Pergamon

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Bioorganic & Medicinal Chemistry 11 (2003) 2415–2419

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis and Activities of Oxidative Metabolites of the Anti-arthritic Drug Candidate S-2474

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Received 9 January 2003; accepted 25 February 2003

Abstract—We have synthesized and characterized some oxidative metabolites of S-2474. In this study, we discovered a novel skeleton, the 2,3-dihydrobenzofuran derivative, which inhibited PGE_2 production at a very low concentration and was effective in the anti-carrageenin footpad edema assay.

Introduction

S-2474 [(*E*)-2-ethyl-5-(3,5-di-*tert*-butyl-4-hydroxy-benzylidene)-1,2-isothiazolidine 1,1-dioxide, **1**], developed in our laboratories,[1] is a cytokine suppressive dual inhibitor of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LO). Drugs are often subjected to metabolic transformation such as oxidation, reduction or conjugate formation. These metabolites may circulate in the bloodstream and be distributed to the site of pharmacological activity. In this work, we studied the metabolism of S-2474 in vitro. HPLC analysis from in vitro metabolic studies with human and rat liver microsomes, revealed the presence of two major (M-1 and M-2) and some minor metabolites. The three portions of S-2474 which may be metabolized by CYPs are shown in Figure 1 in comparison with findings from metabolic studies of this class of compounds.[2,3] Pathway A is hydroxylation of the *tert*-butyl group and further dehydration, giving compounds **2** and **3**, respectively. Pathways B and C are hydroxylations of α-positions of nitrogen atom, giving compounds **5** and **6**, respectively (Fig. 2).

Chemistry

The *tert*-butyl-hydroxylated S-2474 (**2**) was synthesized by a very recently reported method, in which the *tert*-butyl-hydroxylated di-*tert*-butyl-hydroxybenzaldehyde (**7**) was used (Scheme 1).[4] Compound **3** was easily prepared from **2** by intra-molecular etherealization under the mesylation condition.[2] The de-ethyl S-2474 (**5**) was prepared by the improved method described in Scheme 2. This route is much more effective with respect to *E*-selectivity and yield than the previous method.[1] The 3-hydroxylated S-2474 (**6**) was synthesized in a straightforward manner by the methods summarized in Scheme 3. A Weinreb amide[5] **14** was treated with an α-sulfonyl carbanion to react cleanly and produce an adduct.[6] The adduct was treated with $BrCH_2CO_2Bu^t$ to give a mono-alkylated derivative as a single product **15** in 75% yield in two steps. Compound **15** was subjected to $NaBH_4$ reduction and hydrogenolysis with Pearlman's catalyst[7] to afford compound **16** in 84% yield. Removal of two protecting groups of **16** with excess iodotrimethylsilane (TMSI) and subsequent treatment of DBU gave an *E*-benzylidene derivative (**17**) in 57% yield via a lactone intermediate. Intramolecular cyclization of **17** was achieved by treatment with ethyl chloroformate via a mixed-anhydride intermediate to afford **18** in good yield (90%).[8] The 3-hydroxylated S-2474 (**6**) could be obtained by DIBAL reduction of **18** at −78 °C in 87% yield. NMR analysis revealed that the reduction product existed as an equilibrium mixture between the ring-opened aldehyde (**6′**) and the ring-closed aminal (**6**).

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doi:10.1016/S0968-0896(03)00141-X

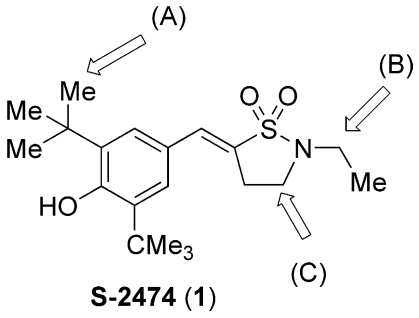


Figure 1.

Results and Discussion

M-1 and M-2 were identified as the de-ethyl S-2474 (**5**) and the *tert*-butyl-hydroxylated S-2474 (**2**) by HPLC analysis, respectively. However, compounds **3** and **6** were not identical to any minor metabolites of S-2474 by HPLC comparison. Structure elucidation of the unknown minor metabolites is now in progress. These synthetic, oxidative derivatives of S-2474 were evaluated for in vitro efficacy according to a previously reported method.[1] The results are summarized in Table 1. Compounds **2** (M-2) and its dehydrating derivative **3** were revealed to be potent inhibitors of PGE_2 production equal to or slightly higher than the parent compound. However, these two compounds were not as effective for LTB_4 production as the parent. These synthetic compounds were revealed to be not effective for LTB_4 and/or IL-1 production. The oral anti-inflammatory activities were further evaluated by carrageenin-induced foot-pad edema assay. The in vivo results are summarized in Table 2. Although all the oxidative derivatives were revealed to be less effective than S-2474, the 2,3-dihydrofurane derivative **3**, which had lost any antioxidant characteristics, displayed moderate activity in both in vitro and in vivo assays. This is noteworthy, because the antioxidant and radical scavenging property of 2,6-di-*tert*-butylphenol groups have been suggested to be relevant to the anti-inflammatory efficacy.[9] Other groups have reported that

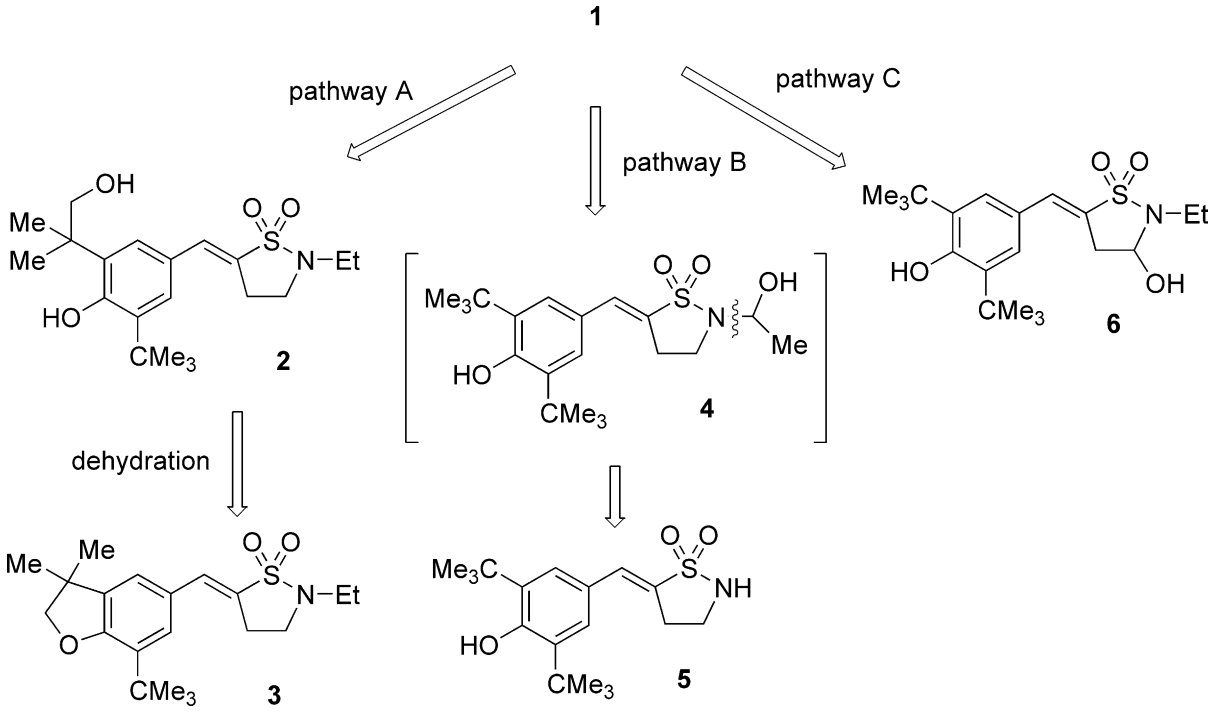
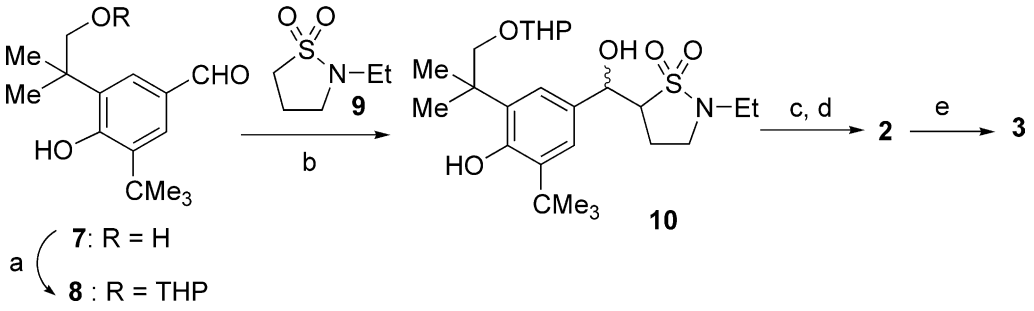
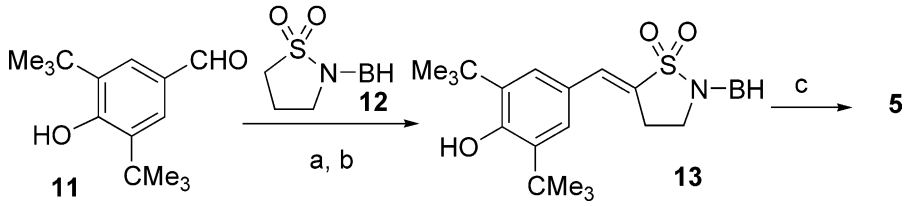


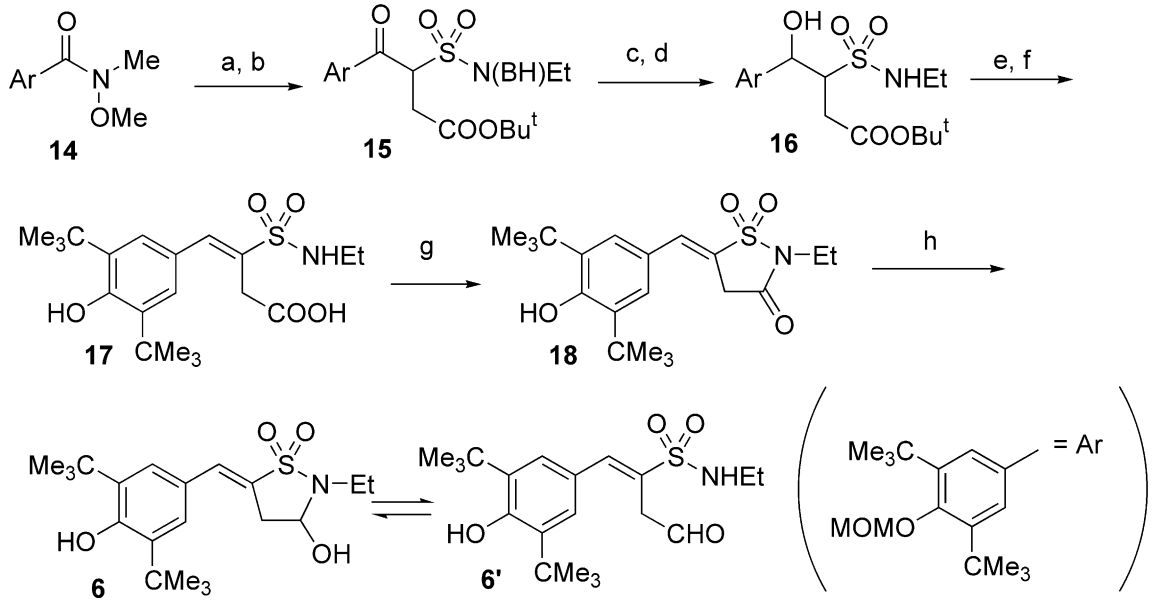
Figure 2.



Scheme 1. Reagents and conditions: (a) dihydropyran, PPTS, CH_2Cl_2, rt (97%); (b) LDA, THF −78 °C; (c) MsCl, Et_3N, AcOEt, 0 °C; (d) *p*-TsOH, MeOH, rt (86% for three steps); (e) MsCl, Et_3N, CH_2Cl_2, 0 °C (94%).



Scheme 2. Reagents and conditions: (a) LHMDS, THF, −78 °C; (b) MsCl, Et_3N, AcOEt, 0 °C (70% for two steps); (c) TFA, anisole, CH_2Cl_2, rt (95%). BH, benzhydryl.



Scheme 3. Reagents and conditions: (a) $CH_3SO_2N(BH)Et$, LHMDS, THF, −50 °C; (b) $BrCH_2CO_2Bu^t$, K_2CO_3, DMF, rt (75% for two steps); (c) $NaBH_4$, CH_2Cl_2-MeOH, rt; (d) $Pd(OH)_2/C$, THF-MeOH, H_2, rt (84% for two steps); (e) TMSI, $CHCl_3$, 0 °C; (f) DBU, benzene; rt (57% for two steps); (g) $ClCO_2Et$, Et_3N, CH_2Cl_2, 0 °C (90%); (h) DIBALH, CH_2Cl_2, −78 °C (87%). BH, benzhydryl.

Table 1. In vitro inhibitory effects on production of PGE_2, LTB_4, and IL-1 by oxidative derivatives of S-2474

Compd	Inhibition of PGE_2 production IC_{50}, μM[a]	Inhibition of LTB_4 production IC_{50}, μM[b]	Inhibition of IL-1 production IC_{50}, μM[c]
1	0.0095	2.5	10
2	0.005	44	15
3	0.002	>100	33
5	0.03	>100	>100
6	>1.0	2.7	69

[a]Concentration (μM) required for 50% inhibition of PGE_2 formation in rat synovial cells.
[b]Concentration (μM) required for 50% inhibition of LTB_4 formation in rat peritoneal cells.
[c]Concentration (μM) required for 50% inhibition of IL-1 formation in human THP-1 cells.

Table 2. In vivo anti-inflammatory effects of oxidative derivatives of S-2474

Compd	Anti-edema (carrageenin) % inhib. at 30 mg/kg[a]	ED_{30} (mg/kg)[b]
1	37.8**	3.5
2	60.3**	6.6
3	50.1**	N.D.[c]
5	17.2	
6	28.6**	

[a]Percent inhibition of carrageenin-induced footpad edema at 30 mg/kg po.
[b]The dose (mg/kg) required for 30% inhibition of carrageenin-induced edema.
[c]Not determined.

compounds with this functionality discovered from metabolic studies of the di-*tert*-butylphenol class compound tebufelone are dual inhibitors of COX and 5-LO.[10]

This study has clarified the primary major metabolic pathways of S-2474: metabolic oxidation via pathways A and B in Figure 1. The presence of the metabolites should not modify the antiinflammatory effect of S-2474 because they do not have potent effects on the production of LTB_4 and IL-1. However, we discovered that a novel, non-antioxidant skeleton, the 2,3-dihydrobenzofuran derivative **3**, was a potent inhibitor of PGE_2 production and effective in the anti-inflammation animal model.

Experimental

Melting points are uncorrected. ^1H NMR spectra were determined at 200 or 300 MHz and ^{13}C NMR spectra

were determined at 75.5 MHz with tetramethylsilane as an internal standard. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere with guaranteed grade solvents that had been dried over type 4A or 3A molecular sieves. Drying of organic extracts over anhydrous sodium sulfate is simply indicated by the word 'dried'. Column chromatography using silica gel (230–400 mesh) is referred to as 'chromatography on silica gel'.

(*E*)-5-(7-*tert*-Butyl-3,3-dimethyl-2,3-dihydrobenzofuran-5-ylmethylene)-2-ethyl-1,2-isothiazolidine 1,1-dioxide (3)

Methansulfonyl chloride (0.39 mL, 4.98 mmol) was added to a stirred solution of **2**[4] (1.58 g, 4.15 mmol), triethylamine (1.45 mL, 12.5 mmol), and CH_2Cl_2 (10 mL) at 0 °C and stirred for 0.5 h. To the reaction mixture were added dil. HCl and AcOEt and the organic layer was separated and washed with H_2O and brine, dried and evaporated. The residue was subjected to chromatography on silica gel (*n*-hexane/AcOEt 70:30) to give the title compound as a colorless solid (1.41 g, 94%). Mp 107–109 °C. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, J = 7.2 Hz, 3H), 1.33 (s, 6H), 1.35 (s, 9H), 3.06–3.33 (m, 6H), 4.28 (s, 2H), 7.01 (d, J = 1.6 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 7.25 (t, J = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 12.89, 23.87, 27.49, 29.10, 34.15, 39.21, 41.23, 43.77, 84.24, 121.34, 126.08, 127.11, 131.01, 131.11, 133.39, 137.82, 158.44. IR (KBr): 3436, 2963, 2871, 1642, 1602, 1453, 1288, 1151 cm^{-1}. Anal. calcd for $C_{20}H_{29}NO_3S$: C, 66.08; H, 8.04; N, 3.85; S, 8.82. Found: C, 65.89; H, 8.01; N, 3.84; S, 8.79.

2-Benzhydryl-1,2-isothiazolidine 1,1-dioxide (12). A solution of 3-chloropropanesulfonyl chloride (20 g, 113 mmol) in AcOEt (50 mL) was added to a stirred mixture of diphenylmethylamine (22.78 g, 124 mmol), triethylamine (18.9 mL, 136 mmol) in AcOEt (100 mL) at 5 °C. The resulting mixture was stirred for 0.5 h at 23 °C. The reaction mixture was washed successively with diluted HCl, H_2O and brine. The organic layer was dried and evaporated to give a crystalline residue. The residue was treated with K_2CO_3 (31.2 g, 226 mmol) and methyl ethyl ketone at refluxing temperature for 18 h. After being cooled to rt, the mixture was passed through a pad of silica gel and the filtrate was concentrated to give a crystalline residue that was recrystallized from AcOEt to give the title compound (24.8 g, 76%) as a colorless crystal. Mp 148–151 °C. ^{1}H NMR (DMSO-d_6): δ 2.22 (quintet, J = 6.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 2H), 3.26 (t, J = 7.2 Hz, 2H), 5.77 (s, 1H), 7.26–7.39 (m, 10H). IR (Nujol): 2925, 1455, 1445, 1377, 1287, 1201, 1166, 1138 cm^{-1}. Anal. calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87; S, 11.16. Found: C, 66.71; H, 5.83; N, 4.85; S, 11.05

(*E*)-2-Benzhydryl-5-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)-1,2-isothiazolidine 1,1-dioxide (13). The title compound was prepared in 70% yield from **11** and **12** by the previously reported method with LHMDS as a base instead of LDA.[4] Mp 192–193 °C. ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 18H), 3.04 (dt, J = 2.1, 6.0 Hz, 2H), 3.17 (t, J = 6.0 Hz, 2H), 5.49 (s, 1H), 5.99 (s, 1H), 7.21 (s, 2H), 7.24–7.38 (m, 11H). IR (Nujol): 3599, 2925, 1597, 1455, 1434, 1377, 1314, 1242, 1215, 1157 cm^{-1}. Anal. calcd for $C_{31}H_{37}NO_3S$: C, 73.92; H, 7.40; N, 2.78; S, 6.37. Found: C, 73.68; H, 7.23; N, 2.83; S, 6.26.

(*E*)-5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-1,2-isothiazolidine 1,1-dioxide (5).[1] A mixture of **13** (10.88 g, 21.6 mmol), TFA (12.6 mL, 164 mmol), anisole (11 mL, 101 mmol), and CH_2Cl_2 (20 mL) was stirred at 23 °C for 1 h. The solid $NaHCO_3$ (13.7 g) was carefully added and then cold water and toluene (100 mL) were added. A precipitate was collected and washed with water and toluene to give the title compound (6.94 g, 95%) as a colorless solid.

3-(Benzhydryl-ethyl-sulfamoyl)-4-(3,5-di-*tert*-butyl-4-methoxymethoxyphenyl)-4-oxo-butyric acid *tert*-butyl ester (15). To a stirred solution of *N*-benzhydryl-*N*-ethylmethansulfonamide (16.82 g, 58 mmol) and THF (200 mL) was added LHMDS solution (1 M in THF, 64 mL, 64 mmol) at −50 °C and the resulting mixture was stirred for 0.5 h at −50 °C. A solution of Weinreb amide **14** (17.7 g, 52.2 mmol) in THF (100 mL) was slowly added to the above reaction mixture at −50 °C. The mixture was allowed to warm to 23 °C and poured into satd NH_4Cl solution. A product was extracted with AcOEt, and the organic layer was washed successively with satd $NaHCO_3$ and brine. After drying and removal of solvents, a residual oil was obtained. The residue was treated with *tert*-butyl bromoacetate (9.25 mL, 57.3 mmol), K_2CO_3 (9.89 g, 71.6 mmol) in DMF at 23 °C for 18 h. To the reaction mixture were added H_2O and AcOEt. The organic layer was separated and washed with H_2O and brine, dried and evaporated to give a yellow crystalline residue, which was washed well with *n*-hexane to give the title compound (26.75 g, 75%). Mp 104–105 °C. ^{1}H NMR ($CDCl_3$): δ 0.77 (t, J = 7.7 Hz, 3H), 1.21 (s, 9H), 1.44 (s, 18H), 2.83 (dd, J = 3.2, 16.8 Hz, 1H), 3.29–3.51 (m, 3H), 3.65 (s, 3H), 4.90 (s, 2H), 5.28 (dd, J = 3.2, 10.4 Hz, 1H), 6.39 (s, 1H), 7.31–7.34 (m, 10H), 7.96 (s, 2H). IR ($CHCl_3$): 3435, 1735, 1677, 1340, 1164, 1147 cm^{-1}. Anal. calcd for $C_{39}H_{53}NO_7S$: C, 68.90; H, 7.86; N, 2.06; S, 4.72. Found: C, 68.80; H, 7.93; N, 2.16; S, 4.55.

4-(3,5-Di-*tert*-butyl-4-methoxymethoxyphenyl)-3-ethylsulfamoyl-4-hydroxy-butyric acid *tert*-butyl ester (16). $NaBH_4$ (1.89 g, 49.9 mmol) was slowly added to a solution of **15** (22.6 g, 33.2 mmol) in MeOH (150 mL) and CH_2Cl_2 (180 mL) at 0 °C. The reaction was allowed to warm to 23 °C and stirred for an additional 0.5 h. Acetone (5 mL) and then satd NH_4Cl solution and CH_2Cl_2 were added to the reaction mixture. The organic layer was separated and washed with H_2O and brine, dried and evaporated to give an almost colorless solid. The residue was dissolved with THF (100 mL) and MeOH (200 mL) and treated with Perlman's catalyst (3.05 g) under H_2 atmosphere for 5 h at 23 °C. The catalyst was removed by filtration and the filtrate was concentrated to afford a crystalline residue, which was recrystallized from ether and *n*-hexane to give the pure title compound (13.7 g, 84%). Mp 96–97 °C. ^{1}H NMR ($CDCl_3$): δ 1.15 (t, J = 7.4 Hz, 3H), 1.36 (9H, s), 1.44 (s, 18H), 2.31 (dd, J = 5.6, 17.6 Hz, 1H), 2.80 (dd, J = 6.6, 17.6 Hz, 1H), 3.00–3.27 (m, 2H), 3.40 (d, J = 4.8 Hz, 1H), 3.64 (s, 3H),

3.97 (ddd, $J=5.6$, 6.6, 8.2 Hz, 1H), 4.19–4.25 (m, 1H), 4.89 (s, 2H), 4.95 (dd, $J=4.8$, 8.2 Hz, 1H), 7.27 (s, 2H). IR (KBr): 3441, 3298, 2966, 1736, 1635, 1367, 1152 cm^{-1}. Anal. calcd for $C_{26}H_{45}NO_7S$: C, 60.56; H, 8.80; N, 2.72; S, 6.22. Found: C, 60.37; H, 8.72; N, 2.69; S, 6.17.

(*E*)-4-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-ethylsulfamoyl-3-butenoic acid (17). To a stirred solution of **16** (1.10 g, 2.13 mmol) in $CHCl_3$ (30 mL) was added TMSI (0.91 mL, 6.39 mmol) in one portion with ice-cooling and stirred for 0.5 h. To the reaction were added 5% aqueous sodium thiosulfate and CH_2Cl_2, and an organic layer was separated and washed with brine, dried and evaporated. The obtained residue was purified by column chromatography on silica gel to give an intermediate lactone (481 mg, 58%) as a colorless solid. Mp 129–131 °C. The lactone (1.52 g, 3.81 mmol) was treated with DBU (1.14 mL, 7.62 mmol) in benzene (50 mL) at 0 °C for 0.5 h. To the reaction were added 1 N HCl and AcOEt, and an organic layer was separated and washed with water and brine, dried and evaporated to afford the title compound (1.52 g, quant) as a colorless solid. Mp 169–172 °C. ^1H NMR (CD_3OD): δ 1.15 (t, $J=7.4$ Hz, 3H), 1.43 (s, 18H), 2.99 (q, $J=7.4$ Hz, 2H), 3.63 (s, 2H), 7.29 (s, 2H), 7.58 (s, 1H). IR (KBr): 3604, 3267, 2958, 1719, 1631, 1596, 1430, 1326, 1158 cm^{-1}. Anal. calcd for $C_{20}H_{31}NO_5S$: C, 60.43; H, 7.86; N, 3.52; S, 8.07. Found: C, 60.36; H, 7.95; N, 3.54; S, 7.87.

(*E*)-5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-3-one 1,1-dioxide (18). To a stirred solution of **17** (1.52 g, 3.81 mmol), triethylamine (0.74 mL, 5.72 mmol) and CH_2Cl_2 (60 mL) was added ethyl chloroformate (0.44 mL, 4.57 mmol) at 0 °C, and stirring was continued for 50 min. To the reaction mixture were added water and CH_2Cl_2. An organic layer was separated and washed with brine, dried and evaporated to give a crystalline residue, which was washed with ether to afford the title compound (1.30 g, 90%) as a colorless crystal. Mp 188–190 °C. ^1H NMR ($CDCl_3$): δ 1.38 (t, $J=7.2$ Hz, 3H), 1.46 (s, 18H), 3.74 (q, $J=7.4$ Hz, 2H), 3.80 (d, $J=2.4$ Hz, 2H), 5.64 (s, 1H), 7.23 (s, 2H), 7.45 (t, $J=2.4$ Hz, 1H). IR (KBr): 3559, 2960, 1715, 1641, 1598, 1434, 1317, 1159 cm^{-1}. Anal. calcd for $C_{20}H_{29}NO_4S$: C, 63.30; H, 7.70; N, 3.69; S, 8.45. Found: C, 63.07; H, 7.71; N, 3.72; S, 8.30.

(*E*)-5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-ethyl-3-hydroxy-1,2-isothiazolidine 1,1-dioxide (6) and (*E*)-4-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-ethylsulfamoyl-3-butenal (6′). To a stirred solution of **18** (870 mg, 2.29 mol) in CH_2Cl_2 (30 mL) was added DIBALH solution (1 M in *n*-hexane, 4.22 mL, 4.22 mmol) at −40 °C and stirred for 5 min. To the reaction mixture was added satd NH_4Cl, and the mixture was allowed to warm to 23 °C slowly. A slurry was removed by filtration and the filtrate was concentrated to give a crystalline residue, which was recrystallized from ether and *n*-hexane to give the title compound (762 mg, 87%) as a colorless crystal. Mp 138–141 °C. **6** : **6′** = 5:1 in acetone-d_6; peaks of **6**; δ 1.27 (t, $J=7.0$ Hz, 3H), 1.48 (s, 18H), 3.07 (dt, $J=2.4$, 16.4 Hz, 1H), 3.27 (q, $J=7.0$ Hz, 2H), 3.57 (ddd, $J=2.4$, 6.2, 16.4 Hz, 1H), 5.23 (m, 1H), 5.35 (br s, 1H), 7.18 (t, $J=2.4$ Hz, 1H), 7.37 (s, 2H); peaks of **6′**; δ 1.12–1.21 (m, 3H), 1.44 (s, 18H), 2.95–3.05 (m, 2H), 3.78 (d, $J=1.6$ Hz, 2H), 7.30 (s, 2H), 7.68 (br s, 1H), 9.78 (t, $J=1.6$ Hz, 1H). IR (KBr): 3610, 3427, 2968, 1653, 1595, 1432, 1261, 1214, 1147 cm^{-1}. Anal. calcd for $C_{20}H_{31}NO_4S$: C, 62.96; H, 8.19; N, 3.67; S, 8.40. Found: C, 63.075; H, 8.26; N, 3.67; S, 8.33.

Acknowledgements

The authors thank Drs. Mitsuaki Ohtani, Kenji Kawada, and Norihiko Tanimoto for their encouragement and helpful discussions throughout this study.

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