# Cesium Fluoride-Induced Intramolecular Michael Addition: Highly Diastereoselective Ring Construction of a *trans*-2,3-Dimethylchroman-4-one

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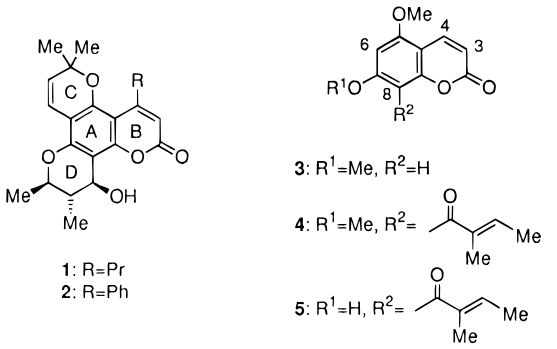
The highly diastereo- and/or enantioselective preparation of the *trans*-2,3-dimethylchroman-4-one ring is attracting much attention[1] because the *trans*,*trans*-2,3-dimethylchroman-4-ol skeleton (rings A, D) in *Calophyllum* coumarins such as calanolide A (**1**)[2] and inophyllum B (**2**)[3] has been suggested to have significant activity against anti-human immunodeficiency virus type 1 (HIV-1).[4] Although the most practical construction of chromanone rings[1,5] would be through intramolecular Michael addition (IMA)[1a−c] of *o*-tigloylphenols like **5**, stereoselective cyclization[6] has not been reported. In this paper, we present the highly diastereoselective ring construction of a *trans*-2,3-dimethylchroman-4-one by the cesium fluoride (CsF)-induced IMA using 7-hydroxy-5-methoxy-8-tigloylcoumarin (**5**) as a model synthetic approach to anti-HIV-1 active *Calophyllum* coumarins (Chart 1).

**Chart 1**




The starting phenol **5** was prepared by initial Friedel−Crafts acylation of limettin (**3**) with tigloyl chloride in the presence of tin(IV) chloride ($SnCl_4$) to afford the expected 8-tigloyl derivative **4** in 64% yield. The structure of the acylated product was determined by NOE enhancements of both methoxy groups at the 5 and 7 positions when a signal due to 6-H at $\delta$ 6.31 was irradiated. Treatment of **4** with boron trichloride led to selective demethylation of the 7-methoxy group to give tigloylphenol **5** in 73% yield.

In a related cyclization to chromanones by IMA, a base such as potassium carbonate ($K_2CO_3$)[1a] or triethylamine (TEA)[1b] was used as an additive. We first examine TEA for the cyclization of **5**, which led to preparation of both diastereoisomers of chromanone **6** (see entry 1 in Table 1). Fractional recrystallization of the products from ethyl acetate afforded the desired *trans*-**6** as a less soluble component. On the other hand, the *cis* isomer *cis*-**6** was separable by flash chromatography of the mother liquor [$CHCl_3$:ethyl acetate (10:1)]. The stereochemistry of each product was determined by examination of the coupling constant[2,3] between the methine protons at the 2 and 3 positions of the formed chromanone ring in the $^1$H NMR spectrum. The larger coupling constant ($J_{2,3}$ = 11.0 Hz) was assigned to *trans*-**6** in which both methine protons should be arranged in a *trans* diaxial relation, while the smaller one ($J_{2,3}$ = 3.3 Hz) was assigned to *cis*-**6**.

Chromanone cyclizations of **5** by IMA under various conditions are summarized in Table 1. The $^1$H NMR spectrum of the crude **6** in entry 1 in Table 1 showed no diastereoselectivity.[1b] Cyclization under acidic conditions failed to improve the diastereoselectivity (entries 2 and 3, Table 1). Interestingly, *cis*-**6** was formed as a slightly major isomer when a catalytic amount of $SnCl_4$ was used as an additive (entry 3, Table 1).

The fluoride atom of CsF can be effectively bonded to an acidic hydrogen atom such as a phenol function.[7] Thus, we focused on the effect of CsF on the chromanone cyclization by IMA. A solution of **5** in either dimethylformamide (DMF) (entry 4, Table 1) or tetrahydrofuran (THF) (entry 5, Table 1) was treated with about a 2-fold excess of CsF at 60 °C under argon. Although a longer time was needed for completion of the reaction,[8] the desired *trans*-**6** was formed both in high chemical yield and with high diastereoselectivity (90% de) in each case. On the other hand, the use of other fluorides (entries 6−9) also led to effective production of **6**. However, the diastereoselectivity for *trans*-**6** was low (30% de) in these cases. A similar result was also obtained when we used cesium carbonate or $K_2CO_3$ as an additive (entries 10 and 11, Table 1). These findings indicated that CsF itself is necessary for the highly diastereoselective *trans*-chromanone formation by IMA.

Monitoring of the CsF-induced IMA by thin layer chromatography (TLC) showed that *trans*-**6** was always the major isomer in the reaction mixture in addition to

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(2) (a) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, J. H., II; McMahon, J. B.; Currens, M. J.; Buckheit, R. W., Jr.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem*. **1992**, *35*, 2735. (b) Fuller, R. W.; Bokesch, H. R.; Gustafson, K. R.; McKee, T. C.; Cardellina, J. H., II; McMahon, J. B.; Cragg, G. M.; Soejarto, D. D.; Boyd, M. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1961. (c) Cardellina, J. H., II; Bokesch, H. R.; McKee, T. C.; Boyd, M. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1011.

(3) Patil, A. D.; Freyer, A. J.; Eggleston, D. S.; Haltiwanger, R. C.; Bean, M. F.; Taylor, P. B.; Caranfa, M. J.; Breen, A. L.; Bartus, H. R.; Johnson, R. K.; Hertzberg, R. P.; Westly, J. W. *J. Med. Chem*. **1993**, *36*, 4131.

(4) Taylor, P. B.; Culp, J. S.; Debouck, C.; Johnson, R. K.; Patil, A. D.; Woolf, D. J.; Brooks, I.; Hertzberg, R. P. *J. Biol. Chem*. **1994**, *269*, 6325.

(5) (a) Polonsky, J. *Bull. Soc. Chim. Fr*. **1956**, 914. (b) Polonsky, J.; Baskevitch, Z. *Bull. Soc. Chim. Fr*. **1958**, 929. (c) Stout, G. H.; Stevens, K. L. *J. Org. Chem*. **1964**, *29*, 3604. (d) Stout, G. H.; Hickernell, G. K.; Sears, K. D. *J. Org. Chem*. **1968**, *33*, 4191.

(6) Although Xu and co-workers[1e,f] reported a diastereoselective 2,3-dimethylchromanone synthesis by the reaction of *o*-propionylphenol with an acetaldehyde derivative, the chemical yield was low (30%). On the other hand, Rao and co-workers[1d] reported enantioselective 2,3-dimethylchromanone synthesis by methylation of a chiral 2-methylchromanone under basic conditions. However, no diastereoselectivity was observed in the methylation.

(7) For example, see: Clark, J. H.; Holland, H. L.; Miller, J. M. *Tetrahedron Lett*. **1976**, 3361.

(8) The use of less than an equimolar amount of CsF led to an incomplete reaction.

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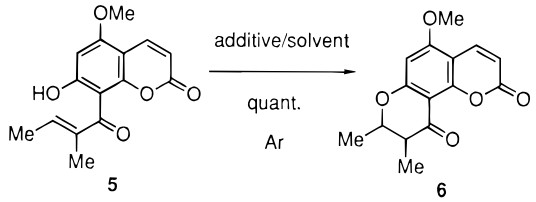
**Table 1. Trials for Cyclization of Phenol 5 to the Chromanone 6 by IMA**




| entry[a] | additive (equiv) | solvent (mol/L) | time | T (°C) | 6[b] (cis : trans) |
|---|---|---|---|---|---|
| 1 | TEA (3.0) | $CHCl_3$ (0.26) | 4 h | rt | 50:50 |
| 2 | TFA[c] (50) | $CHCl_3$ (0.2) | 12 h | rt | NR[d] |
| 3 | $SnCl_4$ (0.01) | THF (0.04) | 4 d | rt | 60:40 |
| 4 | CsF (2.1) | DMF (0.32) | 2 d | 60 | 5:95 |
| 5 | CsF (2.0) | THF (0.07) | 1 d | 60 | 5:95 |
| 6 | KF (2.1) | THF (0.04) | 1 h | 60 | 35:65 |
| 7 | $BaF_2$ (4.1) | THF (0.04) | 1 d | reflux | 35:65 |
| 8 | $CaF_2$ (2.0) | THF (0.03) | 1 d | reflux | 35:65 |
| 9 | TBAF[e] (1.5) | THF (0.06) | 7 h | 60 | 35:65 |
| 10 | $Cs_2CO_3$ (2.0) | THF (0.03) | 1 d | 60 | 30:70 |
| 11 | $K_2CO_3$ (2.0) | THF (0.03) | 1 d | 60 | 30:70 |

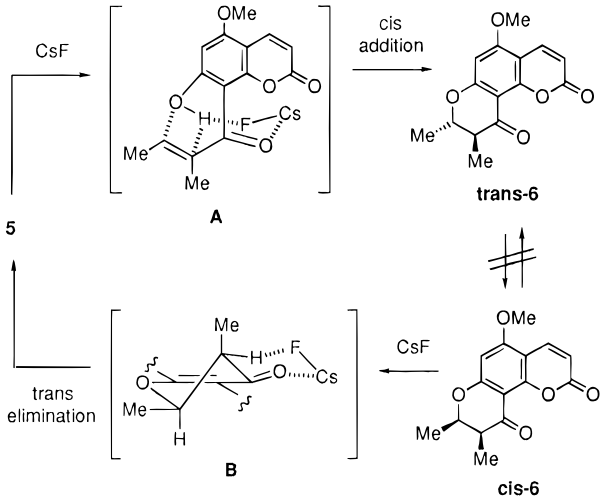
[a] The reaction was carried out under argon except for runs 1 and 2. [b] **6** was given quantitatively except for run 10 (60%). The ratio of diastereoisomers in the product was determined by $^1$H NMR (400 MHz). [c] Trifluoroacetic acid. [d] No reaction. [e] Tetrabutylammonium fluoride.

starting **5**. Furthermore, we found that *cis*-**6** was exclusively isomerized into *trans*-**6** through ring opening to the starting phenol **5**[9] under the conditions of the CsF-induced IMA, whereas *trans*-**6** was inert to this epimerization. On the other hand, further treatment of the crude **6** obtained by treatment with TEA under the same conditions resulted in no change of the diastereomeric ratio of the two stereoisomers, suggesting that they are nearly equal in thermodynamic stability. Thus, strictly stereocontrolled reactions must occur during these CsF-participating reactions (Scheme 1).

For the highly diastereoselective construction of the *trans*-chromanone in the CsF-induced IMA, the phenolic hydroxy group in **5** must be added to the olefinic bond of

(9) An isomeric angeloyl phenol, prepared by photoirradiation of **5**, could not be detected on TLC.

**Scheme 1. Supposed Transition States for the CsF-Participating Reactions**




the α,β-unsaturated ketonic function through a *cis* mode. The cesium atom of CsF may coordinate to a carbonyl oxygen because of its cationic character. Thus, a partial [4.2.0] bicyclic transition structure (**A** in Scheme 1), in which CsF coordinates through the phenolic hydrogen and the carbonyl oxygen atoms, may enforce *cis* addition of the phenolic hydroxyl group to the olefinic bond in the IMA. On the other hand, for the ring opening of only *cis*-**6** to the starting tigloylphenol **5** during the CsF-mediated epimerization, *trans*-1,4-elimination must occur. The methine protons at the 2 and 3 positions of the chromanone ring are axial−equatorial oriented in the stable conformation for *cis*-**6** and *trans* diaxially arranged in *trans*-**6** as mentioned above. Thus, we may also speculate that a CsF-coordinated six-membered cyclic transition state (**B** in Scheme 1) contributes to the stereospecific ring opening in only *cis*-**6**.

In conclusion, we succeeded in identifying a highly diastereoselective ring construction of the *trans*-2,3-dimethylchroman-4-one ring system by the CsF-induced IMA. This product could easily be reduced to the key *trans*,*trans*-2,3-dimethylchroman-4-ol[10] skeleton responsible for anti-HIV-1 activity shown by *Calophyllum* coumarins by Luche reduction.[1a−d,11] The effect of CsF on the highly diastereoselective ring construction of a *trans*-2,3-dimethylchroman-4-one in the CsF-induced IMA suggests another alternative utility[12] of CsF for organic synthesis.

**Supporting Information Available:** The CsF-induced IMA procedure and copies of $^1$H NMR spectra for compounds **4**, **5**, and *cis*- and *trans*-**6** (11 pages).

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(10) Reduction of *trans*-**6** is now in progress. These results, including the biological activities of obtained chromanols, will be reported in the near future.

(11) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(12) We have already reported the CsF-mediated Claisen rearrangement of aryl propargyl ethers, in which CsF acts like a base to exclusively produce 2-(methylaryl)furans instead of arylpyrans, the normal cyclized products in the corresponding thermal Claisen rearrangement: Ishii, H.; Ishikawa, T.; Takeda, S.; Ueki, S.; Suzuki, M. *Chem. Pharm. Bull.* **1992**, *40*, 1148.