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THE SYNTHESIS OF LEUKOTRIENE ANALOGUES VIA ACETYLENE CARBOCUPRATION

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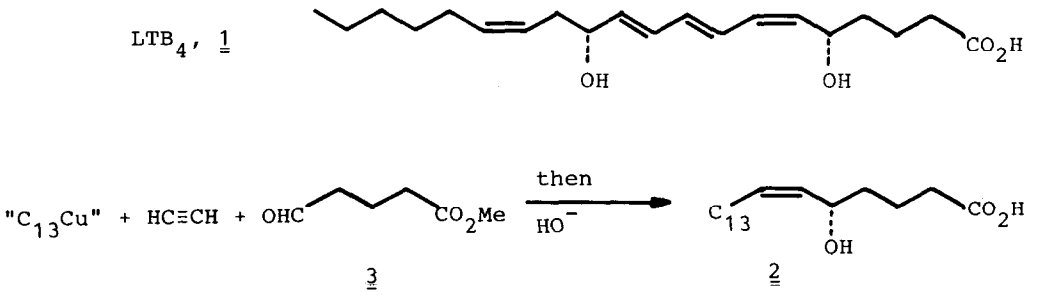
SUMMARY: A general route to simple LTB_4 analogues is reported based on acetylene carbocupration followed by trapping with methyl 5-oxopentanoate.

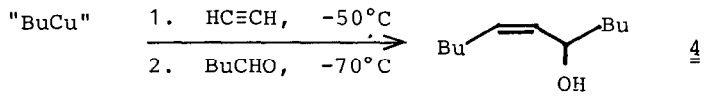
There has been a considerable amount of recent interest in hydroxylated eicosatetraenoic acids derived from arachidonic acid by lipoxygenase metabolic pathways.[1] Leukotriene B_4 (LTB_4, 1), produced by the 5-lipoxygenase pathway, has attracted particular attention because of its potent chemotactic properties and its potential role in inflammation and allergy.[2] We wanted to prepare a series of LTB_4 analogues for structure-activity studies and the first synthetic targets were analogues of general structure 2 which contain the crucial Z-allylic alcohol and terminal carboxylic acid moieties. In designing a synthetic approach to compounds 2 a short, stereospecific route was required which was compatible with wide variation in the C_{13}-chain. Acetylene carbocupration followed by trapping with methyl 5-oxopentanoate (3) seemed to meet these demands in terms of the established Z-stereoselectivity of carbocupration and its scope with respect to the organometallic component:[3]



3 2

However, there had been only two reports of aldehydes being used as trapping agents in carbocupration reactions[4,5] and so model studies were carried out to assess the viability of such an approach. A wide range of butylcopper and butylcuprate reagents were therefore treated with acetylene to product Z-hex-1-enyl organometallics which were trapped with pentanal to produce Z-undec-5-en-6-ol (4)[6,7] in varying amounts (Table). The results in the Table show that the reagents of choice for the carbocupration-aldehyde trapping procedure are the homocuprates (entry ii) and the lithium alkyl(pentynyl)cuprate 5a (entry iv).

TABLE



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	Reagent[a]	Ligands, salts	Equivalents of BuCHO	G.L.C. Yield (%)[b]	Isolated Yield (%)[b]
1.	BuCu	$LiBr.Me_2S$	1		
	BuCu	$LiBr.Me_2S.BF_3$	1	0-5	-
	BuCu[c]	$MgBr_2.Me_2S$	1		
ii	Bu_2CuLi[d]	$LiBr.Me_2S$	2	36	35
	Bu_2CuLi	$LiBr.Me_2S$	1	-	74
	Bu_2CuLi	$LiBr.Me_2S.BF_3$	2	41	37
iii	BuCu(CN)Li	-	1		
	BuCu(SPh)Li	-	1	0-5	-
	$Bu_2Cu(CN)Li_2$	-	2		
iv	BuCuMeLi	$3LiBr.Me_2S$	1	27	-
	BuCu≡CPrLi 5a	$2(Me_2N)_3P$	1	-	86

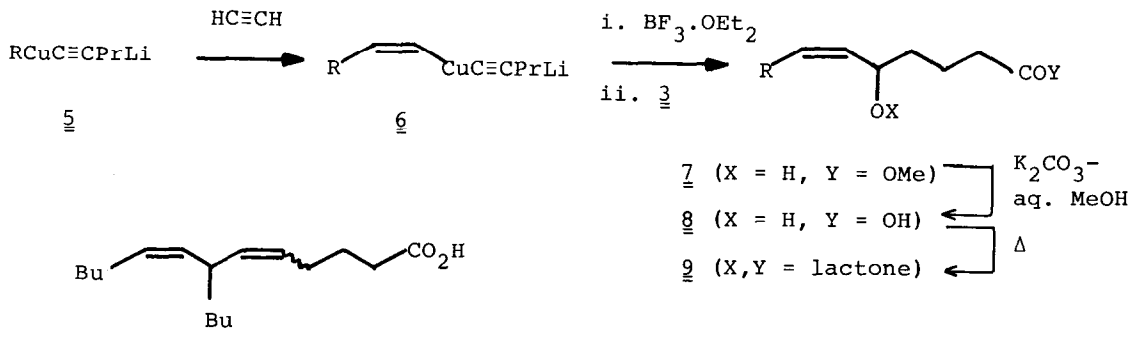
[a] Prepared in diethyl ether unless indicated otherwise. [b] Based on BuCHO. [c] Prepared in THF. [d] Use of THF in place of diethyl ether gave 16% yield.

Having established that the basic strategy was sound we turned our attention to the use of aldehyde ester 3 as a trapping agent, first with the hexenylcuprate 6a (Scheme 1). Three major products were isolated from this reaction, the expected hydroxy-ester 7a (30%) and lactone 9a (5%) together with the dienyl-acid 10 (38%). Compound 10 is presumably formed from lactone 9a and cuprate 6a by an allylic substitution reaction. Similar reactions have been reported with δ-vinyl-δ-valerolactone.[8] In accord with this proposal, treatment of lactone 9a, after isolation, with cuprate 6a produced 10 in 79% yield. Fortunately, we found that this unwanted side reaction could be completely suppressed by the addition of boron trifluoride etherate to the hexenyl cuprate 6a prior to the addition of aldehyde 3. Under these conditions ester 7a was obtained in 55% yield. Ester 7a was readily saponified to hydroxy acid 8a (90%) which was converted to lactone 9a (ca. 100%) by heating in vacuo.

The above protocol was then applied to the synthesis of LTB_4 analogues 2 (Scheme 1 & 2). Firstly, the hexahydro-LTB_4 analogue 8a was prepared starting from lithium di(tridecyl)cuprate 5b. An unusually high temperature, -20°C, was required for acetylene incororation but once formed the alkenylcuprate 6b gave the expected hydroxy ester 7b (48%) on treatment with boron trifluoride etherate followed by aldehyde 3. Saponification of 7b produced the target LTB_4 analogue 8b (90%) which readily lactonised on heating to give 10b in quantitative yield.

A similar procedure was employed for the preparation of the tetrahydro-LTB_4 analogue 14 (Scheme 2). The dienylcuprate 12 was prepared from cuprate 11 by a double carbocupration reaction[9] and then treated with aldehyde 3 in the normal manner to give hydroxy ester 13 in 48% yield. Saponification gave LTB_4 analogue 14 which was characterised as lactone 15 (41% from 3). A wide variety of LTB_4 analogues of type 2 are now accessible via this carbocuprate-aldehyde trapping procedure. The biological properties of compounds 8, 9, 10, 14 and 15 are currently being evaluated.

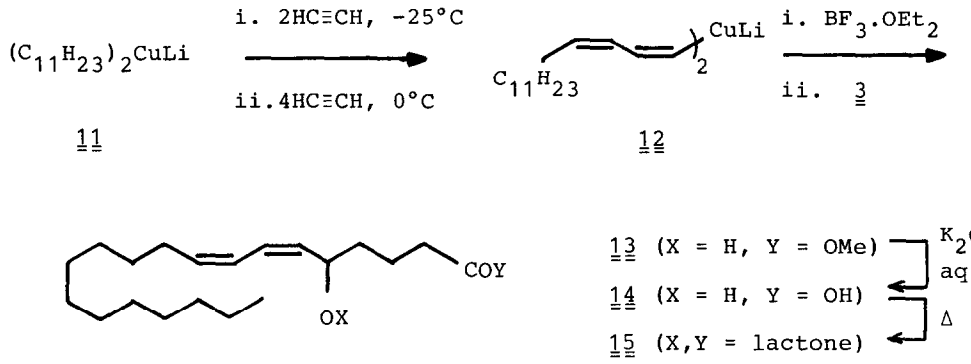
SCHEME 1 (a, R=^{n}Bu; b, R=$^nC_{13}H_{27}$)



5 6

10 (E:Z = 4:1)

SCHEME 2



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2) K. C. Nicolaou, R. E. Zipkin, R. E. Dolle and B. D. Harris, J. Amer. Chem. Soc., 1984, 106, 3548 and references therein.
3) Review: J. F. Normant and A. Alexakis, Synthesis, 1981, 841.
4) J. F. Normant, A. Alexakis and G. Cahiez, J. Organomet. Chem.,1979, 177, 293.
5) J. F. Normant, A. Alexakis and G. Cahiez, Tetrahedron, 1980, 36, 1961.
6) All new compounds gave consistent IR, ^{13}C and ^{1}H NMR spectra together with satisfactory elemental analyses or accurate mass measurements. All compounds are racemic.
7) An authentic sample of compound 4 was prepared from Z-iodohex-1-ene in 76% yield by lithiation followed by treatment with pentanal (see J. F. Normant, G. Cahiez, C. Chuit and J. Villieras, J. Organomet. Chem., 1974, 77, 269 and G. Cahiez, D. Bernard and J. F. Normant, Synthesis, 1976, 245). For comparison, E-undec-5-en-6-ol was prepared from hex-1-yne by sequential treatment with diisobutylaluminium hydride, butyllithium and pentanal (see G. Zweifel and R. B. Steele, J. Amer. Chem. Soc., 1976, 89, 2754). Samples of 4 did not contain any of the E-isomer according to ^{13}C & ^{1}H N.m.r.
8) T. Fujisawa, T. Sato, M. Kawashima, K. Naruse and K. Tamai, Tetrahedron Lett., 1982, 23, 3583.
9) A. Alexakis and J. F. Normant, Tetrahedron Lett., 1982, 23, 5151; M. Furber, R. J. K. Taylor and S. C. Burford, unpublished results.

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