Highly *E*-Selective and Effective Synthesis of Antiarthritic Drug Candidate S-2474 Using Quinone Methide Derivatives

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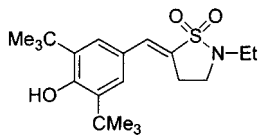
We have developed an efficient and *E*-selective synthesis of an antiarthritic drug candidate (*E*)−(5)−(3,5-di-*tert*-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (S-2474; **1**), in which α-methoxy-*p*-quinone methide is used as a key intermediate. α-Methoxy-*p*-quinone methide was revealed to be an equivalent to a *p*-hydroxy protected benzaldehyde. It reacts smoothly with α-sulfonyl carbanion to give 1,6-addition intermediates, which can be further processed to provide S-2474 directly in the presence of a base. This procedure gives S-2474 as an almost single isomer on the benzylidene double bond in excellent yield and thus is a very practical method adaptable to large-scale synthesis. The detailed mechanistic aspects are studied and discussed.

Introduction

We have recently reported that (*E*)−(5)−(3,5-di-*tert*-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (S-2474, **1**; Figure 1) shows potent inhibitory effects on both cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LO), as well as production of interleukin-1 (IL-1) in in vitro assays and is effective in several animal arthritic models without any ulcerogenic activities.[1] S-2474 has been identified as a new type of antiarthritic drug candidate, acting as an NSAID (nonsteroidal anti-inflammatory drug) with a cytokine modulating property and is now in phase II clinical trials.

Structure−activity relationship studies were conducted by synthesizing various benzylidene-1,2-isothiazoline-1,1-dioxides (γ-sultams) using an aldol-type reaction of γ-sultams and corresponding aldehydes of which hydroxy groups were protected with a methoxymethyl (MOM) group.[1] These procedures were very effective for preparing a wide range of substrates for preliminary biological evaluation. With the identification of **1** as an antiarthritic drug candidate, a more focused synthetic approach was needed. The previous synthetic procedure (Scheme 1) poses problems for the large-scale production of S-2474 required for clinical development. One problem is the protection and deprotection procedures of the formyl group needed to introduce the MOM group to the hydroxy group of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde, because the hydroxy group, sterically hindered by ortho-substituted *tert*-butyl groups, has very weak nucleophilicity and a quinone enolate form is thought to be more favored. Moreover, (MOM)Cl, suspected to be a carcinogen, is unavoidable because MOM ether is the most suitable protecting group with its minimal bulkiness and stability against nucleophiles and strong bases. Another problem is that the dehydration and deprotection reaction



S-2474 (1)

Figure 1.

with a catalytic amount of *p*-TsOH as the last step provided a mixture of *E*- and *Z*- benzylidene sultams as described in Scheme 1. In this paper, we report an efficient short-step synthesis of S-2474 (**1**) using a unique quinone methide derivative **9** as the key intermediate, along with mechanistic discussions of the key reaction in this synthesis.

Results and Discussion

To develop an improved synthesis of **1**, we focused on quinone methides (QMs) as an equivalent of protected *p*-hydroxybenzaldehyde derivatives. QM derivative **3** was detected by NMR analysis when 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**2**) was allowed to react with (MOM)Cl without any protection of its formyl group. QMs[2] are known to be good Michael acceptors of nucleophiles such as dienes,[3] alcohols,[4] phosphates,[5] carbanions,[6] and DNA.[7]

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Scheme 1

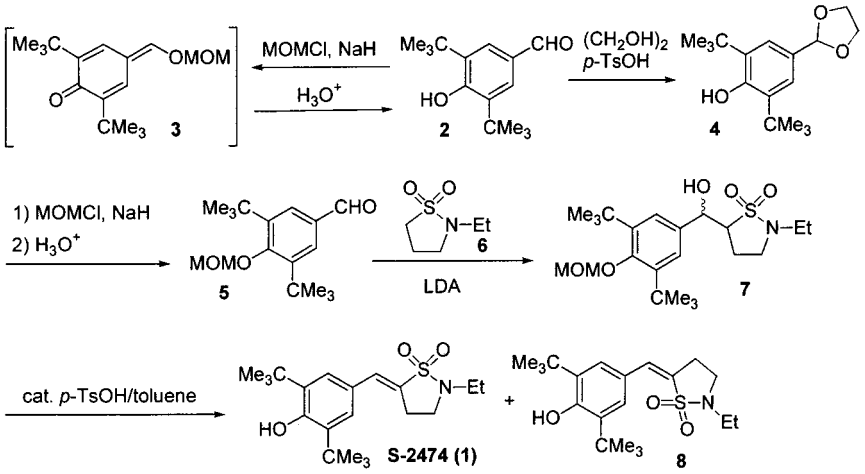
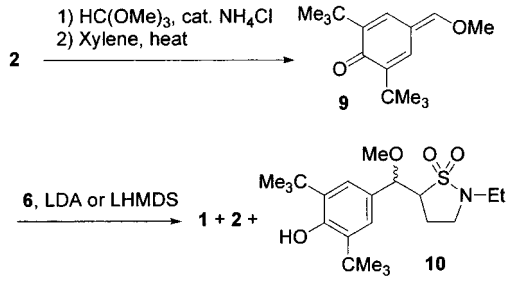


Table 1. Reactions of Quinone Methide and α-Sulfonylcarbanion[a]

entry	base	temp (°C)	time (h)	product (ratio) **1**:**2**(:**10**)	yield of **1** (%)
1	LDA	−78	1	26:2(:72)[b]	(25)[b]
2	LDA	−78	2	9:1[c]	61[d] (88)[c]
3	LDA	0	1	complex mixture	
4	LHMDS	0	2	1.8:1[b]	35[e]
5	NaHMDS	0	1	1:1[b]	
6	KHMDS	0	1	1:2[b]	

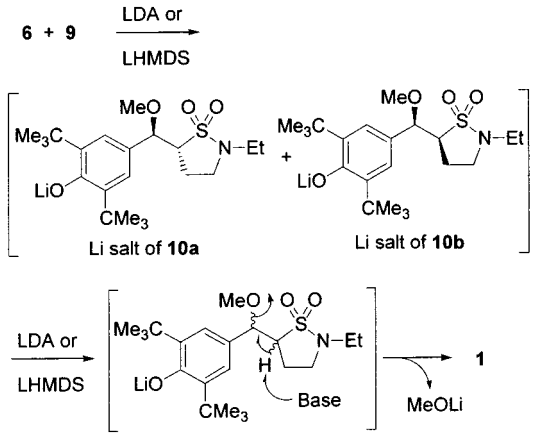
[a] All reactions were carried out in THF with **9**:**6**:base = 1:1.2:2.4 except for entry 1 (the ratio of **9**:**6**:base = 1:1:1.2). [b] Ratio or yield determined by NMR analysis of the crude reaction mixture. [c] Ratio or yield determined by HPLC analysis of the crude reaction mixture. [d] Isolated yield from single crystallization of the crude reaction mixture. [e] Isolated yield after separation by chromatography on silica gel.

Scheme 2



However, to our knowledge, there has been no example of its use as an equivalent of the protected *p*-hydroxybenzaldehyde derivatives. First, we tried a reaction of 2,6-di-*tert*-butyl-α-methoxyquinone methide (**9**) which was simply prepared from thermal decomposition of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde dimethyl acetal[4a] and α-sulfonyl carbanion as a carbon nucleophile. α-Lithio-*N*-ethyl-γ-sultam was prepared from *N*-ethyl-γ-sultam (**6**)[1] and 1.2 equiv of LDA at −78 °C and then treated with 1 equiv of **9**. Interestingly, we obtained not only the 1,6-addition adduct **10** but also **1** after 1 h of stirring (Scheme 2 and entry 1 in Table 1). To our surprise, no *Z*-isomer **8** could be detected in the reaction mixture by NMR analysis. We think **1** was formed from the 1,6-addition adduct **10** by deprotonation with excess base following elimination of MeOLi as described in Scheme 3. To find proof for this, the reaction was carried out with 2 equiv of LDA to **6** and **9**. As expected, **1** was obtained in good yield with excellent *E*-selectivity (entry 2). To

Scheme 3



reduce the cost of the synthesis of **1**, we tried carrying out this reaction at higher temperature. Unfortunately, the reaction with LDA in THF at 0 °C gave a complex mixture which involved a trace amount of the desired product (entry 3). Although the use of LHMDS as a base afforded a better result (entry 4), other bases such as NaHMDS and KHMDS also gave poor results (entries 5 and 6). In each case, a significant amount of **2** was obtained. These results were presumed to occur due to bases such as NaHMDS, KHMDS, and LDA attacking **9** because of their slightly stronger nucleophilicity than that of LHMDS, with their adducts being hydrolyzed to **2** after aqueous workup.[8] To investigate the solvent effects on this reaction, the nonpolar solvent toluene was used instead of THF. The reaction with LHMDS did not proceed smoothly in toluene as a sole solvent (entry 1 in Table 2), but in a combination of toluene and THF gave

(8) Indeed, an amino acetal **11** was observed as a 1,6-addition adduct by NMR analysis when **9** was treated with KHMDS in THF-d_8 in the absence of **6** and changed to **2** with aqueous workup.

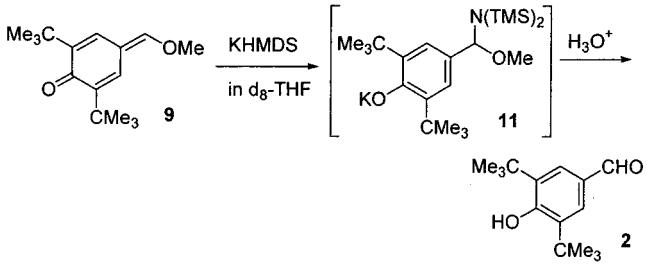


Table 2. Effects of Solvents on Product Ratio[a]

entry	ratio toluene:THF	products (ratio) **1**:**2**	entry	ratio toluene:THF	products (ratio) **1**:**2**
1	toluene only	slaggy	3	4:1	50:1[b]
2	2:3	15:1[b]	4	5:1	97.3:1.4[c]

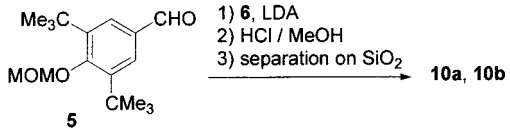
[a] All reactions were carried out with **9**:**6**:LHMDS = 1:1.2:2.4 at 0 °C for 1−4 h. [b] Ratios determined by NMR analysis of the crude reaction mixture. [c] Ratio determined by HPLC analysis of the crude reaction mixture.

Table 3. Effects of Several Bases on Product Ratio[a]

entry	base	time (h)	products (ratio) **1**:**2**
1	LHMDS	4	97.3:1.4[b]
2	NaHMDS	3	10:1[c]
3	KHMDS	3	complex mixture
4	LDA	2	slaggy

[a] All reactions were carried out with **9**:**6**:base = 1:1.2:2.4 at 0 °C in toluene−THF (5:1). [b] Ratio determined by HPLC analysis of the crude reaction mixture. [c] Ratio determined by NMR analysis of the crude reaction mixture.

Scheme 4



better results, with a ratio of toluene/THF of more than 4:1 giving satisfactory results (entries 3 and 4). In the mixed solvent system, LHMDS was revealed to be the best of several bases shown in Table 3. Next, we tried to optimize the reaction temperature in this solvent system with LHMDS as a base (Table 4[9]). The reaction was carried out at −15 °C, to minimize the formation of byproducts **2** and **8** at lower temperature, to afford the intermediate 1,6-addition adduct **10** in 3% yield because the reaction proceeded more slowly than at 0 °C, but at 23 °C gave the *Z*-isomer **8** in 4% yield as the main byproduct. The other leaving groups of QMs, OEt, or Cl[10] gave no better results (50 and 38% yields, respectively) (Table 5[9]). The optimized reaction conditions from these experiments and details are given in the Experimental Section. We can obtain **1** in 80% yield of high quality (>99.9% by HPLC analysis) after a single crystallization.

Studies were done on the reaction details. Careful monitoring of this reaction revealed that the intermediate 1,6-addition adduct **10** was observed when the reaction was stopped before completion. Remarkably, diastereomer **10a** was almost exclusively obtained with only a trace amount of diastereomer **10b**. The stereochemistry of **10a** was determined as the threo form by single X-ray crystallography.[11] These results suggested that the erythro adduct **10b** rapidly changed to **1** but the threo **10a** did so only slowly. In fact, when the threo **10a** and the erythro **10b**, which were synthesized by the method described in Scheme 4, were separately treated with LHMDS, the erythro **10b** changed to **1** in a ratio of 10:1 within 1.5 h, but the threo **10a** changed to **1** as 6:1 over 4 h.

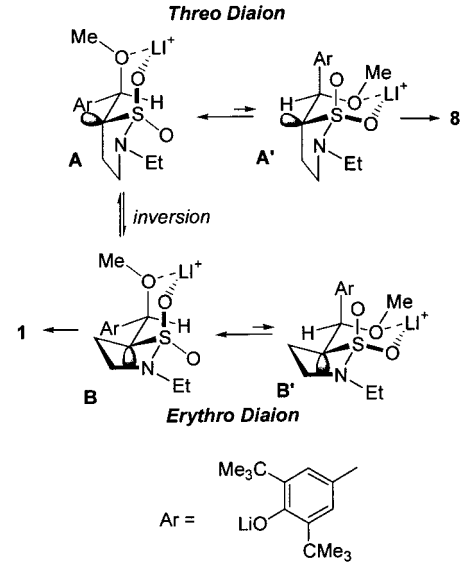


Figure 2.

Another question remained: *why was the E-isomer formed selectively?* Although the reasons for the above outcome have not yet been established, we assume the reaction proceeds via six-membered, chair-form dianions shaped by fixed SO_2−Li−OMe chelation with a bulky substituent in the equatorial position (**A** and **B**, not **A′** and **B′** in Figure 2) and then anti-elimination of MeOLi from the chelated dianion (**B**) gives the *E*-isomer, because non-benzylic type α-sulfonylcarbanions are suggested to have pyramidalized structures and the countercation is bound to the oxygen of the sulfonyl group and solvents, not to the carbanionic center.[12] Intermediate **10b** is suitable for anti-elimination with the bulky aryl substituent in the equatorial position, but **10a** cannot assume a suitable conformation for anti-elimination with the bulky substituent in the equatorial position, as shown in Figure 2. In the case of **10a**, the chelated dianion (**A**) may change slowly with inversion of configuration of the carbanion center[12a,13] to a more suitable dianion (**B**), followed by anti-elimination of MeOLi to give the *E*-isomer.[14] This assumption is supported by the fact that the reaction (**10a,b** → **1**) did not proceed in the presence of HMPA which intercepts the formation of the six-membered dianion intermediate formed by SO_2−Li−OMe chelation.[15]

Summary

We have described the improved short-step synthesis of the antiarthritic drug candidate S-2474 with high

(9) Tables 4 and 5 are given in the Supporting Information.

(10) QMs having OEt and Cl were synthesized as described in the Experimental Section.

(11) X-ray crystallographic data of **10a** is given in the Supporting Information.

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(14) An alternative explanation is intermediate lithium anions of **10a** or **10b** are reversible via a retro-aldol-type reaction. To clarify whether or not this reaction occurred, the lithium salt of **10a** was treated with benzaldehyde to see if cross-coupling adducts were observed. In this reaction, only **10a** was recovered, and no cross-coupling adducts and its diastereoisomer **10b** were detected by NMR analysis.

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E-selectivity, which is the first example of a relatively stable α-methoxyquinone methide being used as an equivalent of the protected *p*-hydroxy benzaldehyde. This procedure resolves the problems arising from protection/deprotection procedures of the formyl group and the dehydration/deprotecion reaction with *p*-TsOH described in the Introduction and gives S-2474 of high quality after a single crystallization.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra were determined at 200 or 300 MHz. ^{13}C NMR spectra were determined at 75.5 MHz. IR spectra were recorded on a Nicolet 20SXB FT-IR spectrometer. Mass spectra were measured on a JEOL JMS−SX/S102A or a HITACHI M-90 mass spectrometer. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere with guaranteed grade solvents that had been dried over type 3A or 4A molecular sieves. Drying of organic extracts over anhydrous sodium sulfate is simply indicated by the word "dried". Column chromatography using Merck silica gel 60 (70−230 or 230−400 mesh) or a Merck Lobar column is referred to "chromatography on silica gel".

HPLC analysis was performed on a Cosmosil 5C18-AR column (4.6 × 150 mm) with UV detection at 230 nm. The mobile phase flow rate was 1 mL/min with a gradient for which solvent A was MeOH/H_2O/AcOH (50:50:1) and B was MeOH/AcOH (100:0.1). Time program: 0−10 min, A:B = 50:50; 10−20 min, A:B = 50:50−30:70; 20−30 min, A:B = 30:70. Retention times: **10a,** 4.9 min; **8,** 5.8 min; **2,** 6.1 min; **1,** 6.8 min.

2,6-Di-*tert*-butyl-4-methoxymethylenecyclohexa-2,5-dienone (9). A mixture of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**2**) (23.4 g, 0.10 mol), NH_4Cl (1.0 g), trimethyl orthoformate (50 mL, 0.46 mol), xylene (50 mL), and absolute MeOH (50 mL) was refluxed for 2 h. Excess trimethyl orthoformate, methyl formate formed during the reaction, and MeOH were removed by distillation. To the residue was added xylene (50 mL), and the mixture was cooled to room temperature. NH_4Cl was removed by filtration, and the filtrate was heated at 160 °C to remove xylene and MeOH formed during the thermal decomposition reaction over 2 h and an additional 2 h under reduced pressure (20−100 mmHg). The reaction was cooled to 50 °C, and then hexane (50 mL) was added. The crystalline product was collected and washed with a small amount of hexane to afford yellow crystals of the title compound (**9**) (22.1 g, 89%); mp 137−139 °C (lit.[4a] mp 136−138 °C). ^{1}H NMR (acetone-d_6): δ 1.27 (s, 9H), 1.29 (s, 9H), 4.08 (s, 3H), 7.02 (d, J = 2.5 Hz, 1H), 7.41 (dd, J = 0.9, 2.5 Hz, 1H), 7.54 (brs, 1H). ^{13}C NMR (acetone-d_6): δ 29.68, 30.24, 35.42, 35.82, 63.03, 114.83, 124.58, 132.42, 145.39, 147.27, 162.62, 186.30. IR (Nujol): 1637, 1558, 1454, 1358, 1290, 1269, 1153, 1088, 1020 cm^{-1}. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.15; H, 9.75.

2,6-Di-*tert*-butyl-4-ethoxymethylenecyclohexa-2,5-dienone. The title compound was prepared from **2** (23.4 g, 0.10 mol), NH_4Cl (2.0 g), triethyl orthoformate (60 mL), absolute EtOH (60 mL), and xylene (60 mL) in 84% yield by the same procedure described above; mp 114−117 °C. ^{1}H NMR (acetone-d_6): δ 1.27 (s, 9H), 1.30 (s, 9H), 1.41 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.03 (d, J = 2.4 Hz, 1H), 7.44 (dd, J = 0.7, 2.4 Hz, 1H), 7.46 (brs, 1H). ^{13}C NMR (acetone-d_6): δ 15.60, 29.67, 29.70, 35.34, 35.74, 72.24, 114.64, 124.64, 132.56, 145.05, 146.98, 161.58, 186.15. IR (Nujol): 1633, 1560, 1450, 1358, 1252, 1149, 1088, 1022 cm^{-1}. HR-FABMS: *m*/*z* 263.2005 $[M + H]^+$ (calcd for $C_{17}H_{27}O_2$, 263.2011).

2,6-Di-*tert*-butyl-4-chloromethylenecyclohexa-2,5-dienone. A mixture of **2** (7.02 g, 30 mmol), triethylamine (8.36 mL, 60 mmol), methansulfonyl chloride (4.7 mL, 60 mmol), and CH_2Cl_2 (70 mL) was refluxed for 5 h. The reaction was cooled to room temperature, and insoluble materials were removed by filtration. The filtrate was concentrated to give a crude form of the title compound (8.16 g), which was used in the next reaction without further purification. ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 9H), 1.32 (s, 9H), 6.81 (s, 1H), 6.83 (d, J = 2.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H).

(*E*)-5-(3,5-Di-*tert*-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (S-2474; 1). A solution of **6** (8.21 g, 55 mmol) in toluene (10 mL) was added to LHMDS (1 M in toluene, 115 mL, 115 mmol) with ice-cooling, and the mixture was stirred for 30 min under the same conditions. Next, to this solution was added a solution of **9** (12.42 g, 50 mmol) in THF (30 mL) and toluene (25 mL) over 30 min with ice-cooling. The reaction was stirred for an additional 4 h under the same conditions and then quenched with cold diluted HCl. The organic layer was separated and washed with water twice. Drying and removal of the solvents gave a residual solid (the purity by HPLC analysis was determined to be 97.31%, with **2** (1.40%) and **8** (1.29%) as impurities of more than 0.1%.). It was crystallized from 2-propanol to give the title compound (14.7 g, 80%) as colorless crystals. The purity was over 99.9% as determined by HPLC analysis; mp 135−137 °C.

(5*R, 1′*R**)-5-[(3,5-Di-*tert*-butyl-4-hydroxyphenyl)methoxymethyl]-2-ethyl-1,2-isothiazolidine-1,1-dioxide (10a; threo) and (5*S**, 1′*R**)-5-[(3,5-Di-*tert*-butyl-4-hydroxyphenyl)methoxymethyl]-2-ethyl-1,2-isothiazolidine-1,1-dioxide (10b; erythro).** To a stirred solution of diastereo mixture of 5-((3,5-di-*tert*-butyl-4-methoxymethyloxyphenyl)-hydroxymethyl)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (**7**) (2.64 g, 6.17 mmol) in MeOH (25 mL), which was prepared by a previously reported method,[1] was added 10 N HCl/MeOH (2.5 mL, 25 mmol) at 0 °C. The resulting mixture was stirred for 15 h at room temperature. The reaction was poured into water, and the product was extracted with diisopropyl ether. The organic layer was washed with water and then brine, dried, and evaporated. The residue was carefully purified by column chromatography on silica gel, eluting with hexane/AcOEt (4:1). The erythro **10b** (1.00 g, 41%) and the threo **10a** (0.30 g, 12%) were obtained as colorless solids from the less polar and polar fractions, respectively. Compound **10a**: mp 204−206 °C. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 3H), 1.43 (s, 18H), 1.65−1.90 (m, 2H), 2.93−3.23 (m, 4H), 3.27 (s, 3H), 3.36−3.48 (m, 1H), 4.34 (d, J = 9.9 Hz, 1H), 5.25 (s, 1H), 7.09 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 13.20, 22.99, 30.30, 34.37, 39.68, 43.90, 56.67, 63.18, 82.66, 123.82, 127.79, 136.25, 154.09. IR (KBr): 3547, 2948, 1434, 1287, 1233, 1198, 1113 cm^{-1}. Anal. Calcd for $C_{21}H_{35}NO_4S$: C, 63.44; H, 8.87; N, 3.52; S, 8.06. Found: C, 63.17; H, 8.74; N, 3.55; S, 8.07. Compound **10b**: mp 90−92 °C. ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J = 7.2 Hz, 3H), 1.44 (s, 18H), 2.21−2.35 (m, 1H), 2.42−2.56 (m, 1H), 3.08−3.34 (m, 5H), 3.27 (s, 3H), 4.65 (d, J = 4.2 Hz, 1H), 5.21 (s, 1H), 7.10 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 13.56, 20.61, 30.27, 34.34, 40.04, 45.03, 57.05, 63.21, 79.49, 122.99, 128.33, 135.89, 153.49. IR (KBr): 3585, 2953, 1431, 1358, 1299, 1234, 1106, 1086 cm^{-1}. Anal. Calcd for $C_{21}H_{35}NO_4S$: C, 63.44; H, 8.87; N, 3.52; S, 8.06. Found: C, 63.16; H, 8.77; N, 3.48; S, 8.09.

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Supporting Information Available: Tables 4 and 5 and tables of X-ray crystallographic data of compound **10a** and a figure showing an ORTEP diagram of **10a**. This material is available free charge via the Internet at http://pubs.acs.org.

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