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AN EFFICIENT SYNTHESIS OF ISOCARBACYCLIN STARTING FROM FURFURAL

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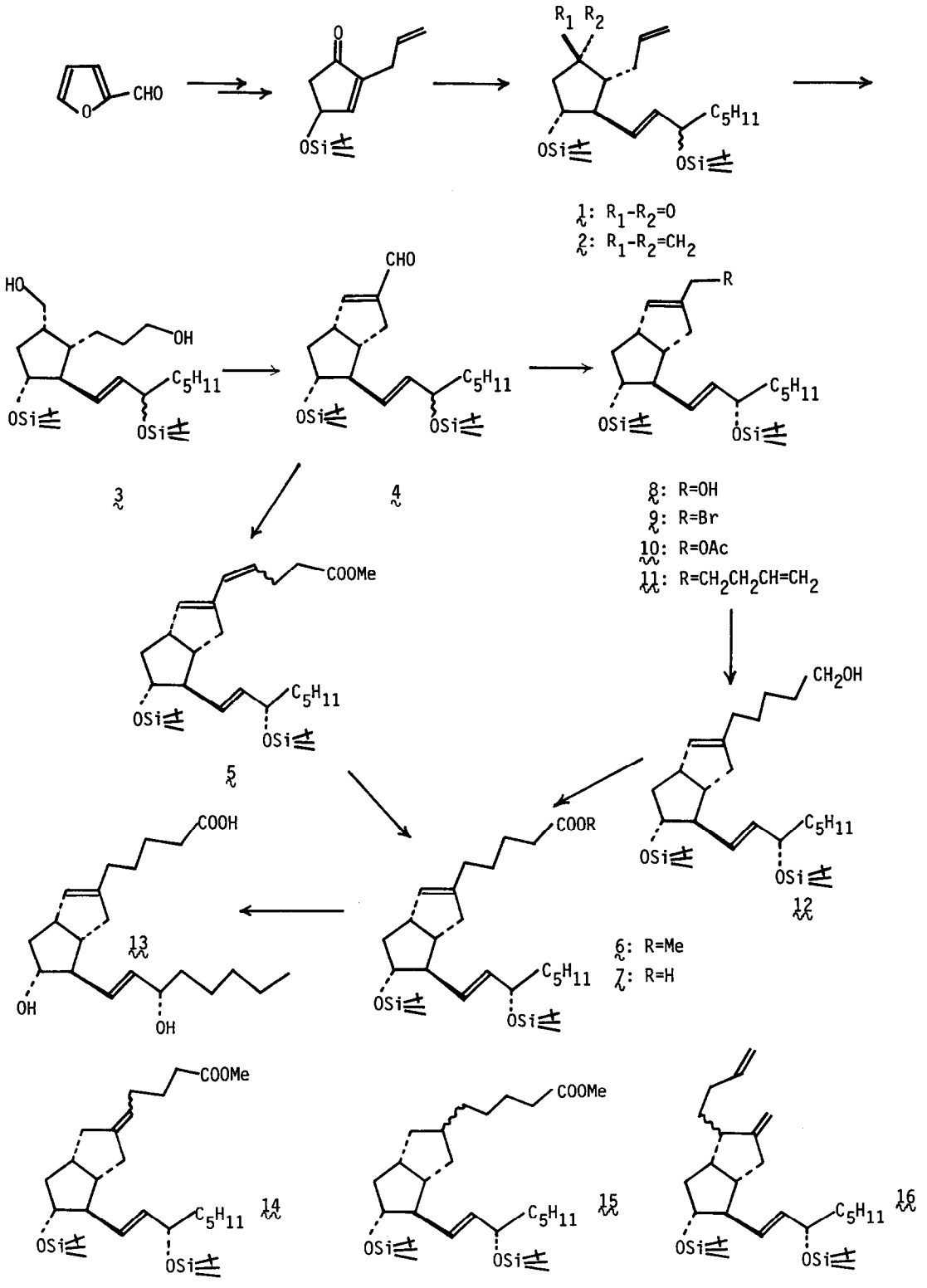
Summary: Two synthetic routes to isocarbacyclin starting from furfural are described. One route involves the regioselective hydrogenation of the disubstituted olefin in the presence of two other olefinic double bonds, and the other includes the highly regioselective organocopper coupling with the allylic electrophile as a key step.

Isocarbacyclin [9(0)-methano-$\Delta^{6(9\alpha)}$-PGI_1] (13) is more potent than carbacyclin in inhibiting platelet aggregation.[1] Recently we have reported two efficient syntheses of 13, both of which involve the Corey lactone as a common key intermediate.[2] Since it became clear that there would be a widespread and continuing demand for 13, we have sought a more direct route, not dependent on the availability of the Corey lactone. An effective and short synthesis of 13 is reported here.

It was anticipated that the conjugated aldehyde (4) would become a key intermediate for the present synthesis. Thus, a large amount of 4 was first prepared by a nine-step sequence starting from furfural as shown below. The allyl-ketone (1), obtainable from furfural in five steps according to the reported procedure,[3] was converted to the diene (2)[4] ($Zn\text{-}CH_2Br_2\text{-}TiCl_4$[5]) (90%). Hydroboration of 2 with 9-BBN followed by treatment with alkaline hydrogen peroxide gave the diol (3)[4] (85%) in a stereo- and regiocontrolled manner. The Swern oxidation of 3 gave a mixture of the dialdehyde and the corresponding aldol, which was subsequently treated with dibenzylammonium trifluoroacetate in benzene at 70 °C to afford the conjugated aldehyde (4)[4] in 85% yield from 3.

With the efficient construction of 4, regiocontrolled transformation of 4 to 13 *via* the 1,3-diene intermediate (5) was first attempted. The diene (5)[4,6] (*E* : *Z* = *ca.* 1 : 2) was prepared from 4 (85%) by treatment with the ylide generated from 3-carboxypropyltriphenylphosphonium bromide[7] and potassium *t*-butoxide in THF followed by esterification with diazomethane. The stereoisomers at C-15 (PG numbering) were separated at this stage, and only the less polar 15-α isomer was used for further transformation. In an attempt toward the regioselective hydrogenation of the 4-5 double bond (PG numbering) in the presence of two other olefinic double bonds, various hydrogenation conditions were examined,[8] revealing that the modified Wilkinson catalyst obtainable from chlorodicyclooctene rhodium(I) and phenyldipiperidylphosphine[9] provides the best result. Namely, hydrogenation of 5 in benzene-ethanol (3 : 1) (7.30 ml/g of 5) by the modified Wilkinson catalyst (24 mol %) under 1 atm of H_2 pressure (25 °C, 4 hr) afforded the desired product (6) (60%)[4] together with the 1,4-reduction product (14)[4] (24%) and the over-reduction product (15)[4] (16%). The desired


CHO
O
OSi
R_1 R_2
C_5H_{11}
1: R_1-R_2=O
2: R_1-R_2=CH_2
HO
OH
CHO
R
3
4
8: R=OH
9: R=Br
10: R=OAc
11: R=CH_2CH_2CH=CH_2
COOMe
CH_2OH
5
12
COOH
COOR
13
OH
6: R=Me
7: R=H
14
15
16

product (6) was easily converted to (±)-isocarbacyclin (13)[4] in two steps (i. aqueous CH_3COOH, ii. aqueous NaOH). Thus, a fourteen steps synthesis of 13 has been accomplished starting from furfural. Although the synthesis described above appears to be the shortest, it suffers from the by-products (14 and 15) whose removal from the desired product (6) is extremely difficult, indicating that this synthesis seems to be unsuitable for the large-scale preparation of 13.

In order to develop a more practical route to 13, we turned our attention to the synthetic approach involving the organocopper coupling with the allylic electrophile. Thus, the conjugated aldehyde (4) was converted to the allylic alcohol (8)[4] (99%) by treatment with $NaBH_4$ in methanol at 0 °C. The stereoisomers at C-15 (PG numbering) were separated at this stage, and the less polar 15-α isomer was used for the next reaction. In the first place, the reaction of the allylic bromide (9)[4] derived from 8 (∿100%) with the reagents such as (a) 3-butenylmagnesium bromide-dilithium tetrachlorocuprate, (b) the Gilman reagent derived from 3-butenyllithium[10] and cuprous iodide, (c) 3-butenyllithium itself[11] was investigated in order to obtain the α-attacked product (11) selectively. However, against our expectations, a large amount of the γ-attacked product (16)[4] was formed in every case (a. α:γ=1:10, b. α:γ=3:2, c. α:γ=3:1). After several attempts, it was found that this selectivity problem was fully overcome by the procedure described below. Thus, the reaction of the allylic acetate (10)[4], obtained from 8 in 94% yield, with the Gilman reagent (2.5 equiv) generated from 3-butenyllithium and cuprous iodide (ether solvent, -78 °C∿r.t.) afforded the α-attacked product (11)[4] (*ca.* 90%) in a highly selective manner together with a small amount of the γ-attacked product (16) (*ca.* 3%) and the allylic alcohol (8) (7%).[12] A mixture of 11 and 16, easily separable from 8 by silica gel column chromatography, was subjected to hydroboration (1.2 equiv of 9-BBN, THF solvent, 0 °C∿r.t.) followed by alkaline hydrogen peroxide oxidation, giving the alcohol (12)[4] in *ca.* 90% yield. At this stage, the γ-attacked product (16) which produced the highly polar diol was easily removed from the desired product. The alcohol (12) was then oxidized to the carboxylic acid (7)[4] by a two-step sequence (65%) (i. SO_3·pyridine complex-triethylamine in DMSO, ii. silver oxide). Finally, treatment of 7 with CH_3COOH-H_2O-THF (3:1:1) afforded (±)-isocarbacyclin (13)[4] in nearly quantitative yield. Thus, a sixteen steps synthesis of 13, which is suitable for the large-scale preparation, has been accomplished starting from furfural. Since the optically active intermediate (1) is also obtainable from furfural,[3,13] it appears that the synthesis presented above provides the most efficient synthetic route to 13 and its analogs.

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References and Notes

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2) (a) Y. Ogawa and M. Shibasaki, Tetrahedron Lett., 25, 1067 (1984); (b) M. Sodeoka and M. Shibasaki, Chemistry Lett., 579 (1984).

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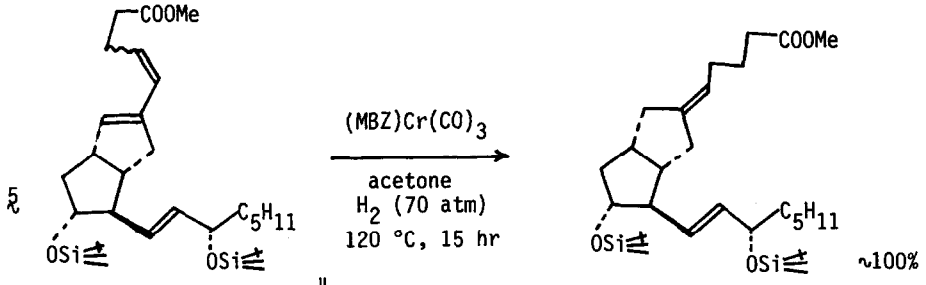
4) Satisfactory infrared, pmr and mass spectral data were obtained on all intermediates described herein using chromatographically homogeneous samples.

5) L. Lombardo, Tetrahedron Lett., 23, 4293 (1982).

6) The diene (5) is also a key intermediate for the stereocontrolled synthesis of carbacyclin , which involves the stereospecific 1,4-hydrogenation of the conjugated diene by $(MBZ)Cr(CO)_3$ catalyst. For the detailed discussion, see: M. Shibasaki, M. Sodeoka, and Y. Ogawa, submitted to J. Org. Chem..



7) W. Seidel, J. Knolle, and H.J. Schäfer, Chem. Ber., 110, 3544 (1977).

8) Among other hydrogenation catalysts examined, the Wilkinson catalyst (benzene solution, 1 atm of H_2 pressure, r.t.~45 °C) provided the rather good result, giving the desired product (6) (45%) together with 15 (50%).

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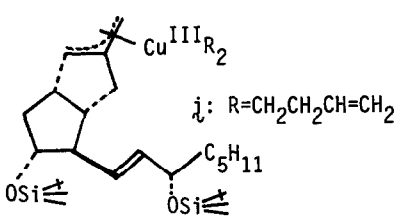
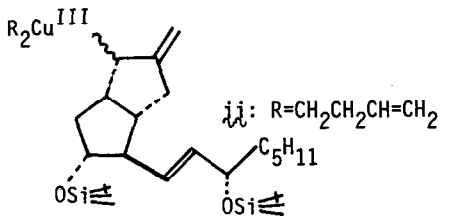
10) R.F. Cunico and Y.-K. Han, J. Organomet. Chem., 174, 247 (1979).

11) Addition of cerium(III) chloride (*ca.* 1 molar equiv.) to the reaction medium increased the α-selectivity slightly.

12) The highly regioselective coupling reaction might be ascribed to the involvement of the η^3 complex (i) rather than ii as an intermediate.





13) The optically active intermediate (1) is also obtainable from 4-*t*-butyldimethylsilyloxy-2-cyclopentenone. See: T. Tanaka, A. Hazato, and S. Kurozumi, Jpn. Kokai Tokkyo Koho, JP 59 44,336.

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