

CYCLIZATION OF  $\omega$ -TRIMETHYLSILYLETHYNYLALKANOYL CHLORIDES.  
APPLICATION OF THE PREPARATION OF LARGE RING YNONES AND dl- AND (R)-MUSCONE

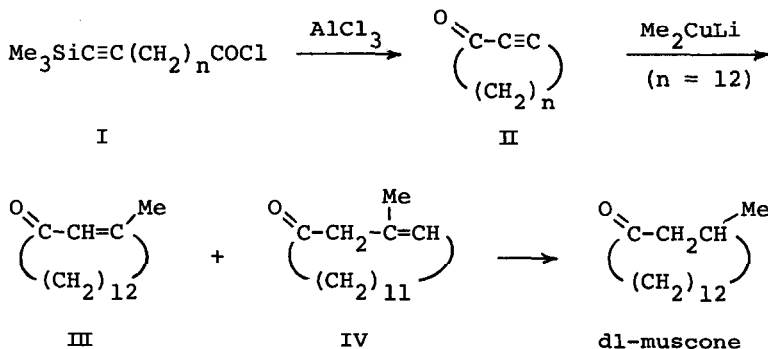
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(Received in UK 27 March 1978; received in UK for publication 27 April 1978)

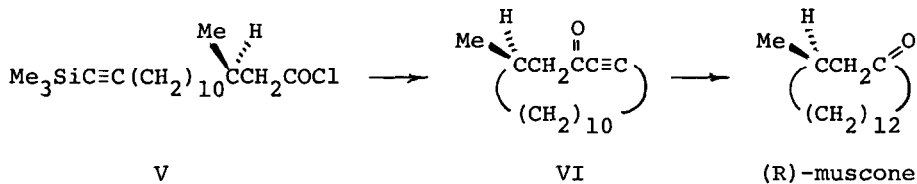
Large ring ketones including muscone and exaltone have been prepared from easily accessible cyclododecanone by ring enlargement<sup>1</sup> or suitably substituted acyclic compounds by ring closure and subsequent transformation.<sup>2</sup> Synthetically applicable cyclization techniques are limited. This paper describes a new procedure for the synthesis of large ring ynones by intramolecular acylation of  $\omega$ -trimethylsilylethynylalkanoyl chlorides (I) whose ready accessibility is discussed in the last section.

The acid chlorides (I) have been cyclized into the corresponding cycloalkynones (II) successfully. Synthesis of 2-cyclopentadecynone (II,  $n = 12$ ) is illustrative. To a refluxing mixture of dichloromethane (200 ml) and freshly sublimed and well ground aluminum chloride (3 mmol) was added a solution of 15-trimethylsilyl-14-pentadecynoyl chloride (329 mg, 1 mmol) in 25 ml of dichloromethane over a period of 2.5 h by means of a high dilution apparatus.<sup>3,4</sup> After additional reflux for 30 min, the reaction mixture was worked up with diluted hydrochloric acid at 0°C. Chromatography (silica-gel, benzene) gave 2-cyclopentadecyne [170 mg, 77% yield (82% yield by glc)].<sup>5</sup> Yields of lower homologs of II were 56% for  $n = 10$ <sup>6</sup> and 46% for  $n = 8$ <sup>7</sup>.

2-Cyclopentadecyne thus obtained was transformed to dl-muscone in almost quantitative yield: treatment of lithium dimethylcuprate afforded a mixture of 3-methyl-2- and 3-cyclopentadecenes (III and IV, about 1:1)<sup>8</sup> whose reduction gave dl-muscone.<sup>9</sup>

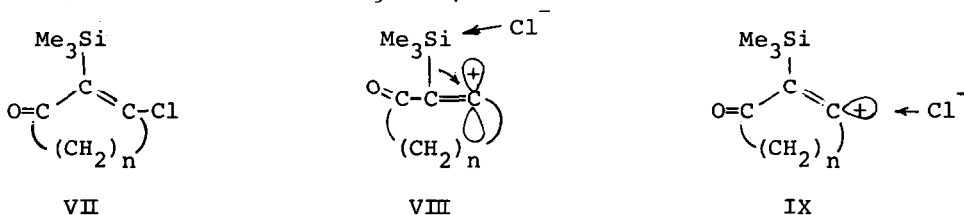


Optically active muscone was similarly prepared. Cyclization of (R)-3-methyl-15-trimethylsilyl-14-pentadecynoyl chloride (V)<sup>10</sup> gave (R)-14-methyl-2-cyclopentadecynone (VI)<sup>11</sup> in 52% yield, which was hydrogenated to (R)-muscone<sup>12</sup> quantitatively. Easy accessibility of V from (R)-citronellol (*vide infra*) confirms the above described transformation to be a procedure for optically active muscone.<sup>13</sup>

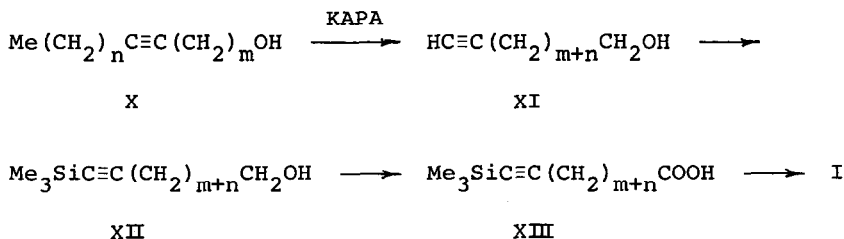


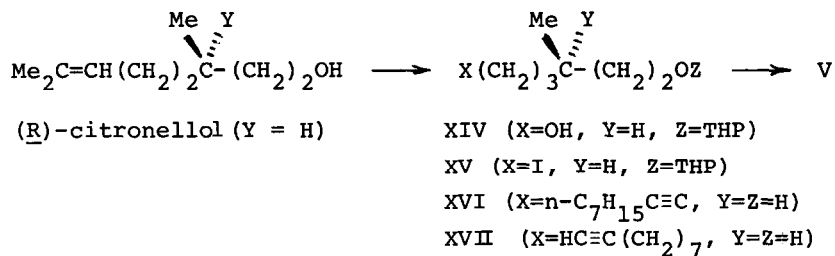
Extension of this reaction to common ring and medium ring formation produced 3-chloro-2-trimethylsilyl-2-cycloalkenones (VII) in varying yields<sup>14</sup>: 31% for  $n = 2$ <sup>15</sup>, 74% for  $n = 3$ <sup>16</sup>, 65% for  $n = 4$ <sup>17</sup> and 40% for  $n = 5$ <sup>18</sup>.

The above described modes of cyclization could be explained by assuming the intermediates VIII and IX. The linear carbocations VIII give II, whereas the bent ones IX lead to VII.



The starting material (I) are easily obtained from alkyne-1-ol (X) with any combination of m and n. Isomerization of 2-pentadecyn-1-ol (X,  $m = 1$ ,  $n = 11$ )<sup>19</sup> with excess potassium 3-aminopropylamide (KAPA) afforded 14-pentadecyn-1-ol<sup>20</sup> in an 89% yield.<sup>21</sup> 10-Pentadecyn-1-ol (X,  $m = 9$ ,  $n = 3$ ) gave a 93% yield. Transformation (XI  $\rightarrow$  XII)<sup>22</sup> followed by oxidation (XII  $\rightarrow$  XIII)<sup>23</sup> and chlorination with oxalyl chloride produced 15-trimethylsilyl-14-pentadecynoyl chloride (I,  $n = 12$ )<sup>24</sup> in 92% overall yield. Other silylated alkynoyl chlorides I were obtained analogously. The optically active alkynoyl chloride V was prepared from (R)-citronellol tetrahydropyranyl ether. Ozonolysis and successive reduction gave XIV ( $Y = \text{H}$ ) which was transformed to acetylenic alcohol XVI ( $Y = \text{H}$ ) via the iodide XV ( $Y = \text{H}$ ). Remarkably, the chiral center of XVI remained perfect intact during the isomerization of XVII. This was confirmed by deuteration experiment. dl-3-D-Citronellol ( $Y = \text{D}$ ,  $d_1$  97%)<sup>25</sup> was transformed to internal acetylenic alcohol XVI ( $Y = \text{D}$ ,  $d_1$  97%)<sup>26</sup>, whose KAPA treatment gave the terminal acetylenic alcohol XVII of identical D-content.<sup>26</sup>





The present cyclization provides a novel strategy in the synthesis of large ring yrones and 3-chloro-2-trimethylsilyl-2-alkenones of common and medium sizes, further synthetic application of which is under investigation.<sup>27</sup>

## REFERENCES AND NOTES

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- (2) (a) V. R. Mamdapur, P. P. Pai, K. K. Chakravarti, U. G. Nayak, and S. C. Bhattacharyya, *Tetrahedron*, 20, 2601 (1964); S. Ställberg-Stenhagen, *Arkiv Kemi*, 3, 517 (1951); (c) J. Nokami, Y. Kusumoto, K. Jinnai, and M. Kawada, *Chem. Lett.*, 715 (1977).
- (3) Intermolecular acylation of trimethylsilylacetylenes has been published: (a) L. Birkofer, A. Ritter, and H. Uhlenbrauck, *Chem. Ber.*, 96, 3280 (1963); (b) H. Newman, *J. Org. Chem.*, 38, 2254 (1973); (c) D. R. M. Walton and F. Wauch, *J. Organomet. Chem.*, 37, 45 (1972); (d) P. Bourgeois, G. Merault, and R. Calas, *ibid.*, 59, C4 (1973).
- (4) High dilution apparatus of Davis was used: A. C. Davis, *Chem. Ind. (London)*, 203 (1977).
- (5) (a) New compounds gave correct elemental analyses; (b) 2-Cyclopentadecynone (II, n = 12): ir (neat) 2220, 1667 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>) δ ppm, 1.2-1.9 (20H, m), 2.2-2.6 (4H, m); ms (prominent ions), m/e (rel. %), 220 (M<sup>+</sup>, 2), 205 (2), 191 (4), 95 (49), 80 (71), 55 (71), 41 (100).
- (6) 2-Cyclotridecynone: ir (neat) 2220, 1666 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>) δ ppm, 1.2-1.9 (16H, m), 2.2-2.6 (4H, m); ms m/e (rel. %), 192 (M<sup>+</sup>, 3), 177 (2), 107 (42), 95 (41), 93 (46), 79 (100).
- (7) 2-Cycloundecynone: ir (neat) 2220, 1666 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>) δ ppm, 1.4-2.0 (12H, m), 2.2-2.6 (4H, m); ms m/e (rel. %), 164 (M<sup>+</sup>, 7), 149 (9), 107 (51), 79 (100).
- (8) Formation of a mixture of the α,β-unsaturated ketone and its β,γ-isomer of 14-membered ring has been reported (ref. la).
- (9) Structure was determined by the comparison of ir nmr, and ms with those of reported.
- (10) Prepared from (R)-citronellol (64% e.e.).
- (11) Ir (neat) 2220, 1670 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>) δ ppm, 0.94 (3H, d, J = 7 Hz), 1.2-1.9 (19H, m), 2.2-2.4 (4H, m).

- (12) Obtained (R)-muscone ( $[\alpha]_D^{20} -7.7^\circ$ , ca. 59% e.e.). Optical purity was doubly checked by  $\text{Eu}(\text{hfc})_3$ -shifted nmr in which two doublets (C-methyl of R and S isomer, respectively) were observed. Synthesis of optically active muscone has appeared (ref. 1e, 2a, and 2b).
- (13) (R)-Citronellol was used as "Chiral Pool" in this synthesis.
- (14) Formation of 3-chloro-2-trimethylsilyl-2-alkenones has not been described yet to the best of authors' knowledge.
- (15) 3-Chloro-2-trimethylsilyl-2-cyclopentenone: ir (neat) 1710, 1575, 1250, 835  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\delta$  ppm, 0.23 (9H, s), 2.3-2.5 (2H, m), 2.7-2.9 (2H, m); ms m/e (rel. %), 188 ( $\text{M}^+$ , 2), 175 (35), 173 (85), 93 (100).
- (16) 3-Chloro-2-trimethylsilyl-2-cyclohexenone: ir (neat) 1665, 1570, 1240, 845  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\delta$  ppm, 0.23 (9H, s), 1.9-2.4 (4H, m), 2.6-2.8 (2H, m);  $\text{Eu}(\text{fod})_3$ -shifted nmr showed singlet (9H), triplet (2H), triplet (2H), and quintet (2H); ms m/e (rel. %), 187 (M-15, 90), 95 (42), 93 (100), 55 (40).
- (17) 3-Chloro-2-trimethylsilyl-2-cycloheptenone: ir (neat) 1690, 1580, 1260, 845  $\text{cm}^{-1}$ , nmr ( $\text{CCl}_4$ )  $\delta$  ppm, 0.18 (9H, s), 1.6-2.0 (4H, m), 2.3-2.5 (2H, m), 2.5-2.8 (2H, m);  $\text{Eu}(\text{fod})_3$ -shifted nmr supported the structure.
- (18) 3-Chloro-2-trimethylsilyl-2-cyclooctenone: ir (neat) 1680, 1600, 1255, 845  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\delta$  ppm, 0.18 (9H, m), 1.5-1.9 (6H, m), 2.1-2.4 (2H, m), 2.4-2.7 (2H, m).
- (19) Prepared from propargyl alcohol and 1-bromododecane in 83% yield.
- (20) Ir (Nujol) 3300, 1050  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\delta$  ppm, 1.2-1.5 (23H, m), 1.75 (1H, J = 3 Hz), 2.0-2.3 (2H, m), 3.55 (2H, t, J = 7 Hz).
- (21) Isomerization of internal acetylenes to the corresponding terminal ones as well as its application to acetylenic alcohols: (a) C. A. Brown and A. Yamashita, J. Am. Chem. Soc., 97, 891 (1975); (b) idem, J. Chem. Soc. Chem. Commun., 959 (1976); (c) C. A. Brown and E. Negishi, ibid., 318 (1977); (d) J. D. Lindhoudt, G. L. van Mourik, and H. J. J. Pabon, Tetrahedron Lett., 2565 (1976); (e) H. Hommes and L. Brandsma, Rec. Trav. Chim., 96, 160 (1977); (f) K. Utimoto, M. Kitai, and H. Nozaki, 33rd Annual Meeting of Chemical Society of Japan. August 28-31, 1976, Sapporo, 1K11.
- (22) Treatment with 2 equiv. of  $\text{EtMgBr}$  in THF (reflux for 2 h), with excess  $\text{Me}_3\text{SiCl}$  then with water gave XII.
- (23) Chromic acid oxidation (Jones reagent) at  $0^\circ\text{C}$ .
- (24) Treatment with oxalyl chloride at  $0^\circ\text{C}$  to room temp. in benzene. Ir (neat) 2190, 1799, 1245, 840, 759  $\text{cm}^{-1}$ .
- (25) Prepared from citral by deuterium addition to  $\alpha,\beta$ -double bond in a modified Noyori's procedure and successive treatment with aqueous alkali and  $\text{LiAlH}_4$  reduction: R. Noyori, I. Umeda, and T. Ishigami, J. Org. Chem., 37, 1542 (1972).
- (26) Deuterium content was determined by ms of the corresponding trimethylsilyl ether.
- (27) The authors wish to thank the Ministry of Education, Japan, for Grant-in-Aid (110309, 203014 and partially 185188).