## STEREOSELECTIVE SYNTHESIS OF HR 780 A NEW HIGHLY POTENT HMG-COA REDUCTASE INHIBITOR

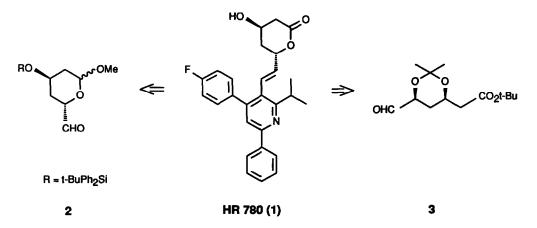
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Abstract: HR 780 (1) a new HMG-CoA reductase inhibitor has been synthesized stereoselectively starting from L-malic acid. Wittig olefination employing phosphonium halides, phosphonates and phosphane oxides have been investigated.

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme-A reductase (HMG-CoA reductase) are highly efficacious cholesterol lowering agents.<sup>1</sup> Lovastatin,<sup>2</sup> Pravastatin<sup>3</sup> and Simvastatin<sup>4</sup> are the most prominent examples of the naturally derived compounds. HR 780 (1), a fully synthetic HMG-CoA reductase inhibitor, is a promising clinical candidate exhibiting higher potency and longer half-life than Lovastatin and its congeners.<sup>5</sup>

Originally, HR 780 was synthesized via Wittig type coupling of aldehyde 2 with phosphonium bromide<sup>6</sup> 10a. Although HR 780 was obtained optically pure, for large scale preparations the synthesis suffers from several disadvantages. We wish to report a new more convenient route to optically pure HR 780 using aldehyde<sup>7</sup> 3 as a key intermediate.



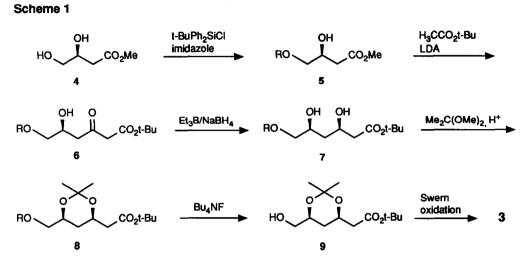
Diol ester 4 (scheme 1) was prepared from L-malic acid according to lit. 8. Reaction of 4 with 1.0 equiv. tert-butylchlorodiphenylsilane in DMF in the presence of 2.0 equiv. imidazole at 23°C gave 5 in 89%

yield after chromatography on silica (cyclohexane/ethyl acetate = 3:1 + 1% triethylamine). Hydroxy ester 5 was converted to hydroxy  $\beta$ -keto ester 6 quantitatively using 3.5 equiv.  $\alpha$ -lithio tert-butylacetate (LDA, tert-butylacetate, THF) in THF at -70°C for 1.5 h and at -15°C for 15 min<sup>9</sup>. Subsequent stereoselective reduction<sup>10</sup> (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<sup>11,16</sup> 9 after chromatography on silica (cyclohexane/ethyl acetate = 1:1). Swern oxidation<sup>12</sup> of 9 provided crystalline aldehyde 3 in 97% yield.<sup>13</sup>

Wittig olefination of 3 with non stabilized phosphoranes generated from phosphonium bromides<sup>6,14</sup> 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 phosphonate<sup>14</sup> 10c gave 11 exclusively (n-BuLi, THF). However, the yield was only 45% along with 30% recovered phosphonate. Phosphane oxide<sup>14</sup> 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<sup>16</sup> in 75% yield after chromatography on silica (cyclohexane/ethyl acetate = 1:1). Diastereomeric and enantiomeric purity of 1 has been proven by HPLC<sup>15</sup> using independently synthesized stereoisomers as references.

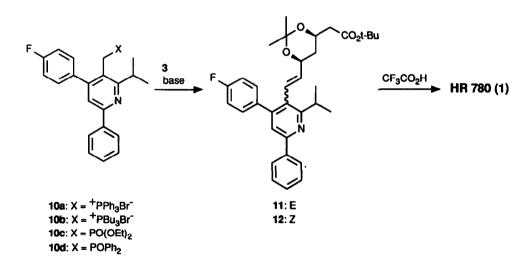
Entry	Reagenta	Temp. [ <sup>o</sup> C]	Yield [%] <sup>b</sup>	11 : 12 <sup>c</sup>
1	10a	0	66	75 : 25
2	10a	- 40	60	55 : 45
3	10a	+40	59	83 : 17
4	10a	+20 <sup>d</sup>	56	76 : 24
5	10b	+40	63	79 : 21
6	10c	+20	45	99:1
7	10d	+40	69	98:2

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 HCI, +20°C) using HPLC (silica, cyclohexane/ethyl acetate = 7 : 3. d) 3.0 equiv. of LiBr were added prior to addition of the aldehyde



R = t-BuPh<sub>2</sub>Si

Scheme 2



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

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- 11. A similar synthetic pathway employing a different protecting strategy has been reported by Sandoz recently (EP 0244364).
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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/RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> according to P. Müller, J. Godoy, Tetrahedron Lett. <u>22</u>, 2361 (1981) turned out to be an alternative to the Swern method.
- 14. Prepared from the corresponding bromide<sup>6</sup> 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. Wattley, I. Shinkai, Tetrahedron Lett. <u>28</u>, 1385 (1987).
- 16. 9: oil; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  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; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  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)