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Diastereoselective Preparation of a *trans, trans* 2, 3-Dimethylchroman-4-ol Skeleton: A Model Synthetic Approach to Anti-HIV-1 Active *Calophyllum* Coumarins

Tsutomu Ishikawa,* Yumie Oku and Ken-Ichiro Kotake

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

Abstract: A model synthetic study of anti-HIV-1 active *Calophyllum* coumarins using 5, 7-dimethoxycoumarin (limettin) is described. Successive reactions of the CsF-induced intramolecular Michael type addition of an *o*-tigloylphenol followed by reduction with lithium tri-*tert*-butoxyaluminum hydride led to easy and diastereoselective access to a *trans, trans* 2, 3-dimethylchroman-4-ol ring, which is suggested to be the most responsible skeleton for the activity. © 1997 Elsevier Science Ltd.

INTRODUCTION

Recently it was reported that some coumarins [calanolide **1** (R=Pr)[1] and inophyllum **2** (R=Ph)[2] series] isolated from *Calophyllum* genus (Guttiferae) showed strong activity against anti-human immunodeficiency virus type 1 (HIV-1).[3] These *Calophyllum* coumarins were basically composed of three skeletal rings, a coumarin (rings A, B), a 2, 2-dimethylchromene (rings A, C) and a 2, 3-dimethylchroman-4-ol (rings A, D). Among the three, the chromanol ring, especially three sequential stereochemistries at the 2, 3 and 4 positions (10, 11 and 12 positions in **1** and **2**), has been suggested the most responsibility for the antiviral activity[1b, 1c, 2g, 4]; *i. e.* in inophyllum series[2g] inophyllum B (**2a**) with *trans, trans* configurations showed the highest activity (IC$_{50}$: 0.038 μM) against HIV-1 reverse transferase, and the activity decreased in order of inophyllum P (**2b**) (IC$_{50}$: 0.13 μM) with *trans, cis*, inophyllum D (**2c**) (IC$_{50}$: 11 μM) with *cis, trans* and inophyllum A (**2d**) (IC$_{50}$: 30 μM) with *cis, cis* configurations at the same positions.[5]

Although several research groups[4, 7] have reported the synthesis of these coumarins including optical active forms,[4c, 7d] satisfactory results in stereoselectivity limited to the asymmetric syntheses.[4c, 7d] We have approached to stereoselective preparation of a 5-methoxycoumarin derivative **9** with a *trans, trans* 2, 3-dimethylchroman-4-ol ring from limettin (**3**) as a model compound of the *Calophyllum* coumarins. In our synthetic strategy a key reaction is an intramolecular Michael type addition (IMA)[7a-c] of an *o*-tigloylphenol for the construction of a chromanone ring,[1a, 2a, 4a-c, 4e, 7a-c] which would be able to easily give access to the

Me Me
6
7 O 5 R
8 C   4 3
A B 2
9 O   O O
10 D 1
Me 11 12 OH
Me
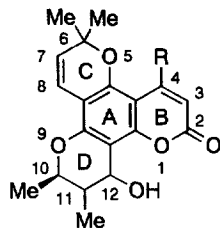
| configuration	calanolides (R=Pr)	inophyllums (R=Ph)
trans, trans (11α-Me, 12β–OH)	calanolide A (**1a**)	inophyllum B (**2a**)
trans, cis (11α-Me, 12α–OH)	calanolide B (**1b**)	inophyllum P (**2b**)
cis, trans (11β-Me, 12α–OH)	————	inophyllum D (**2c**)
cis, cis (11β-Me, 12β–OH)	calanolide C[a] (**1d**)	inophyllum A (**2d**)

[a] Palmer *et al.*[7b, c] noted that the ring C and D in the structure shown here for calanolide C should be interconverted each other based on the precise examination of ^{1}H NMR spectra of the natural products and synthetic coumarins.

corresponding chromanol through a hydride reduction such as Luche reduction ($NaBH_4$-$CeCl_3$).[4a-d, 7a, 8]

In a preliminary communication[9] we reported the highly diastereoselective ring construction of a *trans* 2, 3-dimethylchroman-4-one from the corresponding *o*-tigloylphenol **5** by the cesium fluoride (CsF)-induced intramolecular Michael type addition (the CsF-induced IMA). In this paper we present full accounts of the preliminary results and the following reduction of the formed *trans* 2, 3-dimethylchroman-4-one with lithium tri-*tert*-butoxyaluminum hydride (LTBAH) to afford an intended coumarin **9** with a *trans, trans* 2, 3-dimethylchroman-4-ol skeleton in good selectivity.
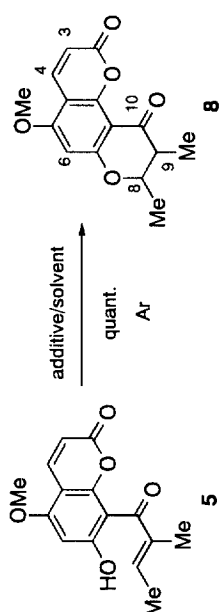
RESULTS AND DISCCUSION

Preparation of *o*-Tigloyl- 5 and *o*-Angeloylphenols 7 for IMA   The starting phenols for IMA were prepared as shown in Scheme 1. We[10] have observed that limettin (**3**) preferentially gave an 8-acylated product when treated with 3, 3-dimethylacryloyl chloride in dichloromethane (CH_2Cl_2) in the presence of tin (IV) chloride ($SnCl_4$). The similar Friedel-Crafts reaction of **3** with tigloyl chloride at 0-2 °C cleanly afforded an intended 8-tigloyllimettin (**4**) in 68% yield. The position of the introduced acyl group was deduced by the chemical shift of a signal due to an aromatic proton (δ 6.32)[11] and unambigously confirmed by NOE enhancements of both methoxy groups at 5 and 7 positions when the aromatic signal was irradiated. Treatment of **4** with 3.0 equivalents of boron trichloride (BCl_3) in CH_2Cl_2 at -70°C led to the selective demethylation of the

Scheme 1. Preparation of the Starting Phenols for IMA
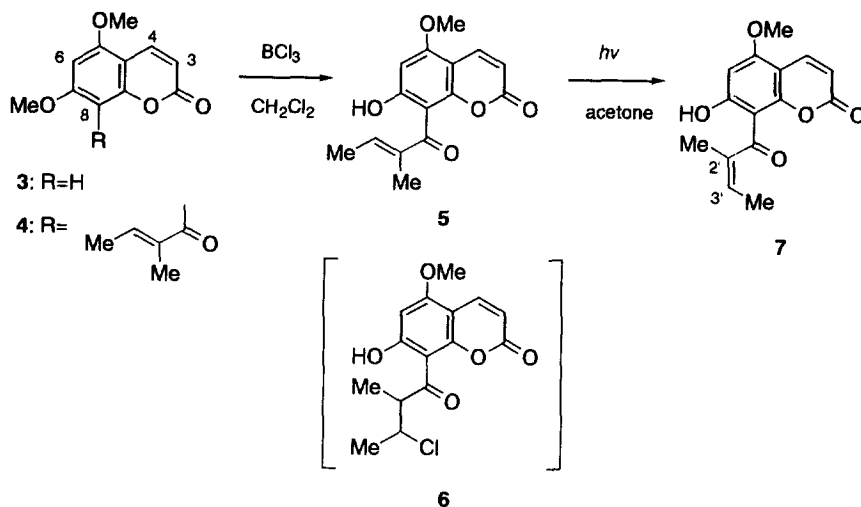
7-methoxy group to give an *o*-tigloylphenol 5^{12} in 73% yield. The use of either a large excess of BCl_3 (10.0 equiv.) or a commercial 1 M solution of BCl_3 in CH_2Cl_2 resulted in producing an HCl adduct **6** as a side product or imcomplete reaction, respectively.

Palmer *et al.*[7c] reported the isomerization of a related *o*-tigloylcoumarin to the corresponding *o*-angeloyl derivative by irradiation of UV light (254 nm) in hexane albeit in low conversion yield (15%). Several trials for photoisomerization of **5** using a low pressure mercury lamp (100 W) as a light source resulted in no production of an *o*-angeloylphenol **7**. On the other hand photoirradiation of **5** in acetone for 40 min using a high pressure mercury lamp (400 W) through Pyrex® filter smoothly afforded an isomerized product **7** in 57% yield. However improvement of the yield failed even if irradiated in nitrogen atmosphere. The use of other solvents such as benzene, chloroform ($CHCl_3$), CH_2Cl_2, diethyl ether and ethyl acetate also led to unsatisfactory photoisomerization. A longer time (5 h) was needed for completion of the reaction when used ethanol (EtOH) in place of acetone. The geometry of a side chain in **7** was confirmed by the higher field-shift (δ 5.63) of the olefinic proton at 3' position compared to that (δ 6.16) in **5** and NOE enhancements of both olefinic methyl groups at 2' and 3' positions on irradiation of the signal at δ 5.63 in the ^{1}H NMR spectrum of **7**.

The Preparation of the 2, 3-Dimethylchroman-4-one 8 by IMA   In the related chromanone construction by IMA using an *o*-tigloylphenol a base such as potassium carbonate $(K_2CO_3)^{7a}$ or triethylamine $(TEA)^{7b, c}$ was used as an additive. In those reactions the corresponding chromanones were smoothly given, but no diastereoselectivity was observed.[7a-c] We applied the basic condition with TEA to the cyclization of an *o*-tigloylphenol **5** for preparation of both diastereoisomers of the chromanone derivative **8** (see run 1 in Table 1). Treatment of a solution of **5** in $CHCl_3$ with TEA (3.0 equiv.) at room temperature (rt) for 4 h gave a cyclized

Table 1. Trials for Cyclization of *o*-Tigloylphenol 5 to the Chromanone 8 by IMA

run[a]	additive (equiv.)	solvent (mol/L)	temp (°C)	time	8[b] (*cis* : *trans*)
1	TEA (3.0)	CHCl$_3$ (0.26)	rt	4 h	50 : 50
2	TFA (50)	CHCl$_3$ (0.2)	rt	12 h	NR[c]
3	SnCl$_4$ (0.01)	THF (0.04)	rt	4 d	60 : 40
4	TMSI (1.1)	CH$_2$Cl$_2$ (0.21)	-70	2 h	an HI adduct
5	CsF (2.1)	DMF (0.32)	60	2 d	5 : 95
6	CsF (2.0)	THF (0.07)	60	3 d	5 : 95
7	KF (2.1)	THF (0.04)	60	1 h	35 : 65
8	BaF$_2$ (4.1)	THF (0.04)	reflux	1 d	35 : 65
9	CaF$_2$ (2.0)	THF (0.03)	reflux	1 d	35 : 65
10	TBAF[d] (1.5)	THF (0.06)	60	7 h	35 : 65
11	Cs$_2$CO$_3$ (2.0)	THF (0.03)	60	1 d	30 : 70
12	K$_2$CO$_3$ (2.0)	THF (0.03)	60	1 d	30 : 70

[a]The reaction was carried out under argon except for runs 1 and 2. [b]8 was given quantitatively except for runs 4 (82%) and 11 (60 %). The ratio of diastereoisomers in the product was determined by ¹H NMR (400 MHz). [c]No reaction. [d]Tetrabutylammonium fluoride.

product quantitatively. Fractional recrystallization of the products from $CHCl_3$-hexane afforded the desired *trans* chromanone *t*-**8** as a less soluble component. On the other hand, the *cis* isomer *c*-**8** was separable by flash chromatography of the mother liquor of the recrystallization using a mixed solvent of $CHCl_3$ and ethyl acetate (10 : 1). The relative stereochemistry of each product was determined by examination of the coupling constant[1b, 1c, 2c-g, 4e] between the methine protons at 8 and 9 positions in the ^{1}H NMR spectrum. The larger coupling constant ($J_{8,9}$=11.0 Hz) was assignable to *t*-**8** in which both methine protons should be arranged in a *trans* diaxial relation, while the smaller one ($J_{8,9}$=3.3 Hz) to *c*-**8** in an axial-equatorial relation of them.

Chromanone cyclizations of **5** by IMA under various conditions are summerized in Table 1. The ^{1}H NMR spectrum of the crude **8** in run 1 in Table 1 showed no diastereoselectivity as previously observed by Palmer *et al.*[7b, 7c] in the related coumarins. The use of trifluoroacetic acid (TFA) (run 2) as an acidic additive led to no chromanone cyclization, while *c*-**8** was interestingly formed as a slightly major isomer when used $SnCl_4$ (run 3). Treatment of **5** with iodotrimethylsilane (TMSI) at -70 °C resulted in the formation of an HI adduct like **6** in 82% yield (run 4).

The fluoride atom of CsF can be effectively bonded to an acidic hydrogen atom such as a phenol function.[13] Independently we[14] observed that CsF caused the exclusive production of 2-methylarylfurans in the Claisen rearrangement of aryl propargyl ethers dependent upon its ability of hydrogen bonding. Thus, we focused on the effect of CsF as a base on the chromanone cyclization by IMA. A solution of **5** in either dimethylformamide (DMF) (run 5) or tetrahydrofuran (THF) (run 6) was treated with about a two-molar excess of CsF at 60 °C under argon. Although a longer time was needed for completion of the reaction,[15] the desired *t*-**8** was given both in high chemical yield and with high diastereoselectivity (90% de) in each case. On the other hand, the use of other fluorides (runs 7-10) also led to effective production of **8**. However, the diastereoselectivity for *t*-**8** was low (30% de) in these cases. A similar result was also given when used cesium carbonate or K_2CO_3 as an additive (runs 11,12). These findings strongly indicated that CsF itself is necessary for the highly diastereoselective construction of a *trans* chromanone *t*-**8** by IMA using an *o*-tigloylphenol **5**.

Trace of the CsF-induced IMA by thin layer chromatography (TLC) showed that *t*-**8** was always distributed as a major isomer in the reaction mixture in addition to the starting **5**. Furthermore, we found that *c*-**8** was exclusively isomerized into *t*-**8** through ring opening to the starting *o*-tigloylphenol **5** under the conditions of the CsF-induced IMA, whereas *t*-**8** was inert to the epimerization. On the other hand, further treatment of a 1 : 1 diastereomeric mixture of **8** obtained in run 1 in Table 1 with TEA resulted in no change of the diastereomeric ratio even if under reflux,[16] suggesting that both isomers are nearly equal in thermodynamical stability. This speculation was supported by the calculation of each final heat of formation of *c*-**8** and *t*-**8**.[17] Therefore, if a phenolate anion is completely generated from **5** in the CsF-induced IMA and an enolate anion from *c*-**8** in the CsF-mediated epimerization, a 1 : 1 diastereomeric mixture of *cis* and *trans* isomers should be given by conjugate addition of the phenolate to an α,β-unsaturated carbonyl group in the former and by simple epimerization without ring opening in the latter reactions, respectively. Thus, strictly stereocontrolled reactions must occur during these CsF-participating reactions. (Scheme 2)

For the highly diastereoselective construction of the *trans* chromanone in the CsF-induced IMA the phenolic hydroxy group in a starting material must be added to the olefinic bond of the α,β-unsaturated ketonic function through a *cis* mode. The cesium atom of CsF may coordinate to a carbonyl oxygen because of its potential cationic character in addition to the hydrogen bonding ability of the fluoride atom of CsF. Thus, a

Scheme 2.
Reactions
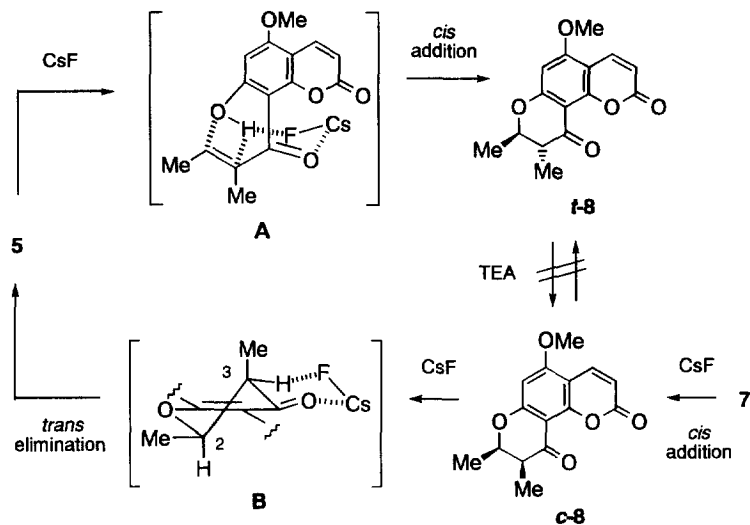
partial [4. 2. 0] bicyclic transition structure (A in Scheme 2), in which CsF coordinates through the phenolic hydrogen and the carbonyl oxygen atoms, may control the *cis* addition of the phenolic hydroxyl group to the olefinic bond in the IMA. On the other hand, for the ring opening of only *c*-**8** to the *o*-tigloylphenol **5** during the CsF-mediated epimerization *trans*-1, 4-elimination must occur. The methine protons at 2 and 3 positions of the chromanone ring are oriented to axial-equatorial arrangement in a stable conformation for *c*-**8** and *trans* diaxial arrangement in *t*-**8** as mentioned above. Thus, we may also speculate that a CsF-coordinated six-membered cyclic transition state (B in Scheme 2) contributes to the stereospecific ring opening in only *c*-**8**.

According to these speculations *t*-**8** could be also yielded in the CsF-induced IMA of an *o*-angeloylphenol **7**, in which *c*-**8** should be initially yielded by the *cis* mode addition through a transition state like A in Scheme 2 and then isomerized into *t*-**8** through the following CsF-mediated epimerization (see Scheme 2). In fact the ¹H NMR spectrum of the crude product obtained after treatment of **7** under the same conditions of the CsF-induced IMA of **5** for 1.5 day showed that *t*-**8** was yielded together with **5** and *c*-**8** in a ratio of 5 : 5 : 4.

On the other hand the close thermodynamical stability between *c*-**8** and *t*-**8** suggested that no diastereoselectivity should be observed for the formation of chromanones in the IMA of **7** with TEA. Treatment of **7** with TEA under the condition in run 1 in Table 1 resulted in the complete production of a 1 : 1 diastereoisomeric mixture of **8** as same as in the case of **5**.

Hydride Reduction of the 2, 3-Dimethylchroman-4-one 8 to the 2, 3-Dimethylchroman-4-ol 9

Hydride reduction of the *trans* chromanone *t*-**8** was examined for the goal of this model synthetic work. (Table 2) In the related reductions[4a-d, 7a, 8b] Luche reduction[8a] has been adopted as a promising method for the stereoselective formation of *trans* chromanols from the corresponding chromanones, although it was also

**Table 2. Trials for Hydride Reduction of the *trans* Chromanone *t*-8**
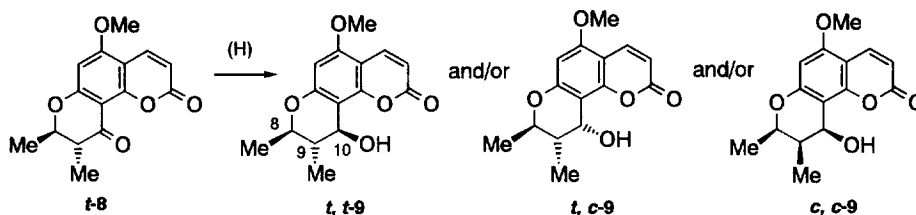
run	reagent (equiv.)	solvent (mol/L)	temp (°C)	time	yield[a] (%)	products (ratio)[b]
1	NaBH$_4$ (2.2) CeCl$_3$ · 7H$_2$O (10)	EtOH (0.04)	rt	1 d	quant.	*t, t*-9/*t, c*-9/*c, c*-9 (4/1/1)
2	NaBH$_4$ (1.3)	EtOH (0.13)	rt	1 d	80	*t, t*-9/*t, c*-9/*c, c*-9 (3/1/1)
3	BH$_3$ (1.3)	THF (0.10)	rt	1 d	quant.	*t, t*-9/*t, c*-9 (3/1)
4	Zn(BH$_4$)$_2$ (10)	Et$_2$O (0.01)	rt	1 d	quant.	*t, t*-9/*t, c*-9 (4/1)
5	K-Selectride® (1.1)	THF (0.07)	0	1 h	decomp.	——
6	9-BBN (1.0)	THF (0.10)	rt	1 d	NR[c]	——
7	LAH (2.2)	THF (0.05)	rt	1 min	52	*t, t*-9/*t, c*-9 (5/1)
8	LAH (2.0) CsF (2.0)	THF (0.06)	(1) -78 (2) -10	(1) 5h (2) 18h	53	*t, t*-9/*t, c*-9 (5/1)
9	LATBH (1.3)	THF (0.06)	-2	2 h	95	*t, t*-9/*t, c*-9 (10/1)

[a] Nonoptimized, isolated yield. [b] The ratio of diastereoisomers was determined by ^{1}H NMR (400 MHz).
[c] No reaction.

reported that the diastereoselectivity could be affected by reaction conditions such as temperature[4a] or scale.[4b] Thus, we firstly applied the Luche reduction to *t*-8.

Treatment of *t*-8 in EtOH with sodium borohydride (NaBH$_4$) in the presence of ceric chloride (CeCl$_3$) at rt for 1 day quantitatively afforded a reduction product, which was found to be composed of three diastereoisomers with close Rf values on TLC in the solvent systems examined by us (run 1). Lowering the reaction temperature caused incomplete reduction because of the low solubility of *t*-8 to EtOH. Although trial for the separation of products failed, the ^{1}H NMR spectrum indicated that their ratio in the crude product was 4 : 1 : 1. The stereochemistries of each isomer were determined by comparison of the ^{1}H NMR data of them to the reported data of *Calophyllum* coumarins.[1b, 1c, 2c-g, 4c] In a major isomer the methine protons at 8, 9 and 10 positions appeared at δ 3.95, 1.92 and 4.73 with large coupling constants of $J_{8,9}$=8.4 Hz and $J_{9,10}$=7.8 Hz.

Scheme 3. Supposed Transition States for the LTBAH Reduction of Chromanones 8
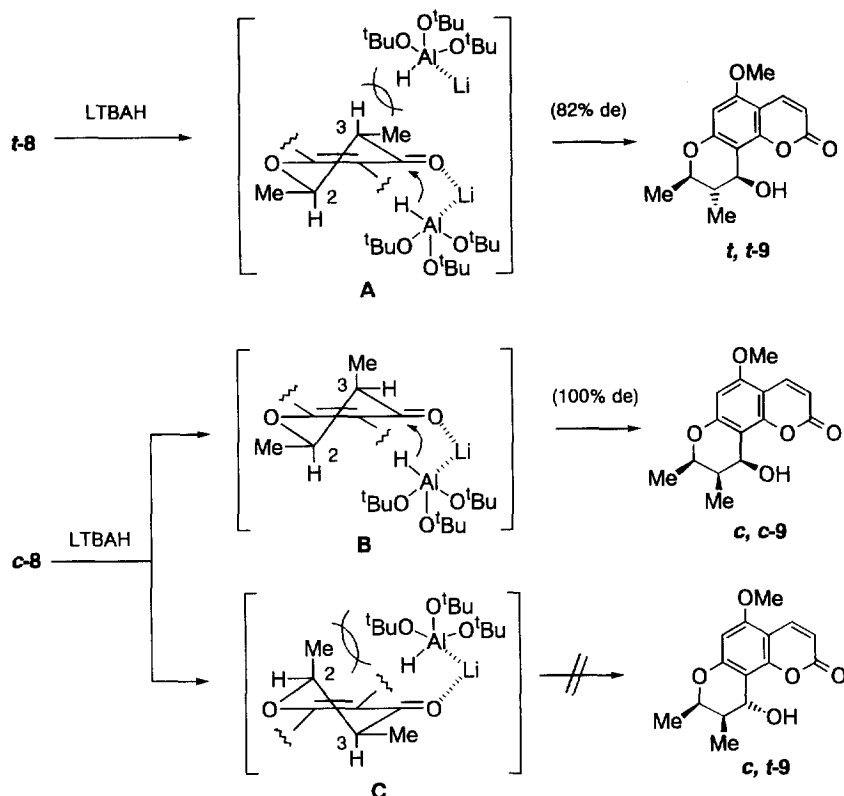
These data indicated that it was an intended *trans, trans* chromanol *t*, *t*-9 like calanolide A (**1a**) or inophyllum B (**2a**). Similarly the minor two components were assigned to be a *trans, cis t*, *c*-9 [δ 4.27 (C_8), 1.76 (C_9), 4.97 (C_{10}); $J_{8, 9}$=8.6 Hz, $J_{9, 10}$=3.3 Hz] like calanolide B (**1b**) or inophyllum P (**2b**) and a *cis, cis* derivatives *c*, *c*-9 [δ 4.35 (C_8), 2.27 (C_9), 5.12 (C_{10}); $J_{8, 9}$=3.2 Hz, $J_{9, 10}$=5.1 Hz] like calanolide C (**1d**) or inophyllum A (**2d**), respectively.

Trial for the reduction with $NaBH_4$ without $CeCl_3$ resulted in lowering both a chemical yield and diastereoselectivity (run 2). Stout *et al.*[1a] reported an epimerization during the $NaBH_4$ reduction of the related chromanones. We also observed a similar epimerization in runs 1 and 2 in Table 2. Thus, we examined reduction under neutral condition such as a borane-THF complex (run 3) or zinc borohydride[18] (run 4). Although no epimerization was observed in both cases, the diastereoselectivity could not be improved. Other reductants such as K-Selectride* or 9-borabicyclo[3. 3. 1]nonane (9-BBN) afforded no chromanols (runs 5, 6).

We next focused on aluminum complexes for the reduction of *t*-8 in spite of no use of them in the related coumarin synthesis. Lithium aluminum hydride (LAH) led to preferred formation of a desired *trans, trans* 2, 3-
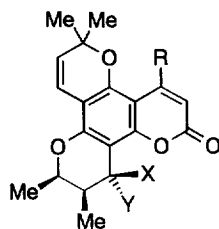
10: R=Pr, X+Y=O
11: R=Pr, X=H, Y=OH
12: R=Ph, X+Y=O

dimethylchroman-4-ol *t, t-9* to the *trans, cis* derivative *t, c-9* in a slightly improved ratio (5 : 1) albeit in unsatisfactory chemical yield (52%) (run 7). Quite rapid completion (1 min) of the reaction at rt indicated that LAH was too highly reactive. Then, we tried the LAH reduction at low temperature in the presence of CsF which might decrease the reactivity of a substrate through hydrogen bonding. Unfortunately no improvement was observed (run 8). Nontheless higher selectivity in the LAH reductions than in the reduction using borane complexes made us examine the reaction using more bulky LTBAH with a weaker reducing power. Treatment of *t-8* with LTBAH at -2°C for 2 h expectedly afforded the desired *t, t-9* in 95% yield with high diastereoselectivity (82% de) (run 9). This fact indicated that the bulky LTBAH could effectively attack on the ketonic function from a less hindered site opposite to the axial proton at the 3 position of the chromanone ring. (see A in Scheme 3)

The successful reduction of the *trans* chromanone *t-8* with LTBAH prompted us to apply the reagent to the reduction of a *cis* chromanone *c-8*, because some discrepancy on the diastereoselectivity appeared in the NaBH$_4$ reduction of a related *cis* chromanones. For example, Chenera *et al.*[7a] reported the exclusive production of calanolide C (**1d**) with a *cis, cis* chromanol skeleton in the reduction of calanolide D (**10**), whereas Zembower *et al.*[4e] the additional formation of an isomeric epicalanolide C (**11**) with a *cis, trans* one. Furthermore in inophyllum series inophyllum D (**2c**) and inophyllum A (**2d**) were obtained in a ratio of 1 : 4 in the reduction of the corresponding *cis* chromanone (**12**).[28]

Treatment of *c-8* with LTBAH under the same condition on *t-8* quantitatively gave a *cis, cis*-chromanol *c, c-9* as a sole reduction product. In the reduction of *c-8* two transition states (B and C in Scheme 3) could be supposed. Between them the axial methyl group at the 2 position of the chromanone ring in the transition state C could effectively block the approach of LTBAH to the ketone group, while smooth attack of the reagent should occur in the transition B. Thus, the exclusive production of *c, c-9* could be reasonably explained by attack of the reagent from a less hindered site as shown in the transition B in Scheme 3.

CONCLUSION

A 2, 3-dimethylchroman-4-one skeleton has been diastereo- and enantioselectively prepared by the reaction of an *o*-propionylphenol with an acetaldehyde derivative[4a] and by methylation of a chiral 2-methylchromanone under a basic condition,[8b] respectively. However, satisfactory results were not given in

these reactions; *i. e.* in the former case[4a] the chemical yield was low (30%) and in the latter case[8b] no diastereoselectivity was observed. As described above we have succeeded in newly exploring easy and diastereoselective construction of a *trans* 2, 3-dimethylchroman-4-one ring by the CsF-induced IMA of an *o*-tigloylphenol. We also found that LTBAH could be a more effective reagent than borane reagents, including a Luche reagent, for the diastereoselective production of *trans, trans* and *cis, cis* chroman-4-ol rings in the reduction of *trans* and *cis* 2, 3-dimethylchroman-4-one derivatives, respectively.

Thus, a model *Calophyllum* coumarin *t*, *t*-9 with a *trans, trans* 2, 3-dimethylchroman-4-ol skeleton, which was supposed to be the most responsible relative stereochemistries against anti-HIV-1 activity, could be easily and effectively prepared from limettin (3). Anti-HIV activity[19] of our synthetic coumarins was tested, but both *trans, trans t*, *t*-9 and *cis, cis* 2, 3-dimethylchroman-4-ol derivatives *c*, *c*-9 showed no activity. Recent studies[4a, 4d, 6] on the structure-activity relationship of *Calophyllum* coumarins and the related compounds suggested that the S configuration of the 4 position in the chromanol ring (position 12 in 1 and 2) could play the most important role for the biological activity. Therefore, we have now been extending this model studies toward asymmetric total synthesis of *Calophyllum* coumarins.

EXPERIMENTAL

General   All melting points were measured on a micro melting point hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded for Nujol mulls on a JASCO IR-300 spectrophotometer and UV spectra in MeOH on a Hitachi U-3400 spectrophotometer, respectively. Shoulder peaks are abbreviated as sh. ^{1}H NMR spectra were recorded in CDCl$_3$ solution with a JOEL JNM GSX-400α or -500α spectrometers, with tetramethylsilane as an internal reference. Peak multiplicities are quoted in Hz. Diffused and broad splitting patterns are abbreviated as dif and br, respectively. MS were measured with a JOEL JMS-HX-110A (EI and FAB modes) spectrometer. For matrix in FABMS was used *m*-nitrobenzyl alcohol. For column and flash chromatographies silica gel 60 (70-230 mesh, Merck) and silica gel 60 (230-400 mesh, Nacalai Tesque), respectively, and for TLC silica gel GF$_{254}$ (Merck) were used. A commercial CsF was purified according to the reported method.[14] In general the extract was washed with brine, dried over magnesium sulfate and filtered. The filtrate was evaporated to dryness under reduced pressure.

8-Tigloyllimettin (4).   A solution of SnCl$_4$ (12.4 ml, 0.11 mol) in dry CH$_2$Cl$_2$ (16 ml) was dropped to a stirred solution of limettin (3) (5.47 g, 26.5 mmol) and tigloyl chloride[20] (7.71 g, 65.0 mmol) in dry CH$_2$Cl$_2$ (33 ml) at -70 °C. The mixed solution was kept to stand in a refrigerator (0-2 °C) for 3 days. After worked up recrystallization of the residue from CH$_2$Cl$_2$-hexane gave colorless prisms (3.69 g, 48%). Purification of the mother liquor by column chromatography using hexane-ethyl acetate (2 : 1) afforded an additional product as colorless prisms [1.50 g (total 5.19 g, 68%)], mp 187-189 °C; IR ν (KBr) (cm^{-1}) 1724, 1656; ^{1}H NMR δ 1.84 (3H, dq, *J*=6.8, 1.0 Hz, 3'-Me), 1.95 (3H, dif s, 2'-Me), 3.85, 3.96 (each 3H, s, OMe), 6.14 (1H, d, *J*=9.8 Hz, 3-H), 6.32 (1H, s, 6-H), 6.44 (1H, dif q, *J*=6.8 Hz, 3'-H), 7.95 (d, 1H, *J*=9.8 Hz, 4-H); EIMS *m/z* 288 (M$^+$, 100%); *Anal.* Calcd for C$_{16}$H$_{16}$O$_5$: C, 66.66; H, 5.59. Found: C, 66.42; H, 5.44.

7-Hydroxy-5-methoxy-8-tigloylcoumarin (5). A solution of BCl_3 in CH_2Cl_2 was prepared by dilution of BCl_3 with four-fold volumes of CH_2Cl_2 under ice-cooling. The BCl_3 in CH_2Cl_2 solution (1.42 ml, 4.2 mmol as BCl_3) was dropped to a mechanically stirred suspension of **4** (0.40 g, 1.4 mmol) in dry CH_2Cl_2 (3.0 ml) at -70 °C under Ar. The mixed solution was stirred at the same temperature for 4 h. After worked up purification of the residue by recrystallization from CH_2Cl_2-hexane gave colorless prisms (0.28 g, 73%), mp 237-238 °C; IR ν (cm^{-1}) 3170, 1737; ^{1}H NMR δ 1.84 (3H, d, J=6.8 Hz, 3'-Me), 1.99 (3H, s, 2'-Me), 3.96 (3H, s, OMe), 6.15 (d, 1H, J=9.8 Hz, 3-H), 6.16 (1H, m, 3'-H), 6.34 (1H, s, 6-H), 7.96 (1H, d, J=9.8 Hz, 4-H), 12.33 (1H, s, OH); UV λmax nm (log ε) 242 (3.96), 272 (4.04)sh, 297 (4.29), 323 (4.25), 344 (4.05)sh; EIMS m/z 274 (M$^+$, 8.6%), 259 (100%); *Anal.* Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.57; H, 5.13.

8-Angeloyl-7-hydroxy-5-methoxycoumarin (7). A solution of **5** (0.039 g, 0.14 mmol) in acetone (40 ml) was irradiated through Pyrex® filter with 400 W high pressure Hg lamp for 40 min under ice-cooling. After worked up purification of the residue by column chromatography using hexane-ethyl acetate (5 : 1) afforded colorless prisms [0.022 g (57%)], mp 143-146 °C; IR ν (cm^{-1}) 3093, 1730; ^{1}H NMR δ 1.56 (3H, dq, J=7.4, 1.4 Hz, 3'-Me), 2.05 (3H, dif q, J=1.4 Hz, 2'-Me), 3.98 (3H, s, OMe), 5.63 (1H, dif q, 3'-H), 6.18 (1H, d, J=9.7 Hz, 3-H), 6.33 (1H, s, 6-H), 7.99 (1H, d, J=9.7 Hz, 4-H), 13.97 (1H, s, OH); UV λmax nm (log ε) 239 (3.81), 244 (3.82), 284 (4.27)sh, 294 (4.36), 322 (4.24), 343 (4.07)sh; FABMS m/z 275 (MH$^+$); *Anal.* Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.46; H, 5.03.

IMA of 7-Hydroxy-5-methoxy-8-tigloylcoumarin (5)

(i) With TEA (Run 1 in Table 1): Separation of *cis*- and *trans*-8, 9-Dihydro-8, 9-dimethyl-5-methoxybenzo[1, 2-*b*; 5, 6-*b'*]dipyran-2(2*H*), 10 (10*H*)-diones (*c*-8 and *t*-8) A mixture of **5** (0.342 g, 1.25 mmol) and TEA (0.52 ml, 3.73 mmol) in CHCl$_3$ (4.8 ml) was stirred at rt for 4 h. After worked up the crude product was given as colorless prisms (0.339 g, quant.), whcih was estimated as a 1 : 1 mixture of *c*-8 and *t*-8 by the ^{1}H NMR spectrum. After addition of ethyl acetate (*ca* 50 ml) to the crude prodcut under ice-cooling, the suspension was divided into an insoluble fraction (Fr. I-1) (0.147 g) and a soluble one (Fr. S-1) (0.192 g). After evaporation of the Fr. S-1 the residue was similarly treated using ethyl acetate (*ca* 20 ml) to further divide into an insoluble fraction (Fr. I-2) (0.060 g) and a soluble one (Fr.S-2) (0.132 g).

(a) *trans* **Chromanone *t*-8**: After combined Fr. I-1 and I-2, recrystallization from CHCl$_3$-hexane gave *t*-8 as colorless prisms (0.116 g, 47%), which was identical with a sample obtained in the CsF-induced IMA mentioned below.

(b) *cis* **Chromanone *c*-8**: After evaporation of the Fr. S-2 flash chromatography of the residue using CHCl$_3$ and ethyl acetate (10 : 1) as a solvent gave *c*-8 (0.085 g, 25%), which were recrystallized from CHCl$_3$-hexane to give colorless prisms, mp 239-241 °C; IR ν (cm^{-1}) 1726, 1680; ^{1}H NMR δ 1.16 (3H, d, J=7.0 Hz, 9-Me), 1.42 (3H, d, J=6.7 Hz, 8-Me), 2.67 (1H, dq, J=7.0, 3.3 Hz, 9-H), 3.96 (3H, s, OMe), 4.70 (1H, dq, J=6.7, 3.3 Hz, 8-H), 6.25 (1H, d, J=9.7 Hz, 3-H), 6.29 (1H, s, 6-H), 7.96 (1H, d, J=9.7 Hz, 4-H); UV λmax nm (log ε) 238 (3.87), 246 (3.84), 264 (4.09)sh, 275 (4.21), 284 (4.25), 321 (4.21), 341 (4.00)sh; EIMS m/z 274 (M$^+$, 100%); *Anal.* Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.34; H, 5.07.

(ii) With TMSI (Run 4 in Table 1): Production of 7-Hydroxy-8-(3-iodo-2-methyl-1-

oxobutyl)-5-methoxycoumarin   TMSI was diluted with ten-fold volumes of CH_2Cl_2. The solution (1.6 ml, 1.1 mmol as TMSI) was added to a stirred mixture of **5** (0.20 g, 0.73 mmol) in CH_2Cl_2 (2.0 ml) at - 70 °C under Ar and then the whole was stirred at the same temperature for 2 h. After worked up recrystallization of the crude product from CH_2Cl_2-hexane gave colorless prisms (0.241 g, 82%), mp 149-150 °C; IR ν (KBr) (cm⁻¹) 1735, 1682; ¹H NMR δ 1.35 (3H, d, *J*=6.4 Hz, 2'-Me), 2.10 (3H, d, *J*=6.8 Hz, 3'-Me), 3.86 (1H, dq, *J*=6.4, 4.5 Hz, 2'-H), 3.97 (3H, s, OMe), 4.68 (1H, dq, *J*=6.8, 4.5 Hz, 3'-H), 6.21 (1H, d, *J*=9.8 Hz, 3-H), 6.33 (1H, s, 6-H), 8.02 (1H, d, *J*=9.8 Hz, 4-H), 14.01 (1H, s, OH); EIMS *m/z* 402 (M⁺, 3.9%), 219 (100%); *Anal.* Calcd for $C_{15}H_{15}IO_5$: C, 44.80; H, 3.76. Found: C, 44.78; H, 3.65.

(iii) With CsF (Run 6 in Table 1): Isolation of the *trans* Chromanone *t*-8   A mixture of **5** (0.533 g, 1.94 mmol) in dry THF (1.5 ml) with CsF (0.589 g, 3.88 mmol) was stirred at 60 °C for 3 days under Ar. After worked up the crude product was given as colorless prisms (0.502 g, 94%), whcih was estimated as a 5 : 95 mixture of *c*-8 and *t*-8 by the ¹H NMR spectrum. Recrystallization of it from CH_2Cl_2 gave colorless prisms, mp 251-252 °C; IR ν (cm⁻¹) 1727, 1681; ¹H NMR δ 1.21 (3H, d, *J*=6.8 Hz, 9-Me), 1.53 (3H, d, *J*=6.4 Hz, 8-Me), 2.56 (1H, dq, *J*=11.0, 6.8 Hz, 9-H), 3.95 (3H, s, OMe), 4.31 (1H, dq, *J*=11.0, 6.4 Hz, 8-H), 6.24 (1H, d, *J*=9.7 Hz, 3-H), 6.28 (1H, s, 6-H), 7.95 (1H, d, *J*=9.7 Hz, 4-H); UV λmax nm (log ε) 237 (3.93), 246 (3.25), 264 (4.09)sh, 274 (4.20), 284 (4.25), 320 (4.21), 339 (4.03)sh; HRFABMS *m/z* 275.0948 (Calcd for $C_{15}H_{15}O_5$: 275.0920); *Anal.* Calcd for $C_{15}H_{14}O_5$•1/8CH_2Cl_2: C, 63.76; H, 5.04. Found: C, 63.63; H, 5.08.

IMA of 8-Angeloyl-7-hydroxy-5-methoxycoumarn (7)

(i) With TEA   A mixture of **7** (0.09 g, 0.02 mmol) in $CHCl_3$ (1.0 ml) with TEA (0.01 ml, 0.07 mmol) was stirred at 60 °C for 1 d under Ar. After worked up the crude product was given as colorless prisms (0.09 g, quant.), whcih was estimated as a 1 : 1 mixture of *c*-8 and *t*-8 by the ¹H NMR spectrum.

(ii) With CsF   A mixture of **7** (0.019 g, 0.07 mmol) in DMF (0.5 ml) with CsF (0.021 g, 0.14 mmol) was stirred at 60 °C for 1.5 days under Ar. After worked up colorless prisms was quantitatively given, whcih was estimated as a 5 : 4 : 5 mixture of **5**, *c*-8 and *t*-8 by the ¹H NMR spectrum.

Reduction of the *trans* Chromanone *t*-8

(i) With $NaBH_4$ in the Presence of $CeCl_3$•$7H_2O$ (Run 1 in Table 2)   A mixture of *t*-8 (0.02 g, 0.07 mmol), $NaBH_4$ (0.006g, 0.16 mmol) and $CeCl_3$•$7H_2O$ (0.265g, 0.71 mmol) in EtOH (2.0 ml) was stirred at rt for 1 d. The crude product (0.02 g, quant.) given after worked up was estimated as a 4 : 1 : 1 mixture of *t*, *t*-9, *t*, *c*-9 and *c*, *c*-9 by the ¹H NMR spectrum.

(ii) With LATBH (Run 9 in Table 2): Isolation of *trans, trans*-8, 9-Dihydro-8, 9-dimethyl-5-methoxybenzo[1, 2-*b*; 5, 6-*b*']dipyran-2(2*H*)-one-10(10*H*)-ol (*t*, *t*-9)   A 1 M solution of LATBH in THF (0.5 ml, 0.5 mmol) was added to a suspension of *t*-8 (0.103 g, 0.375 mmol) in dry THF (6.5 ml) at -2°C and the whole was stirred at the same temperature for 2 h. After worked up the crude product was given as colorless prisms (0.99 g, 95%), which was estimated as a 10 : 1 mixture of *t*, *t*-9 and *t*, *c*-9 by the ¹H NMR spectrum. Recrystallization of it from ethyl acetate-hexane afforded *t*, *t*-9 as colorless prisms, mp 189-190 °C; IR ν (KBr) (cm⁻¹) 3597, 1725; ¹H NMR δ 1.15 (3H, d, *J*=6.6 Hz, 9-Me), 1.45 (3H, d, *J*=6.4 Hz, 8-Me), 1.92 (1H, m, 9-H), 3.58 (1H, d, *J*=2.4 Hz, OH), 3.87 (3H, s, OMe), 3.95 (1H, dq, *J*=8.4, 6.4 Hz,

8-H), 4.73 (1H, dd, J=7.8, 2.4 Hz, 10-H), 6.14 (1H, d, J=9.7 Hz, 3-H), 6.22 (1H, s, 6-H), 8.00 (1H, d, J=9.7 Hz, 4-H); EIMS m/z 276 (M$^+$, 40.9%), 220 (100%); *Anal.* Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.37; H, 5.75.

Reduction of the *cis* Chromanone *c*-6 with LATBH: Isolation of *cis*, *cis*-8, 9-Dihydro-8, 9-dimethyl-5-methoxybenzo[1, 2-*b*; 5, 6-*b*']dipyran-2(2*H*)-one-10(10*H*)-ol (*c*, *c*-9) A 1 M solution of LATBH in THF (0.12 ml, 0.12 mmol) was added to a suspension of **c-8** (0.024 g, 0.089 mmol) in dry THF (1.3 ml) at -2°C and the whole was stirred at the same temperature for 2 h. After worked up the crude product was purified by column chromatography to give ***c***, ***c*-9** as colorless prisms (0.024 g, quant.), mp 125-128 °C; IR ν (KBr) (cm^{-1}) 3420, 1705; ^{1}H NMR δ 1.13 (3H, d, J=7.1 Hz, 9-Me), 1.41 (3H, d, J=6.6 Hz, 8-Me), 2.27 (1H, ddq, J=7.1, 5.1, 3.2 Hz, 9-H), 3.40 (1H, br, OH), 3.87 (3H, s, OMe), 4.35 (1H, dq, J=6.6, 3.2 Hz, 8-H), 5.12 (1H, d, J=5.1 Hz, 10-H), 6.13 (1H, d, J=9.8 Hz, 3-H), 6.22 (1H, s, 6-H), 8.00 (1H, d, J=9.7 Hz, 4-H); EIMS m/z 276 (M$^+$, 41.3%), 164 (100%); *Anal.* Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.06; H, 5.89.

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15. The use of less than an equimolar amount of CsF led to an incomplete reaction.

16. No isomerization was also observed when used diisopropylethylamine instead of TEA in various solvents such as $CHCl_3$, EtOH and acetone.

17. Calculation was performed using a MOPAC AM1 method (*c*-**8**: -141.90888 kcal, *t*-**8**: -142.47974 kcal).

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20. A mixture of tiglic acid (20 g, 0.2 mol) and thionyl chloride (20 ml, 0.27 mol) was stirred at rt for 2.5 h and then at 40 °C for 1 h. Distillation of the mixture at bp 47-48 °C (75-80 mmHg) gave tigloyl chloride as a colorless liquid (14.7 g, 62%).