# Notes

## Synthesis of (Z)-4-Methylhex-3-en-1-ol via the Reaction of Hexyn-1-ol with Trimethylaluminum–Titanium Tetrachloride

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There has been considerable interest in the synthesis of *Cecropia* juvenile hormones.[1] In 1968 Corey et al.[2] reported a stereospecific synthesis of the *d,l*-$C_{18}$ *Cecropia* juvenile hormone methyl *cis*-10,11-oxido-3,11-dimethyl-7-ethyltrideca-*trans*,*trans*-2,6-dienoate. Their synthesis depended on the stereospecific preparation of the intermediate (*Z*)-4-methylhex-3-en-1-ol (I) which was accomplished in several steps starting with *p*-methoxytoluene. In 1972 Mori et al.[3] presented an alternative synthesis of I which depended on the observation of Julia et al.[4] that 2-cyclopropylbut-3-yn-2-ol with hydrogen bromide underwent ring cleavage stereospecifically to give (*Z*)-1-bromo-4-methylhex-3-en-5-yne (95% purity); this compound was then converted to the alcohol and finally to I by selective reductions.

In this paper we report an extremely facile synthesis of (*Z*)-4-methylhex-3-en-1-ol from readily available starting materials.

### Experimental Section

**Preparation of (*Z*)-4-Methylhex-3-en-1-ol.** 3-Hexyn-1-ol, trimethylaluminum (TMA), and titanium tetrachloride were obtained from Farchan, Ethyl Corp., and Fisher Scientific, respectively, and used without further purification. Methylene chloride was distilled from $P_2O_5$. All chemistry was performed under an argon atmosphere, using syringe techniques to transfer reagents.

A three-neck 250-mL round-bottom flask equipped with a gas inlet (vented through a safety bubbler) and a dropping funnel was purged with argon (passed over Ridox (Fisher) and 4-Å molecular sieves) and charged with a solution of 80 mmol of TMA in 75 mL of $CH_2Cl_2$. After the TMA solution was cooled to 0 °C, 40 mmol (4.0 g) of 3-hexyn-1-ol in 25 mL of $CH_2Cl_2$ was added from the dropping funnel over a period of 20 min; the resulting solution (II) was allowed to warm to room temperature.

A second three-neck 250-mL round-bottom flask equipped and purged as above was charged with 100 mL of $CH_2Cl_2$ followed by 5.9 mL (53 mmol) of $TiCl_4$. The mixed methyl(1-oxyhex-3-yne)aluminum solution (II) from above was transferred to the dropping funnel of the second assembly. The $TiCl_4$ solution was cooled to −78 °C and solution II added dropwise over a period of ca. 20 min. The reaction mixture was stirred at −78 °C for 6 h after which it was carefully quenched with 20 mL of $CH_3OH$ followed by 50 mL of 5% $H_2SO_4$ saturated with NaCl. The $CH_2Cl_2$ layer was separated, and the aqueous layer extracted with five 50-mL portions of ether. The organic layers were dried over $MgSO_4$ and the solvents removed under reduced pressure. The yield based on 3-hexyn-1-ol was 81% (90% conversion). Yields were determined by GLC with corrections for response factors.

The only impurity evident from GLC was unreacted starting material from which the title compound was isolated in 60% overall yield by high-performance LC (7.8 mm x 122 cm μ-Bondapak $C_{18}$ column, 50:50 $CH_3CN$–$H_2O$, 4.0 mL/min, 0.20 mL per pass of the product–starting material mixture). No other isolation techniques were attempted: $^1$H NMR δ 0.90 (3 H, t, $J$ = 7 Hz), 1.69 (3 H, d, $J$ = 1.5 Hz), 2.03 (2 H, q, $J$ = 7 Hz), 2.20 (2 H, q, $J$ = 7 Hz), 2.98 (1 H, br s, OH), 3.49 (2 H, t, $J$ = 7 Hz), 5.17 (1 H, t, $J$ = 7 Hz); $^{13}$C NMR δ 12.88 (q, $J_{CH}$ = 125, $C_6$), 22.96 (q, $J_{CH}$ = 125, 4-$CH_3$), 24.96 (t, $J_{CH}$ = 128, $C_5$), 31.35 ($C_2$), 62.52 ($C_1$), 119.94 (d, $J_{CH}$ = 144, $C_3$), 140.07 ($C_4$); GLC $t_R$ 7.6 min (Carbowax 20M, capillary × 15 m, column temperature 90 °C, carrier gas $H_2$, LGR 51 cm/s).

$^1$H (80 MHz) and $^{13}$C (20 MHz) NMR spectra were recorded with a Varian FT-80A spectrometer, using $Me_4Si$ as an internal standard. Gas and liquid chromatography were carried out on Hewlett-Packard 5711A equipped with a 3380S integrator and Waters Associates Model 240 instruments, respectively.

### Results and Discussion

During the past few years several studies have appeared reporting the controlled carbometalation of isolated carbon–carbon multiple bonds using mixed alkylaluminum–titanium or –zirconium reagents.[5-8] With regard to synthetic potential cyclopentadienyl compounds of titanium and zirconium used with organoalanes are promising group IV transition-metal components. Recent detailed studies of ours using titanium tetrachloride–alkylaluminum systems for the carbometalation of 3-buten-1-ol led to the conclusion that $TiCl_4$ was quite nonspecific and had no synthetic promise.[5e,f] With 3-buten-1-ol several products were observed, including those arising from β-hydride elimination after carbometalation and from hydrogenation, as well as the expected terminal and internal alkylation products. Thus, we were surprised to find that the $TiCl_4$–TMA system was very selective in yielding a single

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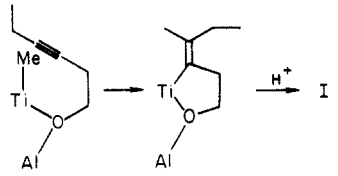
methylated olefinic alcohol (I) with 3-hexyn-1-ol. For reasons summarized previously[5] we favor a reaction scheme involving methylation of a titanium center followed by an intramolecular syn carbotitanation of the yne group which on protonolysis yields I.




The $^1H$ NMR shift data for our product agree with those reported by others,[2,3] and in particular the peak at 1.69 ppm in the absence of one near 1.60 ppm is reliable evidence for the *Z* configuration.[9,10] The occurrence of the olefinic $CH_3$ group at 22.96 ppm in the $^{13}C$ NMR spectrum rather than in the 12–15-ppm region confirms the *Z* configuration arising from a syn addition,[11] which is observed in all group IVa–organoalane alkyne carbometalations.[5,6,8,12]

The NMR spectra do not, to this point, distinguish between the two syn addition possibilities, I and (*Z*)-3-methyl-3-hexen-1-ol. This ambiguity is resolved by reference to the $^{13}C$ NMR shift data for 4-methyl-3-penten-1-ol.[13] For this compound the disubstituted olefinic carbon resonance ($(CH_3)_2C=$) occurs at 134.64 ppm while that of the remaining olefinic carbon occurs at 120.21 ppm. From $^{13}C$ chemical shift additivity relationships one calculates that the chemical shift parameters (relative to ethylene) of the $CH_2CH_2OH$ group in a trisubstituted olefin are $\alpha = 7.48$ and $\alpha' = -1.10$.[14] For I, olefinic carbon shifts ($C_3$ and $C_4$) are calculated to be 119.0 and 141.1 ppm,[15a] which are in excellent agreement with the shifts observed for our product. For the internally substituted product possibility, (*Z*)-3-methyl-3-hexen-1-ol, shifts of 130.5 and 129.6 ppm are calculated,[15b] clearly excluding this isomer from further consideration.

This work and that of others reported recently continues to suggest that early transition metal promoted carbometalation reactions may be synthetically useful and that further study is warranted.

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**Registry No.** I, 21019-60-3; 3-hexyn-1-ol, 1002-28-4; trimethylaluminum, 41561-11-9; titanium tetrachloride, 7550-45-0.

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(13) This compound, which has no stereochemistry, has been synthesized by us via a carbometalation procedure and is unambiguously characterized by proton NMR to be free from the internal addition product, 3-methyl-3-penten-1-ol: $^{13}C$ NMR $\delta$ 62.30 ($C_1$), 31.60 ($C_2$), 120.21 ($C_3$)8 136.64 ($C_4$), 25.78 ($CH_3$ trans to H), 17.81 ($CH_3$ cis to H). Additional details are to be published.
(14) Referring to ref 9 one calculates the $\alpha$ and $\alpha'$ $CH_2CH_2OH$ shift parameters relative to ethylene as follows: $\alpha = 120.2 - 123 - 2(-5.14) = 7.48$; $\alpha' = 134.6 - 123 - 2(6.35) = -1.10$.
(15) (a) $C_3$ shift = 123 + 7.48 + 2(−5.14) + (−1.22) = 119.0; $C_4$ shift = 123 + (−1.10) + 2(6.35) + 6.47 = 141.1; (b) $C_3$ shift = 123 + 7.48 + 6.35 − 5.14 − 1.22 = 130.5; $C_4$ shift = 123 + (−1.10) − 5.14 + 6.35 + 6.47 = 129.6.

## Synthesis of Guanidino-*N*-alkylarginines by the Use of Polymeric Pseudoureas

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Guanidino-*N*-alkyl ($N^G$-alkyl) derivatives of arginine which retain the charge and have different hydrophobicity are required, in order to study the importance of the guanidino groups of arginine in peptides. The only known $N^G$-alkylarginine derivatives which are present in several proteins are $N^G$-methylarginine and $N^G,N'^G$-dimethylarginine.[1] These methylarginines were synthesized in low yield from the corresponding methyl pseudoureas and the copper complex of ornithine. The synthesis was complicated and required more than a week for the reaction and subsequent chromatographic purification.[2,3]

Recently we have shown that the reaction between polysaccharides and cyanogen bromide yields cyanoesters ($ROC{\equiv}N$),[4] which upon reaction with amines give polymeric pseudoureas ($POC(=NH)NR_1R_2$), where $R^1$ and $R^2$ are either H or alkyl groups.[5] These polymeric pseudoureas or N-substituted isoureas can be used for the synthesis of any unsymmetrical or symmetrical guanidine, as described in Scheme I.

In this report the use of the polymeric pseudoureas for the synthesis of the as yet unknown $N^G$-alkylarginines and $N^G$-alkylhomoarginines is described (Table I). The reaction is fast and the yields are high compared to other methods.

The insoluble polysaccharides agarose, Sephadex, and cellulose were activated with cyanogen bromide under conditions which were found to give the highest activation yield.[4] Excess copper complex of ornithine and lysine was added to the activated polymers in order to obtain the maximum coupling yield. The use of the copper complex enabled the binding of the amino acids through the $\omega$-amino groups without covalent protection of the $\alpha$-amino group. The copper complex also enabled the direct isolation of free arginine derivatives. The excess complex was not lost, since after the reaction it was filtered and used again after determination of the amount of complex left. The use of the copper complex also enabled the fast determination of the amount of amino acid coupled to the polymer by titration of the amount of copper bound. The amount of ornithine coupled was also determined by amino acid analysis after total hydrolysis. Of the many polysaccharides checked, the best were Sepharose and cellulose. We chose to continue with cellulose as carrier because of its low price, better stability, and ease of handling. Under optimal conditions the activated cellulose bound about 100 $\mu$mol/g of ornithine or lysine. Incubation of the ornithine- or lysine-containing polymers with different amines for 24 h at 50 °C gave the required arginines in high yield (Table I). No racemization was detected in the arginines synthesized. The optical rotations of the arginine and $N^G$-methylarginine prepared were identical with those of the commercially available products. The polysaccharide, after removal of the arginine, can be used again for the complete

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