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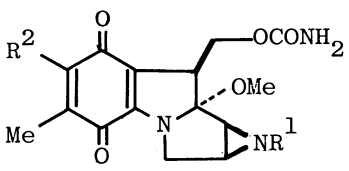
Stereospecific Photochemical Cyclization of Azidoquinone with E,E- and Z,Z-Dienes. Application to the Synthesis of an Important Precursor toward Mitomycins[1)]

Yoshinori NARUTA,* Naoshi NAGAI, Tadafumi YOKOTA,
and Kazuhiro MARUYAMA*
Department of Chemistry, Faculty of Science, Kyoto University,
Kyoto 606

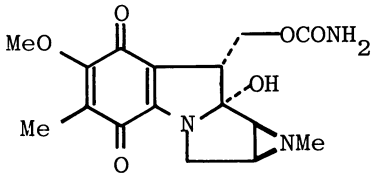
Photochemical reaction of 5-azido-2-methoxy-3-methyl-1,4-benzo quinone with cis,cis-2,4-hexadien-1,6-diol derivatives stereoselectively affords the corresponding 2,3-dihydroindolequinone, which possesses trans configuration at 2,3-position and vinylic double bond preserves the original stereochemistry of the diene. It is efficiently converted to a key precursor in mitomycin synthesis.

Mitomycins (1a-d)[2)] are known to be excellent antibiotics against both gram positive and gram negative bacteria and also against broad range of tumors.[3)] Investigations of their versatile reactivities are one of the recent topics.[4)] Even after the appearance of total synthesis of them,[5)] great number of synthetic works have been published to seek an efficient and shorter route to them.[6)] Our continuous efforts in mitomycin area proved 2 was one of promising candidates toward total synthesis of them.[7)] We designed a new and efficient route to the important precursor 2 based on the following retrosynthetic scheme. C-ring could be cyclized by an appropriate nucleophilic reaction of indole nitrogen to allylic carbon in an intermediate 3, which would be obtained by the cyclization of nitrene equivalent 4 to cis cis-hexadiene derivative. Both to prevent the complexity and to keep high synthetic efficiency in the cyclization stage, cis,cis-hexadiene derivative has to have to high isomeric purity. And also the symmetrical structure in both termini will be helpful for its analysis.

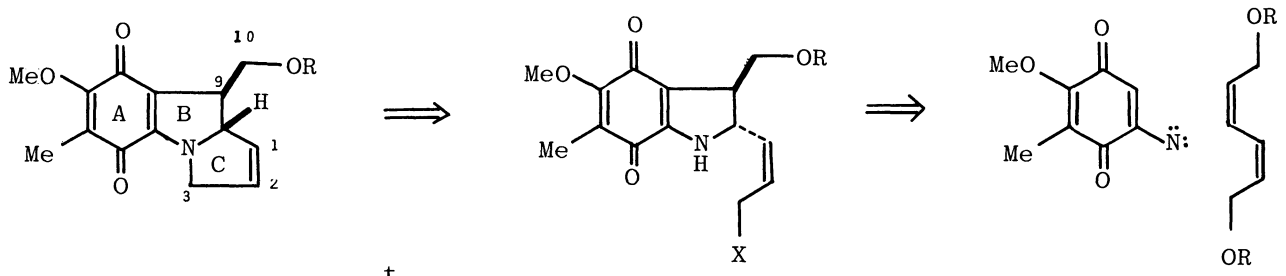
To realize this strategy, the following problems must be solved; (1) cis,cis-2,4-hexadiene derivative with appropriate oxygen functionality at the both termini is prepared with high isomeric purity in quantity, (2) no isomerization of diene double bond should occur under the reaction conditions, (3) in the course of the cyclization the vinylic double bond in 3 must



1a, Mitomycin A
R^1=H, R^2=OMe
b, Mitomycin C
R^1=H, R^2=NH_2
c, porfiromycin
R^1=Me, R^2=NH_2



1d, Mitomycin B



2a, R=Bn **b**, R=$SiMe_3Bu^t$ **3** **4**

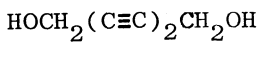
Scheme 1.

preserve cis configuration, and (4) the protecting group of hydroxyl group at C-10 of **2** should be easily removed under neutral conditions.

Recently, we found photochemical reaction of 2-azido-1,4-quinons with conjugated dienes gave the corresponding dihydroindolequinones both with excellent trans stereochemistry concerning 2,3-positions of indole ring and with complete retention of the original stereochemistry of an applied diene in an alkenyl moiety of the photo products.[8,9] We report herein the application of this photochemical cyclization to facile synthesis of a key intermediate **2b** toward mitomycins.

First, we tried synthesis of cis,cis-2,4-hexadien-1,6-diol (**6a**) by partial hydrogenation[11] of hexa-2,4-diyn-1,6-diol (**5**),[10] while it did not afford satisfactory results. Other method of partial reduction[12] did not work well. Consequently, the reduction of monomethyl cis,cis-muconate with diisobutylaluminum hydride in dichloromethane at 0 °C to room temperature successfully gave the desired **6a**[14,15] in 58% isolated yield. This diol was converted to the corresponding t-butyldimethylsilyl ether (**6b**) (94%),[14,15] which was proved to possess >99% cis,cis configuration by analysis with 400 MHz ^{1}H-NMR.

For the comparison of photochemical reaction, trans,trans-isomer (**7a**) (isomeric purity >99%) was easily prepared by hydroalumination of **5** with $LiAlH_4$[13] in THF in



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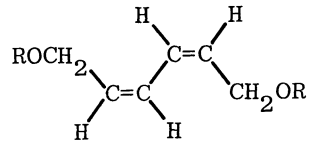
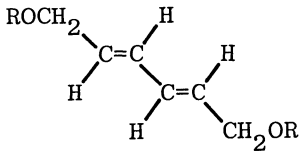
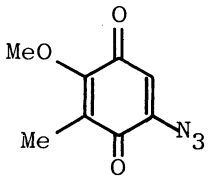


6a, R=H **b**, R=$SiMe_2Bu^t$



7a, R=H **b**, R=$SiMe_2Bu^t$



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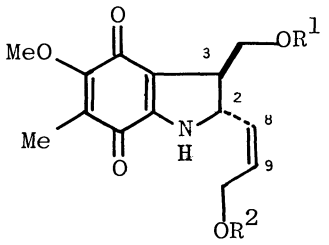
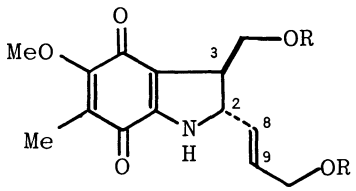


9a, R^1=R^2=$SiMe_2Bu^t$

b, R^1=$SiMe_2Bu^t$, R^2=H

c, R^1=R^2=H

d, R^1=$SiMe_2Bu^t$, R^2=SO_2Me



10, R=$SiMe_2Bu^t$

83% yield.

The photochemical reaction was done as follows; a benzene solution (25 ml) of 5-azido-2-methoxy-3-methyl-1,4-benzoquinone (8) (0.3 mmol) and cis,cis-diene 6b (6.0 mmol) was irradiated with medium pressure mercury lamp through $CuSO_4$ filter at 20 C for 1 h under an argon atmosphere. After chromatographic separation, a single adduct among four possible isomers was obtained in 46% isolated yield. The structure was assigned to be 9a,[14,15] which did not contaminate any other possible stereoisomers. The structure was proved to be 2,3-trans[16] and 8,9-cis configuration. The photoproduct 9a was treated with n-Bu_4NF in THF at 0 °C to afford selectively mono deprotected product 9b (85%)[15] at the allylic alcohol position with trace amount of diol 9c. The monoalcohol 9b was converted to the corresponding mesylate (9d) with treatment of MsCl-Et_3N in ether at 0 °C, and then without isolation of 9d, the reaction mixture was refluxed for 30 min with DBU. After complete disappearance of 9d on TLC, 2b[14,15] was isolated from the reaction mixture in 75% isolated yield. The structure of the final product 2b was also assigned in comparison with the corresponding benzyl ether 2a.[7b] Since the protecting silyl group is easily removable under neutral conditions, 2b is a very useful key intermediate of mitomycins.

As the control experiment of the present photocycloaddition, we examined the reaction of 8 with trans,trans-diene 7b in similar manner. A single photo product was also isolated and its structure was assigned to be 10,[14,15] which possessed trans configuration of the 2,3 positions ($J_{H(2)-H(3)}$=5.8 Hz)[16] and its olefinic double bond at C-2 preserved its original stereochemistry. Consequently, this photocyclization was concluded to proceed in highly stereospecific manner regardless of its original stereochemistry of the applied conjugated dienes.

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14) 400 MHz ^{1}H-NMR data (in $CDCl_3$). 6b: δ 0.06(s, 8H), 0.89(s, 18H), 4.33(d, 4H, J=5.8 Hz), 5.57(m, AA'XX' system, 2H, J=1.4, 2.6, 5.8, 10.1, 11.2 Hz), 6.19(m, AA'XX' system, 2H, J=1.4, 2.6, 10.1, 11.2 Hz).
7b: δ 0.06(s, 12H), 0.90(s, 18H), 4.22(d, 4H, J=4.7 Hz), 5.72(m, AA'XX' system, 4H, J=0.9, 1.9, 4.7, 9.1, 15.3 Hz, CH=C<u>H</u>CH_2), 6.22(m, AA'XX' system, 4H, J=0.9, 1.9, 9.1, 15.3 Hz, C<u>H</u>=$CHCH_2$).
9a: δ 0.05(s, 6H), 0.06(s, 6H), 0.86(s, 9H), 0.91(s, 9H), 1.84(s, 3H, ring Me), 3.19(m, 1H, J=3.6, 5.8, 7.0 Hz, C_3-H), 3.72(dd, 1H, J=7.0, 10.0 Hz, diastereotopic H of CH_2OSi), 3.83(dd, 1H, J=3.6, 10.0 Hz, diastereotopic H of CH_2OSi), 4.08(s, 3H, MeO), 4.20(ddd, 1H, J=1.5, 4.8, 13.4 Hz, diastereotopic H of $C=CH_2OSi$), 4.37(ddd, 1H, J=1.5, 7.0, 13.4 Hz, diastereotopic H of $C=CCH_2OSi$), 4.80(dd, 1H, J= 5.8, 9.1 Hz, C_2-H), 5.36(s, 1H, NH), 5.49(m, 1H, J=1.5, 9.1, 10.6 Hz, C<u>H</u>=$CHCH_2OSi$), 5.64(m, 1H, J=4.8, 7.0, 10.6 Hz, CH=C<u>H</u>CH_2OSi).
2b: δ 0.03(s, 3H), 0.06(s, 3H), 0.87(s, 3H), 0.87(s, 9H), 1.85(s, 3H, ring Me), 3.39(m, 1H, J=3.9, 6.1, 8.5 Hz, $H_{9\alpha}$), 3.60(dd, 1H, J=8.5, 9.4 Hz, diastereotopic H of C_{10}-H), 4.01(m, 1H, $H_{3\alpha}$), 4.03(s, 3H, MeO), 4.08(dd, 1H, J=3.9, 9.4 Hz, diastereotopic C_{10}-H), 4.28(m, 1H, J=1.8, 2.1, 16.7 Hz, $H_{3\beta}$), 4.81(m, 1H, H_{9a}), 5.81 and 5.85(m, 2H, olefinic H).
10: δ 0.00(s, 3H), 0.03(s, 3H), 0.04(s, 6H), 0.84(s, 9H), 1.82(s, 3H, ring Me), 3.21(m, 1H, J=3.9, 5.8, 7.6 Hz, H_3), 3.66(q, 1H, J=7.6, 10.0Hz, diastereotopic H of CH_2OSi), 3.88(q, 1H, J=3.9, 10.0 Hz, diastereotopic H of CH_2OSi), 4.06(s, 3H, MeO), 4.14(d, 2H, J=2.1 Hz), 4.47(m, 1H, H_2), 5.24(br. s, 1H, NH), 5.65(d, 1H, J=15.5 Hz), 5.70(m, 1H, J=2.1, 15.5 Hz).

15) These substances gave satisfactory MS, IR, and ^{1}H-NMR spectra consisted with assigned structures.

16) The corresponding cis isomers of indole ring have lager $J_{H(2)-H(3)}$ (>10 Hz) than the trans isomers ($J_{H(2)-H(3)} \cong 6$ Hz), see Ref. 8.

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