

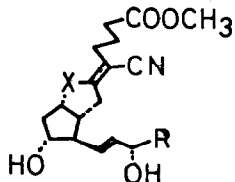
STEREOSPECIFIC CONSTRUCTION OF EXO-TETRASUBSTITUTED OLEFINS.
 THE EFFICIENT SYNTHESIS OF CYANO-CARBACYCLINS¹

Masakatsu Shibasaki* and Mikiko Sodeoka

Sagami Chemical Research Center, Nishi-Onnuma, Sagamihara, Kanagawa 229, Japan

Summary: Cyano-carbacyclins (2 and 3) were efficiently synthesized using the stereospecific 1,4-hydrogenation of the corresponding conjugated diene 1 catalyzed by the arene·Cr(CO)₃ complex as a key step.

Recently we have shown in the synthesis of carbacyclins² that the 1,4-hydrogenation of 1,3-dienes catalyzed by arene·Cr(CO)₃ complexes is an excellent method for the stereospecific construction of exo-trisubstituted olefins. Following and extensive investigation of new functions of arene·Cr(CO)₃ complexes as hydrogenation catalysts³ has led us to find that the 1,4-hydrogenation of 1,3-dienes carrying a cyano functionality at the C-2 position also works smoothly, providing a useful method for the stereospecific construction of exo-tetrasubstituted olefins with a cyano functionality which can be easily converted to a variety of exo-tetrasubstituted olefins.⁴ It is the purpose of this communication to show one application of the above-mentioned method in a stereocontrolled synthesis of cyano-carbacyclins (2 and 3).⁵ Cyano-carbacyclins (2 and 3) are expected to have similar biological profile to that of 1. Nileprost (1) may be of therapeutic value for gastric ulcer because of its potent antiulcer effects with weak antiaggregatory and vasodilating activities.⁶



- 1 X = O , R =
- 2 X = CH₂ , R =
- 3 X = CH₂ , R =

In order to accomplish the stereocontrolled synthesis of cyano-carbacyclins (2 and 3) by using the 1,4-hydrogenation as a key step, the requisite 1,3-diene 1 with the cyano functionality at the C-2 position was efficiently synthesized from 4 as shown in Scheme I. The α,β -unsaturated aldehyde 4 prepared from the Corey lactone⁷ in ca. 70% overall yield was first reduced to the allylic alcohol 5⁸ (DIBAH or NaBH₄) in 98% yield. After conversion of 5 to the bromide 6⁸ (PPh₃ and CBr₄ in CH₂Cl₂ at -60~-25 °C, 89% yield), it was treated with KCN and

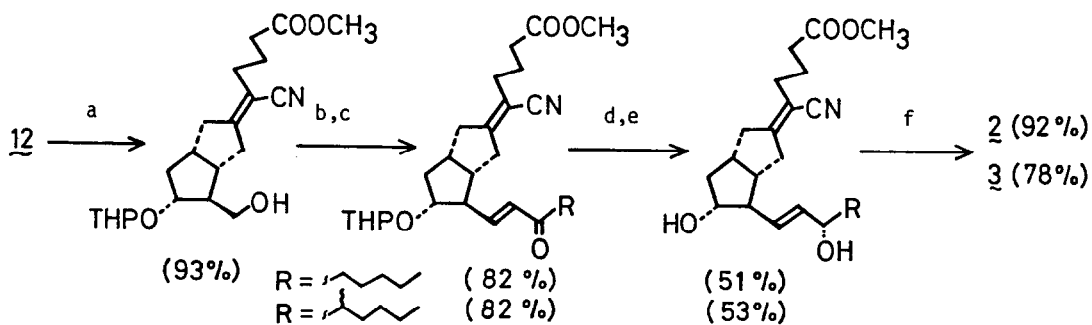
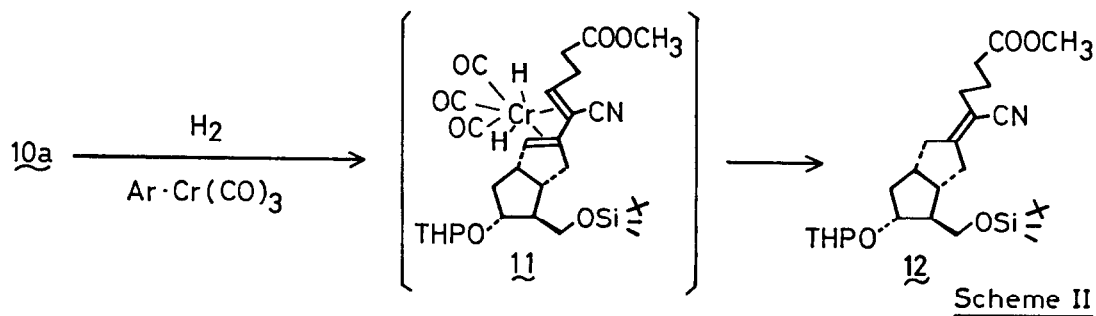
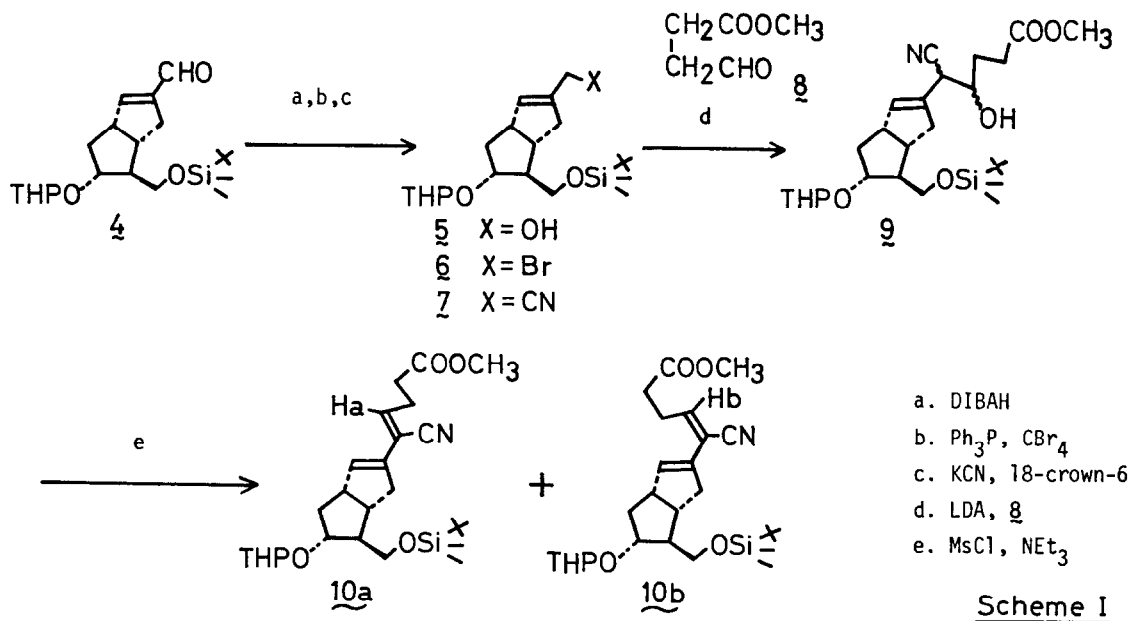
18-crown-6 in CH_3CN to give the allylic cyanide 7^8 in 99% yield. The α -chain was regiospecifically introduced by the coupling reaction of 7 with the aldehyde 8^9 (LDA in THF at -78°C , then 8), furnishing a diastereoisomeric mixture of the cyano-alcohols 9^8 in 64% yield based on conversion of 7 (36% recovery of 7). Subsequently these cyano-alcohols 9 were treated with methanesulfonyl chloride (4 eq) and triethylamine (12 eq) in CH_2Cl_2 . Under these reaction conditions elimination occurred spontaneously to afford a easily separable mixture of the diene $10a^8$ (83%) and $10b^8$ (6%). Stereochemistry of both $10a$ and $10b$ was determined on the basis of their NMR spectra¹⁰ (Ha, δ 6.10, t, $J = 7$ Hz; Hb, δ 6.20, t, $J = 7$ Hz). Furthermore chemical reactivity of $10a$ and $10b$ for the 1,4-hydrogenation reaction supported the above-mentioned stereochemistry.

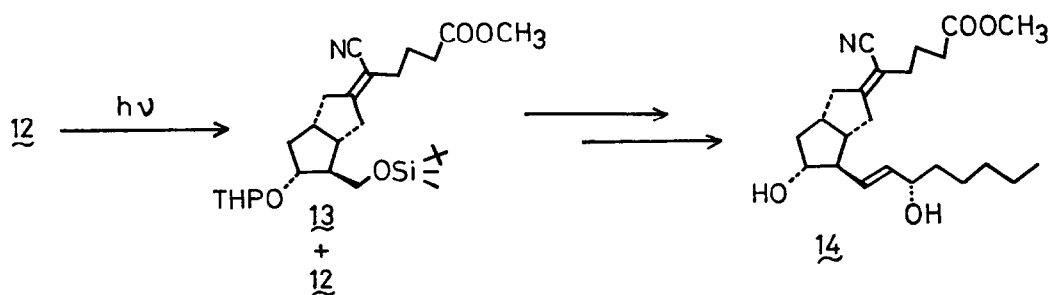
The crucial 1,4-hydrogenation of $10a$ proceeded smoothly via the transition state like 11 by using (methyl benzoate) $\text{Cr}(\text{CO})_3$ as a catalyst to afford the stereochemically homogeneous Z -tetrasubstituted olefin $12^{8,11,12}$ in quantitative yield (20 mol % of the catalyst, degassed acetone solvent, 70 kg/cm^2 of H_2 pressure, 120°C , 15 hr). It was also found that the hydrogenation proceeded under the milder conditions by the use of naphthalene- $\text{Cr}(\text{CO})_3$ as a catalyst (20 mol % of the catalyst, degassed THF solvent, 70 kg/cm^2 of H_2 pressure, 45°C , 21 hr) to give 12 stereospecifically in 97% yield (Scheme II). On the other hand, the 1,4-hydrogenation of $10b$ available in a very low yield remained unchanged under the various 1,4-hydrogenation conditions probably due to steric hindrance around the diene moiety.¹³

Introduction of the ω -chains to the hydrogenation product 12 was accomplished according to the general procedure (Scheme III), and cyano-carbacyclin (2)⁸ and its 16-methyl analogue 3^8 were obtained in 36 and 32% overall yields from 12 respectively.^{14,15}

The absence of the 5- E -stereoisomer 14 in cyano-carbacyclin was confirmed by the following experiments. Irradiation of 12 in benzene at room temperature for 37 hr using a high pressure mercury lamp resulted in the formation of a easily separable mixture of the 5- E -stereoisomer 13^8 and 12 in a ratio of ca. 1 : 1. Subsequently the isolated 5- E -isomer 13 was transformed into 5- E -cyano-carbacyclin (14)⁸ by the same procedure as described above (Scheme IV). Careful TLC analysis of both 14 and 2 showed clearly that cyano-carbacyclin (2) was stereochemically homogeneous, indicating that isomerization of the α,β -conjugated cyanide functionality didn't occur during ω -chain introduction.

On the basis of the arguments presented above, it is concluded that the 1,4-hydrogenation of 1,3-dienes bearing a cyano functionality at the C-2 position provides a useful method for the stereospecific construction of versatile exo-tetrasubstituted olefins.

**Scheme III**

Scheme IVReferences and Notes

- 1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.
- 2) M. Shibasaki, M. Sodeoka, and Y. Ogawa, J. Org. Chem., **49**, 4096 (1984).
- 3) M. Sodeoka and M. Shibasaki, J. Org. Chem., **50**, 1147 (1985).
- 4) Cyano group is easily converted to a variety of functional groups such as aldehyde, carboxylic acid, ester, alcohol and amine etc..
- 5) Cyano-carbacyclin means 5- \underline{Z} -cyano-6 α -carba-PGI₂.
- 6) W. Skuballa, B. Radüchel, and H. Vorbrüggen, Abstracts of Papers, the 5th International Conference, Florence, 1982, p. 515.
- 7) M. Sodeoka and M. Shibasaki, Chemistry Lett., 579 (1984). Recently the process has been optimized, and the overall yield from the Corey lactone has been fairly improved.
- 8) Satisfactory spectral data (NMR, Mass and IR) were obtained.
- 9) The aldehyde 8 was synthesized by hydrogenation of 3-carbomethoxypropionyl chloride, see: A.W. Burgstahler, L.O. Weigd, and C.G. Shaffer, Synthesis, 767 (1976). Since 8 is rather unstable, it is necessary to use freshly prepared 8.
- 10) R.M. Silverstein, G.C. Bassler, T.C. Morrill "Spectrometric Identification of Organic Compounds"; John Wiley & Sons, Inc..
- 11) Stereochemistry of the newly formed olefinic double bond is strongly assumed to be \underline{Z} based on the mechanistic ground of the 1,4-hydrogenation.
- 12) About 10% of the product was obtained as its chromium complex. Although the structure was not clear, this complex was transformed into 12 quantitatively under exposure to air and light.
- 13) In the case of the 1,3-diene bearing no cyano functionality, the 1,4-hydrogenation of the both stereoisomers proceeds smoothly, see reference 2.
- 14) The 15 β -isomers were also obtained (27% with 2 and 33% with 3).
- 15) The biological activities of 2 and 3 will be reported in due course.

(Received in Japan 27 April 1985)