# A NEW APPROACH TO (±)-LEUKOTRIENE A$_4$ METHYL ESTER

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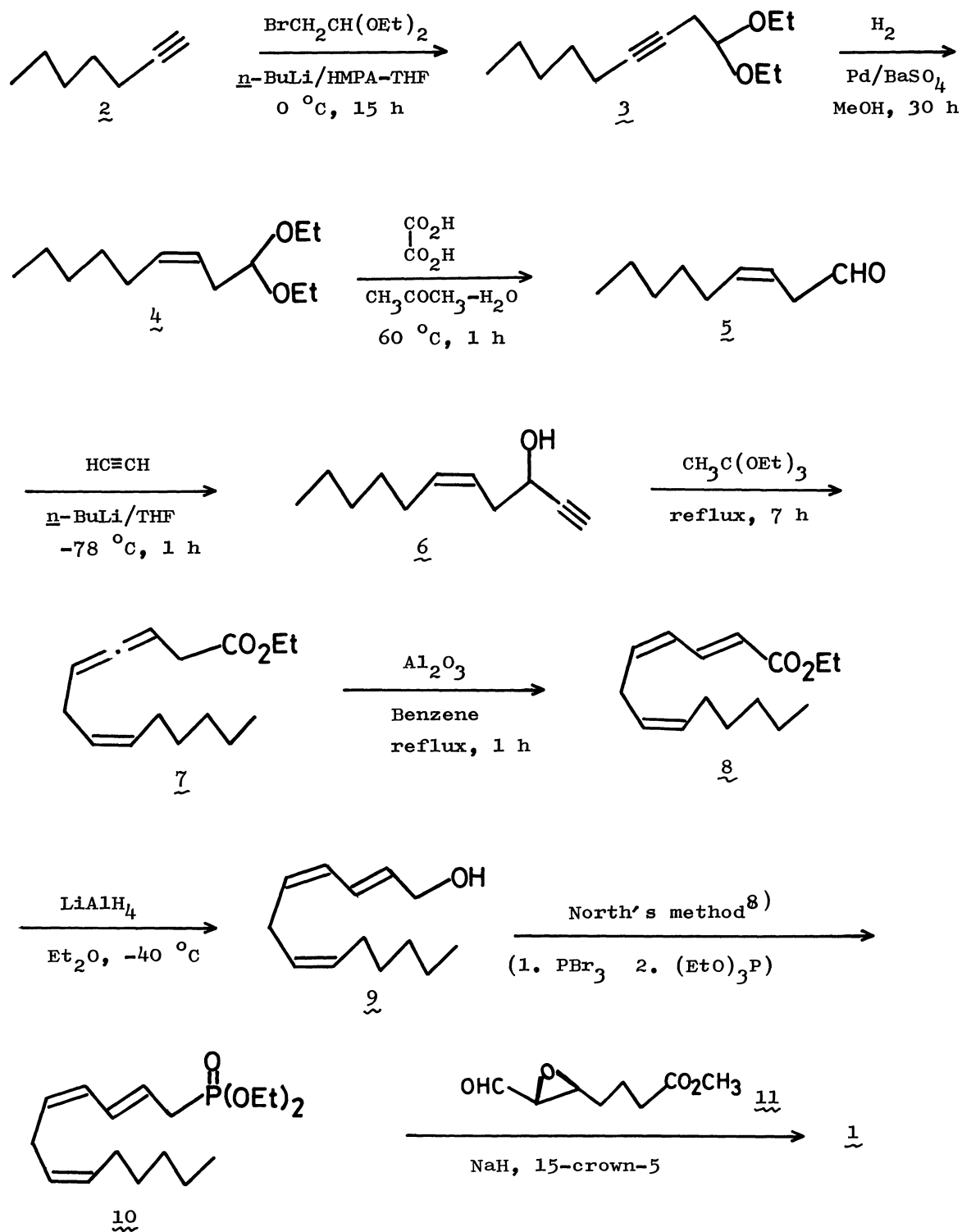
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A stereoselective synthesis of (2E,4Z,7Z)-2,4,7-tridecatrienol, a key intermediate in the synthesis of leukotriene A$_4$ methyl ester, is established via alumina-promoted rearrangement of ethyl (7Z)-3,4,7-tridecatrienoate to ethyl (2E,4Z,7Z)-2,4,7-tridecatrienoate as a key step.

The slow-reacting substance of anaphylaxis (SRS-A) is a highly spasmogenic material and possibly plays an important role in asthma and other diseases of the respiratory system.[1] Since its first total synthesis established by Corey, Samuelsson, and their groups,[2] many syntheses of leukotriene A$_4$ methyl ester (1), the precursor of SRS-A, have been reported.[3]

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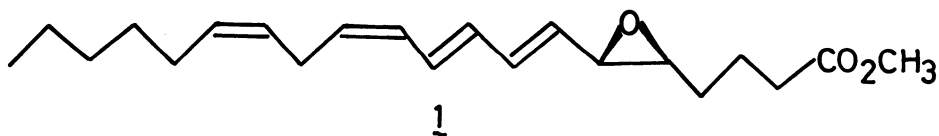
Recently we reported a highly stereoselective rearrangement of β-allenic esters to (2E,4Z)-dienoates promoted with alumina.[4] As a part of its application to the syntheses of natural products,[5] we attempted the synthesis of 1 and describe here a new route to 1 as shown in Scheme 1.

Ethyl (7Z)-3,4,7-tridecatrienoate (7), a key intermediate of the present synthesis, was prepared in 5 steps from 1-heptyne. Commercially available 1-heptyne (2) was allowed to react with bromoacetaldehyde diethyl acetal by using n-butyllithium as a base [THF-HMPA, 0 °C (4 h), 27 °C (40 h)], giving 3-nonynal diethyl acetal (3)[6] in 53% yield.[7] Palladium-catalyzed hydrogenation of 3 in methanol for 30 h afforded stereoselectively (3Z)-3-nonenal diethyl acetal (4) in 83% yield, which was subsequently hydrolyzed with oxalic acid (acetone-H$_2$O, 60 °C, 1 h) to give (3Z)-3-nonenal (5) in 93% yield. Ethynylation of 5 with lithium acetylide at -78 °C (THF, 1 h) afforded (5Z)-5-undecen-1-yn-3-ol (6)[6] in 62% yield. Orthoester-Claisen rearrangement of 6 (7 equiv. of CH$_3$C(OEt)$_3$, reflux, 7 h) yielded β-allenic ester 7[6] in 69% yield. Alumina-promoted rearrangement[4] of 7 to ethyl (2E,4Z,7Z)-2,4,7-tridecatrienoate (8)[6] was carried out under various conditions. Treatment of 7 with 5 equiv. of alumina (benzene, reflux, 3 h) gave

2 →[BrCH$_2$CH(OEt)$_2$ / n-BuLi/HMPA-THF / 0 °C, 15 h]→ **3** →[H$_2$ / Pd/BaSO$_4$ / MeOH, 30 h]→

4 →[CO$_2$H–CO$_2$H / CH$_3$COCH$_3$–H$_2$O / 60 °C, 1 h]→ **5**

→[HC≡CH / n-BuLi/THF / -78 °C, 1 h]→ **6** →[CH$_3$C(OEt)$_3$ / reflux, 7 h]→

7 →[Al$_2$O$_3$ / Benzene reflux, 1 h]→ **8**

→[LiAlH$_4$ / Et$_2$O, -40 °C]→ **9** →[North's method[8] / (1. PBr$_3$ 2. (EtO)$_3$P)]→

10   →[OHC—(epoxide)—CO$_2$CH$_3$ **11** / NaH, 15-crown-5]→ **1**

Scheme 1.

an undesirable product, 3,5,7-tridecatrienoate (12)[6] in 76% yield, of which the

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stereochemistry was not clarified. However, treatment of 7 with 2 equiv. of alumina (benzene, reflux, 1 h) yielded a mixture of the desired product 8, the starting material 7, and 12 (47 : 15 : 32 by HPLC). Pure 8 was isolated in 38% yield (56% yield from the consumed 7) by preparative HPLC and reduced with LiAlH$_4$ (Et$_2$O, -40 °C, 1.5 h) to afford (2E,4Z,7Z)-2,4,7-tridecatrienol (9) in 58% yield along with unidentified products, which were supposed to be the stereoisomers. ^{1}H NMR data (100 MHz, in CDCl$_3$) of 9 purified by preparative HPLC were identical with those of the authentic sample.[8]

The synthesis of 1 by the stereospecific reaction of the phosphonate 10 derived from 9 with the known epoxyaldehyde 11[9] has been established by North et al.[8] Consequently, a sequence of reactions described above presents a formal synthesis of (±)-leukotriene A$_4$ methyl ester (1).

References

1) R. P. Orange and K. F. Austen, Adv. Immunol., 10, 105 (1969).

2) E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, and S. Hammarstrom, J. Am. Chem. Soc., 102, 1436 (1980).

3) For example, see: S. Hashimoto and M. Toda, Yuki Gosei Kagaku Kyokai Shi, 41, 221 (1983); R. H. Green and P. F. Lambeth, Tetrahedron, 39, 1687 (1983). Literatures are cited therein.

4) S. Tsuboi, T. Masuda, and A. Takeda, J. Org. Chem., 47, 4478 (1982).

5) Previous paper: S. Tsuboi, T. Masuda, and A. Takeda, Bull. Chem. Soc. Jpn., in press.

6) Spectral and analytical data for the selected compounds are as follows.
   3: IR (neat) 2225 (C≡C), 1380, 1350, 1130, 1070 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.90 (3H, t, J = 5 Hz, CH$_3$), 1.15 (6H, t, J = 7 Hz, (OCH$_2$CH$_3$)$_2$), 1.40 (6H, m, (CH$_2$)$_3$), 2.10 (2H, m, C≡CCH$_2$C$_4$H$_9$), 2.32 (2H, m, CH$_2$CH(OEt)$_2$), 3.50 (4H, m, (OCH$_2$CH$_3$)$_2$), 4.50 (1H, t, J = 6 Hz, CH(OEt)$_2$). Found: C, 73.23; H, 11.35%. Calcd for C$_{13}$H$_{24}$O$_2$: C, 73.54; H, 11.39%.
   4: IR (neat) 1365, 1340, 1120, 1055 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.90 (3H, m, CH$_3$), 1.20 (6H, t, J = 7 Hz, (OCH$_2$CH$_3$)$_2$), 2.02 (2H, m, CH$_2$CH=), 2.38 (2H, m,

C$\underline{H}_2$CH(OEt)$_2$), 3.52 and 3.58 (4H, 2q, (OC$\underline{H}_2$CH$_3$)$_2$), 4.48 (1H, t, J = 6 Hz, C$\underline{H}$(OEt)$_2$), 5.42 (2H, m, CH=CH).

^{13}C NMR (CDCl$_3$, δ)
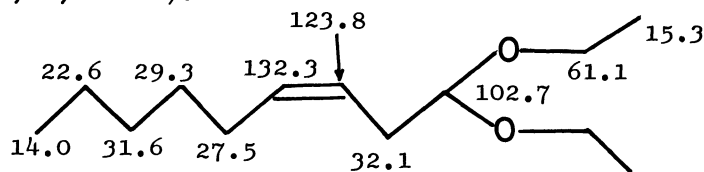
6: IR (neat) 3400, 3320 (C≡CH), 2100 (C≡C), 1050 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 0.90 (3H, t, J = 6 Hz, CH$_3$), 1.31 (6H, m, (CH$_2$)$_3$), 2.08 (4H, m, C$\underline{H}_2$CH=CHC$\underline{H}_2$), 2.38-2.68 (2H, m, C≡CH, OH), 4.37 (1H, dt, J = 2 and 6 Hz, -C$\underline{H}$OH-), 5.54 (2H, m, CH=CH). Found: C, 79.40; H, 10.84%. Calcd for C$_{11}$H$_{18}$O: C, 79.46; H, 10.91%.

7: IR (neat) 1965 (C=C=C), 1738, 1155, 1040, 860 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 0.90 (3H, t, J = 6 Hz, CH$_3$), 1.26 (3H, t, J = 7 Hz, OCH$_2$CH$_3$), 1.30 (6H, m, (CH$_2$)$_3$), 2.00 (2H, m, CH$_3$(CH$_2$)$_3$C$\underline{H}_2$), 2.70 (2H, m, =CHC$\underline{H}_2$CH=), 2.90 (2H, m, C$\underline{H}_2$CO$_2$Et), 4.05 (2H, q, J = 7 Hz, OC$\underline{H}_2$CH$_3$), 4.90-5.47 (m, C$\underline{H}$=C$\underline{H}$CH$_2$C$\underline{H}$=C=C$\underline{H}$).

^{13}C NMR (CDCl$_3$, δ)
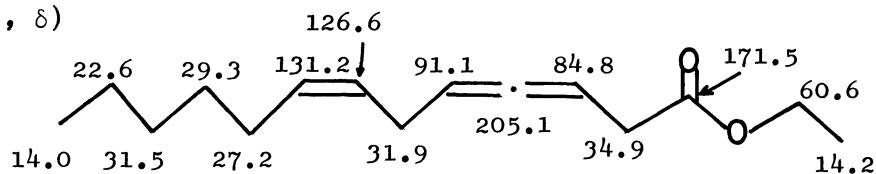
Found: C, 76.20; H, 10.16%. Calcd for C$_{15}$H$_{24}$O$_2$: C, 76.23; H, 10.24%.

8: IR (neat) 1710 (C=O), 1635, 1600, 1260, 1160, 1035 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 0.91 (3H, t, J = 5 Hz, CH$_3$), 1.28 (3H, t, J = 7 Hz, OCH$_2$C$\underline{H}_3$), 4.14 (2H, q, J = 7 Hz, OC$\underline{H}_2$CH$_3$), 5.32 (2H, m,), 5.6-6.3 (3H, m, C$\underline{H}$=C$\underline{H}$CH=C$\underline{H}$CO$_2$Et), 7.5 (1H, dd, J = 11 and 15 Hz, C$\underline{H}$=CHCO$_2$Et).

12: IR (neat) 1740, 1620, 1250, 1160, 985 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 0.93 (3H, t, CH$_3$), 1.1-1.5 (9H, m, (C$\underline{H}_2$)$_3$, OCH$_2$C$\underline{H}_3$), 2.12 (2H, m, C$\underline{H}_2$C$_4$H$_9$), 3.02 (2H, m, J = 7 Hz, C$\underline{H}_2$CO$_2$Et), 5.1-6.3 (6H, m, -(CH=CH)$_3$).

7) All yields of the present paper are isolated yields.

8) J. C. Buck, F. Ellis, and P. C. North, Tetrahedron Lett., **23**, 4161 (1982). This work was reported while the present synthesis was in progress.

9) J. G. Gleason, D. B. Bryan, and C. M. Kinzig, Tetraderon Lett., **21**, 1129 (1980).

(Received September 22, 1983)