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Z,Z-DIENES VIA ACETYLENE CARBOCUPRATION: SYNTHESIS OF NAVEL ORANGEWORM PHEROMONE

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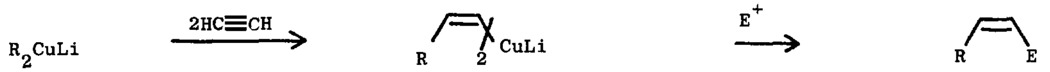
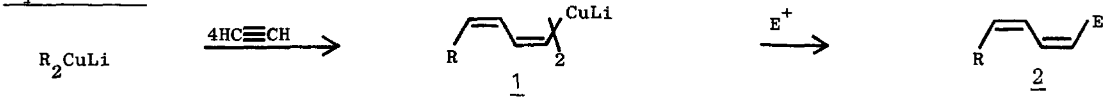
Summary: A range of conjugated Z,Z-dienes have been prepared in a stereospecific manner via acetylene carbocupration: the value of this procedure has been illustrated by an extremely short synthesis of hexadeca-11Z, 13Z-dienal a principle component of Navel Orangeworm Pheromone.

The Normant Reaction, acetylene carbocupration followed by electrophilic trapping of the resulting vinylcuprate, is an extremely versatile procedure for the synthesis of Z-disubstituted alkenes in a stereospecific manner (Equation 1).[1] In view of the number of natural products based on conjugated dienes and trienes (insect pheromones, leukotrienes, etc.) we decided to try to use acetylene carbocupration to prepare these types of compounds.[2,3,4] Initial efforts were concentrated on the synthesis of Z,Z-dienes 2 because of the potential simplicity of the procedure - organocuprate formation followed by double acetylene incorporation and electrophilic trapping of the resultant dienylcuprate (Equation 2).

Equation 1[1]

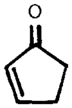
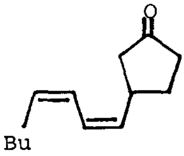
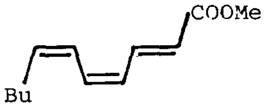
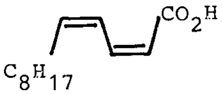


Equation 2



After we had commenced these studies, Alexakis and Normant reported that the double incorporation of acetylene into organocuprates was not a synthetically viable procedure because of a tendency for the intermediate vinylcuprates to metallate acetylene rather than undergo a second insertion reaction.[4] In contrast, we found that by carefully controlling solvent, ligands and, in particular, reaction temperature, lithium dialkylcuprates can be converted into the corresponding dienylcuprates 1 with no noticeable acetylide formation. The first two equivalents of acetylene are readily absorbed at -50°C but the reaction has to be warmed to 0°C in order to incorporate the remaining acetylene at a reasonable rate. Even at this higher temperature only partial absorption occurred and it was found necessary to bubble twice the calculated amount of acetylene through the reaction to maximise the yield of dienylcuprates 1. These cuprates can be trapped with a variety of electrophiles to give fair to good yields of the Z,Z-dienes 2 with total stereospecificity according to GLC and ^{13}C-NMR spectroscopy (Table).[5,6]

TABLE[a]

	R	E^+	Product 2	Isolated Yield[b]
(i)	Bu	CH_3I		71%[c]
(ii)	Bu	$CH_2=CHCH_2Br$		62%[c]
(iii)	Bu	$PhCH_2Br$		59%[c]
(iv)	Bu			52%[c]
(v)	Bu	HC≡C.COOMe		51%[d]
(vi)	^{t}Bu	CO_2		46%[d]
(vii)	C_8H_{17}	CO_2		48%[d]

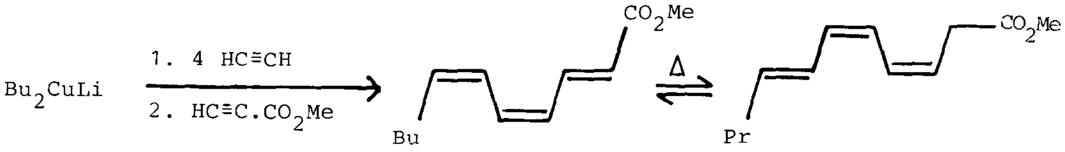
[a] See general experimental procedure for more details.

[b] Of analytically and/or spectroscopically pure material.

[c] Yield based on electophilic trapping reagents.

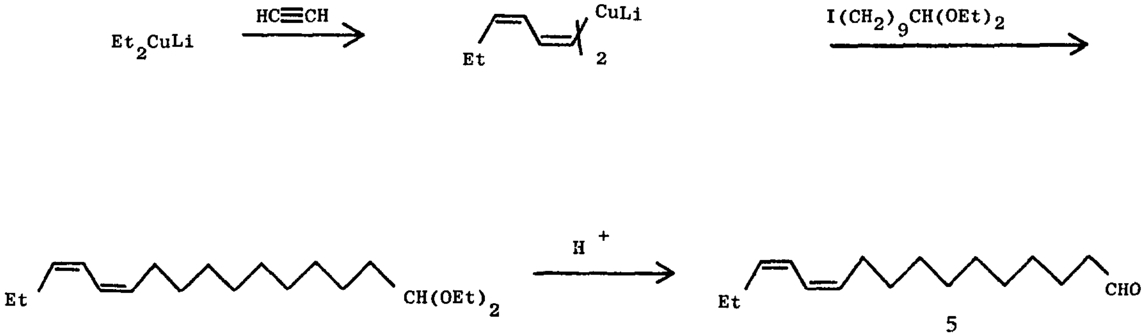
[d] Yield based on organocuprate.

The procedure in Equation 2 therefore represents an extremely useful method of preparing conjugated *Z*,*Z*-dienes and, by judicious choice of the electrophilic trapping reagent, a variety of functional groups can be introduced for subsequent elaboration. The use of methyl propiolate is particularly noteworthy in this respect as it provides a stereospecific route to the conjugated *Z*,*Z*,*E*-triene ester 3. In addition, compound 3 can be equilibrated with the isomeric diene 4 by heating at 90 °C. The resulting mixture of 3 and 4 (*ca.* 1:1) can be separated on silver nitrate impregnated silica gel:



3 4

To illustrate the value of acetylene carbocupration as a means of producing *Z*,*Z*-dienes, the reaction has been employed as the key step in an extremely short synthesis of the recently discovered Navel Orangeworm Pheromone 5[3,7,8] (Scheme 1). Treatment of lithium diethylcuprate with acetylene followed by alkylation with 10-iododecanal diethyl acetal[9] and acidic hydrolysis produced pheromone 5 in 33% overall yield (based on the alkyl iodide) after chromatography and distillation. This extremely short and relatively efficient synthesis contrasts with the existing preparations of pheromone 5 (one[7] is 11 steps long).



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Pheromone 5 is the first insect hormone containing a *Z*,*Z*-conjugated diene unit to be discovered but if, and when, others follow this methodology would appear to be ideally suited to their preparation. Other applications of the methodology described in this paper are currently being investigated.

General Experimental Procedure

Acetylene (0.25L, 11 mmol), measured using a gas burette, was passed through a stirred, colourless solution of lithium dialkylcuprate (5 mmol), prepared from a suspension of $CuBr.SMe_2$ (ex. Fluka) (5 mmol) in dry ether (35 ml) and alkyllithium (10 mmol) in hexane, at -50°C. The reaction was then stirred at -25°C for 30 min and then allowed to warm to 0°C. Acetylene (0.45L, 20 mmol) was then passed into the reaction, only partial absorption occurring. The resulting brown solution was then cooled and the trapping reagent added. [Table, entries (i)-(iii) (5 mmol), HMPA (5 mmol), -40°C; Table, entry (iv) (5 mmol), -40°C; Table, entry (v) (10 mmol), -80°C; Table, entries (vi) and (vii) (excess), HMPA (5 mmol), -40°C.] The reaction was then left to warm to 0°C over 1 h, quenched with acid, given a normal work-up and the products isolated by Kugelrohr distillation. The product from the methyl propiolate reaction (Table, entry (v)) underwent isomerisation on distillation (see text) and so crude 3 was purified by SiO_2-$AgNO_3$ chromatography.

Acknowledgements

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References

1. Review: J. F. Normant and A. Alexakis, Synthesis, 1981, 84.
2. A number of new routes to conjugated dienes have recently been reported, some of which also use organocopper chemistry. See references 3 and 4 and references therein.
3. M. Gardette, N. Jabri, A. Alexakis and J.F. Normant, Tetrahedron, 1984, 40, 2741.
4. A. Alexakis and J.F. Normant, Tetrahedron Lett., 1982, 23, 5151; 1-substituted vinylcuprates, however, were found to add smoothly to acetylene. It has also been shown that "double carbocupration" reactions can be carried out efficiently by treating organocuprates with excess 1-trimethylsilylacetylene (H. Westmijze, H. Kleijn and P. Vermeer, J. Organomet. Chem, 1984, 276, 317).
5. All new compounds gave consistent IR, ^{13}C and ^{1}H NMR spectra together with satisfactory elemental analyses.
6. Under Normant's conditions[4] (i.e. 2.19 molar equivalents of acetylene in the second step rather then 4 molar equivalents), a considerable amount of monoene was isolated along with the expected diene.
7. P. E. Sonnet and R. R. Heath, J. Chem. Ecol., 1980, 6, 221.
8. C. E. Bishop and G. W. Morrow, J. Org. Chem. 1983, 48, 657.
9. The iodoacetal was obtained in 73% overall yield from 9-bromodecanol (P. Chuit, Helv. Chim. Acta, 1926, 9, 266) via the sequence (i) pyridinium chlorochromate oxidation (ii) acetal formation using EtOH, pTSA (iii) halide displacement with NaI / acetone.

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