Communications to the Editor

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SYNTHESIS OF CARBACYCLIN USING RHODIUM(I) COMPLEX

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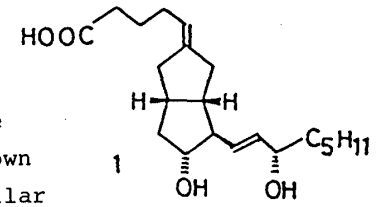
The key intermediate (11) for the synthesis of carbacyclin (1) was synthesized by the application of a new method for stereoselective five-membered ring formation using Wilkinson complex.

KEYWORDS——carbacyclin; Wilkinson complex; cyclization; five-membered ring

As a part of our synthetic studies on biologically active compounds involving a five-membered ring, we have already reported the Rh-complex-catalyzed stereoselective conversion[1] of 3,4-disubstituted 4-pentenals to cis-3,4-disubstituted cyclopentanones. The present paper describes the application of this method to the synthesis of the key intermediate (11) for carbacyclin (1).[2]

For a preliminary ring closure reaction, the aldehyde (2) was prepared from cyclopentanone in 22% overall yield as shown in Chart 1. On heating at 40°C for 20 h in the presence of $RhCl(PPh_3)_3$ (0.4 eq) in CH_2Cl_2 under a nitrogen atmosphere, 2 was converted into the bicyclic ketone (3a) in 51% yield. In this reaction, side products were not detected. The structure of 3a was determined by direct comparison with the authentic sample, which was synthesized from the diketone (3b) via the monothioketal (3c, 1,2-ethanedithiol-BF_3, 27% yield) and subsequent desulfurization (3a, Raney-Ni in EtOH, 63% yield).



The key intermediate (11) was synthesized as follows. The optically active lactone (4) was utilized as starting material, and converted to the aldehyde (5) in 35% overall yield by the manner shown in Chart 2. Ring closure of 5 was performed in similar manner to that of 2 to afford the desired bicyclic ketone (6, 30% yield) accompanied by a side product (7, 23% yield). The structures of 6 and 7 were determined on the basis of spectroscopic analysis [6, IR(neat) 1740cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 4.62(2H,br s,-OCH-O-×2). MS m/z 338(M^+), 253. 7, IR(neat) 1653cm^{-1}. ^{1}H-NMR($CDCl_3$) δ 4.60(2H,br s,-OCH-O-×2), 4.84(2H, br s,=CH_2). MS m/z 310(M^+), 225]. 6 was converted to the key intermediate (11)[3] in the usual manner via 8, 9, and 10 as shown in Chart 3 in 40% overall yield.

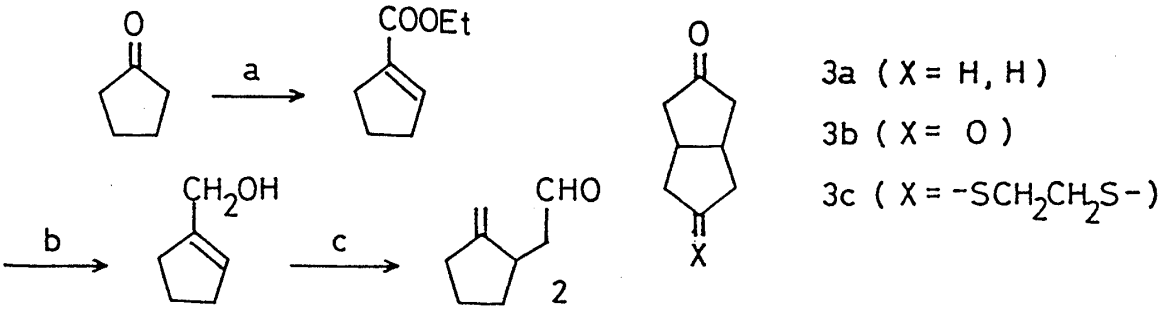


Chart 1 a: i) KCN, 40% H_2SO_4 ii) $POCl_3$ iii) EtOH, H_2SO_4
b; $LiAlH_4$ c; i) $EtOCH=CH_2$, $Hg(OAc)_2$ ii) refluxing in toluene

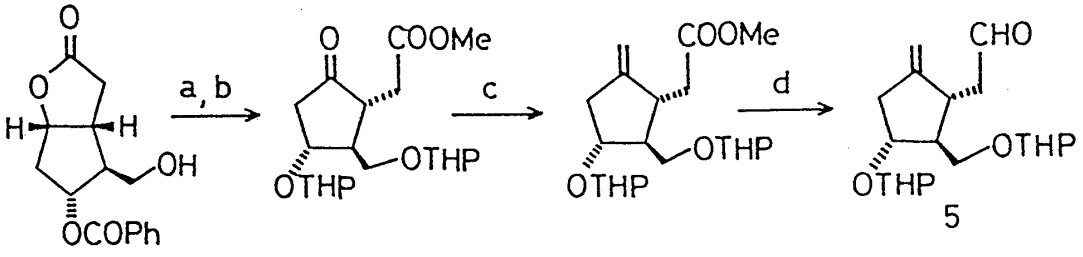
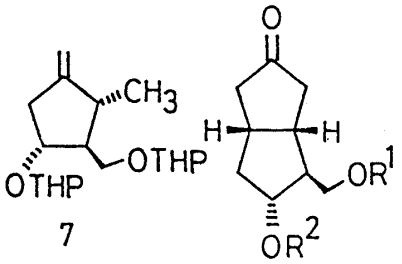


Chart 2 a; i) K_2CO_3, MeOH ii) DHP, p-TsOH b; i) KOH ii) CH_2N_2
iii) Collins oxd. c; i) Ph(Me)S(O)=NMe, MeMgBr ii) Al-Hg
d; i) $LiAlH_4$ ii) Collins oxd.



6 (R^1=R^2= THP)
8 (R^1=R^2= H)
9 (R^1= Tr, R^2= H)
10 (R^1= Tr, R^2= THP)
11 (R^1= H, R^2= THP)

6 $\xrightarrow{a}$ 8 $\xrightarrow{b}$ 9 $\xrightarrow{c}$ 10 $\xrightarrow{d}$ 11

a; p-TsOH, MeOH
b; TrCl, DMAP
c; DHP, PPTS
d; 5% Pd-C, H_2

Chart 3

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REFERENCES AND NOTES

1) K. Sakai, Y. Ishiguro, K. Funakoshi, K. Ueno, and H. Suemune, Tetrahedron Lett., 25, 961(1984).
2) Y. Konishi, M. Kawamura, Y. Arai, and M. Hayashi, Chem. Lett., 1979, 1437.
3) IR and ^{1}H-NMR spectra of 11 were identical with those of an authentic sample.

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