Dianion Methodology for the Construction of Large-Membered Ring Systems: Application to the Synthesis of **Muscone**.

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Summary: A dianion method for the construction of the macrocycles has been developed and applied to the synthesis of natural fragrance muscone. Conformational analysis of the macrocycle using MM2-Monte Carlo method was carried out to evaluate whether the rationally designed intermediate will readily cyclize.

The most crucial problem in the synthesis of macrocyclic compounds is to have an efficient method of cyclization. We have reported a general method for the construction of 10- to l&membered rings by the intramolecular alkylation of cyanohydrin ethers¹⁾ and have shown the utility of this method in total synthesis of natural products.2) The dianion cyclization method described herein (Fig-l) involves the intermolecular alkylation of the dianion 1 with the alkyl dihalide 2. followed by intramolecular alkylation of the monoanion 3 to give the macrocycle 4. The cyclization suffers from the competition of a polymerization through the dialkylated product 5 which comes from the intermolecular alkylation of 3 with the alkyl halide 2. In general, high substrate concentrations favor the intermolecular process whereas the intramolecular process occurs without competition only at low concentrations.



To circumvent this difficulty, molecular mechanics calculations31 **(MM2)** have been employed to design the synthetic intermediate 3 having an enhanced propensity for cyclization. We also describe the synthesis of natural fragrance **muscone**⁴) by using this dianion cyclization methodology.51

The rate of cyclization may be interpreted in terms of the activation energy and the probability of end-to-end encounters. The activation energy is thought to reflect the strain energy of the ring to be formed. The probability of the terminal anion and halide coming close enough to cyclize should decrease as the chain gets longer.61 In terms of entropy, reduction of the degrees of freedom of internal rotations of the open chain precursor 3 by introducing double bond should result in partial compensation for the entropy loss caused by freezing of internal bond rotations upon ring closure. Thus, we introduce the double bond into the open chain monoanion 8 and/or 9 and select the position of the double bond where the minimum ring strain will be experienced when 8 and/or 9 approach to the ring shaped transition state. In order to make a prediction for the location of the double bond, the cyanohydrin ether 8 was selected as a lead compound. Monte Carlo (MC) random-search method71 was applied to finding the lower-energy conformers of 6. The structures generated by MC search were energy minimized by using MM2 force field.81 A total of 47 unique minima were found within 2.4 Kcal/mol of the global minimum. The results of these calculations are shown in Table-l. Among the lowest 10 energy conformers, torsional angles at C5-C6-C7-C8, C9-C10-C11-C12, and C12-C13-C14-C15 in 6 show preferable alignments in which methylene groups are oriented in antiperiplanar fashion except for C9-C10-C11-C 12 torsional angle of the 3rd conformer and C12-C 13-C 14-C 15 torsional angle of the 4th conformer. These conformational properties in the lowest energy conformers of 6 suggest that introduction of the trans double bonds at carbons C6-C7, C10-C11, and/or C13-C14 positions would provide the structural features required for the cyclization to proceed rapidly. Based on the conformational analysis of 6, the dicyanohydrin 7 were selected as the dianion precursor in which the trans double bond was introduced to the position equivalent to the C6-C7 position of 6. Table.1



		Dihedral Angles		
population (%)	(Kcal/mol)	C13-C14	C10-C11	C6-C7
27.7	0.00	173.4	-167.5	-169.4
22.3	0.15	179.0	167.3	-174.7
9.0	0.79	-178.8	-63.9	-175.3
5.6	1.12	-75.5	179.9	-177.8
4.9	1.22	·172.9	179.0	- 175.6
4.5	1.27	-174.4	173.9	160.1
4.0	1.35	-163.9	169.9	171.1
3.9	1.37	-167.3	174.6	167.0
3.4	1.47	-174.6	177.1	177.8
3.0	1.57	176.4	.175.2	165.5

* Energy Difference between global minimum and local minima *Boltzmann Distribution of lowest 15 conformers at 80 °C

First, we examined the dianion cyclization of 7.9) To a solution of LiN(TMS)2 (9.5 mmol) in dioxane (10 mL) was added the protected cyanohydrin 7 (0.86 mmol) and the ditosylate 10 (1.7 mmol) in **dioxane** (10 mL) over 4 h at 80 °C. Removal of the ethoxy ethyl groups (p-TsOH/MeOH), followed by a mild base treatment (2% NaOH) afforded the **diketone** 11 in 64% overall yield. Then a series of the substrates with no conformational bias toward the cyclization was **examined**¹⁰ to compare the tendency for the cyclization of the trans dianion 7 with that of the other substrates. Cyclization of the saturated derivative 14. which decreases the probability of end-to-end encounters, with the ditosylate 10 gave the **diketone15** in 31% overall yield after acid and base treatments. Reaction of the cis derivative **16**, which imposes an extra enthalpic penalty, provided the diketone 17 in 37% overall yield in three steps. To enhance the reactivity of the intramolecular **alkylation** stage, the diallyl halides 19 and 20. which also have the two double bonds in the open chain precursors, were subjected to the dianion cyclization. Comparable results were however obtained. These results indicate that the introduction of the double bond with the correct configuration at an appropriate position in the open chain precursor is effective for assisting the formation of the rings by the dianion. 11)



Next, conversion of the diketone 11 into muscone 13 was carried out. Selective reduction of the saturated ketone present in 11 with NaBH4. followed by tosylation of the resulting alcohol gave the tosylate 12 in 62% yield. Removal of the tosyl group with super-hydride provided the allylic alcohol in 78% yield. Oxidation of the alcohol with PCC. followed by hydrogenation of double bonds with Pd/C led smoothly to muscone 13 in 73% yield.

In summary, we have developed a dianion cyclization method for the construction of macrocyclic rings based on the molecular design of the open chain precursors having a high propensity for cyclization. Other applications of the dianion cyclization for the synthesis of natural products are currently under investigation.

References and Notes

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- 1)
- Takahashi, T.; Nemoto, H.; Tsuji, J. Tetrahedron Lett. 1983, 24, 2005. Takahashi, 'I'. "Studies in Natural Products Chemistry, Stereoselective Synthesis (part E)", Elsevier, 1991, 2Ì
- 3)
- Takahashi, T., 'Neholo, H., Tsuji, J. Fetrahedron Lett. 1963, 24, 2005.
 Takahashi, T. "Studies in Natural Products Chemistry, Stereoselective Synthesis (part E)", Elsevier, 1991, Vol. 8, p.175.
 a) Allinger. N. L. J. Am. Chem. Soc. 1977, 99, 8127. b) Burkent, U.; Allinger, N. L. "Molecular Mechanics", ACS Monograph, 1982, 177. c) Clark, T. "A Handbook of Computational Chemistry", Wiley Interscinence, New York 1985.
 a) Felix, D.; Schreiber, J.; Ohloff, G.; Eschenmoser. A. Helv. Chim. Acta 1971, 54, 2896. b)
 Mookherjee, B. D.; Patel, R. R.; Ledig, W. O. J. Org. Chem. 1971, 36, 4124. c) Baker, R.; Cookson, R. C.; Vinson, J. R. J. Chem. Soc. Chem. Commun. 1974. 515. d) Stork, G.; Macdonald, T. L. J. Am. Chem. Soc. 1975. 97, 1264. e) Bauman, M.; Hoffmann, W.; Muller, N. Tetrahedron Lett. 1976, 3585.
 f) Branca, Q.; Fischli. A. Helv. Chim. Acta 1977, 60, 925. g) Taguchi, H.; Yamamoto, H.; Nozaki, H. Bull. Chem. Soc. Jpn. 1977, 50. 1592. h) Ito, Y.; Saegusa, T. J. Org. Chem. 1977. 42, 2326. i) Uchimoto, K.; Tanaka, M.; Kitai, M.; Nozaki, H. Tetrahedron Lett. 1978, 2301. j) Takahashi T.; Nagashima, T.; Tsuji, J. *ibid.* 1981, 22, 1359. k) Tanaka, K.; Ushino, H.; Suzuki, H. J. Chem. Soc. Chem. Commun. 1990, 795. 1) J. Chem. Soc. 1991. 1438.
 Other dianion cyclizaion methodology : Takahashi, T.; Nagashima, T.; Ikeda, H.; Tsuji, J. Tetrahedron Lett. 1982, 23, 4361.
 Illuminati, G.; Mandolini, L. Acc. Chem. Res. 1981, 14, 95.
 Chang, G.; Guida, 'W. C.; Still, W. C. J. Am. Chem. Soc. 1989, 111, 4379.
 Monte Carlo conformational search and MM2 calculations were carried out by MacroModel V3.1. We are grateful to Professor W. C. Still for providing a copy of this program. Mohamadi, F.; Richards, N. G. J.; 4)
- 5)
- 6)
- 7)
- **8**5 grateful to Professor W. C. Still for providing a copy of this program. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. J. Comp. Chem. **1990**, 11, 440.
- The dicyanohydrin 7 was prepared from geranyl acetate as follows. 9)



a) 1) O3, Mc2S 73% 2) MgCl 59% b) 1) EVE, Hg(OAC)2 then 120 °C 93% 2) K2CO3, MeOH 3) MnO2 46%

- 10) Cyclizations of the compounds 14, 16, and 18 were carried out under the same reaction condition that used for the cyclization of 7 with 10. We also confirmed that yields of the cyclizations were reproducible.
 11) We also examined the cyclization of the ditosylates i and ii with the saturated dicyanohydrin 18. Cyclization of 18 with the ditosylate i gave the 15-membered diketone in 20% overall yield in three steps. The ditosylate ii which contained cis double bond, showed no improvement on the cyclization yield (15%). TsO-(CH2)9-OTs TsO-(CH2)4-CH=CH-(CH2)3-OTs C1S
- 12) Takahashi, T; Kitamura, K.; Nemoto, H.; Tsuji, J.; Miura, I. Tetrahedron Lett., 1983, 24, 3489.

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