Applications of Lewis Acids for the Efficient Syntheses of Diltiazem, Cephems, and Taxoids

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Abstract: An efficient method is described for preparation of diltiazem hydrochloride (Herbesser®), a marketed calcium antagonist widely used for the treatment of ischemic heart disease. In the reaction of 2-nitrothiophenol (**1**) with *trans*-3-phenylglycidic esters (**2**) carrying various substituents on the benzene ring, both reactivity and stereoselectivity of the oxirane ring-opening of the glycidates were markedly influenced by the electronic nature of the substituents. As a result of our investigation on the catalytic effect of various Lewis acids in the reaction of **2a** with **1**, tin compounds were found to be effective catalysts for the *cis*-opening and readily produced the *threo*-nitro ester (**3a-*t***), a key intermediate for the synthesis of diltiazem. Isolation of the crystalline complex from the reaction of **1** and $SnCl_4$; and its efficient catalytic activity similar to that of $SnCl_4$ suggests that the transition state involves co-coordination of tin derivatives both with **1** and the epoxy oxygen of **2a** to result in highly specific *cis*-opening. We have also amplified this chemistry into other fields, leading to applications in the syntheses of cephem and taxoid templates. Med Res Rev, 20, No. 6, 485–501, 2000

Key words: diltiazem; calcium antagonist; Lewis acid; oxirane ring-opening; stereoselectivity; 3-phenylglycidic ester; 2-nitrothiophenol; cephem; taxoid

1. INTRODUCTION

Diltiazem (Herbesser®),[1] a representative calcium antagonist widely used for the treatment of ischemic heart disease, was derived from a lead compound found in an original random screening test and developed by Tanabe researchers. Diltiazem possesses two continuous stereocenters at C-2 and C-3 on 1,5-benzothiazepine skeleton as shown in Figure 1. The coronary vasodilating activity of 1,5-benzothiazepine derivatives was greatly influenced by the stereochemistry of the 2- and 3- substituents. Namely, among the four possible stereoisomers, only the *d-cis*-isomer exhibits potent activity. Consequently, 2,3-*cis*-lactam (**4a-*t***) is a key intermediate for the synthesis of diltiazem. Our prior work has shown that reaction of the *trans*-3-(4-methoxyphenyl)glycidic ester (**2a**) with 2-nitrothiophenol (**1**) mainly gives the *threo*-nitro ester (**3a-*t***), the *cis*-product resulting from front-side opening of the oxirane ring, after prolonged heating in MeCN.[2]

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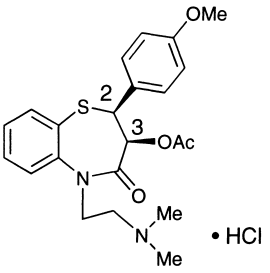


diltiazem hydrochloride (Herbesser®)

Figure 1. Structure of diltiazem.

However, this procedure suffers from flaws such as low yield (<60%), insufficient stereoselectivity, and long reaction time, which have been obstacles in the synthesis of diltiazem. The reaction of **1** and **2a** in the presence of a catalytic amount of $NaHCO_3$, on the other hand, readily gave the undesired *erythro*-isomer (**3a-*e***), the *trans*-opening product resulting from back-side S_N2-type attack of thiolate anion as shown in Figure 2. Classical organic synthesis teaches that epoxides are attacked by nucleophiles via S_N2 mechanism. No stereoselective *cis*-opening of epoxides is currently known.

2. IMPROVEMENTS IN THE SYNTHESIS OF DILTIAZEM

The most important step in the synthesis of diltiazem is the reaction of **2a** with **1** to form the *threo*-nitro ester (**3a-*t***). On the other hand, the mode of opening of the *cis*-glycidic ester (**5a**) and the

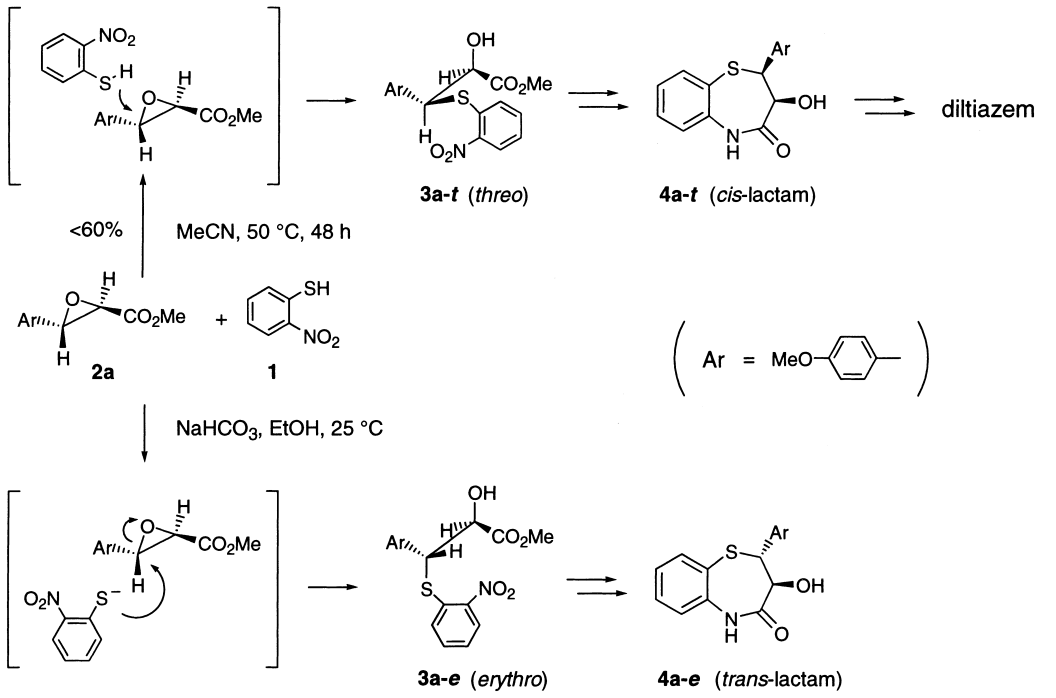


Figure 2. Previous method for the preparation of diltiazem.

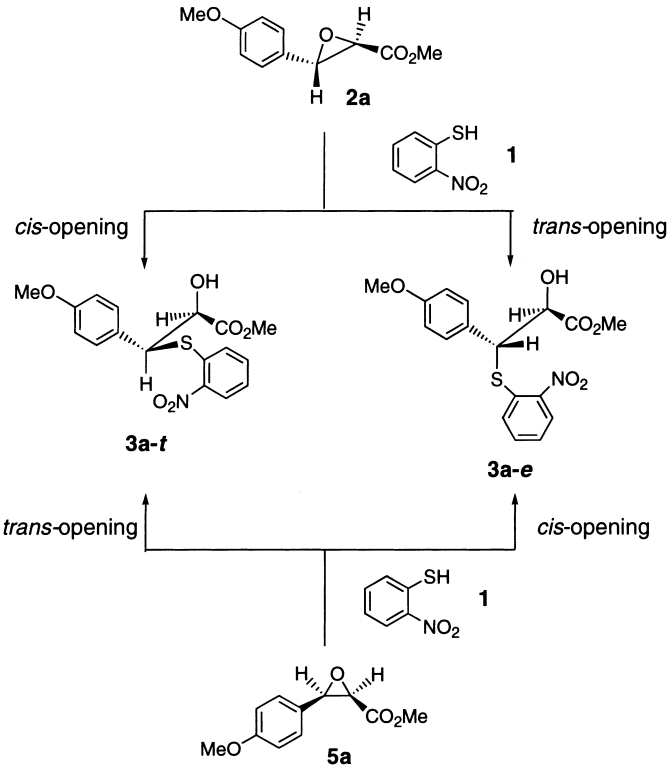


Figure 3. Mode of opening of the glycidic esters.

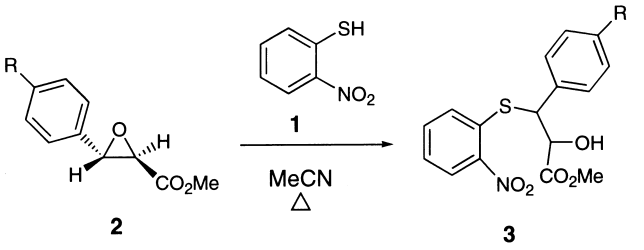
stereochemistry of the product is opposite to those of the *trans*-glycidic ester. Thus, *cis* and *trans* openings of the *cis*-glycidic ester are expected to yield the *erythro* and *threo* isomer, respectively as shown in Figure 3. However, it is difficult to synthesize *cis*-glycidic esters. Therefore, we have investigated *cis*-opening of the *trans*-glycidic ester, which is readily prepared by Darzen's reaction.

A. The Effect of Substituents on the Benzene Ring of trans-3-Phenylglycidic Esters

The reaction of 2-nitrothiophenol (**1**) with *trans*-3-phenylglycidic esters (**2**) carrying various substituents on the benzene ring was examined in MeCN at 50°C, and the results are summarized in Table I.[3]

Both the reactivity and stereochemistry of ring-opening of these glycidates were markedly influenced by the electronic nature of their substituents. Thus, in the case of glycidates with electron-withdrawing substituents[3] or without a substituent (**2d**), no reaction was observed under these conditions. The ester (**2c**) with a 4-methyl substituent scarcely reacted, and the *cis*/*trans* ratio of the oxirane ring-opening reaction (*threo*/*erythro* ratio of the product) was *ca.* 1. On the other hand, the 4-methoxy and 4-thiomethyl analogues (**2a** and **2b**) reacted more smoothly, and gave the *cis*-opening product with moderate selectivity (*cis*/*trans* ratio 3). Therefore, both the reactivity and *cis*/*trans* ratio of oxirane ring-opening of these glycidates mutually related with the substituent constants—values, not-values. In other words, the transition state of the reaction of these glycidates have a carbocationic character on the benzylic carbon.

Table I. Reaction of *trans*-3-Arylglycidates (**2**) with **1** in MeCN



2	*R*	σ	σ^+	*Yield of* **3** *(%)*	**3-*t*/3-*e***
2a[a]	4-MeO	−0.27	−0.78	85	3.0
2b[b]	4-MeS	0	−0.60	47	3.1
2c[b]	4-Me	−0.17	−0.31	21	1.2
2d[a]	H	0	0	—[c)]	

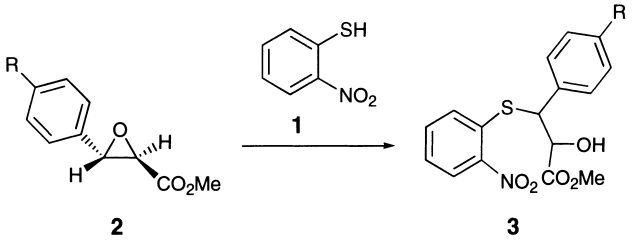
Reaction conditions: [a]50°C, 48 h.
[b]reflux, 20 h.
[c]Nitroester was not obtained.

B. Effect of Catalysts

Our prior work has shown that the reaction of unsubstituted 3-phenylglycidic ester (**2d**) with **1** in the presence of $BF_3 \cdot Et_2O$ gave a low yield of the *trans*-opening product. On the other hand, similar reaction of the 4-methoxy analogue (**2a**) with **1** was found to proceed very rapidly and gave the *cis*-opening product (**3a-*t***) as the major product. However, the stereoselectivity was still unsatisfactory. The results of some ring-substituted glycidates with **1** are summarized in Table II.[3] The unfavorable effect of electron-withdrawing substituents on both the reactivity and the *threo*/*erythro* ratio was still observed under these conditions.

Encouraged by the promising catalytic effect of $BF_3 \cdot Et_2O$ on the reaction of the 4-methoxy derivative (**2a**), we examined a wide variety of Lewis acids as well as Brønsted acids as catalysts in this reaction to obtain better stereoselectivity (Table III).[3] Brønsted acids such as sulfuric acid and

Table II. Reaction of *trans*-3-arylglycidates (**2**) with **1** in the Presence of Catalytic Amounts of $BF_3 \cdot Et_2O$



2	*R*	*Conditions*	*Yield of* **3** *(%)*	**3-*t*/3-*e***
2a	4-MeO	Et_2O, r.t., 0.3 h	69	4.2
2d	H	Et_2O, r.t., 22 h	36	0.68
2e	4-Cl	Dioxane, 50°C, 72 h	11	0/1

Table III. Reaction of Methyl 3-(4-methoxyphenyl)glycidate (**2a**) with 2-nitrothiophenol (**1**) in the Presence of Catalytic Amount of Various Acids

Entry	*Catalyst*	*Solvent*	*Temp. (°C)*	*Time (h)*	*Isolated yield of* **3a** *(%)* **3a-*t***	**3a-*e***	**3a-*t*/3a-*e*** *(whole product)*
1)	—	MeCN	50	48	56		3.0
2)	c-H_2SO_4	Dioxane	10	0.15	43	15	
3)	$HClO_4$	Dioxane	10	0.15	48	18	
4)	BF_3-Et_2O	Et_2O	15	0.3	51	12	4.2
5)	$ZnCl_2$	Dioxane	15	1	50	25	
6)	$MgCl_2$	Dioxane	r.t.	40		65	
7)	$CaCl_2$	Dioxane	r.t.	40		63	
8)	$SnCl_4$	Dioxane	r.t.	20	69		6.7
9)	$SnBr_4$	Dioxane	r.t.	20	63		
10)	SnI_4	Dioxane	r.t.	20	63		
11)	$SnCl_2$	Dioxane	r.t.	20	69		
12)	SnI_2	Dioxane	r.t.	20	68		
13)	SnF_2	Dioxane	r.t.	20	72		
14)	$Sn(OCOC_7H_{15})_2$	Dioxane	r.t.	20	74(82)[a]		9.3
15)	$Sn(OCOC_7H_{15})_4$	Dioxane	r.t.	20	50		
$TiCl_4$, $TiCl_3$, $FeCl_2$, $FeCl_3$, $AlCl_3$, CuCl, $CuCl_2$, $CdCl_2$, $NiCl_2$, $SbCl_3$, $SbCl_5$, $BiCl_3$, $PdCl_2$, TlCl, CsCl, $SnSO_4$, SnO, SnO_2, SnS, $Sn(OCOC_{11}H_{23})_2$, $Sn(OCOC_{15}H_{31})_2$, Sn(OCOCOO), $(Bu_3Sn)_2O$, $(Bu_3Sn)_2S$							ineffective

[a]Corrected yield based on the purity of **3a-*t*** which was determined by titration.

70% aqueous perchloric acid were effective in acceleration of the reaction, but the *threo*/*erythro* ratio of the product was not improved. Surprisingly, $MgCl_2$ readily gave the *trans*-opening product.

Finally, $SnCl_4$ was found to exhibit good catalytic activity with a much improved yield of *cis*-opening product. Both stannous[tin(II)] and stannic[tin(IV)] halides were effective regardless of the nature of the halogen groups. Some carboxylates of tin such as stannous 2-ethylhexanoate were also effective catalysts. Other Lewis acids listed in Table III had no catalytic effect.

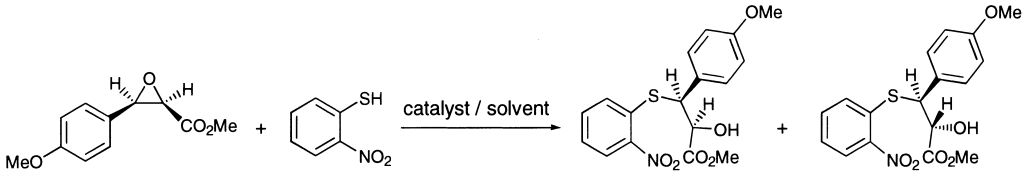
C. Reaction of cis-3-Phenylglycidate (5a) with Thiophenol (1)

We investigated the reaction of *cis*-3-(4-methoxyphenyl)glycidate (**5a**) with ***1*** under various conditions. This results obtained are summarized in Table IV together with the comparative data for the corresponding *trans*-glycidate (**2a**).[4] In the absence of a catalyst, the reactivity and stereoselectivity of the oxirane ring-opening of *cis*-glycidate (**5a**) was lower than those of *trans*-analogue (**2a**). With regard to the effect of catalyst, $BF_3 \cdot Et_2O$ greatly accelerated the reaction of the *cis*-glycidate (**5a**), but the stereoselectivity ramained as low as that in the reaction without catalyst. In contrast, stannous 2-ethylhexanoate showed good catalytic activity with a high *cis*-opening ratio (23.5). The $NaHCO_3$-catalyzed reaction of **5a** proceeded mainly by *trans*-opening, but the selectivity was not as one-sided as that seen with the *trans*-glycidate (**2a**). $MgCl_2$ showed no catalytic effect.

D. Isolation of Adducts of $SnCl_4$ with Thiophenol (1) and the Reaction Mechanism

We attempted to clarify the unique role of tin catalysts in effecting the highly stereospecific *cis*-opening of **2a** with ***1***. When we employed *cis*-glycidate, tin-compounds and $BF_3 \cdot Et_2O$ Lewis acids

Table IV. Reaction of methyl *cis*-3-(4-methoxyphenyl)glycidate (**5a**) with **1**[a]



5a **1** **3a-*t*** (*trans*-opening) **3a-*e*** (*cis*-opening)

Entry	*Solvent*	*Catalyst*	*Temp,*	*Time (h)*	*Yield of* **3** *(%)*	*cis-opening/trans-opening*
1)	MeCN	—	55°C	96 (72)	64 (85)	0.62 (3.0)
2)	Dioxane	$Sn(OCOC_7H_{15})_2$	r.t.	18 (19)	84 (82)	23.5 (9.3)
3)	Dioxane	$BF_3 \cdot Et_2O$	r.t.	5 (0.3)	75 (69)	0.75 (4.2)
4)	EtOH	$NaHCO_3$	r.t.	96 (18)	31 (80)	0.35 (0/1)
5)	Toluene	$MgCl_2$	r.t.	17 (16)	9 (65)	0.63 (0/1)

Values in the parentheses are results obtained in the reaction of the corresponding *trans*-glycidate (**2a**).

showed different catalytic character. Therefore, we speculated that the tin-compounds participate by coordinating with both glycidate and thiophenol (**1**). When 2-nitrothiophenol (**1**) was allowed to react with $SnCl_4$ in a 2:1 molar ratio in toluene at room temperature, a yellow crystalline adduct was obtained. The yellow crystalline adduct was recrystallized from dry benzene to give yellow crystals (adduct A), whose elemental analysis and i.r. spectral data appear to indicate that this adduct is a compound **7** as shown in Figure **4**.[3] When the adduct A (**7**) was repeatedly recrystallized from dry benzene more than three times, it rearranged to the adduct B, whose elemental analysis and i.r. spectral data appear to indicate that this adduct is a compound **8**.

At any rate, addition of a catalytic amount (0.8 mol%) of adduct A to the mixture of **1** and **2a** in toluene at room temperature readily gave a 68% yield of the *threo*-nitro ester (**3a**) with a good *threo*/*erythro* ratio of the whole product (9.2) as shown in Figure 5.[3] Thus, the catalytic effectiveness of adduct A was quite similar to that of $SnCl_4$ in both stereoselectivity and reactivity. In addition, the reaction of adduct A with two equivalents of **2a** in toluene at room temperature proceeded exceedingly fast and gave the *threo*-isomer (**3a-*t***) in 46% yield within 10 min. The low yield appears to suggest that the coordinated thiol group in adduct A is utilized in the reaction. On the other hand,

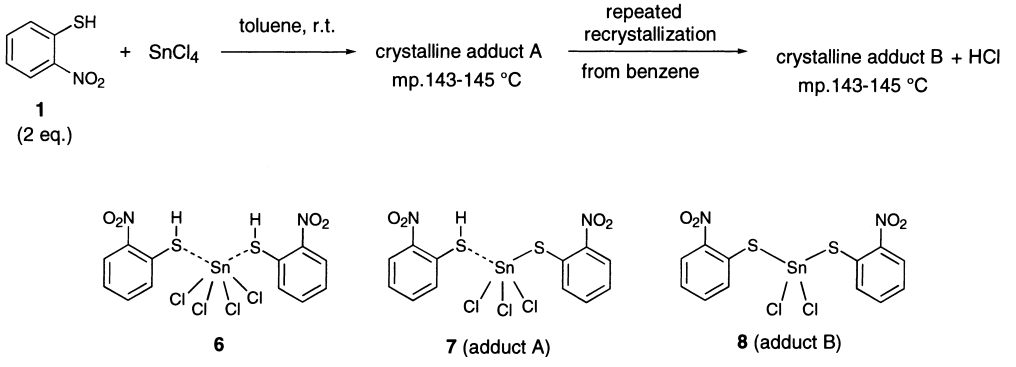


Figure 4. Isolation of adducts of $SnCl_4$ with nitrothiophenol (**1**)

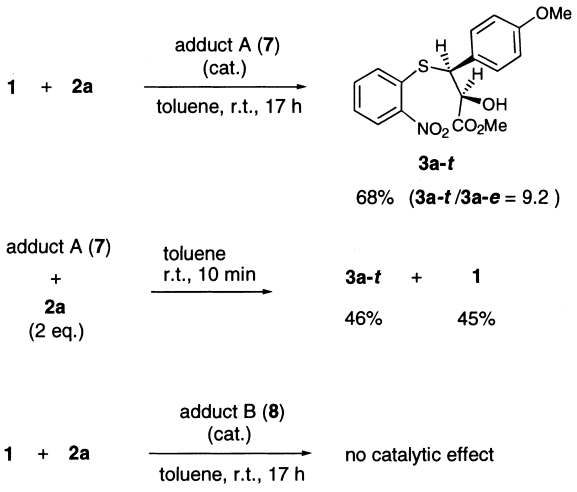


Figure 5. Reactivity of tin-adducts.

adduct B differed markedly from adduct A in its reactivity and showed no catalytic activity. The above results suggest that the catalytically active species in the $SnCl_4$-catalyzed reaction of **2a** with **1** are the tin-2-nitrothiophenol complexes (**6** and/or **7**). Therefore, the thiol group coordinated with tin may play an important role, while an ionically linked thiol group may not.

In conclusion, it appears likely that the balanced coordination of tin with both 2-nitrothiophenol and the oxygen atom of the oxirane ring **2a** leads to the formation of plausible transition states (**9** and **10**). These transition states would provide suitable geometry in the reactants for selective *cis*-opening as well as electronic activation of the oxirane ring in the transition state, leading to highly stereoselective formation of the *threo*-nitro ester (**3a-*t***) and *erythro*-nitro ester (**3a-*e***) respectively.

E. Contribution on the Process Improvement

As described in the previous section, the earlier method of oxirane ring-opening of **2a** resulted in desired *cis*-opening (*threo*-isomer **3a-*t***) as well as concomitant formation of the unwanted *erythro*-

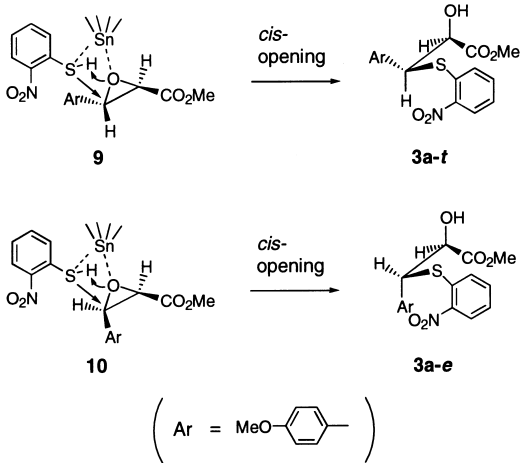


Figure 6. The reaction mechanism.

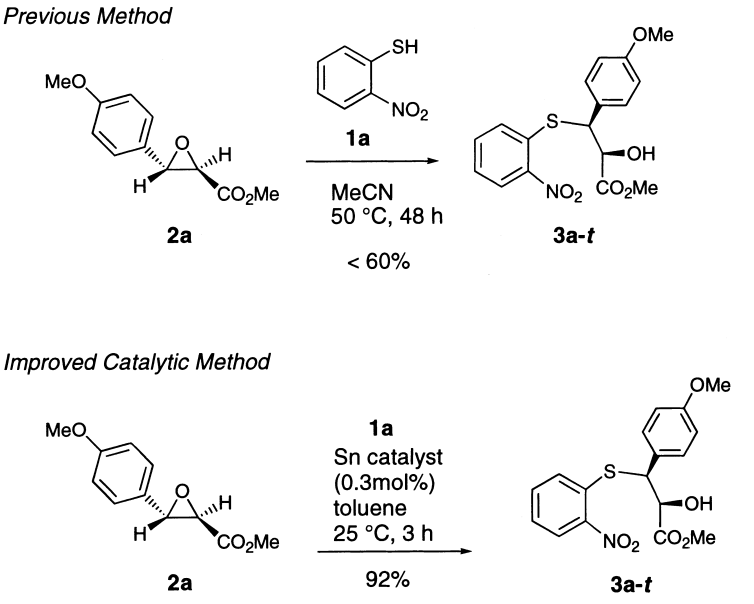


Figure 7. Previous method and catalytic method.

isomer (**3a-*e***) as a minor product. Moreover, the reaction required an extremely long time. On the other hand, the present catalytic method gave a 92% yield of *threo*-nitro ester (**3a-*t***) and the starting materials (**1** and **2a**) were completely consumed within 3 h at room temperature.

3. APPLICATION

A. Reaction of Glycidate (2a) with 2-Nitrophenol (11) and Synthesis of 1,5-Benzoxazepine Derivatives

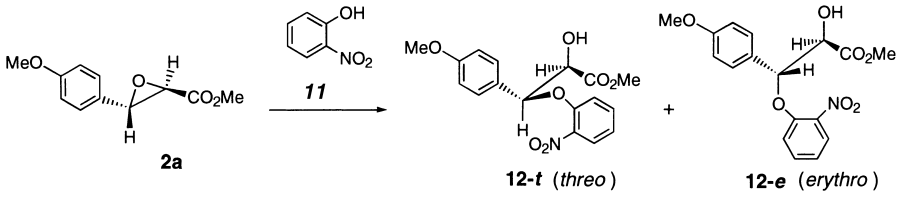
The reaction of glycidate (**2a**) with 2-nitrophenol (**11**) was investigated under various conditions as shown in Table V.[5] Generally, the reaction proceeded predominantly by *cis*-opening of the oxirane ring of **2a** to give the *threo*-nitro ester (**12-*t***). Especially, $MgCl_2$ showed excellent catalytic activity in this reaction. On the other hand, tin-compounds showed little catalytic effect in the reaction with 2-nitrophenol (**11**). This is probably because of the difference in affinity of the catalysts to sulfur and oxygen. We have established the stereoselective synthesis of *threo*-nitro ester (**12-*t***) and *erythro*-nitro ester (**12-*e***), respectively.

Next, some 1,5-benzoxazepine derivatives, 1-oxa analogues of diltiazem, were synthesized from **12-*t*** and **12-*e*** for pharmacological evaluation. Compound **13-*t*** exhibited cerebral vasodilating activity in this series, but it was about 0.7 as active as recemic diltiazem and more toxic than racemic diltiazem.[5]

B. Reaction of Glycidate (2a) with 2-Nitroaniline (14) and Synthesis of 1,5-Benzodiazepine Derivatives

Stereochemical aspects of the oxirane-ring opening of glycidate (**2a**) with 2-nitroaniline (**14**) were investigated. The results of the reaction of **2a** with **14** under a variety of conditions are summarized in Table VI.[6] When **2a** was reacted with **14** in the absence of catalyst, no reaction was observed. The

Table V. Reaction of *trans*-glycidic ester (**2a**) with 2-nitrophenol (**11**)



Entry	***11***[a]	*Catalyst*[b]	*Solvent*	*Temp. (°C)*	*Time (h)*	*Total yield of* **12** *(%)*	**12-*t*/12-*e***
1)	Free	—	MeCN	80	52	87	9.4[c]
2)	Free	$Sn(OCOC_7H_{15})_2$	Toluene	r.t.	22	—[d]	
3)	Free	$MgCl_2$	Toluene	r.t.	22	68	1/0
4)	Na salt	—	MeOH	65	13	38	0.1
5)	Free	—	HMPA	50–60	19	17	1/0

[a]One equivalent of 2-nitrophenol (**11**) was used.
[b]0.2 equivalent of catalysts was added.
[c]When the reaction was carried out at room temperature for 8 days, the *threo*-isomer (**12-*t***) was obtained in 7% yield.
[d]No nitro ester (**12-*t***) or (**12-*e***) was obtained.

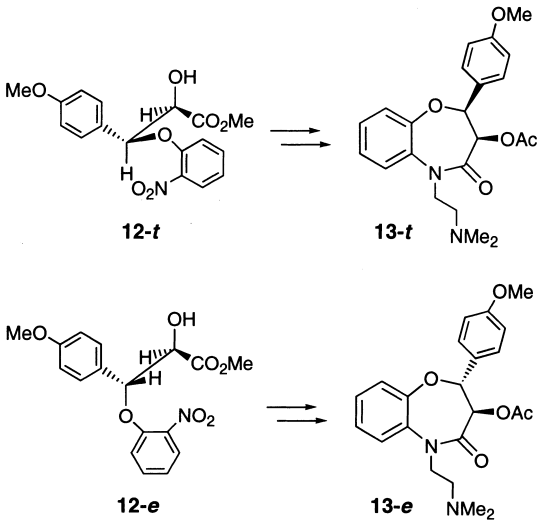
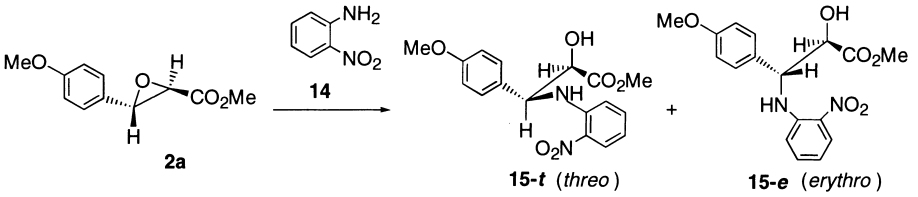


Figure 8. Synthesis of 1,5-benzoxazepine derivatives.

reaction also proved to be refractory in the presence of catalysts such as $MgCl_2$ and stannous 2-ethylhexanoate,[6] which were effective in the reaction **2a** with thiophenols.[3] However, ZnI_2 showed good catalytic activity in this reaction, giving the *cis*-opening product (**15-*t***) predominantly. On the other hand, the reaction on the surface of silica gel proceeded predominantly by *trans*-opening. Some 1,5-benzodiazepine derivatives, 1-aza-analogues of diltiazem, were synthesized from **15-*t*** and **15-*e*** for pharmacological evaluation. The cerebral vasodilating activity of **16-*t***, the most potent compound in this series, was about 0.5 that of racemic diltiazem. Thus, the sulfur atom of diltiazem could not be replaced by nitrogen or oxygen without a decrease in potency.[6]

Table VI. Reaction of *trans*-glycidic ester (**2a**) with 2-nitroaniline (**14**)



Entry	*Solvent*	*Additive*	*Temp. (°C)*	*Time (h)*	*Total yield of* **15** *(%)*	**15-*t*/15-*e***
1)	MeCN	—	60	72	—[b]	
2)	Toluene	$MgCl_2$	r.t.	48	—[b]	
3)	Toluene	$Sn(OCOC_7H_{15})_2$	r.t.	48	—[b]	
4)	Toluene	ZnI_2	r.t.	21	100	2.0
5)	Benzene	SiO_2[a]	r.t.	17	58	0.5

[a]The reaction was carried out in silica gel chromatography column. Stirring of the reaction mixture with the slurry of SiO_2 gave similar result.
[b]No nitro ester **15-*t*** or **15-*e*** was obtained.

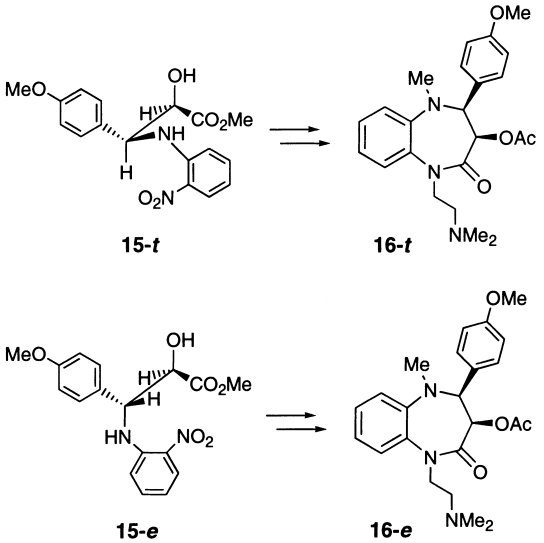


Figure 9. Synthesis of 1,5-benzoxazepine derivatives.

C. A Facile Access to 3-Cephems by Employing a Novel Lewis Acid-Mediated Reaction

In recent year, considerable interest has been focused on altering the C-3 substituent of the cephem nucleus to obtain a variety of analogues with enhanced biological activities. It has long been known that electron-withdrawing groups on the 3-position of cephems enhance antibacterial activity.[7]

We designed a novel cephem (**17**) and tried to synthesize it. However, the reaction of **18** with 1-hydroxybenzotriazole (HOBt) and $NaHCO_3$ in DMF afforded the undesired.^{3}/.^{2}-migration product (**20a**) as a major product. In the field of the cephem chemistry, this well known Δ^3/Δ^2 isomerization represents one of the major obstacles to the synthesis of the desired product. An appropriate Lewis

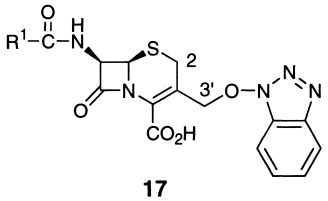


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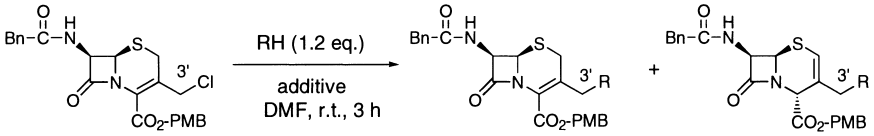
Figure 10. Structure of 3-cephem derivative.

Table VII. Application of Lewis Acid-Mediated Reaction of 3-chloromethyl-3-cephem (**18**) by Nucleophiles



18 **19** **20**

a : R = O-Bt, **b** : R = O-Su

Entry	*RH*	*Additive (mol %)*	*Total yield of* **19** + **20**[a] *(%)*	**19/20**
1)	HOBt[b]	$NaHCO_3$(150)	71	0.6
2)	HOBt	ZnI_2(40)	11	>100
3)	HOBt	ZnI_2(40), $NaHCO_3$(150)	93	>100
4)	HOBt	$ZnCl_2$(40), $NaHCO_3$(150)	63	1.7
5)	HOSu[c]	ZnI_2(40), $NaHCO_3$(150)	70	>100

[a]Isolated yield.
[b]HOBt: 1-Hydroxybenzotriazole.
[c]HOSu: N-Hydroxysuccinimide.

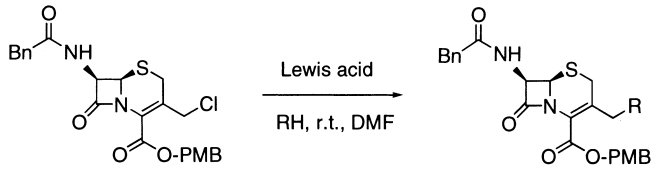
acid would activate the allylic position of **18**, bearing the chlorine atom to be substituted under acidic or neutral conditions. We investigated several conditions including using Lewis acids as shown in Table VII.[8] ZnI_2 was added to the reaction mixture of **18** and HOBt to give **19a** in 11% yield without detecting the side product (**20a**). This process generated HCl which interrupted reaction progression. Therefore, we added $NaHCO_3$ as an acid scavenger to the reaction in the presence of ZnI_2. The reaction proceeded smoothly and the selectivity was dramatically improved. Furthermore, by employing the process, the desired *N*-hydroxysuccinimide derivative (**19b**) was obtained in 70% yield.[8]

Moreover, we have expanded this efficient Lewis acid process toward novel carbon-carbon bond formation reactions as shown in Table VIII.[9]

D. Regioselective Lewis Acid Mediated Ring-Opening of Aryl Orthoacetates

Paclitaxel (Taxol®, **22**) and a semisynthetic analogue, docetaxel (Taxotere®, **23**) are regarded as frontline anticancer agents, especially for the treatment of ovarian, breast, and lung cancer. Extensive studies on structure-activity relationships (SAR) of paclitaxel analogues revealed that the C-13 side chains are extremely important for the outstanding antitumor activity. As the role of C-13 side chain in the biological activity of taxoid became evident, enantioselective synthesis of the C-13 side chain became the focus of many investigators.[10] Among the numerous papers, Sharpless's method was considered to be more efficient and adaptable for industrial scale production, which

Table VIII. A Novel Carbon-Carbon Bond Formation



18 **21**

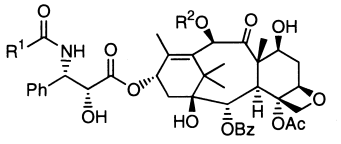
Entry	*RH (eq.)*	*Additive (eq.)*	*Time (h)*	*Yield (%)*
1)	$CH_2(CN)_2$(4.0)	$NaHCO_3$(4.0), SnI_2(1.2)	4	71
2)	$CH_2(CO_2Me)_2$(2.1)	K_2CO_3(1.8), SnI_2(0.7)	8	15
3)	$CH_2(CO_2Me)_2$(2.1)	K_2CO_3(1.8), SnI_2(0.7), H_2O(0.5)	8	70

proceeded through the asymmetric dihydroxylation (AD) reaction.[11] However, they mentioned that the reaction of cyclic orthoacetate (**24a**) with acetyl bromide afforded the bromoacetate (**25a**) with an appreciable amount of the unwanted regioisomer (**26a**), which became the major obstacle in the synthesis of taxoid side chain.

As mentioned above, we found that tin compounds such as $SnBr_2$ exhibited excellent catalytic activity for *cis*-opening of the epoxide (**2a**). Consequently, a Lewis acid would be expected to control the reaction of **24a** to bromoacetate (**25a**) regiochemically. We examined some Lewis acids as a catalyst on this reaction to obtain better regioselectivity. Typical Lewis acids such as $BF_3 \cdot Et_2O$ and $TiBr_4$ were ineffective at improving regioselectivity. Fortunately, mild Lewis acids such as $ZnBr_2$ and $SnBr_2$ were found to exhibit excellent catalytic activity and the bromoacetate (**25a**) was obtained in excellent yield as a sole product. Furthermore, we examined the effect of some fluoro-substituents on the benzene ring of cyclic orthoacetates, and results are summarized in Table IX.[12] In the absence of Lewis acid, the ratio of **25**/**26** was small. On the contrary, in the presence of mild Lewis acids such as $ZnBr_2$ and $SnBr_2$, the reaction proceeded smoothly and selectively to afford the desired bromoacetates (**25**), with the exception of the 3-fluoro derivative.

E. A Novel and Efficient Method for Preparation of Taxoids by Employing cis-Glycidic Acid

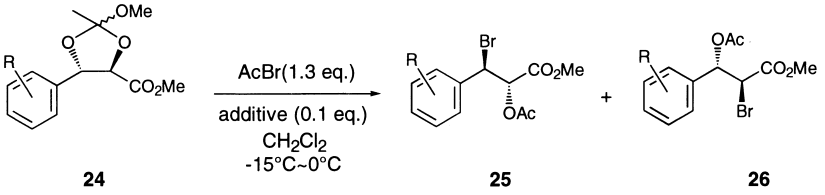
Recently, a number of paclitaxel analogues have been semisynthetically prepared from 10-deacetyl-baccatin III (**27**) which is extracted from renewable yew leaves (Fig 12).[10] However, the taxane skeleton has a very folded structure in which the hydroxyl group at C-13 of **27** is in a hindered position and, it can form a hydrogen bond with the 4-α-acetyl group. Therefore, such circumstances hamper introduction of C-13 side chains into the taxane skeleton. Consequently, only limited



22 R^1=Ph, R^2=Ac : paclitaxel (Taxol®)
23 R^1=O*t*-Bu, R^2=H: docetaxel (Taxotere®)

Figure 11. Structure of paclitaxel and docetaxel.

Table IX. Reaction of the Aryl Orthoacetates (**24**) with Acetyl Bromide



24 **25** **26**

a : R = H
b : R = 4-F
c : R = 2,4-F
d : R = 3-F

Entry	*Substrate*	*R*	*Additive*	*Total yield of* **25** + **26**[a] *(%)*	**25/26**
1)	**24a**	H	—	94	5
2)	**24a**	H	$BF_3 \cdot Et_2O$	44	6
3)	**24a**	H	$TiBr_4$	94	5
4)	**24a**	H	$ZnBr_2$	94	>100[b]
5)	**24a**	H	$SnBr_2$	80	>100[b]
6)	**24b**	4-F	—	89	5
7)	**24b**	4-F	$ZnBr_2$	91	>100[b]
8)	**24c**	2,4-F	—	95	1.5
9)	**24c**	2,4-F	$SnBr_2$	76	20
10)	**24d**	3-F	—	93	2.4
11)	**24d**	3-F	$SnBr_2$	78	4.6

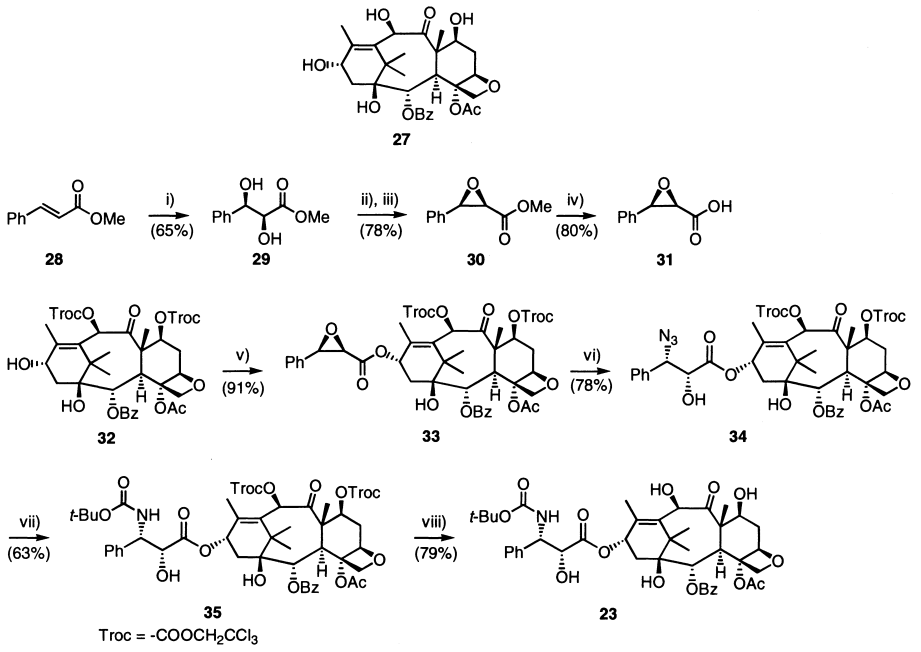
[a]isolated yield.
[b]Regioisomer (**26**) was not detected by 300–MHz ^{1}H-nmr spectrum.

approaches have been established for the conversion of 10-deacetylbaccatin III to paclitaxel analogues: (a) coupling of a suitable β-lactam[13] or (b) direct acylation by a protected oxazolidinecarboxylic acid.[14] However, these processes afforded only 3-nitrogen substituted compounds, preventing more extensive SAR studies of paclitaxel analogues.

We envisaged that the glycidic acid would have relatively less steric hindrance such as to enable it to react with the hydroxyl group at C-13. Therefore, we investigated the synthesis of taxoids using esterification of the glycidic acid with a baccatin III derivative.

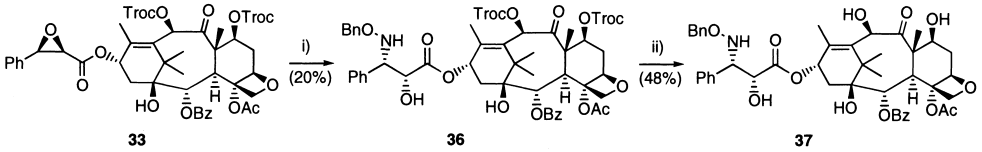
First of all we describe an efficient conversion of 10-deacetylbaccatine III into docetaxel (**23**), which could be converted to paclitaxel (**22**), by employing glycidic acid (**31**) as shown in Figure 12.[15] The optically active glycidic acid (**31**) was synthesized by using the AD process as the key reaction. The critical coupling reaction of **32** with **31** and dicyclohexylcarbodiimide (DCC) in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) in toluene at 80°C afforded the 13-*O*-acylated compound (**33**) in 91% yield. Then, the epoxide (**33**) was reacted with NaN_3 in aqueous MeOH in the presence of methyl formate to give azide derivative (**34**) in good yield. Compound **34** was treated with PPh_3 in the presence of di-*tert*-butyl dicarbonate (Boc_2O) to give **35** in 63%. The final reductive deprotection was performed with Zn in AcOH and MeOH to yield **23** in 79%.

Furthermore, the synthetic intermediate (**33**) was reacted with *O*-benzylhydroxylamine in the presence of a catalytic amount of $Yb(OTf)_3$ to give 3′-hydroxylamine derivative (**36**) (Fig. 13).[15] The deprotection step afforded a taxoid (**37**), which could not be obtained by previous methods. We have accomplished a novel and efficient synthesis of taxoids, which can eliminate the annoying protection-deprotection steps on the 2′,3′ amino alcohol moiety. However, the epoxide (**33**) did not react with ordinary nucleophiles such as thiols.



Reagents and conditions: (i) AD-mix-ß,*t*-BuOH, H_2O, r.t., 18 h; (ii) TsCl, Et_3N, CH_2Cl_2, 0 °C, 38 h; (iii) K_2CO_3, H_2O, DMF, r.t., 24 h; (iv) LiOH, MeOH, H_2O, r.t., 1 h; (v) **31** (1.5 eq.), DCC, DMAP, toluene, 80 °C, 1 h; (vi) NaN_3, HCO_2Me, MeOH, H_2O, 50 °C, 40 h; (vii) PPh_3, Boc_2O, $KHCO_3$, CH_2Cl_2, H_2O, r.t., 19 h; (viii) Zn, AcOH, MeOH, 60 °C, 40 min

Figure 12. Synthesis of docetaxel (**23**) using *cis*-glycidic acid



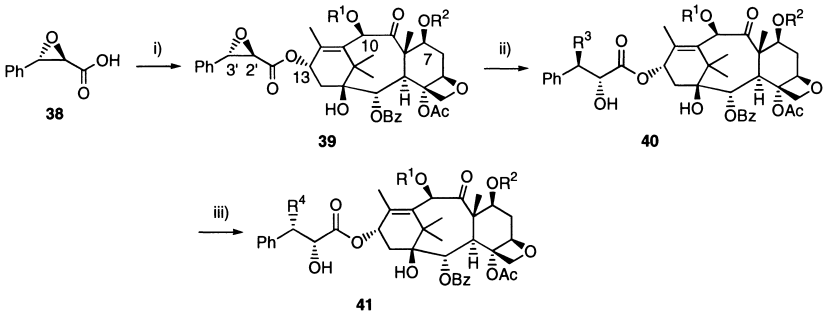
Reagents and conditions: (i) NH_2OBn, $Yb(OTf)_3$ (cat.), CH_2Cl_2, 60 °C, 6d; (ii) Zn, AcOH, MeOH, 60 °C, 30 min.

Figure 13. Synthesis of new taxoid using *cis*-glycidic acid.

F. A Novel and Efficient Method for Preparation of Taxoids by Employing trans-Glycidic Acid

Therefore, next we examined the esterification of **32** by employing *trans*-glycidate, whose reactivity was higher than that of *cis*-glycidate. We describe an improved synthesis of the known taxoid docetaxel (**23**) and novel taxoids using (2*R*,3*S*)-*trans*-glycidic acid (**38**), which is more readily obtained than *cis*-glycidic acid (**31**), by Darzen's reaction of benzaldehyde, followed by enzyme-mediated enantioselective transesterification and hydrolysis.[16] The *trans*-glycidate (**39**) and docetaxel (**23**) have the same 2′ *R*, 3′ *S* stereochemistry, so it is necessary to accomplish a net stereo-retained conversion of epoxide (**39**) to obtain **23**. We designed successive nucleophilic ring-opening and substitution reactions, as shown in Figure 14. When R^3 of the intermediate (**40**) is a good leaving group, it might be possible to synthesize not only docetaxel but also novel taxoids effectively.

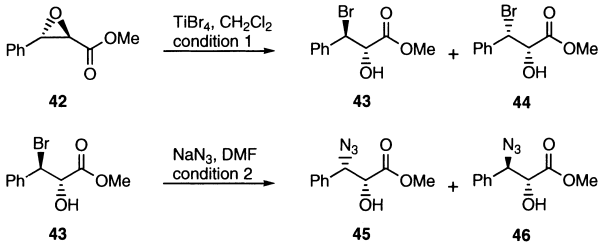
First, we investigated the conversion of glycidate (**42**) to azide (**45**) as a model study shown in Table X.[13] Stereoselective bromination of **42** was achieved by the use of $TiBr_4$ in the presence of



Reagents: (i) 7,10-protected baccatin III; (ii) nucleophile; (iii) nucleophile.

Figure 14. Synthetic strategy of taxoids using *trans*-glycidic acid.

Table X. Stereoselective Synthesis of Azide Derivative by Employing *trans*-Glycidic Ester (Model Study)

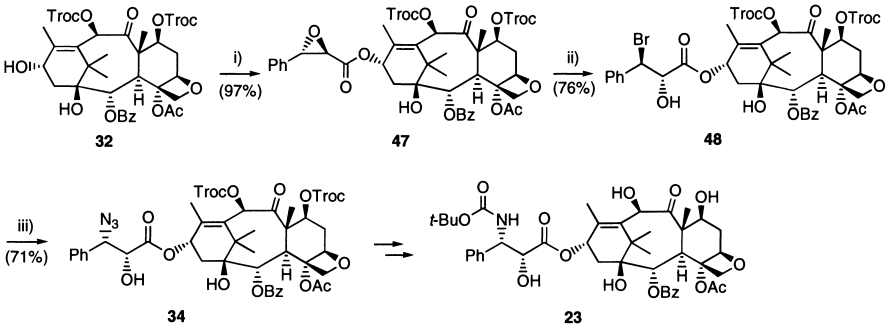


Condition 1	*Additive*	*yield*[a] *(%)*	**43/44**[b]
Bromination of **42**			
−78°C, 15 min	—	99	5/8
−78°C, 3 h then −10°C, 1 h	HMPA[c]	82	>20/1
Condition 2	*Additive*	*yield*[a] *(%)*	**45/46**[b]
Reaction of **43** with NaN_3			
70°C, 20 h	—	67	5/2
0°C, 31 h	15-crown-5[d]	88	>20/1

[a]Isolated yield.
[b]Ratio was determined by 300 Mz ^{1}H-NMR spectrum.
[c]HMPA-CH_2Cl_2 (1:10).
[d]Catalytic amount of 15-crown-5 was added.

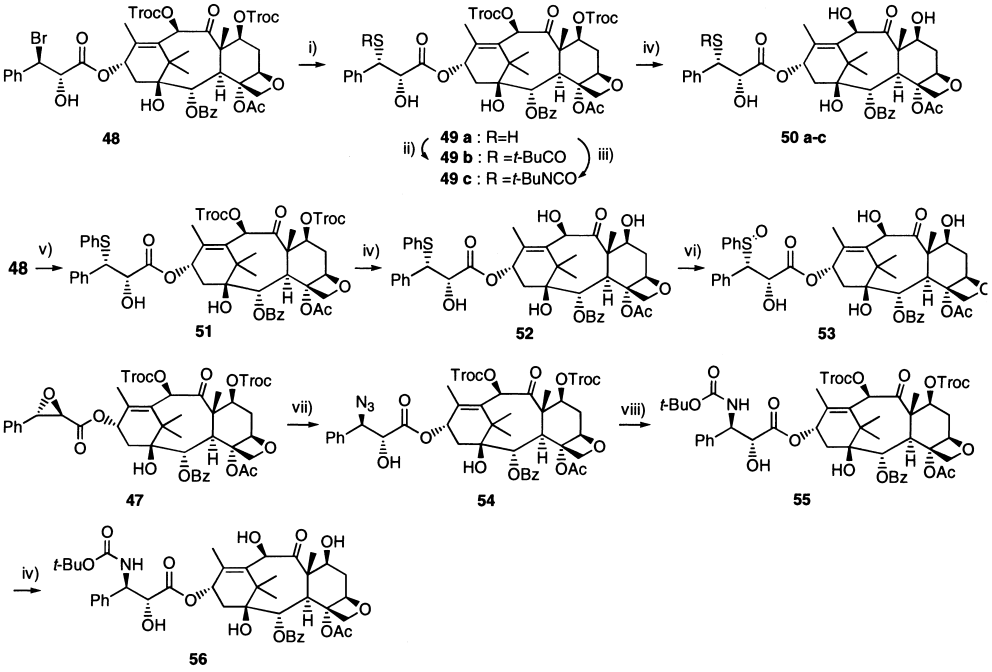
hexamethylphosphoramide (HMPA). Without HMPA, the reaction proceeded in a poorly stereocontrolled manner. Unfortunately, in our experimentation, the reaction of the bromohydrin (**43**) and NaN_3 in DMF afforded an appreciable amount of stereoisomer (**46**) together with the desired product (**45**). The formation of **46** might involve a step through the epoxide (**42**) as a reactive intermediate. Therefore, in order to increase the nucleophilicity of the azide anion, a catalytic amount of crown ether was added to the reaction mixture. Under these conditions the reaction proceeded smoothly and gave **45** predominantly.

Next, we describe an efficient synthesis of docetaxel by employing *trans*-glycidic acid (**38**) (Fig. 15).[13] The coupling reaction of baccatin III derivative (**32**) and **38** in toluene with DCC and DMAP at room temperature proceeded smoothly and gave 13-*O*-acylated compound (**47**) in almost quantitative yield. Surprisingly, **32** was completely consumed within 10 minutes at room



Reagents and conditions : (i) **38** (2 eq.), DCC, DMAP, toluene, r.t., 10 min; (ii) $TiBr_4$, HMPA, CH_2Cl_2, 0 °C, 18 h; (iii) NaN_3, 15-crown-5, DMF, 0 °C, 24 h

Figure 15. Synthesis of docetaxel using *trans*-glycidic acid.



Reagents and conditions : (i) NaSH, 15-crown-5 (0.1 eq.), DMF, -45 °C, 2 h, 79%; (ii)*t*-BuCOCl, Et_3N, CH_2Cl_2, -78 °C, 30 min, 100%; (iii) *t*-BuNCO, Et_3N, CH_2Cl_2, 0 °C, 30 min, 94%; (iv) Zn, AcOH, MeOH, 50~60 °C, 20~60 min, 75~94%; (v) PhSH, NaH, DMF, -10 °C, 30 min, 92%; (vi) 3-chloroperoxybenzoic acid (*m*CPBA), $CHCl_3$, 0 °C~r.t., 2 h, 53%; (vii) NaN_3 , HCO_2Me, MeOH, H_2O, 45 °C, 3.5 h, 92%; (viii) PPh_3, Boc_2O, $KHCO_3$, CH_2Cl_2, H_2O, r.t., 22 h, 86%.

Figure 16. Synthesis of novel taxoids by employing *trans*-glycidic acid.

temperature. Then, the epoxide (**47**) was reacted with $TiBr_4$ in the presence of HMPA at 0°C to give bromohydrin (**48**) in a highly stereo- and regio-selective manner. Stereoselective azidation of the bromohydrin (**48**) was achieved by the use of NaN_3 in DMF in the presence of a catalytic amount of 15-crown-5 at 0 to give **34** in 71% together with the recyclable epoxide (**47**) in 10%. The azide (**34**) is easily converted to docetaxel; hence we established a novel synthesis of docetaxel in only 9 steps.

Furthermore, novel compounds, the synthesis of which could note be obtained by previous methods, can easily be prepared from novel and reactive intermediates (**47,48**). Nucleophilic

substitution of the bromohydrin (**48**) with thiolate anions afforded thiol (**49a**) and phenyl thioether (**51**), which were readily converted to various 3′-thio-derivatives (**50a–c, 52, 53**) (Fig. 16).[15] The epoxide (**47**) reacted with NaN_3 to give azide derivatives (**54**), which was converted to 3′-epi-docetaxel (**56**) which can not be obtained by conventional methods.[17]

4. CONCLUSIONS

As a result of various investigations, *threo*-nitro ester (***3a-t***), a key intermediate for the synthesis of diltiazem, has been successfully synthesized in high yield via regio- and stereoselective opening of the oxirane ring of 3-(4-methoxyphenyl)glycidic ester (**2a**) with 2-nitrothiophenol (**1**) in the presence of a tin-catalyst. The mechanism of this catalytic reaction was elucidated by isolation of the adduct of $SnCl_4$ with **1**. Applications of other Lewis acids and glycidic esters have found utilities, which expand and simplify the chemistry in other fields, including cephems and taxoids.

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