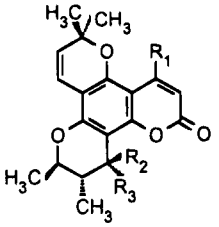
Synthesis of Optically Active Calanolides A and B

Prashant P. Deshpande, Frank Tagliaferri, Samuel F. Victory, Shija Yan, and David C. Baker*

Department of Chemistry, The University of Tennessee, Knoxville, Tennessee 37996-1600

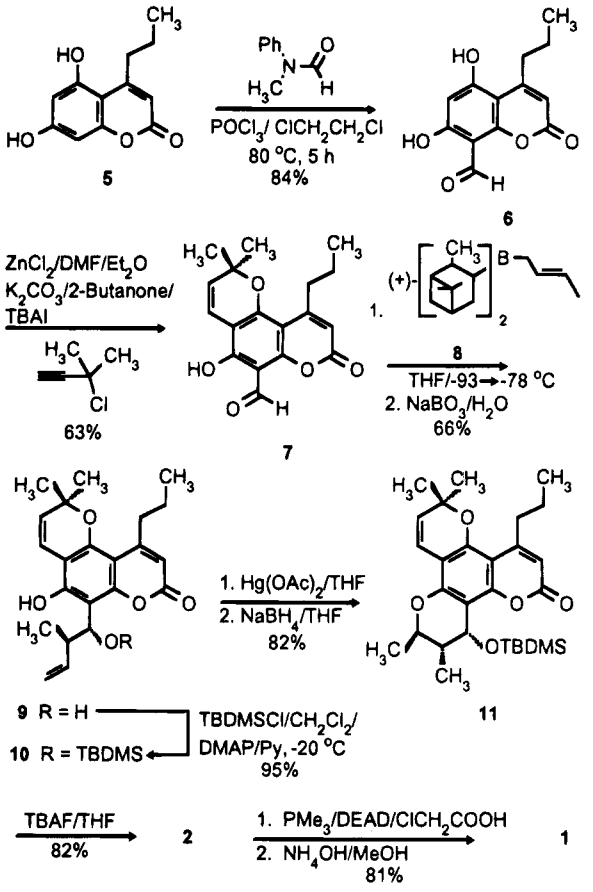
Received January 25, 1995 (Revised Manuscript Received April 11, 1995)

Recently calophyllum coumarins such as the calanolides[1] (**1** and **2**) and the inophyllums[2,3] (**3** and **4**) have attracted considerable attention as potent inhibitors of human immune deficiency virus-1 (HIV-1) reverse transcriptase (RT). Because these compounds show a mechanism of action toward the RT that is distinct from other non-nucleoside inhibitors, they may have potential use in the combination therapy of AIDS.[4] The ring system of these compounds is built around a phloroglucinol core, with common structural features that include a chromene ring, a coumarin ring, and most essential for their optical activity and perhaps their biological activity, a 2,3-dimethylchroman-4-ol (3,4-dihydro-2*H*-benzo[*b*]pyran system) bearing methyl groups at C-2 and C-3 in a trans relationship and a hydroxy group at C-4 (chroman numbering). A number of syntheses of racemic calanolides[5–7] and other calophyllum coumarins[8] have already appeared in the literature. One multistep synthesis of optically active 2,3-methylchroman-4-ones and subsequent diastereoselective reduction to the chroman-4-ols has been recently reported;[9] however, until now the synthesis of optically active calanolides has not been reported. Herein we describe the synthesis of the four stereoisomers of both calanolides A and B using a process that generates all three contiguous chiral centers in a most expeditious manner.



calanolide A (**1**): R_1 = *n*-propyl, R_2 = OH, R_3 = H
calanolide B (**2**): R_1 = *n*-propyl, R_2 = H, R_3 = OH
inophyllum B (**3**): R_1 = phenyl, R_2 = OH, R_3 = H
inophyllum P (**4**): R_1 = phenyl, R_2 = H, R_3 = OH

Scheme 1[a]



[a] In the text a designation of "**a**" after a compound number indicates the structure generated by use of (−)-(*E*)-crotyldiisopinocampheylborane (**8a**).

We have just reported[10] a stereoselective synthesis of the chiral 2,3-dimethylchroman-4-ol ring from a silyl-protected salicylaldehyde. The chiral centers at C-3 and C-4 (chroman numbering) were introduced using (*Z*)-crotyldiisopinocampheylborane, and then a mercury-assisted cyclization of the resulting *o*-alkenyl phenol was implemented to give the required *trans,trans*-Me-Me-OH substituted chroman (benzo[*b*]pyran ring). In this paper we report an application of this process to the first enantioselective total synthesis of (+)-calanolide A (**1**) and (+)-calanolide B (**2**) and their (−)-enantiomers, **1a** and **2a** (the latter is also known as costatolide),[7a,11] respectively.

Given the sensitive nature of the chromanol system,[12] our plan was to introduce the dimethylchromanol ring

(1) (a) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, J. H., II; McMahon, J. B.; Currens, M. J.; Buckhiet, R. W., Jr.; Hughes, S. H.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1992**, *35*, 2735–2743. (b) Fuller, R. W.; Bokesh, H. R.; Gustafson, K. R.; McKee, T. C.; Cardelina, J. H., II; McMahon, J. B.; Cragg, G. M.; Soejarto, D. D.; Boyd, M. R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1961–1964. (c) Newman, R. A.; Costa, M.; Cisneros, A. *J. Chromatogr. B* **1994**, *658*, 129–133.

(2) (a) Kawazu, K.; Ohigashi H.; Mitsui, T. *Tetrahedron Lett.* **1968**, 2383–2385. (b) Kawazu, K.; Ohigashi H.; Takahashi, N.; Mitsui, T. *Bull. Chem. Res. Kyoto Univ.* **1972**, *50*, 160–167; *Chem. Abstr.* 78: 13744.

(3) Patil, A. D.; Freyer, A. J.; Eggleston, D. S.; Haltiwagner, 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*, 4130–4138.

(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*, 6325–6331.

(5) Chenera, B.; West, M. L.; Finkelstein, J. A.; Dreyer, G. B. *J. Org. Chem.* **1993**, *58*, 5605–5606.

(6) Palmer, C. J.; Josephs, J. L. *Tetrahedron Lett.* **1994**, *35*, 5363–5366.

(7) (a) Stout, G. H.; Stevens, K. L. *J. Org. Chem.* **1964**, *29*, 3604–3609. (b) Stout, G. H.; Hickernell, G. K.; Sears, K. D. *J. Org. Chem.* **1968**, *33*, 4191–4200.

(8) Polonsky, J. *Bull. Soc. Chim. Fr.* **1956**, 914–922. Polonsky, J.; Baskevitch, Z. *Bull. Soc. Chim. Fr.* **1958**, 929–944.

(9) Rao, A. V. R.; Gaitonde, A. S.; Prakash, K. R. C.; Rao, S. P. *Tetrahedron Lett.* **1994**, *35*, 6347–6350.

(10) Deshpande, P. P.; Baker D. C. *Synthesis*, in press.

(11) (+)-Calanolide A[1a] and (−)-calanolide B (also known as costatolide)[7a] are firmly established natural products. Recently[1a] (+)-calanolide B has been reported as a natural product; however, subsequent studies to those reported[1a] have indicated that the product was impure. Thus the $[\alpha]_D$ +10° (*c* 1.0, acetone)[1a] is in error.

(12) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins*; Wiley: Bristol, 1982; pp 55–95.

0022-3263/95/1960-2964$09.00/0

near the end of the synthetic sequence. This strategy required a complex salicylaldehyde-like derivative, such as compound **7** that can be obtained from the readily available starting material, 5,7-dihydroxy-4-(*n*-propyl)-coumarin (**5**).[5] Thus our final, concise synthetic plan was carried out as shown in Scheme 1.

The known coumarin lactone **5** was prepared from phloroglucinol.[5] On the basis of the studies reported by Chenera et al.,[5] it was anticipated that a regioselective Vilsmeier reaction[13] with compound **5** would introduce the aldehyde function at the C-8. Treatment of **5** with *N*-methylformanilide in the presence of $POCl_3$ in dichloroethane at 70–75 °C gave clean, formylated product **6** in 84% yield, mp 236–237 °C. The regiochemistry of the formylation was confirmed by NOE studies. Because the phenolic hydroxy group at C-7 was less accessible for substitution[14] due to a presumed hydrogen-bonding interaction, we were able to regioselectively introduce the dimethylchromene ring using the conditions developed by Chenera et al.[5] Thus compound **6** was reacted with 3-chloro-3-methyl-1-butyne, potassium carbonate, Bu_4NI in DMF, and 2-butenone, followed by addition of anhydrous zinc chloride in diethyl ether at 60 °C for 36 h, to afford the crucial intermediate **7** as a yellow solid, mp 116–117 °C.

For construction of the enantiomerically pure *trans*-2,3-dimethyl chroman-4-ol system, our initial plan was to synthesize the *erythro*-β-homoallylic alcohol[10] [from (*Z*)-crotyldiisopinocampheylborane][15] and to protect the newly formed secondary homoallylic alcohol with a silyl group that could easily be removed in the final step without racemizing[12] the chiral center at C-4 (chroman numbering). However, preliminary studies showed that a bulky silyl group at C-4 also controls the stereochemistry of the new chiral center (methyl group) at C-2 (obtained via mercury-assisted cyclization and demercuration), a fact recently demonstrated for another system.[16] The resulting *erythro*-β-homoallylic alcohol was shown to give the undesired stereochemistry at C-2. This prompted the preparation of *threo*-β-methyl homoallylic alcohol **9** using (*E*)-crotyldiisopinocampheylborane[15] (**8**), thus taking advantage of the directing effect of the silyl group to provide easy access to calanolide B. The organoborone reagent (+)-(*E*)-crotyldiisopinocampheylborane (**8**) was prepared according to the procedure of Brown and Bhat[15] and reacted with aldehyde **7** at −93 °C to obtain the *threo*-β-methyl homoallylic alcohol **9**, $[\alpha]^{20}_D$ +78°, in 66% yield. Sodium perborate (THF–H_2O, room temperature)[17] was used during the workup to oxidize the boron–carbon bond instead of the usual conditions (H_2O_2–3 N NaOH, reflux). No racemization of the C-4 (chroman numbering) chiral center was observed by either TLC or ^1H NMR spectroscopy of the product. The silylation of **9** with TBDMSCl–pyridine–DMAP in CH_2Cl_2 at −20 °C was quantitative. It is probable that the phenolic hydroxy group is less accessible than the secondary homoallylic alcohol due to a steric interaction with the alkene proton at C-4, leading to preponderant monosilylation. Although some disilylated product was observed in the crude product (TLC and ^1H NMR spectroscopy), desilylation of the phenolic hydroxy group occurred during the purification over silica gel, giving the monosilylated compound **10** as a syrup, $[\alpha]^{20}_D$ +26.0° (*c* 1.0, acetone).

Mercury-assisted cyclization of the *o*-akenyl phenol[18] **10** was carried out with mercury(II) acetate[19] in THF, and the intermediate organomercurial was reduced with an excess of sodium borohydride to obtain silyl-protected (+)-calanolide B (**11**) in 83% yield, $[\alpha]^{20}_D$ −41.5° (*c* 1.0, acetone). Deprotection of the silyl group with tetrabutylammonium fluoride gave (+)-calanolide B[11] (**2**) in 86% yield {mp 175–176 °C, $[\alpha]^{20}_D$ +44.0° (*c* 1.0, acetone)}. The ^1H and ^{13}C NMR spectra were identical with those reported for the natural product.[1a] The enantiomeric ratio was determined by ^1H, ^{13}C, and ^{19}F NMR analysis of the α-methyl-α-(trifluoromethyl)phenylacetate (i.e., the Mosher ester)[20] of the synthetic (+)-calanolide B (**2**) and was found to be ~98%. A similar value, 97:3 (+):(−)-isomers, was shown by chiral HPLC using a Regis no. 731221 Pirkle D-phenylglycine column (10 × 250 mm, 9:1 hexanes–2-propanol, 5 mL/min, UV_{285}; t_R (+)-**1** = 17.4 min, t_R (−)-**1** = 19.9 min).

The conversion of (+)-calanolide B (**2**) into (+)-calanolide A (**1**) was efficiently carried out with a modified[21] Mitsunobu reaction.[22] Compound **2** was reacted with PMe_3, diethyl azodicarboxylate (DEAD), and chloroacetic acid, and the resulting ester was saponified with ammonium hydroxide in MeOH, giving after purification by silica gel chromatography, (+)-calanolide A (**1**) in 81% yield (mp 45–48 °C), $[\alpha]^{20}_D$ +66° (*c* 0.5, $CHCl_3$), {lit.[1a] $[\alpha]_D$ +60° (*c* 0.5 $CHCl_3$)}. Again, the ^1H and ^{13}C NMR spectra were identical with those reported for the natural product.[1a]

When the process was scaled up [4.81 g (15.3 mmol) of **7**] and better temperature control was achieved during the reaction with **8**, a product that was analyzed by HPLC as >99:1 (+)-calanolide A (**1**) was obtained: $[\alpha]^{20}_D$ = +72° (*c* 0.51, $CHCl_3$).

The entire process in Scheme 1 was repeated using (−)-(*E*)-crotyldiisopinocampheylborane (**8a**) in order to provide (−)-calanolide B [costatolide (**2a**)][7a] {mp 176–177 °C; $[\alpha]^{20}_D$ −45° (*c* 1.0, acetone), (lit.[7a] $[\alpha]^{25}_D$ −50.4° (*c* 1.55, acetone)}. Finally, (−)-calanolide B was treated under our modified Mitsunobu conditions to provide the heretofore unknown (−)-calanolide A (**1a**), $[\alpha]^{20}_D$ −66° (*c* 0.5, $CHCl_3$).

In summary, we have demonstrated an efficient synthesis of the four stereoisomers of the calanolides. Anti-HIV activities, other biological data, and structure–activity relationships will be reported in due course.

Acknowledgment. This work was supported, in part, by contracts N01-CM-17551 and -47038 from the Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program of the National Cancer Institute. Dr. A. Mauger, Project Officer, is thanked for coordinating this work with that of the NCI.

Supplementary Material Available: Experimental procedures and characterization data for all compounds (11 pages).

JO950153I

(13) Vilsmeier, J. C. *Adv. Org. Chem.* **1976**, *9*, 225–342.
(14) Reference 12, pp 131–161.
(15) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923.
(16) Tius, M. A.; Busch-Petersen, J. *Tetrahedron Lett.* **1994**, *35*, 5181–5184.
(17) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930–5933.
(18) Clive, D. L. J.; Chittattu, G.; Curtis, N. J.; Kiel, W. A.; Wong, C. K. *J. Chem. Soc., Chem. Commun.* **1977**, 725–727.
(19) Brown, H. C.; Rei, M.-H. *J. Am. Chem. Soc.* **1969**, *91*, 5646–5649.
(20) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
(21) Saïah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317–4320.
(22) Mitsunobu, O. *Synthesis* **1981**, 1–28.