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A New Carbacyclin Synthesis[1]

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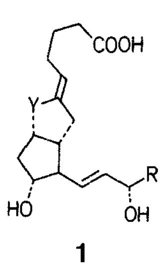
After opening of substituted Corey lactones by alkali, acidification and Jones oxidation to the γ-keto acids, reaction with triphenyl-(phenyliminovinylidene)-phosphorane afforded in 50% overall yield the corresponding unsaturated bicyclo[3.3.0]octane-1-one derivatives, which could be readily reduced to the saturated bicyclic ketones.

Due to the inherent chemical instability of the natural prostacyclin PGI_2[2] (**1a**), a whole range of chemically stable prostacyclin analogs has been synthesized[3]. Among these analogs, carbacyclin (**1b**)[3,4], in which the cyclic enol ether oxygen has been replaced by a methylene group, is of particular interest. Systematic variation of the lower side chain of the carbacyclin led to the clinically useful Iloprost (ZK 36 374)[5] (**1c**) with practically the same biological profile and activity as natural PGI_2[6].



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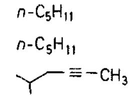
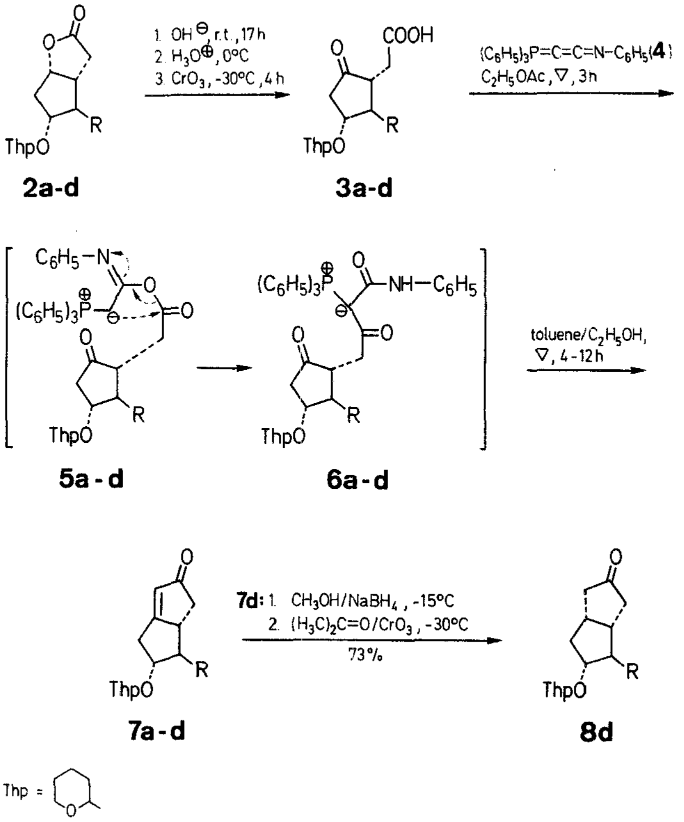
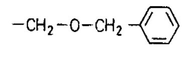
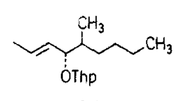
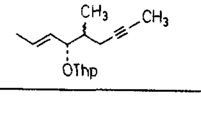
1	Y	R
a	O	n-C_5H_{11}
b	CH_2	n-C_5H_{11}
c	CH_2	

One of the key synthetic problems in carbacyclin chemistry is the synthesis of the bicyclo[3.3.0]octane ring system in its optically active form, for which a number of different synthetic approaches have been reported[3,4,5].

As mentioned in a preliminary report[6], we were intrigued by the facile ring closure of ω-keto acids with triphenyl-(phenyliminovinylidene)-phosphorane (**4**) described by Bestmann et al.[7,8], a method which appeared to be optimally suited for the synthesis of carbacyclins.

Our synthetic pathway started with the Corey lactones **2**, which were opened by alkali followed by careful acidification with citric acid at 0 °C, rapid extraction with dichloromethane, dilution with acetone, and *immediate* addition of Jones reagent to minimize relactonization and elimination of the tetrahydropyranyloxy group. The crude keto acids **3** were then heated for 3 h with triphenyl-(phenyliminovinylidene)-phosphorane (**4**) in boiling ethyl acetate to give **6** via **5**. Heating of **6** with ethanol in boiling toluene for 4–12 h effected elimination of N-phenylurethane for the subsequent internal Wittig reaction, which afforded, after chromatography on silica gel, the desired bicyclo[3.3.0]octane intermediates **7** in 40–50 % overall yield. Only in the case of **2c** containing a dimethyl-t-butylsilyl ether group, which is apparently partially cleaved during alkaline opening of the lactone and subsequent acid treatment, did the overall yield of **7** not exceed 22 %. Since all four reaction steps, including the final chromatography, can be readily performed in less then two days, this sequence to the bicyclo[3.3.0]octane system is an attractive alternative to the existing methods.



2-8	R	Yield [%] of **7**
a		40
b	$-CH_2-O-Si(CH_3)_2C_4H_9$-t	22
c		50
d		54

The compounds **7a**–**7d** show characteristic I.R. bands at 1633 and 1710 cm^{-1} (film) as well as an olefinic proton signal at $\delta = 5.9$ ppm ($CDCl_3$) for their α,β-unsaturated 5-ring ketone in the ^1H-N.M.R. spectra. In addition, the ^1H-N.M.R. spectrum of compound **7d** displays a sharp singlet at $\delta = 1.8$ ppm for its methyl-acetylene group.

The α,β-unsaturated ketones **7** have also been prepared independently via an intramolecular Horner-Wittig cyclization by Aristoff[9], who converted these ketones by 1,4-addition of alkylcopper halides and subsequent Wittig reaction into the biologically potent 9-alkyl carbacyclins[10].

Whereas the *α,β*-unsaturated ketone system in **7c** could be reduced selectively by triethylammonium formate/palladium on carbon[11] in high yields to **8c** without affecting the *trans*-olefin, the same reagent attacked the acetylenic bond in **7d** leading to complicated mixtures. Thus **7d** was reduced with excess sodium borohydride in methanol at −15 °C to the corresponding saturated alcohol followed by Jones oxidation to afford in 73% yield the saturated ketone **8d**, which can be readily converted into Iloprost (**1d**)[5,6]. The reaction of **7d** with other reagents such as sodium borohydride in pyridine, tetra-*n*-butylammonium borohydride, sodium borohydride/nickel(II) chloride, lithium trimethoxyaluminium hydride plus copper(I) bromide, or tri-*n*-butyltin hydride/azobisisobutyronitrile followed by Jones oxidation did not lead to any improvement in the yield of **8d**.

Because of the similarity of the different reaction steps only the preparation of **7d** and its reduction to **8d** is described in the experimental part.

Compound **2d** is prepared from the Corey lactone following standard procedures and using methyl 3-methyl-2-oxo-5-heptynylphosphonate[5] in the Horner-Wittig step.

7*α*-[Tetrahydropyran-2-yl)-oxy]-6*β*-{3′-[(tetrahydropyran-2-yl)-oxy]-4-methyl-6,7-tetradehydro-*trans*-1-octenyl}-bicyclo[3.3.0]oct-1-en-3-one (7d):

Compound **2d** (12.14 g, 27.18 mmol) is stirred in diethyl ether (100 ml) and 1 normal aqueous sodium hydroxide solution (100 ml) at 24 °C for 17 h. The ether phase is separated, the aqueous solution is cooled to 0 °C and carefully acidified to pH = 4–5 with an ice-cold, saturated solution of citric acid in water. The now turbid mixture is rapidly extracted with ice-cold dichloromethane (225 ml) and the extract is filtered through a layer of sodium sulfate in a glass filter funnel. The dried solution is immediately diluted with ice-cold acetone (115 ml), cooled to −30 °C, and then Jones reagent[12] (13.8 ml) is added within 10 min. The mixture is then stirred at −30 °C for 4 h after which time T.L.C. analysis shows only the presence of the *γ*-keto acid **3d** (R_F: 0.40, ethyl acetate) and not the *γ*-hydroxy acid (R_F: 0.16). Excess Jones reagent is then reduced by addition of isopropanol (10 ml) and the resultant green solution is diluted with ice/water (200 ml). Extraction with dichloromethane (600 ml), washing of the extract with ice-cold, saturated, aqueous sodium chloride solution (2 × 100 ml), drying with sodium sulfate, and evaporation affords the crude *γ*-keto acid **3d**. The product is further dried by two successive evaporations with toluene (2 × 50 ml) under vacuum and storage of the residue at 24 °C/0.1 torr; yield: 13.09 g (~100%).

The crude acid **3d** is refluxed for 3 h with triphenyl-(phenyliminovinylidene)-phosphorane (**4**; 11.28 g, 29.89 mmol) in absolute ethyl acetate (250 ml). The ethyl acetate is then evaporated, the crude product **6d** is dissolved in toluene (125 ml) + ethanol (8 ml) and refluxed for 12 h. After evaporation, the residue is extracted with boiling hexane containing acetone to afford, after evaporation, the crude unsaturated ketone **7d** (20.25 g), which is chromatographed on a column of silica gel (1000 g). Elution with 9/1 toluene/ethyl acetate gives impurities (~3 g), subsequent elution with 4/1 toluene/ethyl acetate furnishes the slightly impure, oily product **7d** [yield: 6.44 g (54%); R_F: 0.37 (1/1 toluene/ethyl acetate). Finally, elution with ethyl acetate affords triphenylphosphine oxide.

7*α*-[(Tetrahydropyran-2-yl)-oxy]-6*β*-{3-[(tetrahydropyran-2-yl)-oxy]-4-methyl-6,7-tetradehydro-*trans*-1-octenyl}-bicyclo[3.3.0]octane-3-one (8d):

A solution of the slightly impure **7d** (0.11 g, 0.25 mmol) in methanol (6 ml) is stirred at −15 °C and sodium borohydride (0.047 g, 1.25 mmol) is added in portions during 15 min to control the foaming. After stirring at −30 °C for further 30 min, T.L.C. analysis (ethyl acetate) shows, like **7d**, a spot at R_F: 0.37, which however, has *no* U.V.-adsorption and, besides, a weak spot at R_F: 0.31 for the allylic alcohol. After addition of acetone (5 ml), the mixture is warmed up to 24 °C, evaporated, and taken up in dichloromethane/water (25 ml/25 ml). This mixture is extracted with dichloromethane (2 × 25 ml), the extract is dried with sodium sulfate, and evaporated. The crude product (0.11 g) in acetone (3 ml) is treated at −30 °C with Jones reagent[12] (0.14 ml). After 1 h at −30 °C, isopropanol (0.5 ml) is added and the mixture is kept at −30 °C for 10 min. Work-up with ice/water/diethyl ether gives the crude product (0.14 g) which is chromatographed on a column of silica gel (10 g). Elution with 9/1 toluene/ethyl acetate gives pure **8d** [yield: 0.08 g (73%); physical properties identical to those of an authentic sample[5]], further elution affords slightly impure **7d** [yield: 0.012 g (11%)].

We thank Professor H.J. Bestmann for making triphenyl-(phenyliminovinylidene)-phosphorane (4) available to us. We are further indebted to Dr. D. Rosenberg and Dr. A. Seeger for the physical data.

Dedicated to Professor Dr. H.J. Bestmann on the occasion of his 60th birthday.

Received: June 7, 1985

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