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EREMOPHILANES

PART I. TOTAL SYNTHESES OF (±)-EREMOPHILENOLIDE AND (±)-FURANOEREMOPHILANE[1)]

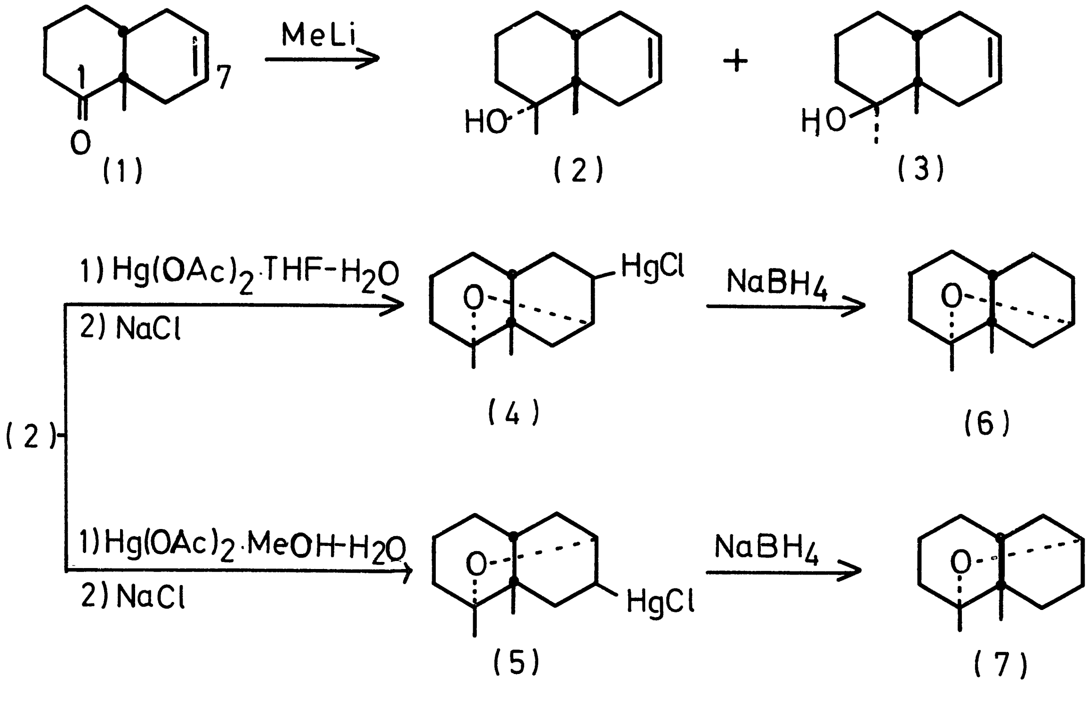
Isao NAGAKURA, Shuichi MAEDA, Masako UENO, Makoto FUNAMIZU, and Yoshio KITAHARA*
Department of Chemistry, Faculty of Science, Tohoku University
Sendai 980

Stereoselective total syntheses of (±)-eremophilenolide (14) and (±)-furanoeremophilane (15) starting from an octalone (1) are described.

Over seventy compounds which belong to eremophilane-type sesquiterpenoids have been isolated from nature. Although at the inception of our work several syntheses had already been published,[2)] we still felt the need for a shorter and more efficient route to eremophilanes because of their physiological activities and their marked structural characteristics. One of the most important problems encountered in carring out our total syntheses of the compounds was stereoselective introduction of adjacent cis-dimethyl groups into the cis-decalin skeleton which is mobile between steroidal and nonsteroidal conformers. We describe here the stereocontrolled total syntheses of (±)-eremophilenolide (14)[3)] and (±)-furanoeremophilane (15).[3a,4)]

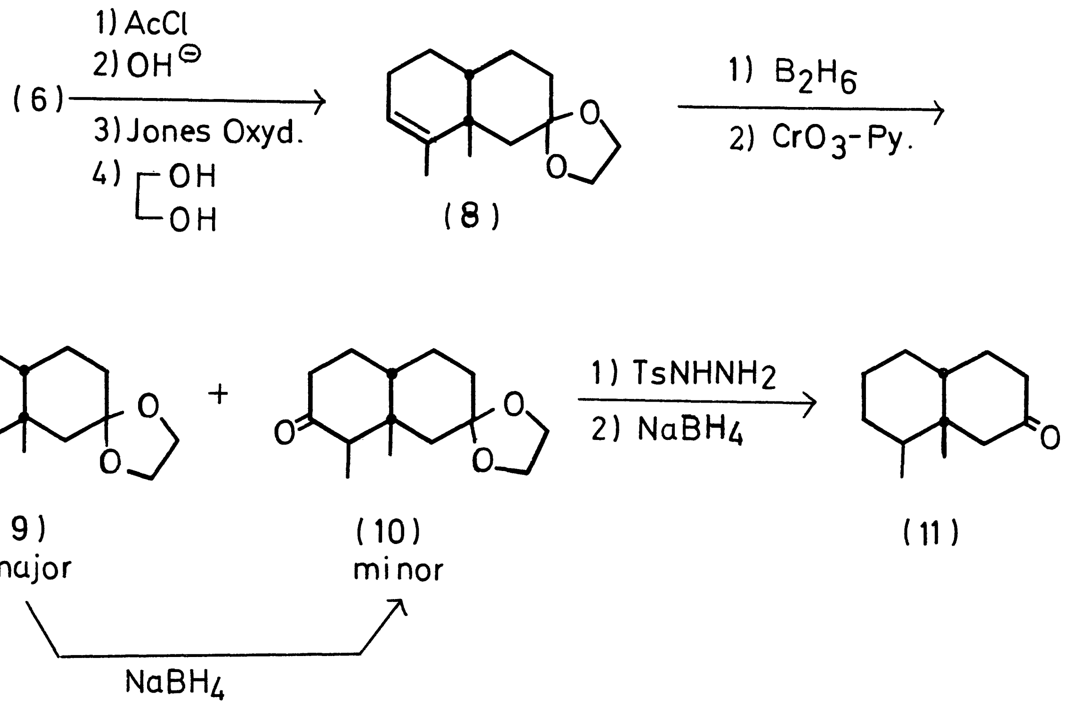
2-Methylcyclohexenone-butadiene Diels-Alder adduct (1)[5)] was methylated with MeLi to give a 63:37 mixture of the epimeric carbinols, (2) and (3), in 94% yield [(2): NMR(CCl_4) δ 0.95(3H, s), 1.03(3H, s); (3): NMR(CCl_4) δ 0.94(3H, s), 1.10(3H, s)]. Although the methylation was not highly stereoselective, the carbinol (2) could easily be separated from its epimer (3) by the formation of the chloromercurial (4), because (3) did not react with $Hg(OAc)_2$. The intramolecular oxymercuration of (2) was markedly influenced by the solvents and reaction time. After addition of (2) in THF to a solution of $Hg(OAc)_2$ in THF-H_2O (1:1), an aqueous NaCl solution was added dropwise to the resultant solution to separate out a five-membered chloromercurial compound (4) as white solid. Using MeOH instead of THF, a six-membered chloromercurial compound (5) was obtained. Reduction of (4) and (5) with $NaBH_4$ afforded oxides, (6) and (7), in 69% and 86% overall yield from (2), respectively [(6): mp 67.5-70.0°C, NMR($CDCl_3$) δ 1.00(3H, s), 1.04(3H, s), 1.38(1H, d, J=12.0 Hz), 2.08(1H, d, d, J=12.0, 6.5 Hz), 4.20(1H, d, t, J=6.5, 2.0, 2.0 Hz); (7): mp 104.5-115°C, NMR(CCl_4) δ 0.86(3H, s), 1.03(3H, s), 3.78(1H, m)]. Prolonged reaction time in THF-H_2O also led to (5) as the major product. These results indicate that (4) is kinetically controlled product and (5) is thermodinamically controlled one. Inspection of models suggests that (4) is more strained than (5).

On treatment with an excess amount of AcCl in the presence of catalytic amounts of $Hg(OAc)_2$, the oxide (6) underwent a ring opening of the ether linkage to give a chloroacetate, which on hydrolysis with NaOH, Jones oxidation and subsequent ketalization with ethylene glycol in the presence of TsOH, gave the unsaturated ketal (8) in 77% overall yield [bp 110°C/1.5 mmHg; NMR(CCl_4) δ 3.84(4H, q), 5.20 (1H, m)]. Thus, by the procedure above described, an O-function could be regiospecifically introduced at C-7 of the octalone (1). (8) was converted to an epimeric mixture of ketones, (9) and (10), by hydroboration and subsequent oxidation with CrO_3-pyridine in 65% yield. The ketone (9) was quantitatively epimerized to (10) by treatment with NaOMe in MeOH at room temperature or by passing through a short alumina column [(9): mp 93.5-94.0°C. IR(KBr) 1700 cm^{-1}, NMR(CCl_4) δ 0.88(3H,

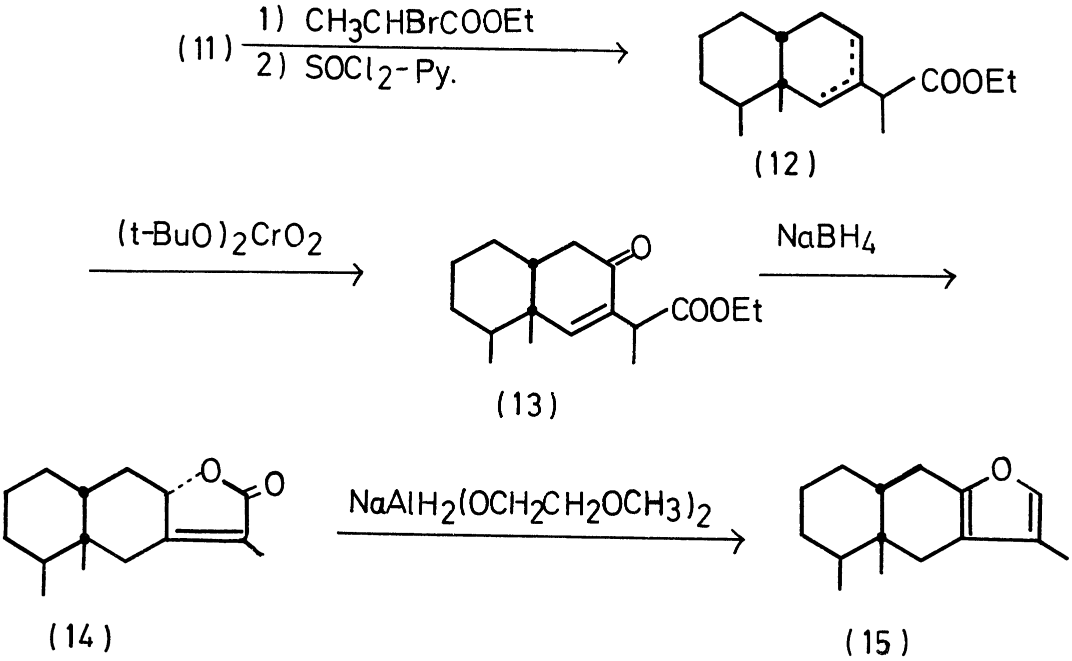


d, J=7.0 Hz), 1.23(3H, s), 2.33(1H, q, J=7.0 Hz), 3.84(4H); (10): mp 81.5-82.0°C, IR(KBr) 1710 cm^{-1}, NMR(CCl_4) δ 0.79(3H, s), 0.87(3H, d, J=6.5 Hz), 3.12(1H, q, J=6.5 Hz), 3.88(4H, s)]. Treatment of (10) with tosylhydrazine in abs. MeOH at room temperature followed by the reaction of the resultant hydrazone (mp 139-143°C, 90% yield) with a large excess of $NaBH_4$ in refluxing dioxane-H_2O (1:1), gave the desired cis-decalone (11) in 67% yield from the tosylhydrazone [(11): bp 69°C (bath temp.)/ 0.1 mmHg: ν_{max} 1710, 1317, 1234 cm^{-1}; NMR(CCl_4) δ 0.85(3H, d, J=6.0 Hz), 0.96(3H, s); 2,4-DNP mp 140-141.5°C (decomp.)]. (11) was spectroscopically (IR and NMR) identical with the ketone prepared by the method of Marshall et al.$^{2a)}$

The decalone (11) was transformed to a mixture of unsaturated esters (12), isomers with respect to double bond, by the Reformatsky reaction with ethyl α-bromopropionate in benzene-toluene (1:1) in the presence of catalytic amounts of $HgCl_2$ and then dehydration with $SOCl_2$-pyridine in 79% yield [(12): bp 80°C (bath temp.)/0.2 mmHg, ν_{max} 1734 cm^{-1}; NMR($CDCl_3$) δ 3.05(1H, q, J=7.0 Hz), 4.16(2H, q, J= 7.0 Hz), 5.50(1H, br. m)]. Allylic oxidation of the esters (12) with $(t\text{-}BuO)_2\text{-}CrO_2$ regiospecifically produced a conjugated enone (13) in 50% yield [(13): bp 110°C (bath temp.)/0.15 mmHg, ν_{max} 1735, 1687, 1635, 1190 cm^{-1}; NMR($CDCl_3$) δ 0.95(3H, d, J=6.5 Hz), 1.14(3H, s), 1.23(3H, t, J=7.0 Hz), 1.28(3H, d, J=7.0 Hz), 6.67(1H, s);



λ_{max}^{MeOH} 239 nm (log ε 4.00)]. Reduction of (13) with $NaBH_4$ in abs. EtOH at room temperature stereospecifically gave (±)-eremophilenolide (14) in 66% yield [mp 111-112°C]. (14) was reduced to give (±)-furanoeremophilane (15) with $NaAlH_2(OCH_2CH_2OCH_3)_2$ in quantitative yield. Our synthetic materials, (14) and (15), were spectroscopically (IR and NMR) identical with the natural compounds.[3,4]



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* To whom correspondence should be addressed.

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