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TOTAL SYNTHESIS OF (±)-EREMOLACTONE

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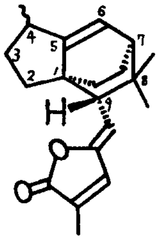
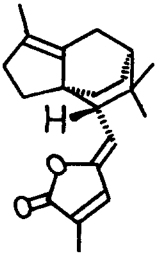
Summary: (±)-Eremolactone and its C-4 epimer were synthesized. By this synthesis, stereochemistry at C-4 is elucidated.

The diterpene eremolactone(1), which has an unusual skeletone, tricyclo-[5.2.2.0^{1,5}]undecane ring system, was isolated from Eremophila fraseri and E. freelingii.1) It was reported that under the recrystallization conditions 1 was partially isomerized to isoeremolactone(2), and the structure of 1 was finally deduced from X-ray studies on 2.2) Therefore the stereochemistry at C-4 has not been assigned yet. In this paper, we will describe the first total synthesis of (±)-eremolactone and its C-4 epimer.3)

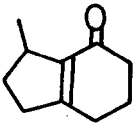


eremolactone
1



isoeremolactone
2

Our synthetic plan involves the double Michael reaction for the construction of the tricyclic ring system. Previous investigations of the double Michael reaction were carried out in basic media in almost all cases,3b,c,4) however, our attempts to synthesize the tricyclic compounds from bicyclic enone(3) and substituted 2-methyl-1-propenes(4) under basic conditions were unsuccessful. Then we applied the Lewis acid promoted Michael reaction5) of silyl enol ether to the double Michael reaction6) using silyl dienol ether, and we achieved success as follows.



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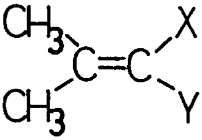
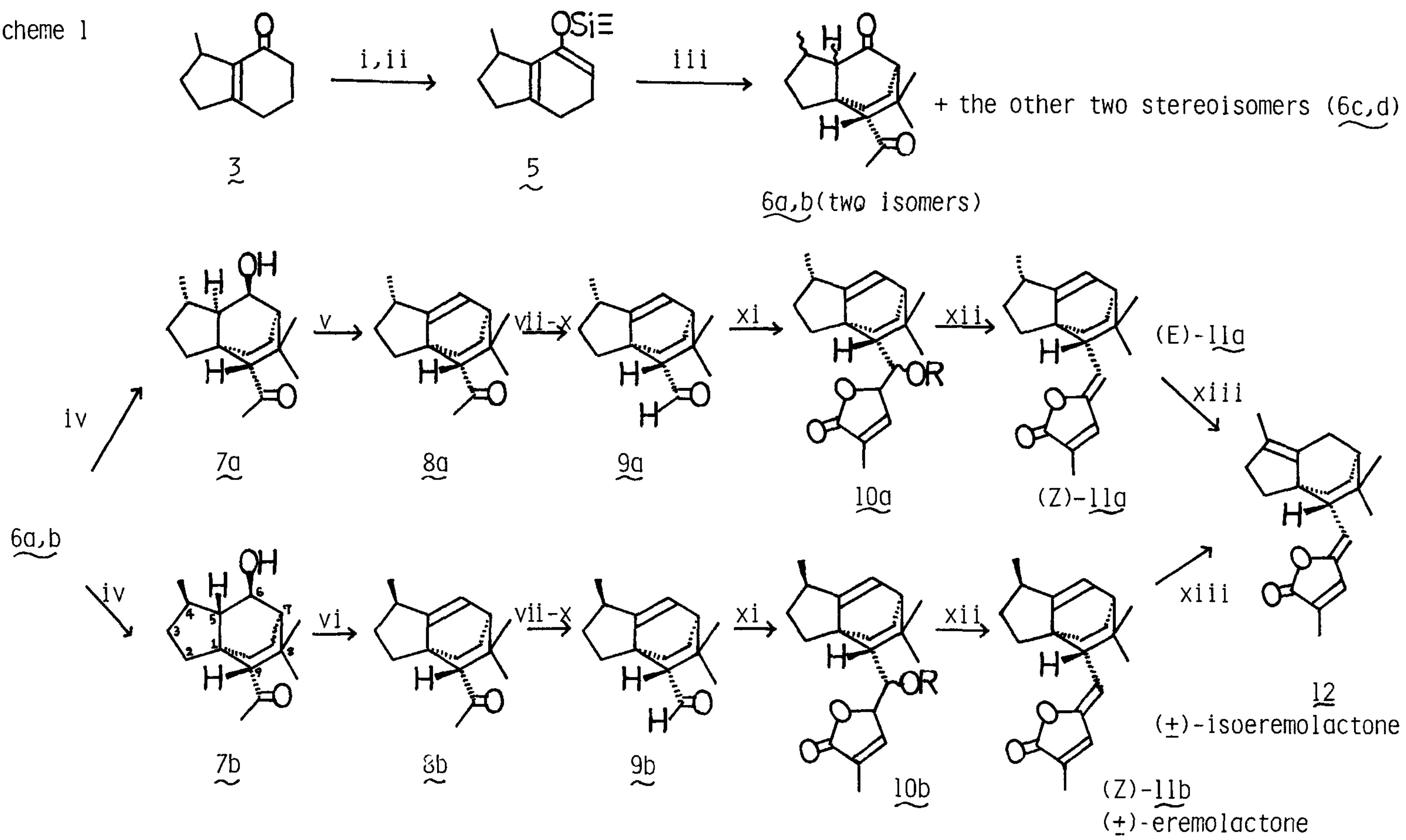


4

Silylation of enone(3)7) under kinetic conditions gave siloxydiene(5, bp 82-83°C/5 mmHg) in 92% yield. The reaction of 5 with mesityl oxide(4, Y=H, X=$COCH_3$) in the presence of titanium(IV) chloride (-78~-40°C, 2h) afforded a ca. 1:2 mixture of 6a and 6b (64% yield)8) and a mixture of the other two stereoisomers (6c and 6d; 17% yield). Sodium borohydride reduction of the former mixture (6a and 6b) gave easily separable two keto alcohols, 7a (29% mp 101-102°C) and 7b (40%, oil), although the latter mixture (6c and 6d) gave

Scheme 1



i) LDA, THF/HMPA, ii) TMSCl, iii) $(CH_3)_2C{=}CHCOCH_3$, $TiCl_4$ CH_2Cl_2 -78°~-40°C, iv) $NaBH_4$. MeOH 0°C, v) $SOCl_2$-PyH, 0°C, vi) $(PhO)_3PCH_3I$,HMPA, vii) LDA, THF/HMPA, TMSCl, viii) MCPBA, CH_2Cl_2 -10°C, then KF/MeOH, ix) $NaBH_4$ MeOH, x) $NaIO_4$, THF/H_2O 0°C, xi) 3-methyl-2-trimethylsiloxyfuran, $SnCl_4$ -78°C, xii) Et_3N, $(CF_3CO)_2O$, PPY, CH_2Cl_2 or DBU, CH_3CN, xiii) EtOH, 2M HCl reflux.

mainly side chain reduced products. The structure of racemic 7a was established as indicated in the scheme by X-ray crystallography.9) The stereochemistry at the C-4 and C-9 positions of 7b was tentatively assigned and later confirmed by the successful transformation to eremolactone and isoeremolactone. The stereochemistry at the C-5 and C-6 of 7b was deduced mainly from the assumption that hydride might attack on the carbonyl group of 6b from less hindered side and from the behavior of the following transformations. Dehydration of 7a with $SOCl_2$-pyridine at 0°C for 4h gave 8a in 72% yield. In contrast to 7a, 7b gave the corresponding dehydration product(8b) only in a very low yield under the same conditions. But the dehydration could be performed in 71% yield by treatment with an excess amount of methyltriphenoxyphosphonium iodide in HMPT at 95°C for 8h, although 8b was contaminated by several percent of double bond migrated isomer. Silylation, oxidation with MCPBA, $NaBH_4$ reduction, and subsequent oxidative cleavage with $NaIO_4$ of 8a gave the aldehyde 9a in 43% yield. Similar treatments of 8b afforded 9b in 45% yield. Reaction of the aldehyde(9a) with 3-methyl-2-trimethylsiloxyfuran in the presence of $SnCl_4$ at -78°C was very slow compared with model reactions,10) probably due to the steric hindrance. To obtain the desired product even in a moderate yield, it required a large excess of the furan (ca. 10eqs.) and a long reaction period(overnight). The reaction mixture was quenched with triethylamine and 10a (R=H, 25% and R=Me_3Si, 42%) were isolated by tlc. Dehydration of 10a (R=H) was carried out by successive treatment with triethylamine-trifluoroacetic anhydride and DBU in dichloromethane to give 11a(E and Z mixture) in 54% yield. The siloxy derivative 10a(R=Me_3Si) also gave 11a(E and Z) in 61% yield by treatment with DBU in acetonitrile at r.t. for 1h. These isomers were separated by tlc from each other. The ratio of (E)- and (Z)-11a was ca. 1:1. Though the mass spectral data of (Z)-11a showed the same fragmentation pattern as those of eremolactone,11) the ^{1}H-nmr spectral data of (Z)-11a12) were apparently different from those of natural eremolactone. Migration of double bond of (Z)-11a to 12 was carried out under acidic condition (2M HCl-EtOH, reflux 2h), and then 12 was found to be (±)-isoeremolactone by the comparison with natural isoeremolactone(2). Therefore (Z)-11a was apparent to be the C-4 epimer of (±)-eremolactone. On the other hand, the reaction of another aldehyde(9b) with the siloxyfuran under the similar conditions gave 10b(R=H) in 50% yield. Dehydration of 10b gave 11b(ca. 1:1 mixture of E- and Z-isomer) in 75% yield. Careful separation of the two isomers by tlc gave (Z)- and (E)-11b. The spectral data (MS, ^{1}H-NMR, IR) of (Z)-11b12) agreed with those of natural eremolactone (1), though the synthetic compound was contaminated with several percent of (±)-isoeremolactone(12). Migration of double bond of (Z)-11b by the treatment with acid gave (±)-isoeremolactone(12), which is identical with that obtained from (Z)-11a. As (Z)-11a was derived from 7a, which structure was confirmed by X-ray analysis, the structure of (Z)-11b, 9b, and 8b, were deduced as shown.

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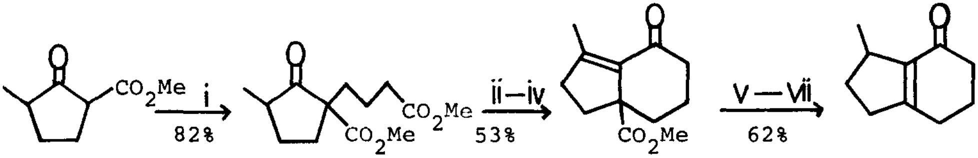
7. The enone **3** was synthesized as follows.



i) $I(CH_2)_3CO_2Me$, K_2CO_3, acetone reflux 24h, ii) cat. TsOH, H_2O-AcOH reflux 7.5h, iii) $NaHCO_3/H_2O$, $NaBH_4$, iv) PPA, Toluene 90°c, 2.5h, v) Pd-C, H_2, vi) LiOH/MeOH, vii) $Pb(OAc)_4$, cat. $Cu(OAc)_2$, benzene reflux 24h.
8. Although these two compounds could not be separated by column chromatography, each of pure samples was obtained by PCC oxidation of **7a** or **7b**. **6a**: Oil; NMR($CDCl_3$): δ=1.04(3H, s), 1.17(3H, s), 1.24(3H, d, J=7 Hz), 2.18(3H, s), 2.54(1H, d, J=2 Hz), 2.82(1H, m). **6b**: Oil; NMR($CDCl_3$): δ= 1.06(3H, s), 1.20(3H, s), 1.24(3H, d, J=6 Hz), 2.20(3H, s), 2.56(1H, d, J=1 Hz).
7a: Mp 101-102°C; NMR($CDCl_3$): δ=0.93(3H, s), 1.08(3H, d, J=7 Hz), 1.46 (3H, s), 2.13(3H, s), 2.85(1H, d, J=2 Hz), 4.26(1H, dd, J=10 Hz, 4 Hz).
7b: Oil; NMR($CDCl_3$): δ=0.96(3H, s), 1.12(3H, d, J=6 Hz), 1.41(3H, s), 2.12(3H, s), 2.48(1H, d, J=1 Hz), 3.81(1H, dd, J=6 Hz, 1 Hz).
9. K. Ishibashi, M. Asaoka, H. Takei, Y. Ohashi, Y. Sasada, to be published, Crystal data: $C_{16}H_{26}O_2$, M=250.37, Monoclinic, space group $P2_1/a$, a=14.607(4)Å, b=9.517(4)Å, c=10.423(3)Å, β=92.27(3)°, V=1447.9(9)$Å^3$, Z=4, Dx=1.149 g cm^{-3}. The structure was solved by direct method and refined by least-squares to the final R facter of 0.093.
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12. (Z)-**11a**: Mp 109-112°C; IR(KBr): 1760 cm^{-1}(C=O); NMR($CDCl_3$): δ=0.90(6H, s), 1.08(3H, d, J=8 Hz), 2.00(3H, s), 2.30(1H, dd, J=12 Hz, 2 Hz), 5.23 (1H, d, J=12 Hz), 5.84(1H, dd, J=8 Hz, 2 Hz), 7.00(1H, d, J=2 Hz).
(Z)-**11b**: Mp 101-105°C; IR(KBr): 1755 cm^{-1}(C=O); NMR($CDCl_3$): δ=0.90(6H, s), 1.14(3H, d, J=8 Hz), 2.02(3H, s), 2.32(1H, dd, J=12 Hz, 2 Hz), 5.24 (1H, d, J=12 Hz), 5.90(1H, dd, J=8 Hz, 2 Hz), 7.02(1H, d, J= 2 Hz).
12: Mp 141-143°C; IR(KBr): 1745 cm^{-1}(C=O); NMR($CDCl_3$): δ=0.91(3H, s), 1.01(3H, s), 1.57(3H, s), 1.99(3H, d, J=2 Hz), 2.66(1H, dd, J=12 Hz, 2 Hz), 5.24(1H, d, J=12 Hz), 7.02(1H, d, J=2 Hz).

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