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DIASTEREOSELECTIVE CYCLIZATION OF 6-OCTEN-1-ALS WITH RHODIUM(I)-COMPLEX

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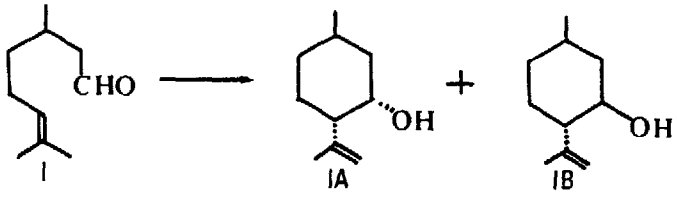
Summary: Rhodium(I)-catalyzed cyclization of 6-octen-1-al with chiral protecting group ((4R,6R)-dimethyl-1,3-dioxane) at the C_3 afforded diastereoselectively the trans-cyclohexanol.

Previously, we reported on Rh(I)-catalyzed stereoselective cyclization[1] of 3,4-disubstituted 4-penten-1-als to cis-3,4-disubstituted cyclopentanones and Rh(I)-catalyzed cyclization[2] of (+)-citronellal (I) to a mixture of the cis-cyclohexanol(IA) and the trans-cyclohexanol (IB) in ratio of 3 to 1.[3]

Now, we report on Rh(I)(Wilkinson complex)-catalyzed diastereoselective cyclization of 6-octen-1-als with chiral protecting group at the C_3-position. Rh(I)-catalyzed cyclization[4] of the aldehydes (IIa,b) with cyclic acetal (1,3-dioxane or 1,3-dioxolane) at the C_3 afforded stereoselectively only the trans-alcohol (IIIa, 60%; IIIb, 55%), and the cis-alcohol was not obtained at all. This trans-cyclization is in contrast to the case of I, 3,3-dimethyl-7-methyl-6-octen-1-al,[5a] and 7-methyl-3-phenyl-4-oxa-6-octen-1-al,[5b] which were cyclized to a mixture (ratio of 3 to 2) of the corresponding cis-alcohols and trans-alcohols[5c] with Rh(I)-complex. This stereocontrolled trans-cyclization



I IA IB

reaction prompted us to cyclize the aldehyde (IV)[6] with chiral protecting group ((4R,6R)-dimethyl-1,3-dioxane) at the C_3. Rh(I)-catalyzed cyclization of IV proceeded to afford only the trans-alcohol (V)($[\alpha]_D^{22}$ -19.79°(c=1.02, EtOH)) in 60% yield, similarly to that of II. Examination of ^{1}H-NMR using shift reagent (Eu(DME))[7] indicated that V should be >99% de. Thus, it was concluded that this cyclization proceeded in diastereoselective manner. Removal of protecting group in V with aq. AcOH (5% aq.AcOH/THF; 5 h at 40°C) afforded the optically active ketone (VI, 75%)($[\alpha]_D^{22}$-11.66° (c=0.24, EtOH). Absolute stereochemistry of (-)-VI was determined to be

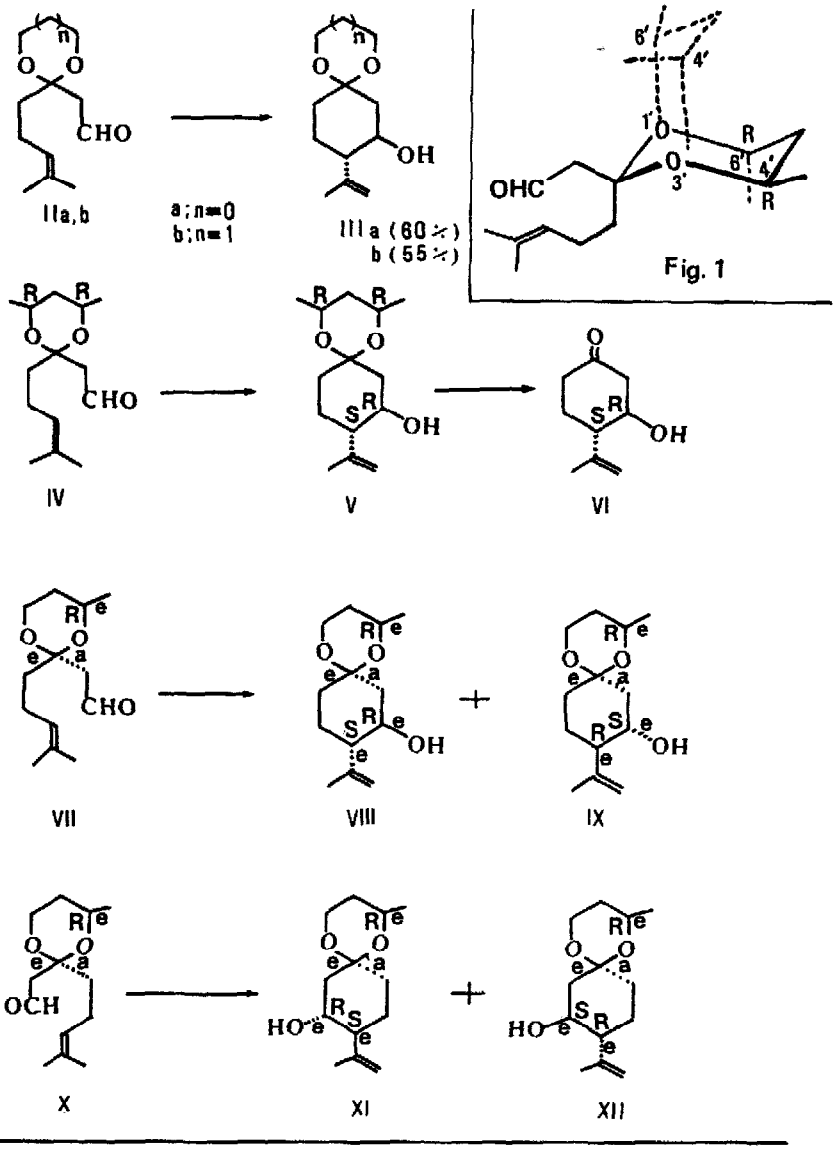
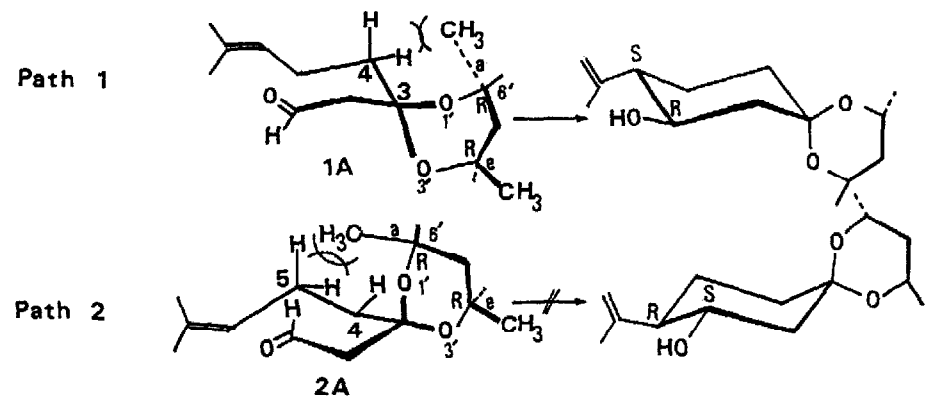

IIa,b
a;n=0
b;n=1
IIIa (60%)
b (55%)
IV
V
VI
VII
VIII
IX
X
XI
XII

Fig. 1


Path 1
1A
Path 2
2A

(3R,4S) by comparison with (+)-VI, in which absolute stereochemistry was established by CD-spectrum to be (3S,4R).[8] The formation of (3R,4S)-(-)-VI allows tentatively to propose the following mechanism. As shown in Fig. 1, a space around the aldehyde function in chair form drawn by full line seems to provide sterically more preferable conditions for cyclization than the dotted line chair form, in which the axial methyl at the C_4, may interrupt the access of bulky Rh(I)-complex. There are two possible path ways (1 and 2) in this cyclization. Consideration of Dreiding stereomodel suggests that 1A conformation causes a steric repulsion between the C_4-H_2 and C_6,-Me(ax). However, the C_6,-Me in 2A conformation occupies sterically more hindered position between the C_4 and C_5. The above difference for steric hinderance allows to proceed via the sterically less hindered 1A to afford (3R,4S)-configuration. Two aldehydes (VII,X)[9] with chiral protecting group (4R-methyl-1,3-dioxane) at the C_3-position were also subjected to Rh(I)-catalyzed cyclization. The aldehydes (VII,X) were cyclized to afford two diastereomeric trans-alcohols; VIII: 40%, $[\alpha]_D^{22}$+6.24° (c=5.00, EtOH); IX: 12%, $[\alpha]_D^{22}$-41.63°(c=3.18, EtOH); and XI: 42%, $[\alpha]_D^{22}$+2.06°(c=1.65, EtOH); XII: 7.0%, $[\alpha]_D^{22}$-42.30°(c=1.68, EtOH), respectively. Independent deprotection[10] of VIII and XI with aq.AcOH afforded (-)-VI (3R,4S)($[\alpha]_D^{22}$-11.64°from VIII, and -11.25°from XI).[11] Thus, chiral protecting group with C_2-axis seems to be effective for diastereoselective cyclization.

References and Notes

1) K.Sakai, J.Ide, O.Oda, and N.Nakamura, Tetrahedron Lett., 1972, 1287; K.Sakai, Y.Ishiguro, K.Funakoshi, K.Ueno, and H.Suemune, ibid., 25, 961 (1984); R.C.Larock, K.Oertle, and G.F.Potter, J. Am. Chem. Soc., 102, 190 (1980); C.F.Lochow, and R.G.Miller, ibid., 98, 1281 (1976).

2) K.Sakai, and O.Oda, Tetrahedron Lett., 1972, 4375.

3) It is well known that Lewis acid-catalyzed cyclization of citronellal afford the trans-alcohol. Y.Nakatani, and K.Kawashima, Synthesis, 1978, 147; S.Sakane, K.Maruoka, and H.Yamamoto, Tetrahedron, 42, 2203 (1986).

4) Each aldehyde was heated at reflux in $CHCl_3$ in the presence of equimolar Wilkinson-complex. Rearrangement of the double bond was not observed under the employed reaction conditions.

5) a; D.J.L.Clive, V.Farina, P.J.Beaulieu, J. Chem. Soc., Chem. Commun., 1981, 643. b; Preparation of the aldehyde will be published elsewhere. c; Structure of the cis- and trans-alcohols was difinitively determined on the basis of ^{1}H-NMR spectra, in which one proton in olefinic protons of cis-alcohol shifted dramatically to the upfield, because of shielding effect by oxygen atom in the alcohol. In the trans-alcohol, this dramatic proton shift was not observed, in accord with the assumption based on stereo-model.

6) Reaction of the dianion of methyl acetoacetate with 4-bromo-2-methyl-2-butene afforded methyl 3-oxo-7-methyl-6-octenoate, which was converted to

to the aldehyde (II, IV, VII and X) by successive treatment with i; ethandiol, or propanediol, or 2R,4R-pentanediol, or R-1,3-butandiol/p-TsOH, ii; $LiAlH_4$, and iii; PCC oxidation.

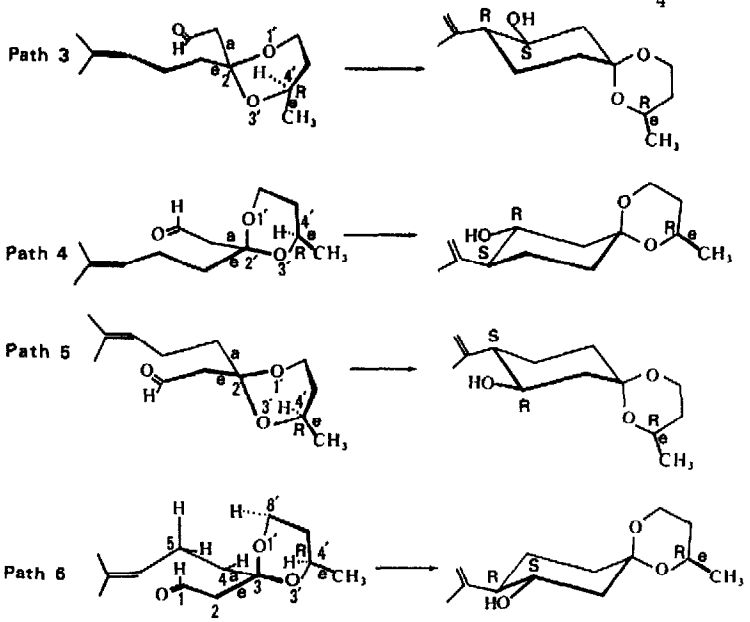
7) P.V.Dermaco, T.K.Elzey, R.B.Lewis, and E.Wenkert, J. Am. Chem. Soc., 92, 5734 (1970).

8) Absolute stereochemistry of (+)-VI ($[\alpha]_D^{22}$+3.0°(27%e.e) obtained by alternative method was determined by CD spectrum ($[\theta]^{24}$= +47.28°(289 nm, MeOH),$\Delta\varepsilon$ = +1.43×10^{-2}) to be (3S,4R).

9) Two aldehydes (VII and X) could be separated by column chromatography on silica gel, and each structure was established by comparison of ^{1}H-NMR spectra with those of two R-1,3-butanedioxy acetals of methyl pyruvate. Based on the finding that, in R-1,3-butanedioxy acetals of methyl pyruvate, axial methyl (δ 1.51) in less polar fraction is observed at the upfield than that of equatrial methyl (δ 1.65) in polar fraction, the formyl methyl function [the C_2-H_2: δ 2.54 (2H, d, J=2.9Hz)] in less polar aldehyde (VII) was assigned to be axial, and more polar aldehyde (X) [the C_2-H_2: δ 2.93 (2H, dd, J=1.5, 3.2 Hz)] was assigned to be equatrial.

10) Independent removal of the protecting group of IX and XII with aq.AcOH afforded (+)-VI.

11) In the cyclization of VII and X, the formation of (3R,4S)-trans-alcohol as main product may be rationalized by the following mechanism. In the cyclization of VII (axial formylmethyl in 1,3-dioxane ring), path 4 may be more favorable than path 3, because the C_4,-H (axial) close to the aldehyde function in path 3 may hinder the access of bulky Rh(I)-complex to the aldehyde function. In X, path 5 (equatrial formylmethyl in 1,3-dioxane ring) seems to be more favorable than path 6, because the C_6,-H (axial) in path 6 causes steric repulsion between the C_4-H and the C_5-H.



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