An Efficient and Simple Procedure for the Preparation of α-Keto-β-lactams

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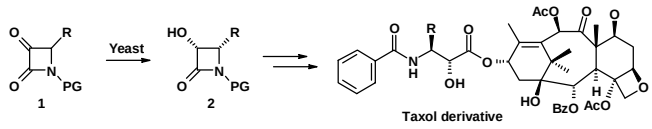
Dedicated to Prof. Fritz Sauter on the Occasion of his 70th Birthday

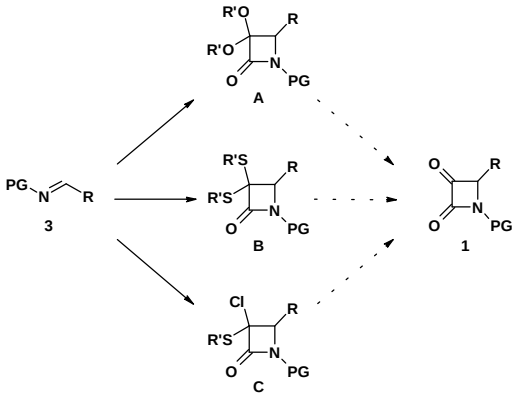
Abstract. The methods for the preparation of α-keto-β-lactams described in the literature are generally specific for a particular target molecule and lack generality. A short route to several of these compounds has been developed and is described in this communication. The protocol based on an efficient cyclization procedure followed by hydrolysis and oxidation allows preparation of α-keto-β-lactams **5a**–**g** with sensitive substituents.

α-Keto-β-lactams **1** are at the crossroads of many important transformations leading to bioactive compounds [1]. Recently, we used yeast-catalyzed reduction of 1-(4-methoxyphenyl)-4-phenyl-2,3-azetidindione as a key step in a biocatalytic approach to the synthesis of the paclitaxel C-13 side chain (Scheme 1) [2]. To investigate other 4-substituted α-keto-β-lactams as substrates for microbial reductions and subsequent conversions to optically pure C-13 side-chain analogs we required a simple, efficient, and general protocol for the synthesis of these compounds.



Scheme 1 α-Keto-β-lactams as key fragments in a biocatalytic approach to paclitaxel analogs

Although numerous α-keto-β-lactams have been successfully prepared, the reported methods were optimized for specific compounds and lacked generality. Usually cyclizations to the lactam ring have been achieved by condensations of activated carboxylic acids with protected imines in *Staudinger* type reactions [3]. In most cases an acid chloride was used as an activated species, however, the reactions did not consistently produce high yields [4]. In an alternative approach, ketal or thioketal protected glyoxylic acid esters were treated with a strong base such as *tert*-BuOK or BuLi providing anions that were condensed with imines to ketal or thioketal protected β-lactams [5]. While the above routes gave satisfactory results for the cyclizations, the deprotection of the resulting intermediates (Scheme 2, A and B), to ketones **1** could be accomplished only under rather harsh conditions such as treatment with concentrated mineral acids [5]. These methods, therefore, are suitable only for the preparation of compounds with acid-resistant substituents. Thus, low reactivity of the quaternary center in the intermediates **A**, **B**, or **C** (the latter accessible *via* cyclization of a thio-precursor followed by chlorination) towards nucleophilic attack limits the applicability of these otherwise simple and straightforward syntheses.



Scheme 2 Possible synthetic routes to α-keto-β-lactams

This paper describes a milder and more general three-step procedure adapted for the preparation of α-keto-β-lactams substituted with fragile functional groups. The protocol is based on the cyclization of an imine **3** with carboxylic acid **4** in the presence of $POCl_3$ *via in situ* generation of acid chloride illustrated in Scheme 3 [6], followed by hydrolysis of the acetate and oxidation of the resulting alcohol (Scheme 4). The cyclization step can be easily controlled and scaled up. The following transformations are carried out under mild conditions tolerated by a variety of sensitive substituents.

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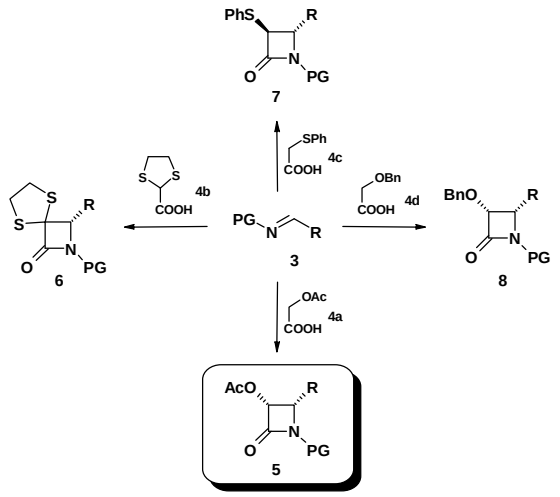
Results and Discussion

Imines **3** were readily accessible by reacting appropriate amines with aldehydes in the presence of magnesium sulfate [7]. The products were isolated in good yields and could be used in subsequent transformations without purification. In the following step a solution of **3** and acetylglyoxylic acid **4a** [8] was treated with $POCl_3$ in the presence of triethylamine as the base. The 3-acetoxy-β-lactams **5a**–**g** were produced in good to excellent yields after recrystallization or flash chromatography (Scheme 3). Even the sterically demanding imine **3g** was successfully converted to the corresponding β-lactam albeit in a lower yield (Scheme 3, entry 7). The two *N*-protecting groups tested, *p*-methoxyphenyl (PMP) and benzyl (Bn), appear to be equally acceptable (Scheme 3, entries 1 and 2). It is noteworthy that the lactams **5** were obtained mainly as *cis*-isomers. Only compounds **5c** and **5e** contained traces of the *trans* β-lactams. Since at this stage the stereochemistry was not an issue the mixtures were used in the following oxidation step.



entry	imine	R	PG	acid	product	yield (%)
1	**3a**	phenyl	PMP	**4a**	**5a**	55
2	**3b**	phenyl	Bn	**4a**	**5b**	84
3	**3c**	2-thienyl	PMP	**4a**	**5c**	59 [a]
4	**3d**	3-thienyl	PMP	**4a**	**5d**	65
5	**3e**	2-furyl	PMP	**4a**	**5e**	56 [b]
6	**3f**	-C(Me)=CHPh	PMP	**4a**	**5f**	83
7	**3g**	*tert*-butyl	PMP	**4a**	**5g**	33
8	**3a**	phenyl	PMP	**4b**	**6a**	86
9	**3c**	2-thienyl	PMP	**4c**	**7c**	59
10	**3e**	2-furyl	PMP	**4c**	**7e**	70
11	**3a**	phenyl	PMP	**4d**	**8a**	69

[a]) mixture of *cis*- and *trans*-isomers 5:1; [b]) mixture of *cis*- and *trans*-isomers 2:1

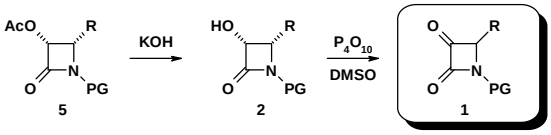
Scheme 3 Cyclizations *via* the $POCl_3$ method

To evaluate the effectiveness of our cyclization protocol, we carried out the alternative cyclizations of imines **3a**, **3c** and **3e** with dithioketal **4b** [9], phenylthioacetic acid **4c** [10], and benzylglyoxylic acid **4d** [11] (Scheme 3, entries 8–11). The yields of lactams **6**, **7**, and **8** were found to be comparable to those obtained in the reactions with acetylglyoxylic acid described above. Interestingly, the thio-compounds **7c** and **7e** were formed as *trans*-isomers exclusively. This stereopreference for sulfur substituted lactams has been noted previously [10].

Our attempts to scale-up the subsequent conversion to the desired ketones *via* the protocol outlines in the literature [10] proved difficult. The furane substituent in **7e** was unstable under chlorination conditions with sulfuryl chloride, and although the chlorination was successfully accomplished with the thienyl substituted **7c** the subsequent heterogeneous hydrolysis on silica gel proceeded very slowly and gave incomplete conversion.

The low reactivity of the quaternary center seemed to be responsible for the problems encountered in the deprotection of the thioketal **6a** especially in the presence of adjacent carbonyl groups [12]. The successful deprotection of a ketal group in compounds of type **A** (Scheme 2) was achieved only with a phenyl substituent. It required prolonged treatment with *conc.* sulfuric acid [2, 5]. Few functional groups can tolerate such drastic conditions.

On the other hand α-acetoxy-β-lactams (**5a**–**g**) were hydrolyzed to alcohols (**2a**–**g**) in excellent yields under very mild conditions [13]. Subsequent oxidations were performed by treatment with DMSO in the presence of phosphorous pentoxide [14] to give the α-keto-β-lactams (**1a**–**g**) in good yields as shown in Scheme 4.



entry	R	PG	hydrolysis	yield (%)	oxidation	yield (%)
1	phenyl	PMP	**2a**	77	**1a**	90
2	phenyl	Bn	**2b**	99	**1b**	99
3	2-thienyl	PMP	**2c**	92 [a]	**1c**	69
4	3-thienyl	PMP	**2d**	74	**1d**	81
5	2-furyl	PMP	**2e**	92 [a]	**1e**	76
6	-C(Me)=CHPh	PMP	**2f**	95	**1f**	82
7	*tert*-butyl	PMP	**2g**	94	**1g**	85

[a]) mixture of *cis*- and *trans*-isomers

Scheme 4 Synthesis of α-keto-β-lactams

In conclusion, the synthetic scheme reported here includes the cyclization protocol applicable to a variety of substrates. The following transformations leading to the target compounds **1** are suitable for a variety of substituents and allow access to several oxy precursors for the taxol C-13 side-chain.

The enantioselective reductions of these compounds using recombinant organisms are presently investigated.

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Experimental

Unless otherwise noted, chemicals were purchased from commercial suppliers and were used without further purification. All solvents were distilled prior to use. Dry methylene chloride was prepared by distillation from P_4O_{10}. Commercially available dry DMSO was treated with molecular sieves (4 Å). Melting points were determined on a *Fisher-Johns* melting point apparatus and are uncorrected. Proton and carbon NMR spectra were recorded either on a BRUKER 200 FT-NMR spectrometer or a Varian Unity 400 FT-NMR spectrometer; chemical shifts are reported in ppm using Me_4Si as internal standard. Mass spectra were obtained on a Kratos MS 550TC mass spectrometer. IR spectra were recorded from thin films on a Nicolet 520 FT-IR spectrometer.

Cyclization Reaction (General Procedure)

A 10% solution of the imine **3** (1 equiv.), the carboxylic acid **4** (1.3 equiv.), and dry triethyl amine (3 equiv.) in dry methylene chloride was cooled to approximately 5 °C and treated under nitrogen atmosphere with a 20% solution of $POCl_3$ (1 equiv.) in dry methylene chloride. After complete addition the solution was stirred at room temperature for 24–48 hrs. The reaction mixture was hydrolyzed with 2N HCl, and extracted with methylene chloride; the combined organic layers were washed with saturated sodium carbonate solution, dried over magnesium sulfate, filtered, and concentrated.

cis-3-Acetoxy-1-(4-methoxyphenyl)-4-phenyl-2-azetidinone (**5a**)

Imine **3a** (2.000 g, 9.467 mmol) reacted with acid **4a** to give 1.609 g (55%) of pure **5a** [11, 15] as colorless crystals after recrystallization from diisopropyl ether (*m.p.* 154–157 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.67 (s, 3H), 3.75 (s, 3H), 5.33 (d, J = 4.9 Hz, 1H), 5.94 (d, J = 4.9 Hz, 1H), 6.80 (d, J = 9.1 Hz, 2H), 7.26–7.35 (m, 7H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 19.8 (q), 55.4 (q), 61.4 (d), 76.3 (d), 114.4 (d), 118.8 (d), 127.9 (d), 128.4 (d), 128.8 (d), 130.3 (s), 132.2 (s), 156.6 (s), 161.3 (s), 169.2 (s).

cis-3-Acetoxy-4-phenyl-1-(phenylmethyl)-2-azetidinone (**5b**)

Imine **3b** (2.000 g, 10.234 mmol) reacted with acid **4a** to give 2.532 g (84%) of **5b** [16, 17] as colorless oil after flash column chromatography (silica gel, petroleum ether : ethyl acetate = 5:1). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.64 (s, 3H), 3.91 (d, J = 14.9 Hz, 1H), 4.75 (d, J = 4.6 Hz, 1H), 4.87 (d, J = 14.9 Hz, 1H), 5.76 (d, J = 4.6 Hz, 1H), 7.13–7.35 (m, 10H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 19.7 (q), 44.4 (t), 60.7 (d), 77.2 (d), 127.9 (d), 128.2 (2d), 128.4 (d), 128.6 (d), 128.7 (d), 132.3 (s), 134.3 (s), 164.5 (s), 168.9 (s).

3-Acetoxy-1-(4-methoxyphenyl)-4-(2-thienyl)-2-azetidinone (**5c**)

Imine **3c** (2.80 g, 12.90 mmol) reacted with acid **4a** to give 2.40 g (59%) of pure **5c** as colorless crystals after flash column chromatography (silica gel, petroleum ether : ethyl acetate = 3:1) as mixture of *cis* and *trans* isomers in a ratio of approx. 5:1 - *cis*-**5c**. – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 1.73 (s, 3H), 3.76 (s, 3H), 5.61 (d, J = 4.8 Hz, 1H), 5.96 (d, J = 4.8 Hz, 1H), 6.83 (d, J = 9.2 Hz, 2H), 6.97–7.05 (m, 1H), 7.08–7.16 (m, 1H), 7.16–7.30 (m, 3H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm = 19.9 (q), 55.3 (q), 57.5 (d), 76.4 (d), 114.3 (d), 118.7 (d), 126.7 (d), 127.0 (d), 128.1 (d), 130.0 (s), 135.6 (s), 156.6 (s), 161.0 (s), 169.2 (s); *trans*-**5c**. – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 2.20 (s, 3H), 3.76 (s, 3H), 5.20 (d, J = 1.5 Hz, 1H), 5.51 (d, J = 1.5 Hz, 1H), 6.83 (d, J = 9.2 Hz, 2H), 6.97–7.05 (m, 1H), 7.08–7.16 (m, 1H), 7.16–7.30 (m, 3H). – ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 20.3 (q), 55.3 (q), 60.3 (d), 82.9 (d), 114.3 (d), 119.0 (d), 126.2 (d), 126.5 (d), 127.3 (d), 129.9 (s), 138.5 (s), 156.6 (s), 160.7 (s), 169.5 (s).

cis-3-Acetoxy-1-(4-methoxyphenyl)-4-(3-thienyl)-2-azetidinone (**5d**)

Imine **3d** (2.000 g, 9.204 mmol) reacted with acid **4a** to give 1.906 g (65%) of pure **5d** as colorless crystals after recrystallization from diisopropyl ether (*m.p.* 145–148 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.79 (s, 3H), 3.76 (s, 3H), 5.44 (d, J = 4.8 Hz, 1H), 5.90 (d, J = 4.8 Hz, 1H), 6.81 (d, J = 9.2 Hz, 2H), 7.01 (d, J = 5.0 Hz, 1H), 7.26–7.31 (m, 4H). – ^{13}C NMR ($CDCl_3$, 100 MHz), δ/ppm = 19.0 (q), 55.4 (q), 57.6 (d), 76.3 (d), 114.4 (d), 118.7 (d), 124.7 (d), 126.2 (d), 126.8 (d), 130.3 (s), 134.0 (s), 156.6 (s), 161.2 (s), 169.4 (s). – IR ($CDCl_3$): ν_{max}/cm^{-1} = 1761, 1523, 1221. – HRMS for $C_{16}H_{15}NO_4S$ (M^+): calcd.: 317.0722, found: 317.0720.

3-Acetoxy-4-(2-furyl)-1-(4-methoxyphenyl)-2-azetidinone (**5e**)

Imine **3e** (6.68 g, 33.19 mmol) reacted with acid **4a** to give 5.60 g (56%) of a 2:1 mixture of *cis*- and trans-**5e** as colorless crystals after flash column chromatography (silica gel, petroleum ether : ethyl acetate = 2:1) - *cis*-**5e**. – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 1.95 (s, 3H), 3.78 (s, 3H), 5.38 (d, J = 5 Hz, 1H), 5.95 (d, J = 5 Hz, 1H), 6.37–6.52 (m, 2H), 6.82 (d, J = 9 Hz, 2H), 7.30 (d, J = 9 Hz, 2H), 7.42–7.47 (m, 1H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm = 19.8 (q), 55.2 (d), 55.3 (q), 76.0 (d), 110.2 (2d), 114.3 (d), 118.5 (d), 130.1 (s), 143.4 (d), 146.7 (s), 156.6 (s), 161.9 (s), 169.1 (s); *trans*-**5d**. – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 2.21 (s, 3H), 3.78 (s, 3H), 4.97 (d, J = 2 Hz, 1H), 5.78 (d, J = 2 Hz, 1H), 6.37–6.52 (m, 2H), 6.82 (d, J = 9 Hz, 2H), 7.30 (d, J = 9 Hz, 2H), 7.42–7.47 (m, 1H). – ^{13}C NMR ($CDCl_3$, 50 MHz), δ/ppm = 20.3 (q), 55.3 (q), 56.6 (d), 79.4 (d), 110.2 (d), 110.7 (d), 114.2 (d), 118.7 (d), 130.2 (s), 143.5 (d), 148.0 (s), 156.6 (s), 161.9 (s), 169.4 (s).

cis-3-Acetoxy-1-(4-methoxyphenyl)-4-(3-phenylprop-2-en-2-yl)-2-azetidinone (**5f**)

Imine **3f** (2.000 g, 7.958 mmol) reacted with acid **4a** to give 2.319 g (83%) of pure **5f** as colorless crystals after recrystallization from diisopropyl ether (*m.p.* 144–145 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.89 (s, 3H), 2.09 (s, 3H), 3.78 (s, 3H), 4.85 (d, J = 5.1 Hz, 1H), 6.01 (d, J = 5.1 Hz, 1H),

6.63 (s, 1H), 6.87 (d, J = 9.0 Hz, 2H), 7.21–7.27 (m, 3H), 7.35 (t, J = 7.5 Hz, 2H), 7.40 (d, J = 9.0 Hz, 2H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 14.9 (q), 20.3 (q), 55.4 (q), 64.4 (d), 75.8 (d), 114.4 (d), 118.3 (d), 127.2 (d), 128.3 (d), 128.8 (d), 130.6 (s), 130.8 (s), 131.5 (d), 136.5 (s), 156.6 (s), 161.4 (s), 169.4 (s). – IR ($CDCl_3$): ν_{max}/cm^{-1} = 1761, 1516, 1221. – HRMS for $C_{21}H_{21}NO_4$ (M^+): calcd.: 351.1470, found: 351.1483.

cis-3-Acetoxy-1-(4-methoxyphenyl)-4-(1,1-dimethylethyl)-2-azetidinone (**5g**)

Imine **3g** (2.000 g, 10.456 mmol) reacted with acid **4a** to give 1.001 g (33%) of pure **5g** as colorless crystals after recrystallization from diisopropyl ether : THF = 3:1 (*m.p*. 186–189 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.01 (s, 9H), 2.18 (s, 3H), 3.79 (s, 3H), 4.24 (d, J = 5.5 Hz, 1H), 6.15 (d, J = 5.5 Hz, 1H), 6.88 (d, J = 9.1 Hz, 2H), 7.29 (d, J = 9.1 Hz, 2H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 20.9 (q), 26.6 (q), 34.7 (s), 55.4 (q), 66.9 (d), 73.4 (d), 114.2 (d), 122.0 (d), 129.9 (s), 157.1 (s), 164.0 (s), 169.3 (s). – IR ($CDC1_3$): ν_{max}/cm^{-1} = 2961, 1747, 1516, 1235, 1123. – HRMS for $C_{16}H_{21}NO_4$ (M^+): calcd.: 291.1470, found: 291.1490.

2-(4-Methoxyphenyl)-3-phenyl-5,8-dithia-2-azaspiro[3.4]octan-1-one (**6a**)

Imine **3a** (0.500 g, 2.367 mmol) reacted with acid **4b** to give 0.698 g (86%) of pure **6a** as colorless crystals after trituration with methanol (*m.p*. 230–232 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 3.11–3.49 (m, 4H), 3.75 (s, 3H), 5.30 (s, 1H), 6.79 (d, J = 9.2 Hz, 2H), 7.23–7.41 (m, 7H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 39.8 (t), 40.1 (t), 55.4 (q), 69.5 (d), 74.1 (s), 114.3 (d), 119.0 (d), 126.9 (d), 128.8 (d), 129.1 (d), 130.5 (s), 134.6 (s), 156.4 (s), 162.4 (s). – IR ($CDCl_3$): ν_{max}/cm^{-1} = 1754, 1510, 1256, 1156. – HRMS for $C_{18}H_{17}NO_2S_2$ (M^+): calcd.: 343.0701, found: 343.0698.

trans-1-(4-Methoxyphenyl)-3-phenylthio-4-(2-thienyl)-2-azetidinone (**7c**)

Imine **3c** (2.000 g, 9.204 mmol) reacted with acid **4c** to give 1.997 g (59%) of pure **7c** as colorless crystals after flash column chromatography (silica gel, petroleum ether : ethyl acetate = 8:1 to 3:1 gradient elution) (*m.p*. 103–106 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 3.72 (s, 3H), 4.40 (d, J = 2.5 Hz, 1H), 5.05 (d, J = 2.5 Hz, 1H), 6.76 (d, J = 9.1 Hz, 2H), 6.96–7.53 (m, 10H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 55.4 (q), 59.4 (d), 62.4 (d), 114.3 (d), 118.8 (d), 126.3 (d), 126.4 (d), 127.4 (d), 128.1 (d), 129.2 (d), 130.4 (s), 132.0 (s), 132.3 (d), 140.1 (s), 156.5 (s), 162.3 (s). – IR ($CDCl_3$): ν_{max}/cm^{-1} = 3059, 1756, 1519, 1381, 1249. – HRMS for $C_{20}H_{17}NO_2S_2$ (M^+): Calcd. 367.0701, found: 367.0689.

trans-4-(2-Furyl)-1-(4-methoxyphenyl)-3-phenylthio-2-azetidinone (**7e**)

Imine **3e** (2.000 g, 9.939 mmol) reacted with acid **4c** to give 2.441 g (70%) of pure **7e** as colorless crystals after flash column chromatography (silica gel, petroleum ether : ethyl acetate = 8:1 to 3:1 gradient elution) (*m.p*. 90–93 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 3.71 (s, 3H), 4.59 (d, J = 2.4 Hz, 1H), 4.80 (d, J = 2.4 Hz, 1H), 6.36 (dd, ^1J = 3.4 Hz, ^2J = 1.8 Hz, 1H), 6.46 (d, J = 3.4 Hz, 1H), 6.75 (d, J = 9.1 Hz, 2H), 7.14–7.51 (m, 8H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 55.4 (q), 56.3 (d), 58.3 (d), 110.4 (d), 110.8 (d), 114.2 (d), 118.6 (d), 128.1 (d), 129.2 (d), 129.8 (s), 130.6 (s), 131.8 (d), 143.6 (d), 148.8 (s), 156.4 (s), 162.5 (s). – IR ($CDCl_3$): ν_{max}/cm^{-1} = 1761, 1500, 1390, 1249.

cis-1-(4-Methoxyphenyl)-3-phenylmethyloxy-4-phenyl-2-azetidinone (**8a**)

Imine **3a** (0.500 g, 2.367 mmol) reacted with acid **4d** to give 0.585 g (69%) of pure **8a** [18] as colorless crystals after recrystallization from ethyl acetate (*m.p*. 197–198 °C). – ^{1}H NMR (acetone-d_6, 400 MHz): δ/ppm = 3.73 (s, 3H), 4.24 (d, J = 11.3 Hz, 1H), 4.42 (d, J = 11.3 Hz, 1H), 5.18 (d, J = 5.1 Hz, 1H), 5.50 (d, J = 5.1 Hz, 1H), 6.83–7.54 (m, 14H).

Hydrolysis of the Acetoxy Group (General Procedure)

A 5% solution of the acetyl compound **5** (1 equiv.) was dissolved in THF and cooled to 0 °C. The reaction mixture was slowly treated with half the volume of 2N KOH and stirred at 0 °C until TLC indicated complete conversion (usually about 1 h). After addition of water the solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and evaporated to dryness.

cis-3-Hydroxy-1-(4-methoxyphenyl)-4-phenyl-2-azetidinone (**2a**)

Compound **5a** (0.200 g, 0.677 mmol) was hydrolyzed according to the above procedure to give 0.140 g (77%) of **2a** [19] as colorless crystals (*m.p*. 204–208 °C). – ^{1}H NMR (DMSO-d_6, 400 MHz): δ/ppm = 3.68 (s, 3H), 5.16 (dd, ^1J = 7.0 Hz, ^2J = 5.1 Hz, 1H), 5.29 (d, J = 5.1 Hz, 1H), 6.09 (d, J = 7.0 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.27–7.37 (m, 5H). – ^{13}C NMR (DMSO-d_6, 100 MHz): δ/ppm = 55.2 (q), 61.8 (d), 76.8 (d), 114.4 (d), 118.2 (d), 127.7 (d), 128.0 (d), 128.1 (d), 130.7 (s), 134.9 (s), 155.6 (s), 166.3 (s).

cis-3-Hydroxy-4-phenyl-1-(phenylmethyl)-2-azetidinone (**2b**)

Precursor **5b** (2.200 g, 7.449 mmol) was hydrolyzed according to the above procedure to give 1.880 g (99%) of **2b** [16, 17] as colorless crystals (*m.p*. 116–120 °C). – ^{1}H NMR (DMSO-d_6, 400 MHz): δ/ppm = 3.91 (d, J = 15.4 Hz, 1H), 4.64–4.68 (m, 2H), 5.02 (dd, ^1J = 4.8 Hz, ^2J = 7.0 Hz, 1H), 5.95 (d, J = 7.0 Hz, 1H), 7.15–7.36 (m, 10H). – ^{13}C NMR (DMSO-d_6, 100 MHz): δ/ppm = 43.4 (t), 62.1 (d), 77.9 (d), 127.4 (d), 127.7 (d), 128.0 (2d), 128.3 (d), 128.6 (d), 135.1 (s), 135.8 (s), 169.0 (s).

3-Hydroxy-1-(4-methoxyphenyl)-4-(2-thienyl)-2-azetidinone (**2c**)

The mixture of *cis*- and *trans*-**5c** (2.00 g, 6.35 mmol) obtained from the above cyclization was hydrolyzed according to the general procedure to give 1.20 g (92%) of *cis/trans*-**2c** as colorless crystals; *cis*-**2c**. – ^{1}H NMR (DMSO-d_6, 200 MHz): δ/ppm = 3.74 (s, 3H), 5.18 (d, J = 4.9 Hz, 1H), 5.50 (d, J = 4.9 Hz, 1H), 6.81 (d, J = 9.2 Hz, 2H), 7.02 (dd, ^1J = 5.1 Hz, ^2J = 3.6 Hz, 1H), 7.14–7.15 (m, 1H), 7.28 (d, J = 9.2 Hz,

2H), 7.37 (dd, ^1J = 5.1 Hz, ^2J = 0.9 Hz, 1H). – ^{13}C NMR (DMSO-d_6, 50 MHz): δ/ppm = 53.8 (q), 57.4 (d), 75.8 (d), 112.8 (d), 117.1 (d), 124.8 (d), 125.4 (d), 126.0 (d), 129.2 (s), 136.5 (s), 154.6 (s), 164.6 (s); *trans*-**2c**. – ^{1}H NMR (DMSO-d_6, 200 MHz): δ/ppm = 3.74 (s, 3H), 4.65–4.70 (m, 1H), 5.16–5.23 (m, 1H), 6.81 (d, *J* = 9.2 Hz, 2H), 7.01–7.07 (m, 1H), 7.16–7.32 (m, 3H), 7.48–7.55 (m, 1H). – ^{13}C NMR (DMSO-d_6, 50 MHz): δ/ppm = 55.2 (q), 60.9 (d), 84.5 (d), 114.4 (d), 118.8 (d), 126.4 (d), 126.7 (d), 126.9 (d), 130.1 (s), 140.5 (s), 155.9 (s), 165.7 (s).

cis-3-Hydroxy-1-(4-methoxyphenyl)-4-(3-thienyl)-2-azetidinone (**2d**)

Precursor **5d** (1.500 g, 4.726 mmol) was hydrolyzed according to the above procedure to give 0.956 g (74%) of **2d** as colorless crystals after trituration with diisopropyl ether (*m.p.* 212–215 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): 3.76 (s, 3H), 5.14 (d, *J* = 5.0 Hz, 1H), 5.34 (d, *J* = 5.0 Hz, 1H), 6.81 (d, *J* = 9.1 Hz, 2H), 7.08 (d, *J* = 5.0 Hz, 1H), 7.21–7.31 (m, 3H), 7.40 (dd, ^1J = 5.0 Hz, ^2J = 2.9 Hz, 1H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 55.4 (q), 58.7 (d), 76.6 (d), 114.4 (d), 118.8 (d), 124.1 (d), 126.6 (d), 127.3 (d), 130.5 (s), 134.9 (s), 156.5 (s), 156.9 (s). – IR ($CDCl_3$) ν_{max}/cm^{-1} = 1726, 1523, 1256. – HRMS for $C_{14}H_{13}NO_3S$ (M^+): calcd. 275.0616, found: 275.0616.

3-Hydroxy-1-(4-methoxyphenyl)-4-(2-furyl)-2-azetidinone (**2e**)

The mixture of *cis*- and *trans*-**5e** (5.00 g, 16.56 mmol) was hydrolyzed according to the above procedure to give 3.95 g (92%) of *cis/trans*-**2e** as colorless crystals; *cis*-**2e**. – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 3.2 (bs, 1H), 3.76 (s, 3H), 5.15–5.30 (m, 2H), 6.40–6.55 (m, 2H), 6.82 (d, *J* = 9 Hz, 2H), 7.30 (d, *J* = 9 Hz, 2H), 7.45–7.50 (m, 1H). – ^{13}C NMR (DMSO-d_6, 50 MHz): δ/ppm = 54.9 (q), 56.1 (d), 76.9 (d), 109.4 (d), 109.7 (d), 113.8 (d), 117.8 (d), 130.5 (s), 142.6 (d), 148.4 (s), 155.6 (s), 165.7 (s); *trans*-**2e**. – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 3.74 (s, 3H), 4.92 (d, *J* = 2 Hz, 1H), 5.05–5.20 (m, 2H), 6.40–6.55 (m, 2H), 6.79 (d, *J* = 9 Hz, 2H), 7.25 (d, *J* = 9 Hz, 2H), 7.40–7.43 (m, 1H). – ^{13}C NMR (DMSO-d_6, 50 MHz): δ/ppm = 54.9 (q), 58.4 (d), 80.6 (d), 109.4 (2d), 113.8 (d), 118.0 (d), 130.4 (s), 142.8 (s), 149.1 (s), 155.7 (s), 165.7 (s).

cis-3-Hydroxy-1-(4-methoxyphenyl)-4-(3-phenylprop-2-en-2-yl)-2-azetidinone (**2f**)

Compound **5f** (1.700 g, 4.838 mmol) was converted according to the above procedure to give 1.425 g (95%) of **2f** as colorless crystals (*m.p.* 173–174 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.98 (s, 3H), 3.64 (bs), 3.77 (s, 3H), 4.72 (d, *J* = 4.8 Hz, 1H), 5.15 (dd, ^1J = 4.8 Hz, ^2J = 8.4 Hz, 1H), 6.54 (s, 1H), 6.84 (d, *J* = 9.1 Hz, 2H), 7.21–7.37 (m, 5H), 7.39 (d, *J* = 9.1 Hz, 2H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 15.9 (q), 55.4 (q), 65.2 (d), 77.1 (d), 114.4 (d), 118.5 (d), 127.0 (d), 128.2 (d), 129.0 (d), 129.3 (d), 130.9 (s), 131.6 (s), 136.5 (s), 156.4 (s), 166.0 (s).

cis-3-Hydroxy-1-(4-methoxyphenyl)-4-(1,1-dimethylethyl)-2-azetidinone (**2g**)

Compound **5g** (0.900 g, 3.089 mmol) was hydrolyzed according to the above procedure to give 0.725g (94%) of **2g** as colorless crystals (*m.p.* 204–205 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.07 (s, 9H), 3.78 (s, 3H), 4.05 (d, *J* = 5.3 Hz, 1H), 5.05 (dd, ^1J = 5.3 Hz, ^2J = 6.5 Hz, 1H), 5.68 (d, *J* = 6.5 Hz, 1H), 6.86 (d, *J* = 9.1 Hz, 2H), 7.30 (d, *J* = 9.1 Hz, 2H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 26.8 (q), 34.5 (s), 55.1 (q), 67.3 (d), 75.4 (d), 113.7 (d), 121.2 (d), 130.5 (s), 156.2 (s), 168.4 (s). – IR ($CDC1_3$): ν_{max}/cm^{-1} = 3298, 1719, 1516, 1256, 1039. – HRMS for $C_{14}H_{19}NO_3$ (M^+): calcd.: 249.1365, found: 249.1369.

Oxidation with Phosphorous Pentoxide (General Procedure)

Phosphorous pentoxide (P_2O_5, 1.5 eq.) was added to dry DMSO and stirred for 10min. The alcohol **2** in little DMSO was added and the resulting mixture (approx. 5% solution of starting material) was stirred at room temperature until TLC indicated complete conversion (usually 24 h). After hydrolysis with cooled saturated sodium bicarbonate solution and extraction with ethyl acetate the combined organic layers were washed three times with brine to remove DMSO, dried over magnesium sulfate, filtered, and evaporated.

1-(4-Methoxyphenyl)-4-phenyl-2,3-azetidindione (**1a**)

Alcohol **2a** (30 mg, 0.111 mmol) was oxidized according to the above procedure to give 27 mg (90%) of **1a** [5] as yellow crystals (*m.p.* 124–126 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 3.78 (s, 3H), 5.55 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.29–7.40 (m, 5H), 7.42 (d, *J* = 8.8 Hz, 2H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 55.5 (q), 74.9 (d), 114.8 (d), 119.8 (d), 126.4 (d), 129.4 (d), 129.5 (d), 129.9 (s), 131.7 (s), 158.0 (s), 160.0 (s), 190.7 (s).

4-Phenyl-1-(phenylmethyl)-2,3-azetidindione (**1b**)

Product **2b** (1.800 g, 7.106 mmol) was oxidized according to the above procedure to yield 1.780g (99%) of **1b** as yellow oil after chromatographic purification (silica gel, petroleum ether : ethyl acetate = 3:1). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 4.19 (d, *J* = 14.7 Hz, 1H), 4.92 (s, 1H), 5.17 (d, *J* = 14.7 Hz, 1H), 7.15–7.50 (m, 10H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 45.3 (t), 73.3 (d), 126.8 (d), 128.6 (d), 128.9 (d), 129.1 (d), 128.3 (d), 129.5 (d), 131.7 (s), 133.2 (s), 163.7 (s), 193.0 (s). – IR ($CDC1_3$) ν_{max}/cm^{-1} = 3032, 2927, 1822, 1756, 1466, 1335, 1308, 1137. – HRMS for $C_{16}H_{13}NO_2$ (M^+): calcd.: 251.0946, found: 251.0930.

1-(4-Methoxyphenyl)-4-(2-thienyl)-2,3-azetidindione (**1c**)

The mixture of *cis*- and *trans*-**2c** (1.60 g, 5.82 mmol) obtained from the hydrolytic step was oxidized according to the above procedure to give 1.09 g (69%) of **1c** as yellow crystals after chromatographic purification (silica gel, petroleum ether : ethyl acetate = 2:1) (*m.p.* 48–50 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 3.80 (s, 3H), 5.81 (s, 1H), 6.89 (d, *J* = 9.1 Hz, 2H), 7.03–7.10 (m, 1H), 7.16 (d, *J* = 3.8 Hz, 1H), 7.36 (d, *J* = 4.5 Hz, 1H), 7.51 (d, *J* = 9.1 Hz, 2H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm = 55.4 (q), 70.4 (d), 114.6 (d), 119.6 (d), 127.0 (d), 127.1 (d), 127.3 (d), 129.4 (s), 134.6 (s), 158.0 (s), 159.4 (s), 189.7 (s). – IR ($CDCl_3$) ν_{max}/cm^{-1} = 1839, 1768, 1516, 1256, 842. – HRMS for $C_{14}H_{11}NO_3S$ (M^+): calcd.: 273.0459, found: 273.0441.

1-(4-Methoxyphenyl)-4-(3-thienyl)-2,3-azetidindione (**1d**)

Alcohol **2d** (0.700 g, 2.542 mmol) was oxidized according to the above procedure to give 0.560 g (81%) of **1d** as yellow crystals after chromatographic purification (silica gel, petroleum ether : ethyl acetate = 2:1) (*m.p.* 102–105 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 3.79 (s, 3H), 5.67 (s, 1H), 6.89 (d, J = 9.1 Hz, 2H), 7.02 (dd, ^1J = 5.1 Hz, ^2J = 1.4 Hz, 1H), 7.34 (dd, ^1J = 3.0 Hz, ^2J = 1.4 Hz, 1H), 7.38 (dd, ^1J = 5.1 Hz, ^2J = 3.0 Hz, 1H), 7.48 (d, J = 9.1 Hz, 2H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 55.5 (q), 70.9 (d), 114.7 (d), 119.6 (d), 124.1 (d), 125.0 (d), 127.9 (d), 129.9 (s), 132.9 (s), 158.0 (s), 159.6 (s), 190.5 (s). – IR ($CDC1_3$): ν_{max}/cm^{-1} = 1825, 1761, 1516, 1256, 1116. – HRMS for $C_{14}H_{11}NO_3S$ (M^+): calcd.: 273.0459, found: 273.0446.

4-(2-Furyl)-1-(4-methoxyphenyl)-2,3-azetidindione (**1e**)

The mixture of *cis*- and *trans*-**2e** (3.95 g, 15.25 mmol) was oxidized according to the above procedure to give 2.96 g (76%) of **1e** [20] as yellow crystals after chromatographic purification (silica gel, petroleum ether : ethyl acetate = 3:1) (*m.p.* 89–91 °C). – ^{1}H NMR ($CDCl_3$, 200 MHz): δ/ppm = 3.80 (s, 3H), 5.63 (s, 1H), 6.37–6.46 (m, 1H), 6.53–6.60 (m, 1H), 6.90 (d, J = 9 Hz, 2H), 7.40–7.55 (m, 3H). – ^{13}C NMR ($CDCl_3$, 50 MHz): δ/ppm = 55.4 (q), 68.1 (d), 111.0 (d), 111.6 (d), 114.7 (d), 119.3 (d), 130.0 (s), 144.3 (d), 145.3 (s), 158.1 (s), 159.8 (s), 189.3 (s).

1-(4-Methoxyphenyl)-4-(3-phenylprop-2-en-2-yl)-2,3-azetidindione (**1f**)

Alcohol **2f** (1.000 g, 3.232 mmol) reacted according to the above procedure to give 0.811 g (82%) of **1f** [21] as yellow crystals after recrystallization from diisopropyl ether (*m.p.* 92–94 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.86 (s, 3H), 3.82 (s, 3H), 5.14 (s, 1H), 6.71 (s, 1H), 6.94 (d, J = 9.4 Hz, 2H), 7.27–7.35 (m, 5H), 7.61 (d, J = 9.4 Hz, 2H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 13.9 (q), 55.5 (q), 76.7 (d), 114.8 (d), 119.1 (d), 127.5 (d), 128.4 (d), 129.0 (d), 129.4 (s), 130.6 (s), 131.7 (d), 135.8 (s), 158.1 (s), 159.9 (s), 193.4 (s).

1-(4-Methoxyphenyl)-4-(1,1-dimethylethyl)-2,3-azetidindione (**1g**)

Compound **2g** (0.700 g, 2.808 mmol) was oxidized according to the above procedure to give 0.811 g (85%) of **1g** as yellow crystals after recrystallization from diisopropyl ether (*m.p.* 130–131 °C). – ^{1}H NMR ($CDCl_3$, 400 MHz): δ/ppm = 1.03 (s, 9H), 3.81 (s, 3H), 4.54 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H). – ^{13}C NMR ($CDCl_3$, 100 MHz): δ/ppm = 26.0 (q), 35.2 (s), 55.5 (q), 80.4 (d), 114.4 (d), 121.4 (d), 129.6 (s), 158.4 (s), 161.0 (s), 195.7 (s). – IR ($CHC1_3$) ν_{max}/cm^{-1} = 2967, 1815, 1762, 1604, 1512, 1262. – HRMS for $C_{14}H_{17}O_3N$ (M^+): calcd. 247.1208, found: 247.1204.

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