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A FACILE ROUTE TO *d,l*-MUSCONE

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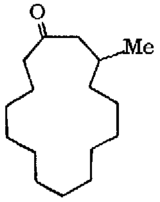
While the search for new synthesis of *d,l*-muscone (**1**) and related macrocycles has generated considerable interest and development in the area of carbocyclic ring enlargement processes,[1] the applications of these methods to the unsymmetrically substituted ketones are few indeed.[2] We now report the synthesis of *d,l*-muscone (**1**) by a novel approach which features the regioselective ring-enlargement. The present pathway depends heavily on the recently described one-carbon ring homologation *via* β-oxido carbenoid intermediate.[3]

Treatment of 2-methylcyclotetradecanone (**2**)[4] in ether containing methylene dibromide (2.2 equiv) with lithium 2,2,6,6-tetramethylpiperidide (2.2 equiv in ether-hexane) for 2 hr at -78°,[5] followed by chromatography on silica gel plate (R_f 0.55, ether:hexane = 2:15) gave the hydroxy dibromide **3** in 78% yield: bp 190° (bath temp, 2 mmHg); ir (film) 3580, 978, 702 cm^{-1}; nmr (CCl_4) δ 0.93 (d, *J* = 6 Hz, CH_3 of major isomer), 1.02 (d, *J* = 6 Hz, CH_3 of minor isomer), 5.78 (s, $CHBr_2$ of major isomer), 5.86 ppm (s, $CHBr_2$ of minor isomer); mass *m/e* 398 (M^+); *Found*: C, 48.1; H, 7.6%. *Calcd*. for $C_{16}H_{30}Br_2O$: C, 48.3; H, 7.6%. The alcohol **3** was transformed into *d,l*-muscone (**1**) in 79% yield by the reaction with *n*-butyllithium (2.1 equiv in hexane) in dry tetrahydrofuran at -78° for 1 hr and 0° for 5 min.[3] The spectral and analytical characteristics of synthetic *d,l*-**1** were identical with those of an authentic specimen of muscone.[1b, 6]



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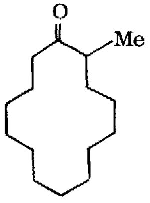

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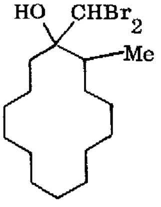
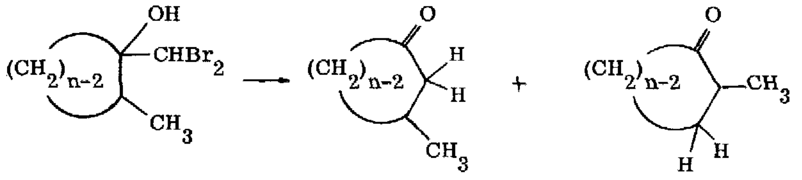


3

The crucial intermediate in this synthesis is the hydroxy dibromide **3** which can a priori undergo rearrangement in either of two directions to give either muscone or 2-methylcyclopentadecanone. It was soon discovered that the direction of methylene insertion was highly selective and muscone was obtained virtually exclusively.[7] The high regioselectivity of the reaction may be further illustrated by the results summarized in Table I. Thus,, the regioselectivity is highly dependent upon the reaction temperature, the nature of the solvent, and the ring size.

Table I. Product Distribution and Yields of Ring-Expansion Products[a]



4 **5** **6**

Dibromide[b] n	Temperature[c] °C	Solvent	Product Isomer Distribution[d] **5**:**6**	 Yield[e] % (**5**+**6**)
5-*trans*[f]	-78	THF	69:31	90
5-*cis*[f]	-78	THF	49:51	73
6[g]	-78	THF	98:2	29[h]
6	-95	THF	99:1	51
6	-45	ether	86:14	62
6	-78	ether	95:5	82
6	-95	ether	97:3	86
6	-78	hexane	66:34	71
6	-95	hexane	65:35	68
12[i]	-78	THF	99:1	(96)
14[j]	-78	THF	~97:3[k]	(79)

a) Most of these reactions were run on a 1 mmol scale using the stoichiometry described above for the preparation of muscone. b) Prepared according to the previously reported procedure (ref. 3): To an ethereal solution of polyhalomethane (2.2 equiv) and carbonyl compound (1.0 equiv) was added a THF (or ether)-hexane solution of lithium 2,2,6,6-tetramethylpiperidide (2.2 equiv) over a period of 1 hr at -78°, and the solution was stirred for 1 hr at the same temperature. c) Cooling bath temperature. d) Determined by glpc assay from analytical samples before bulk purification. e) The yields were determined by analytical glpc using an internal standard: isolated yields in parentheses. f) Reaction of cyclopentanone with dibromomethyllithium afforded **4** (n = 5) in a ratio of *trans*:*cis* = ~7:3. The isomers were separated by preparative tlc. The stereochemical course of the reaction was estimated by the analogy in similar systems; see, for example, E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, **75**, 521 (1975). g) Only one isomer was detected from the reaction of dibromomethyllithium and 2-methylcyclohexanone. 2-methylcyclohexanone is known to be attacked from the equatorial side to a large extent. It has been suggested that the 2-methyl group introduces a pseudo-axial hydrogen into the molecule which increases hindrance of attack from the axial side; see, G. Chauviere, Z. Welvart, D. Eugene, and J. Richer, *Can. J. Chem.*

47, 3285 (1969). h) Low yield of this reaction was due to the thermal lability of β-alkoxy dibromide **4** (n = 6) even at -78°. i) Mixture of stereoisomers (~4:1 by nmr assay). j) Mixture of stereoisomers (~8:1 by nmr assay). k) Estimated by nmr analysis.

When the reaction of **4** (n = 6) is conducted at -95° in ether, 3-methylcycloheptanone is obtained with high regioselectivity (97:3). At -45° the reaction produced a significant amount of 2-methylcyclohexanone.

The nature of the solvent influences the regioselectivity of the reaction. In tetrahydrofuran, reaction is highly selective, and 3-methyl ketone is obtained almost exclusively. In diethyl ether, 3-methyl ketone still dominates, but 2-methyl ketone is also produced significantly even at -78°. In hexane as solvent the regioselectivity is less than in ether solvents, and the yield is lower.

Since the solvation of the lithium atom or low reaction temperature are of decisive importance to increase the stability of carbenoids,[8] in the absence of better solvating ether solvents or at relatively higher reaction temperature, the kinetically formed β-oxido carbenoid might lead directly to product with lower regioselectivity. Thus, the relative conformational or configurational energies of the intermediate β-oxido carbenoids might play an important role to determine the product ratio,[9] although there is at present no basis for mechanistic conclusion.

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3. H. Taguchi, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, **96**, 6510 (1974); *idem*, *ibid.*, **96**, 3010 (1974).
4. Prepared from cyclotetradecanone (R_2NLi and CH_3I in THF-HMPA). For the convenient synthesis of cyclotetradecanone, see (a) T. Mori, T. Nakahara, and H. Nozaki, *Can. J. Chem.*, **47**, 3266

(1969); (b) ref. 1a and references cited therein.

5. R. A. Olofson and C. M. Dougherty, J. Amer. Chem. Soc., **95**, 583 (1973).

6. 2-Methylcyclopentadecanone was also prepared by the basic alkylation of exaltone (lithium diisopropylamide in THF-HMPA). Unfortunately, d,l-**1** and 2-methylcyclopentadecanone behave quite similarly on glpc assay, but nmr analysis of two isomers indicate slight differences on methyl signals: nmr ($CDCl_3$, 100 MHz) muscone: δ 0.922 (d, J = 6.5 Hz); 2-methylcyclopentadecanone: 0.994 ppm (d, J = 7.0 Hz).

7. The ratio >97:<3 by nmr assay.

8. G. Köbrich, Angew. Chem. Internat. Ed. Engl., **11**, 473 (1972). See also A. Amaro and K. Grohmann, J. Amer. Chem. Soc., **97**, 3830 (1975).

9 Figure 1 shows a view of β-oxido carbenoid (from dibromide **4** (n = 6)) in what appeares to be the energetically favorable molecular form.

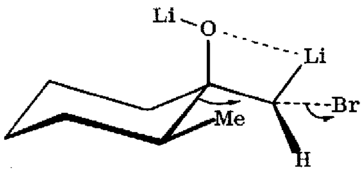

Figure 1