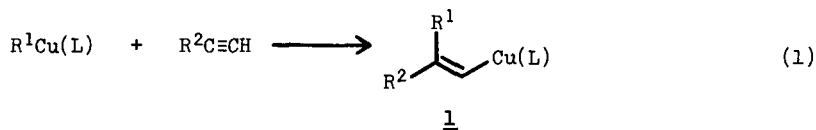


DETERMINATION OF THE CONFIGURATIONS OF TRISUBSTITUTED OLEFINS  
 OBTAINED FROM ADDITION OF ALKYL COPPER COMPLEXES TO ACETYLENES.  
 USE OF A LANTHANIDE NMR SHIFT REAGENT

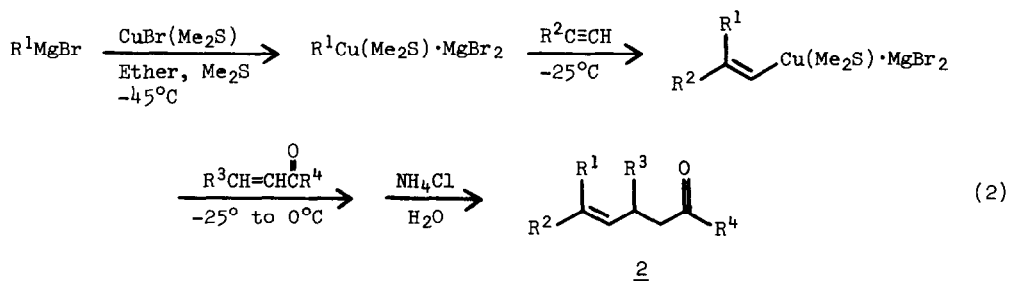
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The addition of alkylcopper complexes to acetylenes (equation 1), originally developed by Normant<sup>1</sup> and later investigated by Westmijze,<sup>2</sup> is a very useful approach to the synthesis of olefins. More recently we<sup>3</sup> and others<sup>4</sup> have modified this reaction through use of

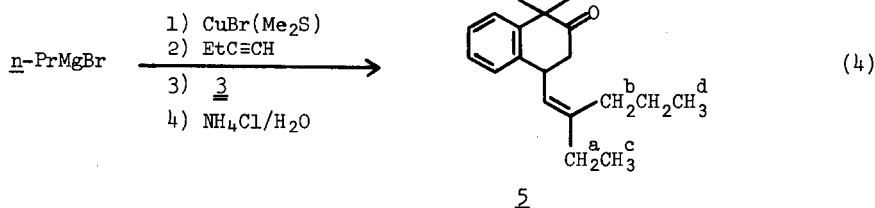
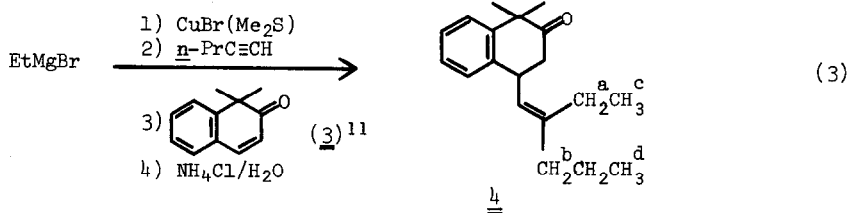


dimethyl sulfide complexes of the copper-containing intermediates. Under our conditions the previously unfeasible addition of a methylcopper complex occurs,<sup>5</sup> and the vinylcopper intermediates (1) react efficiently with various electrophiles, including epoxides<sup>6</sup> and  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>3</sup> Because the one-flask sequence of reactions involving the latter compounds (equation 2)<sup>7</sup> produces functionalized trisubstituted olefins (2)<sup>8</sup> that are potentially applicable to the synthesis of a wide variety of olefinic natural products,



firm knowledge of the stereochemistry of the resulting olefins (2) is desirable. Although our earlier work indicated that the products are formed with high stereospecificity (up to ca. 99.5%), the actual configurations of the olefins were not determined. Instead, we relied heavily upon two precedents: (1) Normant had shown that alkylcopper complexes undergo cis-addition to acetylenes,<sup>9</sup> and (2) vinylcopper complexes retain their configurations during conjugate addition reactions.<sup>10</sup> However, before our reaction sequence was applied to natural products synthesis, we wished to investigate more fully the stereochemistry of our olefinic products.

For these studies we chose to prepare separately compounds 4 and 5 (equations 3 and 4), which we believed would serve as suitable substrates for lanthanide nmr shift investigations. The examination of this pair of E- and Z-isomers would provide more convincing stereochemical



evidence than the study of only a single isomer. Study of molecular models indicates that the methylene groups  $\text{CH}_2^{\text{a}}$  and  $\text{CH}_2^{\text{b}}$  in several conformations of these compounds are located at significantly different distances from the carbonyl groups, the sites of coordination of a shift reagent. Also, the methylene groups are potentially distinguishable by  $^1\text{H}$ -nmr because the protons  $\text{H}^{\text{a}}$  are expected to appear principally as quartets and  $\text{H}^{\text{b}}$  as triplets. Furthermore, in decoupling experiments, if the upfield regions of the spectra in which the resonances of  $\text{H}^{\text{c}}$  and  $\text{H}^{\text{d}}$  appear were irradiated, the signals for  $\text{H}^{\text{a}}$  would collapse to singlets, but the signals for  $\text{H}^{\text{b}}$  would remain essentially unchanged. Therefore, a lanthanide shift experiment would consist of observing the relative shifts of the  $\text{H}^{\text{a}}$  and  $\text{H}^{\text{b}}$  as the shift reagent is added to samples of 4 and 5. For compound 4, the signal for  $\text{H}^{\text{a}}$  would be shifted to a larger extent than for  $\text{H}^{\text{b}}$ , and the reverse would be true for 5. Further reasons for the choice of 4 and 5 are that their  $^1\text{H}$ -nmr spectra have somewhat simplified aliphatic regions compared to adducts of other  $\alpha,\beta$ -unsaturated compounds that we have studied,<sup>3</sup> and the two methyl substituents adjacent to the carbonyl group may possibly direct the coordination of the lanthanide reagent to a position which would maximize the difference in shifts of  $\text{H}^{\text{a}}$  and  $\text{H}^{\text{b}}$ .

The magnitude of shifts of nmr peak positions induced by lanthanide reagents is given by the simplified expression shown in equation 5 in which  $\theta$  is the angle between the

$$\Delta\delta = K \left\langle \frac{(3 \cos^2\theta - 1)}{r^3} \right\rangle_{\text{time}} \quad (5)$$

principal magnetic axis of the lanthanide-substrate complex and the vector of length  $r$  joining the lanthanide ion and the nuclei under consideration ( $\text{H}^{\text{a}}$  and  $\text{H}^{\text{b}}$  in our case).<sup>12</sup> By inspection of molecular models of lanthanide complexes of 4 and 5,  $\theta$  may be estimated to possess a range of values ( $\leq 37^\circ$ ) which will assure that only downfield shifts are observed

for  $H^a$  and  $H^b$ . Also, through use of equation 5, the differences in downfield shifts of  $H^a$  and  $H^b$  should lie within the range of 0.21 to 0.53 ppm, depending mainly upon conformations resulting from rotation about the single bonds joining the vinyl groups to the alicyclic rings of 4 and 5. These estimates of  $\theta$  and  $\Delta\delta$  are made with the simplifying assumption that the principal magnetic axis is colinear with the Ln-O bond of the complex and, in turn, colinear with the C=O bond.<sup>12</sup> Deflection of the lanthanide to the side of the carbonyl group away from the gem-dimethyl groups would not alter the qualitative results of the work described below.

By the reaction sequence shown in equations 3 and 4, compounds 4 and 5 were each obtained in ca. 50% yield (not optimized) after distillation (bp 110°C, 0.005 Torr) or preparative glpc, and both were fully characterized spectroscopically.<sup>13</sup> Each product contained no detectable amount (< 0.4%) of the opposite isomer according to glpc analysis (when mixed together the two isomers are cleanly separable on a 12-ft x 1/8-in 10% Carbowax 20M column at 250°C). Thus, with both isomers on hand in pure form we were in a position to demonstrate more rigorously the stereochemistry of our synthesis of olefins.

The lanthanide shift experiments were performed using a Varian HFT-80 spectrometer equipped with a Hewlett-Packard Model 3320A frequency synthesizer for spin decoupling experiments. Samples of 4 and 5 (ca. 20 mg of each) were dissolved in dry  $CDCl_3$ , and spectra were recorded after addition of incremental amounts of  $Eu(fod)_3$ .<sup>14</sup> The triplet and quartet signals of  $H^a$  and  $H^b$  progressively became further separated from each other. The spin decoupling experiments described above were performed to identify these peaks unambiguously. The results of these studies are shown in Figures 1 and 2.<sup>15</sup>

Figure 1. Lanthanide Shift Studies of Compound 4.

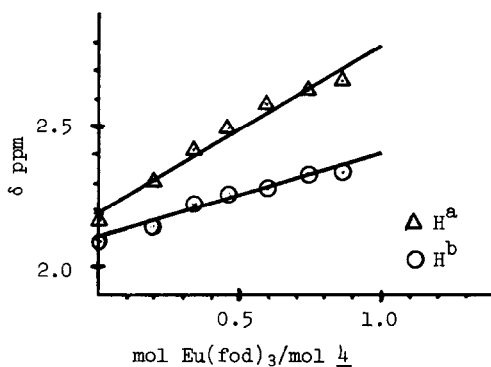
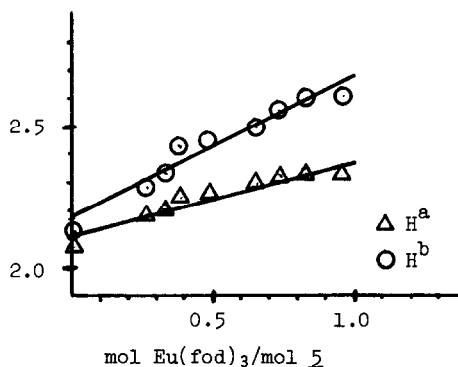


Figure 2. Lanthanide Shift Studies of Compound 5.



The observed differences in shifts of  $H^a$  and  $H^b$  are 0.38 and 0.31 ppm (extrapolated to mol  $Eu(fod)_3$ /mol substrate = 1.0) for 4 and 5, respectively. These values agree with those predicted on the basis of equation 5. The greater shifts of  $H^a$  in 4 and of  $H^b$  in 5 are consistent with the given olefin configurations of these compounds. These results are also in agreement with our earlier ones involving the positions of methyl group resonances in methyl-substituted olefins derived from addition of alkylcopper complexes to acetylenes.<sup>6</sup>

As a result of these stereochemical studies, our method for the synthesis of functionalized trisubstituted olefins may now be employed with greater confidence in the synthesis of complex natural products. Also, with the assumption that conjugate addition of vinylcopper complexes occurs with retention of configuration of the vinyl groups,<sup>10</sup> this work serves to confirm the observation that alkylcopper complexes undergo cis-addition to acetylenes.<sup>9</sup>

Acknowledgement is made to Professor Charles S. Springer of this department for very helpful discussions concerning the lanthanide shift reagent studies and to the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

#### FOOTNOTES AND REFERENCES

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6. P. R. McGuirk, A. Marfat, and P. Helquist, submitted for publication.
7. We do not intend to imply any specific structures of intermediates involved in this work.
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13. For example, the spectroscopic data for 4 are as follows: ir (neat film) 1714, 1665, 1600, 1485, 1463, 1444, and 846  $\text{cm}^{-1}$ ;  $^1\text{H}$ -nmr ( $\text{CDCl}_3$ ) 7.08-7.50 (m, 4 H), 5.05 (d,  $J = 9.7$  Hz, 1 H), 4.05 (m, 1 H), 2.42-2.92 (m, 2 H), 1.85-2.32 (m, 4 H), and 0.72-1.77 (several overlapping signals, 14 H); ms (70eV) m/e 270.1981 ( $M^+$ , calculated for  $\text{C}_{19}\text{H}_{26}\text{O}$ , 270.1984).
14. The  $\text{Eu}(\text{fod})_3$  was obtained from Aldrich and handled under a dry nitrogen atmosphere. The reagent was added as a stock solution (0.54 M) in  $\text{CDCl}_3$  to the samples of 4 and 5.
15. According to a linear least squares analysis, in Figure 1 the  $\text{H}^a$  plot has a slope of 0.59 and a y-intercept of 2.19; for  $\text{H}^b$  the values are 0.30 and 2.10. In Figure 2,  $\text{H}^a$  has values of 0.26 and 2.11, and  $\text{H}^b$  has values of 0.51 and 2.17. For the purposes of our work, a more rigorous curve-fitting analysis of the data was not deemed necessary.

(Received in USA 08 April 1978; received in UK for publication 20 June 1978)