

Total Synthesis of Methyl 14-Hydroxy-(all-*cis*)-5,8,11-Tetradecatrienoate: A Useful Intermediate For the Synthesis of Arachidonic Acid Analogues.

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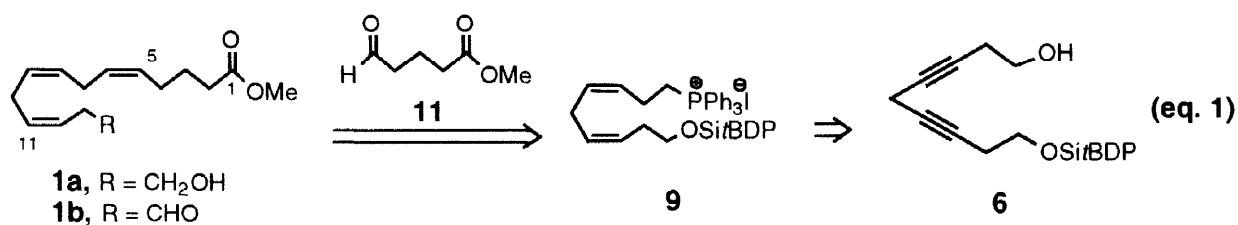
Abstract: The first total synthesis of methyl 14-hydroxy-(all-*cis*)-5,8,11-tetradecatrienoate (**1a**) was accomplished in 11 steps with an overall yield of 14%. Major sequences involve Cu(I) catalyzed propargylic substitution of propargyl bromide **5** by 3-buten-1-ol, followed by partial reduction of the diyne **6** to the *cis,cis*-diene **7**, and Wittig reaction of the phosphonium iodide **9** with aldehyde **11** to the all-*cis* skipped triene **10**.

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Anandamide (AN) is an endogenous ligand which binds to the cannabinoid receptor (CB₁) in the brain.¹ It is an arachidonic acid derivative, namely *N*-2-hydroxyethyl arachidonamide. In vivo studies have shown that AN mimics the biological activities of Δ⁹-tetrahydrocannabinol (THC), the active constituent of marihuana, but with some differences.² AN has a faster onset and shorter duration of action, and is less potent than Δ⁹-THC. As a part of our ongoing study of the structure-activity relationships (SAR) in the AN series, we have synthesized several analogues which are more potent than AN in both binding affinity and pharmacological tests.³ In the syntheses of these analogues, the alcohol, methyl 14-hydroxy-(all-*cis*)-5,8,11-tetradecatrienoate (**1a**), and the corresponding aldehyde **1b**, which is unstable, were key intermediates,^{3,4} and although procedures have been reported for their synthesis from arachidonic acid,^{3,4} we wish to report their total synthesis. This flexible and convergent synthetic procedure not only allows us to prepare more readily larger amounts of the above mentioned AN analogues for further pharmacological and behavioral studies, but also allows for the syntheses of analogues unattainable when starting from arachidonic acid. It is also noteworthy that both **1a** and **1b** have been used as key intermediates in the syntheses of several other arachidonic acid analogues not mentioned above.⁴

Our retrosynthetic strategy (eq. 1) involves building up the C₆-C₁₄ section of the molecule through 1,4-diyne **6**, followed by partial reduction of the diyne to the *cis,cis*-diene. Wittig reaction of the derived

phosphonium iodide **9** with aldehyde **11** would generate the *cis* C₅-C₆ double bond of the target molecule **1**.

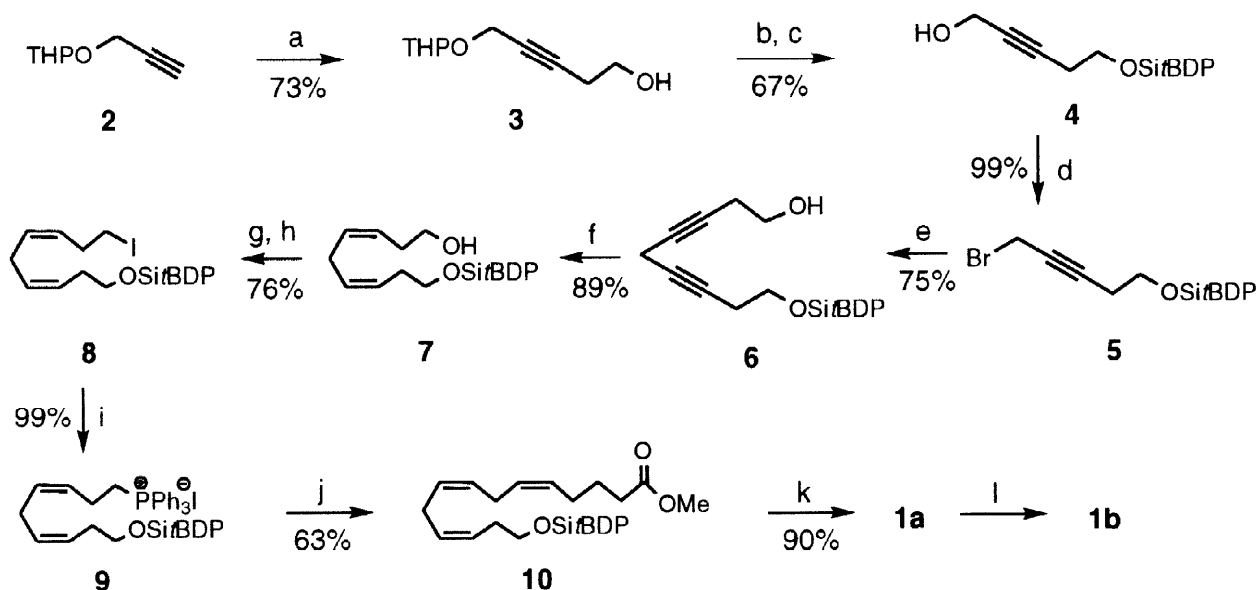


The synthesis of **1a** and **1b** was accomplished as follows (scheme 1). Commercially available tetrahydro-2-(2-propynyloxy)-2*H*-pyran (**2**) was alkylated with ethylene oxide to give mono protected diol **3**.⁵ Protection of the alcohol **3** with a *t*-butyldiphenylsilyl group followed by deprotection of the THP ether with Dowex 50 × 8-100 ion exchange resin in methanol provided propargyl alcohol **4**. Bromination of **4** with triphenylphosphine and carbon tetrabromide gave propargylic bromide **5** quantitatively,⁶ which with 3-butyne-1-ol in the presence of copper(I) iodide, sodium carbonate and tetra-*n*-butylammonium chloride in DMF led to the skipped diyne **6**⁷ in 75% yield directly without the protection of the alcohol.^{8,9} Partial reduction of the triple bonds over the "nickel boride" catalyst¹⁰ provided *cis* skipped diene **7**. The terminal alcohol of **7** was converted to the iodide **8** via the mesylate, and then converted to the phosphonium salt **9** quantitatively. Wittig reaction of the corresponding ylide of **9** with 4-carbomethoxybutyraldehyde¹¹ (**11**) furnished all *cis* skipped triene **10**.¹² Fluoride deprotection of **10** afforded alcohol **1a**¹³ (overall yield 14% for 11 steps), which was identical in all respects (¹H and ¹³C NMR, TLC, mass spectra, elemental analysis) to the sample prepared from arachidonic acid via the unstable aldehyde **1b** by borohydride reduction.³ Oxidation of alcohol **1a** with MnO₂ gave the aldehyde **1b**.

In summary, the total synthesis of the key intermediate **1a** provides an efficient and economical route to various biologically active compounds.

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Scheme 1



(a) *n*-BuLi, THF, -10 °C; ethylene oxide; (b) *t*-BDPSiCl, imidazole, DMF, rt; (c) Dowex-MeOH, rt; (d) CBr₄, Ph₃P, CH₂Cl₂, 0 °C; (e) CuI, *n*-Bu₄Ni, Na₂CO₃, DMF, 3-butyn-1-ol, rt; (f) 2Ni(OAc)₂-NaBH₄, H₂, rt; (g) MsCl, Et₃N, CH₂Cl₂, rt; (h) NaI, acetone, reflux; (i) Ph₃P, MeCN, reflux; (j) *n*-BuLi, HMPA, THF, -78 °C; 11; (k) *n*-Bu₄NF-THF, AcOH, rt; (l) MnO₂, ether, rt.

Reference and Notes

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5. Satisfactory spectral data were obtained for all new compounds using chromatographically homogeneous samples. NMR data were recorded at 100 MHz in CDCl₃. Chemical shifts are reported in δ and coupling constants in Hz. Data for **3**: ¹H NMR 4.80 (m, 1H), 4.26 (dt, 2H, *J* = 2.1, 2.1), 3.88-3.45 (m, 4H), 2.51 (tt, 2H, *J* = 6.2, 2.1), 1.92-1.45 (m, 7H). ¹³C NMR 96.7, 83.2, 77.3, 61.8, 60.6, 54.5, 30.0, 25.1, 22.9, 18.8.
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 7. Data for **6**: ¹H NMR 7.74-7.62 (m, 4H), 7.43-7.34 (m, 6), 3.75 (t, 2H, *J* = 7.0), 3.63 (t, 2H, *J* = 6.3), 3.09 (tt, 2H, *J* = 2.4, 2.4), 2.50-2.31 (m, 4H), 2.28 (br s, 1H, OH), 1.06 (s, 9H). ¹³C NMR 135.4 (4C), 133.5 (2C), 129.5 (2C), 127.6 (4C), 77.5, 76.9, 76.3, 75.3, 62.4, 60.9, 26.7 (3C), 22.9, 22.7, 19.1, 9.6.
 8. Attempts to prepare **6** from the 1,4-diyne, HC≡CCH₂C≡CCH₂CH₂OSi^tBDP, by treatment with ethylene oxide failed under a variety of conditions presumably due to the acidity of the doubly propargylic protons. For the unstability of the 1,4-diyne unit, see references (a) Gensler, W. J.; Casella, J. Jr. *J. Am. Chem. Soc.* **1958**, *80*, 1376. (b) Taniguchi, H.; Mathai, I. M.; Miller, S. I. *Tetrahedron*, **1966**, *22*, 867.
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 12. Data for **10**: ¹H NMR 7.73-7.61 (m, 4H), 7.46-7.35 (m, 6), 5.47-5.27 (m, 6H), 3.67 (t, 2H, *J* = 6.8), 3.66 (s, 3H), 2.77-2.71 (m, 4H), 2.39-2.00 (m, 6H), 1.76-1.62 (m, 2H), 1.05 (s, 9H).
 13. Data for **1a**: ¹H NMR 5.51-5.27 (m, 6H), 3.67 (s, 3H), 3.67 (br t, 2H, *J* = 6 Hz), 2.91-2.75 (m, 4H), 2.46-1.98 (m, 6H), 1.85-1.54 (m, 2H), 1.41 (br s, 1H, OH). ¹³C NMR 174.2, 131.0, 128.9 (2C), 128.3, 127.9, 125.6, 62.2, 51.5, 33.4, 30.9, 26.5, 25.7, 25.6, 24.7. Anal. Calcd for C₁₅H₂₄O₃: C, 71.39; H, 9.59. Found: C, 71.16; H, 9.82. HRMS Calcd for C₁₅H₂₅O₃ (M+1) 253.1804. Found 253.1822.