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Synthesis of the Calophyllum Coumarins

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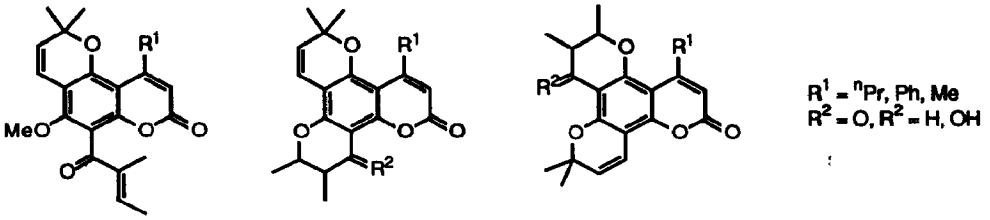
Key Words: HIV-1 RT Inhibitors; Calanolides; Calophyllolide; Inophyllums; Tomentolides

Abstract: *Synthetic routes leading to the synthesis of the natural 4-alkyl and 4-phenyl coumarins isolated from* Calophyllum sp. *are reported. The reported structures of calanolides C and D and oblongulide are incorrect and have been corrected by unambiguous synthesis.*

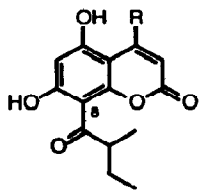
Extraction of several tropical plants of the genus *Calophyllum* (Guttiferae) has over the last 30 years led to the isolation of coumarins of the general type (**1-3**).[1, 2, 3, 4, 5, 6]



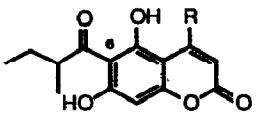
(1) (2) (3)

Interest in these compounds has arisen as a result of their indentification as potent inhibitors of human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT).[6] We have therefore sought a general method of preparation for these compounds and their natural relatives.[7] 8 and 6-(2-Methylbutyryl) coumarins (**4**) and (**5**) were prepared as previously described.[8] Assignments to the 8 or 6-acyl series have been unequivocally confirmed by U.V. spectra and X-ray crystal structure determination.[8, 9]

(4a) R = nPr
(4b) R = Ph
(4c) R = Me



(5a) R = nPr
(5b) R = Ph
(5c) R = Me



Chromenes (**6**) (yields 73-93%) and (**7**) (yields 33-79%) were obtained on heating (**4**) and (**5**) with the dimethylacetal of 3-methyl-3-hydroxybutyraldehyde in pyridine,[10] followed by methylation with methyl iodide.

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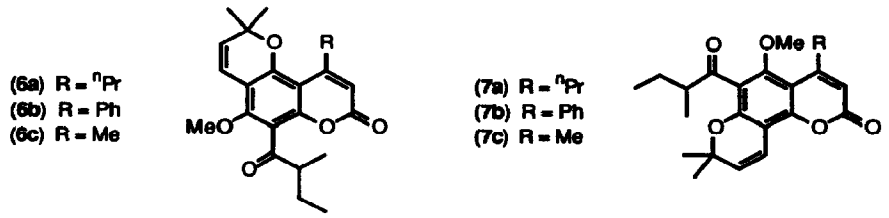
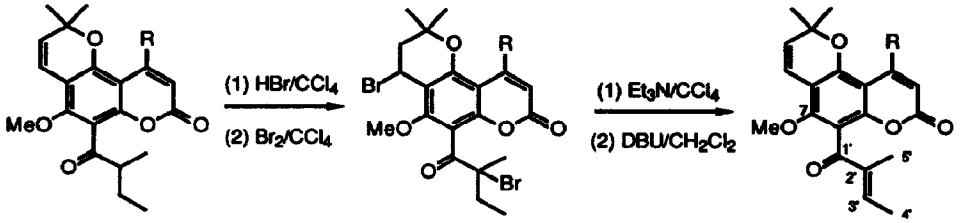
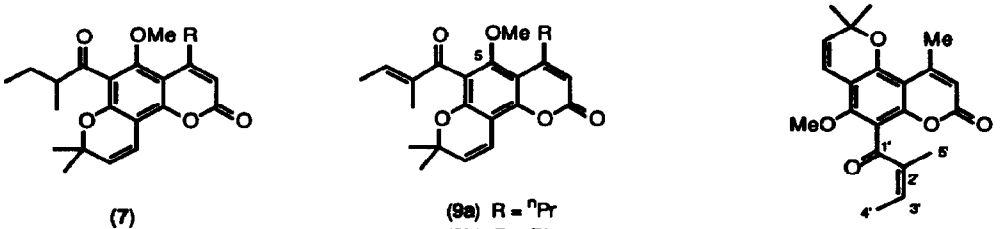


A 4-step hydrobromination-bromination-double dehydrobromination sequence converted the 2-methylbutyryl side chain in (6) and (7) to the (*E*)-2-methylbut-2-enoyl (tigloyl) group to form coumarins (8) (yields 39-58%) and (9) (yields 14-33%).



(6)

(8a) R = nPr
(8b) R = Ph
(8c) R = Me



(7)

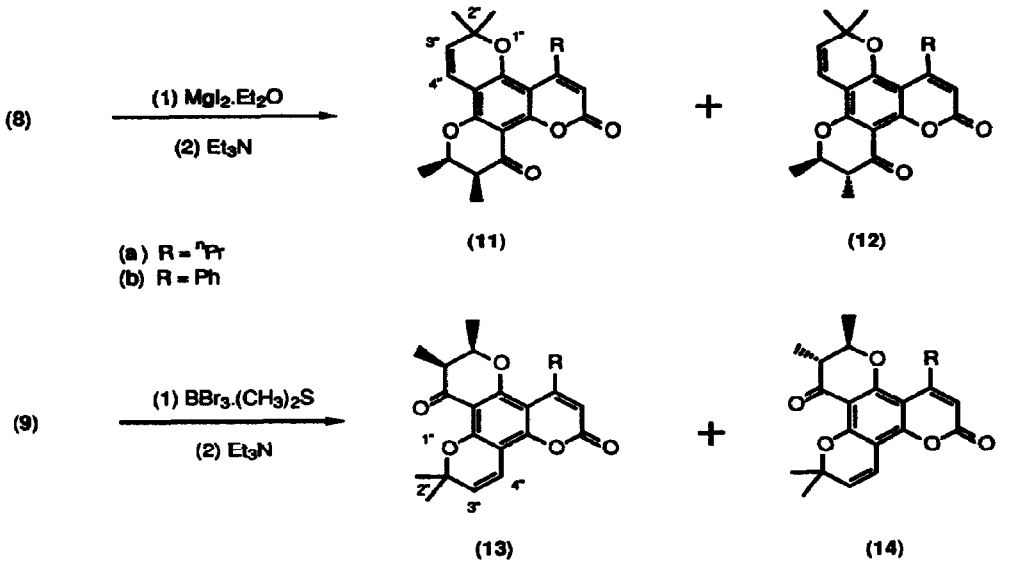
(9a) R = nPr
(9b) R = Ph

(10)

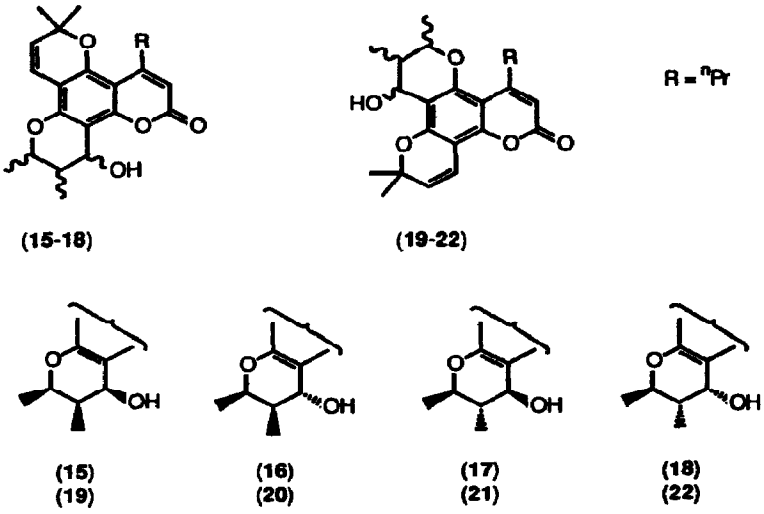
Coumarin (8a) is identical in all respects to the natural product isolated from *C. inophyllum*.[2] Coumarin (8b) is identical in all respects to calophyllolide isolated from *C. inophyllum* and *C. bracteatum*.[1, 11] Coumarin (8c) on irradiation with UV light (254 nm) in hexane gave coumarin (10). However this compound is not identical to oblongulide isolated from *C. cortato-oblongum*.[5] Examination of the ^{1}H, ^{13}C and HETCOR NMR spectra for compounds (8c) and (10) revealed that the structure proposed for oblongulide had been based on incorrect assignment of signals in the ^{13}C NMR by the authors. The correct structure for oblongulide in agreement with the published spectral data is coumarin (8c).[12] Coumarin (9b) is reported to be the structure of apetalolide isolated from *C. apetalum*.[3] Our spectroscopic and physical data for coumarin (9b) (m. p. 168°) are consistent with the structure shown, but are not consistent with the spectroscopic and physical data reported for apetalolide (m. p. 203-205°). The assignment of structure (9b) to apetalolide is therefore thought to be incorrect.

Demethylation of 8-acyl coumarins (8) with magnesium iodide etherate and 6-acyl coumarins (9) with boron tribromide-dimethyl sulphide complex gave the corresponding 7-hydroxy and 5-hydroxy coumarins.

Treatment with triethylamine afforded the respective *cis* and *trans* dipyranocoumarins (11) and (12) (yields 62-98%); and (13) and (14) (yields 27-34%) which were separated chromatographically.



$NaBH_4$/potassium biphthalate reduction[13] of the keto compounds (11) and (12), (13) and (14) affords the hydroxy epimers (15-18) and (19-22) respectively.



Dipyranocoumarins (11a), (12a), (15) and (17) have been recently synthesised by another route.[14] The authors claiming that compounds (11a), (15) and (17) are the first syntheses of calanolides D, C and A respectively, reportedly isolated from *C. lanigerum*.[6] Our synthesis of dipyranocoumarins (11a) and (15)

reveals that the physical and spectral properties are in agreement with these compounds recently synthesised. However careful examination of the published spectra and data has revealed that these are not calanolides D and C isolated from *C. lanigerum*.[6] The structures proposed for calanolides D and C are incorrect. (A discrepancy in the ^{1}H NMR between the natural calanolide C and the synthetic dipyranocoumarin (**15**) was noted but the possibility that the structures might be incorrect has apparently not been considered).[14] Our experience in this area led us to believe that calanolides C and D are regioisomers of (**15**) and (**11a**) and belong to the 6-acyl series, i.e. they are (**19**) and (**13a**) respectively.[15] Examination of the physical and spectral properties of (**19**) and (**13a**) confirmed that they are indeed the correct structures of calanolides C and D respectively. Additionally, dipyranocoumarins (**14a**) and (**14b**) have spectral data in agreement with that published for tomentolide B and tomentolide A respectively, both isolated from *C. tomentosum*.[3] The previously unknown stereochemistry about the 2,3-dimethylchromanone ring of both compounds being established as *trans*. Dipyranocoumarins (**11b**) and (**12b**) are identical to inophyllum E and inophyllum C respectively isolated from *C. inophyllum*.[4]

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12. ^{13}C ($CDCl_3$, 75 MHz, ∂ ppm) values for angeloyl chain in (**10**), tigloyl chain in (**8c**) and 2-methylbut-2-enoyl group in natural oblongulide;[5] C-1' (194.53, 194.28, 193.48) C-2' (136.67, 139.88, 139.43), C-3' (137.49, 144.02, 143.05), C-4' (15.44, 15.15, 15.06), C-5' (20.65, 10.68, 10.54).
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15. The ^{1}H NMR ($CDCl_3$, 300MHz, ∂ ppm) signals for the protons at position 4" of the 2", 2"-dimethylchromene ring in calanolides C (**19a**) and D (**13a**) appear at 6.85 and 6.78 respectively as they do in other 6-acyl chromeno-coumarins from this class. The corresponding 4" signals in (**11a**) and (**15a**) appear at 6.62 and 6.63 respectivly as they do in other 8-acyl chromeno-coumarins from this class.

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