Tetrahedron Letters, Vol. 34, No. 40, pp. 6489-6492, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

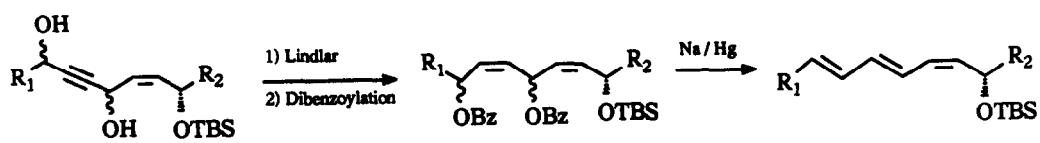
Application of Sodium Amalgam Reductive Elimination of Allylic Dibenzoates to the Total Synthesis of 5(S)-12 (R) Leukotriene B_4

Guy Solladié*, Antonio Urbano[a], Guy B. Stone

Ecole Européenne des Hautes Etudes des Industries Chimiques,
Laboratoire de Stéréochimie, associé au CNRS, 1 Rue Blaise Pascal, F-67008-Strasbourg, France.

Abstract : *A stereoselective synthesis of 5(S)-12(R) LTB_4 is described in this paper using a novel reaction, the sodium amalgam induced reductive elimination of allylic dibenzoates for the selective synthesis of the E,E,Z - triene moiety. The creation of the chiral centers was controled by a chiral sulfoxide group.*

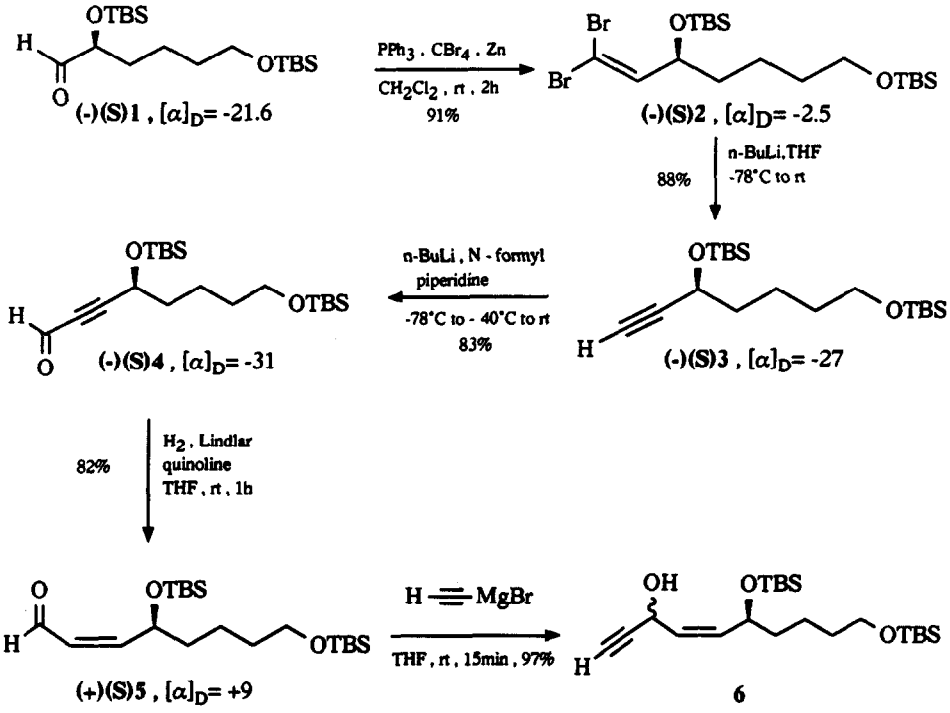
In most syntheses of LTB_4[1], the conjugated E,E,Z triene moiety was prepared by Wittig reactions, additions of vinyl cuprates, triple bond reduction or a combination of theses methods. We recently reported[2] our discovery that a conjugated E,E,Z-triene could be prepared with a stereoselectivity higher than 95% and in almost quantitative yield via Na/Hg reductive elimination of allylic dibenzoates, readily made by coupling an allylic aldehyde with a propargylic alcohol:



We report in this paper a stereoselective total synthesis of 5(S), 12(R) LTB_4 in which the conjugated triene unit is prepared using this novel reaction and the chiral centers obtained by asymmetric synthesis monitored by a chiral sulfoxide group.

The synthesis is based on the condensation of the optically active lithium acetylide of 6 to the aldehyde 7 followed by reduction of the triple bond. Protection of the alcohols as benzoate esters followed by sodium amalgam reductive elimination of the allylic dibenzoates lead to the isolation of the trienic compound 11 in 81% yield (scheme 2) with no sign of the other possible double bond isomers.

The optically active acetylenic compound 6 was prepared from the chiral aldehyde 1, which was made by asymmetric synthesis and already described[3] for the synthesis of (6E) LTB_4. Condensation of the aldehyde 1 with Ph_3P/CBr_4 gave the corresponding vinylic dibromide in 88% yield (scheme 1). Dehydrohalogenation with butyl lithium in THF lead to the propargylic alcohol 3 in 88% yield. The formylation was carried out with N-formyl piperidine in 83% yield. Finally the triple bond was reduced with Lindlar catalyst (82%) and acetylene magnesium bromide added to afford compound 6 in 97% yield.

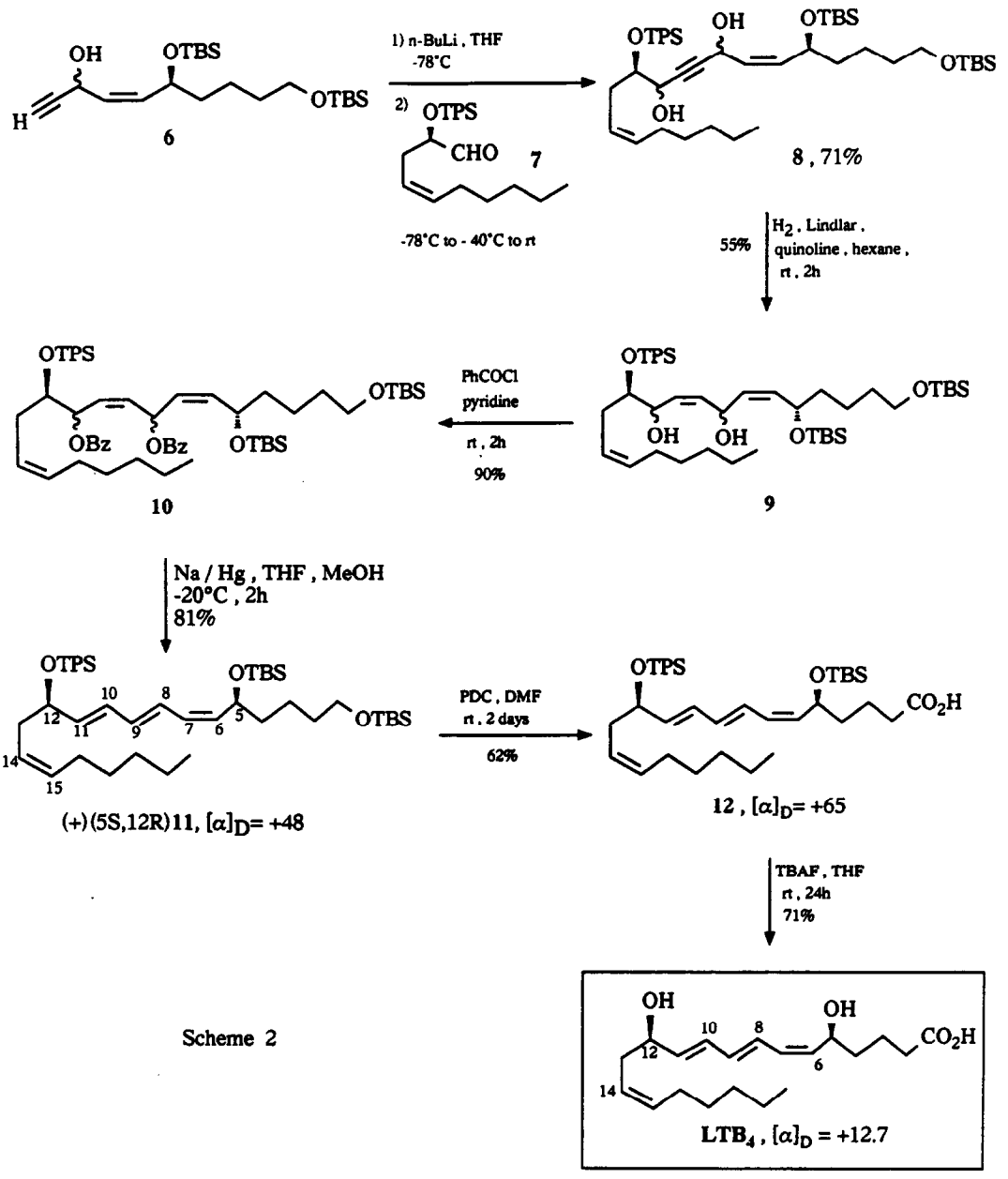


Scheme 1

The aldehyde **7** was already made by asymmetric synthesis[4] and used also in the synthesis of (6E)-LTB_4[3].

Condensation of the lithium acetylide of **6** to the aldehyde **7** afforded the diol **8** as a mixture of diastereoisomers in 71% yield. Triple bond reduction with Lindlar catalyst (55%) and diol benzoylation with benzoyl chloride in pyridine lead to the dibenzoate **10** in 90% yield. Following our recent discovery[2], the dibenzoate **10** in a 3/10 methanol/THF solution was treated[5] at -20°C with 6% sodium-amalgam[6] for 2h giving the triene **11** in 81% yield. By ^1H NMR and spin decoupling it was possible to show the Z geometry of the C_{6-7} (J=10.9Hz) and C_{14-15} (J=11Hz) double bonds and the E geometry for the C_{8-9} (J=15Hz) and C_{10-11} (J=14.7Hz) double bonds. The absence of any other isomer was confirmed by ^{13}C NMR showing only one set of 8 vinylic carbons (136.5, 135.5, 133.4, 132.1, 130.2, 127.5, 127.3 and 124.5). The primary hydroxyl group was oxidized without deprotection by using PDC in DMF at room temperature in 62% yield ; the secondary t-butyldimethylsilyloxy group did not react under these conditions. Finally deprotection with TBAF afforded LTB_4 (71% yield) showing all the characteristics[7] reported in the literature[1e,h,i,j,m].

Hence this application showed the synthetic promise of the sodium amalgam reductive elimination of allylic dibenzoates, easily made, to prepare conjugated E,E,Z-trienes in high yield and high stereoselectivity. We are currently investigating extension of this methodology towards higher polyenes as well as continuing our synthetic applications of this method.


OH
OTBS
H
OTBS
6
1) n-BuLi, THF
-78°C
2) OTPS
CHO
7
-78°C to - 40°C to rt
OTPS
OH
OTBS
OTBS
OH
8, 71%
55%
H2, Lindlar,
quinoline, hexane,
rt, 2h
OTPS
OTBS
OH
OH
OTBS
9
PhCOCl
pyridine
rt, 2h
90%
OTPS
OTBS
OBz
OBz
OTBS
10
Na / Hg, THF, MeOH
-20°C, 2h
81%
OTPS
OTBS
OTBS
12
11
10
9
8
7
6
5
14
15
(+)(5S,12R)11, [α]D= +48
PDC, DMF
rt, 2 days
62%
OTPS
OTBS
CO2H
12, [α]D= +65
TBAF, THF
rt, 24h
71%
OH
OH
CO2H
12
10
8
6
14
LTB4, [α]D = +12.7

Scheme 2

Acknowledgments : we thank CNRS and L'OREAL for financial support.

References and Notes.

a) On leave from the Universidad Autonoma of Madrid.

1) a) Corey, E.J. ; Marfat, A.; Goto, G.; Brion, F.; *J. Am. Chem. Soc.*, **1980**, *102*, 7984-85. b) Corey, E.J.; Marfat, A.; Munroe, J.; Kim, K.S.; Mopkius, P.B.; Brion, F.; *Tetrahedron Lett.* **1981**, *22*, 1077-80. c) Guindon, Y.; Zamboni, R.; Lau, C.; Rokach, J.; *Tetrahedron Lett.* **1982**, *23*, 739-42. d) Zamboni, R.; Rokach, J.; *Tetrahedron Lett.* **1982**, *23*, 2631-34. e) Mills, L.S.; North, P.C.; *Tetrahedron Lett.* **1983**, *24*, 409-10. f) Nicolaou, K.C. ; Zipkin, R.E.; Dolle, R.E.; Harris, B.D.; *J. Am. Chem. Soc.* **1984**, *106*, 3448-51. g) Han, C.K.; Di Tullio, D.; Wang, Y.F.; Sih, C.J.; *J. Org. Chem.* **1986**, *51*, 1253-58. h) Le Merrer, Y.; Gravier, C.; Languin-Micas, D.; Depezay, J.C.; *Tetrahedron Lett.* **1986**, *27*, 4161-64. i) Kobayashi, Y.; Shimazaki, T.; Sato, F.; *Tetrahedron Lett.* **1987**, *47*, 5849-52. j) Guindon, Y., Delorme, D.; Lau, C.K. ; Zamboni, R., *J. Org. Chem.* **1988**, *53*, 267-275. h) Le Merrer, Y.; Gravier, C.; Languin-Micas, D.; Depezay, J.C.; *Tetrahedron Lett.* **1986**, *27*, 4161-64. i) Kobayashi, Y.; Shimazaki, T.; Sato, F.; *Tetrahedron Lett.* **1987**, *47*, 5849-52. j) Guindon, Y.; Delorme, D.; Lau, C.K.; Zamboni, R., *J. Org. Chem.* **1988**, *53*, 267-275. h) Le Merrer, Y.; Gravier-Pelletier, C.; Micas-Languin, D.; Mestre, F.; Dureault, A.; Depezay, J.C., *J. Org. Chem.* **1989**, *54*, 2409-16. l) Avignon-Tropis, M.; Treilhou, M.; Lebreton, J.; Pougny, J.R.; Frechard-Ortuno, I.; Huyh, C. Linstrumelle, G., *Tetrahedron Lett.* **1989**, *30*, 6335-39. m) Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, F.; *J. Org. Chem.* **1990**, *55*, 5324-35. n) Avignon-Tropis, M.; Berjeaud, J.M.; Pougny, J.R.; Frechard-Ortuno, I.; Guillerm, D. Linstrumelle, G.; *J. Org. Chem.* **1992**, *57*, 651-54. O) Treilhou, M.; Fauve, A.; Pougny, J.R.; Promé, J.C.; Veschambre, H., *J. Org. Chem.* **1992**, *57*, 3203-08. p) Borer, B.C.; Taylor, R.J.K., *Synlett*, **1992**, 117-8. q) Nunn, K.; Mosset, P.; Grée, R.; Saalfrank, R.W., *J. Org. Chem.* 1992, *57*, 3359-64.

2) Solladié, G.; Stone, G.B.; Urbano, A.; Andrès, J.M., *Tetrahedron Lett.* **1993**, *34*, 2835-38.

3) Solladié, G.; Stone, G.B.; Hamdouchi, C., *Tetrahedron Lett.* **1993**, *34*, 1807-10.

4) Solladié, G.; Hamdouchi, C.; Ziani-Chérif, C., *Tetrahedron Asymmetry* **1991**, *2*, 457.

5) Dibenzoate **10** (210 mg, 0.2 mmol) in solution in a mixture THF (10 mL) - MeOH (3 mL) was treated with Na_2HPO_4 (200 mg) and cooled at -20°C. Then 6% Na/Hg (1g, 2.6 mmol, 13 equiv.) was added and stirred for 2h. The reaction mixture was diluted with ether and filtrated on silica gel. After solvent evaporation, the crude product was purified by chromatography (130 mg, 81%).

6) Fieser and Fieser, Reagents for Organic Chemistry, J. Wiley, NY **1967**, Vol. 1, p 1030.

7) $[\alpha]_D$+12.7 (c=0.3, $CDCl_3$), Lit.[1m] +13.1 (c=0.26, $CDCl_3$) and +12.6 (c=0.46, $CDCl_3$)[1g]. ^1H NMR ($CDCl_3$, 200MHz) : δ : 6.49 (dd, 1H, J=11.7 and J_{8-9}=14.0Hz, H-8), 6.27 (m, 2H, H-9 and H-10), (m, 3H, H-6, H-14, H-15), 4.60 (m, 1H, H-5), 4.22 (q, 1H, J=6.4Hz, H-12), 2.5-2.2 (m, 4H, H-2, H-13), 2.5-1.35 (m, 2H, H-16), 1.8-1.2 (m, 12H), 0.88 (t, 3H, J=6.5Hz, H-20). ^{13}C NMR ($CDCl_3$) : δ : 178.9 (C-1), 137.1, 134.8, 134.1, 132.9, 130.4, 127.7, 127.0 and 124.4 (8 vinylic C), 72.9 and 68.1 (C-5 and (C-12), 36.9, 35.6, 33.9, 31.5, 29.2, 27.3, 22.6 and 20.5 (8 aliphatic H), 14.1 (C-20).

(Received in UK 5 July 1993; accepted 5 August 1993)