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Technical Notes

Process Development of a Dual MMP/TNF Inhibitor (SDZ 242-484)

Guido Koch,* Georg Kottirsch, Bernhard Wietfeld, and Ernst Küsters

Process Research and Development, Chemical and Analytical Development, Novartis Pharma AG, CH 4002, Basel, Switzerland

Abstract:

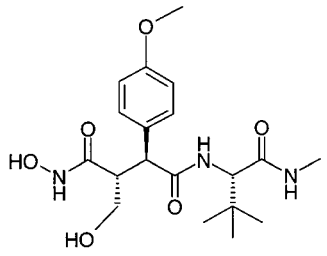
The compound (2*R*,3*S*)-*N*-4-((*S*)-2,2-Dimethyl-1-methylcarbamoyl-propyl)-*N*-1-hydroxy-2-hydroxymethyl-3-(4-methoxy-phenyl)-succinamide (1; SDZ 242-484) shows antiinflammatory effects due to inhibition of matrix metalloproteases (MMP) and tumor necrosis factor-α activity (TNF). We describe the development of a chromatography-free process for a multikilogram-scale pilot-plant production. Two of the three chiral centers are introduced in a diastereoselective Claisen−Ireland rearrangement. It was found that the selectivity of this step was significantly enhanced by the addition of catalytic amounts of Lewis acids. The resulting enantiomeric carboxylic acids were resolved with (*S*)-(−)-phenylethylamine. The use of osmiumtetroxide was considered to be problematic for pilot-plant use. Therefore, it was necessary to find an alternative method for the oxidative cleavage of the terminal olefin functionality. For the last chemical transformation, a hydrogenolytic cleavage of a benzyl group in the presence of a hydroxamate, a selective hydrogenation protocol was developed. To improve drug substance properties a series of hydroxamic acid salts were synthesized, and their physical behaviors were investigated.

Introduction

SDZ 242-484 (**1**) (Figure 1) was discovered by Kottirsch et al. at Novartis Pharmaceuticals Corporation. It is a direct inhibitor of the release of tumor necrosis factor-α (TNF) from the cells. TNF triggers a variety of proinflammatory events in rheumatoid arthritis; its inhibition (by antibodies of receptor constructs) has been shown to be beneficial for rheumatoid arthritis patients. In addition, SDZ 242-484 (**1**) is a direct and potent inhibitor of matrix metalloproteinases (MMP), the enzymes that are largely responsible for the destruction of cartilage and bone in rheumatoid arthritis and osteoarthritis.[1] The dual TNF/MMP inhibitor SDZ 242-484 (**1**) is therefore expected to have combined antiinflammatory and joint-protective effects.

Results and Discussion

(a) The Medicinal Chemistry Synthesis. The original nine-step synthesis of **1** (Scheme 1)[1] started from *trans*-1,4-dibromobutene (**2**) which was used in excess to alkylate benzyl alcohol. After chromatographic separation the allylbromide **3** and *p*-methoxyphenyl acetic acid were treated with DBU in dichloromethane followed by silica gel chromatography to give allylic ester **4**. The silyl enol ether was generated in situ at −78 °C by deprotonation of the ester **4** with LDA followed by TMSCl quench. If the solution was warmed quickly to reflux, the rearrangement product **5** could be isolated as a 2.8−9/1 mixture of racemic *erythro*-/*threo*-isomers in variable 60−80% yield. However, these conditions were not suitable for scale-up, most likely due to the limited thermal stability of the silyl ketene acetal intermediate. The resulting isomeric mixture of **5** was coupled to L-*tert*-leucine-*N*-methylamide under standard peptide coupling conditions (EDC, DMAP) to form a mixture of four diastereomeric acids **6** in 4/4/1/1 ratio. A three-step oxidation protocol was used for the cleavage of the terminal olefin. Osmylation, followed by periodate cleavage and chlorite oxidation of the resulting aldehyde, gave the corresponding carboxylic acid **7** in high yield. The benzyl-protected hydroxamate was obtained after coupling of *N*-benzylhydroxylamine hydrochloride to acid **7** in the presence of EDC, HOBT, and triethylamine. After chromatographic purification, the final debenzylation was achieved by catalytic hydrogenation (Pd−$BaSO_4$). The mixture of four diastereomeric hydroxamates was subjected to reverse phase chromatography, providing the desired product in moderate yield (1% over nine steps).



SDZ 242-484 (1)

Figure 1.

(b) Process R&D (Scheme 2). Due to the limited availability of *trans*-dibromobutene (**2**) an alternative synthesis for the construction of ester **4**, the precursor for the Claisen−Ireland rearrangement, had to be established. Propargylic alcohol (**10**) was chosen as starting material. After alkylation in a biphasic system under phase-transfer condi-

* Corresponding author: Dr. Guido Koch, Novartis Pharma AG, WSJ-507.704, Postfach, CH-4002 Basel, Switzerland, Telephone: ++41 61 324 42 38. Fax: ++41 61 324 42 36. E-mail: guido.koch@pharma.novartis.com.

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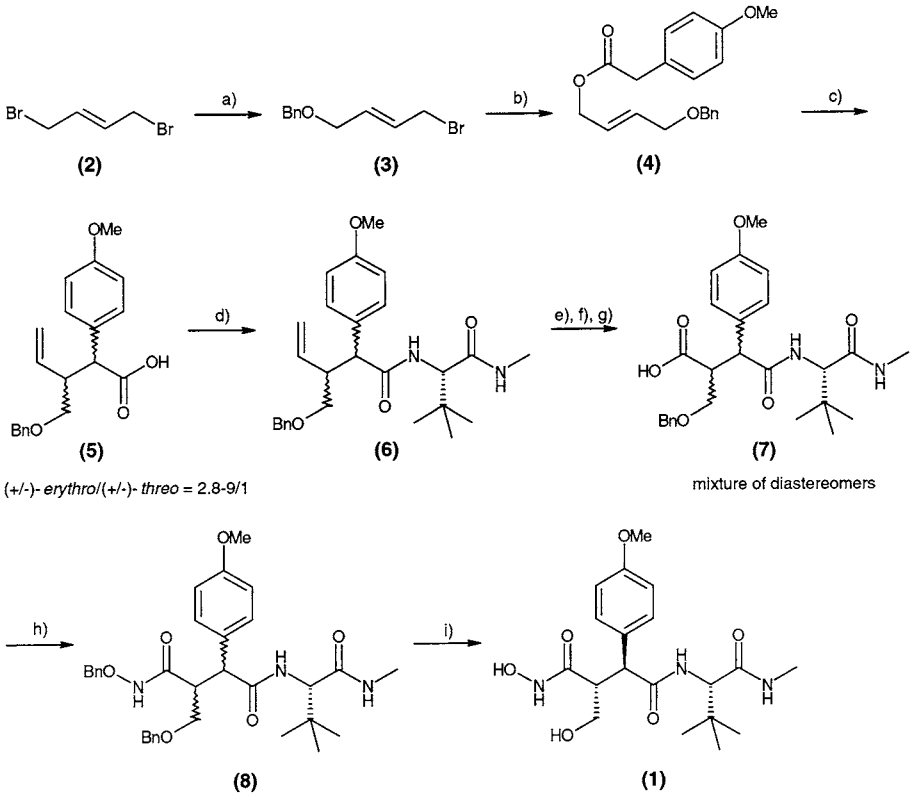
Scheme 1. **Medicinal chemistry synthesis**[a]



[a] Reagents and conditions: a) BnOH, Bu_4NHSO_4, NaOH, H_2O, CH_2Cl_2, 23 °C, flash chromatography, 50%; b) *p*-methoxyphenylacetic acid, DBU, CH_2Cl_2, 23 °C, flash chromatography, 82%; c) LDA, TMSCl, THF, −78 °C−66 °C, 80%; d) EDC, DMAP, L-*tert*-leucine-*N*-methylamide, CH_2Cl_2, 23 °C, flash chromatography, 60%; e) OsO_4, NMO, acetone, H_2O, *tert*-butyl alcohol, 23 °C, 90%, f) $NaIO_4$, acetone, H_2O, 23 °C, 90%; g) $NaClO_2$, HaH_2PO_4, 2-methyl-2-butene, H_2O, *tert*-butyl alcohol, 23 °C, 80%; h) *O*-benzylhydroxylamine hydrochloride, EDC, HOBt, Et_3N, DMF, 23 °C, flash chromatography, 60%; i) 1 bar H_2, $Pd/BaSO_4$, MeOH, 23 °C, reverse phase chromatography, 30%.

tions, prop-2-ynyloxymethyl-benzene (**11**)[2] was subjected to deprotonation with hexyllithium followed by reaction with paraformaldehyde to give monobenzylated butynediol (**12**)[3a] in a clean reaction. The resulting alkyne is selectively reduced to the *trans*-allylic alcohol **13**[3] with RedAl in THF at 0 °C. The mono-benzyl-protected butenediol can be purified by distillation under reduced pressure. Esterification with *p*-methoxyphenylacetic acid was achieved using dicyclohexylcarbodiimid as coupling reagent in the presence of catalytic amounts of DMAP[4] in toluene. Addition of heptane forced the urea byproduct to precipitate from the reaction mixture. After a simple filtration and evaporation of the solvents, the allylic ester could be used for the Claisen−Ireland[5] rearrangement without further purification.

There was some evidence that the conditions previously described for the rearrangement reaction were suitable for scale-up. However, most likely due to the thermal instability of the silylketene acetal intermediate first scale-up experiments were not reproducible. In regard to achieving a highly selective, robust process, this step was closely investigated. The addition of catalytic amounts of Lewis acids was beneficial in terms of both yield and selectivity.[6]

Due to the thermal instability of the intermediate silylketene acetal reaction monitoring is rather difficult using conventional methods. However, when using online FT-IR spectroscopy the process could be followed step-by-step. When generating the enolate with LiHMDS the expected *E*-enolate is formed selectively, clearly identified by a single IR absorption band 1598 cm^{-1}. Treatment with TMSCl gave the corresponding (*Z*)-silylenolether as a single isomer (1656 cm^{-1}). In the presence of a catalytic amount of $TiCl_4$ the diastereoselective rearrangement starts at about 0 °C. The IR spectrum clearly shows the expected carbonyl absorption at 1718 cm^{-1} (Figure 2) for the resulting carboxylic acid silylester. A highly diastereoselective titaniumtetrachloride-catalyzed Ireland−Claisen rearrangement was developed, which yields the racemic diastereomeric carboxylic acids (*erythro*/*threo*=13:1) in high yield.

The racemic acid can be effectively resolved with (*S*)-(−)-phenylethylamine.[7] (one recrystallization: 88.0% ee, yield: 32%; two recrystallizations: 98.5% ee, yield: 90%). The application of such a chiral resolution process prior to the peptide-coupling step allowed us to minimize the amount of rather expensive L-*tert*-leucine-*N*-methylamide. The free

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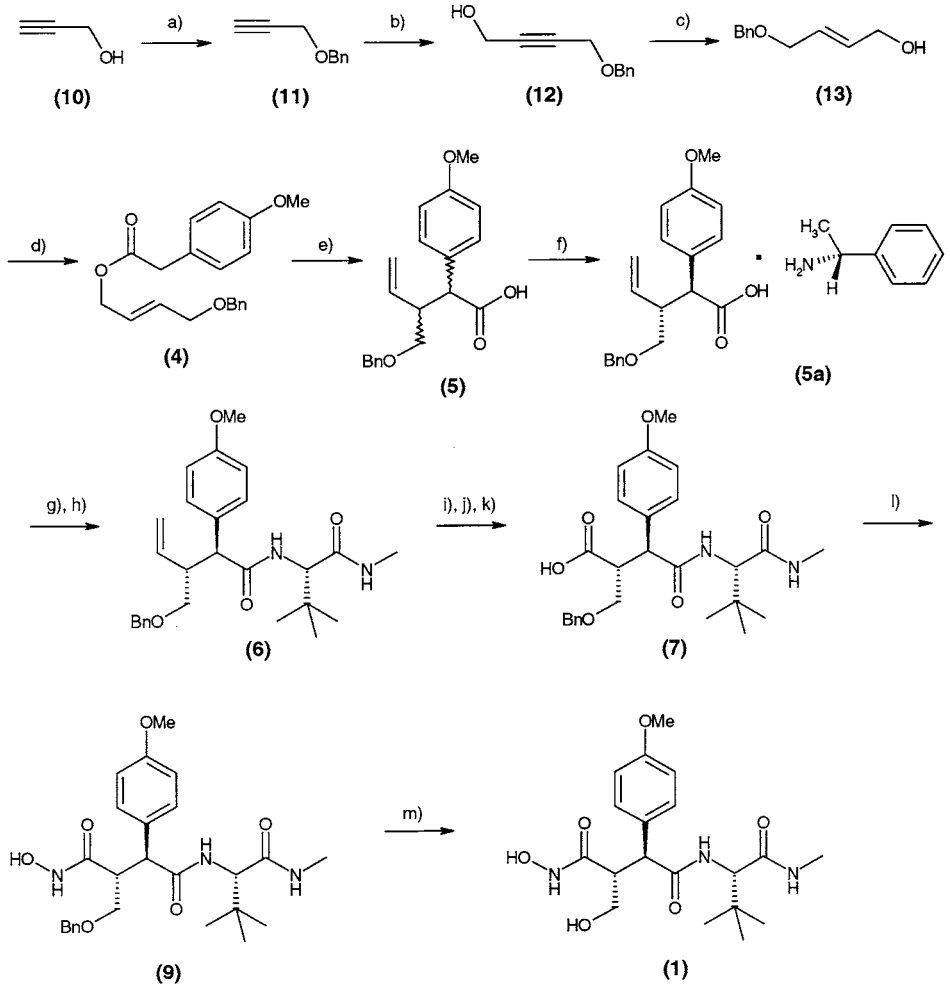
Scheme 2: **Manufacturing process of SDZ 242-484**[a]



[a] Reagents and conditions: a) BnBr, NaOH, Bu_4NBr, H_2O, toluene, 50 °C, 98%; b) Hexyl-Li, THF, paraformaldehyde, −78 °C−23 °C, 96%; c) Red-Al, THF, 0 °C, distillation, 80%; d) DCC, DMAP, *p*-methoxyphenylacetic acid, toluene, 23 °C, 88%; e) LHMDS, TMSCl, $TiCl_4$, THF, −78 °C−23 °C, 77%; f) (*S*)-(−)-phenylethylamine, EtOAc; g) 1 N HCl, toluene, 23 °C; h) Vilsmeier reagent, *N*-methylmorpholine, L-*tert*-leucine-*N*-methylamide, THF, 23 °C, 98%; i) O_3, MeOH, −78 °C; j) $(CH3)_2S$, MeOH, −78 °C−23 °C; k) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *tert*-butanol, H_2O, 23 °C, crystallization, 62%; l) DIC, HOBt, H_2NOH, H_2O, TBME, DMF, 23 °C, crystallization, 64%; m) H_2, Pd/C, MeOH, 23 °C, crystallization, 74%.

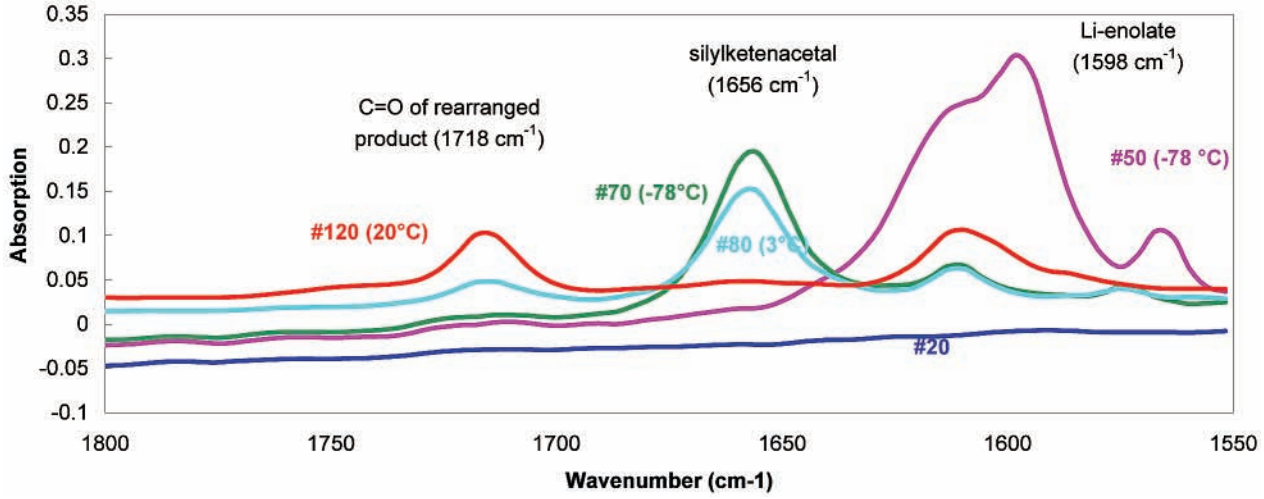
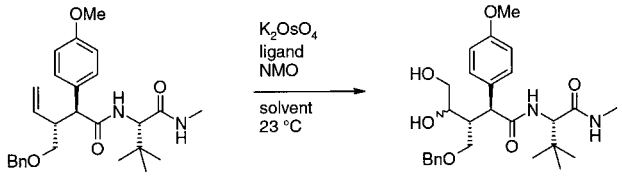


Figure 2. **FT-IR monitoring of the rearrangement of ester 4. Reaction profile from React-IR.**

acid was generated by treating a suspension of the phenylethylamine salt in toluene with aqueous HCl (1.0 N). In the medicinal chemistry synthesis the coupling with L-*tert*-leucine-*N*-methylamide was performed under standard peptide chemistry conditions using EDC, DMAP.[1] Careful HPLC and NMR analysis indicated that significant epimerization

Table 1. **Dihydroxylation: catalyst screening**



(6) (14)

entry	K_2OsO_4 (mol %)	ligand	solvent	reaction time (h)
1	1	–	acetone/H_2O	>15
2	1	DABCO (5 mol %)	acetone/H_2O	15
3	1	$(DHQD)_2PHAL$ (2.5 mol %)	acetone/H_2O	15
4	0.5	DABCO (5 mol %)	acetone/H_2O	20
5	0.5	quinuclidine (5 mol %)	Acetone/H_2O	20
6	0.5	$(DHQD)_2PHAL$ (2.5 mol %)	Acetone/H_2O	4
7	0.25	$(DHQD)_2PHAL$ (1 mol %)	Acetone/H_2O	15
8	0.4	$(DHQD)_2PHAL$ (2 mol %)	*t*-BuOH/H_2O	18
9	0.25	$(DHQD)_2PHAL$ (1 mol %)	*t*-BuOH/H_2O	>24

(>5%) occurred under the employed reaction conditions. Therefore, and also because of the significant cost factor of EDC, we were looking for alternative coupling procedures. The use of isobutylchloroformate[8] to form a mixed anhydride intermediate was not successful. The formation of the anhydride was found to be clean and complete; however, competitive nucleophilic attack to the carbonate carbon resulted in regeneration of significant amounts of starting material. Carbonyldiimidazole[9] and dimethoxychlorotriazine[10] gave unsatisfactory results as well. A very clean reaction without any detectable epimerization was observed when using the commercially available Vilsmeier reagent[11] for the activation of the carboxylic acid functionality. The desired product (**6**) was isolated in quantitative yield and could be used in the following step without further purification.

The terminal olefin was cleaved to the carboxylic acid in a three-step procedure.[1] Osmium catalyzed dihydroxylation using NMO as cooxidant (Upjohn process),[12] followed by periodate cleavage and $NaClO_2$ oxidation. The use of highly toxic osmium compounds in the pilot-plant environment was accompanied with safety and environmental issues. We therefore made an effort to reduce the amount of osmium catalyst as much as possible. It is well-known that the dihydroxylation process can be significantly accelerated by amine ligands coordinating to the catalytically active osmium species.[13] Results with some ligands investigated are summarized in Table 1.

Under Sharpless asymmetric dihydroxylation conditions[14] osmium loading as low as 0.25 mol % still gave high yields

Table 2. **Osmium balance**[a]

layer	volume [ml]	Os-content [ppm]	Os-amount [mg]
distilled acetone	225	<0.1	0
sodiumsulfite layer (pH 9)	227	205	46
first HCl layer (pH 1)	110	35	4
second HCl layer (pH 1)	54	12	1
sodium bicarbonate layer (pH 8)	150	22	3
first brine layer (pH 8)	105	<1	0
second brine layer (pH 7)	100	<1	0
distilled isopropyl acetate	375	<1	0
crude diol	50.42 g	320	16

[a] Batch: 0.1 mol of alkene **6** (44 g). Total amount of osmium used: 74 mg found: 70 mg.

Table 3. **Osmium reduction**

entry	resin	Os-content of diol [ppm]
1		367
2	PureLite S930	363
3	PureLite S920	240
4	IONAC SR-3	217
5	IONAC SR-4	237
6	Na_2SO_3-wash (5 times)	273

of the corresponding isolated diol. Surprisingly, the diastereoselectivity of the process was very low for both the mismatched and the matched ligand enantiomers. The process was very carefully investigated for environmental reasons. The osmium flow was monitored (Table 2). In total, 95% of the osmium introduced in the reaction could be found and localized. Unfortunately it was found that even after extensive wash of the product layer and treatment of the crude diol with ion-exchange resins (Table 3), significant amounts of the heavy metal was still found in the diol after recrystallization. Not surprisingly the molecule acts as an excellent chelating ligand for metal ions such as osmium.

Therefore, we decided to look for other possibilities to achieve double bond cleavage. In a first attempt we applied von Rudloff−Lemieux conditions.[15] The reaction with catalytic amounts of $KMnO_4$ in the presence of HIO_4 offers a one-step transformation to the corresponding carboxylic acid. However, the reaction proceeded with low yield most likely due to undesired aromatic ring cleavage reactions and product isomerization. After crystallization the acid **7** was isolated in 20% yield (Table 4).

A very efficient and clean reaction was obtained when treating the alkene with ozone in methanol. After reduction with dimethyl sulfide the resulting aldehyde was directly oxidized without any purification. The carboxylic acid was effectively purified by crystallization from ethyl acetate in 62% overall yield over the three steps. The coupling with *N*-benzylhydroxylamine using a standard protocol (EDC, HOBt) resulted in smooth formation of the benzylhydroxamate **8**. However, selective debenzylation proved to be

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Table 4. **von Rudloff−Lemieux reaction conditions**[a]

entry	solvent (v/v)	$KMnO_4$ [eq]	temperature [°C]	time [h][b]	yield (**7**) [%]	remarks
1	*t*-BuOH/H_2O (1:2)	0.16	50	1	7.8	
2	*t*-BuOH/H_2O (1:3)	0.48	50	1	36	20% isolated yield after crystallization
3	*t*-BuOH/H_2O (1:3)	0.48	50	1	29	reaction at pH 8−8.5 by adding NaOH
4	*t*-BuOH/H_2O (1:3)	0.48	50	1	19	reaction in buffer at pH 7
5	*t*-BuOH/H_2O (1:3.5)	0.16	0	24	17	
6	*t*-BuOH/H_2O (1:3.5)	0.48	0	24	22	
7	*t*-BuOH/H_2O (1:3.5)	0.48	−6	48	34	
8	acetone/H_2O (1:3.5)	0.16	0	24	0	
9	acetone/H_2O (1:3.5)	0.48	0	24	0	

[a] 6 equiv of $NaIO_4$ and 1.3 equiv of K_2CO_3 were used. [b]Conversation of starting material **6** was in all cases greater than 95% for that time.

rather difficult. Significant N−O-reduction was observed. To avoid these selectivity problems in the bis-debenzylation step a new synthetic strategy was chosen. Instead of introducing *O*-benzylhydroxylamine the free hydroxamate was synthesized using simply aqueous hydroxylamine solution in the presence of DIC, HOBt. The highly crystalline hydroxamic acid derivative could be effectively purified by a simple recrystallization. The debenzylation step was carried out on 5% Pd/C in methanol at atmospheric hydrogen pressure providing the drug substance (**1**) in quantitative yield and high purity. Selectivity problems, for example hydrogenolytic cleavage of the N−O bond vs benzyl hydrogenation, were not detected upon applying these conditions. The final synthetic route is shown in Scheme 2.

(c) Drug Substance Properties. The drug substance SDZ 242-484 crystallizes from water as tetra-hydrate (15.5 wt %) which is in agreement with the theoretical amount (15.4 wt %). This crystal modification, further mentioned as modification A, melts at 88.2 °C and is characterised by single X-ray powder diffraction (XRPD), thermogravimetry (TG), and differential scanning calorimetry (DSC). Strong drying of the tetra-hydrate leads to amorphous material. The water sorption isotherm of the amorphous form resembled that of modification A which shows that under humid conditions the amorphous form can recrystallize into the tetra-hydrate. Crystallization of amorphous material (from the melt at 123 °C) yielded modification B with a melting point of 150.7 °C and a water content of only 6.5 wt %. The water content corresponds to a 1.5-hydrate and is constant between 30 and 95% relative humidity Unfortunately, modification B, which exhibits better physicochemical properties, could not be obtained in conventional crystallization experiments.

All crystallization experiments with other solvents to obtain a solvent and water-free crystal form failed so far. As illustrated in Table 5, at least five additional crystalline forms have been identified which all present solvate forms and which are all characterised by a strong water uptake.

Transformation of SDZ 242-484 into its sodium, calcium, and magnesium salts yielded higher-melting compounds

Table 5. **Crystal modifications of SDZ 242-484 (manufacturing conditions and analytical characterisation)**

solvent	cryst. temp [°C]	XRPD	DSC [°C]	TG [%]
water	60	modification A	88.2	15.5
(melt)	123	modification B	150.7	6.5
tetrahydrofuran/methanol = 10/1 (V/V)	60	modification C	67.7	0.5
methanol/toluene = 1.5/10 (V/V)	65	modification D	82.5	3.0
methanol/ethyl acetate = 0.5/20 (V/V)	65	modification E	66.2	2.8
tetrahydrofuran/water = 100/2 (V/V)	70	modification F	107.5	2.0
methanol/2-propanol = 1/10 (V/V)	65	modification G	96	1.1

(between 150 and 190 °C). Nevertheless, all salts were again solvates that exhibited a strong tendency to take up water and to become amorphous under drying conditions. It should be mentioned that until now the preparation of a solvent-free crystal modification has not been accomplished.

Conclusions

In summary, a robust process for a large-scale, chromatography-free preparation of **1** was developed. The key step in the reaction sequence utilized a Lewis acid-mediated diastereoselective Claisen−Ireland rearrangement followed by a chiral resolution. One batch of 4.5 kg of drug substance (**1**) was produced in pilot-plant equipment. The physicochemical properties of the drug substance were optimized.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. All the melting points are uncorrected and determined on a Büchi apparatus. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz on a Bruker DPX 300 instrument. IR spectra were measured on a Bruker IFS660 spectrometer. The enantiopurity of **5** was determined on a Hewlett-Packard Series 1100 HPLC system using a *Daicel Chiralcel OD* column.

Prop-2-ynyloxymethylbenzene (11).[2] To a solution of propargylic alcohol **10** (22.1 mL, 0.37 mol) in 170 mL of toluene was added a solution of NaOH (10.0 M, 37.5 mL,0.37 mol) followed by the addition of 11.93 g (37 mmol) Bu_4NBr. The resulting mixture was heated to 50 °C and treated with benzylbromide (40.0 mL, 0.34 mol) over 1 h. The biphasic solution was stirred for additional 14 h at 50 °C and then cooled to 23 °C. The two layers were separated, and the organic phase was washed three times with brine. After evaporation of the solvent 47.6 g (98%) of a pale yellow oil was obtained. Purity: 97% (GC). R_f = 0.82 (EtOAc/heptane = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.49 (t, J = 2.4 Hz, 1 H), 4.20 (d, J = 2.4 Hz, 2 H), 4.64 (s, 2 H), 7.30−7.39 (m, 5 H).

4-Benzyloxy-but-2-yn-1-ol (12).[3a] In a 1.5-L flask equipped with a mechanical stirrer, prop-2-ynyloxymethylbenzene (**11**)

(39.3 g, 0.27 mol) was dissolved in 220 mL of THF and cooled to −78 °C. *n*-Hexyllithium (33% in hexanes, 118 mL, 0.30 mol) was added over a period of 1 h. The resulting yellow solution was stirred for 2 h. Paraformaldehyde (9.73 g, 0.32 mol) was added in one portion, and the yellow suspension was warmed to 23 °C over 2 h. The reaction mixture was stirred for 16 h and then quenched with aqueous NH_4Cl solution (20%, 175 mL). TBME (260 mL) was added, and the two layers were separated. After extraction of the aqueous layer with TBME (80 mL) the organic phases were combined and washed three times with 170 mL of brine. Concentration and azeotropic removal of water with toluene (2 times 60 mL) afforded 45.54 g (96%) of crude alcohol **12** as a yellow oil. R_f = 0.44 (EtOAc/heptane = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69 (s, *br*, 1 H), 4.24 (t, J = 1.6 Hz, 2 H), 4.35 (t, J = 1.6 Hz, 2 H), 4.62 (s, 2 H), 7.32−7.39 (m, 5 H).

(*E*)-4-Benzyloxy-but-2-en-1-ol (13).[3] A solution of alkyne **12** (40 g, 0.23 mol) in 185 mL of THF was cooled to 0 °C. RedAl (70% in toluene, 85.2 g, 0.30 mol) was slowly added over 1 h. After complete addition the reaction mixture was immediately transferred into a solution of aqueous H_2SO_4 (20%, 300 mL) at 0 °C. Toluene was added (260 mL), and the biphasic system was vigorously stirred for 5 min. The two phases were separated, and the aqueous layer was extracted with 40 mL of toluene. The combined organic layers were washed with aqueous $NaHCO_3$ (8%, 150 mL) and brine (150 mL), concentrated, and dried by azeotropic distillation of toluene to afford 36.40 g (90%) of crude *trans*-alcohol **13**. The product was purified by distillation (110 °C, 0.3 mbar) to yield 80% of a yellow oil. Purity: 83% (GC). R_f = 0.37 (EtOAc/heptane = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, *br*, 1 H), 3.97 (d, J = 5.3 Hz, 2 H), 4.09−4.10 (m, 2 H), 4.46 (s, 2 H), 5.73−5.90 (m, 2 H), 7.32−7.39 (m, 5 H).

(4-Methoxyphenyl)acetic Acid (*E*)-4-Benzyloxy-but-2-enyl ester (4). A 2.5-L flask was charged with a solution of (*E*)-4-benzyloxy-but-2-en-1-ol (**13**) (100 g, 0.56 mol), 4-methoxyphenylacetic acid (93.03 g, 0.56 mol) and 4-DMAP (3.425 g, 28 mmol) in 550 mL of toluene. Dicyclohexylcarbodiimide (50% in DMF, 222.6 mL, 0.56 mol) was added slowly. The reaction temperature was kept between 23 and 27 °C. When the addition was finished, heptane (225 mL) was added. The resulting suspension was cooled to −10 °C, stirred for 10 min, and filtered. The filter cake was washed with 300 mL of heptane. Water (1275 mL) was added to the filtrate, the layers were separated, and the organic phase was washed with an additional 640 mL of water. Filtration of the organic solution through a pad of aluminum oxide (500 g), elution with toluene/heptane (1:1, 1110 mL), and concentration of the filtrate afforded 161.41 g (88%) of a yellowish oil. R_f = 0.38 (heptane/EtOAc = 50:25). IR (film, cm^{-1}) 2930m, 1736s, 1613w, 1514s, 1454m, 1302m, 1249s, 1152m, 1034m, 976m, 821w, 739w, 699w. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.57 (s, 2 H), 3.77 (s, 3 H), 3.99−4.03 (m, 2 H), 4.50 (s, 2 H), 4.57−4.62 (m, 2 H), 5.82−5.86 (m, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 7.19 (d, J = 8.6 Hz, 2 H), 7.28−7.39 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.4, 55.2, 64.6, 69.7, 72.3, 114.0, 126.0, 126.6, 127.0, 127.7, 127.8, 128.4, 130.3, 130.9, 138.1, 158.7, 171.6. MS (EI) *m*/*z* 326 (M^+), 166, 148, 121, 91, 65.

(±)-3-Benzyloxymethyl-2-(4-methoxy-phenyl)-pent-4-enoic Acid (±-5). A solution of 38.4 mL (184.3 mmol) 1,1,1,3,3,3-hexamethyldisilazane in 100 mL of THF was treated with *n*-hexyllithium (63.65 g, 184.0 mmol, 26.6% in hexanes) at 0 °C over a period of 14 min. The LHMDS solution was stirred for 5 min and cooled to −78 °C. Then chlorotrimethylsilane (23.3 mL, 184.0 mmol) was added over 15 min. To the resulting mixture a solution of ester **4** (50.0 g, 153.2 mmol) in 50 mL of THF was slowly added (43 min). The reaction mixture was treated with 0.31 mL (0.31 mmol) of a $TiCl_4$ solution (1.0 M in toluene), warmed to 23 °C over 90 min, and stirred at room temperature for 1 h. The reaction was quenched by the addition of a 1.0 M solution of NaOH (400 mL). The layers were separated, and the organic layer was extracted once with 72 mL of 1.0 M NaOH. The combined aqueous solutions were acidified to pH 1.0 by slow addition of 5% HCl (390 mL) at 0 °C. Then 286 mL of toluene were added, the layers were separated, and the organic solution was concentrated in vacuo to afford 38.35 g (77%) of a yellow oil (*anti*/*syn* = 13:1 (HPLC)). The crude mixture was subjected to the resolution with *L*-(−)-α-methylbenzylamine. HPLC t_R (*anti*-isomer) = 17.3/22.7 min/t_R (*syn*-isomer) = 15.4/20.1 min (*Chiralcel OD n*-hexanes/*i*-PrOH/TFA = 95:5:0.1).

(2*S*,3*R*)-3-Benzyloxymethyl-2-(4-methoxyphenyl)-pent-4-enoic Acid *L*-(−)-α-Methylbenzylammonium salt (5a). Crude racemic acid **5** (45.17 g, 138.3 mmol) was dissolved in 1760 mL of ethyl acetate and treated with 19.4 mL (152.2 mmol) of *L*-(−)-α-methylbenzylamine. The resulting suspension was heated to reflux. A clear solution was obtained, from which upon cooling to 20 °C over a period of 2 h crystallization occurred (seeding if necessary). After additional stirring of the suspension for 2 h the mixture was filtered, and the white crystals were washed with 90 mL of cold (−20 °C) ethyl acetate in two portions. The product was dried under vacuum (50 mbar) at 50 °C for 8 h to afford 25.35 g (41%) of the *L*-(−)-α-methylbenzylammonium salt (86% ee; HPLC). Recrystallization from 1075 mL of ethyl acetate yielded 15.5 g (62%) of enantiomerically pure (98.5% ee) white crystals. Mp = 177 °C.

(2*S*,3*R*)-3-Benzyloxymethyl-2-(4-methoxyphenyl)-pent-4-enoic Acid (5). A 2-L flask equipped with a mechanical stirrer was charged with 34.2 g (76.4 mmol) of *L*-(−)-α-methylbenzylammonium salt (**5a**) and suspended in 780 mL of toluene. HCl (240 mL of a 1.0 M solution, 240 mmol) was added. Stirring was continued until a clear biphasic solution was observed (0.5−3.0 h). The two layers were separated, the aqueous phase was subjected to reextraction (vigorous stirring for 25 min) with 250 mL of toluene, and the combined toluene layers were washed with 400 mL of water followed by a second wash with 200 mL of water. After concentration in vacuo 25.73 g (100%) of a colorless oil was obtained. R_f = 0.49 (heptane/EtOAc/AcOH = 60:40:2). HPLC t_R = 22.7 min (*Chiralcel OD n*-hexanes/*i*-PrOH/TFA = 95:5:0.1). IR (film, cm^{-1}) 2935m, 1704s,

1611m, 1512s, 1454m, 1363w, 1251s, 1179m, 1105m, 1034m, 922w, 828w, 738w, 699w. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.13−3.18 (m, 1H), 3.43 (dd, J = 9.4, 6.2 Hz, 1 H), 3.56 (dd, J = 9.4, 5.3 Hz, 1 H), 3.72−3.78 (m, 1H), 3.75 (s, 3 H), 4.47 (s, 2 H), 4.94 (dd, J = 15.5, 12.3 Hz, 2 H), 5.48 (ddd, J = 15.5, 12.3, 8.8 Hz, 1 H), 6.81 (d, J = 8.8 Hz, 2 H), 7.19 (d, J = 8.8 Hz, 2 H), 7.27−7.30 (m, 5 H), 8.60−9.80 (s, *br*, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.1, 52.1, 55.2, 72.0, 73.1, 113.8, 117.8, 127.5, 127.6, 128.3, 130.3, 136.1, 138.1, 158.9, 179.4. MS (EI) *m*/*z* 326 (M^+), 282, 217, 165, 137, 121, 91.

(2*S*,3*R*)-3-Benzyloxymethyl-2-(4-methoxy-phenyl)pent-4-enoic Acid ((*S*)-2,2-Dimethyl-1-methylcarbamoylpropyl)amide (6). To a suspension of (chloromethylene)dimethylammonium chloride (21.4 g, 167 mmol) in 156 mL of THF was added a solution of 36.2 g (111 mmol) of carboxylic acid **5** in 144 mL of THF at 0 °C. The slurry was stirred at 0 °C for 1 h before *N*-methylmorpholine (49.1 mL, 445 mmol) was added, followed by the addition of a solution of L-*tert*-leucine-*N*-methylamide (17.7 g, 122 mmol) in 100 mL of THF and 4 mL of DMF over 15 min. The reaction mixture was warmed to 23 °C over 25 min and stirred for additional 2 h. A 1.0 M solution of HCl (180 mL) was added. After dilution with 120 mL of isopropyl acetate the two layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed once with 120 mL of 1.0 M NaOH and three times with brine (120 mL). The solvent was removed, and 49.1 g (98%) of a yellow foam was obtained. R_f = 0.33 (heptane/EtOAc/AcOH = 60:40:2). IR (KBr, cm^{-1}) 3307s, 2955m, 1634s, 1569m, 1538m, 1511s, 1454w, 1384w, 1249m, 1179w, 1100w, 1036w, 698w. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9 H), 2.52 (d, J = 4.7 Hz, 3 H), 3.12−3.16 (m, 1 H), 3.44−3.48 (m, 1 H), 3.59−3.67 (m, 1 H), 3.69−3.77 (m, 1 H), 3.73 (s, 3 H), 4.33 (d, J = 9.4 Hz, 1 H), 4.48 (dd, J = 21.9, 12.0 Hz, 2 H), 4.94 (dd, J = 19.7, 10.6 Hz 2 H), 5.56−5.68 (m, 1 H), 6.60−6.63 (m, 2 H), 6.75 (d, J = 8.7 Hz, 2 H), 7.16 (d, J = 8.7 Hz, 2 H), 7.25−7.33 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 34.6, 46.3, 53.1, 55.1, 60.5, 71.8, 73.3, 113.7, 117.3, 127.6, 127.7, 128.3, 129.4, 129.6, 130.1, 137.2, 138.3, 158.7, 170.8, 172.9. MS (ESI) *m*/*z* 475 ($M + Na^+$), 453, 422, 366, 290, 200.

(2*S*,3*R*)-4,5-Dihydroxy-3-hydroxymethyl-2-(4-hydroxy-phenyl)pentanoic Acid ((*S*)-2,2-Dimethyl-1-methylcarbamoylpropyl)amide. To a solution of 143.7 mg (0.39 mmol) K_2OsO_4 in 220 mL of H_2O was added a solution of 760 mg (0.98 mmol) of $(DHQ)_2PHAL$ in 20 mL of acetone, followed by the addition of a solution of 44.14 g (97.5 mmol) alkene **6** in 200 mL of acetone. The resulting mixture was treated slowly with an aqueous solution (50%) of *N*-methylmorpholine-*N*-oxide (27.0 mL, 127 mmol) at 23 °C. Stirring was contiued for 17 h. For the workup, a solution of 2.2 g of sodium hydrogen sulfite (38−40%) was dissolved in 11 mL of H_2O and added to the reaction mixture. After 3 h the solution was concentrated in vacuo to a total volume of 340 mL. The residue was extracted with 150, 100, and 75 mL of isopropyl acetate. The combined organic layers were washed with 100 mL of 1 N HCl (100 and 50 mL), 180 mL of $NaHCO_3$ (8%) and twice with 100 mL of NaCl (20%). The organic layer was concentrated to give a diastereomeric mixture of crude diol (50.42 g, 106%) which was subjected directly to the next step.

(2*S*,3*R*)-*N*-((*S*)-2,2-Dimethyl-1-methylcarbamoylpropyl)-3-hydroxymethyl-2-(4-hydroxy-phenyl)-4-oxobutyramide. A solution of 16.33 g (33.6 mmol) of crude diol was dissolved in 160 mL of acetone and treated with a solution of 7.89 g (36.9 mmol) of $NaIO_4$ in 80 mL of H_2O. The reaction mixture was stirred for 3 h at 23 °C, diluted with 200 mL of isopropyl acetate and 200 mL of H_2O, and the resulting layers were separated. The aqueous phase was extracted with 120 mL of isopropyl acetate, and the combined organic phases were washed with 160 mL of NaCl (20%). Concentration in vacuo afforded 14.52 g (95%) of a yellowish foam, which was directly further oxidized with sodium chlorite to the corresponding carboxylic acid as described in the following procedure.

(2*R*,3*S*)-2-Benzyloxymethyl-*N*-((*S*)-2,2-dimethyl-1-methylcarbamoylpropyl)-3-(4-methoxy-phenyl)succinamic Acid (7). Alkene **6** (6.0 g, 11.3 mmol) was dissolved in 230 mL of methanol and cooled to −78 °C. The solution was treated with a stream of ozone for 1 h until a blue-coloured solution was obtained. The reaction mixture was purged with nitrogen for 5 min to remove the excess of O_3. To the clear, colourless solution was added dimethyl sulfide (4.9 mL, 66.8 mmol). The reaction mixture was warmed to 23 °C over 1 h and stirred for additional 14 h. After concentration under reduced pressure 8.20 g of crude aldehyde were obtained, which was subsequently dissolved in 80 mL of *tert*-butanol and treated with 3.83 g (46.6 mmol) of 2-methyl-2-butene (85%) and a solution of 3.61 g (39.9 mmol) of sodium chlorite and 3.51 g (29.3 mmol) sodium dihydrogenphosphate in 35 mL of water at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and for 2 h at 23 °C. Sodium hydrogen sulfite solution (10%, 98 mL) was slowly added, and the pH was adjusted to 3.0 by the addition of 1 N HCl (15 mL). The mixture was extracted three times with ethyl acetate (50 mL each). Concentration of the combined organic extracts afforded 6.61 g (72%) of crude acid **7**. Purity: 69% (HPLC). Crystallization: Crude acid **7** (55 g, 118 mmol) was disolved in 400 mL of refluxing ethyl acetate. Cooling to 0 °C over 4 h and stirring at 0 °C for 2 h followed by filtration afforded crystalline product. The cake was washed with cold ethyl acetate (50 mL) and dried for 15 h at 50 °C at 10 mbar. White crystals (34.63 g, 62%) were obtained. Purity: 93% (HPLC). R_f = 0.30 (heptane fractions/EtOAc/AcOH = 20:80:1). Mp = 201 °C. IR (KBr, cm^{-1}) 3305m, 2963m, 1712m, 1638s, 1545m, 1513s, 1369m, 1253m, 1180m, 110w, 1030w. ^{1}H NMR (300 MHz, DMSO) δ 0.86 (s, 9 H), 2.45 (s, 3 H), 3.28−3.35 (m, 1 H), 3.48−3.52 (m, 1 H), 3.61 (t, J = 9.5 Hz, 1 H), 3.70 (s, 3 H), 3.90 (d, J = 11.5 Hz, 1 H), 4.15 (d, J = 9.6 Hz, 1 H), 4.45 (s, 2 H), 6.08 (d, J = 8.5 Hz, 2 H), 7.28−7.36 (m, 7 H), 7.84 (d, *br*, J = 4.3 Hz, 1 H), 8.14 (d, J = 9.4 Hz, 1 H), 11.98 (s, *br*, 1 H). ^{13}C NMR (75 MHz, DMSO) δ 23.7, 25.4, 32.9, 47.5, 48.2, 53.6, 58.4, 68.9, 70.8, 112.0, 126.15, 126.21, 126.9, 128.1, 128.8, 136.6,

156.9, 168.7, 169.6, 172.3. MS (ES) *m*/*z* 469 (M − H)$^-$, 235.

(2*R*,3*S*)-2-Benzyloxymethyl-*N*-((*S*)-2,2-dimethyl-1-methylcarbamoylpropyl)-3-(4-methoxy-phenyl)succinamic Acid (7) (von Rudloff−Lemieux Conditions). Alkene **6** (3.6 g, 8.0 mmol) was dissolved in 45 mL of *tert*-butanol at room temperature. Potassium carbonate (1.4 g, 10.4 mmol) dissolved in water (40 mL) was added, and the mixture was heated to 50 °C (pH 13). To this mixture a solution of sodium periodate (10.2 g, 47.8 mmol) in water (55 mL) was added followed by the additon of a solution of potassium permanganate (0.6 g, 3.8 mmol) in water (40 mL). Thereafter, the reaction mixture was stirred for 1 h until no alkene **6** was detectable (TLC: EtOAc/heptane/AcOH = 60:40:2 v/v). The red-brown solution (pH 6) was cooled to room temperature, sodium sulfite solution (20%, 100 mL) was added, and the two-phase mixture was concentrated under reduced pressure until no *tert*-butanol distilled. Ethyl acetate (200 mL) was added, and the pH was adjusted to 3.0 by the addition of 1 N HCl (110 mL). After phase separation, the ethyl acetate layer was washed one time with sodium sulfite solution (20%, 40 mL) and two times with brine (20%, 75 mL each). Concentration of the ethyl acetate phase afforded 3.2 g (84%) of the crude acid **7** as a yellow foam. Purity: 37% (HPLC). The foam was dissolved in toluene (150 mL) and extracted twice with 1 N NaOH (50 mL each). The combined alkaline phases were adjusted to pH 1 by the additon of HCl (10%, 30 mL) and extracted two times with ethyl acetate (150 mL each). The combined ethyl acetate extracts were washed three times with brine (10%, 100 mL each). Concentration in vacuo afforded 2.2 g (57%) of a yellowish foam. Purity: 44% (HPLC). Crystallisation: Crude acid **7** (2.2 g) was dissolved in 100 mL of refluxing ethyl acetate. The solution was concentrated to 11 mL and cooled to 0 °C over 4 h. At this temperature the slurry was stirred overnight. Filtration afforded a crystalline product, which was washed with cold ethyl acetate (20 mL) and dried for 15 h at 50 °C at 10 mbar. White crystals (0.7 g, 20%) were obtained. Purity: 87% (HPLC).

(2*R*,3*S*)-2-Benzyloxymethyl-*N*-4-((*S*)-2,2-dimethyl-1-methylcarbamoylpropyl)-*N*-1-hydroxy-3-(4-methoxy-phenyl)succinamide (9). A solution of carboxylic acid **7** (15.62 g, 33.2 mmol) in 66 mL of DMF was cooled to 0 °C, treated with 1-hydroxybenzotriazole (6.73 g, 49.8 mmol), followed by the addition of diisopropylcarbodiimide (12.57 g, 126.2 mmol). Stirring was continued for 2 h at 0 °C and for 1 h at 23 °C. The mixture was diluted with TBME (330 mL) and reacted with a hydroxylamine solution (50% in water) (4.39 g, 66.4 mmol). The resulting suspension was stirred for 1 h and filtered. The product was washed twice with 50 mL of TBME each. The crude product was dried in vacuo at 50 °C overnight to give 27.40 g of a white solid. This was added to 1350 mL of ethyl acetate and 1350 mL of 0.1 N HCl and stirred for 1 h until all solids completely dissolved. The layers were separated, and the organic phase was washed twice with 100 mL of 0.1 N HCl. The organic layer was concentrated to a total volume of 700 mL. The resulting suspension was heated to reflux and cooled to 0 °C over 2 h. Crystallization was initiated by seeding at 45−50 °C. The white crystals were filtered and washed twice with cold ethyl acetate (100 mL). Drying under vacuum (10 mbar) at 50 °C for 15 h afforded 10.42 g (64%) of hydroxamic acid **9**. Additional 8% yield could be recovered by washing the mother liquor with 0.1 N HCl and recrystallization following the described procedure. R_f = 0.33 (EtOAc/AcOH = 100:1). Mp = 209 °C. IR (KBr, cm^{-1}) 3339m, 3277s, 2963m, 1705m, 1678m, 1628s, 1512s, 1455w, 1407w, 1367m, 1250m, 1179w, 1105m, 1036m, 747. ^{1}H NMR (300 MHz, DMSO) δ 0.85 (s, 9 H), 2.45 (s, 3 H), 3.16 (t, J = 10.6 Hz, 1 H), 3.29−3.31 (m, 1 H), 3.60 (t, J = 9.9 Hz, 1 H), 3.70 (s, 3 H), 3.88 (d, J = 11.5 Hz, 1 H), 4.10 (d, J = 9.4 Hz, 1 H), 4.42 (s, 2 H), 6.78 (d, J = 8.5 Hz, 2 H), 7.28−7.36 (m, 7 H), 7.78 (d, *br*, J = 4.3 Hz, 1 H), 8.08 (d, J = 9.4 Hz, 1 H), 8.61 (s, 1 H), 10.35 (s, 1 H). ^{13}C NMR (75 MHz, DMSO) δ 25.0, 26.6, 34.0, 45.9, 48.7, 54.8, 59.7, 67.0, 71.9, 113.1, 127.3, 127.4, 128.1, 129.4, 130.1, 138.0, 158.0, 167.6, 168.0, 171.3. MS (ESI) *m*/*z* 486 (MH$^+$), 470, 453.

(2*R*,3*S*)-*N*-4-((*S*)-2,2-Dimethyl-1-methylcarbamoylpropyl)-*N*-1-hydroxy-2-hydroxymethyl-3-(4-methoxy-phenyl)-succinamide (1). The benzyl ether **9** (25.0 g, 51.5 mmol) was dissolved in 125 mL of methanol and hydrogenated over 2.5 g of Pd/C (5%) at 1.1 bar and 22 °C for 1.25 h. The catalyst was removed by filtration over Celite and was washed with MeOH. Concentration of the filtrate resulted in 19.66 g (97%) of crude drug substance. Recrystallization from 72 mL of water afforded the desired tetrahydrate (17.80 g) in 74% yield. R_f = 0.14 (toluene/EtOAc/AcOH = 50:50:10). Mp = 88.2 °C, IR (KBr, cm^{-1}) 3583m, 3243s, 3099m, 2965m, 1658s, 1635s, 1536m, 1513s, 1372w, 1253m, 1235m, 1086m, 1040m. ^{1}H NMR (300 MHz, DMSO) δ 0.91 (s, 9 H), 2.45 (2, J = 4.5 Hz, 3 H), 2.88−2.96 (m, 1 H), 3.40 (s, 1 H), 3.45−3.60 (m, 1 H), 3.70 (s, 3 H), 3.84 (d, J = 11.5 Hz 1 H), 4.13 (d, J = 9.4 Hz 1 H), 4.64 (s, *br*, 1 H), 6.77 (d, J = 8.7 Hz, 2 H), 7.26 (d, J = 8.7 Hz, 2 H), 7.75 (d, J = 4.5 Hz, 1 H), 8.01 (d, J = 9.4 Hz, 1 H), 8.47 (s, 1 H), 10.20 (s, 1 H). ^{13}C NMR (75 MHz, DMSO) δ 25.4, 27.1, 34.5, 48.9, 49.2, 60.2, 62.0, 113.5, 129.8, 130.9, 158.3, 168.8, 170.5, 172.0. MS (ES) *m*/*z* 394 (M − H)$^-$, 367, 209.

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