

yield after chromatography on silica (cyclohexane/ethyl acetate = 3:1 + 1% triethylamine). Hydroxy ester **5** was converted to hydroxy β -keto ester **6** quantitatively using 3.5 equiv. α -lithio tert-butylacetate (LDA, tert-butylacetate, THF) in THF at -70°C for 1.5 h and at -15°C for 15 min⁹. Subsequent stereoselective reduction¹⁰ (1.6 equiv. triethylborane, THF, 23°C , 15 min; -70°C , 20 equiv. methanol, 2.0 equiv. sodium borohydride; workup with aqueous hydrogen peroxide) provided syn diol **7** in 92% yield after chromatography on silica (cyclohexane/ethyl acetate = 1:1). Acetonide formation (1.5 equiv. 2,2-dimethoxypropane, cat. p-toluenesulfonic acid, acetone, 23°C , 2 h, chromatography on silica, cyclohexane/ethyl acetate = 5:1, 70%) and removal of the silyl group (1.2 equiv. tetrabutylammonium fluoride, THF, 0°C , 3 h, 80%) gave alcohol^{11,16} **9** after chromatography on silica (cyclohexane/ethyl acetate = 1:1). Swern oxidation¹² of **9** provided crystalline aldehyde **3** in 97% yield.¹³

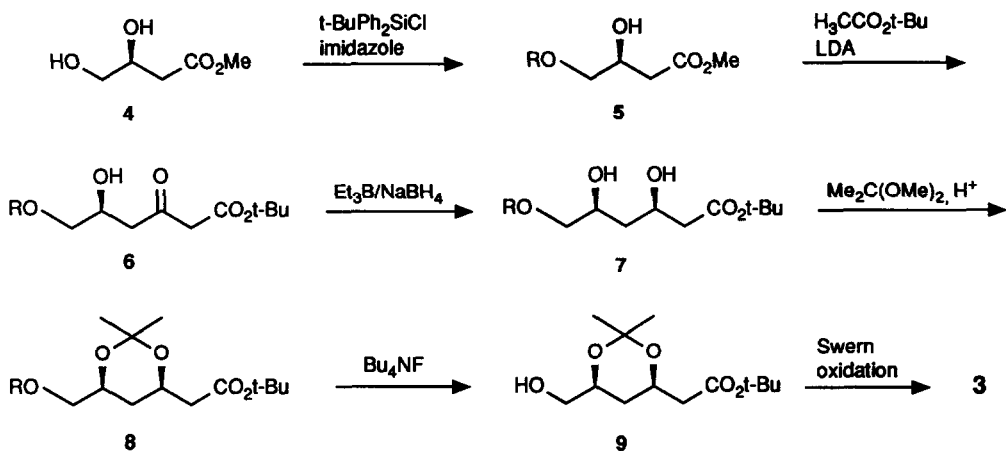
Wittig olefination of **3** with non stabilized phosphoranes generated from phosphonium bromides^{6,14} **10a** and **10b** (n-BuLi, THF) led to mixtures of E- and Z-isomers (**11** and **12**, table 1 and scheme 2). The desired E-isomer was obtained with 83:17 selectivity by raising the reaction temperature. Addition of lithium bromide had no effect. Horner olefination with phosphonate¹⁴ **10c** gave **11** exclusively (n-BuLi, THF). However, the yield was only 45% along with 30% recovered phosphonate. Phosphane oxide¹⁴ **10d** sufficiently stabilized for E selectivity, but still reactive enough, gave **11** in 69% yield with an E/Z ratio of 98:2 (n-BuLi, THF). Deprotection/lactonization of **11** with trifluoroacetic acid (15 equiv., dichloromethane, 23°C , 24 h) gave **1**¹⁶ in 75% yield after chromatography on silica (cyclohexane/ethyl acetate = 1:1). Diastereomeric and enantiomeric purity of **1** has been proven by HPLC¹⁵ using independently synthesized stereoisomers as references.

Table 1: Wittig olefination of 3

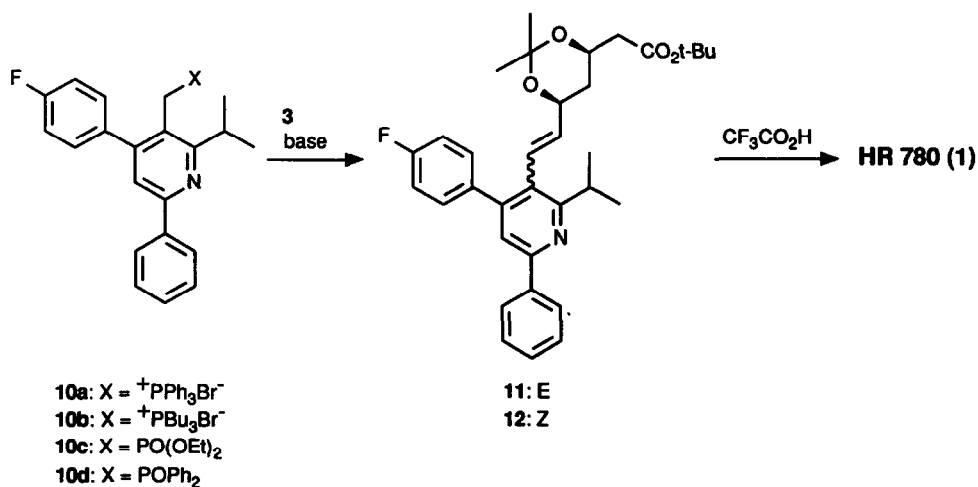
Entry	Reagent ^a	Temp. [$^{\circ}\text{C}$]	Yield [%] ^b	11 : 12 ^c
1	10a	0	66	75 : 25
2	10a	- 40	60	55 : 45
3	10a	+40	59	83 : 17
4	10a	+20 ^d	56	76 : 24
5	10b	+40	63	79 : 21
6	10c	+20	45	99 : 1
7	10d	+40	69	98 : 2

a) all reactions were performed in THF using n-BuLi. b) refers to chromatographed material. c) determined after cleavage of the acetonide (THF, 2 M HCl, $+20^{\circ}\text{C}$) using HPLC (silica, cyclohexane/ethyl acetate = 7 : 3. d) 3.0 equiv. of LiBr were added prior to addition of the aldehyde

Scheme 1

R = t-BuPh₂Si

Scheme 2



Acknowledgments: We wish to thank Dr. Fehlhaber, Dr. Kogler and Dr. Teetz for analytical support.

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13. Aldehyde **3** was found to be acid labile and could not be prepared using chromium(VI)-based oxidants. However, oxidation with iodosobenzene diacetate/RuCl₂(PPh₃)₃ according to P. Müller, J. Godoy, *Tetrahedron Lett.* **22**, 2361 (1981) turned out to be an alternative to the Swern method.
14. Prepared from the corresponding bromide⁶ by reaction with 1.0 equiv. tri-*n*-butylphosphine (**10b**), triethylphosphite (**10c**) or diphenylethoxyphosphane (**10d**) in toluene at reflux.
15. Diastereomeric purity: silica, *n*-heptane/2-propanol = 95:5; enantiomeric purity: Chiraspher (E. Merck), methylcyclohexane/DME = 4:1; ent-**1** was synthesized according to the method of J. E. Lynch, R. P. Volante, R. V. Wattlely, I. Shinkai, *Tetrahedron Lett.* **28**, 1385 (1987).
16. **9**: oil; ¹H NMR (DMSO-d₆) δ 1.1 (m, 1H), 1.2 (s, 3H), 1.4 (s, 9H), 1.4 (s, 3H), 1.6 (m, 1H), 2.2 (dd, 1H, J=15Hz, 8Hz), 2.4 (dd, 1H, J=15Hz, 5Hz), 3.2-3.4 (m, 2H), 3.9 (m, 1H), 4.2 (m, 1H), 4.6 (t, 1H, J=5Hz); **1**: mp 141°C; ¹H NMR (CDCl₂) δ 1.4 (m, 6H), 1.5 (s, 1H), 1.6 (m, 1H), 1.8 (m, 1H), 2.6 (m, 1H), 2.7 (m, 1H), 3.4 (h, 1H, J=7Hz), 4.3 (m, 1H), 5.2 (m, 1H), 5.4 (dd, 1H, J=16Hz, 6Hz), 6.7 (dd, 1H, J=16Hz, 1Hz), 7.1 (m, 2H), 7.3-7.5 (m, 6H), 8.1 (m, 2H).

(Received in Germany 1 February 1990)