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Novel Antiarthritic Agents with β -Sultam Skeleton: Structure-activity Relationships¹⁾ and Practical Synthetic Studies²⁾

MASANAO INAGAKI^{1,2} AND TATSUO TSURI¹

Received May 21, 2004

Various 1,2-isothiazolidine-1,1-dioxide (β -sultam) derivatives containing an antioxidant moiety, a 2,6-di-*tert*-butylphenol substituent, were prepared. Some compounds, with a lower alkyl group at the 2-position of the β -sultam skeleton, showed potent inhibitory effects on both cyclooxygenase (COX)-2 and 5-lipoxygenase (5-LO), as well as the production of interleukin-1 (IL-1) in *in vitro* assays. They also proved to be effective in several animal arthritic models without any ulcerogenic activities. Among these compounds, (*E*)-(5)-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)-2-ethyl-1,2-isothiazolidine-1,1-dioxide (S-2474) was selected as an antiarthritic drug. The structure-activity relationships (SAR) were examined and some pharmacological evaluations are described. We also developed an efficient and *E*-selective method of synthesizing S-2474, in which β -methoxy-*p*-quinone methide is used as a key intermediate. β -Methoxy-*p*-quinone methide, revealed to be equivalent to a *p*-hydroxy protected benzaldehyde, reacts smoothly with β -sulfonyl carbanion to give a 1,6-addition intermediate, which can be further processed to provide S-2474 directly in the presence of 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 discussed.

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed in drug therapy for rheumatoid arthritis (RA). Currently available NSAIDs are thought to inhibit both isoforms of a constitutive form of cyclooxygenases (COXs), COX-1, and an inducible form, COX-2, to offer anti-inflammatory therapeutic effects.³⁾ However, NSAIDs generally have adverse effects, especially gastrointestinal ulceration,⁴⁾ because COX-1 is believed to be responsible for the synthesis of cytoprotective prostaglandins in the gastrointestinal tract.⁵⁾ COX-2, on the other hand, is induced by many kinds of inflammatory mediators and plays an important role in prostaglandin biosynthesis associated with inflammatory responses.⁶⁾ Therefore, NSAIDs having selective COX-2 inhibitory activity should be more useful for the treatment of inflammatory diseases.⁷⁾ NSAIDs which have dual inhibitory activities against COX and 5-lipoxygenase (5-LO) such as KME-4,⁸⁾ E-5110,⁹⁾ BF-389,¹⁰⁾ and CI-1004¹¹⁾ (Fig.1) may be better than simple COX inhibitors. They are hypothesized to be superior because leukotrienes, produced through the 5-LO enzyme pathway, may contribute to both inflammation and NSAID-induced side effects.¹²⁾

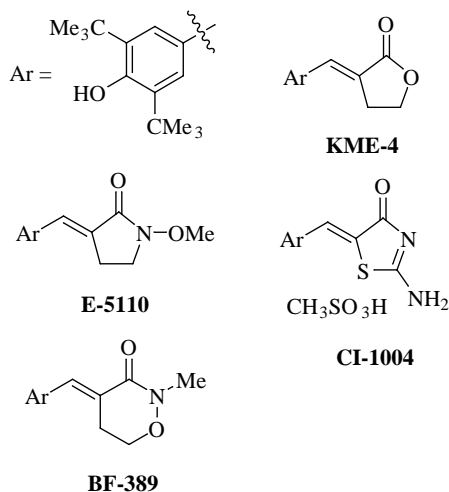


Fig. 1

Methotrexate, the clinical efficacy of which is thought to be related to its inhibitory activities on the production of inflammatory cytokines such as IL-1, IL-6, and TNF- α ¹³⁾ has been used as the first choice in drug therapy for RA. However, the possibility of drug side effects and difficulties in determining the adequate dosage demand particular caution and careful monitoring of patients.

From the pharmaco-economic viewpoint and the need for better compliance of patients with RA, an antiarthritic drug having both NSAID and disease modifying antirheumatic drugs (DMARD) activities with lesser adverse effects is desirable. The first promising agent was tenidap,¹⁴⁾ but its development had to be suspended due to some adverse effects.¹⁵⁾ What is needed is a drug which has multiple inhibitory effects on both COX, especially COX-2, and 5-LO, as well as on cytokine production.

To develop an alternative anti-arthritis agent with a tenidap-like profile, we conducted exploratory research focusing on antioxidant-based lead compounds having di-*tert*-butylphenol functionality, such as KME-4, E-5110, BF-389, and CI-1004. These antioxidants were chosen because they are known to inhibit both COX and 5-LO. Also, antioxidant drugs, as exemplified by the antiatherosclerotic drug probucol, display the possibility of suppressing cytokine production under inflammatory stimuli.¹⁶⁾ These compounds have the common structure of a 3,5-di-*tert*-butyl-4-hydroxy benzylidene moiety and five- or six-membered lactone or lactam rings. To

develop anti-inflammatory drugs in this area, we selected the sulfonyl group as an isostere of carbonyl function. Five- or six-membered sulfonamide ring systems are very unique and had not yet been prepared.

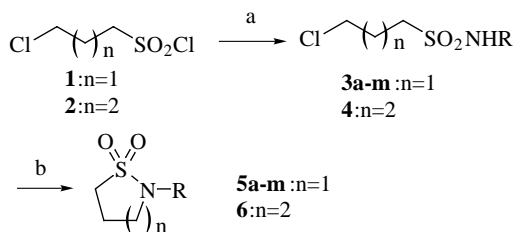
Our work led us to the discovery of novel anti-arthritis agents having the unique β -sultam skeleton with di-*tert*-butylphenol substituent as an antioxidant moiety. We conducted SAR study on the substituents at the 2-position of the β -sultam skeleton and the antioxidant moieties. We here report the synthesis and SAR study of the β -sultam derivatives, and the development of a new type of antiarthritic drug candidate, S-2474.

2. Structure-activity relationship studies

2.1 Chemistry

The compounds listed in Table 1 were synthesized by procedure A or B. Procedure A consists of the construction of an *N*-substituted- β -sultam ring¹⁷⁾ by cyclization of 3-chloropropanesulfonamide, followed by coupling with antioxidant aldehydes by an aldol-like reaction and dehydration to the benzylidene derivatives.

N-Alkyl- β -sultam derivatives **5a-m** (**a-m**, for structures see Table 1 and Scheme 3) were prepared in good yields from commercially available 3-chloropropanesulfonyl chloride (**1**) by reacting with various primary amines in the presence of a base, followed by treatment with sodium hydride (NaH) or diazabicycloundecene (DBU) as shown in Scheme 1.

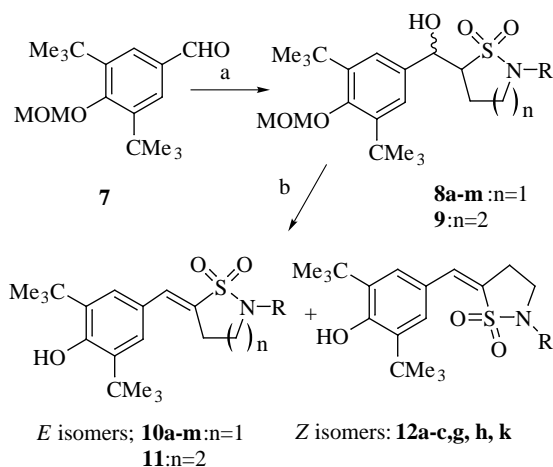
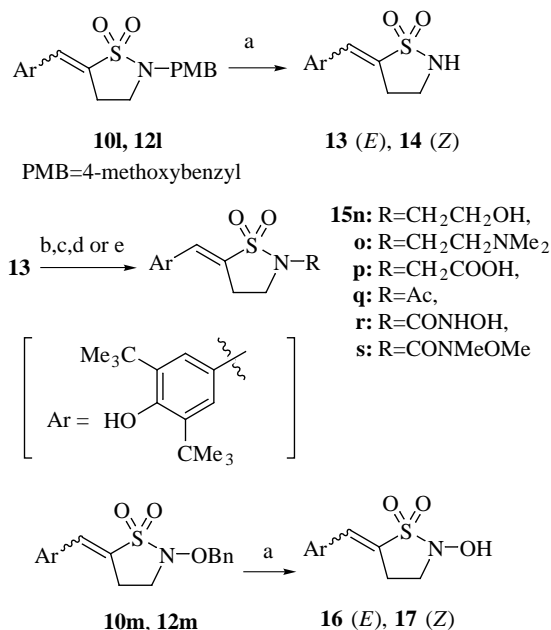


Scheme 1 ^a. ^a Reagents: (a) RNH₂, aq. K₂CO₃ or NaHCO₃; (b) NaH or DBU

The aldol-like condensation reaction of 3,5-di-*tert*-butyl-4-methoxymethoxybenzaldehyde (**7**) with *N*-alkyl- β -sultams **5a-m** in the presence of lithium diisopropylamide (LDA) in THF, smoothly proceeded to give the corresponding adducts **8a-m** as diastereo-isomeric mixtures. Treatment of the crude aldol adducts with a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) resulted in dehydration and removal of the methoxymethyl (MOM) group yielding a mixture of *E*- and *Z*-isomers of 5-benzylidene- β -sultam derivatives **10** and **12** as shown in Scheme 2. Their geometry of the double bond was determined by nuclear Overhauser effect (NOE) experiments¹⁸⁾ or X-ray crystallography.¹⁹⁾ In most cases, *E*-isomers **10a-m** were the major products and both isomers were separated by column chromatography on silica gel.

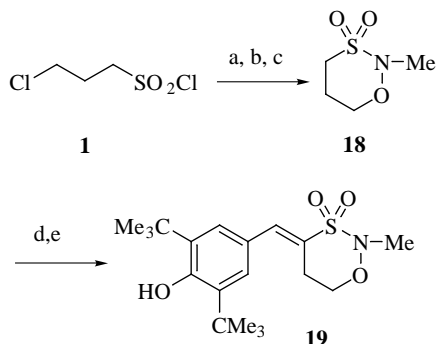
Compounds **20-24**, having other antioxidant moieties, with the structures shown in Table 3, were also prepared using procedure A. The corresponding protected aldehydes were coupled with *N*-ethyl- β -sultam **5b**, followed by the reaction with *p*-TsOH to give **20-24**.

Procedure B consists of construction of the *N*-protected-5-benzylidene- β -sultam derivative **13**, followed by deprotection and introduction of an alkyl or acyl substituent at the nitrogen atom as shown in Scheme 3. An isomeric mixture of 4-methoxybenzyl derivative **101** and **121** was prepared according to procedure A, and then the 4-methoxybenzyl group was removed with titanium tetrachloride (TiCl₄) to give **13** and **14** in good yield. *N*-Alkylated derivatives **15n** and **15o** were synthesized from the corresponding alkyl halides and **13** in the presence of sodium hydroxide. Carboxymethyl derivative **15p** was synthesized by hydrolysis of the corresponding ethyl ester, obtained by the coupling reaction of **13** and ethyl iodoacetate, using aqueous sodium hydroxide in methanol. Acetyl derivative **15q** was prepared by using Ac₂O in pyridine. Carbamoyl derivatives **15r** and **15s** were prepared by treatment of **13** with lithium hexamethyldisilazide (LHMDS) and the

Scheme 2^a. ^a Reagents: (a) **5a-m**, or **6**, LDA; (b) cat.*p*-TsOHScheme 3^a. ^a Reagents: (a) TiCl₄; (b) alkyl halide, aq.NaOH; (c) ethyl iodoacetate, K₂CO₃ then aq. NaOH in MeOH; (d) Ac₂O, pyridine; (e) LHMDS, phenyl carbamate

corresponding phenyl carbamates.²⁰ *N*-Hydroxy- -sultam derivatives **16** and **17** were prepared by removal of the benzyl group of an isomeric mixture of **10m** and **12m** with TiCl₄.

As a ring-expanded six-membered analog of the -sultam derivative, the -sultam derivative **11** was obtained starting from 4-chlorobutylsulfonyl chloride (**2**),²¹ similarly to the method used for the synthesis of -sultam derivatives in Scheme 1 and 2. As a sulfonamide isostere of BF-389, 1,3,2-oxathiazine derivative **19** was prepared as a major isomer from **1** by the procedure shown in Scheme 4 in moderate yield.



Scheme 4. Reagents: (a) MeNHOH, aq. K₂CO₃; (b) NaI; (c) DBU; (d) **7**, LDA; (e) *p*-TsOH

2.2 Biological results and discussions

For the primary screening, we used tenidap and indomethacin as reference compounds in the following *in vitro* assays: inhibitory activity against IL-1 induced PGE₂ production in rat synovial cells,²² calcium ionophore (A23187)-induced LTB₄ productions in rat peritoneal cells,^{22,23} and lipopolysaccharide (LPS)-induced IL-1 production in human THP-1 cells.²⁴ The compounds which showed sufficient *in vitro* potency were advanced to the secondary screening in the rat carrageenin-induced foot-pad edema model,²⁵ and some of the effective compounds were further evaluated by the rat adjuvant arthritic model.²⁶ Furthermore, the ulcerogenic activity^{25b} of compounds, which showed oral activity comparable to that of tenidap in these inflammatory model animals, was also assessed in rats. For the selected compound **10b** and reference compounds, the ratio of IC₅₀ against COX-2 / IC₅₀ against COX-1 *in vitro* assays²⁷ was calculated and their inhibitory activities of COX-1 and COX-2 were also assessed by *in vivo* assay.²⁸

2.2.1 *In vitro* primary screening assays

The results of inhibitory effects on PGE₂ production from *in vitro* assay by the synthesized compounds, containing the di-*tert*-butylphenol substituent, are summarized in Table 1. As for the substituents at the 2-position of -sultam, good inhibitory activity was obtained in the case of sterically small groups, such as hydrogen, hydroxy, methyl, ethyl, propyl, cyclopropyl methoxy, and acetyl, as illustrated by compounds **13**, **16**, **10a-c**, **10e**, **10k**, and **15d**. On the other hand, polar groups and large alkyl groups were not suitable for the 2-position as illustrated by compounds **10d**, **10f**, and **15a-c**. Carbamoyl derivatives **15e** and **15f** showed moderate effects. In the case of aromatic groups, 4-chlorophenyl derivative **10g** was also effective, but pyridyl derivatives **10h-10j** were not. As for the geometry of the double bond of the benzylidene groups, *E*- and *Z*-isomers showed a potency almost equal to that of the corresponding compounds. As for six-membered analogs, -sultam derivative **11** showed almost equal inhibitory potency to its corresponding five-membered -sultam derivative **10k**, but 1,3,2-oxathiazine derivative **19**, the sulfonamide isostere of BF-389, showed relatively weak activity.

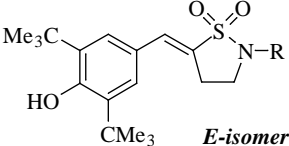
In vitro inhibitory effects on LTB₄ and IL-1 production of some selected compounds which showed good inhibitory effects on PGE₂ productions are summarized in Table 2. The compounds having the di-*tert*-butylphenol substituent and the -sultam skeleton with sterically small alkyl groups at the 2-position, showed better or nearly equal inhibitory activities compared with those of tenidap. However, the hydroxy derivative **16**, 4-chlorophenyl derivative **10g**, and -sultam derivative **11** showed lesser inhibitory activities on both LTB₄ and IL-1 production. As for the geometry of the double bond of the benzylidene groups, *Z*-isomers showed slightly stronger activities than those of the corresponding *E*-isomers.

Among the evaluated antioxidant phenol moieties, the di-*tert*-butyl phenol group was found to be the most effective in each of the *in vitro* assays as shown in Table 3, suggesting that the activities might be related to

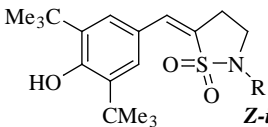
their free radical scavenging potency.

From the viewpoint of combined inhibition of PGE₂, LTB₄, and IL-1 production, compounds having the di-*tert*-butylphenol moiety and small alkyl groups on the 2-position of the β -sultam skeleton were found to show good biological activities.

Table 1. In vitro inhibitory effect on production of PGE₂ by 3,5-di-*tert*-butyl-4-hydroxy benzylidene- β - and γ -sultam derivatives and reference compounds.



E-isomer



Z-isomer

compd	R	E / Z	IC ₅₀ (μM) ^a	compd	R	E / Z	IC ₅₀ (μM) ^a
13	H	<i>E</i>	0.03	15r	CONHOH	<i>E</i>	0.024
10a	Me	<i>E</i>	0.0091	15s	CONMeOMe	<i>E</i>	0.1
10b	Et	<i>E</i>	0.0095	16	OH	<i>E</i>	0.01
10c	Pr	<i>E</i>	0.013	14	H	<i>Z</i>	<0.0010
10d	<i>i</i> -Pr	<i>E</i>	0.32	12a	Me	<i>Z</i>	<0.0010
10e	cyclo-Pr	<i>E</i>	0.0025	12b	Et	<i>Z</i>	0.0021
10f	<i>i</i> -Bu	<i>E</i>	0.41	12c	Pr	<i>Z</i>	0.012
10g	4-Cl-Ph	<i>E</i>	<0.0010	12g	4-Cl-Ph	<i>Z</i>	<0.0010
10h	2-pyridyl	<i>E</i>	1	12h	2-pyridyl	<i>Z</i>	4.4
10i	3-pyridyl	<i>E</i>	0.32	12k	OMe	<i>Z</i>	0.0025
10j	4-pyridyl	<i>E</i>	0.41	17	OH	<i>Z</i>	0.7
10k	OMe	<i>E</i>	<0.0010	11		<i>E</i>	0.0062
15n	CH ₂ CH ₂ OH	<i>E</i>	0.24	19		<i>E</i>	0.2
15o	CH ₂ CH ₂ NMe ₂	<i>E</i>	0.34				
15p	CH ₂ COOH	<i>E</i>	3.4	Tenidap ^b			0.053
15q	Ac	<i>E</i>	<0.0010	Indomethacin			0.0029

^a Concentration (μM) required for 50% inhibition of PGE₂ formation in rat synovial cells. ^b Tenidap was synthesized at our laboratories by a reported method.³²⁾

2.2.2 In vivo screening assays

The *in vivo* screening results are summarized in Table 4. In the *E*-isomers, the oral anti-inflammatory activities were found to be largely influenced by the substituent at the 2-position of the β -sultam skeleton, being limited to small alkyl or alkoxy groups such as methyl, ethyl, cyclopropyl, and methoxy. They exhibited anti-inflammatory effects on rat carrageenin-induced foot-pad edema and the rat adjuvant arthritic model at 30 mg/kg and 10 mg/kg po, respectively. However, *N*-aryl derivative **10g** and hydroxy derivative **16** were less active in the animal models, suggesting the importance of their inhibitory activity on IL-1 production. *Z*-isomers, showing more potent activities than the corresponding *E*-isomers in the *in vitro* assays, were found to be less effective than the *E*-isomers in the *in vivo* assays. We think these tendencies result from the low oral bioavailability of *Z*-isomers, because in the case of *N*-ethyl derivatives, no **12b** could be detected in the plasma after oral administration.²⁹⁾

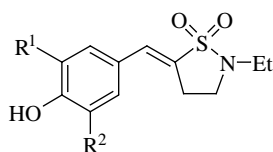
2.2.3 Further pharmacological evaluations

Next, three selected compounds **10a**, **10b**, and **10e**, and reference compounds were tested for their ulcerogenic activity as presented in Table 5. Most notably, in spite of the strong inhibitory effects on PGE₂

Table 2. In vitro inhibitory effects on production of LTB₄ and IL-1 by β - and γ -sultam derivatives and reference compounds.

compd	IC ₅₀ (μ M) ^a	
	LTB ₄	IL-1
13	>100	>100
10a	2.8	28
10b	2.5	10
10c	1.9	19
10e	3.2	9
10g	21	>100
10k	3	>100
15d	4.9	28
15e	6	20
15f	28	>100
16	9.5	90
14	1.8	27
12a	1.8	29
12b	2.5	10
12c	0.8	23
12k	1.5	20
11	74	56
Tenidap	45	16
Ind. ^b	>100	>100

^a Concentration (μ M) required for 50% inhibition of LTB₄ formation in rat peritoneal cells and IL-1 formation in human THP-1 cells. ^b Ind.: indomethacin

Table 3. In vitro inhibitory effects on production of PGE₂, LTB₄ and IL-1 by β -sultam derivatives with various antioxidant moieties.

compd	R ¹	R ²	IC ₅₀ (μ M) ^a		
			PGE ₂	LTB ₄	IL-1
10b	t-Bu	t-Bu	0.0095	2.5	10
20	i-Pr	i-Pr	>1.0	>100	>100
21	Me	Me	>1.0	21	>100
22	OMe	OMe	>1.0	2.6	>100
23	OMe	H	>1.0	>100	>100
24	H	H	>1.0	>100	>100

^a Concentration (μ M) required for 50% inhibition of production of PGE₂, LTB₄, and IL-1.

Table 4. In vivo antiinflammatory effects of - and -sultam derivatives and reference compounds.

compd	anti-edema (carrageenin)		anti-arthritis (adjuvant. proph.)	
	% inhib. 30 mg/kg ^a	ED ₃₀ mg/kg ^b	% inhib. 10 mg/kg ^c	ED ₃₀ mg/kg ^b
13	17.2		8.8	
10a	61.4**	5.4	39.4**	0.64
10b	49.4**	3.5	37.8**	0.76
10c	0.3		11.4	
10e	21.4*	11.9	32.9**	1.7
10g	6.3			
10k	26.5**	34.7	35.2**	2.4
15d	21.0**			
15e	14.9			
15f	11.2			
16	15.8*		3.6	
14	10.8			
12a	25.2**			
12b	7.3		11.4	
12c	11.2			
12k	6		5	
11	14.7			
Tenidap		4		1
Indomethacin		0.8		0.06

^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 Percent inhibition of adjuvant-induced arthritis at 10 mg/kg po. ^d The dose (mg/kg) required for 30% inhibition of adjuvant-induced arthritis. * $p < 0.05$, ** $p < 0.01$: significantly difference vs vehicle control.

Table 5. Ulcerogenic effects of selected compounds and reference compounds

compd	dose (mg/kg)	ulcer index (mm) ^a
10a	400	26.8 ± 4.92
10b	400	1.6 ± 0.41
10e	400	0.7 ± 0.28
Ind. ^b	30	19.5 ± 2.10
Tenidap	30	12.9 ± 2.38

^a Lengths of bleeding ulcer of drug-administrated group, 6 animals/group. ^b ind.: indomethacin. Details are given in the Experimental Section of reference 1a.

production, **10b** and **10e** showed little ulcerogenic activity compared with the reference compounds. Among these three compounds, *N*-ethyl derivative **10b** (S-2474) was selected as a candidate for further pharmacological evaluations because it has well balanced suppressive effects on PGE₂, LTB₄, and IL-1 productions without any ulcerogenic activities. To clarify this mechanism of lesser side effects despite its remarkable inhibitory effect on PGE₂ production, the inhibitory actions against COX-1 and COX-2 by **10b** were compared with selective COX-2 inhibitors, NS-398³⁰⁾ and celecoxib,³¹⁾ and the COX-1 and COX-2 inhibitor, indomethacin, in an *in vitro* system previously reported by Kawai et al.²⁷⁾ As shown in Table 6, **10b**, NS-398 and celecoxib were over 2000 times more potent against COX-2 than COX-1, but indomethacin was approximately equipotent as an inhibitor of COX-1 and COX-2. In addition, we assessed the inhibitory activity of **10b**, NS-398, tenidap and

Table 6. Comparison of IC₅₀ values of various NSAIDs for COX-1 and COX-2 in human intact cells.

compd	COX-1	COX-2	COX-1/COX-2
	TXB ₂ (μ M) ^a	PGE ₂ (μ M) ^b	ratio
10b	27	0.011	2500
NS-398 ^c	6.8	0.0019	3600
Celecoxib ^d	19	0.0079	2400
Ind. ^e	0.0058	0.0046	1.3

^a Concentration (μ M) required for 50% inhibition of TXB₂ production in human platelet cells.

^b Concentration (μ M) required for 50% inhibition of PGE₂ production in human IL-1 stimulated synovial cells. Details of these assays are described in the Experimental Section. ^{c,d} NS-398 and celecoxib were synthesized at our laboratories by reported methods.^{33,31} ^e Ind.: indomethacin

Table 7. Comparison of ED₅₀ values of various NSAIDs for COX-1 and COX-2 activities in rats.

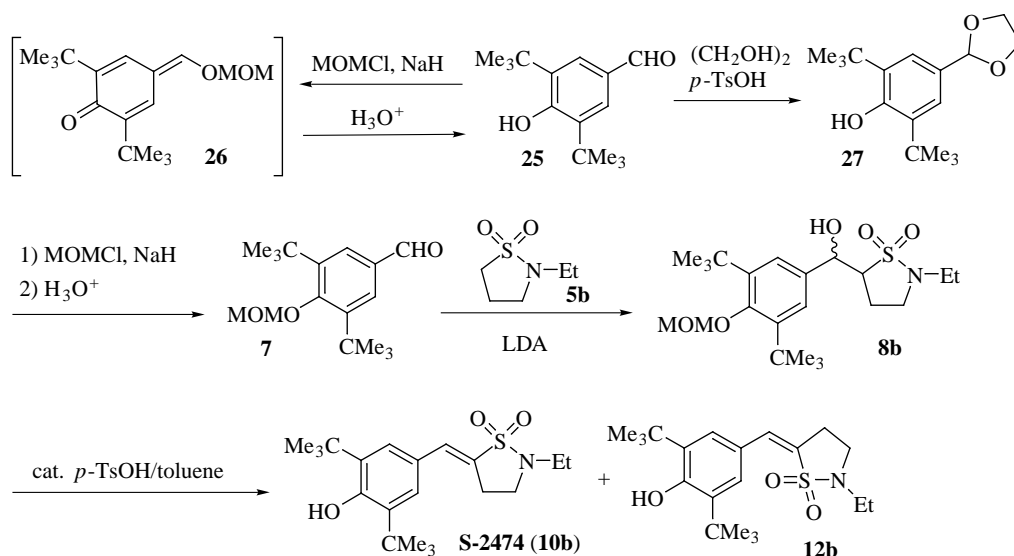
compd	ED ₅₀ value (mg/kg) ^a	
	COX-1 (a)	COX-2 (b)
10b	>30	3.19
NS-398	>30	1
Tenidap	0.025	0.05
Ind. ^b	0.37	0.15

^a ED₅₀ values required for 50% inhibition of increase in plasma PGE₂ level after arachidonic acid (AA) injection into non-LPS treated rats (a) and LPS-treated rats (b). Details of these assays are described in the Experimental Section of reference 1a. ^b Ind.: indomethacin

indomethacin against COX-1 and COX-2 in the *in vivo* system previously described by Futaki et al.²⁸ **10b** and NS-398 selectively inhibited COX-2, while tenidap and indomethacin suppressed both COX-1 and COX-2 activities (Table 7). These results indicate that **10b** is a highly selective COX-2 inhibitor.

3. Practical synthesis of S-2474

Structure-activity relationship studies were conducted by synthesizing various benzylidene-1,2-isothiazoline-1,1-dioxides (β -sultams) using an aldol-type reaction of β -sultams and corresponding aldehydes having hydroxy groups protected with a methoxymethyl (MOM) group.^{1a} These procedures were very effective for preparing a wide range of substrates for preliminary biological evaluation. With the identification of **10b** as an antiarthritic drug candidate, a more focused synthetic approach was needed. The previous synthetic procedure (Scheme 5) poses some problems for the large-scale production of S-2474 required for clinical development. One problem is that the protection and deprotection procedures of the formyl group required introduction of 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, thus leading to the favoring of quinone enolate form. Moreover, MOMCl, suspected to be a carcinogen, is unavoidable because MOM ether is the most suitable protecting group with minimal bulkiness and stability against nucleophiles and strong bases. Another problem is that the dehydration and deprotection reaction with a catalytic amount of *p*-TsOH as the last step provided a mixture of *E*- and *Z*- benzylidene sultams as described in



Scheme 5

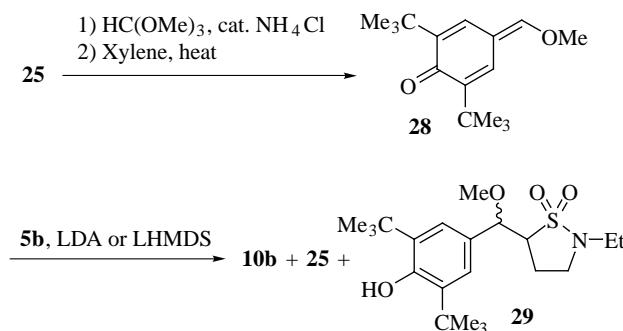
Scheme 5. In this chapter, we report an efficient short-step synthesis of S-2474 (**10b**) using a unique quinone methide derivative **28** as the key intermediate, along with mechanistic discussions on the key reaction of this synthesis.

3.1 Chemistry

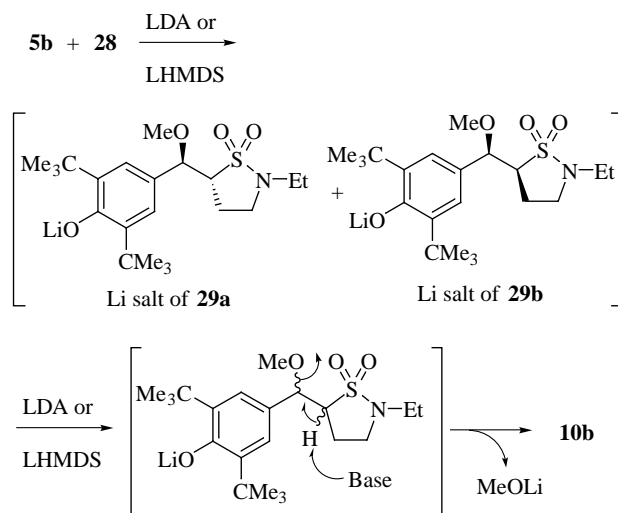
In order to improve the synthesis of **10b**, we focused on quinone methides (QMs) as an equivalent of protected *p*-hydroxybenzaldehyde derivatives. QM derivative **26** was detected by NMR analysis when 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**25**) was allowed to react with MOMCl without any protection of its formyl group. QMs³⁴ are known to be good Michael acceptors of nucleophiles such as dienes,³⁵ alcohols,³⁶ phosphates,³⁷ carbanions³⁸ and DNA.³⁹ However, to our knowledge, there has been no example of their use as an equivalent of the protected *p*-hydroxybenzaldehyde derivatives. First, we tried a reaction of 2,6-di-*tert*-butyl-4-hydroxyquinone methide (**28**) which was simply prepared from thermal decomposition of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde dimethyl acetal,³⁶ and *N*-lithio *N*-ethyl-sulfam as a carbon nucleophile. *N*-Lithio *N*-ethyl-sulfam was prepared from *N*-ethyl-*N*-sulfam (**5b**) and 1.2 equivalents of LDA at -78°C and then treated with 1 equivalent of **28**. Interestingly, we obtained not only the 1,6-addition adduct **29** but also **10b** after 1-hour stirring (Scheme 6 and entry 1 in Table 8).

To our surprise, no *Z*-isomer **12b** could be detected in the reaction mixture by NMR analysis. We think **10b** was formed from the 1,6-addition adduct **29** by deprotonation with slight excess base following elimination of MeOLi as presented in Scheme 7.

To find proof for this hypothesis, the reaction was carried out with 2 equivalents of LDA to **5b** and **28**. As expected, **10b** was obtained in good yield with excellent *E*-selectivity (entry 2). To reduce the cost of the synthesis of **10b**, 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 at 0°C (entry 4), other bases such as NaHMDS and KHMDS also gave poor results (entry 5, 6). In each case, a significant amount of **25** was obtained. These results were presumed to occur due to bases such as NaHMDS, KHMDS, and LDA attacking **28** because of their slightly stronger nucleophilicity than that of LHMDS, with their adducts being hydrolyzed to **25** after aqueous working-up.⁴⁰ To investigate the solvent effects on this reaction, the non-polar solvent toluene was



Scheme 6



Scheme 7

Table 8. Reactions of Quinone Methide and α -Sulfonylcarbanion^a

entry	Base	Temp. ($^{\circ}$)	Time (h)	Product (ratio) 10b : 25 (: 29)	Yield of 10b (%)
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 ^c
5	NaHMDS	0	1	1 : 1 ^b	
6	KHMDS	0	1	1 : 2 ^b	

^a All reactions were carried out in THF with **28** : **5b** : base = 1 : 1.2 : 2.4 except for entry 1 (the ratio of **28** : **5b** : 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.

used instead of THF. The reaction with LHMDS did not proceed smoothly in toluene as a sole solvent (entry 1 in Table 9), but better results were obtained in a combination of toluene and THF, with a ratio of toluene/THF of more than 4:1 giving satisfactory results (entry 3, 4). In the mixed solvent system, LHMDS was revealed to be the best of several bases shown in Table 10. Next, we tried to optimize the reaction temperature in this solvent system with LHMDS as a base (Table 11). The reaction was carried out at -15°C , to minimize the formation of by-products **25** and **12b** at lower temperature, to afford the intermediate 1,6-addition adduct **29** in 3% yield because the reaction proceeded more slowly than at 0°C , but at 23°C gave the *Z*-isomer **12b** in 4% yield as the major by-product. The other leaving groups of QMs, OEt or Cl⁽¹⁾ gave no better results (50 and 38% yields, respectively) (Table 12). The optimized reaction conditions from these experiments and details are given in the Experimental Section of reference 2a. We were able to obtain **10b** of high quality (>99.9% by HPLC

Table 9. Effects of Solvents on Product Ratio^a

Entry	Ratio toluene : THF	Products (ratio) 10b : 25
1	toluene only	slaggy
2	2 : 3	15 : 1 ^b
3	4 : 1	50 : 1 ^b
4	5 : 1	97.3 : 1.4 ^c

^a All reactions were carried out with **28** : **5b** : LHMDS = 1 : 1.2 : 2.4 at 0°C for 1 to 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 10. Effects of Several Bases on Product Ratio^a

entry	Base	Time (h)	Products (ratio) 10b : 25
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 **28** : **5b** : 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.

Table 11. Effects of Reaction Temperature on Product Ratio^a

entry	Temp. ($^{\circ}\text{C}$)	Products (ratio) 10b : 12b : 29
1	0	97.3 : 1.3 : 0.1 ^b
2	-15	97 : : 3 ^c
3	23	96 : 4 : : ^c

^a All reactions were carried out with **28** : **5b** : LHMDS = 1 : 1.2 : 2.4 for 2 to 4 h in toluene - THF (5 : 1). ^b Ratio determined by HPLC analysis of the crude reaction mixture. ^c Ratios determined by NMR analysis of the crude reaction mixture.

Table 12. Effects of Leaving-Group (LG) of QMs on Yield

entry	LG ^a	yield (%) ^b
1	OMe	80
2	OEt	50 ^c
3	Cl	38 ^d

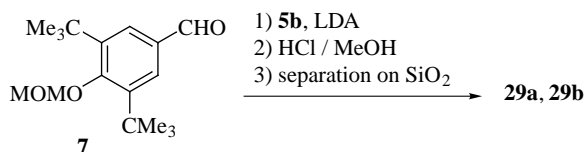
^a QMs having OEt or Cl were synthesized as described in the Experimental Section of reference 2a.

^b Isolated yields of **10b**. Reactions were all carried out in toluene - THF (5 : 1) at 0 °C. ^c The reaction was slow compared to LG = OMe. ^d The reaction gave a larger amount of *Z*-isomer and other by-products.

analysis) in 80% yield after a single crystallization.

3.2 Mechanistic studies

Studies were done on the reaction details. Careful monitoring of this reaction revealed that the intermediate 1,6-addition adduct **29** was observed when the reaction was stopped before completion. Remarkably, diastereomer **29a** was almost exclusively obtained with only a trace amount of diastereomer **29b**. The stereochemistry of **29a** was determined as the *threo* form by single X-ray crystallography.⁴²⁾ These results suggested that the *erythro* adduct **29b** rapidly changed to **10b** but the *threo* **29a** did so only slowly. In fact, when the *threo* **29a** and the *erythro* **29b**, which were synthesized by the method described in Scheme 8, were separately treated with LHMDS, the *erythro* **29b** changed to **10b** in a ratio of 10:1 within 1.5 hours, but the *threo* **29a** changed to **10b** as 6:1 over 4 hours.

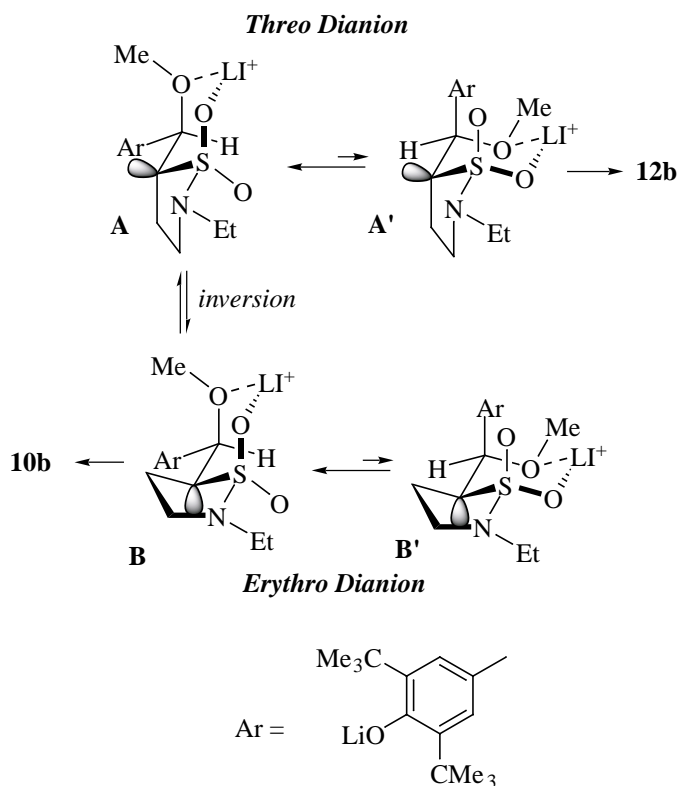


Scheme 8

Another question remained: *why was the E-isomer formed selectively?* Although the reasons for this have not yet been established, we assume that the reaction proceeds *via* 6-membered, chair-form dianions shaped by fixed SO₂-Li-OMe chelation with a bulky substituent at 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 β -sulfonylcarbanions are thought to have pyramidal structures and the counter cation is bound to the oxygen of the sulfonyl group and solvents, not to the carbanionic center.⁴³⁾ Intermediate **29b** is suitable for *anti*-elimination with the bulky aryl substituent at the equatorial position, but **29a** cannot assume a suitable conformation for *anti*-elimination with the bulky substituent at the equatorial position as shown in Figure 2. In the case of **29a**, the chelated dianion (**A**) may change slowly with inversion of configuration of the carbanion center^{43a,44)} to a more suitable dianion (**B**), followed by *anti*-elimination of MeOLi to give the *E*-isomer.⁴⁵⁾ This assumption is supported by the fact that the reaction (**29a, b** → **10b**) did not proceed in the presence of HMPA, which intercepts the formation of the 6-membered dianion intermediate formed by SO₂-Li-OMe chelation.⁴⁶⁾

4. Summary

We have described the synthesis of novel β -sultam derivatives containing the di-*tert*-butylphenol antioxidant moiety. Several compounds with lower alkyl groups at the 2-position of the β -sultam skeleton

Fig. 2. Mechanistic Proposal for *E*-Selectivity

showed potent inhibitory activities against PGE₂ production via the COX pathway and LTB₄ production via the 5-LO pathway, as well as production of IL-1 in *in vitro* assays. Extensive pharmacological characterizations revealed that the 2-ethyl-*o*-sultam derivative **10b** displays multiple inhibition of COX, 5-LO, and IL-1 production similar to tenidap and also good selective COX-2 inhibition like NS-398 and celecoxib. It exerted excellent anti-inflammatory activity without any ulcerogenic effects and was designated as S-2474, an agent having both NSAID and cytokine modulating properties. S-2474 is now being developed as a promising alternative anti-arthritis drug candidate.

We have also described the improved short-step synthesis of the antiarthritic drug candidate S-2474 with high *E*-selectivity, which is the first example of a relatively stable *o*-methoxyquinone methide being used as an equivalent of the protected *p*-hydroxy benzaldehyde. This procedure resolves the problems arising from the protection/deprotection procedures of the formyl group and the dehydration/deprotection reaction with *p*-TsoH and gives S-2474 of high quality after a single crystallization.

Acknowledgements

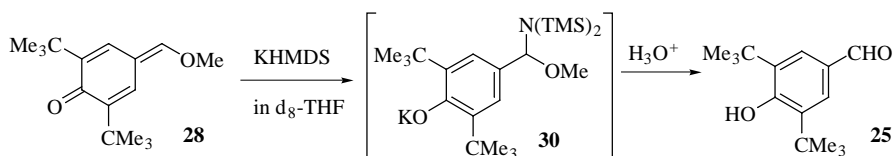
We wish to dedicate this small article with the greatest respect and gratitude to all the people who participated in the development of S-2474. This work is the compilation of collaborations with Dr. Takashi Ono, Katsutoshi Yamada (*in vitro* assay), Hirokuni Jyoyama, Mika Kobayashi, Dr. Yozo Hori, Dr. Akinori Arimura, Dr. Kiyoshi Yasui (*in vivo* assay), Hiroshi Nakai (X-ray), Dr. Masanori Nishiuchi (pharmacokinetics), Dr. Nobuhiro Haga, Makoto Kobayashi, Naoki Ohta, Dr. Susumu Kamata (synthesis). The authors thank Drs. Mitsuaki Ohtani, Hitoshi Arita, Kenji Kawada, Toshiro Kounoike, Hirohisa Kondou, and Saichi Matsumoto for their encouragements and helpful discussions throughout this study.

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