Total Synthesis of (±)-Calanolide A, a Non-Nucleoside Inhibitor of HIV-1 Reverse Transcriptase

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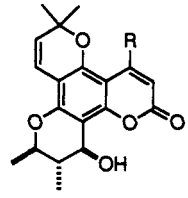
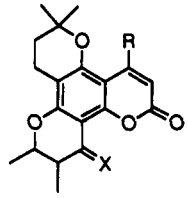
Summary: The first syntheses of (±)-calanolide A and the related (±)-calanolides C and D have been carried out in a short sequence using a Lewis acid-promoted Claisen rearrangement to establish the chromene ring.

The dipyranocoumarins,[1] a group of natural products from several tropical plants of the genus *Calophyllum*, are characterized by coumarin, chromane, and chromene ring systems assembled about a phloroglucinol core.[2-6] Calanolide A (1)[6] and inophyllum B (2)[4] are two dipyranocoumarins recently identified in screening assays as potent inhibitors of human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT).[6,7] As with other non-nucleoside HIV-1 RT inhibitors[8] such as TIBO[9] and nevirapine,[10] RT mutants resistant to calanolide A and inophyllum B have quickly been found.[7,11] However, these dipyranocoumarins differ from the other non-nucleosides in the distinct pattern of amino acid changes required to confer resistance,[7,11] indicating that the RT binding sites for these compounds[12] are overlapping but not identical.



1 (R = n-Pr)
2 (R = Ph)



3 (R = Ph; X = O)
4 (R = n-Pr; X = H, OH)

Further study of dipyranocoumarin analogues and their RT binding site could therefore aid in identifying drugs or drug combinations less prone to eliciting viral resistance.

Syntheses of two non-natural dipyranocoumarins, dihydroinophyllolide (3) and dihydrocostatolide (4), were described by Polonsky[2] and Stout[3] in connection with their original structure-elucidation studies. Both syntheses used methyl ether protection of phloroglucinol to control the regiochemistry of ring formation and a low-yielding Fries rearrangement to establish the 2,3-dimethylbenzopyran ring—conditions likely to be incompatible with the chromene system of the natural products, as well as impractical for analogue preparation. We describe here a short synthesis of (±)-calonolide A that avoids the use of protecting groups.

The coumarin lactone was formed in the first step using a Pechmann reaction[13] (Scheme I). Product yield and purity were improved by using neat triflic acid in place of the more usual sulfuric acid catalyst, affording **5** quantitatively. Similarly good results were achieved in triflic acid-mediated condensations of phloroglucinol with ethyl acetoacetate and ethyl benzoylacetate, yielding precursors to additional members of the dipyranocoumarin family.[2,4-6] Friedel–Crafts acylation[14] of coumarin **5** with tigloyl chloride then led to a single product, **10** (mp 266–268 °C), in 87% yield. The regiochemistry of acylation in **10** was established by NOE studies showing reciprocal enhancement between the aromatic proton H_b (δ_{TMS} 6.44 ppm; $CDCl_3$/acetone-d_6) and both phenolic hydroxyl protons H_a and H_c (δ_{TMS} 9.50, 9.87 ppm). The fortunate regiochemical preference of this Friedel–Crafts reaction thus ensured the desired final arrangement of rings and obviated protection stategies. Base treatment of **10** then led in high yield to a 1:1 epimeric mixture of 2,3-dimethylbenzopyranones **6**.

Initially we considered that C-acylation of **6** with dimethylacryloyl chloride followed by ring closure and deoxygenation would lead to the chromene ring of the dipyranocoumarins,[15] but this approach was not successful. Compound **6** was too deactivated for Friedel–Crafts reaction, and sodium borohydride reduction of **6** led to complex mixtures. Following esterification of **6** with dimethylacrylic acid, ketone reduction proceeded readily using $NaBH_4$, but attempted Fries rearrangement of the protected alcohol **11** ($AlCl_3$, CS_2, $PhNO_2$)[2,16] resulted in decomposition.

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(1) At the advice of a reviewer we use the generic name dipyranocoumarins to describe this group of structurally analogous but etymologically heterogeneous natural products, which includes the inophyllums,[2,4] costatolide,[3] cordatolides,[5] calanolides,[6] and others.

(2) Polonsky, J. *Bull. Soc. Chim. Fr.* **1956**, 914. Polonsky, J.; Baskevitch, Z. *Bull. Soc. Chim. Fr.* **1958**, 929.

(3) Stout, G. H.; Stevens, K. L. *J. Org. Chem.* **1964**, *29*, 3604. Stout, G. H.; Hickernell, G. K.; Sears, K. D. *J. Org. Chem.* **1968**, *33*, 4191.

(4) Kawazu, K.; Ohigashi, H. *Bull. Inst. Chem. Res. Kyoto Univ.* **1972**, *50*, 160.

(5) Gunasekera, S. P.; Jayatilake, G. S.; Selliah, S. S.; Sultanbawa, M. U. S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1505. Dahrmaratne, H. R. W.; Sotheeswaran, S.; Balasubramaniam, S.; Waight, E. S. *Phytochemistry* **1985**, *24*, 1553.

(6) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, J. H.; 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.

(7) Taylor, P. B.; Culp, J. S.; Debouck, C.; Johnson, R. K.; Patil, A. D.; Woolf, D. J.; Bartus, H. R.; Brooks, I.; Hertzberg, R. P., submitted for publication.

(8) DeClercq, E. *Med. Res. Rev.* **1993**, *13*, 229.

(9) Pauwels, R.; Andries, K.; Desmyter, A. K.; Schols, D.; Kukla, M. J.; Breslin, H. J.; Raeymaeckers, A.; Van Gelder, J.; Woestenborghs, R.; Heykants, J.; Schellenkens, K.; Jannsen, M. A. C.; DeClercq, E.; Janssen, P. A. *Nature* **1990**, *343*, 470.

(10) Wu, J. C.; Warren, T. C.; Adams, J.; Proudfoot, J.; Skiles, J.; Palayakotai, R.; Perry, C.; Potocki, I.; Farina, P. R.; Grob, P. M. *Biochemistry* **1991**, *30*, 2022.

(11) Boyer, P. L.; Currens, M. J.; McMahon, J. B.; Boyd, M. R.; Hughes, S. H. *J. Virol.* **1993**, *67*, 2412.

(12) Kohlstaedt, L. A.; Wang, J.; Friedman, J. M.; Rice, P. A.; Steitz, T. A. *Science* **1992**, *256*, 1783.

(13) Sethna, S.; Phadke, R. *Org. React.* **1953**, *7*, 1.

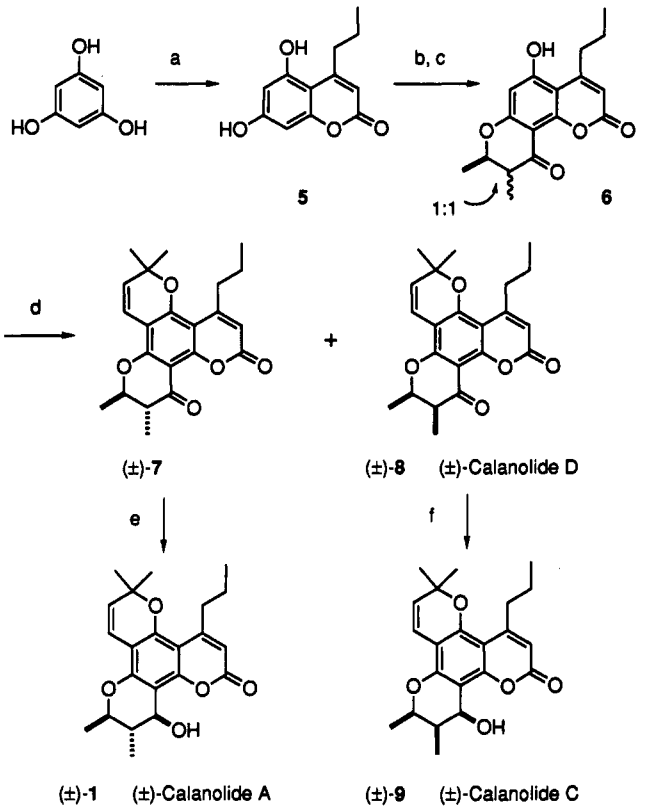
(14) *Friedel Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley: New York, 1963; Vol. 3.

(15) For examples of chromene synthesis from 2-acyl phenols see ref 17 and: Buckle, D. R.; Arch, J. R. S.; Fenwick, A. E.; Houge-Frydrych, C. S. V.; Pinto, I. L.; Smith, D. G.; Taylor, S. G.; Tedder, J. M. *J. Med. Chem.* **1990**, *33*, 3028. A somewhat related chromene synthesis involves condensation of α,β-unsaturated aldehydes with phenols: Clarke, D. G.; Crombie, L.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1007.

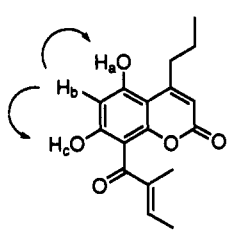
(16) Blatt, A. H. *Org. React.* **1954**, *1*, 342.

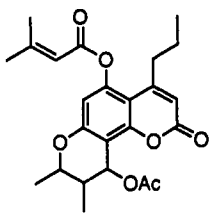
0022-3263/93/1958-5605$04.00/0

Scheme I[a]



[a] Key: (a) $C_3H_7COCH_2CO_2Et$, CF_3SO_3H (neat), 0 → 25 °C, 16 h (99%); (b) tigloyl chloride, $AlCl_3$ (4 equiv), CS_2, $PhNO_2$, 75 °C, 14 h (87%); (c) K_2CO_3, 2-butanone, 70 °C, 2 h (89%); (d) 3-chloro-3-methyl-1-butyne (5 equiv), $ZnCl_2$ (1.3 equiv), K_2CO_3 (2.5 equiv), $(n\text{-}Bu)_4NI$ (1 equiv), 2-butanone/DMF/Et_2O (10:1:1), 70 °C, 16 h ((±)-7, 34%; (±)-8, 27%); (e) $NaBH_4$ (2 equiv), $CeCl_3(H_2O)_7$ (1 equiv), EtOH, 25 °C (59%); (f) $NaBH_4$, EtOH, 25 °C (100%).





We next examined a Claisen rearrangement approach to the chromene. Aryl propargyl ethers typically undergo Claisen rearrangement at 160–215 °C to form *o*-allenylphenol intermediates, which cyclize to chromenes.[17] In the case of **6**, standard conditions for dimethylpropargyl ether formation (3-chloro-3-methyl-1-butyne, K_2CO_3, KI or $(n\text{-}Bu)_4NI$, 10% DMF in Me_2CO or 2-butanone, 50–70 °C)[17] led to no reaction. However, addition of anhydrous zinc chloride to the reaction mixture resulted in clean formation of chromenes (±)-**7** (mp 130–132 °C) and (±)-**8** (mp 130–131 °C) in a 1.3:1 ratio and 61% combined yield after chromatographic separation. Without $(n\text{-}Bu)_4NI$ the reaction proceeded less cleanly and in lower yield, and omitting K_2CO_3 resulted in gradual decomposition with no apparent product formation. We were unable to detect the presumed propargyl ether intermediate, but the mild reaction conditions (70 °C) suggest that both propargyl ether formation and Claisen rearrangement are catalyzed by zinc chloride.[18] Claisen rearrangements of allyl aryl ethers are strongly catalyzed by a variety of Lewis acids[19] including $ZnCl_2$, BCl_3, Et_2AlCl, and $TiCl_4$, as well as protic acids.[20] In addition, rearrangement of aryl propargyl ethers to chromenes has been shown to be catalyzed by mercury and silver salts[21,22] and by $AlCl_3$.[22]

The ^1H NMR and mass spectral data for compound (±)-**8** were identical with those reported for calanolide D.[6] Sodium borohydride reduction of (±)-**8** proceeded quantitatively to (±)-**9** (mp 54–56 °C), whose spectral data matched those of calanolide C.[6,23] Sodium borohydride reduction of ketone (±)-**7** was less selective, affording a 7:3 mixture of (±)-calanolide A ((±)-**1**) and its hydroxy epimer (90% yield), which were not easily separable. However, Luche reduction[24] of ketone (±)-**7** was highly stereoselective, providing (±)-**1** (mp 56-58 °C) in 59% yield (unoptimized) after chromatography, with the remainder consisting mainly of polar material. The ^1H NMR and mass spectra of (±)-**1** were in full agreement with the data reported for natural calanolide A.[6] Additionally, (±)-**1** proved to be a highly potent inhibitor of purified HIV-1 RT.[25] This five-step synthesis of (±)-calanolide A (ca. 15% overall yield) forms a practical basis for medicinal chemical studies of the dipyranocoumarin class of potential AIDS therapeutics.

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Supplementary Material Available: Experimental procedures, 400-MHz ^1H NMR and mass spectra, and elemental analysis data for compounds (±)-**1**, **5**, **6**, (±)-**7**, (±)-**8**, (±)-**9**, and **10** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1962**, *10*, 926. Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1510. Hlubucek, J.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1971**, *24*, 2347. Harfenist, M.; Thom, E. *J. Org. Chem.* **1972**, *37*, 841. Anderson, W. K.; LaVoie, E. J. *J. Org. Chem.* **1973**, *38*, 3832. Attwood, M. R.; Churcher, I.; Dunsdon, R. M.; Hurst, D. N.; Jones, P. S. *Tetrahedron Lett.* **1991**, 811. Brown, P. E.; Lewis, R. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 573.

(18) We have not ruled out the alternative mechanism of Friedel-Crafts alkylation to form an *o*-allenyl phenol, followed by ring closure. However, there is ample precedent for the Claisen rearrangement pathway to the chromene.[19-22]

(19) Karrer, P.; Fritzsche, H.; Ringier, B. H.; Salomon, H. *Helv. Chim. Acta* **1938**, *21*, 520. Smith, L. I.; Ungnade, H. E.; Prichard, W. W. *Science* **1938**, *88*, 37. Fahrni, P.; Habich, A.; Schmid, H. *Helv. Chim. Acta* **1960**, *43*, 448. Sonnenberg, F. M. *J. Org. Chem.* **1970**, *35*, 3166. Wherli, P. A.; Fryer, R. I.; Metlesics, W. *J. Org. Chem.* **1971**, *36*, 2910. Borgulya, J.; Madeja, R.; Fahrni, P.; Hansen, H.-J.; Schmid, H.; Barner, R. *Helv. Chim. Acta* **1973**, *56*, 14. Schmid, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 105. Narasaka, K.; Bald, E.; Mukaiyama, T. *Chem. Lett.* **1975**, 1041. Tachibana, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2477.

(20) Karrer, P.; Fritzsche, H.; Ringier, B. H.; Saloman, H. *Helv. Chim. Acta* **1938**, *21*, 1234. Widmer, U.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2644. Svanholm, U.; Parker, V. D. *J. Chem. Soc., Perkin Trans. 2* **1974**, 169. Ismail, F. M. D.; Hilton, M. J.; Stefinovic, M. *Tetrahedron Lett.* **1992**, 3795.

(21) Koch-Pomeranz, U.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2981.

(22) Bates, D. K.; Jones, M. C. *J. Org. Chem.* **1978**, *43*, 3856.

(23) There is one discrepancy, which we assume to be a typographical error in ref 6 or an artifact. The ^1H NMR chemical shift of chromene proton H_8 in (±)-**9** at 400 MHz (δ 6.63, in $CDCl_3$) disagrees with the reported value[6] for H_8 in calanolide C at 500 MHz (δ 6.83, in $CDCl_3$).

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

(25) Taylor, P. B. Personal Communication. More detailed potency and mechanistic comparisons between natural and synthetic calanolide A are currently underway.