Pergamon

Tetrahedron Letters 41 (2000) 10229–10232

TETRAHEDRON LETTERS

Enantioselective total synthesis of anti HIV-1 active (+)-calanolide A through a quinine-catalyzed asymmetric intramolecular oxo-Michael addition

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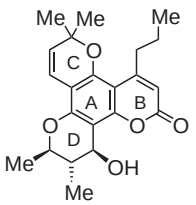
Received 4 September 2000; revised 10 October 2000; accepted 12 October 2000

Abstract

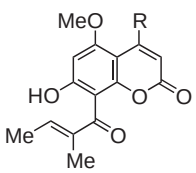
Enantioselective total synthesis of anti HIV-1 active (+)-calanolide A was achieved by a quinine-catalyzed asymmetric intramolecular oxo-Michael addition as a key step. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: asymmetric synthesis; Michael reactions; isomerizations; coumarins.

(+)-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 the clinical level in USA.[2] The (10*R*,11*S*,12*S*) stereochemistry of the 2,3-dimethyl-4-chromanol skeleton (the ring D) in **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 skeleton 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 coumarin **2** lacking a 4-propyl group.[4] However, not only was there no diastereoselectivity between *cis*- and *trans*-products **3** but also the enantioselectivity in the *trans*-chromanone cyclization was poor.

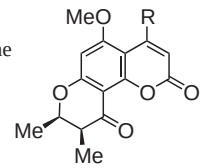


(+)-calanolide A (**1**)



2: R=H
4: R=Pr

(-)-quinine



cis-**3**: R=H (87% ee; 0% de in THF)
cis-**5**: R=Pr (98% ee; 60% de in PhCl)

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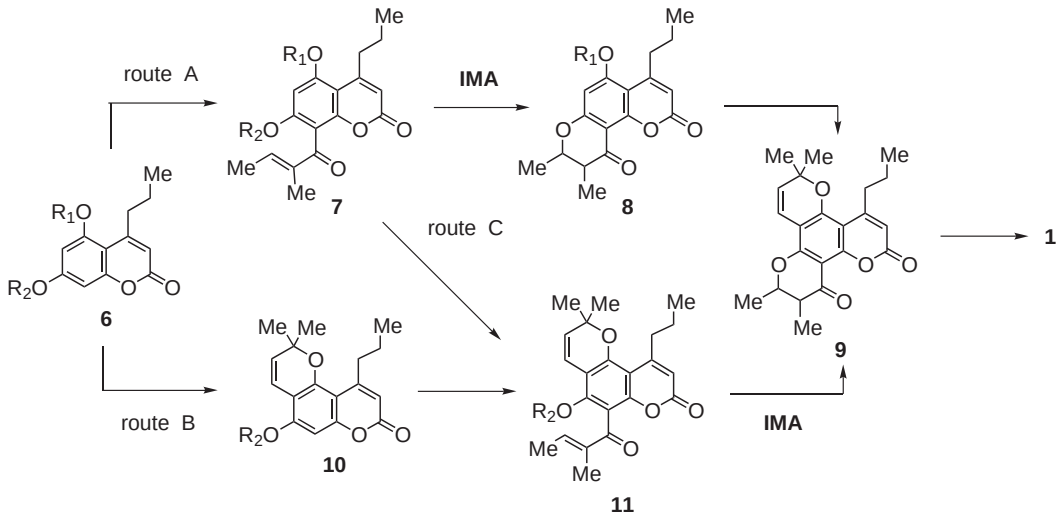
PII: S0040-4039(00)01820-7

Further examination of the quinine-catalyzed IMA using coumarin **4** in various solvents toward (+)-calanolide A (**1**) synthesis led to predominant formation (60% de) of (+)-enantiomer-rich *cis*-chromanone *cis*-**5** (98% ee) when chlorobenzene was used as a solvent.[5] In this communication we present the enantioselective total synthesis of **1** by application of the quinine-catalyzed IMA in chlorobenzene followed by *cis–trans* epimerization of the formed chromanones as the key steps.

For the total synthesis of calanolide A (**1**) composed of a four-ring system (rings A–D) from coumarin substrates, two basic routes of either IMA followed by C ring construction (route A) or the reverse order of the reactions (routes B or C) are available (Scheme 1). We have found that *cis*-chromanone–coumarin *cis*-**5** [*cis*-form in **8** (R_1 = Me)] was enantioselectively given by the quinine-catalyzed IMA of **4**;[5] however, trials for demethylation of the 5-methoxy group in **5** according to route A was not successful. Furthermore, introduction of a tigloyl group into a pyranocoumarin like **10** according to route B resulted in formation of a complex mixture.[5] Thus, a new access to a 10-tigloylpyranocoumarin like **11** by route C, in which 5,7-oxygenated coumarin **7** with different substituents at the 5- and 7-positions such as alkoxy and silyloxy groups is needed for selective cleavage of the 5-oxygen function, should be examined. Methoxy and triisopropylsilyl (TIPS) groups were chosen as the protecting groups for this purpose.



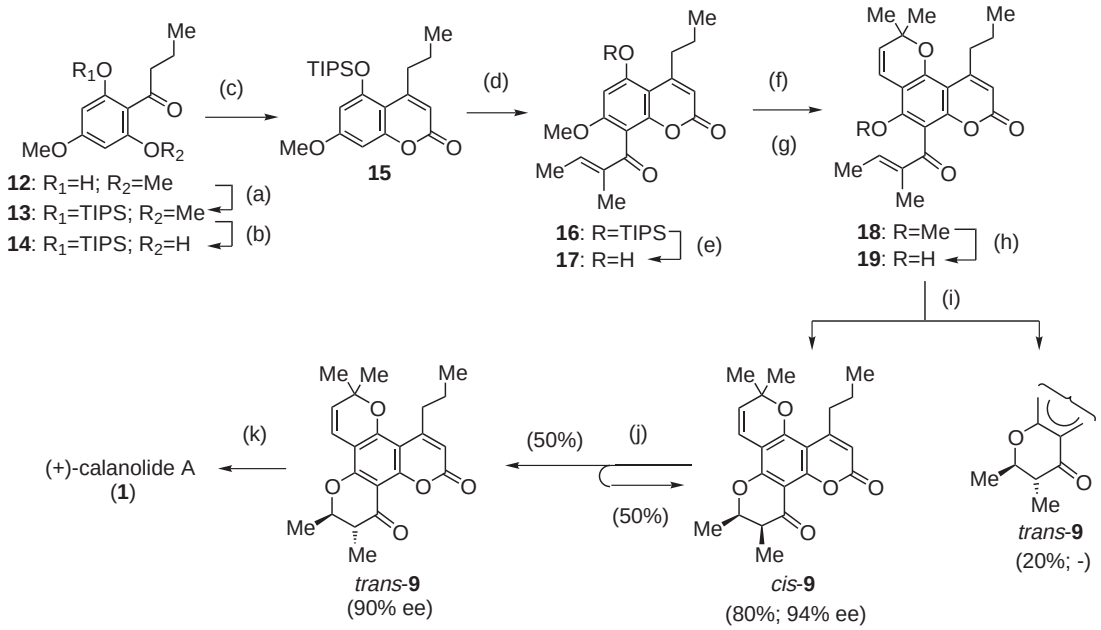
Scheme 1.

Treatment of **12**[5] with triisopropylchlorosilane (TIPCS) in the presence of benzyltriethylammonium chloride[6] as a phase transfer catalyst afforded the silylated derivative **13**. Selective demethylation of the *ortho* methoxy group in **13** was achieved by treatment with boron trichloride to give the desired product **14** in 71% yield,[7] which was converted into coumarin **15** in 58% yield[8] by Wittig-type reaction.[9] Friedel–Crafts reaction of TIPS-protected coumarin **15** with tigloyl chloride followed by deprotection of the TIPS group with tetrabutylammonium fluoride afforded 5-hydroxy-8-tigloylcoumarin **17**.[10] 2,2-Dimethylpyran ring formation on **17** by propargylation[11] and then Claisen rearrangement[12] gave the desired 10-tigloylpyranocoumarin[13] **18**, demethylation of which yielded **19**, the starting substrate for IMA. Application of the quinine[15]-catalyzed asymmetric IMA in chlorobenzene[5] to *o*-tigloylphenol **19** at 4–5°C[16] for 23 h afforded a cyclization product quantitatively, in which *cis*-chromanone *cis*-**9** was, as expected,

yielded in 60% de and 94% ee.[17] The stereochemistry of *cis*-**9** could be deduced to be (10*R*,11*S*) from the results in the model studies.[4]

(+)-Calanolide A (**1**) has a *trans*-2,3-dimethyl-4-chromanol system in its molecule, for the reductive construction of which a *trans*-chromanone ring should be needed. Treatment of *cis*-**9** (94% ee) with $MgI_2 \cdot 6H_2O$[18] in refluxing benzene successfully afforded *trans*-**9** with satisfactory ee (90%).[19] Although in this isomerization the starting *cis*-**9** was recovered in 50% yield, this method should be practically valuable because of the recovery of *cis*-**9** as a re-useable form without loss of optical activity.

Reduction of the enantiomerically rich *trans*-**9** with lithium tri(*tert*-butoxy)aluminum hydride[20] afforded (+)-calanolide A (**1**) in 41% yield after purification (see Scheme 2), which showed $[\alpha]_{589}^{24}$ +72 ($c = 1.1 \times 10^{-3}$, $CHCl_3$)[21] in good accordance with the reported data.



Scheme 2. *Reagents and conditions*: (a) TIPCS, $BnEt_3NCl$ in PhH-20% NaOH, rt , 20 min (100%); (b) BCl_3 in CH_2Cl_2, −78°C, 1 h (71%); (c) $Ph_3P{=}CHCO_2Et$ in $PhNEt_2$, 215°C, 30 min (72%); (d) tigloyl chloride, $SnCl_4$ in CH_2Cl_2, 7∼8°C, 7 days (72%); (e) TBAF in CH_2Cl_2–THF, 0°C, 5 min (58%); (f) 3-chloro-3-methyl-1-butyne, DBU, CuCl in MeCN, 7∼8°C, 16 h (71%); (g) $PhNEt_2$, 150°C, 80 min (93%); (h) MgI_2 in PhH, reflux, 2.5 h (77%); (i) (−)-quinine in PhCl, 3∼4°C, 23 h (100%); (j) $MgI_2 \cdot 6H_2O$ in PhH, reflux, 2.5 h (100%); (k) $LiAl(OBu^t)_3H$ in THF, −15∼−10°C, 2 h (41%)

In conclusion, we have succeeded in enantioselective total synthesis of (+)-calanolide A (**1**) through the quinine-catalyzed asymmetric IMA of *o*-tigloylphenol followed by MgI_2-mediated isomerization of the formed *cis*-chromanone into *trans*-one. Although (+)-calanolide A (**1**) has been prepared by two groups,[22,25] it is noteworthy that our method described here would be applicable to operationally simple, large-scale production.

Acknowledgements

We thank the Futaba Electron Memorial Foundation for partial financial support to this work.

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5. The details will be reported elsewhere.
6. No reaction was observed by treatment either with TIPCS and imidazole or with triisopropylsilyl triflate and 2,6-lutidine.
7. The hydroxybutyrophenone **12** was also obtained in 29% yield as a simply desilylated product.
8. Deprotection of the TIPS group was observed during the coumarin construction to give 5-hydroxycoumarin in 8% yield, which could be used as a source of **15**.
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15. A commercially available (−)-quinine [purchased from Nacalai Tesque Co. Ltd. (Japan)] was used after its azeotropic dehydration using toluene and then drying.
16. The cyclization was smoothly proceeded at rt (10 h) and *cis*-**9** was obtained with high ee (93%). However, de was lowered to 50%.
17. Each enantiomer of *cis*-**9** 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.
18. Treatment of *cis*-**9** (88% ee) with LDA afforded a complex mixture composed of *cis*-**9** (37%; 77% ee), *trans*-**9** (11%), and retro-Michael product **19** (39%), in which *trans*-**9** was obtained in a racemic form.
19. Each enantiomer of *trans*-**9** 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.
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