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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/op400211t • Publication Date (Web): 20 Sep 2013

Development of a Practical and Scalable Synthesis of the side chain for ASP9726, a Successor of Micafungin

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ABSTRACT

Here, we describe a practical and scalable synthesis of **1,** which is a useful side chain of ASP9726 (**2**), a successor of Micafungin. For large-scale synthesis of **1**, reaction conditions were optimized to control impurities and increase yield. In particular, we utilized a high-yield thiadiazole ring formation to prepare thiadiazole **12**, a step which was improved by optimization of reaction conditions and isolation method. Further, the number of steps was reduced from 10 to 9, and hazardous reactions were also avoided. Consequently, this process was scaled to produce 21.7 kg of **1** with overall yield improvement from 36.7% to 56.6%.

INTRODUCTION

ASP9726 (**2**, Figure 1) is expected to be a novel echinocandin with potent *Aspergillus* hyphal growth inhibition properties and significantly improved MIC (minimum inhibitory concentration) against *Candida parapsilosis* and echinocandin-resistant *Candida*. Developed as a potential successor of Micafungin, which was launched by Astellas Pharma Inc. (Fujisawa Pharmaceutical Co.) in 2002, ASP9726 has shown potent efficacy in treating systemic Candidiasis and Aspergillosis with no concerns of side effects.[1]

Trans-4-{5-[4-(4-cyclohexyl-4-methoxypiperidin-1-yl)phenyl]-1,3,4-thiadiazol-2-yl}cyclohexane-1-carbaldehyde (**1,** Figure 2) was identified as a potentially useful side chain of ASP9726,[2] and the original medicinal chemistry-based synthetic route of **1** is outlined in Scheme 1.

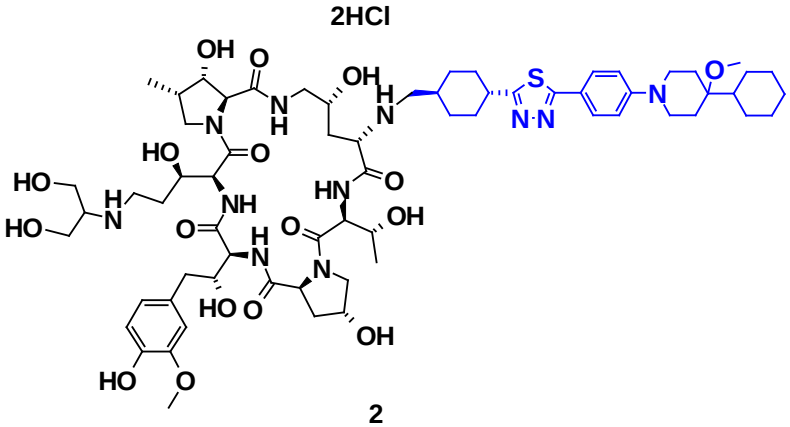


Figure 1. Structures of ASP9726 (**2**)

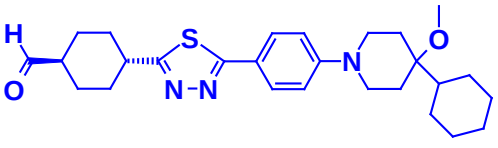
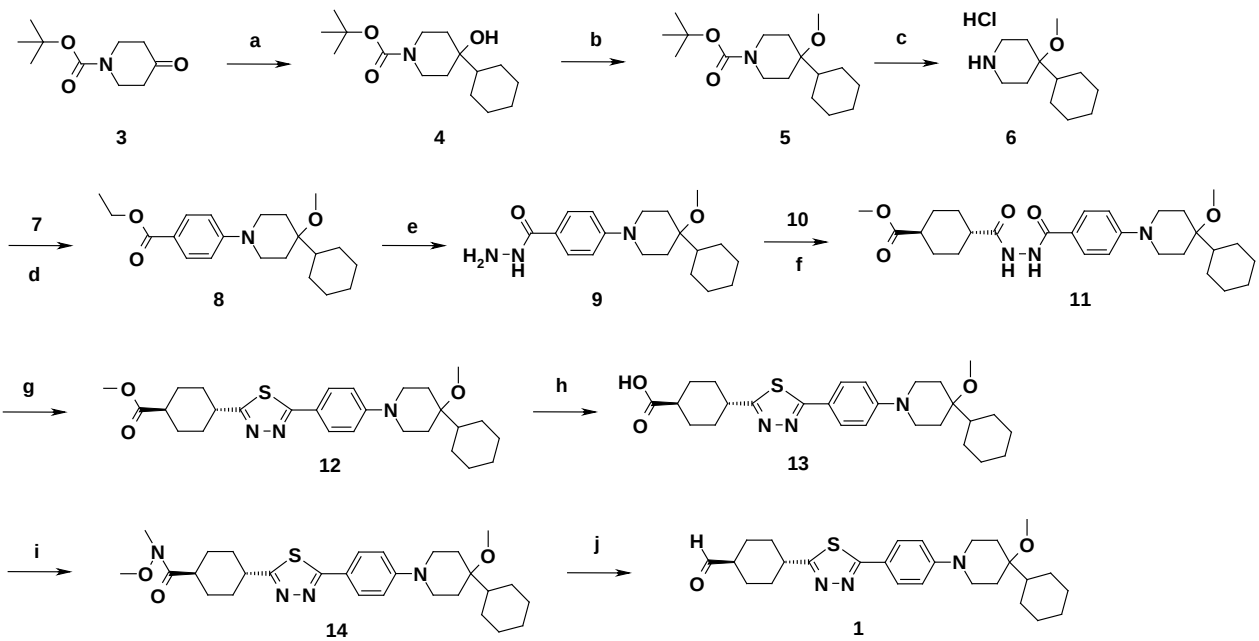


Figure 2. Side chain aldehyde (**1**)

Scheme 1. Medicinal synthetic method of **1** [a)]



[a)] Reagents and conditions: (a) chloro(cyclohexyl)magnesium, $CeCl_3$, THF, 95%; (b) MeI, NaH, DMF, 89%; (c) TFA, anisole, CH_2Cl_2; (d) ethyl 4-fluorobenzoate (**7**), K_2CO_3, DMSO, 76% (2 steps); (e) hydrazine monohydrate, EtOH, THF, 97%; (f) *trans*-4-(methoxycarbonyl)cyclohexanecarboxylic acid (**10**), EDC·HCl, HOBt, TEA, DMF, quant.; (g) P_2S_5, THF, 81%; (h) KOH, THF, EtOH, 86%; (i) *N*, *O*-dimethylhydroxylamine hydrochloride, HBTU, *i*-Pr_2NEt, DMF, 88%; (j) $LiAlH_4$, THF, 96%, overall yield: 36.7%.

However, this medicinal chemistry method presents several drawbacks: $LiAlH_4$ as a reducing agent and methylation conditions involving combination of NaH with DMF should be avoided from a safety point of view.[3] In addition, the relatively low yield for synthesis of thiadiazole **12** (typically 81%) should be improved. Further, HBTU as a coupling agent should be avoided due to low cost-efficiency. Moreover, hydrolysis of ethyl ester to carboxylic acid followed by the amide

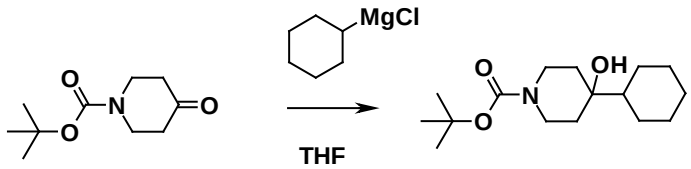
formation, and reduction of amide to aldehyde were required in this sequence, so the number of steps makes it less efficient.

Given the above, urgent demand has risen for a practical and scalable method of preparing the desired side chain aldehyde **1** for GMP campaign. We therefore developed a more efficient method of synthesizing **1** than the original protocol that avoids the aforementioned shortcomings. Here, we describe our efforts to obtain the desired side chain aldehyde **1.**

RESULTS AND DISCUSSION

Development of Grignard reaction (Scheme 2)

Scheme 2. Preparation of **4**.



3 **4**

Commercially available *tert*-butyl 4-oxopiperidine-1-carboxylate **3** was treated with the organocerium reagent[4] derived from cyclohexylmagesium chloride and $CeCl_3$ in THF. Conducting this reaction without $CeCl_3$ typically results in generation of 30 to 40% of aldol adduct impurity A (Figure 3) on GC analysis, hampering isolation of the desired compound without using SiO_2 column chromatography purification. We attempted to use $ZnCl_2$[5] instead of $CeCl_3$ to reduce the cost of reagent; however, 10% of aldol adduct impurity A was observed on GC analysis. Consequently, the synthetic method using $CeCl_3$ was demonstrated in the large-scale synthesis, and 28.4 kg of the desired **4** was prepared in a quantitative yield (GC assay) without forming impurity

A.

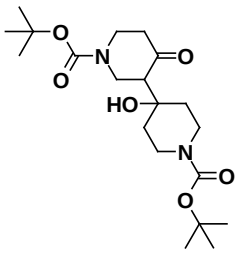
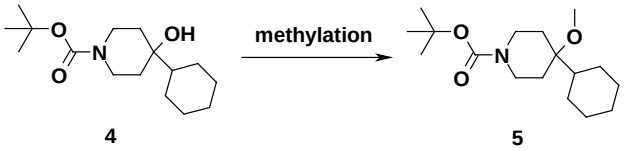


Figure 3. Structure of aldol adduct impurity A.

Development of methylation (Scheme 3)

Scheme 3. Development of methylation.



In the medicinal chemistry synthetic method, methylation is conducted with methyl iodide and NaH as a base in DMF, conditions which should be avoided in large-scale synthesis due to hazards associated with the use of NaH in DMF; indeed, plant-scale incidents involving these reagents have been reported, with onset of exotherm at 40 °C followed by rapid self-heating and eventual explosion.[3] To resolve this issue, a number of candidate bases and solvents were screened for this reaction (Table 1), with the combination of NaH and THF ultimately providing the best reaction profile (entry 1). Yield of desired compound **5** was improved from 89% to 95%, and scale-up synthesis was successfully accomplished, yielding 28.4 kg of **5**.

Table 1. Preparation of **5**[a]

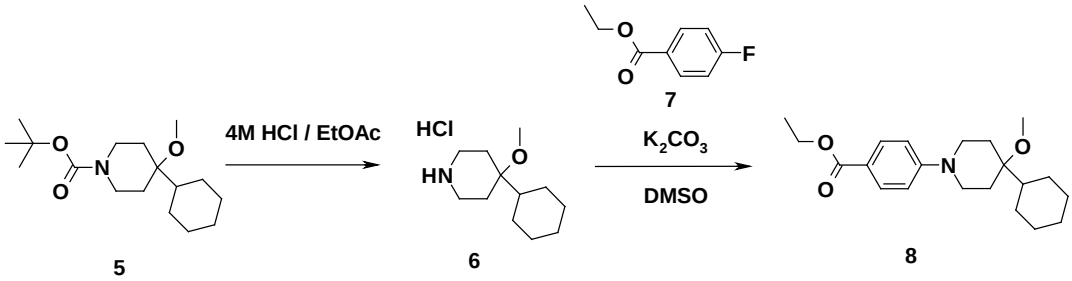
Entry	Base (equiv.)	Solvent	GC yield (%)[b]
1	NaH	THF	95
2	LiOH	THF	77
3	KOH	THF	64
4	Bu_4NOH	THF	78
5	*t*-BuOK	THF	40
6	*t*-BuOK	DMF	23

[a] Reaction temp: 0 to 50 °C.

[b] Determined by GC method A (see the Experimental Section).

Development of deprotection and S_NAr reaction (Scheme 4)

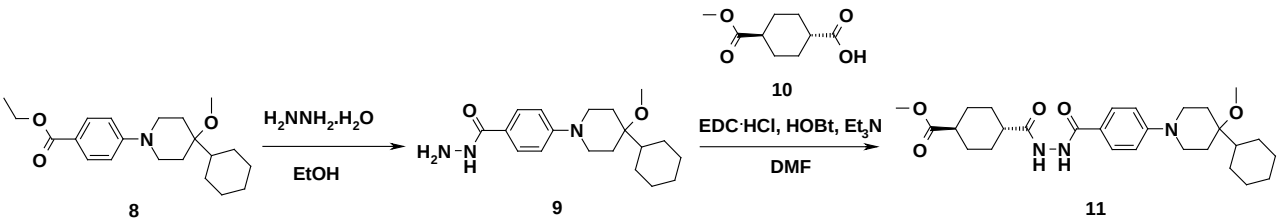
Scheme 4. Development of deprotection and S_NAr reaction.



Deprotection of the *N*-Boc group was successfully accomplished with HCl/EtOAc at 20 °C, and the desired amine HCl salt **6** was isolated as a crystalline solid at >90% yield with an overall 87% yield from **3**, yielding 20.4 kg upon scale-up. The subsequent S_NAr reaction also achieved good yield with potassium carbonate in DMSO heated to approximately 110 °C. The target intermediate **8** was isolated in 90.7% yield simply by adding water to the reaction mixture, and consequently, 27.3 kg of desired **8** was prepared in large-scale synthesis.

Development of acid hydrazide formation and amidation (Scheme 5)

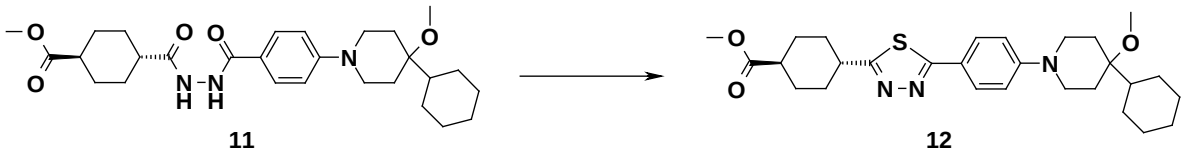
Scheme 5. Development of acid hydrazide formation and amidation.



The formation of acid hydrazide was accomplished by the reaction of compound **8** and hydrazine hydrate by heating the reaction mixture to 80 °C in EtOH, the target intermediate **9** was isolated in 95.9% yield simply by adding water to the reaction mixture, ultimately providing 25.1 kg of **9** in large-scale synthesis. Subsequent amidation with *trans*-4-(methoxycarbonyl)cyclohexanecarboxylic acid (**10**) was accomplished using EDC·HCl, TEA, and HOBt in DMF. While 1 eq. of HOBt was used in the medicinal chemistry method, we attempted to reduce the amount of HOBt. The catalytic amount of HOBt (0.3 equiv.) demonstrated a favorable reaction profile, and the reaction proceeded as in the medicinal chemistry method, with the target intermediate **11** isolated in 94.2% yield simply by adding water to the reaction mixture, ultimately providing 34.1 kg of **11** in large-scale synthesis.

Development of thiadiazole ring formation (Scheme 6)

Scheme 6. Development of thiadiazole ring formation.



In the medicinal chemistry synthetic method, thiadiazole **12** was prepared from amide **11** with P_2S_5 but produced rather unsatisfactory yield, typically less than 80%. To improve yield of this reaction, thiadiazole ring formation was attempted using P_2S_5 under a range of different reaction conditions or Lawesson's reagent[6] (Table 2).

Table 2. Preparation of thiadiazole **12** [a]

Entry	Reagents/solvents	Temperature/ time	HPLC ratio (%) 11/11a/11b/11c/12 [a]	Comments
1	P_2S_5 × 1.2 mol/THF	25 °C/21 h	medicinal method	78% isolated yield
2	P_2S_5 × 0.25 mol/THF	25 °C/2 h	25/44/ 23/<1/8	-
3	P_2S_5 × 1.2 mol/THF	50 °C/3 h	0.4/1.5/n.d./<1/97	94% isolated yield
4	P_2S_5 × 1.2 mol Pyridine × 1.2 mol/DME	25 °C/16 h	97/1/n.d./<1/2	-
5	P_2S_5 × 1.2mol. Na_2CO_3 × 1.2 mol/THF	50 °C/3 h then 50 °C/3 h	21/53/n.d./<1/26 21/53/n.d./<1/26	-
6	P_2S_5×1.2mol. basic Al_2O_3 ×1 wt./THF	50 °C/6 h	21/4/n.d./<1 /85	-
7	Lawesson's reagent × 1.2 mol./THF	60-65 °C/3 h	n.d./n.d./Tr/2/97	Isolation difficulty

[a] Determined by HPLC method C (see the Experimental Section)

During the reaction, formation of monothioamide **11a** and dithioamide **11b** was observed by LC-MS analysis (Figure 4). It was observed that the desired cyclization from dithioamide **11b** to **12** was much faster than that of **11a**, so at the higher temperature reaction condition such as 50 °C, **11b** was not detected on HPLC (entries 1-3). Further, during the reaction, trace amounts of oxadiazole **11c** were detected on LC-MS as an impurity; fortunately, however, this contaminant was purged into the mother liquid during filtration. Using bases such as pyridine, Na_2CO_3, and basic Al_2CO_3 (entries 4-6) prevented performing the desired cyclization, leaving behind large amounts of starting material **11** and monothioamide **11a** in the reaction mixture. Given the above, we hypothesized that optimum cyclization would require acid to improve the reaction rate because the addition of base did not work well. To confirm this hypothesis, cyclization of monothioamide **11a** and dithioamide **11b** were conducted under acidic conditions, such as in the presence of methanesulfonic acid. As expected, the reaction was indeed accelerated under the acidic condition. Use of Lawesson's reagent was also attempted (entry 7), and while the desired reaction proceeded well in comparison with the case of P_2S_5, removing the residue left by the reagent was difficult without SiO_2 column chromatography purification. As such, using P_2S_5 will likely prove to be the optimum condition in this case.

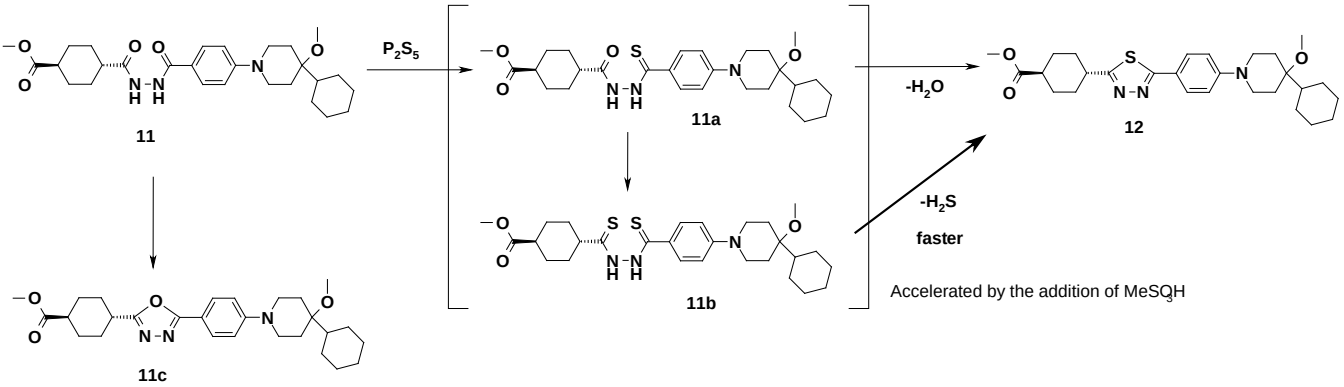


Figure 4. Thiadiazole ring formation.

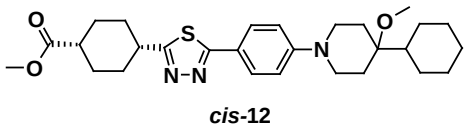


Figure 5. Structure of ***cis*-12**.

However, we noted a significant issue hampering large-scale synthesis during reaction with P_2S_5 in THF: namely, undesired isomerization and an unacceptable level of ***cis*-12** on HPLC analysis (Figure 5). Further, removing ***cis*-12** via crystallization proved quite difficult. To solve these issues, the stability of the product **12** was measured and results were shown in Figure 6. As results, ***cis*-12** was gradually increased after the completion of the reaction at 50 °C after the completion of the reaction.

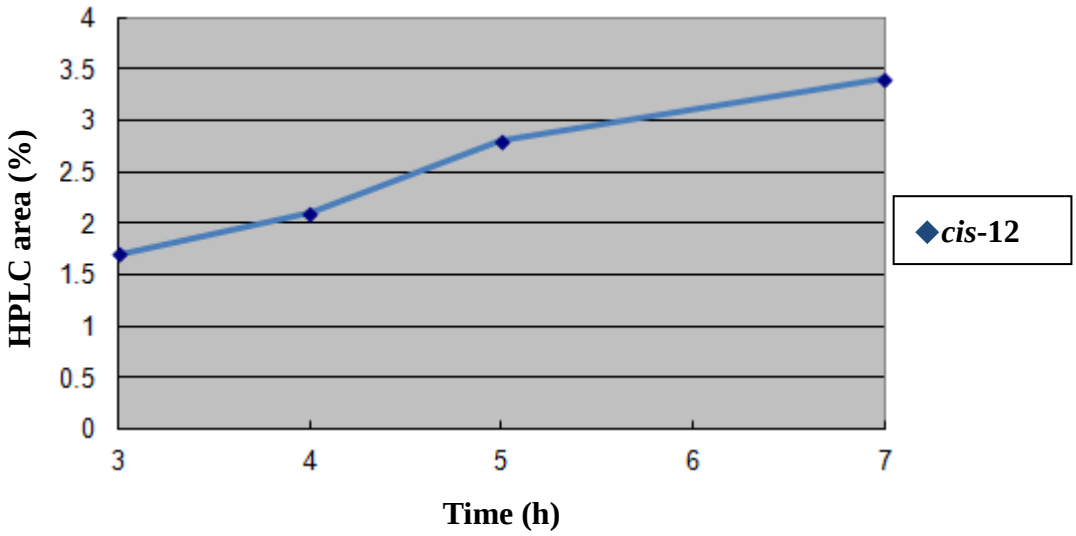


Figure 6. Stability test of **12** in the reaction mixture.

To minimize the undesired isomerization, qunching methods were investigated as shown in Table 3.

Table 3. Minimization of the formation of ***cis*-12**.

Entry	conditions	additional 1 h at 50°C[a]
		12 / ***cis*-12**[b]
1	without quenching	97.9 : 2.1
2	water (× 0.5 v /wt.)	98.1 : 1.9
3	Et_3N (×3 mol.)	98.3 : 1.7
4	aqueous solution of Na_2CO_3 (×3 mol.)	98.3 : 1.7

[a] After completion of the reaction (50°C / 3h) **12** / ***cis*-12** = 98.3 / 1.7,

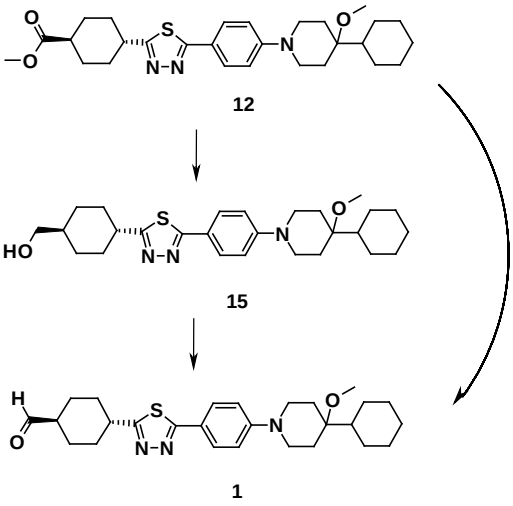
[b] Determined by HPLC method D (see the Experimental Section)

Ultimately, the addition of triethylamine (Et_3N) and an aqueous solution of Na_2CO_3 prevented the isomerization well. After the quenching process with aqueous solution of Na_2CO_3, desired **12** was isolated in 93.8% yield simply by filtration of the resulting slurry. Further, this procedure was demonstrated in a large scale synthesis and yielded 31.9 kg of **12** that contained 0.5 % of ***cis*-12**.

Preparation of aldehyde 1

*Direct preparation of aldehyde **1** from ester **12*** (Scheme 7).

Scheme 7. Direct reduction pass from methyl ester **12** to aldehyde **1**.



Direct reduction of methyl ester **12** to aldehyde **1** was investigated as shown in Table 4. The method using sodium bis (2-methoxyethoxy) aluminum hydride (SMEAH) with pyrrolidine[7] did not work well in this case, with extremely low reaction conversion and an unacceptable level of unknown impurities observed (entries 2 and 3). Further, DIBAL-H reduction also provided poor results, as the double-bond on thiadiazole ring was reduced by hydride, an unacceptable level of over-reduced alcohol **15** was observed on HPLC analysis (entry 1), and controlling formation of **15**

was difficult.

Table 4. Direct reduction of ester **12** to aldehyde **1**.

Entry	**Reagents (× mol)/solvents**	**Conditions**	**HPLC area (%)[a]** **12/15/1**
1	DIBAL-H (1.1) Toluene-CH_2Cl_2	−78 to −70 °C	2/22/ 76
2	SMEAH [7] 1) Red-Al (× 1.49 mol., 65% toluene solution) pyrrolidine (1.74)/THF 2) *t*-BuOK (0.1)/THF 3) 2) was added to a solution of **12** in THF	0 to 25 °C	74/n.d./8; many unknown peaks observed on HPLC
3	SMEAH [7] 1) Red-Al (2.9, 65% Toluene solution) pyrrolidine (3.47)/MTBE 2) *t*-BuOK (0.2)/THF 3) 2) was added to a solution of **12** in THF	0 to 25 °C	52/n.d./2; many unknown peaks observed on HPLC

[a] Determined by HPLC method D (see the Experimental Section)

*Development of an alternative method for aldehyde **1**.*

Given aldehyde **1**, we considered that a step-wise method might be suitable for this compound, therefore reduction of methyl ester **12** to alcohol **15** was investigated (Table 5). DIBAL-H did not work well for this reaction (entries 1 and 2), producing large amounts of impurity B produced from reduction of the double bond on the thiadiazole ring (Figure 7). In contrast, Red-Al worked well, and the reaction proceeded properly at 0 to 15 °C to produce the desired alcohol **15** in 93% yield. In addition, no impurity B was observed on HPLC analysis (entry 3), and the large-scale synthesis of alcohol **15** was successfully accomplished, producing 27.9 kg of alcohol **15** in 93.1% yield.

Table 5. Preparation of **15**.

Entry	Reagents (× mol.)/solvents	Conditions	HPLC area (%) 12/15/1/impurity B
1	DIBAL-H (2), then DIBAL (1)/ Toluene-CH_2Cl_2	−78 °C, then −55 °C	n.d./36/64/n.d. n.d./83/17/n.d.
2	DIBAL-H (3)/Toluene-CH_2Cl_2	−75 °C/0.5 h, then −75 °C/1 h, then −55 °C/0.5 h	n.d./59/ 40/1 n.d./70/25/5 n.d./56/n.d./44
3	Red-Al (1.5)/THF	0 °C then 15 °C	n.d./> 99/n.d./n.d. isolated yield: 93%

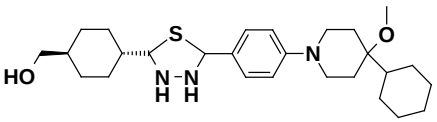


Figure 7. Structure of the over-reduced impurity B.

End-game for preparation of aldehyde 1

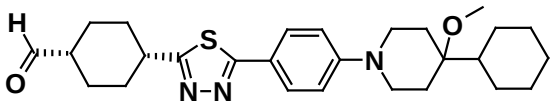
The investigation of the oxidation conditions is shown in Table 6. Oxidizing agents such as TEMPO-NaOCl (entry 1) and TEMPO-Oxone method (entry 2) did not give a good reaction profile. On the other hand, the use of SO_3-Pyridine-TEA with DMSO have the best reaction profile (entries 3 and 4). The reaction was performed under mild conditions, and the yield of desired aldehyde **1** was over 90%.

Table 6. Investigation of oxidizing agent.

Entry	**Reagents (× mol.)/ solvent (v/wt.)**	**Conditions**	**Results**
1	TEMPO (0.01), NaOCl (1.1) KBr (0.1)/CH_2Cl_2 (50), water (20).	−15 °C, then 25 °C, 0.5h	Level of unknown impurities was unacceptable
2	TEMPO (0.01), Oxone (2.2) Bu_4NBr (0.04)/CH_2Cl_2 (60)	-15 °C, then 25 °C, 6 h	no reaction
3	SO_3-Pyridine[a] (3.4) DMSO (4.4), TEA (6.7)/CH_2Cl_2 (50)	20 to 25 °C, 3 h	90% yield
4	SO_3-Pyridine [a] (3.0), DMSO (4), TEA (6)/CH_2Cl_2 (20)	20 to 25 °C, 3 h	91% yield

[a] sulfur trioxide pyridine complex

In large-scale synthesis, 21.7 kg of desired aldehyde **1** was obtained, results comparable to those achieved in lab-scale operations. No undesired isomerization occurred during operations, and the level of ***cis*-1** was < 0.05 % in aldehyde **1** (Figure 8).



***cis*-1**

Figure 8. Structure of ***cis*-1**.

CONCLUSION

In summary, we have developed a practical and scalable method for synthesizing the side chain of ASP9726 that may prove useful as a successor of Micafungin **2**. This new synthesis method was deemed to be the optimum large-scale route due to its improved safety and yield over medicinal chemistry method. Employing our method in large-scale synthesis produced 21.7 kg of desired side chain aldehyde **1**, with overall yield improved from 36.7% to 56.6%.

EXPERIMENTAL SECTION

General

Starting materials, reagents, and solvents were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in the specified deuterated solvent. Chemical shifts of ^{1}H NMR spectra are reported in parts per million on the δ scale from an internal standard of residual solvent ($CHCl_3$ 7.26 ppm; DMSO-*d6* 2.50 ppm) or TMS. Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; dd, doublet doublet; t, triplet; m, multiplet; br, broad), coupling constant (hertz), and integration. Chemical shifts of proton-decoupled ^{13}C NMR spectra are reported in parts per million from the central peak of $CDCl_3$ (77.0 ppm), DMSO-*d6* (39.5 ppm) on the δ scale. Mass spectra were measured using UPLC/SQD-LC/MS, JEOL JMS-GC mate II, Waters ZQ 2000, and JEOL JMSLX2000 instruments. KF were measured using the JP method. HPLC was performed using a Hitachi D-2500 or D-7500 system via methods described below. Gas chromatograph model GC-17A with Static-Headspace and FID detector were obtained from Shimadzu for GC analysis, and GC methods are also described below. Glass lined reactors were used for all steps.

GC Method A - Column: DB-WAX, 0.25 mm × 30 m, 0.25 μm (GL Sciences), carrier gas: He 1.41mL/min. (37 cm/sec.), column temp.: 150 °C, injection temp.: 200 °C, detector temp.: FID 250 °C, split ratio: 1/30, time program: 150 °C (0 min), 5 °C/min., 250 °C (10 min), injection: 1 μm, operation time: 30 min; **3**: 6.8 min, **4**: 19.5 min, **5**: 14.8 min

GC Method B - Column: DB-1, 0.25 mm × 30 m, 0.25 μm (GL Sciences), carrier gas: He 1.74

mL/min. (40.2 cm/sec.), column temp.: 100 °C, injection temp.: 250 °C, detector temp.: FID 300 °C, split ratio: 1/30, time program: 100 °C (0 min), 10 °C/min., 300 °C (10 min.), injection: 1 μm, operation time: 30 min; **5**: 13.9 min, **6**: 8.8 min, **7**: 4.7 min, **8**: 24.4 min

HPLC Method A - Column: YMC-Pack ODS-AM, 5 μm, 4.6 mm × 150 mm (YMC), elution with water/CH_3CN (1/4), over 30 min, 1.0 mL/min, at 40 °C, with UV detection at 254 nm; **8**: 10.9 min; **9**, 2.9 min

HPLC Method B - Column: Unison UK-Phenyl, 5 μm, 4.6 mm × 250 mm (Imtakt), elution with 50 mmol/L $HClO_4$ buffer (adjusted to pH 2.0)/CH_3CN (27/13), over 30 min, 1.0 mL/min., at 50 °C, with UV detection at 254 nm; **9**: 11.9 min; **11**, 23.1 min

HPLC Method C - Column: Unison UK-Phenyl, 5 μm, 4.6 mm × 250 mm (Imtakt), elution with 50 mmol/L $HClO_4$ buffer (adjusted to pH 3.0)/CH_3CN (1/1), over 30 min, 1.0 mL/min, at 50 °C, with UV detection at 254 nm; **11**: 8.4 min; **12**, 23.3 min

HPLC Method D - Column: COSMOSIL® Cholester, 5 μm, 4.6 mm × 250 mm (Nacalai Tesque), elution with 50 mmol/L $HClO_4$ buffer (adjusted to pH 2.0)/CH_3CN (1/3), over 30 min, 1.0 mL/min, at 45 °C, with UV detection at 254 nm; **12**: 16.7 min; ***cis*-12**: 13.3 min; **15**, 9.4 min

HPLC Method E - Column: Unison UK-Phenyl, 5 μm, 4.6 mm× 250 mm (Imtakt), elution with 50 mmol/L $HClO_4$ buffer (adjusted to pH 2.0)/CH_3CN (23/17), over 60 min, 1.0 mL/min, at 45 °C, with UV detection at 254 nm; **15**: 13.8 min; **1**, 19.1 min, ***cis*-1**: 22.1 min

tert-butyl 4-cyclohexyl-4-hydroxypiperidine-1-carboxylate (**4**)

A suspension of cerium (III) chloride anhydrous (37.1 kg, 151 mol) and THF (326 kg) was agitated at 20 °C for 16 h. Cyclohexyl magnesium chloride (20% [w/w] in toluene-THF, 107.6 kg, 151 mol) was added at 20 °C, and the mixture was aged for 1 h and then cooled to 7 °C. A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate **3** in THF (20.0 kg, 100.4 mol/THF 78.1 kg) was then added at 6 to 8 °C, and the mixture was aged for 3 h at the same temperature; GC analysis subsequently indicated that < 1% starting material **3** remained (GC method A). After the completion of the reaction, the batch was poured into an aqueous solution of AcOH (AcOH: 37.0 kg / water: 333 kg) at around 10 °C and EtOAc (100 kg) was added to this mixture. After the phase separation, the resulting aqueous layer was extracted with EtOAc (100 kg). Organic layers were combined and washed with aqueous solution of NaCl (NaCl: 22.4 kg/ water: 89.6 kg). The resulting organic layer was then washed with aqueous solution of $NaHCO_3$ ($NaHCO_3$: 9.0 kg/ water 103 kg) and then with aqueous solution of NaCl (NaCl: 22.4 kg/ water: 89.6 kg). The organic later was concentrated in *vacuo* using a vacuum pump to 60 L. To the residue was added THF (88.7 kg). The mixture was then concentrated in *vacuo* using a vacuum pump to 100 L. To the residue was added THF (88.7 kg), and the resulting solution was concentrated in *vacuo* using a vacuum pump to 100 L. The resulting solution was added THF (88.7 kg) and concentrated in *vacuo* using a vacuum pump to 100 L. The resulting solution was used in the next step without purification and isolation (28.4 kg from GC assay, quantitative yield). An analytical sample of **4** was prepared by concentration in labs (oily material).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.65-3.76 (2H, m), 2.81-3.10 (2H, m), 1.68-1.78 (4H, m), 1.55-1.62 (2H, m), 1.41 (1H, br), 1.38 (9H, s), 1.31-1.37 (5H, m), 1.09-1.18 (2H, m), 0.90-1.01 (2H, m)

^{13}C NMR (100 MHz, DMSO-*d6*) δ 154.4, 78.8, 70.0, 48.7, 33.7, 30.9 (2 carbons), 28.6 (3 carbons), 26.9 (2 carbons), 26.7 (2 carbons), 26.6 (2 carbons)

MS (FAB, positive mode) m/z 284.1; MS (FAB, negative mode) m/z 282.1

tert-butyl 4-cyclohexyl-4-methoxypiperidine-1-carboxylate (**5**)

THF (141 kg) was added to a solution of compound **4** in THF (from previous step), with sodium hydride (60%, 11.9 kg, 301 mol) and more THF (10.1 kg) added subsequently at 20 °C. This mixture was then heated to 33 °C, and methyl iodide (28.5 kg, 201 mol) was added at 30 to 40 °C; GC analysis subsequently indicated that < 1% compound **4** remained (GC method A). After the completion of the reaction, the batch was poured into the mixture of ice and water (134 kg). To the batch was added EtOAc (100 kg). After the phase separation, the resulting aqueous layer was extracted with EtOAc (100 kg). The combined organic layer was washed with aqueous solution of NaCl (NaCl: 27.0 kg / water 104 kg). The resulting organic layer was concentrated in *vacuo* using a vacuum pump to 60 L. The residue was treated three times each with EtOAc (56.4 kg), evaporating each time in *vacuo* using a vacuum pump to 60L. The resulting solution was used in the next step without purification and isolation. (28.4 kg from GC assay, 95% yield). An analytical sample of **5** was prepared by concentration in labs (oily material).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.66-3.80 (2H, m), 3.32 (3H, s), 2.75-2.90 (2H, m), 1.70-1.78 (2H, d, *J* = 12.8 Hz), 1.48-1.64 (6H, m), 1.38 (9H, s), 1.00-1.25 (5H, m), 0.90-1.01 (2H, m)

^{13}C NMR (100 MHz, DMSO-*d6*) δ 154.5, 78.8, 75.2, 47.6, 42.0, 29.5 (3 carbons), 28.6, 27.0 (2 carbons), 26.9 (2 carbons), 26.7 (2 carbons), 26.5 (2 carbons)

MS (FAB, positive mode) m/z 298.1; MS (FAB, negative mode) m/z 296.1

4-cyclohexyl-4-methoxypiperidine monohydrochloride (**6**)

EtOAc (5.4 kg) and 14.6% (w/w) HCl in EtOAc (72.3 kg, 289 mol) were added to a solution of compound **5** in EtOAc (from previous step) at 10 °C, and the mixture was aged for 1 h at 20 °C; GC analysis subsequently indicated that < 0.5% compound **5** remained (GC method B). After reaction completion, *n*-heptane (71.5 kg) was added to the cooled reaction mixture at 20 °C and aged for 3 h at 20 °C, and the mixture was then filtered and washed with *n*-heptane (71.5 kg). Loss to the filtrate was < 7%. The wet cake was dried *in vacuo* at 45 °C to afford the desired **6** at 98.0% purity via GC method B (20.4 kg, 87.0% yield from **3** in three steps).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.08 (1H, br), 3.04 (3H, s), 3.00-3.10 (2H, m), 2.85 (2H, dd, *J* = 12.4, 11.6 Hz), 1.84 (2H, dd, *J* = 13.8 Hz), 1.74 (2H, *J* = 12.8 Hz), 1.50-1.71 (6H, m), 1.14-1.28 (2H, m), 1.02-1.13 (1H, m), 0.88-1.01 (2H, m)

^{13}C NMR (100 MHz, DMSO-*d6*) δ 73.9, 47.8, 41.7, 39.1, 26.9 (2 carbons), 26.7 (2 carbons), 26.6 (2 carbons), 26.3 (2 carbons)

MS (ESI, positive mode) m/z; 198.0, MS (ESI, negative mode) m/z; 196.0

Anal. Calcd for $C_{12}H_{23}NO.HCl$: C (61.65%), H (10.35%), Cl (15.17%), N (5.99%). Found: C (61.75%), H (10.43%), Cl (15.11%), N (5.88%); mp: 218 °C (by DSC)

ethyl 4-(4-cyclohexyl-4-methoxypiperidin-1-yl)benzoate (**8**)

Compound **6** (20.4 kg, 87.3 mol), ethyl 4-fluorobenzoate **7** (15.4 kg, 91.6 mol), and potassium carbonate (24.1 kg, 174.5 mol) were added to stirred DMSO (112 kg), and the mixture was heated to 110 °C and aged for 24 h; GC analysis subsequently indicated that < 1.5% compound **6** remained (GC method B). After reaction completion, the batch was cooled to 65 °C, and water (143 kg) was added. The resulting slurry was then cooled to 25 °C, aged for 2 h, filtered, and washed with water (143 kg). Loss to the filtrate was less than < 0.01%. The wet cake was dried *in vacuo* at 40 °C to afford the desired **8** at 94.0% purity via HPLC method A (27.3 kg, 90.7% yield).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.76 (2H, d, *J* = 9.2 Hz), 6.97 (2H, d, *J* = 9.2 Hz), 4,23 (2H, dd, *J* = 7.0, 6.8 Hz), 3.67 (2H, d, *J* = 12.8 Hz), 3.08 (3H, s), 2.29-3.02 (2H, m), 1.73 (2H, d, *J* = 12.8 Hz), 1.52-1.66 (8H, m), 1.28 (3H, t, *J* = 7.0 Hz), 0.88-1.20 (5H, m)

^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.2, 154.3, 131.2 (2 carbons), 118.1 (2 carbons), 113.7 (2 carbons), 75.1, 60.3, 47.7, 43.2, 41.9, 29.0 (2 carbons), 27.1 (2 carbons), 26.9 (2 carbons), 26.7 (2 carbons)

MS (ESI, positive mode) m/z; 346.0, MS (ESI, negative mode) m/z; 344.0

Anal. Calcd for $C_{21}H_{31}NO_3$: C (73.01%), H (9.04%), N (4.05%). Found: C (73.31%), H (9.00%), N (3.98%); mp: 250 °C (by DSC)

4-(4-cyclohexyl-4-methoxypiperidin-1-yl)benzohydrazide (**9**)

Compound **8** (27.3 kg, 79.0 mol) and hydrazine monohydrate (79.1 kg, 1580 mol) were added to stirred EtOH (108 kg), and the mixture was heated to 80 °C and aged for 20 h; HPLC analysis subsequently indicated that < 0.5% compound **8** remained (HPLC method A). After reaction completion, water (191 kg) was added at 50 °C, and the mixture was cooled to 25 °C. The resulting slurry was then aged for 2 h, filtered, and washed with water (137 kg). Loss to the filtrate was 1.0%. The wet cake was dried *in vacuo* at 40 °C to afford the desired **9** at 100.0% purity via HPLC method A (25.1 kg, 95.9% yield).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.45 (1H, s), 7.69 (2H, d, *J* = 8.8 Hz), 6.91 (2H, d, *J* = 9.2 Hz), 4.35 (2H, br), 3.59 (2H, d, *J* = 12.0 Hz), 3.07 (3H, s), 2.80-2.95 (2H, m), 1.73 (2H, d, *J* = 12.4 Hz), 1.52-1.68 (8H, m), 1.20-1.26 (3H, m), 0.88-1.02 (2H, m)

^{13}C NMR (100 MHz, DMSO-*d6*) δ 166.5, 153.2, 128.7 (2 carbons), 122.3, 114.1 (2 carbons), 75.0, 47.6, 43.7, 41.9, 29.1 (2 carbons), 27.1 (2 carbons), 26.9 (2 carbons), 26.8 (2 carbons)

MS (ESI, positive mode) m/z; 332.30, MS (ESI, negative mode) m/z; 330.30

Anal. Calcd for $C_{19}H_{29}N_3O_2$: C (68.85%), H (8.82%), N (12.68%). Found: C (68.80%), H (8.88%), N(12.77%); mp: 210 °C (by DSC)

methyl

trans-4-{2-[4-(4-cyclohexyl-4-methoxypiperidin-1-yl)benzoyl]hydrazine-1-carbonyl}cyclohexane-1-carboxylate (**11**)

Compound **9** (24.0 kg, 72.4 mol) and *trans*-4-(methoxycarbonyl)cyclohexanecarboxylic acid **10** (14.8 kg, 79.7 mol) were added to DMF (182 kg), and then HOBt (2.94 kg, 21.7 mol), triethylamine (11.0 kg, 109 mol), EDC·HCl (20.8 kg, 109 mol), and DMF (22.8 kg) were added. The reaction mixture was aged for 3 h at 25 °C; HPLC analysis subsequently indicated that < 0.1% compound **9** remained (HPLC method B). After reaction completion, water (120 kg) was added to the mixture, and the resulting slurry was aged for 18 h at 25 °C, then filtered and washed with water (240 kg). Loss to the filtrate was < 0.01%. The resulting wet cake was then added to water (240 kg), and the mixture was agitated for 0.5 h and filtered followed by washing with water (120 kg). Loss to the filtrate was < 0.01%. The wet cake was dried *in vacuo* at 55 °C to afford desired **11** at 100.0% purity via HPLC method B (34.1 kg, 94.3% yield).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.95 (1H, s), 9.68 (1H, s), 7.73 (2H, d, *J* = 8.8 Hz), 6.94 (2H, d, *J* = 9.2 Hz), 3.64 (2H, d, *J* = 12.0 Hz), 3.60 (3H, s), 3.08 (3H, s), 2.88-3.00 (2H, m), 2.10-2.34 (2H, m), 1.92-1.98 (2H, m), 1.80-1.88 (2H, m), 1.70-1.78 (2H, m), 1.56-1.67 (6H, m), 1.30-1.50 (5H, m), 1.11-1.22 (4H, m), 0.90-1.02 (2H, m)

^{13}C NMR (100 MHz, DMSO-*d6*) δ 175.8, 174.8, 165.7, 153.5, 129.3 (2 carbons), 121.2, 113.9 (2 carbons), 75.1, 51.9, 47.6, 43.6, 42.1, 41.9, 41.8, 29.0 (2 carbons), 28.6 (2 carbons), 28.3 (2 carbons), 27.1 (2 carbons), 26.9 (2 carbons), 26.8 (2 carbons)

MS (ESI, positive mode) m/z; 500.0, MS (ESI, negative mode) m/z; 498.0

Anal. Calcd for $C_{28}H_{41}N_3O_5$: C (67.31%), H (8.27%), N (8.41%). Found: C (67.45%), H (8.38%), N (8.22%); mp: 207 °C (by DSC)

methyl

trans-4-{5-[4-(4-cyclohexyl-4-methoxypiperidin-1-yl)phenyl]-1,3,4-thiadiazol-2-yl}cyclohexane-1-carboxylate (**12**)

Compound **11** (34.1 kg, 68.3 mol) was added to THF (424 kg), followed by phosphorus pentasulfide (P_2S_5, 19.7 kg, 88.8 mol) at 30 °C, and the mixture was aged for 2 h at 30 °C; HPLC analysis subsequently indicated that < 0.7% compound **11** remained (HPLC method C and method D). After reaction completion, an aqueous solution of Na_2CO_3 (Na_2CO_3: 21.7 kg, 205 mol/water: 512 kg) was added to the reaction mixture at 7 °C, and the resulting slurry was agitated for 17 h, filtered, and then washed with water (68.0 kg). Loss to the filtrate was 0.7%. The resulting wet cake was then added to a solution of water (205 kg) and THF (121 kg), and the mixture was then agitated for 1 h at 10 °C, filtered, and washed with water (68.0 kg). Loss to the filtrate was < 0.03%. The wet cake was dried *in vacuo* at 60 °C to afford the desired **12** at 99.4% purity via HPLC method C (31.9 kg, 93.8% yield). ***cis*-12** (0.5%) was observed on HPLC method D.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, J = 8.8 Hz), 6.91 (2H, d, J = 8.8 Hz), 3.67 (3H, s), 3.60 (2H, d, J = 12.4 Hz), 3.14 (3H, s), 3.04-3.14 (2H, m), 2.35-2.42 (2H, m), 2.24-3.32 (2H, m), 2.08-2.17 (2H, m), 1.50-1.84 (14H, m), 1.14-1.26 (3H, m), 0.92-1.04 (2H, m)

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 172.9, 168.3, 153.1, 129.1 (2 carbons), 119.9, 114.9 (2 carbons), 75.3, 68.1, 51.8, 47.7, 43.9 (2 carbons), 42.5, 42.3, 39.2, 32.8 (2 carbons), 29.2, 28.6 (2 carbons), 27.1 (2 carbons), 27.0 (2 carbons), 26.7

MS (ESI, positive mode) m/z; 498.0, MS (ESI, negative mode) m/z; 496.0

Anal. Calcd for $C_{28}H_{39}N_3O_3S$: C (67.57%), H (7.90%), N (8.44%), S (6.44%). Found: C (67.45%), H (7.99%), N (8.22%), S (6.55%); mp: 173 °C (by DSC)

(*trans*-4-{5-[4-(4-cyclohexyl-4-methoxypiperidin-1-yl)phenyl]-1,3,4-thiadiazol-2-yl}cyclohexyl)methanol (**15**)

Compound **12** (31.8 kg, 63.9 mol) was added to THF (536 kg), and then the mixture was cooled to 6 °C. Red-Al (70% in toluene, 27.7 kg, 95.8 mol) was then added, followed by washing with THF (28.2 kg) and aging for 1 h at 15 °C; HPLC analysis subsequently indicated that < 0.1% compound **12** remained (HPLC method D). After reaction completion, the batch was cooled to 3 °C, and MeOH (12.6 kg) and aqueous hydrochloric acid (*conc*. HCl: 93.8 kg/water 398 kg) were added. The batch was then warmed to 25 °C, and dichloromethane (527 kg) was added. After the phase separation, the resulting aqueous layer was first extracted with dichloromethane (316 kg) and then re-extracted with dichloromethane (211 kg) again. After combining these resulting organic layers and washing with water (159 kg), anhydrous $MgSO_4$ (32.0 kg) and activated charcoal (1.59 kg) were then added, and the batch was filtered through Celite® 545 (6.4 kg). After the resulting filtrate was concentrated *in vacuo* using a vacuum pump to 320 L, MeOH (252 kg) was added. After this

solution was concentrated *in vacuo* using a vacuum pump to 320 L, more MeOH (252 kg) was added, and the solution was concentrated again *in vacuo* using a vacuum pump to 320 L. The residue was then warmed to 47 °C, and water (95.0 kg) was added to the batch. The resulting slurry was cooled to 2 °C, agitated for 2 h, and filtered followed by washed with MeOH (63.0 kg)/water (79.5 kg). Loss to the filtrate was 0.7%. The wet cake was dried *in vacuo* at 60 °C to afford the desired **15** at 100.0% purity via HPLC method D (27.9 kg, 93.1% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 9.2 Hz), 6.91 (2H, d, *J* = 8.4 Hz), 3.56 (2H, d, *J* = 12.0 Hz), 3.49 (2H, d, *J* = 6.0 Hz), 3.14 (3H, s), 3.01-3.12 (3H, m), 2.18-2.28 (2H, m), 1.90-1.99 (2H, m), 1.86 (1H, br), 1.50-1.82 (13H, m), 1.08-1.26 (4H, m), 0.90-1.13 (3H, m)

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 168.2, 153.0, 129.0 (2 carbons), 119.9, 114.9 (2 carbons), 75.3, 68.2, 47.7, 43.9 (2 carbons), 42.3, 40.1, 39.8, 33.4 (2 carbons), 29.5 (2 carbons), 29.3, 29.1, 27.1 (2 carbons), 26.9 (2 carbons), 26.7

MS (ESI, positive mode) m/z; 470.0, MS (ESI, negative mode) m/z; 468.0

Anal. Calcd for $C_{27}H_{39}N_3O_2S$: C (69.04%), H(8.37%), N(8.95%), S(6.83%). Found: C (69.15%), H (8.39%), N(8.79%), S(6.85%); mp: 195 °C (by DSC)

trans-4-{5-[4-(4-cyclohexyl-4-methoxypiperidin-1-yl)phenyl]-1,3,4-thiadiazol-2-yl}cyclohexane-1-carbaldehyde (**1**)

Compound **15** (24.0 kg, 51.1 mol), dichloromethane (572 kg), and triethylamine (31.0 kg, 307 mol) were added to DMSO (106 kg), and then dichloromethane (31.8 kg) was added to the batch. Sulfur

trioxide pyridine complex (24.4 kg, 153 mol) was then added to the mixture, followed by washing with dichloromethane (31.8 kg) at 25 °C and aging for 3 h at 25 °C; HPLC analysis subsequently indicated that 0.4% compound **15** remained (HPLC method E). After reaction completion, an aqueous solution of ammonium chloride (48.0 kg/water 480 kg) was added to the mixture, followed by dichloromethane (318 kg). After the phase separation, the resulting aqueous layer was then extracted with dichloromethane (159 kg). The combined organic layer was concentrated *in vacuo* using a vacuum pump to 240 L. CH_3CN (188 kg) was added to the residue at 30 °C, and the material was concentrated *in vacuo* using a vacuum pump to 240 L. More CH_3CN (94.0 kg) and water (120 kg) were then added at 30 °C, and the resulting slurry was agitated for 3 h at 25 °C, and then filtered and washed with CH_3CN (28.2 kg)/water (36.0 kg). Loss to the filtrate was 1.1%. The resulting wet cake was then added to CH_3CN (188 kg) and agitated for 1 h at 50 °C, cooled to 25 °C, and then filtered and washed with CH_3CN (37.5 kg). Loss to the filtrate was 0.2%. The wet cake was dried *in vacuo* at 40 °C to afford the desired **1** at 99.9% purity via HPLC method E (21.7 kg, 90.9% yield). ***cis*-1** (0.02%) was observed on HPLC method E.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (1H, d, *J* = 0.4 Hz), 7.76 (2H, d, *J* = 8.8 Hz), 6.91 (2H, d, *J* = 8.8 Hz), 3.57 (2H, d, *J* = 12.4 Hz), 3.14 (3H, s), 3.02-3.13 (3H, m), 2.28-2.38 (3H, m), 2.10-2.20 (2H, m), 1.72-1.82 (3H, m), 1.62-1.71 (8H, m), 1.38-1.61 (3H, m), 1.05-1.26 (3H, m), 0.92-1.04 (2H, m)

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 172.7, 168.3, 153.1, 129.1 (2 carbons), 119.8, 114.9 (2 carbons), 75.3, 49.4, 47.7, 43.9 (2 carbons), 42.3, 39.4, 32.4 (2 carbons), 29.3 (2 carbons), 27.1 (2

carbons), 27.0 (2 carbons), 26.7 (2 carbons), 25.6

MS (ESI, positive mode) m/z; 468.0, MS (ESI, negative mode) m/z; 466.0

Anal. Calcd for $C_{27}H_{37}N_3O_2S$: C (69.34%), H(7.97%), N(8.99%), S(6.86%). Found: C (69.25%), H (7.88%), N(8.93%), S(6.82%). Water: 0.04% (KF); mp: 211 °C (by DSC)

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Notes: The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to Mr. H. Morikawa and Dr. K. Washizuka for their helpful discussions about the medicinal synthetic method for **1**.

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