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E- OR Z-SELECTIVE HORNER-WITTIG REACTIONS OF SUBSTITUTED BICYCLO[3.3.0]OCTANE-3-ONES WITH CHIRAL PHOSPHONOACETATES

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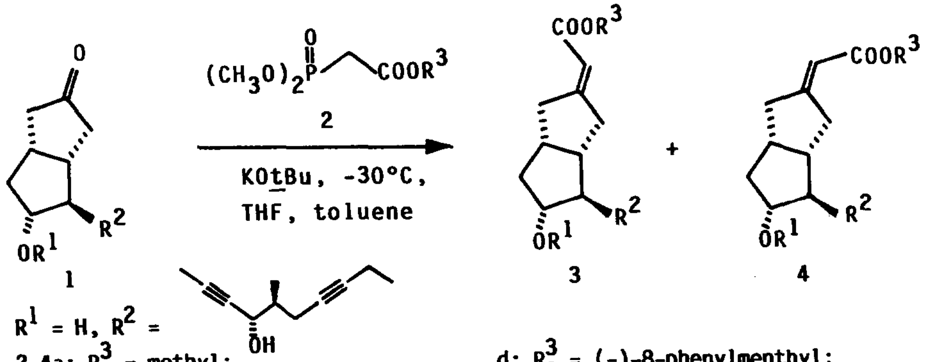
Summary - The Horner-Wittig reaction of substituted bicyclo[3.3.0]octane-3-ones with chiral phosphonoacetates **2** gave the corresponding unsaturated esters in E/Z-ratios of up to 91 : 9.

A major problem in the synthesis of cicaprost[1], a chemically and metabolically stable, biologically potent prostacyclin analogue, is the stereoselective generation of the exocyclic 5,6- double bond. Horner-Wittig reaction gives approximately an 1 : 1 mixture of the E- and the undesired Z-isomers. A logical approach to influence this ratio is the use of optically active phosphonates **2**[2]. Surprisingly only a small number of chiral Wittig type methods have been described[3].

The ketone **1** gave with **2a** a 60 : 40 mixture of **3a** and **4a** in 90% yield, whereas (+)-menthyl phosphonoacetate **2b**[4], $[\alpha]_D^{22}$ + 55.0° (c=1, MeOH), afforded a 72 : 28 ratio[5] of **3b** and **4b** in 90% yield.



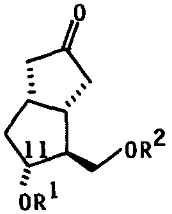
R^1 = H, R^2 =

2-4a: R^3 = methyl;
b: R^3 = (+)-menthyl;
c: R^3 = (+)-8-phenylmenthyl;
d: R^3 = (-)-8-phenylmenthyl;
e: R^3 = (+)-8-phenylneomenthyl;
f: R^3 = (-)-trans-2-phenylcyclohexyl.

The application of (-)-8-phenylmenthyl phosphonoacetate **2c**[6], $[\alpha]_D^{22}$-9.0° (c=1.1, MeOH), improved the ratio of **3c** : **4c** to 86 : 14 in 92% yield. Using the enantiomeric phosphonate **2d**[6], $[\alpha]_D^{22}$ + 8.9° (c=1.07, MeOH), produced the inverse ratio of **3d** : **4d** (15 : 85, 95% yield). **2e**[7], $[\alpha]_D^{22}$+31.2° (c=2.02, MeOH), gave an 88 : 12 mixture of **3e** : **4e** in 94% yield. **2f**[8], $[\alpha]_D^{22}$-20.1° (c=1.08, MeOH), afforded a 71 : 29 ratio of **3f** : **4f** (94% yield).

At -30°C the olefinations were usually complete within 18h, whereas at -60°C the reactions took 6 days, without changing the ratios of the isomers. Only in the case of **2f** the ratio was improved from 71 : 29 to 86 : 14. DIBAH reduction of the E/Z-mixtures **3c** and **4c** or **3e** and **4e** gave the corresponding allylic alcohols, from which the desired E-isomer could be readily separated by chromatography[1].

Horner-Wittig reaction of ketones **5** afforded with **2a** - **2f** under analogous conditions the unsaturated esters in similar or better E/Z-ratios. It is noteworthy, that compounds with a free 11α-hydroxy group (prostaglandin numbering), such as **5c** or **5d**, gave the best E/Z-ratios of up to 91 : 9.



5a: R^1 = t-BuMe$_2$Si, R^2 = t-BuMe$_2$Si;
b: R^1 = H, R^2 = t-BuMe$_2$Si;
c: R^1 = H, R^2 = t-BuPh$_2$Si;
d: R^1 = H, R^2 = trityl.

The monocyclic 4-tert.-butylcyclohexanone provided with **2e** the allylic esters in a ratio[9] of 73 : 27.

Potassium tert.-butylate or potassium hexamethyldisilazide as bases gave better E/Z-ratios than n-butyllithium, lithium- or sodium hexamethyldisilazide, whereas variation of the solvent had no marked effect on the E/Z-ratio.

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This communication is dedicated to Professor Rudolf Wiechert on the occasion of his 60th birthday.

REFERENCES AND NOTES

1. W. Skuballa, E. Schillinger, C.-St. Stürzebecher, and H. Vorbrüggen, J. Med. Chem. **29**, 313 (1986).
2. We thank Professor H.-J. Gais, who independently obtained similar results, for the discussion of his work prior to publication. See preceding communication: H.-J. Gais, G. Schmiedl, W. A. Ball, J. Bund, G. Hellmann, and I. Erdelmeier.
3. I. Tömösközi and G. Janzso, Chem. Ind. **1962**, 2085; H. J. Bestmann and J. Lienert, Angew. Chem. **81**, 751 (1969); Angew. Chem. Int. Ed. Engl. **8**, 763 (1969); S. Hanessian, D. Delorme, S. Beaudoin, and Y. Leblanc, J. Am. Chem. Soc. **106**, 5754 (1984); I. Erdelmeier, H.-J. Gais, and H. J. Lindner, Angew. Chem. **98**, 912 (1986); Angew. Chem. Int. Ed. Engl. **25**, 935 (1986).
4. All chiral phosphonoacetates **2b** - **2f** were synthesized according to: S. Hatakeyama, K. Satoh, K. Sakurai, and S. Takano, Tetrahedron Lett. **28**, 2713 (1987).
5. All E/Z-ratios were determined by capillary GC analysis and/or NMR spectroscopy. The purity of all samples was greater than 98%. The assignment of the configuration of the double bond has previously been described (ref. 1).
6. **2c** was obtained from (+)-8-phenylmenthol, **2d** from (-)-8-phenylmenthol.
7. (+)-8-Phenylneomenthol, $[\alpha]_D^{22}$ +36.6° (c=1.24, CHCl$_3$), was synthesized from R-(+)-pulegone. See: G. Quinkert, H.-G. Schmalz, E. M. Dzierzynski, G. Dürner, and J. W. Bats, Angew. Chem. **98**, 1023 (1986); Angew. Chem. Int. Ed. Engl. **25**, 992 (1986).
8. (-)-trans-2-Phenylcyclohexanol, $[\alpha]_D^{22}$ -59.0° (c=1, MeOH), mp 65-66.5°C (pentane), was prepared according to: J. K. Whitesell and R. M. Lawrence, Chimia **40**, 318 (1986).
9. It is not yet clear, which diastereomer makes up the greater proportion of the mixture.

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