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Solvent effects on stereoselectivity in 2,3-dimethyl-4-chromanone cyclization by quinine-catalyzed asymmetric intramolecular oxo-Michael addition

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Abstract

Examination of the quinine-catalyzed asymmetric intramolecular oxo-Michael addition of *o*-tigloylphenol in various solvents led to high stereoselectivity in chromanone cyclization when chlorobenzene was used as a solvent, giving *cis*-2,3-dimethyl-4-chromanone with 60% de and 98% ee.

(+)-Calanolide A **1**, isolated as a strong anti-HIV-1 active coumarin from *Calophyllum lanigerum* var. *austrocoriaceum* (Guttiferae),[1] is presently being examined as a possible candidate for an AIDS drug at clinical level in USA.[2] The (10*R*,11*S*,12*S*) stereochemistry of the D ring in (+)-calanolide A **1** is suggested to be the most responsible function for anti-HIV-1 activity.[1,3] We have approached the enantioselective construction of the chromanone ring, easily leading to the corresponding chromanol function by hydride reduction, by intramolecular oxo-Michael addition (IMA) of an *o*-tigloylphenol in the presence of chincona alkaloids such as (−)-quinine, and effective asymmetric induction (up to 87% ee) was achieved in *cis*-chromanone cyclization in model studies using a coumarin lacking a 4-propyl group.[4] However, not only was there no diastereoselectivity between *cis*- and *trans*-products but also the enantioselectivity in the *trans*-chromanone cyclization was poor. Examination of the quinine-catalyzed IMA of 7-hydroxy-5-methoxy-4-propyl-8-tigloylcoumarin **3** in various solvents toward (+)-calanolide A **1** synthesis led to predominant formation (60% de) of (+)-enantiomer-rich *cis*-chromanone (98% ee) when chlorobenzene was used as a solvent. In this communication we present remarkable solvent effects on both diastereo- and enantioselectivities for a 2,3-dimethyl-4-chromanone ring construction in the quinine-catalyzed IMA.

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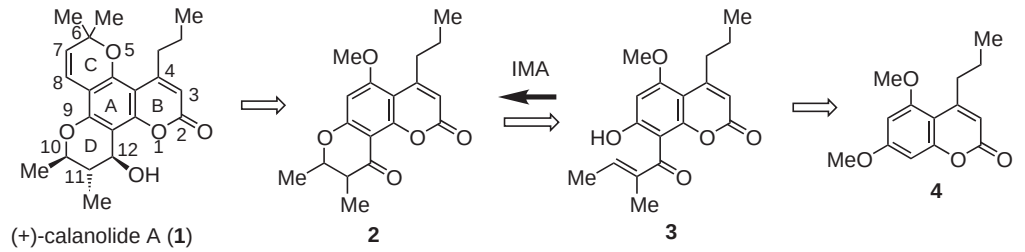
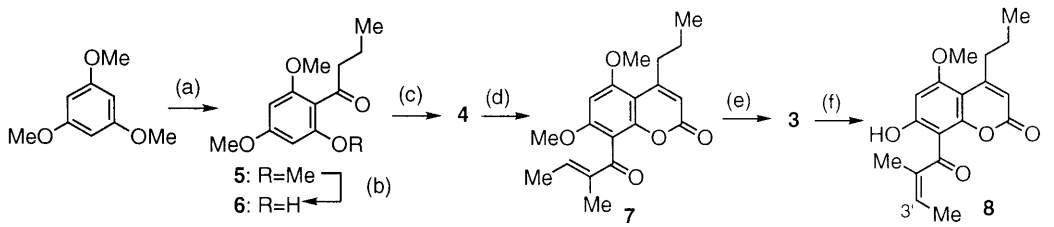
In synthetic trials for the total synthesis of (+)-calanolide A **1** we planned a retrosynthesis shown in Scheme 1, in which a 2,2-dimethylpyran ring (the ring C) would be prepared after the IMA of 5-methoxycoumarin derivative **3** because of successful IMA using a structurally related methoxycoumarin in the model experiments.[4]



Scheme 1.

The starting *o*-tigloylphenol **3** for the IMA was similarly prepared according to the reported method[5] (Scheme 2). Friedel–Crafts reaction of 1,3,5-trimethoxybenzene with butyryl chloride, selective demethylation, and treatment[6] with carbethoxymethylenetriphenylphosphorane afforded 5,7-dimethoxy-4-propylcoumarin **4**. Regioselective introduction[7] of a tigloyl function into **4** followed by demethylation at the 7-methoxy group with magnesium iodide[8] yielded the *o*-tigloylphenol **3**. Furthermore, an isomeric *o*-angeloylcoumarin[9] **8** was prepared by the photoirradiation[8] of **3** in acetone using a 400 W mercury lamp.



Scheme 2. Reagents and conditions: (a) butyryl chloride, $SnCl_4$ in CH_2Cl_2, −15 to −10°C, 2 h (96%); (b) BCl_3 in CH_2Cl_2, 0–5°C, 2.5 h (85%); (c) $Ph_3P{=}CHCO_2Et$ in $PhNEt_2$, 215°C, 6.5 h (82%); (d) tigloyl chloride, $SnCl_4$ in CH_2Cl_2, 0°C, 6 d (60%); (e) MgI_2 in PhH, reflux, 1 d (62%); (f) hν (400 W Hg) in acetone, 0°C, 40 min (60%)

We have suggested that ion pair formation in transition states as shown in Fig. 1 could play an important role for the effective stereoselectivity of *cis*-chromanone cyclization in the quinine-catalyzed IMA.[4] The use of polarizable solvents would be expected to cause stabilizisation of the chiral complex. Thus, we examined the IMA in the presence of 10 mol% of (−)-quinine[10] in various solvents (Table 1). According to a model experiment[4] *o*-tigloylphenol **3** was firstly subjected to the IMA in tetrahydrofuran for 7 days to afford a 56:44 mixture of *cis*- and *trans*-chromanones in 87% isolated yield (run 1). Each isomer was separated by preparative TLC.[11] As expected, *cis*-derivative *cis*-**2** was produced with relatively high enantioselectivity (77% ee).[12] A similar result was obtained when acetone was used as a solvent (run 2). Slight rate accelerations were observed in the reactions using chloroform or ethanol (runs 3 and 4) and the use of 2-trifluoroethanol led to large rate acceleration (run 5). However, enantioselectivities were lowered in these cases.

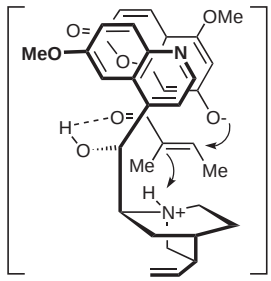
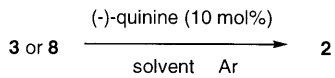


Figure 1.

Table 1
Solvent effects on quinine-catalyzed asymmetric IMA of *o*-tigolylphenol **3** or *o*-angeloylphenol **8** to chromanone cyclization

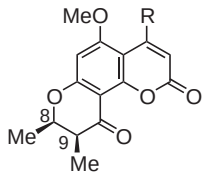


run	3 or 8	solvent	temp (°C)	time (h)	2 yield (%)[a]	2 *cis* (ee%)[b] : *trans*[c]
1	3	THF	24	168	87	56 (77) : 44
2		acetone	20	156	89	53 (73) : 47
3		$CHCl_3$	20	70	92	53 (45) : 47
4		EtOH	25	72	73	63 (1) : 37
5		CF_3CH_2OH	24	20	79	67 (17) : 33
6		benzene	20	14	80	44 (46) : 56
7		toluene	20	17	84	50 (46) : 50
8		$PhCF_3$	24	15	77	78 (94) : 22
9		PhF	25	20	74	80 (76) : 20
10		PhCl	14	21	100	80 (98) : 20
11		PhOMe	16	42	95	79 (92) : 21
12		C_6F_6	16	520	45	72 (95) : 28
13		1,3-di(trifluoromethyl)-benzene	24	160	78	76 (94) : 24
14		1,4-di(trifluoromethyl)-benzene	24	120	68	66 (92) : 34
15	8	PhCl	50	240	64	32[c] : 68 (78)[b]

[a] Non-optimized, isolated yield. A diastereoisomer ratio of *cis*- and *trans*-**2** was determined by ^1H NMR spectra. [b] The ee was determined by a chiral HPLC. (+)-Enantiomer was preferentially formed. [c] The ee was not determined.

On the other hand, aromatic solvents remarkably affected the IMA (runs 6–14). Interestingly the use of either halobenzenes or anisole greatly improved diastereo- and/or enantioselectivities of the cyclized products, leading the predominant production of *cis*-chromanone *cis*-**2** in ca. 60% de (runs 8–11). In particular, the use of chlorobenzene resulted in satisfactory asymmetric induction (98% ee) with smooth chemical conversion (run 10). Similar high selectivities were observed when trifluoromethylbenzene (run 8) and anisole (run 11) were used

as solvents, indicating that polarizability[13] of solvents rather than the electronical character of substituent(s) on the benzene ring could affect the quinine-catalyzed IMA. Furthermore, although perfluorobenzene or di(trifluoromethyl)benzenes resulted in improved stereoselectivities, slow chemical conversions were observed in these cases (runs 12–14). Thus, we concluded that chlorobenzene would be the most suitable solvent for the quinine-catalyzed IMA.[14] The absolute stereochemistry of an optically active *cis*-**2** with 98% ee obtained in run 10 was determined to be (*8R*,*9S*) configuration by comparison of its $[\alpha]_D$ +156.7 ($CHCl_3$) with that of a model *cis*-chromanone **9**, $[\alpha]_D$ +132.5 ($CHCl_3$).[4,15]



cis-**2**: R=Pr; **9**: R=H

We applied the above IMA in chlorobenzene to *o*-angeloylphenol **8** as a comparable experiment. Heating **8** at 50°C for 10 days expectedly afforded a 32:68 mixture of *cis*- and *trans*-**2** in 64% yield, in which *trans*-**2** was obtained in 78% ee (run 15).[16] Resistance of the reaction[17] in this case may be attributable to the predominant conformation as an s-*cis* isomer due to compensation of steric repulsion between the 7-hydroxy group and 3′-methyl one in the angeloyl residue. These facts indicated that the tigloylphenol **3** was a more suitable substrate than the angeloylphenol **8** for quinine-catalyzed intramolecular oxo-Michael reaction not only in the efficiency of the reaction but also in the selectivity of chromanone formation, in spite of predominant production of undesired *cis*-**2** for (+)-calanolide A **1** synthesis.[15]

In conclusion, the use of chlorobenzene in the quinine-catalyzed asymmetric IMA led to satisfactory diastereo- and enantioselectivities in chromanone cyclization. Thus, *cis*-2,3-dimethyl-4-chromanone *cis*-**2** could be derived from *o*-tigloylphenol **3** with 60% de and 98% ee.

Acknowledgements

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7. The coumarin **7** obtained in this reaction had been isolated from natural source [McKee, T. C.; Fuller, R. W.; Covington, C. D.; Cardelline, II, J. H.; Gulakowski, R. J.; Krepps, B. L.; McMahon, J. B.; Boyd, M. R. *J. Nat. Prod.* **1996**, *59*, 754–758].
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9. Up-shield shifted signals due to 3′-Me (δ 1.54) and 3′-H (δ 5.57–5.63) in **8** was observed compared to those (3′-Me: δ 1.84 and 3′-H: δ 6.14–6.17) in **3** in their ^{1}H NMR spectra. In addition, the presence of a strong hydrogen bond in **8** was suggested by appearance of a signal at δ 13.71. The corresponding signal in **3** was resonated at δ 11.86.
10. A commercially available (–)-quinine [purchased from Nacalai Tesque Co. Ltd (Japan)] was used after its azeotropic dehydration using toluene and then drying.
11. A mixed solvent of $CHCl_3$ and EtOAc (20:1) was used for the separation. The *cis*- and *trans*-isomer were obtained as a more polar and a less polar component, respectively.
12. Each enantiomer of *cis*-**2** was observed at retention times of 22.2 and 28.4 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.
13. The dipole moment of chlorobenzene is reported to be 1.69 D, whereas that of anisole is 1.38 D. (*Handbook of Chemistry and Physics*, 55th ed. West, R. C., Ed.; CRS Press: Ohio, 1974; E-63)
14. Chlorobenzene-assisted enantioselection was recently noted in a review of base-catalyzed asymmetric Diels–Alder reaction using 3-hydroxy-2-pyrone [Okamura, H.; Iwagawa, T.; Nakatani, M. *J. Synth. Org. Chem. (Jpn)* **1999**, *57*, 84–91].
15. Recently we succeeded in the total synthesis of (+)-calanolide A **1** by application of the quinine-catalyzed intramolecular oxo-Michael reaction of an *o*-tigloylphenol followed by MgI_2-mediated isomerization of *cis*-chromanone to the *trans*-one (Tanaka, T.; Kumamoto, T; Ishikawa, T. *Tetrahedron Lett*., in press).
16. Each enantiomer of *trans*-**2** was observed at retention times of 12.2 and 13.4 min, respectively, when CHIRALPAK AD-RH (Daicel Co. Ltd) was used as a column under the following conditions; eluent: MeOH, flow rate: 1.0 ml/min, detection: 254 nm.
17. No reaction was observed at room temperature.