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# SIMPLE TOTAL SYNTHESES OF (±)-ACORAGERMACRONE AND (±)-MUKULOL BY INTRAMOLECULAR ALKYLATION OF PROTECTED CYANOHYDRIN

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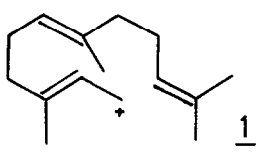
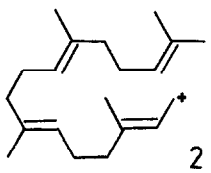
Summary: Total syntheses of (±)-Acoragermacrone (5) and (±)-Mukulol (10) by the intramolecular alkylation of a carbanion generated from protected cyanohydrin with secondary tosylate are presented.

Cyclizations of the farnesy cation 1 and the geranylgeranyl cation 2 to the germacrane type sesquiterpenoids and cembrane type diterpenoids such as Acoragermacrone (5) and Mukulol (10), respectively, are one of the most fundamental and important pathways in the biosynthesis of sesqui- and diterpenoids. So far, two kinds of novel biogenetic type syntheses of macrocyclic sesqui- and diterpenoids have been reported. The first one is the anion-induced cyclization of epoxy sulfides, reported by Kodama and Ito[1] who, however, encountered serious problems with double bond migration and isomerization during both the alkylation and desulfurization steps. The second one, reported by Kato,[6b] is the cation-induced cyclization of acyl halides. This cyclization proceeded without isomerization of double bond in the case of 14-membered rings, but no cyclization took place in the case of 10-membered rings.[2] Thus acceptable methods of the biogenetic type cyclizations, which are effective for both syntheses of macrocyclic sesqui- and diterpenoids, are few.[3]



1

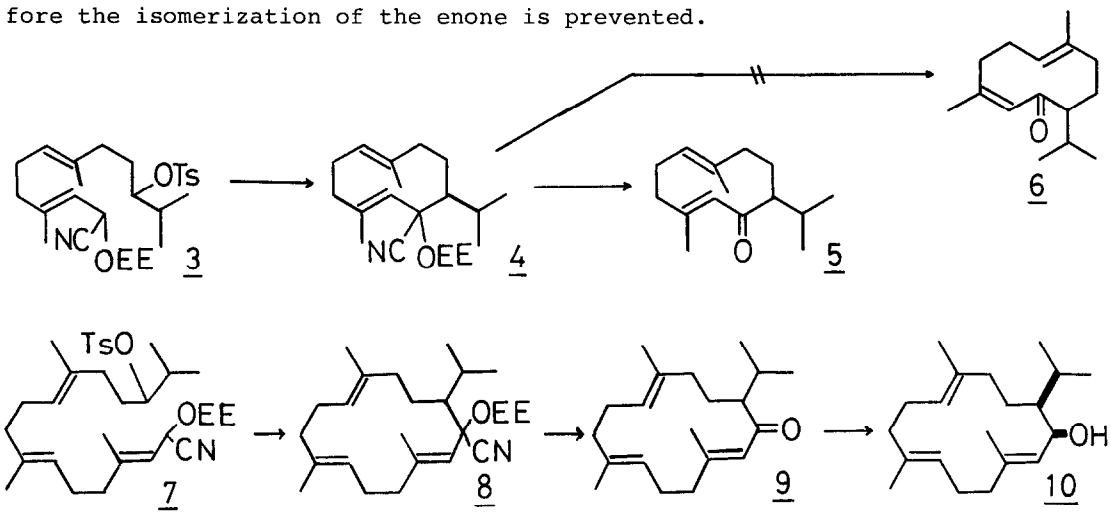


2

Recently we have reported a general synthetic method for the (*E*,*E*)- and (*Z*,*E*)-2,6-cyclodecadienones based on the intramolecular alkylation of protected cyanohydrin with *primary* tosylates.[4] In this paper we wish to report the total syntheses of Acoragermacrone (5)[5a] and Mukulol (10)[6a] based on the intramolecular alkylation with *secondary* tosylates. Acoragermacrone was

synthesized by Still,[5b] but in this method the chemically and thermally labile (*E*,*E*)-2,6-cyclodecadienone system was elaborated by the isomerization of the more stable (*Z*,*E*)-dienone (6), generated by oxy-Cope rearrangement, to the less stable (*E*,*E*)-dienone by 1,4-addition of organotin and oxidation sequence. Thus this synthetic method is indirect for the preparation of the desired (*E*,*E*)-dienone. Mukulol was synthesized by Kato using cation-induced cyclization method.[6b] However, this cyclization proceeds as Friedel-Crafts type reaction and hence the formation of the chiral center at the ring carbon bearing isopropyl group would be difficult.

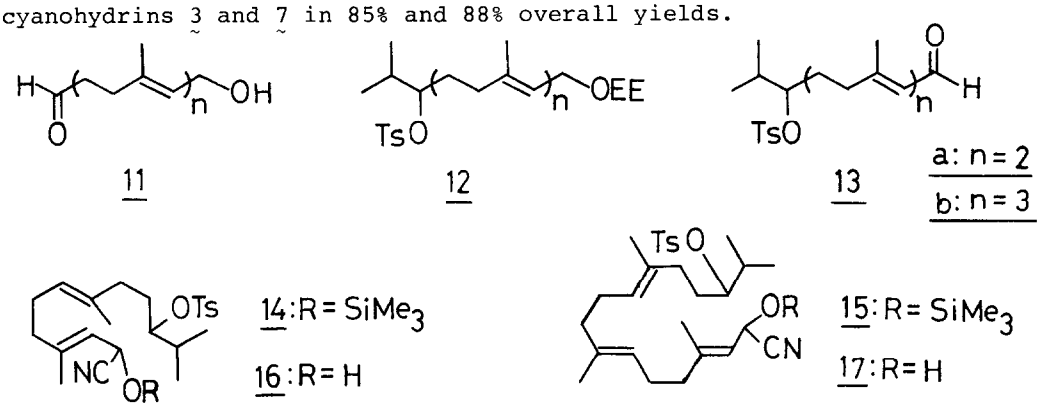
Our cyclizations (Scheme 1) with the secondary tosylates 3 and 7 have the following characteristic feature. (1) High yield of cyclization and efficient introduction of isopropyl groups. (2) The present alkylation proceeds rapidly with inversion of configuration at the carbon atom originally bonded to the tosyl group[7] without undergoing intermolecular alkylation, and hence it is possible to generate the chiral center at α'-position of the labile enone if the secondary tosylate is used as an optically active form. Moreover the labile enone under basic conditions is protected as cyanohydrin ether. Therefore the isomerization of the enone is prevented.




Scheme 1

The key intermediates (*E*,*E*)-dienal 13a and (*E*,*E*,*E*)-trienal 13b were prepared in the following way. Addition of isopropylmagnesium bromide to the ethoxyethyl ethers of 11a and 11b, prepared from geranyl acetate and farnesyl acetate by the method developed in our laboratory[4] and tosylation of the resultant alcohols gave the secondary tosylates 12a and 12b in 83% and 60% overall yields respectively. Removal of 1-ethoxyethyl group of 12a and 12b, and subsequent oxidation of the allyl alcohols with $MnO_2$ gave the enals 13a and 13b in 85% and 78% overall yields respectively. Transformation of the enals 13a and 13b to the protected cyanohydrins 3 and 7 was carried out in the following way. The enals 13a and 13b were converted to the cyanohydrin trimethylsilyl ethers 14 and 15 respectively (trimethylsilyl cyanide, KCN/dicyclohexyl-18-

crown-6-complex, 0°C, 5 min). Removal of trimethylsilyl group in 14 and 15 (benzyltrimethylammonium fluoride in THF/$H_2O$, 0°C, 20 min) and reprotection of the resulting cyanohydrins 16 and 17 with ethyl vinyl ether gave the protected cyanohydrins 3 and 7 in 85% and 88% overall yields.




The cyclization of 3 under various conditions was examined. The use of lithium bis(trimethylsilyl)amide in refluxing benzene proved to be effective to yield the cyclization product 4 in 57% yield. It is noteworthy that the same cyclization using sodium bis(trimethylsilyl)amide was unsuccessful, while the cyclization of 7 using sodium bis(trimethylsilyl)amide in refluxing THF gave the cyclization product 8 in 83% yield. Acid treatments (PPTS/MeOH, 40°C, 1 h) of 4 and 8, and following base treatments (1% aq. NaOH, 0°C, 1 min) of the corresponding cyanohydrins gave Acoragermacrone (5) [IR (neat) 1675, 1600 $cm^{-1}$; Mass 225($M^+$); $^1$H-NMR (400 MHz, $CDCl_3$) see Fig. 1], without formation of isoacoragermacrone (6), and the enone 9 [IR (neat) 1680, 1620 $cm^{-1}$; $^1$H-NMR (270 MHz, $CDCl_3$) δ 2.11, 1.60, 1.52 (vinyl methyls)] in 92% and 86% yields, respectively, after column chromatography. We examined the crude mixtures in both cases by HPLC and none of other isomers could be detected.[9] The structures of the synthetic 5 and 9 were fully confirmed by comparison of their spectra with those of natural Acoragermacrone[10] and an authentic sample of the enone 9,[10] respectively.

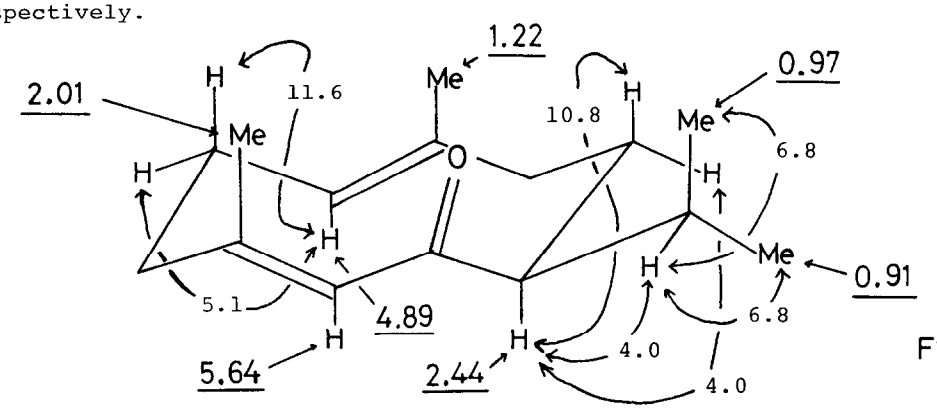



Fig.1

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References and Notes:

1) M. Kodama, Y. Matsuki, S. Ito, Tetrahedron Lett., 1975, 3065; 1976, 1121.

2) Private communication from Prof. T. Kato (Tohoku University).

3) Non-biogenetic type syntheses of 10-membered rings, such as ring-cleavage of bi- or tricyclic compounds, ring-expansion based on Cope, oxy-Cope, and Cope-Claisen rearrangements have been reported (see foot note 4), 5), 6), and 7) in ref. 4). However most of these ring-expansion methods were indirect approaches to the syntheses of (*E*,*E*)-2,6-cyclodecadienones. Another approaches based on nickel,[a] palladium,[b] and titanium[c]-induced cyclization methods were also reported.
   a) E. J. Corey, E. Hamanaka, J. Am. Chem. Soc., 89, 2258 (1976).
   b) Y. Kitagawa, A. Itoh, S. Hashimoto, H. Yamamoto, H. Nozaki, ibid, 99, 3864 (1976); B. M. Trost, R. W. Warner, ibid, 104, 6112 (1982).
   c) J. E. McMurry, J. R. Matz, Tetrahedron Lett., 23, 2723 (1982).

4) T. Takahashi, H. Nemoto, J. Tsuji, Tetrahedron Lett., 24, 2005 (1983).

5) Isolation: a) M. Niwa, A. Nishiyama, M. Iguchi, S. Yamamura, Bull. Chem. Soc. Jpn., 48, 2930 (1975).
   Synthesis: b) W. C. Still, J. Am. Chem. Soc., 99, 4186 (1977).

6) Isolation: a) R. S. Prasad, S. Dev, Tetrahedron, 32, 1437 (1976).
   Synthesis: b) T. Kato, M. Suzuki, T. Kobayashi, B. P. Moore, J. Org. Chem., 45, 1126 (1980).

7) a) T. Takahashi, H. Yamada, J. Tsuji, J. Am. Chem. Soc., 103, 5259 (1981).
   b) K. Deuchert, U. Hertenstein, S. Hunig, G. Wehner, Chem. Ber., 112, 2045 (1979).

8) The reduction of the enone 9 to (±)-Mukulol is known (see ref. 6b)).

9) The longer base treatment (10% aq. NaOH/THF at room temp for 3 days) of 9 gave a mixture of (*E*)-enone 9 and (*Z*)-enone 9 (8 : 1).

10) We wish to thank Prof. M. Niwa of Meijo University and Prof. W. C. Still of Columbia University for NMR, IR, and Mass spectra of natural and synthetic Acoragermacrone and thank Prof. T. Kato of Tohoku University for an authentic sample of the enone 9.

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