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A New Approach to the Total Synthesis of Rosuvastatin[‡]

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A new multi-step synthesis of the lipid-lowering agent rosuvastatin, involving two homogeneously catalyzed reaction steps, is described. The key building block, *N*-[4-(4-fluorophenyl)-5-formyl-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (**2**), was prepared by Pd-catalyzed formylation with CO/H_2 (1:1, 50 bar, phosphane ligand/substrate ratio of 1:10). Several alternative pathways for the preparation of **2** were also tested, but were found to be inferior. Rosuvastatin precursor **1** was assembled by Wittig coupling of aldehyde **2** and ylide (*R*)-**3**, derived from a Ru-catalyzed asymmetric hydrogenation. The second stereogenic center was finally created by stereoselective reduction with Et_2BOMe and $NaBH_4$ to afford rosuvastatin ethyl ester.

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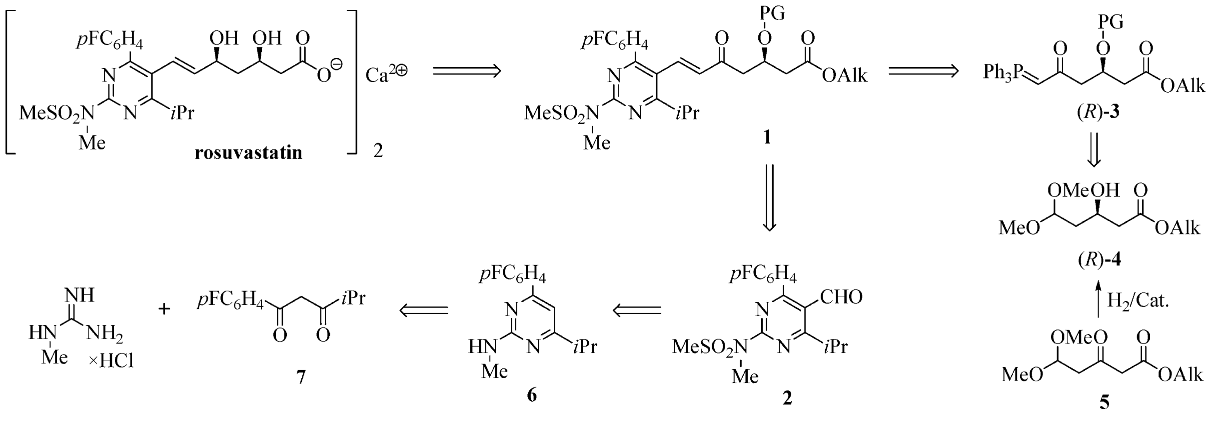
Introduction

Statins such as atorvastatin[1,2] and rosuvastatin[3] are very effective inhibitors[4] of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (HMGR) and are the most powerful lipid-lowering agents in use as pharmaceutical agents for reducing cholesterol levels in people with or at risk of cardiovascular disease.[5] The development of new and efficient strategies for their synthesis, capable of providing the drug in a cheaper and more convenient manner, is therefore extremely important and relevant. The newest of the statins, rosuvastatin,[6] has been called a *super-statin*, because it appears to reduce low-density lipoprotein (LDL) cholesterol to a greater degree than rivals in its class without additional adverse effects. Rosuvastatin is approved for the treatment of elevated LDL cholesterol (dyslipidemia),[7] total cholesterol (hypercholesterolemia),[8] and/or triglycerides (hypertriglyceridemia).[6]



Scheme 1. Retrosynthetic analysis of rosuvastatin calcium salt [Alk = Et as follows below or other alkyl group could be used; *tert*-butyldiphenylsilyl (TBDPS) was considered as protecting group (PG)].

From the retrosynthetic analysis of rosuvastatin calcium salt depicted in Scheme 1 it follows that the possible precursor **1** with a stereogenic center at C-3 must have the indicated (*R*) configuration. It is obvious that this chalcone de-

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[‡] Part IV of a series dedicated to the synthesis of statins. Part III: Ref.[14]

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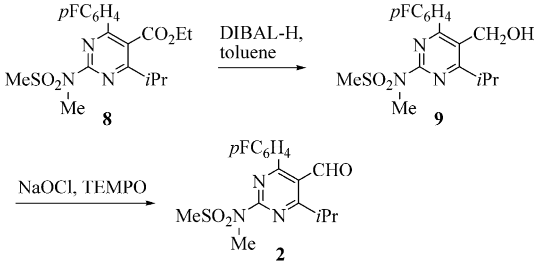
rivative might be easily assembled through Wittig coupling of aldehyde **2** and ylide (*R*)-**3**. The second stereogenic center at C-5 in rosuvastatin can later be created by diastereoselective reduction of the oxo group as described in the literature.[9] Protected hydroxy ylides of type **3** were formulated as possible building blocks[10] for the preparation of **1** as soon as Wittig coupling could be performed with the corresponding aldehyde **2** without or in the presence of a strong base[11] and subsequent cleavage of the HO-protective group.[12] Nowadays this synthetic pathway is commonly employed for the preparation of rosuvastatin.[9,13]

In a parallel paper we report on the highly enantioselective hydrogenation of ethyl 5,5-dimethoxy-3-oxopentanoate (**5**) to ethyl (*R*)-3-hydroxy-5,5-dimethoxypentanoate [(*R*)-**4**] as one of the alternative pathways for the synthesis of a precursor for the chiral side chain of rosuvastatin.[14] The transformation of alcohol (*R*)-**4** into ylide (*R*)-**3** is also considered.

On the other hand, it is known that aldehyde **2** can be prepared by chemoselective catalytic oxidation of alcohol **9** with NaOCl as an oxidant in the presence of catalytic amounts of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) free radical (Scheme 2).[13a,15] The required alcohol **9** can be synthesized by DIBAL reduction of the corresponding ester **8** as reported by Watanabe et al.[9]



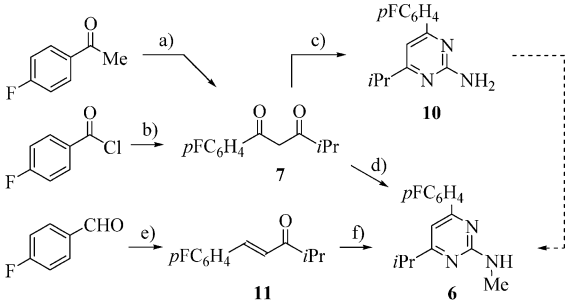
Scheme 2. Synthesis of aldehyde **2** by chemoselective catalytic oxidation of alcohol **9**.

Alternatively, aldehyde **2** could be derived from 2-(methylamino)pyrimidine derivative **6** by introduction of the formyl group into the C-5 position of the pyrimidine ring and subsequent mesylation of the secondary amine functionality, as shown in Scheme 1.

Here we report an entirely new and concise strategy for the synthesis of aldehyde **2**, based on the cyclization of methylguanidine hydrochloride with 1-(4-fluorophenyl)-4-methylpentane-1,3-dione (**7**), followed by regioselective iodization of the pyrimidine and final substitution of the halogen atom by a CHO group. For the last of these conversions the Pd-catalyzed formylation procedure with CO/H_2 (1:1), recently suggested by Beller et al. for a range of (preferentially nonheterocyclic) aromatic compounds,[16] was envisaged. The application of aldehyde **2** in the Wittig reaction with ylide (*R*)-**3** and the final transformation into rosuvastatin is also considered here.

Results and Discussions

One of the shortest routes to substituted 2-aminopyrimidines is the cyclocondensation of guanidine salts with 1,3-diketones (Scheme 3). We synthesized 1,3-diketone **7** by a Claisen-type acylation of 4-fluoroacetophenone with *i*$PrCO_2Et$ in the presence of NaH in Et_2O at room temperature in 70% yield.[17] An alternative approach in dioxane at 80–90 °C for 4 h gave the product only in 51% yield.[18] Acylation of 3-methylbutan-2-one with 4-fluorobenzoyl chloride in the presence of $NaNH_2$ as a base in Et_2O at room temperature afforded 1,3-diketone **7** in 35% yield.[19]



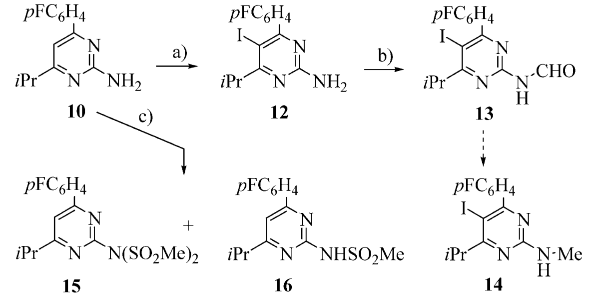
Scheme 3. Synthesis of 1,3-diketone **7** and enone **11** and their cyclization with guanidinium salts. (a) *i*$PrCO_2Et$, NaH, Et_2O, room temp., 1.5 h, 70%; (b) *i*PrCOMe, $NaNH_2$, Et_2O, room temp., 1 h, 35%; (c) $[NH_2C(NH)NH_2]_2SO_4$ (1 equiv.), Na (2 equiv.), *i*PrOH, 51%; (d) $MeNHC(NH)NH_2{\cdot}HCl$ (1 equiv.), Na (1 equiv.), *i*PrOH, 65%; (e) *i*PrCOMe, NaOH, 0 °C, MeOH, 85% (conv. 93%); (f) $MeNHC(NH)NH_2{\cdot}HCl$ (1 equiv.), Na (2 equiv.), *i*PrOH, O_2 (air), (9%).

The cyclization of guanidine sulfate with **7** in the presence of 2 equiv. of *i*PrONa provided 2-aminopyrimidine **10**.[20] Unfortunately, the application of the same reaction conditions (2 equiv. of *i*PrONa) for the reaction of *N*-methylguanidine hydrochloride with **7** failed, and only traces of the desired heterocycle **6** were observed. Unexpectedly, the use of 1 equiv. of *i*PrONa in *i*PrOH at 82 °C for 11 h proved much more successful. The thus obtained 2-(methylamino)-pyrimidine **6** was purified by flash chromatography to give the material in 65% yield.

Another possibility for the synthesis of 2-(methylamino)-pyrimidine **6** is the cyclization of *N*-methylguanidine hydrochloride with (*E*)-1-(4-fluorophenyl)-4-methylpent-1-en-3-one (**11**) (Scheme 3). The starting material could easily be prepared from 4-fluorobenzaldehyde and 3-methylbutan-2-one under basic conditions.[21] According to Wendelin et al., alkenones with hydrogen atoms in their β-positions condense with guanidine to afford labile dihydropyrimidines that easily undergo aromatization to yield the corresponding pyrimidines.[22] In accordance with this protocol, the β-substituted alkenone **11** was transformed into the substituted 2-(methylamino)pyrimidine **6** by treatment with $MeNHC(NH)NH_2{\cdot}HCl$ in the presence of air, but unfortunately the isolated yield was extremely low. Rapid formation of aminopyrimidine derivative **6** in the reaction between methylguanidine and **11** may be a consequence of the relatively strong basicity of the unsaturated intermediates. The application of *t*BuOK as a base for the cyclization led to decomposition.

The monoalkylation of amine **10** was also tested. Unfortunately, the formic acid/formaldehyde methylation protocol[23] led to the formation of a mixture of products that could not be separated.

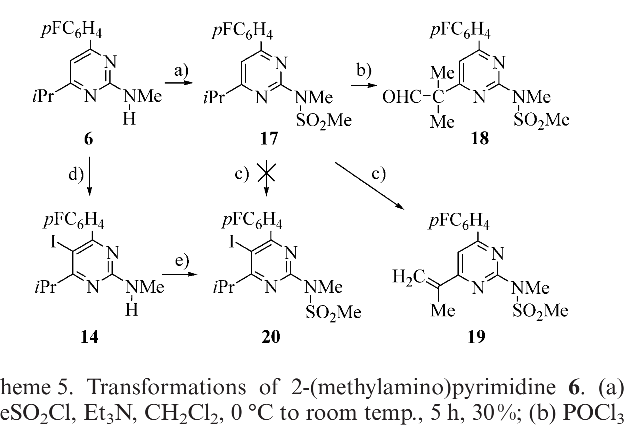
As an alternative pathway the formylation of a suitably halogenated pyridine derivative of **6** was investigated. The required iodide **12** was prepared in 31% yield by treatment of 2-aminopyrimidine **10** with I_2 in DMSO (Scheme 4).[24] Compound **12** was converted into formamide **13** by treatment with $POCl_3$ in DMF. However, because of the low overall yield of this reaction sequence, the further conversion of amide **13** into amine **14** by reduction with $LiAlH_4$ or $NaBH_4$ was not investigated.



Scheme 4. Transformations of 2-aminopyrimidine **10**. (a) I_2, DMSO, 100 °C, 1 h, then room temp., 3 d, 31%; (b) $POCl_3$, DMF, 100 °C, 1.5 h, 54%; (c) $MeSO_2Cl$, Et_3N, room temp., overnight, 55% (compound **15**).

Moreover, mesylation of **10** did not lead to the desired monosulfonamide **16**. Under the conditions applied ($MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C), the bis(sulfonated) compound **15** was formed as a main product. All attempts to introduce iodine at the C-5 position in pyrimidine **15** either with I_2 in DMSO or with I_2/K_2CO_3 in $CHCl_3$ at reflux were unsuccessful.

The mesylation of 2-(methylamino)pyrimidine **6** led to the formation of sulfonamide **17** (Scheme 5). After purification, this compound was obtained in 30% yield as a colorless solid. As a by-product the corresponding ammonium methanesulfonate was detected.



Scheme 5. Transformations of 2-(methylamino)pyrimidine **6**. (a) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to room temp., 5 h, 30%; (b) $POCl_3$ (5 equiv.), DMF, 100 °C, 3 h, 10%; (c) I_2, DMSO, 135 °C, 11 h; (d) I_2, DMSO, 100 °C, 3 h, 33%; (e) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to room temp., 1.5 h, 30%.

Attempted selective formylation of pyrimidine **17** with $POCl_3$ (1 equiv.) in DMF at 100 °C failed. An increase in the amount of $POCl_3$ (5 equiv.) led to the formation of a mixture of products, from which the aliphatic aldehyde **18** was isolated in 10% yield. Treatment of **17** with I_2 in DMSO at 135 °C led to the degradation of the isopropyl group (**19**) and did not afford the desired iodide **20**. The inertness of compound **17** in the iodination reaction could be explained by the electron-withdrawing nature of the sulfonamide group.

A more promising route for the formation of aldehyde **2** involves the insertion of iodine into the C-5 position of **6** in the first step, this reaction then being followed by *N*-mesylation and a final formylation step. Thus, treatment of **6** with I_2 in DMSO at 100 °C led to the formation of iodide **14**. After separation from unreacted initial compound **6** by column chromatography, **14** was obtained as a solid. An additional recrystallization from $CHCl_3$ gave **14** as yellowish crystals in 33% yield. The structure of iodide **14** was confirmed by X-ray analysis and is shown in Figure 1.

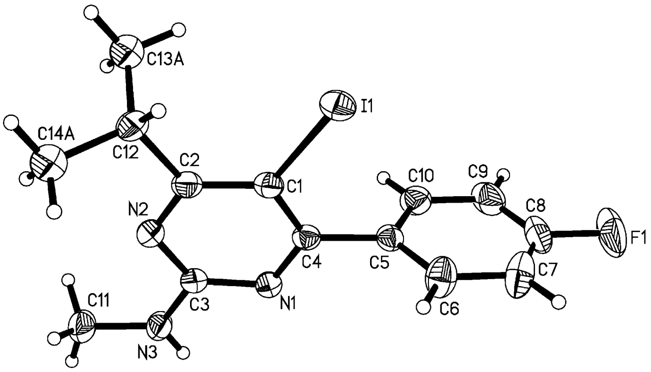
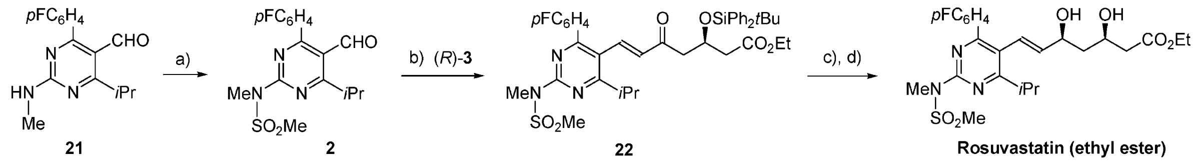


Figure 1. Molecular structure of 2-(methylamino)-4-(4-fluorophenyl)-5-iodo-6-isopropylpyrimidine (**14**). The thermal ellipsoids correspond to 30% probability.

Esterification of **14** with $MeSO_2Cl$ gave sulfonamide **20** (Scheme 5). This was subjected to Pd-catalyzed formylation with CO/H_2 (1:1) at a pressure of 5 bar in toluene as suggested by Beller et al.[16] The catalyst was prepared in situ from $Pd(OAc)_2$, and a number of mono- and bidentate phosphanes were tested. Unfortunately, under these conditions the reaction did not proceed; neither was any reaction observed when an isolated $Pd(dppe)Cl_2$ complex was used.

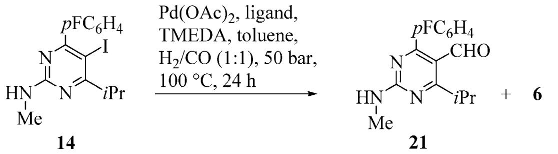
A systematic search for appropriate conditions for the Pd-catalyzed formylation of **14** gave evidence that the nature and the concentration of the phosphane ligand and the CO/H_2 pressure are crucial for the progress of the reaction and the ratio of the desired carbaldehyde **21** and the dehalogenation product **6**. The most important results are shown in Table 1.

With dppe as a ligand in toluene at 100 °C and a substrate/ligand ratio of 10:1, only traces of aldehyde **21** were detected even at a very high ligand/substrate ratio (Entry 1). The application of a catalyst prepared in situ from $Pd(OAc)_2$ and PPh_3 and a substrate/ligand ratio of 100:1 was more promising (Entry 2). Replacement of the ancillary ligand Ph_3P by Ad_2nBuP improved the results in favor of the formation of desired aldehyde **21** (Entry 3). An increase in the substrate concentration to 0.5 $mol\,L^{-1}$ and the applica-



Scheme 6. Synthesis of rosuvastatin ethyl ester. (a) Method 1: $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to room temp., 2 h, 30%; Method 2: NaH, DMF, 0 °C 30 min, then $MeSO_2Cl$ at 0 °C, 3 h room temp., 55%; (b) Method 1: MeCN, reflux, 14 h, 70%; Method 2: toluene, reflux, 48 h, 52%; (c) HF (aq.), MeCN; (d) Et_2BOMe, $NaBH_4$, THF/MeOH, –78 °C, 85% (over two steps).

Table 1. Pd-catalyzed formylation of iodide **14**.



Entry	Ligand[a]	Ratio l/s[b]	Conc. [mol/L]	Conv. [%] (isol. yield) [%]	Ratio **21/6/14**
1	dppe	1:10	0.5	traces	–
2	Ph_3P	1:100	0.05	22 (n.d.)	6:3:16
3	Ad_2*n*BuP	1:100	0.05	14 (n.d.)	9:1:40
4	Ad_2*n*BuP	1:10	0.5	61 (46)	8:1:3
5	Ad_2*n*BuP	1:10	0.5	ca. 99 (70)[c]	84:16:0[c]

[a] dppe = 1,2-bis(diphenylphosphanyl)ethane, Ad = adamantyl. [b] l/s = ligand/substrate. [c] Reaction time 72 h.

tion of a substrate/ligand ratio of 10:1 further enhanced the yield of **21** (Entry 4). Prolongation of the reaction time to 72 h under the same conditions led to nearly complete conversion. After chromatographic purification, aldehyde **21** was obtained in 70% yield (Entry 5).

Mesylation of **21** with $MeSO_2Cl$ in the presence of NEt_3 as a base in CH_2Cl_2 at 0 °C afforded aldehyde **2** in 30% yield (Scheme 6). A significant improvement of the conversion could be achieved in the presence of NaH in DMF.[25] After purification, the desired aldehyde **2** was obtained in 55% yield.

Wittig coupling of aldehyde **2** and ylide (*R*)-**3** was performed according to the literature procedure.[9] The reaction proceeded at reflux in CH_3CN over 14 h and gave the rosuvastatin precursor **22** in a yield of 70% (Scheme 6). Other conditions for the Wittig reaction tested did not improve the yield: the reaction in toluene at reflux, for example, for 48 h gave only 52% of **22**. Removal of the *t*$BuPh_2Si$ protective group in **22** by treatment with aqueous HF in CH_3CN and final reduction of the carbonyl group with $Et_2B(OMe)$ and $NaBH_4$ in THF/MeOH at –78 °C[9] afforded rosuvastatin ethyl ester in 85% yield.

Conclusions

A new and convenient synthetic protocol for the preparation of pyrimidinecarbaldehyde **2** by iodization of 2-(methylamino)4-(4-fluorophenyl)-6-isopropylpyrimidine (**6**) followed by Pd-catalyzed formylation with H_2/CO has been developed. For the first time, evidence has been found that this catalytic reaction, recently discovered by Beller et al., can also be successfully applied for the production of highly functionalized heterocyclic carbaldehydes, provided that appropriate conditions have been identified. Together with the chiral ylide (*R*)-**3**, which was produced by an Ru-catalyzed asymmetric hydrogenation[14] the resulting carbaldehyde **2** is a useful building block for the synthesis of the cholesterol-lowering drug rosuvastatin.

Experimental Section

General: Reactions and manipulations involving air- and moisture-sensitive compounds were performed under dry argon by standard Schlenk techniques. Commercial reagents were used without additional purification. Solvents were distilled from appropriate drying agents before use. Chromatographic purification of products was accomplished by flash column chromatography on Macherey–Nagel silica gel 60 (230–400 mesh ASTM) and on neutral Al_2O_3 with various mixtures of solvents as mobile phases. TLC was carried out on Merck plates with aluminium backing and silica gel 60 F_{254}. NMR spectra were recorded with Bruker ARX 400 and/or ARX 300 spectrometers. Chemical shifts are reported in ppm (δ) and referred to internal TMS for ^1H NMR and to deuterated solvents for ^{13}C NMR spectroscopy. Elemental and mass spectrometric analyses were performed by the analytic laboratory of the Leibniz-Institut für Katalyse e.V. at the Universität Rostock. 1-(4-Fluorophenyl)-4-methylpentane-1,3-dione (**7**) was prepared according to ref.[17] The synthesis of (*E*)-1-(4-fluorophenyl)-4-methylpent-1-en-3-one (**11**) was carried out according to ref.[21]

2-Amino-4-(4-fluorophenyl)-6-isopropylpyrimidine (10): A detailed procedure is given in ref.[20] Purification was carried out by column chromatography (silica gel; *n*-hexane/EtOAc, 1:1; $R_f = 0.38$). Yield: 51% (ref.[20] 56%).

4-(4-Fluorophenyl)-6-isopropyl-2-(methylamino)pyrimidine (6): Sodium (0.21 g, 9 mmol) was added to anhydrous *i*PrOH (35 mL), and the suspension was heated at 80 °C until the metal had dissolved. The solution was cooled to 70 °C, and 1-methylguanidine hydrochloride (1 g, 9 mmol) was added. The suspension was heated at 82 °C for 2.5 h and then cooled again to 70 °C. A solution of 1,3-diketone **7** (1.9 g, 9 mmol) in *i*PrOH (10 mL) was added, and the resulting mixture was heated at 82 °C for 11 h. After cooling to room temp., the reaction mixture was concentrated in vacuo, and the residue was diluted with saturated aqueous NH_4Cl (20 mL). The crude product was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried with $MgSO_4$ and concentrated. The residue was purified on a silica gel column with *n*-hexane/EtOAc (9:1; $R_f = 0.16$) or *n*-hexane/EtOAc (1:1; $R_f = 0.45$) to afford the product **6** (1.44 g, 65%) as a colorless powder. M.p. 75–76 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.8 Hz, 6 H, Me_2CH), 2.86 (m, 1 H, Me_2CH), 3.08 (d, *J* = 5.1 Hz, 3 H, *Me*NH), 5.15 (br. s, 1 H, NH), 6.82 (s, 1 H, CH, pyrimidine), 7.14 (m, 2 H, CH, Ar), 8.05 (m, 2 H, CH, Ar) ppm. ^{13}C NMR (100 MHz,

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$CDCl_3$): δ = 21.75 (*Me*$_2$CH), 28.41 (*Me*NH), 36.16 (Me$_2$*C*H), 102.92 (CH, pyrimidine), 115.50 (d, $J_{C,F}$ = 21.14 Hz, CH), 128.89 (CH), 128.98 (CH), 134.26 (C), 163.23 (CH), 163.63 (CH), 164.12 (d, $J_{C,F}$ = 249.96 Hz, CF), 177.26 (*C*CHMe$_2$) ppm. MS (EI): *m*/*z* (%) = 245 (76) [M]$^+$, 230 (100), 217 (83), 201 (14), 173 (11), 146 (12). $C_{14}H_{16}FN_3$ (245.30): calcd. C 68.55, H 6.57, N 17.13; found C 69.10, H 6.30, N 16.57.

2-Amino-4-(4-fluorophenyl)-5-iodo-6-isopropylpyrimidine (12):[24] A solution of **10** (50 mg, 0.216 mmol) and I_2 (110 mg, 0.43 mmol) in DMSO (0.3 mL) was heated at 100 °C for 1 h and was then left standing at room temp. for 3 d. The solution was diluted with an equal amount of H_2O, shaken with $Na_2S_2O_3$ solution (1 N) for 5 min, and washed with saturated $NaHCO_3$. After extraction with CH_2Cl_2 (2 × 2 mL), the organic phase was dried with $MgSO_4$. The crude product was purified by column chromatography (neutral Al_2O_3; *n*-hexane/EtOAc, 1:1; R_f = 0.56) to afford **12** (24 mg, 31 %) as a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.75 Hz, 6 H, *Me*$_2$CH), 3.50 (m, 1 H, Me$_2$C*H*), 5.37 (br. s, 2 H, NH_2), 7.15 (m, 2 H, CH, Ar), 7.51 (m, 2 H, CH, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.06 (*Me*$_2$CH), 38.48 (Me$_2$*C*H), 92.87 (CI, pyrimidine), 115.50 (d, $J_{C,F}$ = 21.15 Hz), 128.9 (CH), 129.0 (CH), 130.79 (C), 163.23 (CH), 163.63 (CH), 164.12 (d, $J_{C,F}$ = 248.5 Hz, CF), 185.82 (Me$_2$CH*C*) ppm.

***N*-[4-(4-Fluorophenyl)-5-iodo-6-isopropylpyrimidin-2-yl]formamide (13):** A mixture of **12** (25 mg, 0.07 mmol) and $POCl_3$ (72 mg, 0.47 mmol) in DMF (1 mL) was heated at 100 °C for 1.5 h. After cooling, the solution was poured into ice-cold water (5 mL). The crude product was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine. After drying of the CH_2Cl_2 solution with $MgSO_4$, the solvent was evaporated and the residue purified by column chromatography (silica gel; Et_2O/MeOH, 10:1; R_f = 0.91) to give **13** (14.6 mg, 54 %) as yellowish solid. M.p. 163–164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 6.81 Hz, 6 H, *Me*$_2$CH), 3.58 (m, 1 H, Me$_2$C*H*), 7.17 (m, 2 H, CH, Ar), 7.57 (m, 2 H, CH, Ar), 7.8 (br. s, 1 H, NH), 9.52 (s, 1 H, CHO) ppm.

***N*-[4-(4-Fluorophenyl)-6-isopropylpyrimidin-2-yl]-*N*-(methylsulfonyl)methanesulfonamide (15):** A solution of $MeSO_2Cl$ (50 mg, 0.43 mmol) in dry CH_2Cl_2 (1 mL) was added at 0 °C to a solution of amine **10** (100 mg, 0.433 mmol) and NEt_3 (48 mg, 0.48 mmol) in dry CH_2Cl_2 (3 mL). The reaction mixture was warmed to room temp. and stirred overnight. The solvent was evaporated, and the residue was dried under high vacuum. After column chromatography (silica; hexane/EtOAc, 1:1; R_f = 0.76), amide **15** (92 mg, 55 %) was obtained as a colorless solid. M.p. 154–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.84 Hz, 6 H, *Me*$_2$CH), 3.11 (m, 1 H, Me$_2$C*H*), 3.72 [s, 6 H, (*Me*SO$_2$)$_2$N], 7.20 (m, 2 H, CH, Ar), 7.5 (s, 1 H, CH, pyrimidine), 8.05 (m, 2 H, CH, Ar) ppm. MS (EI): *m*/*z* (%) = 387 (38) [M]$^+$, 372 (25), 359 (13), 308 (25), 294 (100), 276 (33), 230 (18), 214 (19).

***N*-[4-(4-Fluorophenyl)-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (17):** A solution of $MeSO_2Cl$ (0.28 g, 2.45 mmol) in dry CH_2Cl_2 (5 mL) was added at 0 °C to a solution of amine **6** (0.6 g, 2.45 mmol) and Et_3N (0.32 g, 3.2 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was warmed to room temp. and stirred for an additional 5 h. The solvent was evaporated, and the residue was dried under high vacuum. Purification by column chromatography (silica gel; toluene/EtOAc, 10:1; R_f = 0.45 or *n*-hexane/EtOAc, 4:1; R_f = 0.22) afforded **17** (237 mg, 30 %) as a colorless solid. M.p. 138–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.8 Hz, 6 H, *Me*$_2$CH), 3.02 (m, 1 H, Me$_2$C*H*), 3.55 (s, 3 H, *Me*N), 3.62 (s, 3 H, *Me*SO$_2$N), 7.18 (m, 3 H, CH, Ar + pyrimidine), 8.08 (m, 2 H, CH, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.77 (*Me*$_2$CH), 28.25 (*Me*N), 36.22 (Me$_2$*C*H), 42.29 (*Me*SO$_2$N), 107.86 (CH, pyrimidine), 115.67 (d, $J_{C,F}$ = 23.23 Hz), 129.13 (CH), 129.25 (CH), 129.36 (C), 163.23 (CH), 159.25 (CH), 163.66 (d, $J_{C,F}$ = 249.96 Hz, CF), 177.49 (Me$_2$CH*C*) ppm. MS (EI): *m*/*z* (%) = 323 (8) [M]$^+$, 308 (12), 245 (41), 244 (100), 230 (47), 217 (30), 57 (19).

4-(4-Fluorophenyl)-6-isopropyl-*N*-methylpyrimidin-2-ylaminium Methanesulfonate: This compound was additionally isolated by column chromatography (silica gel; *n*-hexane/EtOAc, 4:1; R_f = 0.09). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.79 Hz, 6 H, *Me*$_2$CH), 3.03 (m, 1 H, Me$_2$C*H*), 3.29 (s, 3 H, *Me*H$_2$N$^+$), 3.71 (s, 3 H, MeSO$_2^-$), 7.18 (m, 2 H, CH, Ar), 7.25 (s, 1 H, pyrimidine), 8.03 (m, 2 H, CH, Ar) ppm.

***N*-[4-(4-Fluorophenyl)-6-(2-methyl-1-oxoprop-2-yl)pyrimidin-2-yl]-*N*-methylmethanesulfonamide (18):** A solution of **17** (100 mg, 0.31 mmol) and $POCl_3$ (285 mg, 1.86 mmol) in DMF (5 mL) was heated at 100 °C for 3 h. After cooling to room temp., the reaction mixture was poured into ice-cold water, washed with saturated $NaHCO_3$, and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried with $MgSO_4$; after evaporation of the solvent, the product was purified by column chromatography (silica gel; toluene/EtOAc, 10:1; R_f = 0.62) to give **18** (11 mg, 10 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 6 H, C*Me*$_2$CHO), 3.50 (s, 3 H, *Me*N), 3.61 (s, 3 H, *Me*SO$_2$N), 7.20 (m, 2 H, CH, Ar), 7.29 (s, 1 H, pyrimidine), 8.08 (m, 2 H, CH, Ar), 9.77 (s, 1 H, CMe$_2$C*H*O) ppm. MS (CI/isobutene): *m*/*z* (%) = 353 (14), 352 (100), 340 (57), 324 (15), 302 (14), 274 (8).

***N*-[4-(4-Fluorophenyl)-6-(prop-1-en-2-yl)pyrimidin-2-yl]-*N*-methylmethanesulfonamide (19):** A solution of **17** (105 mg, 0.32 mmol) and I_2 (165 mg, 0.65 mmol) in DMSO (2.5 mL) was heated at 135 °C for 11 h. The reaction mixture was poured into water (3 mL), shaken with $Na_2S_2O_3$ solution (1 N) for 5 min, and washed with saturated $NaHCO_3$. After extraction with CH_2Cl_2 (2 × 3 mL), the organic phase was dried with $MgSO_4$. The solvent was evaporated and the residue subjected to purification by column chromatography (silica gel; *n*-hexane/EtOAc, 4:1). Besides initial compound **16**, the decomposition product **19** was isolated (R_f = 0.33). M.p. 135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (m, 3 H, *Me*C=CH$_2$), 3.54 (s, 3 H, *Me*N), 3.64 (s, 3 H, *Me*SO$_2$N), 5.52 (m, 1 H, MeC=C*H*H), 6.18 (m, 1 H, MeC=CH*H*), 7.19 (m, 2 H, CH, Ar), 7.46 (s, 1 H, pyrimidine), 8.09 (m, 2 H, CH, Ar) ppm.

4-(4-Fluorophenyl)-5-iodo-6-isopropyl-2-(methylamino)pyrimidine (14): A solution of **6** (1.08 g, 4.4 mmol) and I_2 (2.24 g, 8.8 mmol) in DMSO (25 mL) was heated at 100 °C for 3 h and left overnight at room temp. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3 × 15 mL). The combined extracts were washed successively with $Na_2S_2O_3$ solution (1 N, 2 × 10 mL), saturated $NaHCO_3$ (2 × 10 mL), and brine (2 × 10 mL) and then dried with $MgSO_4$. After evaporation of the solvent, the mixture of the crude product and unreacted initial compound was separated by column chromatography (silica gel; toluene/EtOAc, 10:1; R_f = 0.54 and/or silica gel; *n*-hexane/EtOAc, 1:1; R_f = 0.61). Additional recrystallization from $CHCl_3$ afforded pure **14** (0.461 g, 33 %) as yellowish crystals. M.p. 195–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.69, Hz, 6 H *Me*$_2$CH), 2.99 (d, *J* = 4.95 Hz, 3 H, *Me*NH) 3.47 (m, 1 H, Me$_2$C*H*), 5.15 (br. s, 1 H, N*H*), 7.12 (m, 2 H, CH, Ar), 7.52 (m, 2 H, CH, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.12 (*Me*$_2$CH), 28.41 (*Me*NH), 38.26 (Me$_2$*C*H), 80.91 (CI, pyrimidine), 114.89 (d, $J_{C,F}$ = 21.93 Hz, CH, Ar), 130.84 (CH), 130.92 (CH), 138.13 (C), 162.04 (CH), 168.77 (CH), 163.00 (d, $J_{C,F}$ = 248.72 Hz, CF), 177.24 (Me$_2$CH*C*) ppm. MS (EI): *m*/*z* (%) = 371 (87) [M]$^+$, 356 (20), 245 (22), 244 (100), 146 (14).

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X-ray Crystallographic Study of Compound 14: Data were collected with a STOE-IPDS diffractometer by using graphite-monochromated Mo-K_α radiation. The structure was solved by direct methods (SHELXS-97: G. M. Sheldrick, University of Göttingen, Germany, **1997**) and refined by full-matrix, least-squares techniques against F^2 (SHELXL-97: G. M. Sheldrick, University of Göttingen, Germany, **1997**). XP (Bruker AXS) was used for graphical representation. Space group $P2_1/n$, monoclinic, a = 11.8954(12), b = 5.5807(4), c = 22.887(2) Å, β = 102.431(7)°, V = 1483.7(2) Å^3, Z = 4, $\rho_{calcd.}$ = 1.662 g cm^{-3}, 18258 reflections measured, 2907 symmetry-independent reflections, of which 2305 were observed [$I > 2\sigma(I)$], $R1$ = 0.024, wR^2 (all data) = 0.063, 175 parameters. CCDC-659030 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

***N*-[4-(4-Fluorophenyl)-5-iodo-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (20):** A solution of amine **14** (20 mg, 0.054 mmol) and Et_3N (7.1 mg, 0.07 mmol) in dry CH_2Cl_2 (2 mL) was cooled to 0 °C, and a solution of $MeSO_2Cl$ (6.2 mg, 0.054 mmol) in dry CH_2Cl_2 (0.5 mL) was added. The reaction mixture was warmed up to room temp. and stirred for 1.5 h. The solvent was evaporated, and the crude product was purified by column chromatography (silica gel; toluene/EtOAc, 10:1; R_f = 0.40 or *n*-hexane/EtOAc, 4:1; R_f = 0.31). Yield of **20**: 7.3 mg (30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, J = 6.59 Hz, 6 H, Me_2CH), 3.02 (m, 1 H, Me_2CH), 3.39 (s, 3 H, *Me*N), 3.47 (s, 3 H, $MeSO_2N$), 7.16 (m, 2 H, CH, Ar + pyrimidine), 8.10 (m, 2 H, CH, Ar) ppm.

4-(4-Fluorophenyl)-6-isopropyl-2-(methylamino)pyrimidine-5-carbaldehyde (21):[16] Under argon a 10-mL flask was charged with $Pd(OAc)_2$ (29.6 mg, 0.132 mmol), Ad_2nBuP (14.3 mg, 0.04 mmol), and toluene (4 mL). The resulting mixture was vigorously stirred at room temp. for 1–1.5 h, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 34.9 mg, 0.3 mmol) and iodide **14** (148.5 mg, 0.4 mmol) were added. The solution was placed in a 25-mL autoclave together with a magnetic stirring bar. The autoclave was flushed 3 times with syngas (CO/H_2, 1:1) and pressurized to 50 bar. The reaction mixture was stirred at 100 °C for 72 h. After cooling to room temp. and releasing of the excess of CO/H_2, the solvent was evaporated and the crude product was purified by column chromatography (silica gel; toluene/EtOAc, 10:1; R_f = 0.44) to give **21** (76.5 mg, 70%) as a colorless solid. M.p. 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, J = 6.60 Hz, 6 H, Me_2CH), 3.11 (d, J = 5.11 Hz, 3 H, *Me*NH), 4.03 (m, 1 H, Me_2CH), 5.62 (br. s, 1 H, N*H*), 7.17 (m, 2 H, CH, Ar), 7.54 (m, 2 H, CH, Ar), 9.82 (s, 1 H, C*H*O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.36 (Me_2CH), 28.31 (*Me*NH), 38.26 (Me_2CH), 115.58 (d, $J_{C,F}$ = 23.90 Hz, CH, Ar), 130.35 (CH), 131.67 (CH), 137.86 (C), 162.05 (CH), 168.41 (CH), 163.00 (d, $J_{C,F}$ = 246.5 Hz, CF), 177.36 (Me_2CHC), 190.12 (*C*HO) ppm. MS (EI): *m*/*z* (%) = 273 (100), 256 (33), 244 (20), 230 (63), 217 (77). $C_{15}H_{16}FN_3O$ (273.31): calcd. C 65.92, H 5.90; found C 65.80, H 6.34.

***N*-[4-(4-Fluorophenyl)-5-formyl-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (2). Method 1:** A solution of $MeSO_2Cl$ (18.9 mg, 0.16 mmol) in dry CH_2Cl_2 (1 mL) was added at 0 °C to a solution of aldehyde **21** (40 mg, 0.15 mmol) and Et_3N (24.9 mg, 0.25 mmol) in dry CH_2Cl_2 (3 mL). The reaction mixture was warmed to room temp. and stirred at this temperature for an additional 2 h. The solvent was evaporated, and the residue was purified by column chromatography (silica gel; toluene/EtOAc, 10:1; R_f = 0.52) to afford aldehyde **2** (15.5 mg 30%) as a colorless solid. **Method 2:** Sodium hydride (NaH, 11 mg, 0.46 mmol) was added at 0 °C to a solution of aldehyde **21** (60 mg, 0.22 mmol) in dry DMF (1 mL). The solution was stirred for 30 min, and then a solution of $MeSO_2Cl$ (37.7 mg, 0.336 mmol) in DMF (1 mL) was added. The mixture was stirred at 0 °C for 30 min and at room temp. for 3 h. Water (2 mL) was then added to quench the reaction, and the mixture was extracted with EtOAc (3 × 3 mL). The organic layer was washed with brine and dried with $MgSO_4$. After evaporation of the solvent, the product was purified by column chromatography (silica gel; toluene/EtOAc, 10:1; R_f = 0.52) to give aldehyde **2** (42.4 mg, 55%) as a colorless solid. M.p. 147–148 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (d, J = 6.62 Hz, 6 H, Me_2CH), 3.55 (s, 3 H, *Me*N), 3.64 (s, 3 H, $MeSO_2N$), 4.03 (m, 1 H, Me_2CH), 7.23 (m, 2 H, CH, Ar), 7.63 (m, 2 H, CH, Ar), 9.97 (br. s, 1 H, C*H*O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.38 (Me_2CH), 28.32 (*Me*N), 38.26 (Me_2CH), 42.29 ($MeSO_2N$), 115.58 (d, $J_{C,F}$ = 23.5 Hz, CH, Ar), 130.35 (CH), 131. 7 (CH), 137.86 (C), 162.05 (CH), 168.41 (CH), 163.00 (d, $J_{C,F}$ = 246.5 Hz, CF), 177.36 (Me_2CHC), 190.12 (*C*HO) ppm. MS (EI): *m*/*z* (%) = 351 (22), 273 (18), 272 (100).

Ethyl (3*R*,6*E*)-3-(*tert*-Butyldiphenylsilyloxy)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-5-oxohept-6-enoate (22). Method 1: According to a modified procedure given in ref.[9] A solution of aldehyde **2** (16 mg, 0.046 mmol) and ylide (*R*)-**3** (30 mg, 0.046 mmol) in MeCN (1 mL) was heated at reflux for 14 h. The solvent was removed in vacuo, and the crude product was purified by column chromatography (silica gel; EtOAc; R_f = 0.92) to yield **22** (24 mg, 70%) as a viscous oil. **Method 2:** A solution of aldehyde **2** (16 mg, 0.046 mmol) and ylide (*R*)-**3** (30 mg, 0.046 mmol) in toluene (1 mL) was heated at reflux for 48 h, and the solvent was then evaporated. The product was purified by column chromatography (silica gel; EtOAc; R_f = 0.92) to afford **22** (18 mg, 52%) as a colorless, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (s, 9 H, Me_3C), 1.26 (m, 3 H + 6 H, Me_2CH + CH_2Me), 3.52 (s, 3 H, *Me*N), 3.59 (s, 3 H, $MeSO_2N$), 2.49 (m, 2 H, CH_2CO_2Et), 2.69 [dd, J = 15.75, J = 5.53 Hz, 1 H, C(O)C*H*H], 2.83 [dd, J = 15.75, 7.48 Hz, 1 H, C(O)CH*H*], 3.25 (m, 1 H, Me_2CH), 4.05 (q, J = 7.11 Hz, CH_2Me), 4.59 (m, 1 H, CH), 5.95 (d, J = 16.50 Hz, 1 H, CH=CH), 7.07 (m, 2 H, Ar), 7.36 (m, 7 H, CH, CH=CH + Ar), 7.55 (m, 2 H, CH, Ar), 7.65 (m, 4 H, CH, Ar) ppm.

Ethyl (3*R*,5*S*,6*E*)-7-{4-(4-Fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoate: This compound was prepared according to the procedure given in ref.[9] Yield 85%.

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