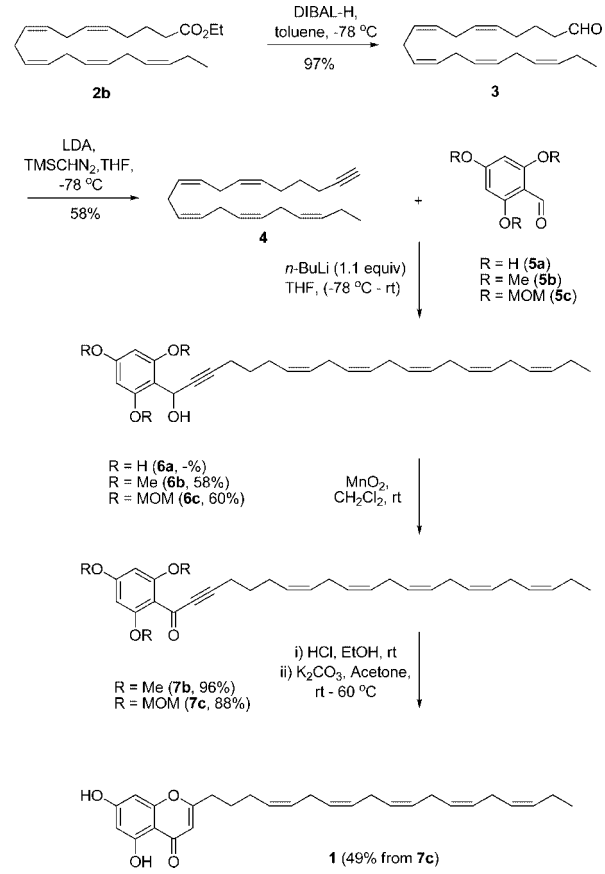
(11) Graybill, T. L.; Casillas, E. G.; Pal, K.; Townsend, C. A. *J. Am. Chem. Soc.* **1999**, *121*, 7729.

Scheme 1. Synthesis of Chromone **1**



from 2,4,6-trihydroxybenzaldehyde and ethyl ester of eicosapentaenoic acid with an overall 14% yield. The synthesis confirmed the assigned structure of **1** and provided sufficient material for biological testing. These efforts will be reported in due course.

Acknowledgment. Financial support to H.F.A. from the University of Oslo (The Quota Scheme) is gratefully acknowledged. Helpful discussions with Professor Lars Skattebøl, Department of Chemistry, University of Oslo, are gratefully acknowledged.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802635A