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Development of One-Pot Synthesis of New Antiarthritic Drug Candidate S-2474 with High *E*-Selectivity

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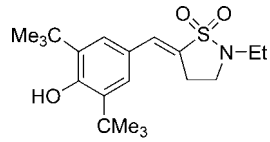
Abstract:

A one-pot synthesis of S-2474 was developed to overcome the problems of a large number of steps, low stereoselectivity, low yield, a large amount of waste, and severe reaction conditions. Aldol-type condensation of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde and *N*-ethyl-γ-sultam was carried out with LDA and then quenched with water. Dehydration proceeded under basic conditions, providing S-2474 directly as a single isomer on the benzylidene double bond. The reaction mechanism appears to involve a quinone methide intermediate. Environmental assessment of the development of this compound is also discussed in this paper.

Introduction

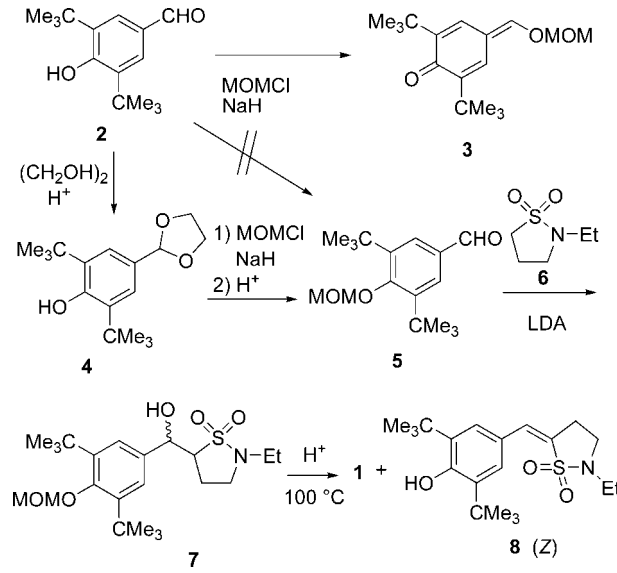
(*E*)-(5)-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (S-2474, **1**), which was discovered at Shionogi Research Laboratories, shows potent inhibitory effects on both cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LO) and is anticipated to be promising as an antiarthritic drug.[1] Study of its structure−activity relationships in in vivo assays shows that the *tert*-butyl group on benzene, *N*-alkylated γ-sultam and the *E*-isomer are essential for its high bioavailability.[1] The *E*-isomer is particularly indispensable for oral bioavailability because the *Z*-isomer is not detected in plasma after oral administration.[1]



S-2474 (**1**)

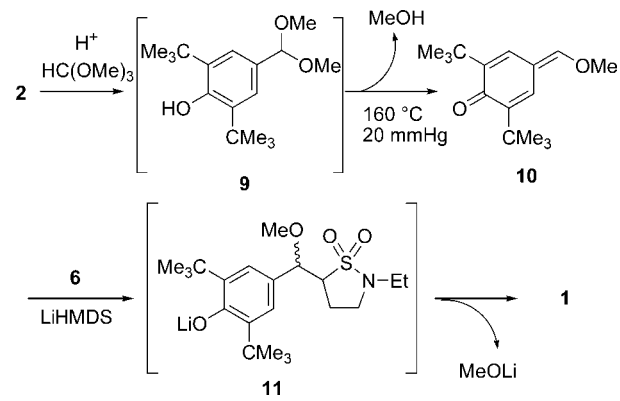
The original synthetic route (Scheme 1) required five reactions, including protection and deprotection of the formyl group to introduce the MOM group to the hydroxy group of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde **2**, because methoxymethylation of **2** gave the quinone enolate **3**.[2] This route required chromatographic purification because dehydration of **7** produced the *Z*-isomer **8** of S-2474 as a byproduct (*E*/*Z* = 84/16). The overall yield was only 19.8%. Another synthetic route was

Scheme 1. **Original synthesis (first-generation route) of S-2474 (1)**



developed by Inagaki et al. using a quinone methide derivative as an equivalent of the protected *p*-hydroxybenzaldeyde derivative (Scheme 2).[2] It required four reactions and the overall yield rose to 71.2%. Although the overall yield was improved and the generation of **8** could be controlled, this route had a problem with respect to scale-up manufacturing. Quinone methide derivative **10** underwent sublimation, and its preparation required a very high temperature reaction in vacuo (160 °C,

Scheme 2. **Second-generation route of S-2474 (1)**



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(1) Inagaki, M.; Tsuri, T.; Jyoyama, H.; Ono, T.; Yamada, K.; Kobayashi, M.; Hori, Y.; Arimura, A.; Yasui, K.; Ohno, K.; Kakudo, S.; Koizumi, K.; Suzuki, R.; Kato, M.; Kawai, S.; Matsumoto, S. *J. Med. Chem.* **2000**, *43*, 2040.

(2) Inagaki, M.; Haga, N.; Kobayashi, M.; Ohta, N.; Kamata, S.; Tsuri, T. *J. Org. Chem.* **2002**, *67*, 125.

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Table 1. **Screening of base on condensation of 2 and 6[a]**

entry	base	product **12** (%)[b]
1	NaHMDS	46
2	KHMDS	59
3	LiHMDS	75
4	*n*-BuLi	80
5	LDA	90

[a] All reactions were carried out in THF at −60 °C. [b] Determined by HPLC. *threo*-**12a** and *erythro*-**12b** mixture.

Table 2. **Effect of temperature and solvent on condensation of 2 and 6[a]**

entry	solvent	temp (°C)	ratio[b] of **12a/12b**	**12a**+**12b** (%)[c]
1	THF	−60	6/1	90
2	THF	25	1/1	74[d]
3	DMI	25	1/1	97

[a] All reactions were carried out with 2.2 mol equiv of LDA. [b] Determined by H NMR. [c] Determined by HPLC. [d] Slaggy lithium salt of **2** and **12** separated out in the course of reaction, and the aldol reaction did not proceed completely.

20−100 mmHg). In sum, these two routes are not suitable for industrial production. We thus aimed at the development of a new synthetic route which could be used for pilot-scale manufacturing.

Results and Discussion

Development of a New Synthetic Route of S-2474. First, screening of the base of aldol-type condensation of **2** and *N*-ethyl-γ-sultam **6** was investigated (Table 1). The countercation of the base was screened by using hexamethyldisilazane (HMDS), which showed that lithium was better than sodium and potassium (entries 1−3). Lithium diisopropylamide (LDA) gave a better yield than LiHMDS and *n*-butyl lithium and was thus chosen as an aldol reaction reagent (entry 5). The reaction using LDA in THF required a very low temperature (Table 2, entry 1) because lithium phenolate easily aggregates[3] and separates out at room temperature. The reaction did not proceed to completion (entry 2). However, we found that lithium phenolate dissolved in 1,3-dimethyl-2-imidazolidinone (DMI) at room temperature, and the reaction could proceed smoothly (entry 3). The ratio of *threo*-isomer **12a** and *erythro*-isomer **12b** was dependent on the reaction temperature (Table 2). As the temperature decreased, the ratio of *threo*-isomer increased. These results show that steric hindrance of the sulfonyl group and di-*tert*-butyl phenoxide seems to affect the stereoselectivity; the reaction is controlled kinetically (Figure 1). The lithium salt of **12** was quenched under acidic condition. The hydroxy group of **12** was chlorinated and then eliminated with base. On using potassium carbonate (K_2CO_3), *Z*-isomer **8** was generated at 20% as a byproduct. Anti-elimination of *threo*-isomer **12a** seemed to proceed in the presence of a base such as K_2CO_3 (Figure 2). Dechlorination with $NaHCO_3$ did not give **8** even though the reaction mixture included *threo*-isomer **12a**, which provided **1** in good yield with high *E*-selectivity. These three reactions can be carried out by a telescoped process (82.5%, Scheme 3), without isolation of the intermediates.

(3) Jackman, L. M.; Chen, X. *J. Am. Chem. Soc.* **1992**, *114*, 403.

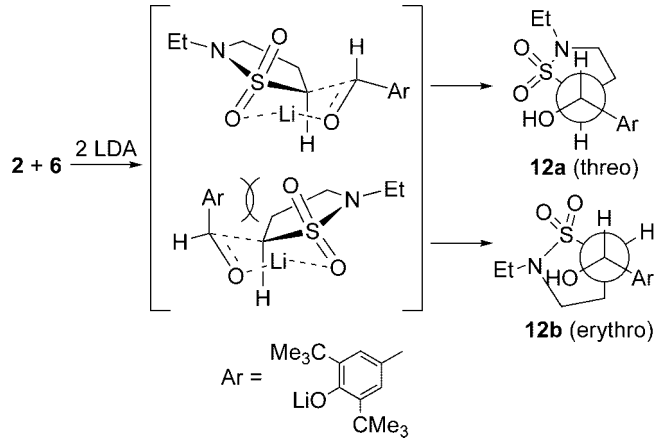


Figure 1. **Proposed mechanism of generation of *threo*- and *erythro*-isomers on aldol-type reaction.**

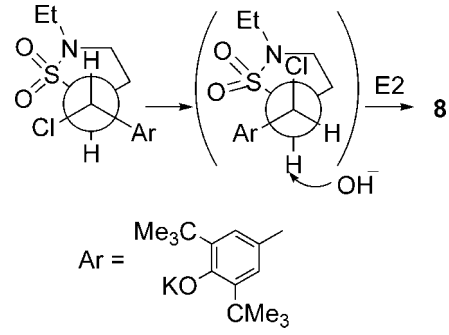
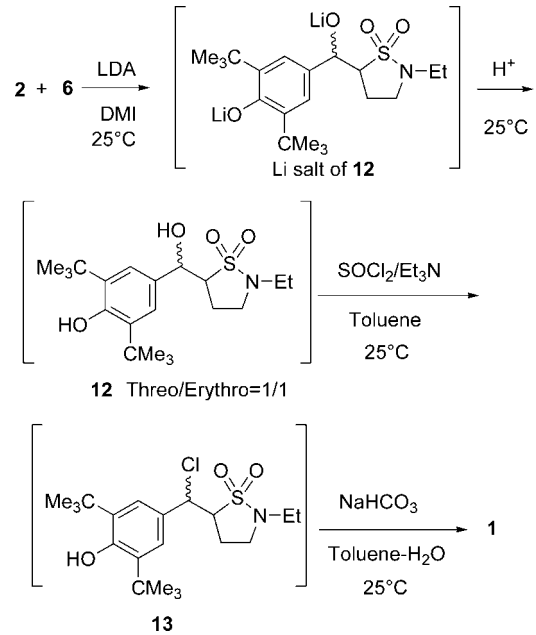


Figure 2. **Anti-elimination of *threo*-isomer 13a using K_2CO_3.**

Scheme 3. **Telescoped process of S-2474 (1)**



Development of a One-Pot Process for Making S-2474. Careful monitoring of the reaction showed that a very small amount of **1** was generated when the lithium salt of **12** was quenched. The yield of **1** seemed to be affected by the exothermic heat of quenching. We estimated that **1** was obtained directly without chlorination and dechlorination. Next, the reaction conditions for dehydration of **12** were examined. The dehydration preferred the basic condition over the acidic as shown in Table 3. Addition of water and heating to 50−90 °C

Table 3. **Optimization of quenching and dehydration of 12**[a]

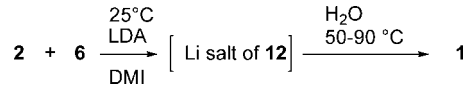
entry	quenching reagent	temp (°C)	product **1** (%)[b]
1	none	60	0[c]
2	HCl	60	0[d]
3	water	50	93
4	water	90	99

[a] All reactions were carried out using the aldol type condensation reaction mixture. [b] Determined by HPLC. [c] Retro aldol reaction proceeded. **2** and **6** were obtained. [d] No reaction. **12** was recovered.

gave **1** (entries 3 and 4). The pH value in this reaction was over 13. To our surprise, *Z*-isomer **8** was not generated in spite of such a strong basic condition. This means that E2 elimination of *threo*-isomer **12a** did not occur. The reaction details are discussed in the next section.

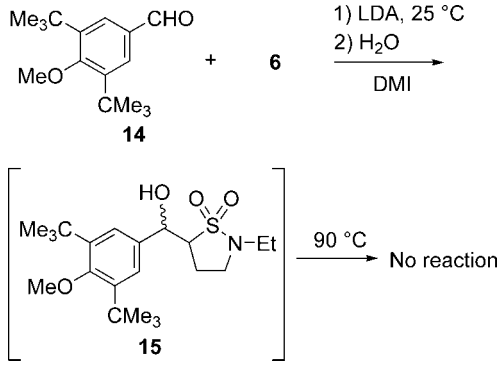
This one-pot synthesis provided **1** in 84.1% isolated yield with high quality (>99.9% purity, Scheme 4). This process did not require extraction of the product, and crystals of **1** were obtained directly on pH adjustment of the reaction mixture to 4.5.

Scheme 4. **One-pot process of S-2474 (1)**



Reaction Mechanism of Dehydration with *E*-Selectivity. The dehydration mechanism details were examined. **1** and **8** did not undergo interconversion even if heated at 100 °C. Thus, the *E*-selectivity did not seem to be controlled by the thermodynamic factor of the products. We focused on the unique character of the phenol derivative which easily forms the quinone methide.[2] Dehydration of **12** proceeded even using 1 mol equiv of $NaHCO_3$ with *E*-selectivity. On the other hand, the *p*-methoxy derivative **14** did not undergo dehydration via the aldol adduct **15** (Scheme 5). These results mean that the dehydration mechanism is not normal E2 elimination. We speculated that this dehydration would also proceed via the quinone methide form as shown in Figure 3. A similar reaction has been known to exist; for example, elimination of the acetoxy group at the benzylic position of the phenol derivative gives the *p*-quinone methide derivative.[5] The quinone methide intermediate quickly equilibrates with phenol compounds.[6] In addition, this quinone methide-type elimination seems to affect the high *E*-selectivity. We hypothesized that phenoxide anions,

Scheme 5



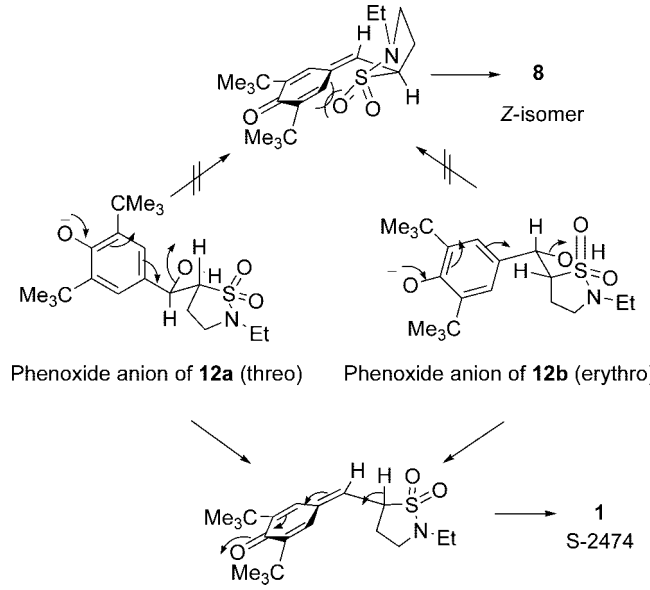


Figure 3. **Proposed dehydration mechanism.**

threo-isomer **12a** and *erythro*-isomer **12b**, would give the same intermediate. Our hypothesis was supported by molecular mechanical (MM) calculation for dihedral angle rotation. The dihedral angle energy of the quinone methide intermediate corresponding to *Z*-isomer **8** was higher than that of the *E*-isomer (Figure 4). This means that the conformation of the quinone methide intermediate is controlled by steric hindrance of the sulfonyl and the aryl groups. From this finding, we propose a dehydration mechanism via a quinone methide intermediate corresponding to the *E*-isomer (Figure 3). If the mechanism were normal E2 elimination, the *Z*-isomer **8** would be produced by anti-elimination of the *threo*-isomer **12a**.

Environmental Assessment of Synthetic Route. This one-pot process does not require chromatographic purification because dehydration proceeds without generation of the *Z*-isomer. Since it requires only two reactions without any protection or introduction of a leaving group, the process has a shorter operation time and is environmentally friendly. Also, this one-pot process does not require any severe reaction conditions. From the viewpoint of environmental assessment, the preparation of **1** via four different routes is compared in Table 4. With the one-pot process, atom economy[3] and reaction mass efficiency (RME)[4] increase dramatically.

Conclusion

A one-pot synthesis of S-2474 for pilot-scale manufacturing was developed. This route consisting of only two reactions gave an overall yield of 84.1% with excellent *E*-selectivity. The excellent stereoselective dehydration to form *E*-olefin was clarified by examination and MM calculation, which relies on

(4) Trost, B. M. *Science* **1991**, *254*, 1471 Atom economy is defined by the following expression: [FW (g mol^{-1}) product]/[FW of all reactants used in reaction] ×100.
(5) Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. *Green Chemistry* **2001**, *3*, 1 Reaction mass efficiency is defined by the following expression:[mass of isolated product (kg)] /[total mass of reactants used in reaction (kg)] ×100.
(6) Takao, K.; Sasaki, T.; Kozaki, T.; Yanagisawa, Y.; Tadao, K.; Kawashima, A.; Shinonaga, H. *Org. Lett.* **2001**, *3*, 4291.
(7) Hunter, S. E.; Savage, P. E. *J. Org. Chem. Soc.* **2004**, *69*, 4724.

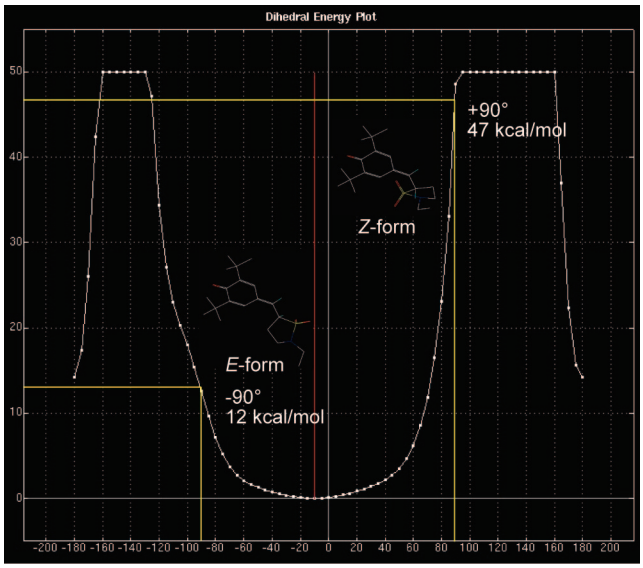


Figure 4. **Dihedral energy plot of the quinone intermediate. This was obtained using the dihedral energy plot of MOE 2006.06, and the structure of the quinone methide intermediate was minimized using MMFF94x. The dihedral angle energy of the quinone methide intermediate corresponding to the *E*-isomer (−90°) was about 12 kcal/mol based on the energy of the most stable conformation (dihedral angle −9°), and that of the *Z*-isomer (+90°) was about 47 kcal/mol.**

Table 4. **Comparison of enviromental assessment for routes of S-2474 (1)**

route	reaction number	atom economy (%)	RME (%)	overall yield (%)
first generation Scheme 1	5	31.8	3.1	19.8
second generation Scheme 2	4	48.9	21.2	71.2
telescoped process Scheme 3	3	46.2	20.2	82.5
one-pot process Scheme 4	2	69.3	48.0	84.1

the unique character of the phenol derivative that can easily form the quinone methide under basic conditions. This process is environmentally friendly and practical for large-scale manufacturing.

Experimental Section

NMR spectra were measured on Varian Unity Inova-600 and Varian Mercury 300 spectrometers. High-resolution mass spectra were recorded on JEOL JMS-SX/SX102A. Di-*tert*-butylbenzaldehyde was obtained from Tokyo Chemical Industry. Lithium diisopropylamide (LDA) was obtained from Chemetall Gmbh. *N*-Ethyl-γ-sultam was prepared by a procedure described in ref 1. HPLC analysis was carried out using Shimadzu 10A-VP. S-2474 **1** and (*Z*)-S-2474 **8** were identified by melting point range and NMR spectra in comparison with reference data.[1] Its purity was determined by HPLC: column, Capcell Pak C18 (5 μm) 4.5 mm × 150 mm (Shiseido); eluent, water/methanol/acetonitrile = 7:10:3; flow rate, 1.2 mL/min; column oven temperature, 25 °C; wavenumber, 230 nm; t_R of S-2474, 18 min. t_R of (*Z*)-S-2474, 16 min.

Procedure for a Telescoped Process of S-2474 Synthesis (Scheme 3). Into a solution of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde **2** (15.0 g, 64.0 mmol) and *N*-ethyl-γ-sultam **6** (10.0 g, 73.4 mmol) in DMI (120 mL) was added dropwise 25% LDA (60.3 g, 140.8 mmol) at 25 °C. This was stirred for 30 min, and then water (144 mL) was added dropwise at 25 °C. After toluene (150 mL) and 62% H_2SO_4 (27.44 g) had been added, the organic layer was separated and washed with water (75 mL, twice). The organic layer was concentrated to 154 g under reduced pressure. Into the residue were added DMI (7.5 mL) and triethylamine (11.7 g, 115.6 mmol), and then thionyl chloride (8.38 g, 70.5 mmol) was slowly added dropwise at 0 °C. Into this reaction mixture, 8.2% $NaHCO_3$ solution (196.1 g, 192.0 mmol) was slowly added dropwise, followed by heating to room temperature. After monitoring of the end-point of the elimination, the organic layer was separated, washed with water (75 mL, twice), and concentrated to 50 g under reduced pressure. The residue was cooled to −10 °C, and white crystals were obtained by filtration. They were recrystallized from 2-propanol. By this procedure, 19.3 g (52.8 mmol) of S-2474 **1** was obtained (isolated yield: 82.5%). The purity was over 99.9% as determined by HPLC; mp 135−137 °C.[1] *Z*-isomer **8** was not detected.

Procedure for a One-Pot Process to S-2474 (Scheme 4). Into a solution of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde **2** (18.0 g, 76.8 mmol) and *N*-ethyl-γ-sultam **6** (12.0 g, 80.4 mmol) in DMI (144 mL) was added dropwise 25% LDA (77.5 g, 180.9 mmol) at 25 °C. This was stirred for 30 min; then water (144 mL) was added, and the mixture was heated to 90 °C for an hour. After monitoring of the end-point of the reaction, the mixture was cooled, then water (108 mL) and 2-propanol (145 mL) were added. Adjustment of the pH to 4.5 with 20% hydrochloric acid gave a slurry and white crystals by filtration. Crystallization from 2-propanol gave 23.6 g (64.6 mmol) of S-2474 **1** (isolated yield: 84.1%). The purity was over 99.9% as determined by HPLC; mp 135−137 °C.[1] *Z*-isomer **8**[1] was not detected.

(5*R,1′*R**)-5-[3,5-Di-*tert*-butyl-4-hydroxyphenyl)hydroxymethyl]-2-ethyl-1,2-isothiazolidine-1,1-dioxide 12a (*threo*) and (5*S**,1′*R**)-5-[3,5-Di-*tert*-butyl-4-hydroxyphenyl)hydroxymethyl]-2-ethyl-1,2-isothiazolidine-1,1-dioxide 12b (*erythro*).** LDA was prepared with diisopropylamine (118 mL) in THF (282 mL) and 1.7 mol/L of *n*-butyl lithium/hexane solution (500 mL). In a 2-L flask, a solution of **2** (94 g), **6** (71.8 g) and THF (1410 mL) was cooled to −60 °C and LDA was added dropwise for 40 min. After the dropwise addition, the reaction mixture was heated to 15 °C followed by stirring for 4.5 h. The mixture was poured into 1 N HCl (3760 mL) and ethyl acetate (3760 mL). The organic layer was separated, washed with water (1880 mL × 2), and evaporated. The residue (226 g) was dissolved in ethyl acetate (1630 mL) and methanol (1130 mL), then methanol (2000 mL) including Girard's reagent T (146 g) was added. The mixture was left standing for 40 h at room temperature. Next, ethyl acetate (1500 mL) and water (1000 mL) were added, and the mixture was stirred. The organic layer was separated and washed with water (1500 mL × 4). Evaporation of the organic layer gave 145 g of residue of which 133 g was crystallized using ethyl acetate and hexane to yield

the *threo*-isomer **12a** (63.39 g). The filtrate included the *erythro*-isomer **12b**. It was evaporated to a residue (66.39 g) from which 58 g was crystallized from hexane to give crude **12b** (42.5 g). The crude crystals (30 g) were purified by silica gel chromatography (70−230 mesh, 240 g, dichloromethane as eluent). Crystallization with diethylether gave **12b** (23.35 g). Compound **12a**: mp 160−162 °C. ^{1}H NMR (500 MHz, ($CDCl_3$ δ) 1.25 (t, J = 7.3 Hz, 3H), 1.43 (s, 18H), 1.84 (m, 1H), 1.94 (m, 1H), 3.03 (ddd, J = 9.1, 8.2, 7.2 Hz, 1H), 3.08 (dq, J = 13.4, 7.2 Hz, 1H), 3.18 (ddd, J = 9.1, 8.0, 3.5 Hz, 1H), 3.23 (dq, J = 13.4, 7.2 Hz, 1H), 3.53 (m, 1H), 4.84 (d, J = 9.7 Hz 1H), 5.27 (s, 1H), 7.16 (s, 2H). ^{13}C NMR (150 MHz, ($CDCl_3$ δ) 13.18, 23.09, 30.24, 34.41, 39.42, 43.92, 63.67, 74.64, 123.58, 129.99, 136.38, 154.22. Elemental analysis: Calcd for $C_{20}H_{33}O_4NS$: C; 62.63, H; 8.67, N; 3.65, S; 8.36, Found: C; 62.58, H; 8.62, N; 3.66, S; 8.32. Compound **12b**: mp 78−96 °C. ^{1}H NMR (500 MHz, ($CDCl_3$ δ) 1.25 (t, J = 7.3 Hz, 3H), 1.44 (s, 18H), 2.08 (m, 1H), 2.60 (dq, J = 13.0, 8.5 Hz, 1H), 3.07 (m, 1H), 3.08 (m, 1H), 3.21 (dq, J = 13.3, 7.2 Hz, 1H), 3.28 (m, 1H), 3.31 (d, J = 2.6 Hz, 1H), 3.38 (td, J = 8.5, 2.1 Hz 1H), 5.21 (s, 1H), 5.40 (brs, 1H), 7.15 (s, 2H). ^{13}C NMR (150 MHz, ($CDCl_3$ δ) 13.18, 18.30, 30.28, 34.43, 39.46, 44.56, 63.21, 69.19, 122.41, 129.94, 136.14, 153.54. Elemental analysis: Calcd for $C_{20}H_{33}O_4NS$: C; 62.63, H; 8.67, N; 3.65, S; 8.36, Found. C; 62.19, H; 8.63, N; 3.62, S; 8.10.

Examination of Reaction Mechanism Study (Scheme 5). 3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde (7.0 g, 29.9 mmol), ethylene glycol (2.8 g, 45.2 mmol), toluene (70 mL), and *p*-toluene sulfonic acid monohydrate (113 mg, 0.59 mmol) were stirred and heated. The water formed during the reaction was removed azeotropically over the 7 h. The reaction mixture was poured into saturated $NaHCO_3$, and a product was extracted with ethyl acetate. The organic layer was separated and washed with water. This organic layer was dried and concentrated to give 6.1 g of (3,5-di-*tert*-butyl-4-hydroxybenzaldehyde)-1,3-dioxolane as white crystals. The crystals (5.0 g) were dissolved with THF (5 mL) and DMF (5 mL), and this solution was slowly added dropwise to a stirred suspension of NaH (60% in mineral oil, 0.80 g, 20 mmol) in THF (5 mL) with ice-cooling and stirred for 15 min at 0 °C. Iodomethane (10.2 g, 71.9 mmol) was added to the reaction mixture at 0 °C, and stirring was continued for 1 h. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. Into the residue, acetone (15 mL) and 1 N HCl (5 mL) were added for hydration of acetal. The reaction mixture was extracted with ethyl acetate, and then the organic layer was evaporated to give 3,5-di-*tert*-butyl-4-methoxybenzaldehyde 14 (3.25 g).

Aldol-type condensation of **14** and **6** and dehydration were tried according to the "Procedure for a One-Pot Process to S-2474". However, no dehydration was detected with HPLC. The reaction mixture was extracted with toluene, and evaporation gave white crystals of **15** as a diastereomer mixture (the *threo*-isomer was the major product). ^{1}H NMR (600 MHz, $(CD_3)_2SO$ δ) 1.10 (t, J = 7.2 Hz, 3H), 1.38 (s, 18H), 1.61 (m, 1H), 1.69 (m, 1H), 2.95 (m, 2H), 2.98 (m, 2H), 3.38 (minor) and 3.43 (major) (ddd, J = 11.9, 9.7, 8.4 Hz, 1H), 3.61 (s, 3H), 4.65 (major) and 4.80 (minor) (dd, J = 9.7, 4.8 Hz, 1H), 5.65 (minor) and 5.72 (major) (d, J = 4.8 Hz, 1H), 7.26 (major) and 7.28 (minor) (s, 2H). ^{13}C NMR (150 MHz, $(CD_3)_2SO$ δ) 13.0 (major) and 13.1 (minor), 21.7 (minor) and 22.7 (major), 31.8, 35.3, 39.2, 43.4 (major) and 44.2 (minor), 63.2 (major) and 62.9 (minor), 63.9 (minor) and 64.0 (major), 70.1 (minor) and 72.3 (major), 124.7 (minor) and 125.0 (major), 135.8 (major) and 136.1 (minor), 142.2 (minor) 142.7 (major), 158.3. HRMS (FAB$^+$) Calcd for $C_{21}H_{35}NO_4S$: ([M + Na]$^+$), 420.2185: Found. *m/z* 420.2183.

Acknowledgment

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Supporting Information Available

HPLC chart of S-2474 **1**; copies of ^{1}H NMR spectra of S-2474 **1**; copies of ^{1}H and ^{13}C NMR spectra of (5*R**,1′*R**)-5-[3,5-di-*tert*-butyl-4-hydroxyphenyl)hydroxymethyl]-2-ethyl-1,2-isothiazolidine-1,1-dioxide **12a** (*threo*), (5*S**,1′*R**)-5-[3,5-di-*tert*-butyl-4-hydroxyphenyl)hydroxymethyl]-2-ethyl-1,2-isothiazolidine-1,1-dioxide **12b** (*erythro*), 5-[(3,5-di-*tert*-butyl-4-methoxyphenyl)hydroxymethyl]-2-ethyl-1,2-isothiazolidine-1,1-dioxide **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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