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An Approach to Anti-HIV-1 Active *Calophyllum* Coumarin Synthesis: An Enantioselective Construction of 2,3-Dimethyl-4-chromanone Ring by Quinine-Assisted Intramolecular Michael-Type Addition

Tsutomu Ishikawa,* Yumie Oku, Tomohiro Tanaka, and Takuya Kumamoto

Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi, Inage, Chiba 263-8522, Japan

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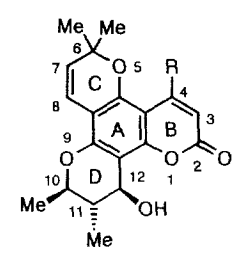
Abstract: (-)-Quinine effectively catalyzes an intramolecular Michael-type addition of 7-hydroxy-8-tigloylcoumarin to give a diastereoisomeric mixture of the corresponding cyclized coumarin with a 2,3-dimethyl-4-chromanone skeleton. Satisfactory enantioselectivity was observed in a *cis*-chromanone construction, but not in a *trans*-one. © 1999 Elsevier Science Ltd. All rights reserved.

A 2,3-dimethyl-4-chromanol skeleton (the ring A-D in Fig. 1) is responsible for anti HIV-1 activity of *Calophyllum* coumarins[1,2] and especially the absolute stereochemistries at three chiral centers play a crucial role. Thus, the strongest activities have been observed in (+)-calanolide A[2a] (**1**) and (+)-inophyllum B[2b] (**2**) with (10*R*,11*S*,12*S*) configuration.[3] It is known that the chromanol ring can be readily given from the corresponding chromanone function by hydride reduction.[4] We have reported a model synthetic route to *Calophyllum* coumarins through a chromanone construction by intramolecular Michael-type addition (IMA) of an *o*-tiglolylphenol in the presence of a base like triethylamine (TEA) as a key step.[5] The use of (-)-quinine in place of TEA led to an asymmetric induction (the quinine-assisted IMA) in a 2,3-dimethyl-4-chromanone construction, in which only a *cis*-chromanone skeleton was built in high enantioselectivity. In this communication we present the first effective asymmetric oxo-Michael addition.



R=^{n}Pr: (+)-calanolide A (**1**)
R=Ph: (+)-inophyllum B (**2**)

In the previous IMA of 7-hydroxy-5-methoxy-8-tigloylcoumarin (**3**) we had used two equivalents of TEA as a base, in which both *cis*- and *trans*-2,3-dimethyl-4-chromanones were given with no diastereoselectivity.[5] Similar treatment of **3** in tetrahydrofuran (THF) using two equivalents of (-)-quinine[6] at 60 °C quantitatively gave a 1 : 1 diastereomeric mixture of a (+)-enantiomer-enriched *cis*-chromanone[7] (+)-*cis*-**4** (see below) and an optically-inactive *trans* one (±)-*trans*-**4** (run 1 in Table 1). The enantiomeric excess (ee) of the (+)-enantiomer in *cis*-**4** was determined to be 75% by HPLC analysis.[8] Trials for the asymmetric IMA using other commercially available chiral amines resulted in unsatisfactory asymmetric induction in all cases examined (runs 2-8 in Table 1).

Thus, we further elaborated the asymmetric IMA induced by (-)-quinine at lower temperature (0-2 °C) (Table 2). The reaction using two equivalents of (-)-quinine improved the enantioselectivity of (+)-*cis*-**4** up to 87% ee (run 1 in Table 2). The use of (+)-quinidine[9] in place of (-)-quinine expectedly gave (-)-*cis*-**4** in 75% ee

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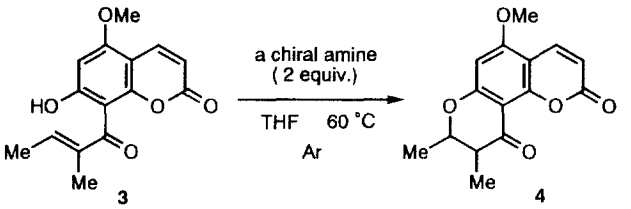
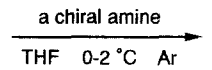
Table 1. Trials for Asymmetric IMA of o-Tigolylphenol 3 in the Presence of a Chiral Amine



run	chiral amines	time (h)	4	
			yield (%)[a]	cis (ee %)[b] : trans (ee %)[b]
1	(-)-quinine	2	quant.	1 (75)[c] : 1 (0)
2	(-)-2-amino-1-butanol	1	quant.	1 (2)[c] : 5 (0)
3	(R)-1-phenylethylamine	2	quant.	3 (6)[c] : 5 (5)
4	sparteine	1	93	7 (0)[c] : 10 (7)
5	strychnine	24	quant.	2 (4)[c] : 5 (7)
6	nicotine	24	quant.	3 (2)[c] : 5 (0)
7	L-proline methyl ester	24	quant.	7 (8)[c] : 10 (6)
8	L-prolinol	1	complex mixture	—

[a] Nonoptimized, isolated yield. [b] The ee was determined by a chiral HPLC. [c](+)-Enantiomer was preferentially formed.

Table 2. Further Examination of the Quinine-assisted IMA

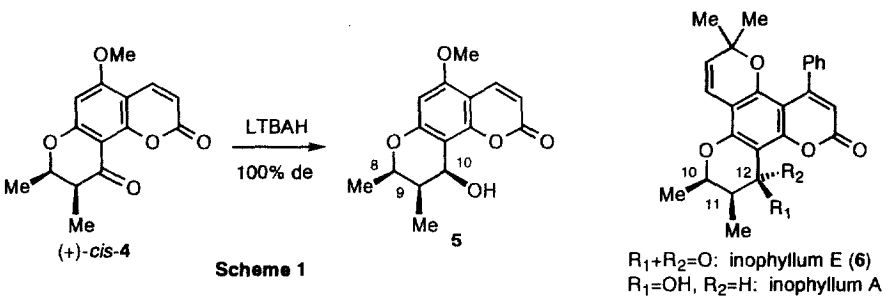


run	chiral amines (equiv.)	time (d)	4	
			yield (%)[a]	cis (ee %)[b] : trans (ee %)[b]
1	(-)-quinine (2)	2	quant.	3 (87)[c] : 2 (0)
2	(+)-quinidine (2)	2	quant.	10 (75)[d] : 7 (0)
3	(-)-quinine (0.2)	6	64[e]	1 (87)[c] : 1 (0)

[a] Nonoptimized, isolated yield. [b] The ee was determined by a chiral HPLC. [c] (+)-Enantiomer was preferentially formed. [d] (-)-Enantiomer was preferentially formed. [e]The starting phenol **3** was recovered in 18% yield.

(run 2 in Table 2). Next we examined the IMA in the presence of a catalytic amount (0.1 mol equiv.) of (-)-quinine (run 3 in Table 2). The high ee was also observed in the (+)-*cis*-chromanone construction albeit slightly lower chemical conversion.

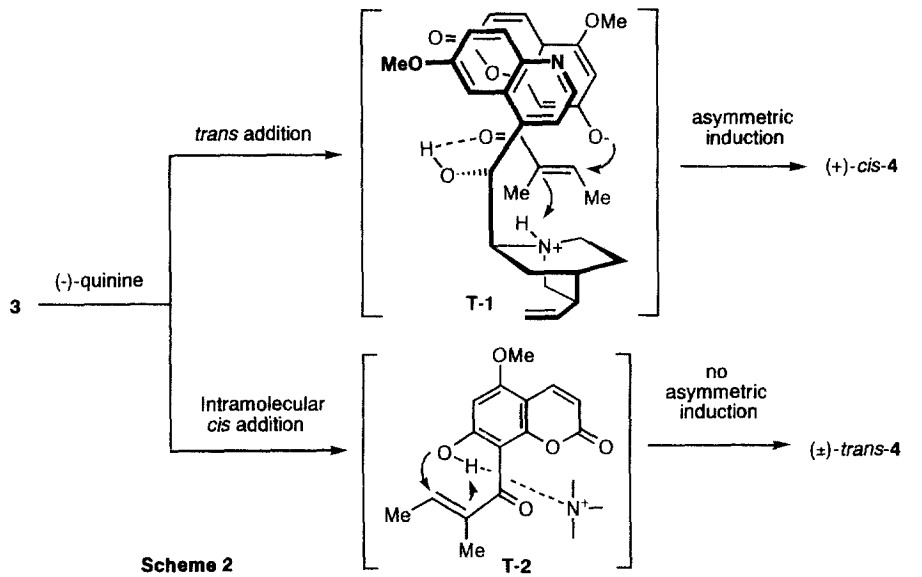
The (+)-*cis*-chromanone (87% ee) obtained in run 1 in Table 2 showed the specific rotation of $[\alpha]_{589}$ +132.5 ($CHCl_3$).[10] The stereoselective hydride reduction of (+)-*cis*-**4** with lithium tri(*t*-butoxy)aluminohydride (LTBAH)[5b] afforded the corresponding (+)-*cis,cis*-chromanol **5**, $[\alpha]_{589}$ +114.4 ($CHCl_3$) [10] (Scheme 1). Inophyllum E[11] (**6**), one of natural *Calophyllum* coumarins with a *cis*-chromanone skeleton, showed the specific rotation of $[\alpha]_D$ +70 ($CHCl_3$). Its absolute configuration has been established as (10*R*,11*S*).[2b] Furthermore,



Scheme 1

the absolute configuration of (+)-inophyllum A (**7**) {$[\alpha]_D$ +43 (acetone)[11]; +68.8 ($CHCl_3$)[12]} with a *cis,cis*-chromanol skeleton has been also established as (10*R*,11*R*,12*S*).[2b] These facts allowed us to assign the absolute configuration of the (+)-*cis*-chromanone obtanied in the quinine-assisted IMA as (8*R*,9*S*).[13]

A conjugate addition is generally accepted as a mode of Michael addition reaction, in which an enolate should be formed in the first step under base-catalyzed condition. If asymmetric induction occurs at the addition step, similar enantioselectivities must be observed in both diastereoisomers of *cis*- and *trans*-chromanones produced by the quinine-assisted IMA. The fact that asymmetric induction was observed in only the construction of a *cis* derivative strongly indicated that the cyclization should be controlled by two independent paths. We have proposed a concerted *cis* addition in the diastereoselective *trans*-chromanone construction by the CsF-induced IMA of **3**.[5] Thus, in the quinine-assisted IMA the *trans*-chromanone was also produced by the *cis* addition, while the *cis*-chromanone by *trans* addition of completely dissociated phenolate and ammonium ions under chiral environment. (Scheme 2)



Scheme 2

The effective asymmetric induction in the *cis*-chromanone construction can be reasonably explained by supposing the transition state **T-1** of the quinine-assisted IMA. In the **T-1** there could be non-bonding π–π

interaction between each aromatic ring of quinine and **3**, in which an electron-deficient pyridine unit in the quinoline skeleton is interacted with an electron-rich dimethoxybenzene unit of the coumarin one, while an electron-rich methoxybenzene unit in the quinoline skeleton with an electron-deficient lactone unit in the coumarin one. Furthermore, each component is fixed by a hydrogen bond[14] between an alcoholic function in the quinine unit and a carbonyl group in the tigloyl group. Thus, concerted *trans* addition in the relatively rigid complex would be able to lead to high enantioselectivity.

Chinchona alkaloids were shown to be good catalysts for asymmetric thio-Michael addition[14, 15] to α, β-unsaturated carbonyl compounds. However, there are, to our knowledge, no reports on the asymmetric oxo-Michael addition. Further trials toward the stereoselective synthesis of *Calophyllum* coumarins using the quinine-assisted IMA are at present under investigation.

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6. A commercially available (-)-quinine [purchased from nacalai tesque Co. Ltd. (Japan)] was used after its azeotropic dehydration using toluene and then drying.
7. All new compounds were fully characterized by spectroscopic data and combustion analysis.
8. Each enantiomer was observed at retention times of 13.5 and 15.5 min, respectively when CHIRALCEL AS (Daicel Co. Ltd.,) was used as a column under the following conditions; eluent: *n*-hexane: EtOH=9 : 1, flow rate: 1.0 ml/min, detection: 254 nm.
9. A commercially available (+)-quinidine [purchased from nacalai tesque Co. Ltd. (Japan)] was used after its azeotropic dehydration using toluene and then drying.
10. Optical rotation was measured with JASCO J-20.
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13. Unfortunately derivatization of (+)-*cis*-**4** and **5** for X ray analysis has never been successful. Preparation of Mosher's ester on **5** was also failed.
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