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High Stereoselectivity in the Wittig Reaction Induced by the Interaction of Charges

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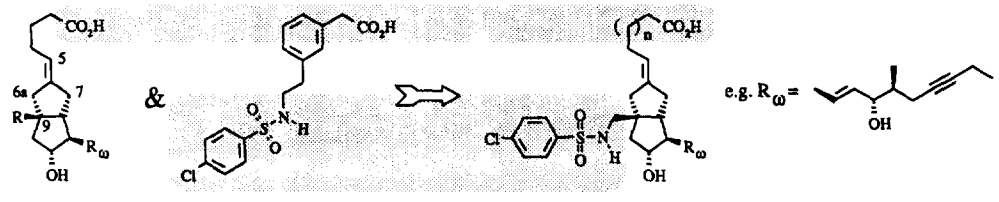
Abstract: The synthesis of carbacyclin analogues **I** based on the introduction of an α-chain to a suitable substituted bicyclo[3.3.0]octan-3-one derivative like **5** by a Wittig reaction leads generally to nearly 1:1-mixtures of E/Z-isomers. This lack of selectivity will change dramatically, if an acidic sulfonamide in the bicyclic framework is present. The observed Z-selectivity can be explained by an interaction of charges of the deprotonated sulfonamide and the electrophilic phosphorous atom in the Wittig reagent. Copyright © 1996 Elsevier Science Ltd

In the course of our cardiovascular program to find new and more selective PGI_2-agonists we synthesized 9-substituted carbacyclin analogues[1] like **I**. Different alkyl-type substituents R are well tolerated by the prostacyclin (IP) receptor as has been demonstrated by several biological assays[2]. In addition we were interested in the synthesis of pure thromboxane receptor (TP) antagonists devoid of any partial agonist activity which, in combination with carbacyclins, might act in a synergistic manner. In such a combination the dose and therefore the side effects of the IP component might be reduced so that the spectrum of therapeutic applications can be expected to be broadened. Because a variety of potent TP receptor antagonists like BM 135033, S-145[4] and Bay-u-3405[5] combine a carboxylic acid and an aryl sulfonamide moiety separated by different types of spacers within one molecule, we tried to add a TP-antagonistic quality to the carbacyclin skeleton by introducing an aryl sulfonamide in position 9, to obtain hybrid compounds of type **II**[6].



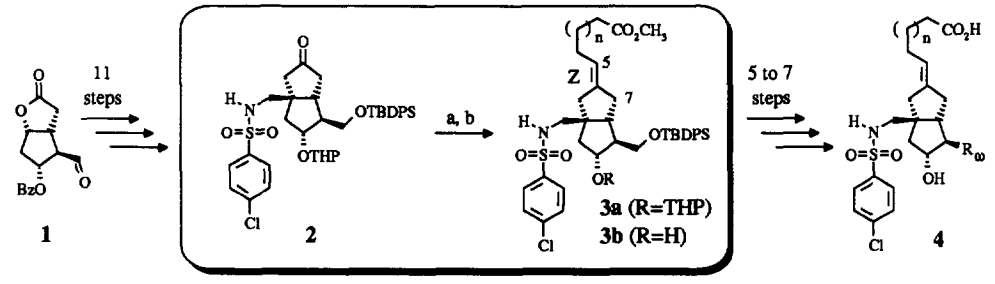
I (R: H, subst. alkyl, alkinyl) — **IP-agonist**

BM 13505 (Daltroban) — **TP-antagonist**

hybrid-system **II** (n: 0, 1) — **IP-agonist & TP-antagonist ?**

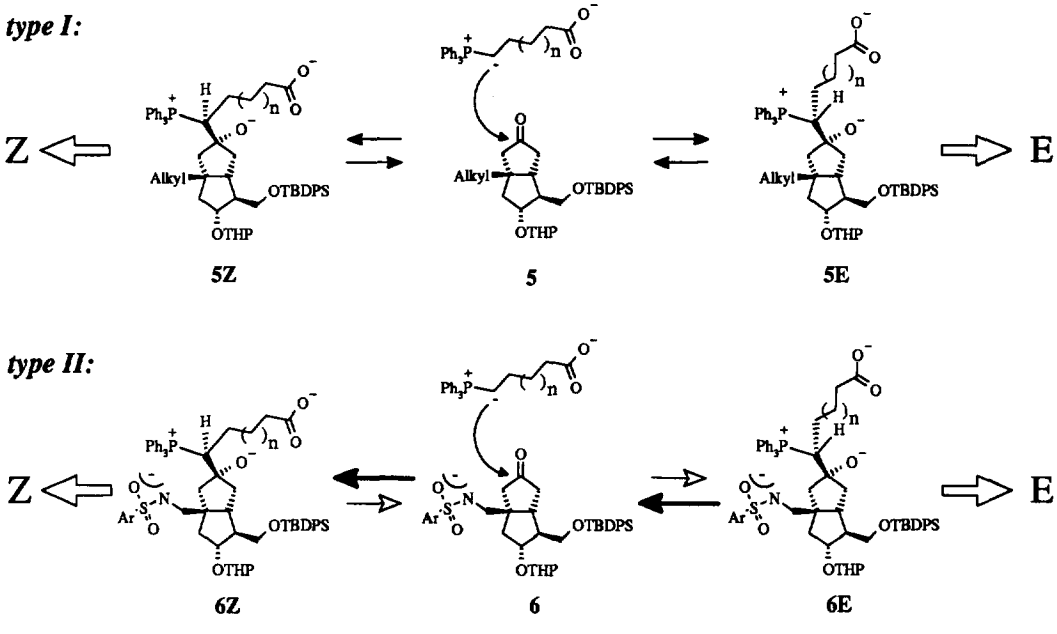
Although the synthesis of type I compounds was already reported in detail[2], it should be emphasized that the α-chain is normally introduced in an unselective manner by a Wittig reaction leading to a nearly 1:1-mixture of double bond isomers at position 5 which, in general, can be readily separated by column chromatography after all protecting groups have been removed at the final step of the synthesis.

From the viewpoint of the attacking nucleophilic ylide-carboxylate the rooflike bicyclic ketone might therefore be considered as a "prochiral" molecule, since the alkyl substituents at positions 9 and 12 are quite remote.
In contrast to these prior results, the Wittig reaction of ketone **2** under the previously used conditions proceeded in a highly stereoselective manner regardless of the length of the α-chain (n= 0,1). After the tetrahydropyranyl ether of **3a** was removed, only a single isomer was isolated which was assigned the Z-configuration based on a strong nuclear Overhauser effect between the proton at C-5 and one proton at C-7[7] of **3b**[8].



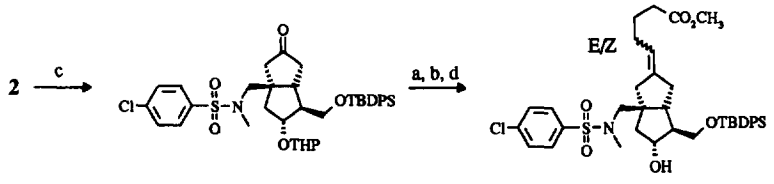
a: LiHMDS, carboxybutyltriphenylphosphonium bromide (for n=1) or carboxypropyltriphenyl-phosphonium bromide (for n=0), THF, 30°C-60°C, 2-6h; b: CH_2N_2, ether, CH_2Cl_2, 3°C, 1h; SiO_2.

Mechanisms involving special interactions in which the ω-carboxylate salts participate[9] cannot account for the observed selectivity, since these interactions which were supposed to depend also upon the carboxylate chain length, should be the same in both types of compounds discussed here.



To explain this unexpected selectivity one has to consider the major differences between type I and type II compounds. In both cases, the nucleophilic attack of the bulky ylene from the β-face may be assumed to be predetermined by the convex conformation of the bicyclic ketone. The geometry of the olefin is controlled by the absolute configuration of the chiral center at the carbon α to the phosphorous atom formed as an intermediate, so that the E/Z-ratio must reflect the energetic differences leading to or stabilizing intermediates **5Z/6Z** versus **5E/6E** before the elimination of triphenylphosphinoxide from the betaine and/or oxaphosphetane can occur. The observed Z-selectivity for type II compounds might therefore be explained by an *intermolecular interaction* of the charges at the deprotonated sulfonamide and phosphorous prior to the stereoselective C-C bond forming step, leading *a priori* to the preferential formation of intermediate **6Z**. In addition, a charge induced *intramolecular stabilization* can be supposed shifting the equilibrium to **6Z** from which the Z configuration is generated as indicated in the sketch above.

As a consequence, on replacing the acidic arylsulfonamide proton by a methyl group a loss in selectivity should be expected. In accordance with this hypothesis, the methylated arylsulfonamide **7** on Wittig reaction gave a nearly 1:1-mixture of E/Z-isomers **8** as it was already observed in the synthesis for type I carbacyclins.



7 **8**

a: LiHMDS, carboxybutyltriphenylphosphonium bromide, THF, 30°C-60°C, 2-6h; b: CH_2N_2, ether, CH_2Cl_2, 3°C, 1h; SiO_2; c: NaH, CH_3I, DMF, 23°C, 1h; SiO_2; d: cat. PPTs, ethanol, 55°C, 10h; SiO_2.

Similar interactions may be responsible for the observed selectivities with a number of quite different substrates[10], emphasizing the generality and potential of this principle.

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References and Notes:

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3) Lefer A.M. *Drugs Future* **1988**, *13*, 999-1005.
4) Ohtani M.; Matsuura T.; Watanabe F.; Narisada M. *J.Org. Chem.* **1991**, *56*, 2122-2127.
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6) For a detailed description of the synthesis see WO 93/07,118 Schering AG.
7) To simplify the discussion, the carbacyclin numbering concerning the bicyclo[3.3.0]octane-skeleton will be maintained even for the truncated α-chain (n=0).

8) Spectral data of methyl 5-[(3Z,1R,5R,6S,7R)-1-(4-chlorophenylsulfonylaminomethyl)-6-(tert-butyl-diphenylsilyloxymethyl)-7-hydroxy-bicyclo[3.3.0]oct-3-ylidene]pentanoate (**3b**, n=1):

^{1}H NMR (500 MHz, $CDCl_3$): δ= 1.04 (s, 9H, t-butyl), 1.42 (dd, 1H, H-10α), 1.56-1.73 (m, 5H), 1.84 (d, 1H), 1.90-2.02 (m, 2H), 2.06 (m, 2H), 2.20 (d, 1H), 2.26 (m, 1H), 2.29 (t, 2H, H-2), 2.66 (broad, 1H, OH), 2.76 (m, 2H, CH_2-N), 3.62 (dd, 1H, H-12), 3.68 (s, 3H, OCH_3), 3.77 (dd, 1H, H-12), 3.97 (q, 1H, H-11β), 4.82 (t, 1H, NH), 5.15 (m, 1H, H-5), 7.37-7.50 (m, 8H), 7.65 (m, 4H), 7.76 (d, 2H) ppm.

^{13}C NMR (125,80 MHz, $CDCl_3$): δ= 19.08 (q, t-butyl), 25.01 (C-4), 25.86 (CH_3 of t-butyl), 28.50 (C-3), 33.39 (C-2), 38.28 (C-7), 40.00 (C-6a), 44.12 (C-10), 45.14 (C-8), 49.70 (C-9), 51.63 (OCH_3), 51.72 (CH_2-N), 54.72 (C-12), 66.00 (C-13), 75.45 (C-11), 121.93 (C-5), 127.83 (m-C_6H_5-Si), 128.41 (o-SO_2-C_6H_4-Cl), 129.43 (p-C_6H_5-Si), 129.90 (m-SO_2-C_6H_4-Cl), 132.91 (q, C_6H_5-Si), 135.52 (o-C_6H_5-Si), 138.42 (C-6), 139.11 (q, C_6H_4-Cl), 141.16 (q, C_6H_4-SO_2), 174.31 (C-1) ppm.

IR (film): 3450 (OH), 3280 (NH), 3070 (=C-H), 2940, 2860 (-C-H), 1735, 1720 (C=O), 1585 (C=C), 1440, 1425, 1330 (SO_2-N), 1160, 1330 (SO_2-N), 1110-1070, 820, 790, 750, 700, 615, 505 and 485 cm^{-1}.

9) For an excellent discussion of the directing effects in the Wittig reaction see: Maryanoff B.E.; Reitz A.B.; Duhl-Emsweiler B.A. *J. Am. Chem. Soc.* **1985**, *107*, 217-226.

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