

OLEFINIC CYCLIZATION PROMOTED BY BECKMANN REARRANGEMENT OF OXIME SULFONATE
SYNTHESIS OF dl-MUSCONE[†]

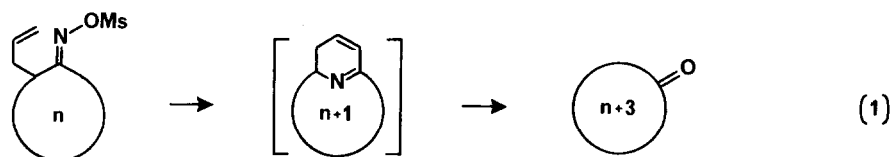
Soichi Sakane, Keiji Maruoka, and Hisashi Yamamoto*

Department of Applied Chemistry, Nagoya University

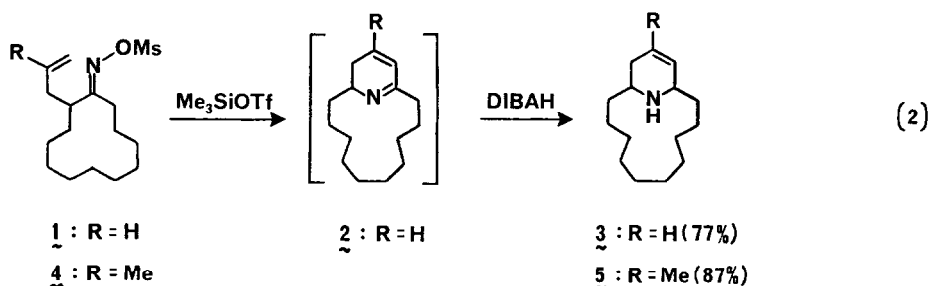
Chikusa, Nagoya 464, Japan

Summary: The acid-catalyzed cyclization of olefinic oxime mesylates has been successfully applied for the synthesis of dl-muscone and related macrocycles.

We have recently shown that a double bond may become involved in the Lewis acid-catalyzed rearrangement of a suitably constituted olefinic oxime sulfonate and four distinct cyclization modes (Endo(B)-endo, Endo(B)-exo, Exo(B)-endo, Exo(B)-exo) were disclosed.¹ At the outset of these works, we were interested in the possibility that Endo(B) cyclizations might serve as a powerful tool for ring-transformation reactions. Thus, the produced enimine might be reductively cleaved to the ring-expansion product (eq 1). We wish to report herein the realization of this goal with facile synthesis of dl-muscone and related macrocycles.²



We chose to test the above possibility by studying the acid-catalyzed rearrangement of the specific oxime sulfonate 1. The synthesis of the latter was carried out starting with cyclododecanone in three steps.³ Upon treatment of 1 with trimethylsilyl trifluoromethanesulfonate (1.1 equiv) in CDCl₃ in the NMR tube at 20°C for 1 h, quantitative formation of the enimine 2 was observed⁴: ¹H NMR (CDCl₃) δ 7.09 (1H, m, N=C-C=CH), 6.39 (1H, d, J = 9.6 Hz, N=C-CH=), 4.16 (1H, br s, NCH). This unusually high efficacy might be attributed in part to the steric effects of medium ring structure. Direct reduction of the enimine with excess diisobutylaluminum hydride gave the tetrahydropyridine structure 3 in 77% yield (eq 2). Under the similar conditions, 2-methallylcyclododecanone oxime mesylate (4) was smoothly transformed into the amine 5 in 87% yield.



With these new heterocycles $\underline{3}$ and $\underline{5}$ at hand, efficient and unique synthesis of dl-muscone was accomplished by two independent routes (Scheme 1). Thus, both $\underline{3}$ and $\underline{5}$ were converted in three steps to the amines $\underline{6}$ (57%) and $\underline{7}$ (70%), respectively: (1) methylation using 37% aq CH_2O - NaBH_3CN in CH_3CN -THF,⁶ (2) treatment with m-chloroperbenzoic acid (1 equiv) in methylene chloride,⁷ (3) Melsenheimer rearrangement of the resulting amine oxides (benzene reflux, 1~3 h).⁸

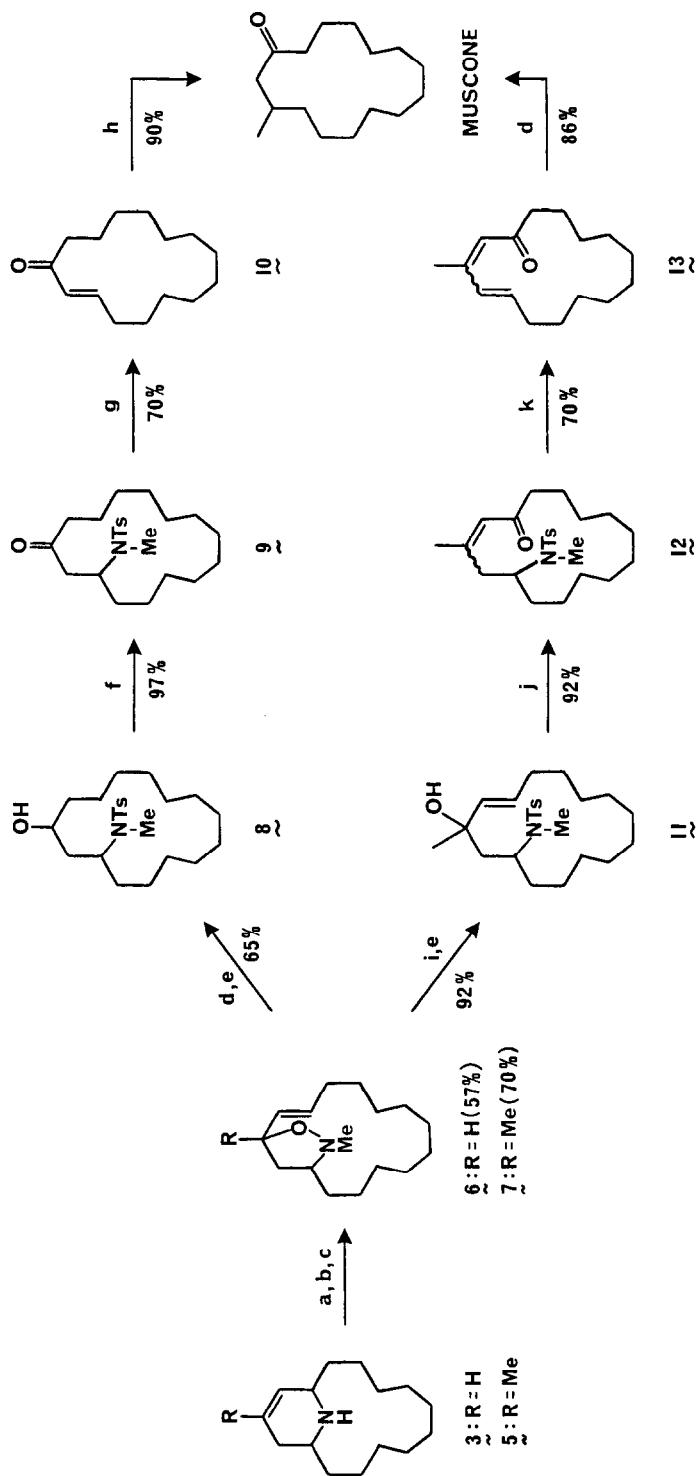
Hydrogenation of $\underline{6}$ in ethanol over 10% palladium on charcoal at 25°C and 1 atm of H_2 for 10 h, followed by selective protection of the amino group with p-toluenesulfonyl chloride (1 equiv) in methylene chloride in the presence of triethylamine (1.5 equiv) at 25°C for 1 h provided the alcohol $\underline{8}$ in 65% yield. Collins oxidation of $\underline{8}$ gave rise to the ketone $\underline{9}$ (97% yield) which was treated with potassium carbonate (3 equiv) in isopropanol at 50°C for 1 h producing trans-2-cyclopentadecenone ($\underline{10}$) exclusively in 70% yield.⁹ Finally, the enone $\underline{10}$ was converted to dl-muscone¹⁰ in 90% yield by exposure with lithium dimethylcuprate (2 equiv) at -20°C for 10 min.¹¹

Muscone was also prepared from the amine $\underline{7}$. Reductive cleavage of $\underline{7}$ with excess sodium in boiling ethanol followed by selective tosylation as described above were accomplished to furnish the alcohol $\underline{11}$ in 92% yield. Oxidation of $\underline{11}$ was effected in 92% yield by using sodium dichromate (2 equiv) in sulfuric acid-water-ether system¹² at 25°C for 2 h. The enone $\underline{12}$,¹³ thus obtained, was treated with potassium carbonate in sec-butanol at reflux for 5 h to form 3-methyl-2,4-cyclopentadecadienone ($\underline{13}$) in 70% yield which led to muscone¹⁰ in 86% yield by hydrogenation over 10% palladium on charcoal at 25°C and 1 atm of H_2 for 10 h.

It is clear that the Endo(B) cyclization followed by reductive cleavage of the tetrahydropyridines described herein serves a new approach to ring expansion and chain extension as illustrated in the synthesis of dl-muscone and related macrocycles.

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Scheme I



(a) aq CH_2O , $NaBH_3CN$. (b) MCPBA. (c) heat. (d) H_2 , Pd/C. (e) $p-TsCl$, NEt_3 . (f) $CrO_3 \cdot Py_2$.
 (g) K_2CO_3 , $(CH_3)_2CHOH$. (h) Me_2CuLi . (i) Na, EtOH. (j) $Na_2Cr_2O_7$. (k) K_2CO_3 , $sec-BuOH$.

REFERENCES AND NOTES

- † This communication is dedicated to Professor Hitosi Nozaki on the occasion of his 60th birthday.
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 3. The oxime mesylate 1 was synthesized by the following sequence: (1) alkylation of cyclododecanone with lithium diisopropylamide-allyl bromide in THF-HMPA; (2) oximation of the crude 2-allylcyclododecanone using $\text{NH}_2\text{OH}\cdot\text{HCl}$ -NaOH in ethanol at reflux (84% yield from cyclododecanone); (3) mesylation of the oxime by treatment with methanesulfonyl chloride-triethylamine in methylene chloride at -20°C (~100%). The oxime mesylate, thus obtained, is pure enough for the next reaction.
 4. The enimine 2 is quite labile, and attempted isolation of 2 was unsuccessful.
 5. A variety of Lewis acids (Et_2AlCl , SnCl_4 , Me_3SiI etc.) were examined for the present rearrangement-cyclization process and Me_3SiOTf has proven to be the most efficacious.
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 9. Only the trans-isomer ($J = 15.0$ Hz) was detected by GC assay (Silicone OV-101, 160°C); t_{R} of 10 = 14.3 min.
 10. The TLC and GC behavior of the synthetic dl-muscone were superimposable on those of the authentic sample.
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 13. The enone 12 was obtained as two isomers, which were separated by column chromatography on silica gel in a ratio of 1:3.

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