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Lactone Pathway to Statins Utilizing the Wittig Reaction. The Synthesis of Rosuvastatin

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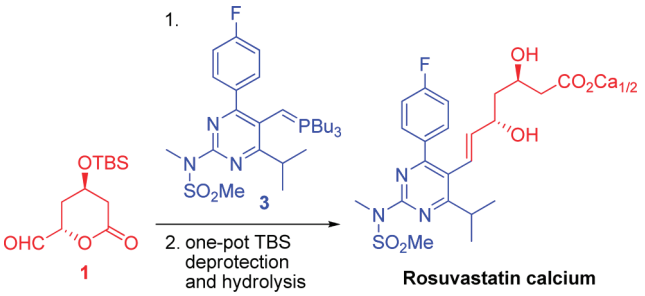
Received May 30, 2010



The first entry to statins via lactonized side chain is reported, exemplified by the synthesis of rosuvastatin. The key step is Wittig coupling of (2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-6-oxotetrahydro-2*H*-pyran-2-carbaldehyde and phosphonium salt of an appropriately functionalized pyrimidine heterocycle. One-pot deprotection and hydrolysis of the resulting 4-*O*-TBS rosuvastatin lactone provided rosuvastatin in high yield.

Statins are among the most commonly prescribed drugs worldwide for the treatment of lipid disorders.[1,2] Initially, they were discovered as fungal metabolites and were composed of a chiral decaline core attached to a β-hydroxy lactone moiety.[3,4] Chemical evolution to structurally refined molecules led to semisynthetic analogues[4] and later on to fully synthetic derivatives with the decaline core being replaced by heteroaromatic motifs (superstatins, Figure 1).[5] In these molecules, the β-hydroxy lactone moiety generally remained unmodified as it is essential for the biological activity.[6] Several superstatins are currently marketed including fluvastatin,[7] pitavastatin,[8] atorvastatin,[9] and rosuvastatin.[10] The value of rosuvastatin is growing with new approved indications in phase III studies, which raises it high on the list of synthetic targets.[11]

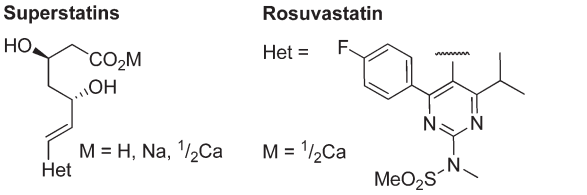


FIGURE 1. Left: general formula of superstatins (Het = heterocycle). Right: rosuvastatin calcium.

Over the last three decades, diverse strategies to the synthetic statins have been developed including those utilizing the Wittig reaction.[5] Unfortunately, many of these are long, multistep linear reaction sequences, often involving late and unselective functional group transformations and protection/deprotection steps with difficult purification procedures. Tedious preparation of chiral precursors, several synthetic steps, and a need of cryo-chemistry render these approaches less attractive (see Supporting Information for detailed discussion).[7,8,10,12−17]

Interestingly, the most obvious formyl functionalized lactonized side chain precursor **1** (Scheme 1) has not yet

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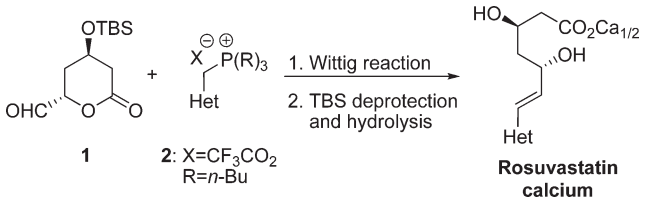
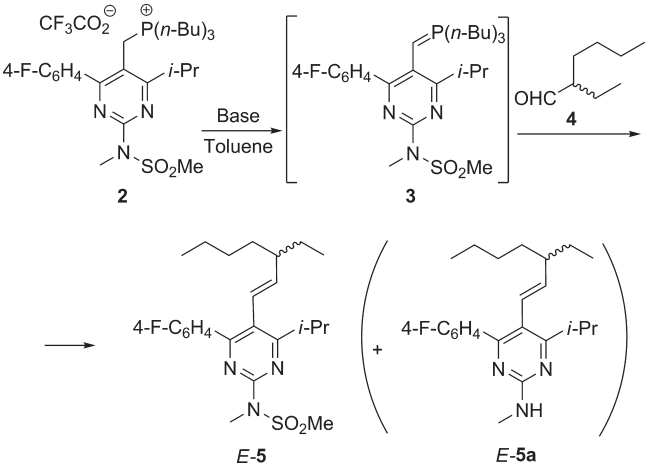
DOI: 10.1021/jo101050z Published on Web 09/03/2010

SCHEME 1. Lactone Pathway to Rosuvastatin Calcium



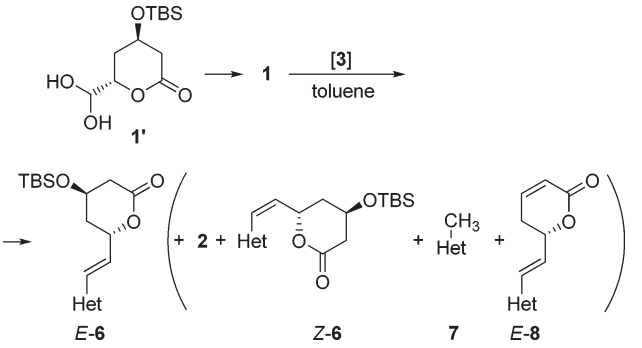
SCHEME 2. Wittig Experiments with 2 and Model Aldehyde 4



been applied for the construction of statins. This is because all previous attempts in the preparation of **1** failed. It was even suggested that **1** is not synthesizable because of the β-substituted δ-lactone ring instability.[18] Followed by our recent success in the preparation of **1**,[19,20] now accessible via an efficient, green, and highly stereoselective enzymatic approach,[21] here we report its application to the synthesis of rosuvastatin. A highly convergent approach is presented, taking advantage of the Wittig reaction between a methylphosphonium-substituted heterocycle **2** and aldehyde **1** and subsequent one-pot deprotection/hydrolysis step (Scheme 1).

Our study began by the selection of phosphonium salt **2** and optimization of its ylide formation. Although substituents R at the phosphorus atom and the counterion X^- may have influence on the course of the Wittig reaction,[22,23] these also greatly affect the solubility of the salt, which is an important factor in a potential industrial application. Out of several combinations of R and X^-, tributyl phosphonium trifluoromethanesulfonate **2** (R = *n*-Bu, $X^- = CF_3CO_2^-$)[13] was chosen on the basis of its relatively high solubility in a solvent as apolar as toluene.

SCHEME 3. Synthesis of TBS-Protected Rosuvastatin Lactone *E*-6



To identify optimal reaction conditions for the ylide **3** formation, we decided to trap this intermediate for analytical purposes in a form of a Wittig reaction product. To minimize the complexity of the trapping reaction, which could arise at this stage from the fragile δ-valerolactone part of **1**, we decided to utilize a non-epimerizable, non-lactone/ester model aldehyde, (±)-2-ethylhexanal (**4**, Scheme 2). After careful addition of NaHDMS (1.0−1.1 equiv) into a toluene solution of **2** (1 mmol) at −35 °C, followed by the introduction of aldehyde **4** (1 equiv) at −45 °C, only a sluggish fade of the orange-red color of ylide **3** was observed, indicating low reactivity of the Wittig components (Supporting Information, Table S1, entries 1−3). In subsequent experiments, this led us to gradually increase the temperatures of both steps, the ylide formation and the olefination. Optimal reaction conditions were identified by conducting both steps at room temperature with olefin *E*-**5** formed exclusively and isolated in yields of up to 80% (Table S1, entries 4 and 5). No isomeric *Z*-**5** could be detected by NMR of the crude reaction product. Similarly, *n*-BuLi, LiHDMS, and NaH were examined for the ylide **3** formation (Table S1, entries 6−10). In all instances, *E*-**5** isomer was formed exclusively albeit in slightly lower yields than by using NaHDMS. *n*-BuLi caused a partial removal of *N*-methylsulfonyl group from *E*-**5**, resulting in byproduct *E*-**5a** (Table S1, entries 7 and 8).

With these results, we next performed the study with aldehyde **1** (Scheme 3; for "Het", see Figure 1). As reported previously,[20] the optimal way for its preparation and storage is in the form of hydrate **1′**, which after being dissolved in an appropriate solvent, equilibrates to aldehyde **1** liberating an equivalent of water. On the basis of the relatively low reactivity of ylide **3**, we surmised that an equimolar amount of water, liberated from **1′**, might not be detrimental to the Wittig reaction. Hence, a toluene solution of **1′** was initially used in the reactions with equimolar ylide **3**. From the results shown in Table 1, entry 1, one can see that the formation of the desired *E*-**6** was accompanied by the isomeric *Z*-**6**, phosphonium salt **2**, and methylpyrimidine **7**.[24] If 2 equiv of **3** was employed, only phosphonium salt **2** and pyrimidine **7** were detected in the reaction mixture (entry 2). The appearance of both **2** and **7** can be ascribed to the reaction of **3** with either water or even hydrate **1′**, which could potentially remain in the solution.[25] This was confirmed by

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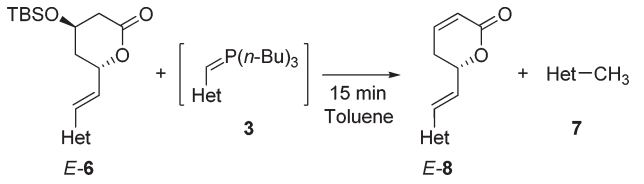
TABLE 1. Wittig Reaction of In Situ Generated Ylide 3 with Aldehyde 1[a]

			yield (%)[c]				
entry	T,[b] °C	ylide **3**(equiv)	*E*-**6**	*Z*-**6**	**2**	**7**	**8**
1[d]	20	1	33	4	52	11	0
2[d]	20	2	0	0	47	53	0
3	20	1	39	5	33	10	13
4	0	1	25	10	2	28	35
5	40	1	49	7	10	12	22
6	65	1	57	6	19	8	10
7	110	1	84 (62)[e]	7 (5)[e]	4	5	0

[a]Average data from several consecutive runs are given. Dry toluene solution of **1** was used (see text), unless otherwise noted. [b]Temperature for the olefination step. For details, see the Experimental Section. [c]Determined as ratio by ^{1}H NMR analysis of the crude products. [d]Toluene solution of **1′** was used. [e]Isolated pure product.

SCHEME 4. Ylide 3 Mediated TBSOH Elimination from *E*-6



an independent experiment in which ylide **3**, generated from **2** and 3-fold excess of NaHDMS, was treated with a 10-fold excess of water. Products **2** (44%) and **7** (56%) were confirmed by ^{1}H NMR analysis of the crude reaction mixture.

Adopting the above findings, we carried out experiments with a dry toluene solution of aldehyde **1**, (see "Preparation of Aldehyde **1**" in the Experimental Section), and a decrease in the formation of byproduct **2**, *Z*-**6**, and **7** was observed. In this case, however, TBSOH elimination product *E*-**8** (13%) appeared (Scheme 3, Table 1, entry 3).

Concomitant formation of **7** in nearly the same amounts as **8** suggested that ylide **3** as a base[23] could cause TBSOH elimination from *E*-**6**. This was confirmed by an independent experiment in which *E*-**6** was treated with equimolar ylide **3** at room temperature for 15 min (Scheme 4). Complete consumption of the starting compounds was observed, and on the basis of ^{1}H NMR analysis of the reaction mixture, compounds **7** (40%) and *E*-**8** (20%) were formed along with several unidentified byproducts. We did not investigate further whether the ylide **3** mediated TBSOH elimination also occurs at aldehyde **1** to give (*S*)-6-oxo-3,6-dihydro-2*H*-pyran-2-carbaldehyde, which would after Wittig reaction afford *E*-**8**, as well. It is known that α,β-dehydro-δ-formyl-δ-valerolactones undergo Wittig reaction.[26] Interestingly, base (NaH, DBU)-promoted TBSOH elimination has been reported to occur at β-TBSO-substituted cyclohexanones,[27] whereas at the valerolactones, it has only been achieved by the action of *p*-toluenesulfonic acid.[28]

Different reaction conditions for the Wittig olefination of **1** were examined to minimize the formation of *E*-**8**. Experiments conducted at different temperatures ranging from 0 to 110 °C are shown in Table 1, entries 4−7. At elevated temperatures, the formation of *E*-**8** was greatly suppressed. This suggests different temperature profiles of the two competing reactions of ylide **3**: as an olefination partner with aldehyde **1**, and as a base in TBSOH elimination at *E*-**6**. Optimal results were seen when toluene solution of aldehyde **1** was added to ylide **3** (1 equiv) at 110 °C. In the crude reaction product, the desired *E*-**6** and the isomeric *Z*-**6** were detected by ^{1}H NMR in 84 and 7% yield, respectively, and after chromatographic purification isolated in 62 and 5% yield, respectively (entry 7). No *E*-**8** could be detected in the reaction mixture.

SCHEME 5. TBS Deprotection of *E*-6

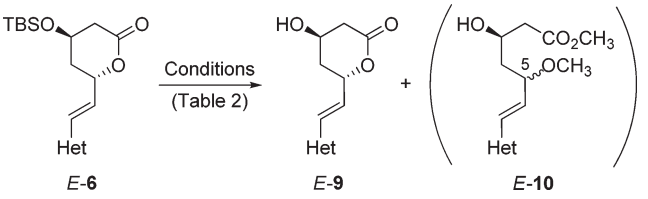


TABLE 2. Selected Results at Desilylation of *E*-6

entry	reagent (equiv)	solvent	T, °C	time, h	product[a]
1	CEC (0.05)	MeOH	25	0.8	*E*-**10** (71)[b]
2	AcCl (0.15)	MeOH	25	48	*E*-**10** (100)
3	*n*-Bu_4NF (3.4)[c]	THF	25	24	*E*-**9** (99)

[a]Percent yield, determined by ^{1}H NMR analysis of the crude reaction mixtures with 1,3,5-trimethoxybenzene as an internal standard for integration. [b]Starting *E*-**6** (7%) was also detected. [c]In the presence of AcOH (5.5 equiv).

Several methods were tested for desilylation of *E*-**6**. By employing HCl generated in situ either from 1-chloroethyl chloroformate (CEC)/MeOH[29] or from acetyl chloride and MeOH,[30] TLC analyses of the reaction mixtures indicated very clean transformations, but instead of the desired alcohol *E*-**9**, these afforded methyl ether *E*-**10** (Scheme 5, Table 2). NMR spectral analysis of *E*-**10** revealed two sets of signals in the ratio of 4:6, indicating partial epimerization at C-5. The mechanism of this ester ether formation may proceed by acid-catalyzed transesterification at the lactone ring of either *E*-**6** or *E*-**9** with methanol, followed by S_N1 substitution of the liberated C-5 hydroxyl group with methanol via allylic carbocation intermediate. Similar lactone ring opening has been documented at a δ-vinyl-δ-valerolactone,[31] and acid-catalyzed allylic alcohol etherification has been reviewed.[32] In our case, we have provided the evidence of the above suggested mechanism by the experiment in which rosuvastatin methyl ester[10] was in the presence of catalytic amounts of HCl incubated in methanol for 19 h. A mixture of diastereomeric ethers *E*-**10** (authentic to the above-mentioned) was produced in quantitative yield. Attempts at desilylation of *E*-**6** mediated by TMSCl/KF·$2H_2O$,[33] $FeCl_3$,[34] or $CuCl_2$[35] gave the desired compound *E*-**9**, but in unsatisfactory yields (Table S2). On the other hand, nearly quantitative conversion

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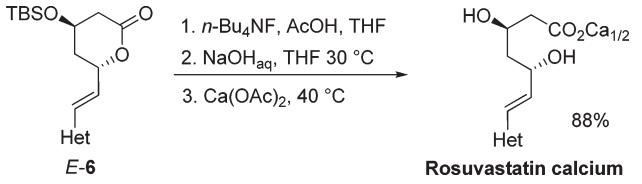
SCHEME 6. Synthesis of Rosuvastatin Calcium from *E*-6



into *E*-**9** was achieved by using *n*-Bu_4NF/AcOH/THF[36] (Table 2, entry 3).

Having established this highly efficient protocol for TBS deprotection and expecting that lactone hydrolysis with an appropriate base should proceed without difficulties, we decided to probe the preparation of rosuvastatin calcium in a one-pot reaction starting from *E*-**6** (Scheme 6). Thus, after the TBS deprotection into *E*-**9** was complete, the resulting reaction mixture was made alkaline with aqueous NaOH to give a solution of rosuvastatin sodium. From this solution, pure amorphous rosuvastatin calcium[10] was precipitated with $Ca(OAc)_2$ in 88% overall yield from *E*-**6**.

In conclusion, we have demonstrated a practical synthesis of rosuvastatin. The key step of our approach is highly selective Wittig olefination between the appropriate heterocyclic ylide and β-TBSO functionalized δ-formyl-δ-valerolactone into 4-*O*-TBS-protected rosuvastatin lactone. Deprotection, lactone hydrolysis, and cation exchange reaction into rosuvastatin calcium has been achieved in one-pot reaction in excellent overall yield and without any detectable epimerization. Owing to the recent advances in remarkably efficient synthesis of β-TBSO-δ-formyl-δ-valerolactone[19,20] and highly stereoselective enzymatic preparation of its acetyloxy lactone precursor,[21] this convergent and cryo-chemistry-free approach is superior to other methods[5] for the preparation of rosuvastatin. Moreover, it seems unlikely that this chemistry is restricted to rosuvastatin, selected herein. Instead, we believe it opens new perspective in efficient, economically and ecologically sustainable statin synthesis in general.

Experimental Section

Synthesis of *E*-6. (a). Preparation of Aldehyde 1: A solution of **1′**[20] (271 mg, 0.98 mmol) in dry CH_2Cl_2 (30 mL) was stirred at ambient temperature for 23 h. Volatiles were removed by atmospheric evaporation at 40 °C, and the residue (**1**, 253 mg, 0.98 mmol) was dissolved in dry toluene (30 mL).

(b). Wittig Reaction: A toluene solution of NaHDMS (1.85 mL of 0.6 M, 1.11 mmol) was added at room temperature to a stirred suspension of **2**[13] (638 mg, 0.98 mmol) in dry toluene (29 mL). The reaction mixture was within 15 min warmed to 110 °C, and the above prepared toluene solution of aldehyde **1** (0.98 mmol), kept at room temperature, was added under vigorous stirring. The reaction mixture was stirred for 5 min and chilled to room temperature. Volatiles were removed in vacuo, and the oily residue was subjected to chromatography (EtOAc/hexanes 3:5) to give *E*-**6** (350 mg, 62%) and *Z*-**6** (30 mg, 5%) as white glassy solids after removal of volatiles.

(***E*-6**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si), 0.89 (s, 9H, $(CH_3)_3C$), 1.27 (d, J = 6.7 Hz, 6H, $(CH_3)_2C$), 1.51−1.83 (m, 2H, H-5), 2.53−2.68 (m, 2H, H-3), 3.34 (septet, J = 6.7 Hz, 1H, CH_3CH), 3.51 (s, 3H, CH_3SO_2), 3.58 (s, 3H, CH_3N), 4.23−4.33 (m, 1H, H-4), 5.12−5.25 (m, 1H, H-6), 5.49 (dd, J = 16.1, 5.8 Hz, 1H, =CH-(C-6)), 6.70 (dd, J = 16.1, 1.3 Hz, 1H, =CH-(C-5′)), 7.03−7.17 (m, 2H, H-3″, H-5″), 7.55−7.70 (m, 2H, H-2″, H-6″); ^{13}C NMR (75 MHz, $CDCl_3$) δ = −4.90, −4.82 (2 × CH_3Si), 18.0 ($(CH_3)_3C$), 21.6, 21.7 (2 × CH_3C), 25.7 ($(CH_3)_3C$), 32.3 (CH_3CH), 33.1 (CH_3N), 36.4 (C-5), 39.4 (C-3), 42.5 (CH_3SO_2), 63.3 (C-4), 75.4 (C-6), 115.1 (d, J = 21.7 Hz, C-3″, C-5″), 120.6 (C-5′), 125.5 (=CH-(C-5′)), 132.1 (d, J = 8.4 Hz, C-2″, C-6″), 134.3 (d, J = 3.3 Hz, C-1″), 134.8 (=CH-(C-6)), 157.6 (C-2′), 163.3 (d, J = 250 Hz, C-4″), 163.7 (C-4′), 169.6 (C-2), 175.0 (C-6′). Anal. Calcd for $C_{28}H_{40}FN_3O_5SSi$: C, 58.21; H, 6.98; N, 7.27. Found: C, 58.25; H, 7.17; N, 7.24.

Synthesis of Rosuvastatin Calcium. To a stirred solution of *n*-$Bu_4NF \cdot 3H_2O$ (3.66 g, 11.6 mmol) and AcOH (1.05 mL) in dry THF (60 mL) was added *E*-**6** (3.80 g, 6.6 mmol). The reaction mixture was stirred at 25 °C for 48 h. Then the mixture was concentrated under reduced pressure to give an oily residue, which was diluted with EtOAc (50 mL). The obtained solution was washed successively with water (25 mL), saturated $NaHCO_3$ solution (25 mL), brine (25 mL), and water (25 mL), followed by removal of EtOAc under reduced pressure to give an oily residue. The residue was dissolved in a mixture of THF/H_2O (4:1, 60 mL), warmed to 30 °C, and NaOH (8.0 M, 0.92 mL, 0.73 mmol) was added. The reaction mixture was stirred at 30 °C for 2 h. Then THF was evaporated completely under reduced pressure, and water was added to give 30 mL of clear rosuvastatin sodium solution. The resulting solution was washed with EtOAc (2 × 12 mL), and water layer was distilled under reduced pressure to remove dissolved EtOAc. The resulting clear solution of rosuvastatinate sodium was diluted with H_2O to 30 mL of total volume, warmed to 40 °C, and $Ca(OAc)_2 \cdot H_2O$ (0.88 g, 5.0 mmol in 6 mL of H_2O) was added under vigorous stirring at 40 °C over 5 min. The reaction mixture was stirred for 30 min at 40 °C. The precipitate was filtered off, washed with water (5 mL), and resuspended in H_2O (20 mL), followed by vigorous stirring for 1 h at room temperature. The product was collected by filtration and dried in vacuo to give pure rosuvastatin calcium (2.88 g, 88%) with specific rotation and spectroscopic properties in accordance with the literature data.[10]

Acknowledgment. The authors gratefully acknowledge Mr. P. Drnovšek for support of this project, Dr. Bogdan Kralj and Dr. Dušan Žigon (Mass Spectrometry Center, Jožef Stefan Institute, Ljubljana, Slovenia) for mass spectrometry measurements, Mr. S. Borišek for acquiring some of the NMR spectra, Mrs. D. Jereb, Mrs. J. Anžel (Dipl. Ing.), and Miss A. Vesković for technical assistance.

Supporting Information Available: Detailed discussion on synthetic strategies to statins, experimental procedures, Tables S1 and S2, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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