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ONE-STEP CONVERSION OF TERMINAL ACETYLENES INTO TERMINALLY FUNCTIONALIZED (E)-3-METHYL-2-ALKENES VIA ZIRCONIUM-CATALYZED CARBOALUMINATION. A SIMPLE AND SELECTIVE ROUTE TO TERPENOIDS[1]

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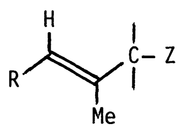
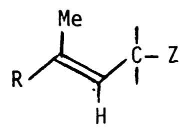
A wide variety of natural products, in particular terpenoids, are either represented by or readily obtainable from terminally functionalized (E)-2-methyl-2-alkenes (1) and/or (E)-3-methyl-2-alkenes (2).



1

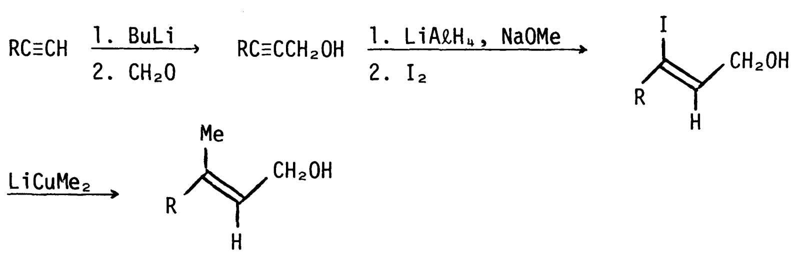


2

Z = hetero-functional group

Whereas various satisfactory methods for the synthesis of 1 are now available, there are only a very limited number of highly stereoselective routes to 2, various widely used carbonyl-olefination reactions being generally of low stereoselectivity as routes to 2.[2]

Corey and his coworkers[3] have previously developed a stereoselective method for the conversion of terminal acetylenes into (E)-3-methyl-2-alken-1-ol (3) shown in eq 1.



3

(1)

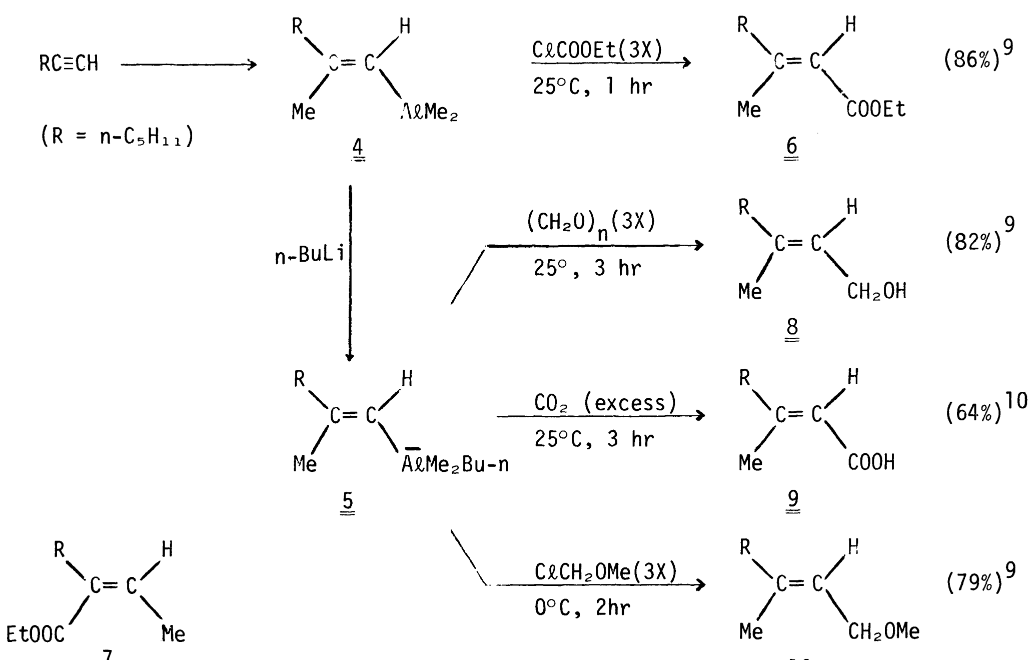
While it has been successfully applied to the syntheses of certain natural products,[3] the multi-step nature of the procedure makes it desirable to develop simpler routes to 3 and related tri-substituted olefins represented by 2.

We have recently reported that terminal acetylenes react in a stereo- and regioselective manner with Me_3Al-Cl_2ZrCp_2 to produce (*E*)-2-methylalkenylmetal derivatives.[1] Our finding that the carbometallated products consist essentially of (*E*)-2-methylalkenylalanes (4) prompted us to test the feasibility of converting 4 to 2 *via* known one-carbon homologation reactions of alkenylalanes.[4-8] We therefore chose 1-heptyne as a test system, carbometallated it with Me_3Al-Cl_2ZrCp_2 as described previously,[1] and reacted the product 4 with carbon electrophiles, either directly or after *in situ* conversion into the ate complex 5. As all alkenylaluminums previously employed in these reactions are either β-monoorgano-substituted or α,β-diorgano-substituted,[4-8] one aspect of our initial concern was whether or not the β,β-diorgano-substituted nature of 4 might seriously affect the yield and/or the stereoselectivity.

Happily, we have found that 4 or 5 reacts with selected one-carbon homologating agents quite satisfactorily, thereby providing a highly convenient entry into terminally functionalized (*E*)-3-methyl-2-alkenes (2) which, we believe, is considerably more stereoselective and/or efficient than any of the previously known procedures for the synthesis of 2. An additional attractive feature of the present methodology lies in the fact that various types of 2 can be obtained in one step *via* the key intermediate 4 or 5.

The experimental results obtained with 1-heptyne are summarized in Scheme I.

Scheme I



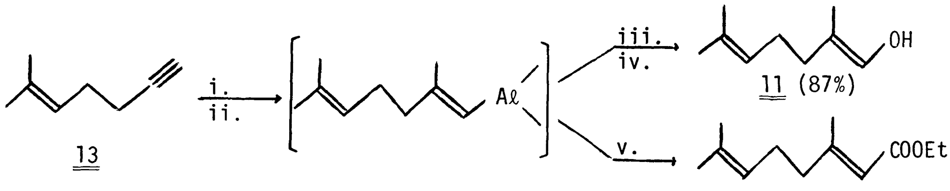
4 6 8 5 9 7 10

All isolated products (6, 8~10) have been adequately characterized by spectroscopic means: 6: bp 83-86°C (3 mm); $n^{23}D$ 1.4506; 8: bp 75-78°C (0.5 mm); $n^{23}D$ 1.4543; 9: bp 91-94°C (0.4 mm); $n^{23}D$ 1.4690; 10: bp 88-90°C (8 mm); $n^{23}D$ 1.4362.

The following observations are worth noting. (1) The product yields based on the starting acetylenes are roughly comparable to the corresponding values reported for β-monoalkyl-substituted alkenylalanes.[4-8] (2) The stereoselectivity in each case was ≥ 98%, as judged by ^1H and ^{13}C NMR and GLC. (3) As established earlier, the carbometallation of simple terminal acetylenes with Me_3Al-Cl_2ZrCp_2 produces ca. 95:5 mixtures of terminal and internal alkenylalanes. Somewhat unexpectedly, however, the one-carbon homologated products were not contaminated with any more than traces (< 2%) of their regioisomers, except for ethyl (E)-3-methyl-2-octenoate (6) which was contaminated with a minor by-product, presumably 7,[11] to the extent of ca. 5%. The use of a restricted amount (0.8 equiv) of ethyl chloroformate merely lowered the product yield by ca. 35% without improving the product purity. (4) Although stereochemically and regiochemically ≥ 98% pure, (E)-3-methyl-2-octen-1-ol (8) was also contaminated with a minor amount (ca. 5%) of an acetylenic by-product which distilled together with 8. The product, however, was readily purified by column chromatography over Florisil. (5) (E)-3-Methyl-2-octenoic acid (9) and (E)-3-methyl-2-octenyl methyl ether (10) were formed essentially uncontaminated with any by-product which would interfere with their purification by simple distillation. (6) The methyl ether 10 was also formed in 72% yield by reacting 4 with chloromethyl methyl ether, as reported recently by Zweifel.[8] Unfortunately, however, the product obtained by the organoalane reaction was contaminated with two unidentified by-products having similar GLC retention times on an SE-30 column which were not readily separated by simple distillation. Thus, at least in this case, the organoaluminate procedure[6] offers a distinct advantage over the organoalane procedure.

One of the most significant features of the procedures reported here lies in their ready applicability to the synthesis of various natural products and related compounds. We chose geraniol (11) and ethyl geranate (12) as target molecules and synthesized them in one step from 13[12] as shown in eq 2. Geraniol (11) was identified by comparing its spectral and GLC properties with those of an authentic sample, and the preparation and characterization of ethyl geranate (12) are described below as a representative example.

To a solution of Cl_2ZrCp_2 (2.92g, 10 mmol) and Me_3Al (1.22g, 1.63 ml, 17 mmol) in 1,2-dichloroethane (25 ml), was added 6-methyl-5-hepten-1-yne[12] (13) (1.08g, 10 mmol) at room temperature, and the mixture was stirred for 2 hr at the same temperature. After the removal of the volatile components under reduced pressure (0.5 mn Hg) at 50°C, the carbometallated compound 4 was extracted with hexane (5 x 6 ml), and transferred into another flask. To this extract was added ethyl chloroformate (3.26g, 30 mmol), and the mixture was stirred for 1 hr at room temperature. After treatment with 3N hydrochloric acid, ether, and aq. sodium carbonate, distillation gave ethyl geranate (12) (1.53g, 98% pure by GLC, 78% isolated yield, 85% GLC yield): bp 72-74°C (0.5 mm) [lit.[13] bp 63-68°C (0.4 mm)]; $n^{23}D$ 1.4677; ^1H NMR (CCl_4, TMS) δ 1.23 (t, J = 7 Hz, 3H), 1.61 and 1.70 (broad s, 3H and 3H), 2.06-2.16 (m, 7H). 4.06 (q, J = 7 Hz, 2H), 5.01 (m, 1H) and 5.54 (q, J = 1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$,TMS) δ 14.44, 17.66, 18.74, 25.67, 26.32, 41.10, 59.34, 115.97, 123.32, 132.32, 159.35, and 116.63 ppm; IR (neat) 1710(s), 1640(m) and 1140(s) cm^{-1}.



13 11 (87%) 12 (85%) (2)

i. $Me_3Al\text{-}Cl_2ZrCp_2$, $ClCH_2CH_2Cl$, 25°C, 2 hr. ii. Evaporation followed by addition of hexane and filtration of Cl_2ZrCp_2. iii. n-BuLi. iv. $(CH_2O)_n$, THF, 25°C, 3 hr. v. ClCOOEt, 25°C, 1 hr.

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References and Notes

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9. GLC yield.
10. Isolated yield.
11. Although no attempt was made to fully identify this compound, the ^{13}C and ^{1}H NMR spectra as well as the GLC behavior are consistent with 7.
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