Tetrahedron Letters No. 31, pp 2901 - 2904. 0040-4039/79/0729-2901$02.00/0

REGIO- AND STEREOSELECTIVE CYCLIZATION OF LINALOOL AND NEROLIDOL WITH MERCURIC SALTS. SYNTHESIS OF IRIDANOLS AND CYCLONERODIOL

Yasuo Matsuki, Mitsuaki Kodama and Shô Itô*

Department of Chemistry, Tohoku University

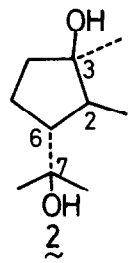
Sendai 980, Japan

Linalool was cyclized in aqueous solvents with Hg(II) salts, thereby iridanediols were formed in ~55% yield with ~85% stereoselectivity, favoring the cis,trans-isomer 2. Utilizing the reaction, cyclonerodiol, a fungal metabolite, was synthesized in a single reaction starting from nerolidol.

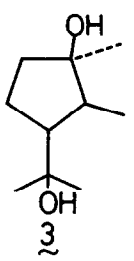
Solvomercuration-demercuration reaction of olefins is widely studied and its use in organic synthesis is well documented[1]. Though the C-C bond formation was observed in the reaction of some polyenes[2], its selectivities are discouraging except in a few cases[3] as a method for the syntheses of cyclic natural products. The Hg(II)-induced cyclization of 3,7-dimethylocta-1,6-diene to iridane carbon skeleton[2c], though a low yield (24%), has attracted our attention because it can be used in biomimetic synthesis of natural cyclopentanoids, if we can improve the yield and control the stereochemistry of the reaction. In view of the known stereocontrol by a neighboring hydroxyl group in oxymercuration[4], we have applied the reaction to allylic alcohols. This paper describes regio- and stereoselective cyclization of linalool to cis, trans-iridane-3,7-diol and of nerolidol to cyclonerodiol, a metabolite isolated from Trichotecium and other fungi[5]. Although thermal cyclization of linalool has been reported to proceed in 56% yield, stereoselectivity is about 50% favoring plinol C, the cis,cis-isomer[6].

Cyclization of linalool Linalool 1 was allowed to react at room temperature for 12 hr under vigorous stirring with 2 molar equivalents of $Hg(OAc)_2$ in aq. THF (75%), the typical conditions for oxymercuration. After alkaline $NaBH_4$ reduction of the organomercurials formed, the products were separated by SiO_2 chromatography and/or preparative GLC. The compounds 2-8 were identified besides some recovery of 1. Their structures were assigned on the following bases: 2 (17% yield); epoxidation and subsequent LAH reduction of known plinol A 9[6,7]: 3 (1%), 4 (1%), 5 (2%) and 6 (7%); comparison of PMR spectra with authentic specimens[6]: 7 (27%, diastereomeric mixture) and 8 (22%, possibly diastereomeric mixture); their PMR analysis and that of the corresponding methyl ketones[8], the CrO_3 oxidation products. The stereoselectivity of the reaction for the cis,trans-iridane-3,7-diol formation was 90%, but their yield was only 19%[9].

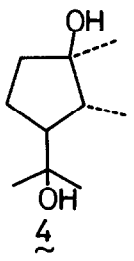
In order to improve the yield of cis,trans-iridanediol 2, we have performed the reaction under various conditions. Some representative results are shown in Table[10]. Plinol A 9[6] and the vinyl ether 10



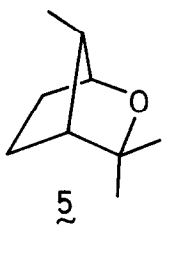
2



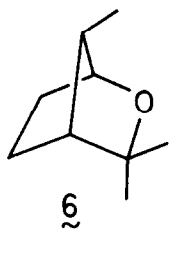
3



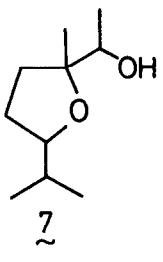
4



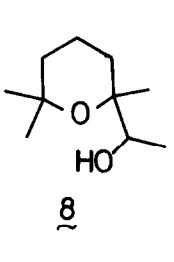
5



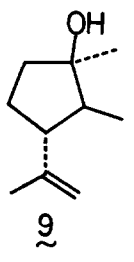
6



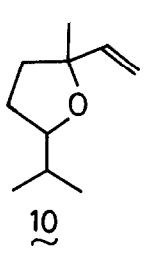
7



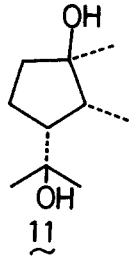
8



9



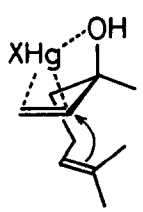
10



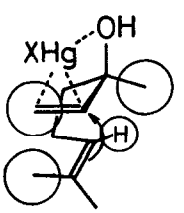
11

(diastereomeric mixture)[11] were newly identified. The analysis revealed that 1) all combinations of the reagents, addends and solvents induce cyclization to iridanols, 2) the kind of mercuric reagents and the presence of a base have little effect, 3) the stereoselectivity in iridanol formation is ~85% favoring 2 in almost all solvents used, 4) the most important factor is the solvent system; H_2O and aq. HOAc give the best result with $Hg(OAc)_2$, while aq. HOAc, aq. t-BuOH and aq. CH_3CN are the best with $HgCl_2$, 5) the reaction period is also important; the reactions in aq. HOAc require less than 1 hr to give the best yield, while in aq. t-BuOH it takes nearly 12 hr and 6) in CH_3CN, the formation of acetamide corresponding to 2 was always observed. Thus, the conversion of linalool to iridanols was achieved with sufficient regioselectivity (56%) and stereoselectivity (85%); much improvement compared with the McQuillin's[2c] and Ohloff's results[6].

Stereoselectivity in iridanol formation The Table discloses the preferential formation of cis,trans-iridanol, and the absence of the fourth (trans,cis) isomer 11 under the all conditions used. This can be explained by the interaction of the hydroxyl group with the Hg atom in π-type complex. Inspection of molecular model reveals that the conformations 2a-4a and 11a, leading to the respective products 2-4 and 11, have steric hindrance to different extents when two reacting centers approach. While 2a has little hindrance, the other three, especially 11a, have considerable hindrance between the circled groups. Thus the steric hindrance in the cyclization step explains the stereocontrol of the iridanol formation.

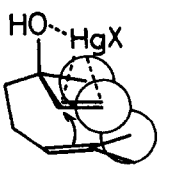


2a(c,t)



3a(c,c)

4a(t,t)



11a(t,c)

Table Products of Hg(II)-induced cyclization of linalool at room temperature

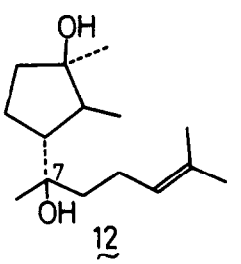
Hg(II)	solv.*2	time(hr)	Iridanols (2+3+4+9) yield*3 %	stereoselectivity (% ratio) 2+9	3	4	recovered 1	5+6	7+8	other products(% yield)*1 10	α-Terpineol
$Hg(OAc)_2$	H_2O	12	52(7)*4	81	8	11	2	6	11		-
	aq. HOAc	1/4	44	73	15	12	4	2	29		-
		1	39(1)	75	12	13	6	3	37		-
		12	56	75	12	13	-	5	-		
	aq. t-BuOH	12	20(2)	80	11	9	2	4	71		-
	aq. CH_3CN	12	24*5	89	11	-	2	1	46		-
$HgCl_2$	H_2O	12	43	49	9	42	4	6	-	1	5
	aq. HOAc	1/4	53(2)	79	13	8	16	6	2	trace	2
		1	40(3)	80	12	8	5	2	3	-	5
	aq. t-BuOH	1	42(4)	84	12	4	10	2	4		2
		12	56(4)	85	11	4	12	2	4		5
		96	54	83	14	3	11	6	1		-
$HgCl_2$+$CaCO_3$	H_2O	12	43(6)	76	12	12	5	7	2	1	6
	aq. t-BuOH	12	56	79	11	10	12	4	7	2	5
$HgCl_2$+$CdCO_3$	H_2O	12	40	79	11	10	12	6	7	2	5
	aq. CH_3CN	12	57*5	77	11	12	3	4	3	trace	1

*1 The rest is nonvolatile polymeric substance. *2 Aq. solvents are 75% vol/vol concentration.

*3 Inclusive yield of 9. *4 Yield of 9 in parentheses.

*5 In addition, acetamide corresponding to 2 is always formed up to 1/3 of 2.

Synthesis of cyclonerodiol Cyclonerodiol 12 is a fungal metabolite isolated from Trichotecium roseum and other fungi[5], and already synthesized by Nozoe[5a] as a diastereomeric mixture in 4 steps starting from linalool. As an extention of our study discussed above, neroridol 13 was subjected to the Hg(II)-induced cyclization reaction. The reaction at room temperature with $HgCl_2$ in aq. HOAc for 30 min. or $HgCl_2$-$CdCO_3$ in aq. acetonitrile for 8 hr, and subsequent reduction and chromatographic separation afforded 12 in 16% and 22% yield, respectively, as a diastereomeric mixture at C_7 [PMR (CCl_4) δ 0.98 (3H, d, J=7), 1.11 (3H, s), 1.20 (3H, s), 1.62 (3H, bs), 1.66 (3H, bs), 5.06 (1H, bt), MS (m/e) 222, 204, 139, 109 (base peak), 82. IR (liq.) 3425, 1450, 1370, 915, 886 cm^{-1}]. In the latter reaction, the vinyl ether (19%) corresponding to 10 was also identified as diastereomeric mixture. Thus, a biomimetic synthesis of cyclonerodiol was achieved.



12

Acknowledgement Thanks are due to Dr. G. Ohloff, Firmenich Cie, for his gift of plinols and to Professor S. Nozoe, Tohoku University, for the authentic sample of cyclonerodiol.

References and Notes

1) Inter al., W. Kitching, Organometal. Chem. Rev., 3, 61 (1968). D. Seyferth, J. Organometallic Chem., 41, 155 (1972). R.C. Larock, Angew. Chem. Intern. Ed., 17, 27 (1978).

2) a. M. Julia et al , Bull. soc. chim. France, 2397 (1966), Ann. Quim., 67, 199 (1971), Tetrahedron Letters, 3429 (1973). b. H.C. Brown, P.J. Geoghegan, G T. Lynch and J.T. Kurek, J. Org. Chem. 37, 1941 (1972). c. F.J McQuillin and D.G. Parker, J. Chem. Soc. Perkin I, 809 (1974).

3) M. Kurbanov, A.V. Semenovskii, W.A. Smit, L.V. Shmelev and V.F. Kucherov, Tetrahedron Letters, 2175 (1972), A.I. Dyadchenko, A.V. Semenovskii, W.A. Smit and M. Kurbanov, Isv. Akad. Nauk, SSSR, Ser. Khim., 1345 (1977).

4) H.B. Henbest and B. Nicholls, J. Chem. Soc., 227 (1959), H.B. Henbest and R.S. McElhinney, ibid., 1834 (1959), S. Moon and B.H. Waxman, Chem. Commun., 1283 (1967).

5) a. S. Nozoe, M. Goi and N. Morisaki, Tetrahedron Letters, 1293 (1970). b. B.E. Cross, R.E. Markwell and J.C. Stewart, Tetrahedron, 27, 1663 (1971).

6) H. Strickler, G. Ohloff and E.sz. Kovats, Helv. Chim. Acta, 50, 759 (1967).

7) Methyl signals in PMR spectra ($CDCl_3$) of 2, 3 and 4 are listed below together with those of the fourth stereoisomer 11 derived from plinol D (Ref. 6). 2: δ 1.05 (d, J=6), 1.20, 1.20, 1.27. 3: δ 1.13 (d, J=7), 1.15, 1.20, 1.34. 4: δ 0.91 (d, J=7), 1.18, 1.21, 1.24. 11: δ 0.93 (d, J=7), 1.23, 1.28, 1.31.

8) 7: ν (liq.) 3450, 1375 cm^{-1}. 8: ν (liq.) 3450, 1385 cm^{-1}, δ (CCl_4) 0.98 (1Me, d, J=6.5), 1.13 (1Me, s), 1.17 (1Me, s), 1.23 (1Me, s), 3.37 (1H, q, J=6.5). Methyl ketone from 7: ν (liq.) 1710, 1365 cm^{-1}, δ (CCl_4) 0.82, 0.93 (2Me, d, J=7.0), 1.12, 1.20 (1Me, s), 2.10 (1Me, s), 3.55 (1H, m). Methyl ketone from 8: ν (liq.) 1712, 1350 cm^{-1}, δ (CCl_4) 1.06 (1Me, s), 1.16 (1Me, s), 1.19 (1Me, s), 2.11 (1Me, s).

9) If the ethers 5 and 6, also iridane derivatives, are included, stereoselectivity for 2 is reduced to 61%, though yield increases to 28%.

10) After the reaction under the conditions shown in Table, pentadecane, an internal standard, was added. The reaction mixture was reduced with alkaline $NaBH_4$ and extracted with ether. Yield of each product was calculated from GLC (chromosorb G-AW-DMCS coated by 5% Apiezon-L and 0.002% Carbowax 20M, temperature, 150°C) with reference to the internal standard.

11) In PMR spectrum of 10 many signals appear as pairs of nearly equal intensity: δ (CCl_4) 0.84 (1Me, d, J=6.5), 0.85 (d, J=6.0); 0.97 (1Me, d, J=6.5), 0.94 (d, J=6.0); 1.23 (1Me, s), 3.54 (1H,m), 4.87 (1H, dd, J=10.5, 2), 4.88 (J=10.5, 2); 5.08 (1H, dd, J=17.0, 2), 5.13 (J=17.0, 2); 5.86 (1H, dd, J=17.0, 10.5), 5.82 (J=17.0, 10.5).

(Received in Japan 25 April 1979)