Pergamon

Tetrahedron Letters 39 (1998) 771–774

TETRAHEDRON LETTERS

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

Luning Han and Raj K. Razdan*

Organix, Inc., 65 Cummings Park, Woburn, Massachusetts 01801

Received 30 September 1997; revised 4 November 1997; accepted 5 November 1997

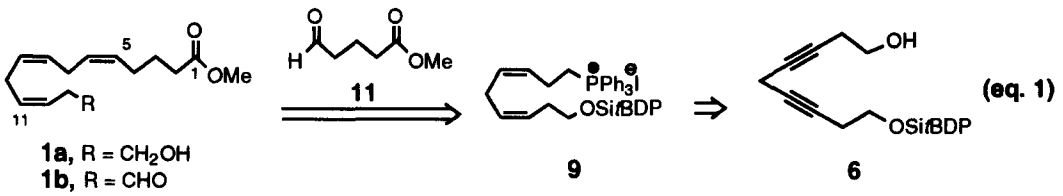
***Abstract:*** *The first total synthesis of methyl 14-hydroxy-(all-cis)-5,8,11-tetradecatrienoate (**1a**) was accomplished in 11 steps with an overall yield of 14%. Major sequences involve Cu(I) catalyzed propargylic substitution of propargyl bromide **5** by 3-butyn-1-ol, followed by partial reduction 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**.*


Anandamide (AN) is an endogenous ligand which binds to the cannabinoid receptor ($CB_1$) 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 acivities of $\Delta^9$-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 $\Delta^9$-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 $C_6$-$C_{14}$ 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

0040-4039/98/$19.00 
*PII:* S0040-4039(97)10607-4

phosphonium iodide **9** with aldehyde **11** would generate the *cis* $C_5$-$C_6$ double bond of the target molecule **1**.




**1a**, R = $CH_2OH$
**1b**, R = CHO

**9**

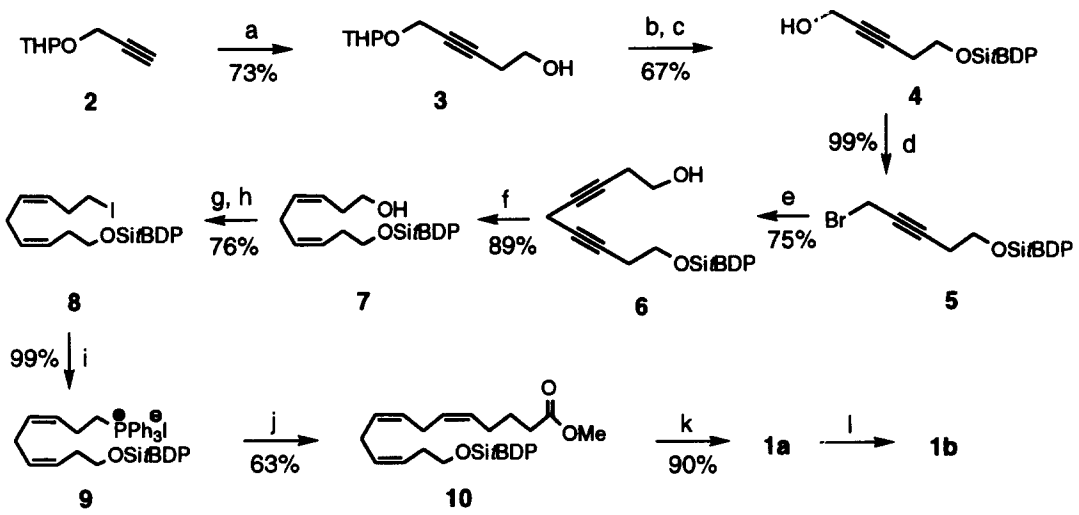
**6**

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-butyn-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" catalyst[10] 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-carbomethoxybutyraldehyde[11] (**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 $^{13}C$ 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 $MnO_2$ 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.

**Acknowlegment:** This work was supported by NIDA grants DA 09789 and 08904. We thank Dr. Peter Crocker for valuable suggestions.

**Scheme 1**




(a) *n*-BuLi, THF, -10 °C; ethylene oxide; (b) *t*-BDPSiCl, imidazole, DMF, rt; (c) Dowex-MeOH, rt; (d) $CBr_4$, $Ph_3P$, $CH_2Cl_2$, 0 °C; (e) CuI, *n*-$Bu_4NI$, $Na_2CO_3$, DMF, 3-butyn-1-ol, rt; (f) $2Ni(OAc)_2$-$NaBH_4$, $H_2$, rt; (g) MsCl, $Et_3N$, $CH_2Cl_2$, rt; (h) NaI, acetone, reflux; (i) $Ph_3P$, MeCN, reflux; (j) *n*-BuLi, HMPA, THF, -78 °C; **11**; (k) *n*-$Bu_4NF$-THF, AcOH, rt; (l) $MnO_2$, ether, rt.

## Reference and Notes


1. Devane, W. A.; Hannus, L.; Breuer, A.; Pertwec, R. G.; Stevenson, L. A.; Griffin, G.; Gibson, D.; Mandelbaum, A.; Etinger, A.; Mechoulam, R. *Science* **1992**, *258*, 1946.
2. Smith, P. B.; Compton, D. R.; Welch, S. P.; Razdan, R. K. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 219 and references cited therein.
3. Ryan, W. J.; Banner, W. K.; Wiley, J. L.; Martin, B. R.; Razdan, R. K. *J. Med. Chem.* in press.
4. (a) Manna, S.; Falck, J. R.; Chacos, N.; Capdevila, J. *Tetrahedron Lett.* **1983**, *24*, 33. (b) Corey, E. J.; Iguchi, S.; Albright, J. O.; De, B. *Tetrahedron Lett.* **1983**, *24*, 37. (c) Falck, J. R.; Sun, L.; Blair, I.; Dishman, E.; Martin, M. V.; Waxman, D. J.; Guengerich, F. P.; Capdevila, J. H. *J. Biol. Chem.* **1990**, *265*, 10244. (d) Falck, J. R.; Sun, L.; Lee, S-G.; Heckmann, B.; Mioskowski, C.; Karara, A.; Capdevila, J. H. *Tetrahedron Lett.* **1992**, *33*, 4893. (e) Heckmann, B.; Mioskowski, C.; Sun, L.; Falck, J. R.; Wei, S.; Capdevila, J. H. *Tetrahedron Lett.* **1996**, *37*, 1425. (f) Seltzman, H.; Fleming, D. N.; Thomas, B. F.; Gilliam, A. F.; McCalliom, D. S.; Pertwec, R. G.; Compton, D. R.;

Martin, B. R. *J. Med. Chem.* in press.

5. Satisfactory spectral data were obtained for all new compounds using chromatographically homogeneous samples. NMR data were recorded at 100 MHz in $CDCl_3$. Chemical shifts are reported in δ and coupling constants in Hz. Data for **3**: $^1$H 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). $^{13}$C NMR 96.7, 83.2, 77.3, 61.8, 60.6, 54.5, 30.0, 25.1, 22.9, 18.8.
6. Hooz, J.; Silani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.
7. Data for **6**: $^1$H 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). $^{13}$C 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, $HC{\equiv}CCH_2C{\equiv}CCH_2CH_2OSi$*t*BDP, 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.
9. Jeffery, T.; Gueugnot, S.; Linstrumelle, G. *Tetrahedron Lett.* **1992**, *33*, 5757.
10. Brown, H. C.; Brown, C. A. *J. Am. Chem. Soc.* **1963**, *85*, 1005.
11. Labelle, M.; Falgueyret, J. P.; Riendeau, D.; Rokach, J. *Tetrahedron* **1990**, *46*, 6301.
12 Data for **10**: $^1$H 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**: $^1$H 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). $^{13}$C 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 $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.16; H, 9.82. HRMS Calcd for $C_{15}H_{25}O_3$ (M+1) 253.1804. Found 253.1822.