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STEREO- AND REGIOCONTROLLED CONSTRUCTION OF 3-ALKYL-*CIS*-BICYCLO[4.3.0]NON-3-ENE DERIVATIVES. AN EFFICIENT SYNTHESIS OF THE POTENT HOMOISOCARBACYCLIN ANALOG

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Abstract: The stereo- and regiocontrolled synthesis of the potent homoisocarbacyclin analog 2 has been achieved by a general strategy that hopefully will allow the synthesis of other 3-alkyl-cis-bicyclo[4.3.0]non-3-ene derivatives.

In the course of our synthetic studies on chemically stable prostacyclin analogs, we were confronted with the synthetic problem that the Corey lactone 1 had to be transformed into the homoisocarbacyclin analog 2 in a stereo- and regiocontrolled manner[3]. In this communication we wish to report a solution to this synthetic problem, which utilizes 1,4-hydrogenation of the conjugated diene 7 having the dimethyl(phenyl)silyl functionality by Ar•Cr(CO)$_3$ catalyst[4] and protodesilylation of the resulting allylsilane derivative 12 as key steps. By the use of this versatile synthetic technology various 3-alkyl-*cis*-bicyclo[4.3.0]-non-3-ene derivatives are now readily available.

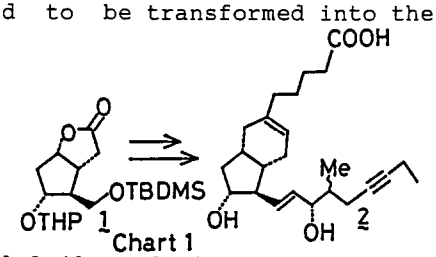
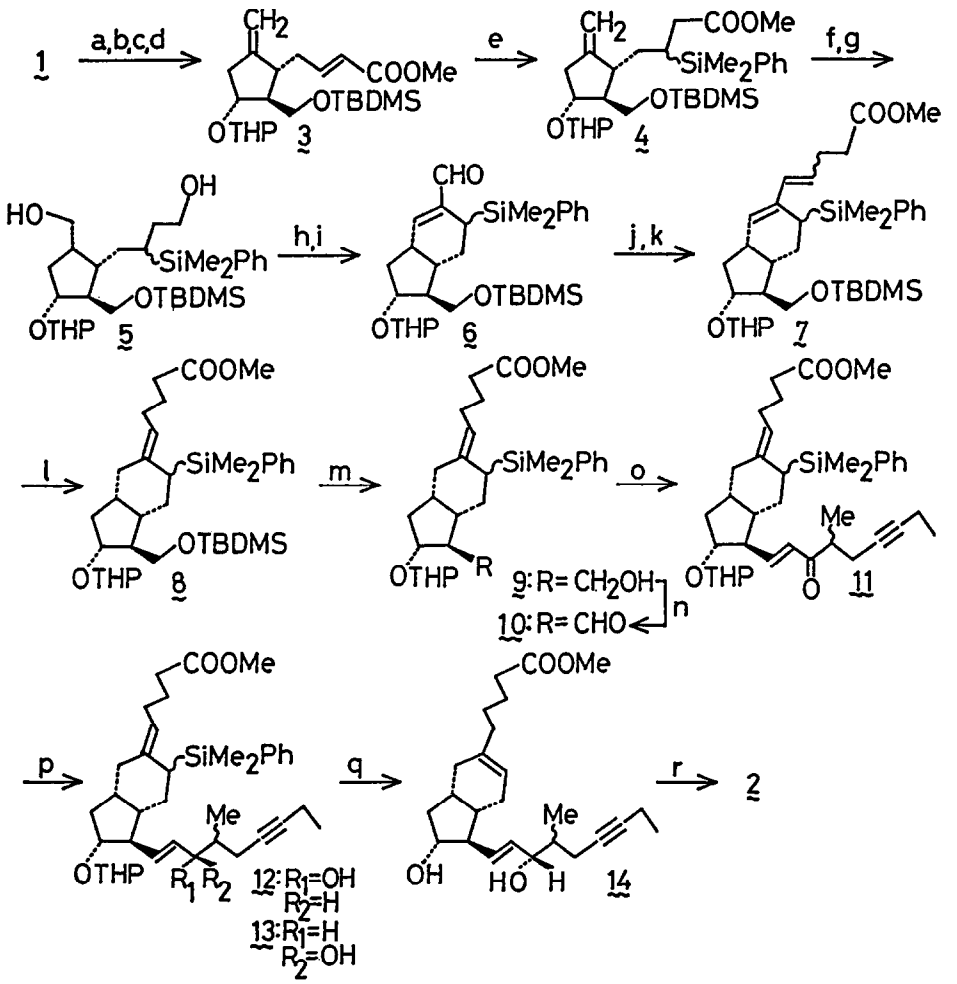


Chart 1

The Corey lactone (1) was efficiently converted to the α,β-unsaturated ester 3[5] in four steps (67% overall yield). Treatment of 3 with dimethyl(phenyl)silyllithium and copper(I) cyanide[6] in THF at 0 °C for 20 min afforded the β-dimethyl(phenyl)silyl-ester derivative 4[5] as a diastereomeric mixture (99% yield). Hydroboration of 4 with $Siam_2BH$ followed by oxidative workup gave the α-hydroxymethylcyclopentane derivative in a stereocontrolled manner (92% yield),[7] which was then reduced with lithium aluminum hydride in THF to furnish the diol 5[5] (98% yield). Swern oxidation of the diol 5 provided the dialdehyde, which, after workup, was heated in toluene at 110 °C in the presence of dibenzylammonium trifluoroacetate to afford the versatile enal 6[5] in a fully regiocontrolled manner (70% yield from 5).[8]

Treatment of 6 with the Wittig reagent derived from 3-carboxypropyltriphenylphosphonium bromide[9] and potassium *t*-butoxide in THF and subsequent reaction with ethereal diazomethane provided the conjugated diene 7[5] in 74% yield (*cis:trans*=2:1). 1,4-Hydrogenation of the conjugated diene 7 with naphthalene•Cr(CO)$_3$ (0.3 eq.) in degassed THF at 50 °C for 12 hr (100 atm of H_2 pressure) afforded the *E*-allylsilane 8[5] in 97% yield.[10] The stereochemistry of 8



(a) Dibah, toluene, -78°C (b) $Ph_3P{=}CHCO_2Me$, toluene, 60°C (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C (d) Zn-CH_2Br_2-$TiCl_4$, r.t. (e) $(Me_2PhSi)_2Cu(CN)Li_2$, THF, 0°C (f) $Siam_2BH$, THF, 0°C, then 6N-NaOH, 30%-H_2O_2, THF, 0°C (g) $LiAlH_4$, THF, 0°C (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C (i) $(PhCH_2)_2NH_2^+ \cdot TFA^-$, toluene, 110°C (j) $Ph_3P{=}CH(CH_2)_2COO^-K^+$, THF, r.t. (k) CH_2N_2, ether, 0°C (l) H_2, Np·$Cr(CO)_3$, THF, 50°C (m) TBAF, THF, r.t. (n) $SO_3 \cdot Py$, Et_3N, DMSO, r.t. (o) $(MeO)_2P(O)CH_2C(O)CH(Me)CH_2C{\equiv}CEt$, NaH, THF, r.t. (p) $NaBH_4$, MeOH, -25°C (q) 1 molar eq. of *p*-TsOH·H_2O, wet-MeCN(MeCN:H_2O=98:2), r.t. (r) 10%-NaOH, MeOH, 0°C

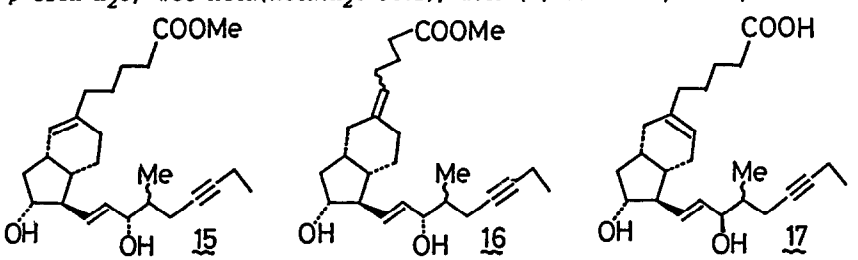


Chart 2

was tentatively determined to be *E* on the basis of the mechanistic ground of 1,4-hydrogenation.[4,11] Removal of a *t*-butyldimethylsilyl group by reaction with tetrabutylammonium fluoride in THF (25 °C, 2.5 hr) led to the versatile alcohol **9**[5] in 81% yield. Oxidation of **9** with sulfur trioxide pyridine complex in DMSO containing triethylamine afforded the aldehyde,[12] which was immediately condensed with the β-keto phosphonate anion derived from racemic dimethyl (2-oxo-3,7-dimethyl-5-heptynyl)phosphonate[13] and sodium hydride in THF to furnish the enone **11**[5] in 86% overall yield. The enone **11** was then reduced with sodium borohydride in methanol , giving the more polar alcohol **12**[5] (48%) together with **13**[5](46%). Treatment of **12** with *p*-toluenesulfonic acid in wet acetonitrile[14] provided the diol **14**[5] in 71% yield. The 400-MHz NMR spectrum of **14** strongly indicated the absence of the regioisomers **15**[3] and **16**,[15] hereby giving the unequivocal proof of regiochemistry of the present synthetic technology. Hydrolysis of **14** with sodium hydroxide in aqueous methanol afforded the homoisocarbacyclin analog **2**[5] in a nearly quantitative yield.

In summation, the efficient synthesis of the homoisocarbacyclin analog **2** has been accomplished by a general strategy that hopefully will allow the synthesis of other 3-alkyl-*cis*-bicyclo[4.3.0]non-3-ene derivatives. Preliminary biological results indicate that the potency of the homoisocarbacyclin analog **2** is a eighth as active as that of prostacylin in inhibiting platelet aggregation induced by ADP in rabbit platelet rich plasma, while the stereoisomer **17** shows essentially no biological activity in this test. These results are extremely instructive in developing a new drug as well as understanding structure-activity relationships of the carbon analogs of prostacyclin.

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References and Notes

1) Visiting scientist from Toa Eiyo Co. Ltd..
2) Present Address: Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan.
3) We have also accomplished the synthesis of potent homoisocarbacyclin **iv** by the strategy shown below, and have found that separation of **2** and **iv** is extremely difficult.
4) M. Shibasaki and M. Sodeoka, *J. Synth. Org. Chem., Jap.*, **43**, 877 (1985), and references cited therein.
5) All structural assignments were confirmed by proton magnetic resonance, infrared and mass spectral data.
6) D.J. Ager, I. Fleming, and S.K. Patel., *J. Chem. Soc., Perkin Trans. 1*, 2520 (1981).
7) Stereochemistry of the α-hydroxymethylcyclopentane derivative was tentatively determined on the basis of the many precedents [e.g. M. Shibasaki and M. Sodeoka, *Chem. Lett.*, 579 (1984)], and was confirmed at the

later stage by comparing with the authentic material. See reference 8.

8) Stereochemistry of the aldehyde **i** discussed in ref. 3 was unequivocally determined by taking the 400-MHz NMR spectrum of **v** derived from **i** (1. Dibah 2. KH, BzBr 3. Et_2AlCl). The aldehyde **i** was further converted to **vi** and **vii**(1. $Ph_3P{=}CH(CH_2)_2CO_2^-K^+$, 2. CH_2N_2, 3. H_2/10%Pd-C, 4. Et_2AlCl, 5. TBDMSCl, Im.). Conversion of the enal **6** to **vi** and **vii** was also carried out(1. $Ph_3P{=}CH(CH_2)_2CO_2^-K^+$, 2. CH_2N_2, 3. H_2/10% Pd-C, 4. *p*-TsOH·H_2O, MeCN, 5. TBDMSOTf, 2,6-Lut. 6. H_2/10% Pd-C). Comparison of both the samples synthesized by the two methods confirmed stereochemistry of the enal **6**.

9) W. Seidel, J. Knolle, and H.J. Schäfer, *Chem. Ber.*, **100**, 3544 (1977).

10) Catalytic hydrogenation of **7** with 10% Pd-C in methanol (1 atm of H_2 pressure, 25°C) provided the less satisfactory result, giving **viii** (60%), **ix** (19%), and **x** (13%).

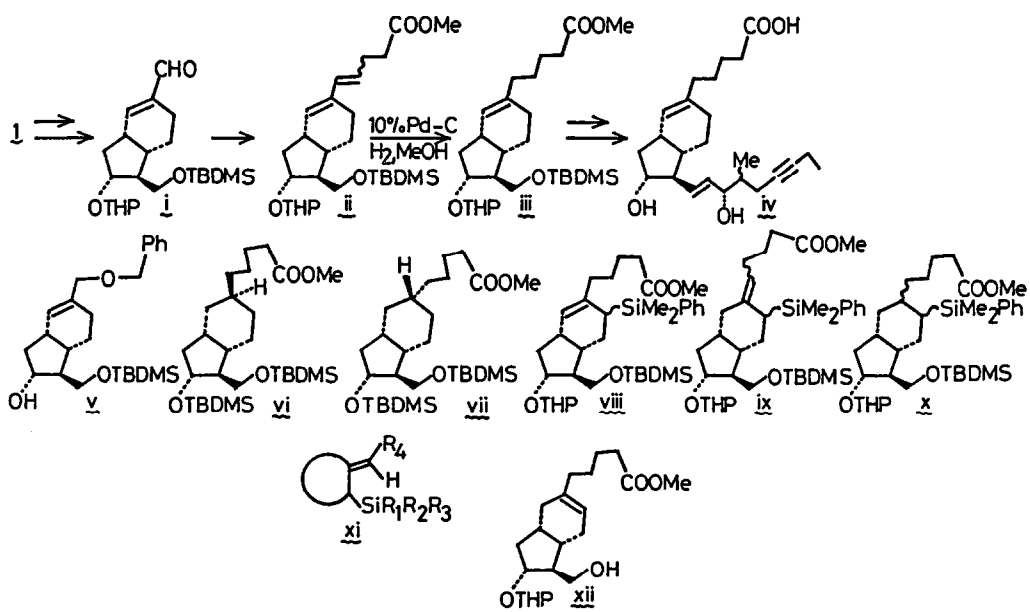
11) This methodology should be useful for the stereocontrolled synthesis of allylsilanes such as **xi**.

12) Oxidation of the alcohol **xii** gave the less satisfactory result, producing the tricyclic products.

13) Separation of the diastereomers at C-17 was found to be impossible. The use of optically pure dimethyl (2-oxo-3,7-dimethyl-5-heptynyl)phosphonate is under investigation. : W. Skuballa, E. Schillinger, C.-St. Stürzebecher, H. Vorbrüggen. *J. Med. Chem.*, **29**, 313 (1986).

14) G.Büchi and H.Wuest, *Tetrahedron Lett.*, 4305 (1977).

15) J.C. Sih, *J. Org. Chem.*, **47**, 4311 (1982).



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