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ARTICLE

Total syntheses of gerberinol I and the pterophyllins 2 and 4 using the Casnati-Skattebøl reaction under different conditions

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The concise and efficient total syntheses of the naturally-occurring coumarin derivatives gerberinol I, and the pterophyllins 2 and 4, from 5-methyl-4-hydroxycoumarin as a common precursor employing different Casnati-Skattebøl reaction conditions, are reported. The synthesis of the key intermediate coumarin was achieved by the organocatalytic condensation of acetylacetone and crotonaldehyde followed by a LiCl-assisted cyclization, $CuCl_2$-promoted aromatization and a final Et_2CO_3-mediated cyclization. A Casnati-Skattebøl formylation under high-temperature conditions afforded gerberinol I, whereas milder conditions resulted in an unstable 3-formyl-4-hydroxycoumarin derivative, which was subjected to a basic alumina-mediated one pot *O*-alkylation with chloroacetone and intramolecular aldolization to furnish pterophyllin 4. Wittig methylenation of the latter conveniently afforded pterophyllin 2.

Introduction

The coumarin framework is a privileged structure with high biological relevance. This motif is embodied in numerous natural products and important heterocycles, including pharmaceuticals and intermediates toward bioactive compounds.[1] Coumarins tend to be associated to anticoagulant activity;[2a] however, they have recently emerged as scaffolds for novel antimycobacterial,[2b] anti-oxidant, antiviral,[2c] anti-inflammatory,[2d] and anticancer agents.[2e]

The furo[3,2-*c*]coumarin motif, an angular tricyclic coumarin structure, is found in many natural products which constitute an important class of furan derivatives.[3a-c] Some furo[3,2-*c*] coumarins exhibit important biological activities, such as antioxidant, insecticidal, antitumor,[3d] antimicrobial and antifungal. They are also NF-κB inhibitors[3e] and agents that prevent age-related neurodegenerative diseases.[3f]

These heterocycles are inherently photosensitive,[4a-e] and some of them possess photo-chemotherapeutic effects, resulting from their ability to intercalate with the pyrimidine bases of the DNA of the target microorganisms.[4f] Selected examples are neo-tanshinlactone (**1**), isolated from *Salvia miltiorrhiza* (Figure 1), which displays potent and selective anti-breast cancer activity,[5a,b] and osthole derivatives **2a-d** which proved to be antifungal agents.[5c]

The pterophyllins 1-5 (**3a,b**, **4a,b** and **5a**) are furo[3,2-*c*]coumarin derivatives carrying a 5-methyl group (numbering of the isolation paper), which have been isolated from the bark and wood of *Ekebergia pterophylla* (C.D.C.) Hofmeyr (Meliaceae), a small evergreen tree known as Rock Ash, which grows on the Natal Group Sandstone outcrops, in South Africa.[5d] The isolated amounts were so minute that some signals could not be observed in the ^{13}C NMR spectra of **4a** and **4b**.

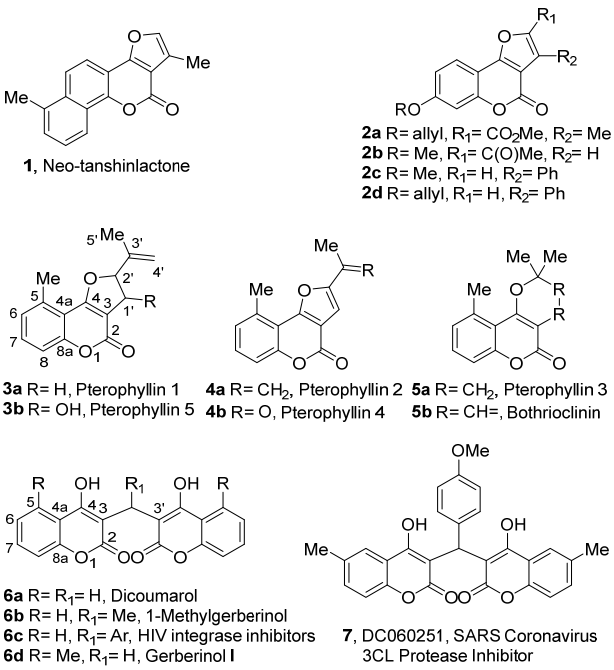

Figure 1. Chemical structures of some naturally-occurring and synthetic 4*H*-furo[3,2-*c*]chromen-4-ones (**1-5**) and 3,3'-bis-coumarin (**6**,**7**) derivatives.

To date, the bioactivity profile of the pterophylins remains unknown; however, it has been shown that analogues of **4a** are active against phytopathogenic fungi,[5c] and the related rare plant metabolite bothrioclinin (**5b**) proved to be cytotoxic.[5e,f] In addition,

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Electronic Supplementary Information (ESI) available: NMR spectra of the intermediates and final products and spectral data tables of the natural and synthetic pterophyllins 2 and 4. See DOI: 10.1039/x0xx00000x

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the syntheses of pterophyllin 1 (**3a**),[6a] pterophyllin 2 (**4a**)[6b] and pterophyllin 3 (**5a**)[6a] have been achieved, albeit in rather moderate to low yields, and accompanied by undesired isomers, through sequences that employed endangered metal catalysts, hazardous solvents and/or extreme temperatures.

The interest of Chemists in the 4*H*-furo[3,2-*c*]chromen-4-one skeleton has resulted in the development of various synthetic approaches to this target. These include the rearrangements of 3-formyl-[7a] and 3-halo- chromones,[7b] the oxidative cyclization of 3-substituted 4-hydroxycoumarins,[7c] the cyclization of 4-hydroxy coumarins with olefins under Ag(I)-catalysis,[4c] and the Cu-catalyzed intramolecular decarboxylative functionalization of α-carbonyl compounds.[8a]

Other alternatives, such as Pd-catalyzed annulation of 3-alkynyl-4-methoxy coumarins with haloarenes,[8b] and the cyclization of 3-alkynyl chromones,[4b,8c] as well as cycloaddition,[9a] tandem[9b] and multicomponent[4e,9c] processes, have also been proposed.

On the other hand, the bis-coumarins are a comparatively small group among the coumarin derivatives; naturally, they are mostly found in plants.[10a,b] The anticoagulant dicoumarol (**6a**) and 1-methyl gerberinol (**6b**)[11a] are two of the few and scattered examples of natural bis-coumarins where both heterocyclic units are linked at the C3-C3' level through a one carbon atom unit (methylene/ methine bridge).

Analogues of dicoumarol differ widely in their anticoagulant activity,[10c] whereas coumarin dimers containing an aryl substituent on the central methylene linker were found to inhibit the HIV-integrase (**6c**),[10d] the severe acute respiratory syndrome (SARS) coronavirus 3CL protease (**7**)[10e] and the c-Met tyrosine kinase receptor,[10f] among other relevant targets.

Gerberinol I (**6d**) is a unique bis-coumarin within this group, which was isolated in minor amounts from different sources, growing in a wide region between Japan and West Africa, and including *Gerbera laniculata* Benth (Compositae),[11b] *Diospyros canaliculata* De Wildeman (Ebenaceae),[11c] *D. crassiflora* Hien,[11d] and *D. kaki* var. *sylvestris* (persimmon, Ebenaceae).[11a]

The natural product, which has been totally synthetized only twice,[12a,b] demonstrated to possess antifungal and strong antibacterial activity, especially against *Shigella dysenteriae* and *Salmonella typhi* (MIC < 5 μg/mL). Interestingly, a study revealed that human intestinal bacteria transform the glycoside gerberinside into gerberinol I.[12c,d]

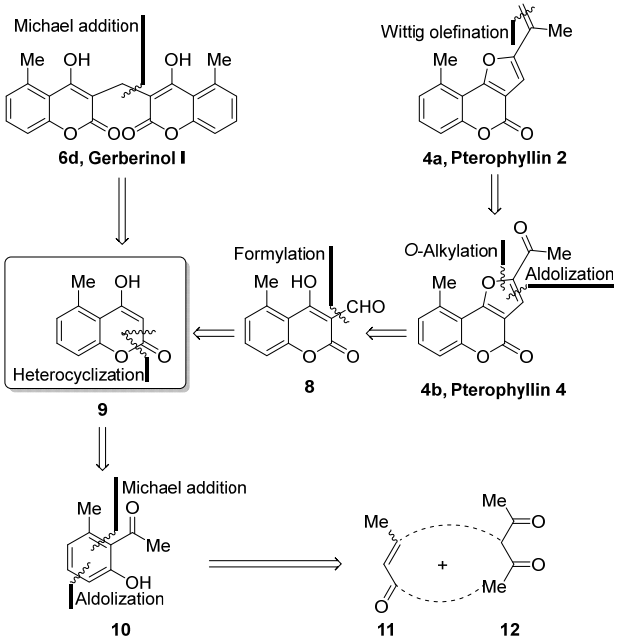
Further, based on docking results, recent theoretical studies have forecasted that this natural product may act as antimicrobial and anticancer agent, and inhibit a target associated with neurodegenerative diseases.[12e,f]

In pursuit of our continuous interest in the development of concise syntheses of structurally interesting natural products[13] and considering that bis-coumarins and furo[3,2-*c*]coumarins are synthetically connected,[8a,9c] herein we report the total syntheses of pterophyllin 2 (**4a**), pterophyllin 4 (**4b**), and gerberinol I (**6d**) from coumarin derivative **9** as the common synthetic precursor, through the use of different Casnati-Skattebøl reaction conditions.

Results and discussion

The syntheses were carried out according to the guidelines provided by the corresponding retrosynthetic analyses (Scheme 1). These analyses suggested the use of acetophenone **10** as the first key intermediate. This is a valuable product that has been recorded as the result of the light-promoted Fries rearrangement of an aryl acetate,[14] as well as the Pd-catalyzed ketone-directed *ortho*-hydroxylation of arenes,[15a] and the Lewis acid-promoted addition of organolithium or Grignard reagents to a 6-methylsalicylic ester,[15b] among others.[15c]

However, in our hands, the ketone-directed hydroxylation took place on the methyl group and the Fries rearrangement under various conditions and promoters gave mixtures of ketones, not unexpectedly containing mainly the undesired isomer.



Scheme 1. Retrosynthetic analyses of the pterophyllins 2 (**4a**) and 4 (**4b**), and gerberinol I (**6d**). Coumarin derivative **9** as a common precursor.

Therefore, and as part of our continued effort of substituting hazardous or less available reagents with simpler and more environmentally conscious surrogates,[13e,16] we opted to devise an alternative approach to **10**, as shown in Scheme 2.

Thus, based on previous findings,[17] we performed the L-proline organocatalyzed Michael addition between crotonaldehyde (**11**) and acetylacetone (**12**), to afford 58% of the tricarbonylic intermediate **13**, along with 28% of the related diene **13a**, resulting from direct addition-elimination of **12** to the carbonyl group of **11**.

Interestingly, running the reaction under neat (solventless) conditions proved advantageous, since the use of anhydrous DMF as solvent furnished diene **13a**[18] as the exclusive product. On the other hand, however, it was serendipitously discovered that the use of approximately 0.1 equiv. of 1-phenylbutane-1,4-diol as organocatalyst furnished good yields of **13**. The best performance (91% yield) was attained when 0.14 equiv were employed, also under solventless conditions. Similarly, the best temperature condition was 0 °C, since running the reaction at room temperature caused a marked increase in the amounts of **13a** and the formation

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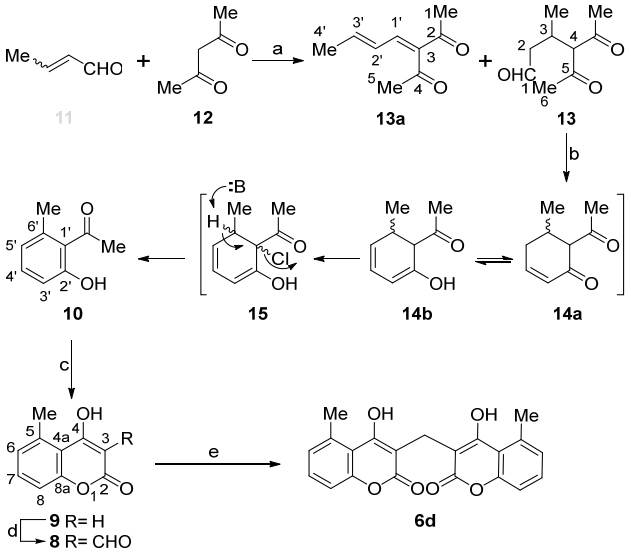
of other unidentified products.

This was followed by reaction of **13** with LiCl and $CuCl_2$ in DMF to effect the sequential intramolecular aldol condensation toward **14a,b** (observed by NMR as a complex mixture of diastereoisomers and tautomers), and further oxidative aromatization of the latter to give 54% of **10**. Presumably, the transformation would proceed through an α-carbonyl chlorination process to afford the intermediate **15**, which would further undergo a final dehydrochlorination with concomitant aromatization.[19]

The sequence was continued with the uneventful acquisition of **9** in 79% yield,[6a,20] by reaction of **10** with diethyl carbonate in DMF, using K^{t}BuO (3 equiv.) as base. Interestingly, the use of metallic sodium (5 equiv.) for this Claisen reaction gave essentially the same results.



Scheme 2. *Reagents and conditions:* a) L-proline (0.1 equiv.), 0 °C, 20 h (**13**, 58%; **13a**, 28%) or 1-phenylbutane-1,4-diol (0.14 equiv.), 0 °C, 20 h (**13**, 91%); b) LiCl, $CuCl_2$, DMF, 90 °C, 3 h (54%); c) Et_2CO_3, K^{t}BuO, r.t., 12 h (79%); d) $POCl_3$ (3 equiv.), DMF, 0 °C, 12 h (59%); e) $MgCl_2$ (anh.), Et_3N, $(CH_2O)_n$, THF, 80 °C, 1 h (75%).

The formylation of 4-hydroxycoumarins has been recorded to proceed under Vilsmeier-Haack conditions ($POCl_3$, DMF, 0 °C),[21] and with the $(MeO)_3CH$/TsOH reagent system.[22] Intriguingly, however, despite the reactions with 4-hydroxycoumarin as model performed acceptably, when the same transformations were carried out on compound **9** they furnished disappointing results.

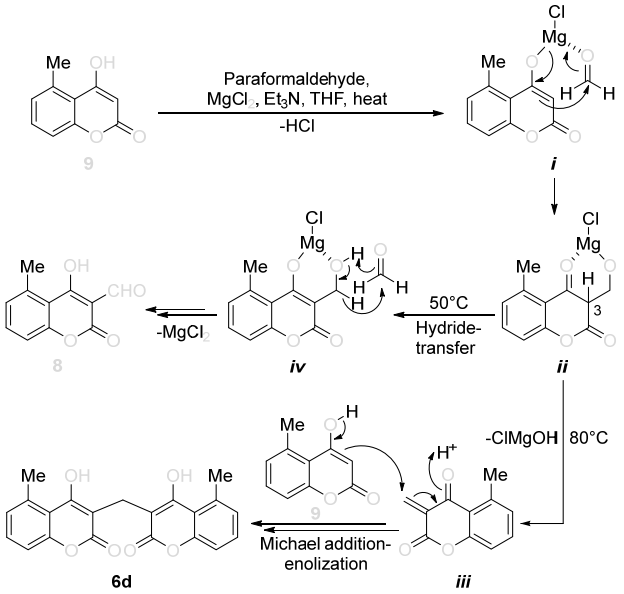
Employing the $(MeO)_3CH$/TsOH approach afforded a meagre 32% yield of 3-(methoxymethylene)-5-methylchromane-2,4-dione, as stemmed from its diagnostic singlets at δ= 8.57 (=C-H), 3.91 (OMe) and 2.86 (ArMe) ppm, whereas the Vilsmeier-Haack formylation gave rather erratic results and the use of 3 equiv. $POCl_3$ gave at best 59% of **8**. Interestingly, the production of 4-4'-ether type dimeric side products during the Vilsmeier-Haack formylation of 4-hydroxycoumarin has been previously reported.[21d]

Observing that the 4-hydroxycoumarins are acidic compounds with pK_a values similar to that of AcOH, the Casnati-Skattebøl reaction was deemed suitable for C-3 functionalization of **9**.[23] To our delight, heating in a closed vessel a mixture of **9** with $MgCl_2$, paraformaldehyde and Et_3N in THF at 80 °C afforded gerberinol I (**6d**) as the main product in 75% yield after 1 h. The NMR spectra of the heterocycle **6d** were in full agreement with the literature. This is the first synthesis of gerberinol I under non-aqueous conditions.

Although the exact mechanism for the formation of the coumarin dimer **6d** remains unknown, a mechanistic picture (Scheme 3) can be drawn based on some literature precedents. In this proposal, the Et_3N-$MgCl_2$ base system can pick-up the acidic proton of the starting heterocycle **9**, triggering a reaction with $MgCl_2$ to afford the magnesium complex ***i***, with concomitant loss of HCl. In turn, this intermediate could interact with formaldehyde (resulting from the *in situ* de-polymerization of the added paraformaldehyde), and induce a vicinal hydroxymethylation, to afford the magnesium complex ***ii***.

Under relatively high temperature conditions (80 °C), and due to the acidity of H-3, the intermediate ***ii*** could decompose through a retro-Michael reaction to a mixture of ClMgOH and the strong Michael acceptor ***iii***, which as soon as it is formed could react with the 4-hydroxy coumarin **9**, furnishing the methylene-bridged bis-coumarin **6d** after a final enolization step.

The proposed path is a known and useful, but little explored and scarcely exploited side reaction of the Casnati-Skattebøl formylation, which seldom proceeds in more than 65% yield.[24a-c] Further, it is mechanistically reminiscent of those reactions put forward for the formation of analogous bis-coumarins by the action of the DMSO/Ac_2O reagent system, and under enzymatic conditions.[12c]



Scheme 3. Proposed mechanism for the synthesis of the bis-coumarin **6d** under Casnati-Skattebøl conditions.

Interestingly, a milder treatment of **9** (50 °C, 1 h) with the same Casnati-Skattebøl mixture of reagents furnished **8** in 87% yield.[24d] Oddly enough, careful ^{1}H NMR analysis of the crude of the reaction revealed the presence of traces of **6d**.

Therefore, we explored the scope of the Casnati-Skattebøl reaction, finding that the transformation turns considerably slower when the reaction temperature is lower than 40 °C, and that at a

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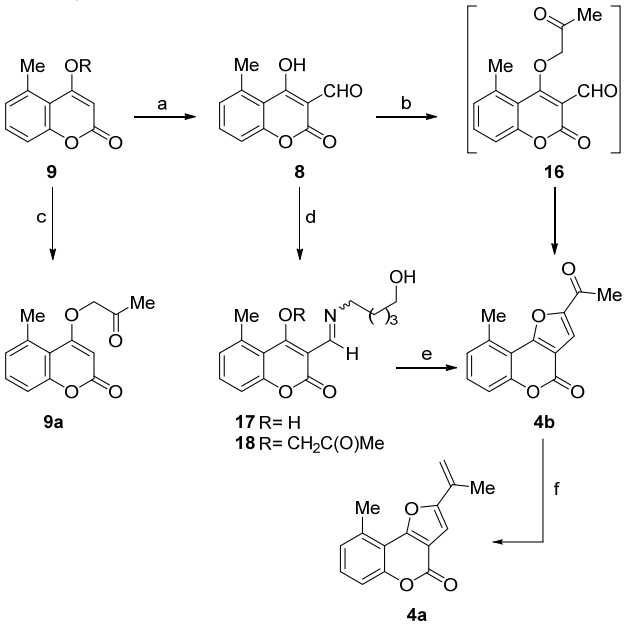
higher temperature (≈ 70 °C) compound **6d** became the major product, being formed exclusively at 80 °C.

In addition, it was observed that the Casnati-Skattebøl reaction can also be applied to other 4-hydroxycoumarins. For example, the reaction with 4-hydroxycoumarin itself at 50 °C gave 91% of the expected 3-formyl-4-hydroxycoumarin, whereas under the more strenuous conditions, the reaction outcome shifted toward the dimer (dicoumarol).

Mechanistically, in this case the common intermediate ***ii*** could undergo a formaldehyde-mediated hydride abstraction as depicted in ***iv***, leading to dehydrogenation of the latter, in a process reminiscent of the Duff formylation,[25] finally affording the formyl derivative **8**. To the best of our knowledge this is the first example entailing access to a 3-formylcoumarin derivative through the Casnati-Skattebøl reaction.

There are some scattered examples about the *O*-alkylation of 4-hydroxycoumarins[4e,5b,26] and 3-acetyl-4-hydroxy- coumarins,[27] generally under very mild conditions; however, the analogous *O*-alkylation of the more unstable and highly reactive 3-formyl-4-hydroxycoumarins, bearing a tricarbonylic motif, seems to have no direct precedent. Thus, it was not surprising that when the *O*-acetonylation of **8** with chloroacetone was procured under conventional conditions (K_2CO_3, EtOH or DMF),[13b] it met with failure, leading to complete destruction of the starting heterocycle.[7a]



Scheme 4. *Reagents and conditions:* a) $MgCl_2$ (anh.), Et_3N, $(CH_2O)_n$, THF, 50 °C, 1 h (87%); b) $ClCH_2COCH_3$, Al_2O_3, CH_2Cl_2, 40 °C, 72 h (**4b**, 88%); c) $ClCH_2COCH_3$, K_2CO_3, DMF, 65 °C, overnight (50%); d) $H_2N(CH_2)_4CH_2OH$, PhMe, 90 °C, 1 h (85%); e) $ClCH_2COCH_3$, K_2CO_3, DMF, 65 °C, overnight (15%); f) $Ph_3PMe^+I^-$, K^tBuO, LiCl, THF, rt, 1 h (**4a**, 58%; **4b**, 25%; **4a**, 78%, based on recovered starting material).

Oppositely, the *O*-alkylation of its precursor **9** was possible under the same conditions, affording the expected product **9a** in 50% yield (Scheme 4), as concluded from examination of the diagnostic signals at δ = 2.31 (s, 3H, MeCO) and 4.75 (s, 2H, OCH_2CO) ppm in its ^1H NMR spectrum.

With scarce literature precedents due to their rather poor stability, imines have been previously employed as carbonyl protecting groups.[28] Therefore, with the aim of reducing the reactivity of the molecule, the formyl moiety of compound **8** was masked as the corresponding imine (**17**), which was prepared in 85% yield by condensation of the aldehyde with 5-aminopentan-1-ol in toluene at 90 °C.

The imine **17**, which proved to be remarkably stable and withstood column chromatographic purification, was obtained as an inseparable 7:3 (*anti-syn*) mixture of geometric isomers, which in turn were observed in their ^1H NMR spectra, as the corresponding ~1:1 mixtures of rotamers. The diagnostic signals of the aldiminic hydrogen appeared as singlets at δ = 8.37 and 8.33 ppm for the *anti* isomer and more deshielded, at δ = 8.50 and 8.45 ppm, for the *syn* isomer. Luckily, exposure of **17** to the conventional acetonylation conditions [$ClCH_2C(O)Me$, K_2CO_3, DMF, 65 °C, overnight] afforded the expected furo[3,2-*c*]coumarin **4b**, albeit in low yield (15%), presumably through the intermediacy of **18**, which could not be unequivocally identified (TLC reaction monitoring) nor isolated.

In view of the instability of the starting material toward the reaction conditions and in search of an improved alternative, the use of a milder and insoluble base was attempted,[29a] opting for $MgCO_3$ which would act "on demand" as an acid scavenger, because of its insolubility in the reaction medium. However, this approach gave a complex and inseparable mixture of unidentifiable products.

Ultimately, however, the paradigm of acid scavenging by means of an insoluble base proved fruitful, since the reaction of **8** with chloroacetone in refluxing CH_2Cl_2, in the presence of a ten-fold excess of Brockmann I activated basic alumina (pH of the aqueous suspension ≥ 9), afforded the desired tricycle **4b** in 88% yield.[7a,29b,c]

Interestingly, the detection of the acetonyl ether intermediate **16** by TLC proved very difficult and all attempts at its isolation were fruitless. However, an *in-tube* NMR experiment employing anhydrous $CDCl_3$ as solvent revealed that the starting coumarin is completely consumed within 1 h at room temperature affording a complex mixture of intermediates.

Finally, the Wittig olefination of **4b** was undertaken. After several attempts with $Ph_3PMe^+I^-$ in THF, using K^tBuO as base, it was observed that the reactions did not reach completion, affording rather low yields of product. This was attributed to a ready enolization of the ketone moiety. Fortunately, however, the addition of LiCl afforded the isopropylidene derivative **4a** in 78% yield, based on recovered starting material. This additive proved relevant for attaining suitable product yields, presumably by affecting the reaction rate or the enolization equilibrium of the methyl ketone moiety.[30]

The ^1H NMR spectra of the natural and synthetic pterophyllins were fully coincident. However, the observed melting points of the synthetic **4a** and **4b** were widely different and higher than those reported for the corresponding natural products, whereas the ^{13}C NMR spectral signatures of these compounds were in good agreement with those published for the corresponding natural products, except for some resonances (Table 1).

These discrepancies probably stem from the lack of proper purity and small sample size of the original isolates, the latter

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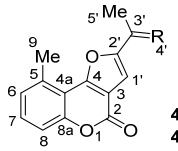
precluding a more accurate analysis. Hence, unlike other cases where spectral differences resulted from structures other than those proposed,[S4124] in this case, the chemical synthesis helped to complete and correct the NMR spectral data sets of the natural products and to obtain their unequivocal assignment.

Table 1. Comparison among the ^{13}C NMR chemicals shifts recorded for natural and synthetic pterophyllins 2 and 4.[a]



4a R= CH_2, Pterophyllin 2
4b R= O, Pterophyllin 4

Position	Pterophyllin 4		Pterophyllin 2	
	Natural	Synthetic	Natural	Synthetic
C-2	—[b]	157.4	—[b]	158.4
C-3	**125.9**	**111.8**	**122.1**	**112.2**
C-4	**157.8**	**160.2**	**162.7**	**157.9**
C-4a	112.0	111.3	**108.9**	**112.0**
C-5	135.1	135.3	134.0	134.0
C-6	127.1	127.0	126.5	126.5
C-7	131.9	131.8	130.0	130.0
C-8	115.2	115.3	115.1	115.1
C-8a	**153.1**	**154.4**	153.8	153.4
C-9	21.1	21.0	**22.7**	**21.0**
C-1'	114.4	114.5	103.7	103.7
C-2'	**154.2**	**153.2**	—[b]	157.3
C-3'	186.1	185.9	—[b]	131.7
C-4'	—	—	113.4	113.4
C-5'	26.4	26.4	19.1	19.1

[a]All spectra were taken at 75 MHz, in $CDCl_3$. Pairs of signals exhibiting the greatest differences are shown in bold.
[b]The authors informed that these signals were not observable in their spectra.

Experimental

General information

The reactions were executed under anhydrous argon atmospheres, employing oven-dried glassware and freshly distilled anhydrous solvents. Anhydrous THF and toluene were obtained by reflux of the AR solvents over sodium metal (benzophenone as indicator), followed by distillation. Anhydrous CH_2Cl_2 was obtained from an M. Braun solvent purification and dispenser system. Anhydrous Et_3N was prepared by refluxing the solvent over CaH_2 for 4 h, followed by distillation.

Anhydrous DMF was prepared by heating and reduced pressure distillation from dry BaO. All the anhydrous solvents were transferred via cannula and stored in dry Young ampoules containing activated molecular sieves. Anhydrous para-formaldehyde was obtained from the commercial product, by drying under vacuum to remove most of the moisture, followed by sublimation under reduced pressure.

The reactions were monitored by TLC run in different hexane-EtOAc solvent mixtures. The chromatographic spots were detected by exposure to 254 nm UV light, and by spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent, followed by careful heating to improve selectivity. The flash column chromatographies were run with silica gel 60 H (particle size 63–200 μm), eluting with hexane-EtOAc mixtures, under positive pressure and employing gradient of solvent polarity techniques.

Equipment

The melting points were measured on an Ernst Leitz Wetzlar model 350 hot-stage microscope and are informed uncorrected. The FT-IR spectra were recorded, as solid dispersions in KBr disks or as thin films held between NaCl cells, on a Shimadzu Prestige 21 spectrophotometer.

The nuclear magnetic resonance spectra were acquired in $CDCl_3$ unless otherwise noted, on a Bruker Avance 300 NMR spectrometer, at 300.13 (^{1}H) and 75.48 (^{13}C) MHz. The chemical shifts are informed in parts per million in the δ scale. TMS was used as the internal standard (resonances of $CHCl_3$ in $CDCl_3$: δ 7.26 and 77.0 for ^{1}H and ^{13}C NMR, respectively). The coupling constants (*J*) are given in Hertz. Pairs of signals marked with asterisk (*) or numeral (#) symbols indicate that their assignments may be exchanged. Some 2D-NMR experiments were also performed to aid unequivocal signal assignment. Structure numbering of the final products is according to the literature.[5d]

The high-resolution mass spectra were obtained from ICYTAC (Córdoba, Argentina) with a Bruker MicroTOF-Q II instrument. Detection of the ions was performed in electrospray ionization, positive ion mode.

4-Acetyl-3-methyl-5-oxohexanal (13)

Method A: Crotonaldehyde (**12**, 1.05 g, 15 mmol) was added to a cooled mixture of acetylacetone (1.5 g, 15 mmol) and L-proline (173 mg, 1.5 mmol), and the reaction was stirred for 20 h at 0 °C. Then, the reaction was diluted with 1M HCl (100 mL) and the reaction products were extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue gave **13a** (638 mg, 28%), as a yellow oil.[18a,18c] ^{1}H NMR δ: 7.00 (d, *J* = 10.1, 1H, H-1'), 6.39 (dd, 1H, *J* = 5.4 and 10.1, (H-2'), 6.28-6.46 (m, 1H, H-3'), 2.35 (s, 3H, Me-1),* 2.34 (s, 3H, Me-5)* and 1.91 (d, 3H, *J* = 5.4, H-4'),. ^{13}C NMR δ: 203.2 (C-2),* 197.3 (C-4),* 144.8 (C-1'), 142.8 (C-3'), 140.3 (C-3), 127.4 (C-2'), 31.7 (C-1),# 26.2 (C-5)# and 19.2 (C-4'). Increasing the solvent polarity furnished **13** (1.48 g, 58%) as a yellow oil;[17c] IR (film, ῡ): 2963, 2732, 1693, 1417, 1360, 1254, 1192, 1024 and 957 cm^{-1}. ^{1}H NMR δ: 9.69 (dd, 1H, *J* = 2.0 and 1.2, H-1), 3.67 (d, 1H, *J* = 9.4, H-4), 2.81-2.96 (m, 1H, H-3), 2.47 (dd, 1H, *J* = 17.2 and 4.0, H-2), 2.31 (ddd, 1H, *J* = 17.2, 8.2 and 2.0, H-2), 2.17 (s, 6H, H-6, H-2') and 0.97 (d, 3H, *J* = 6.8, Me-3). ^{13}C NMR δ: 203.8 (C-5), 203.5 (C-1'), 200.8 (C-1), 73.8 (C-4), 48.0 (C-2), 30.2 (2C, C-6 and C-2'), 28.1 (C-3) and 18.0 (Me-3).

Method B: Crotonaldehyde (**12**, 0.04 mL, 0.49 mmol) was added to a cooled mixture of acetylacetone (0.05 mL, 0.49 mmol) and 1-phenylbutane-1,4-diol (8 mg, 0.05 mmol), and the reaction was stirred for 20 h at 0 °C. Then, the reaction was diluted with 1M HCl (10 mL) and the reaction products were extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine,

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dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography of the residue gave **13** (76 mg, 91%) as a yellow oil which NMR spectra agreed with those of the aldehyde obtained through *Method A*.

2'-Hydroxy-6'-methylacetophenone (10)[15a]

Compound **11** (1.30 g, 7.7 mmol) was added portion-wise, over a period of 30 min., to a stirred mixture of LiCl (325 mg, 7.7 mmol) and $CuCl_2$ (1.45 g, 10.8 mmol) in DMF (5 mL). The reaction was further stirred for 2.5 h at 90 °C, when it was allowed to attain room temperature, diluted with brine (20 mL), and extracted with EtOAc (4 × 30 mL). The combined organic extracts were washed with H_2O (3 × 30 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue gave **10** (620 mg, 54%), as a yellow oil which crystallized on standing to give a solid, mp.: 97-99 °C (Lit.: 93-98 °C).[15c] IR (film, ῡ): 3358, 2926, 1620, 1446, 1360, 1286, 1213 and 789 cm^{-1}. ^1H NMR δ: 7.27 (t, 1H, *J* = 8.0, H-4'), 6.84 (d, 1H, *J* = 8.0, H-5'), 6.72 (d, 1H, *J* = 8.0, H-3'), 2.67 (s, 3H, CO*Me*) and 2.60 (s, 3H, Me-6'). ^{13}C NMR δ: 206.1 (*C*OMe), 162.8 (C-2'), 139.5 (C-6'), 134.7 (C-4'), 123.1 (C-3'), 121.6 (C-1'), 116.6 (C-5'), 33.3 (CO*Me*) and 24.5 (Me-6').

4-Hydroxy-5-methyl-2*H*-chromen-2-one (9)

A solution of **10** (900 mg, 6 mmol) in THF (15 mL) was added to a stirred suspension of K^{t}BuO (2.02 g, 18 mmol) in THF (30 mL). The mixture was treated drop-wise with diethyl carbonate (2.2 mL, 18 mmol) and the reaction was stirred overnight, when the solvent was evaporated under reduced pressure and the residue was treated with 1M HCl (25 mL). The reaction products were extracted with EtOAc (4 × 25 mL) and the combined organic extracts were washed with brine (1 × 10 mL, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography of the residue gave **9** (834 mg, 79%) as a yellow solid, mp.: 232-234 °C (Lit.: 232-234 °C).[20] IR (KBr, ῡ): 3383, 2974, 1641, 1599, 1558, 1340, 1211, 1043 and 793 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 7.44 (t, 1H, *J* =7.9, H-7), 7.16 (d, 1H, *J* = 7.9, H-8), 7.08 (d, 1H, *J* = 7.9, H-6), 5.53 (s, 1H, H-3), 3.33 (br s, $w_{1/2}$= 12.8, O*H*) and 2.65 (s, 3H, Me-5). ^{13}C NMR (DMSO-d_6) δ: 169.1 (C-4), 161.9 (C-2), 155.4 (C-8a), 137.6 (C-5), 132.2 (C-7), 127.6 (C-6), 115.2 (C-8), 114.7 (C-4a), 91.6 (C-3) and 23.1 (Me-5). HRMS *m/z* calcd for $C_{10}H_7O_3$ 175.0375 $[M - 1]^+$; found: 175.0365.

4-Hydroxy-5-methyl-2-oxo-2*H*-chromene-3-carbaldehyde (8)

Anhydrous $MgCl_2$ (217 mg, 2.27 mmol) was added at once to a stirred solution of 2*H*-chromen-2-one **9** (200 mg, 200 mmol) and anhydrous Et_3N (0.475 mL) in anhydrous THF (9 mL). After further stirring for 10 min, anhydrous paraformaldehyde (102 mg, 3.4 mmol) was added to the resulting suspension, and the reaction was heated at 65 °C for 1 h. The mixture was then cooled to room temperature, diluted with 1M HCl (10 mL), and the products were extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a brownish solid. Recrystallization from EtOAc gave **8** (202 mg, 87%), as a light brown solid, mp.: 130-132 °C (dec.). IR (KBr, ῡ): 3383, 2974, 1641, 1599, 1558, 1340, 1211, 1043 and 793 cm^{-1}. ^1H NMR δ: 9.96 (s, 1H, CO*H*), 7.55 (t, 1H, *J* =7.8, H-7), 7.17 (d, 1H, *J* = 7.8, H-8), 7.11 (d, 1H, *J* = 7.8, H-6) and 2.77 (s, 3H, Me). ^{13}C NMR δ: 194.7 (*C*OH), 179.8 (C-4), 160.8 (C-2), 157.2 (C-8a), 141.4 (C-5), 135.8 (C-7), 128.1 (C-6), 115.8 (C-8), 113.5 (C-4a), 101.9 (C-3) and 23.0 (Me). HRMS *m/z* calcd for $C_{11}H_8O_4$ 204.0373 $[M]^+$; found: 204.0365; *m/z* calcd for $C_{11}H_7O_4$ 203.0339 $[M - H]^+$; found: 203.0349.

3,3'-Methylenebis(4-hydroxy-5-methyl-2*H*-chromen-2-one) (6d, gerberinol I)

Anhydrous $MgCl_2$ (300 mg, 3.15 mmol) was added at once to a stirred solution of 2*H*-chromen-2-one **9** (260 mg, 1.48 mmol) and anhydrous Et_3N (0.65 mL, 4.67 mmol) in dry THF (5 mL). After further stirring for 10 min, anhydrous paraformaldehyde (150 mg, 5.0 mmol) was added to the resulting suspension, the reaction vessel was tightly closed and the system was heated at 80 °C for 1 h. The mixture was then cooled to room temperature, diluted with 1M HCl (10 mL), and the products were extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford a brownish solid. Recrystallization from EtOAc gave **6d** (210 mg, 75%), as a light brown solid, mp.: 230-232 °C (dec.); Lit.: 229-231 °C.[12c] IR (KBr, ῡ): 3447, 2930, 1653, 1599, 1464, 1350, 1302, 1234, 1119, 1042 and 789 cm^{-1}. ^1H NMR δ: 11.83 (s, 2H, 2 x OH), 7.41 (t, 2H, *J* = 8.3, H-7 and H-7'), 7.22 (d, 2H, *J* = 8.3, H-8 and H-8'), 7.11 (d, 2H, *J* = 8.3, H-6 and H-6'), 3.80 (s, 2H, C-C*H*$_2$-C) and 2.81 (s, 6H, Me-5 and Me-5'); ^{13}C NMR δ: 168.5 (2C, C-2 and C-2'),* 167.7 (2C, C-4 and C-4'),* 153.7 (2C, C-8a and C-8a'), 138.5 (2C, C-5 and C-5'), 131.7 (2C, C-7 and C-7'), 128.2 (2C, C-6 and C-6'), 115.2 (2C, C-4a and C-4a'), 115.1 (2C, C-8 and C-8'), 102.7 (2C, C-3 and C-3'), 23.3 (2C, Me-5 and Me-5') and 20.1 (C-*C*H$_2$-C). The spectroscopic data of synthetic **6d** were in full agreement with those of the literature for gerberinol I.[11a]

4-Hydroxy-3-{[(5-hydroxypentyl)imino]methyl}-5-methyl-2*H*-chromen-2-one (17)

A stirred solution of aldehyde **8** (24 mg, 0.12 mmol) in toluene (1 mL) was treated 5-aminopentan-1-ol (12 mg, 0.12 mmol) and the mixture was heated at 90 °C for 1 h. The solvent was then evaporated, water (5 mL) was added and the organic compounds were extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Silica gel column chromatography (Hexane:EtOAc, 95:5, containing 0.1% Et_3N) of the residue gave a 7:3 (*anti:syn*) isomeric mixture of imines **17** (29 mg, 85%), as a brown oil. IR (film, ῡ): 3439, 2926, 2850, 1714, 1643, 1593, 1435, 1385, 1042 and 783 cm^{-1}. *Anti*-isomer - ^1H NMR δ: 8.37 (s, 0.5H, H-1' rotamer-1), 8.33 (s, 0.5H, H-1' rotamer-2), 7.37 (t, 1H, *J* = 7.7, H-7), 6.98 (d, 1H, *J* = 7.7, H-8), 7.00 (d, 1H, *J* = 7.7, H-6), 3.67 (t, 2H, *J* = 6.2, H-7'), 3.51 (q, 2H, *J* = 6.6, H-3'), 2.77 (s, 3H, Me), 1.69-1.82 (m, 2H, H-4'), 1.55-1.67 (m, 2H, H-6') and 1.43-1.55 (m, 2H, H-5'). ^{13}C NMR δ: 183.9 (C-4), 164.1 (C-2), 162.0 (C-1'), 156.1 (C-8a), 140.9 (C-5), 133.0 (C-7), 127.3 (C-6), 118.7 (C-4a), 115.6 (C-8), 97.4 (C-3), 62.3 (C-7'), 50.9 (C-3'), 32.0 (C-6'), 30.0 (C-4'), 22.8 (C-5')* and 22.7 (Me-5)*. *Syn*-isomer - ^1H NMR δ: 8.50 (s, 0.5H, H-1' rotamer-1), 8.45 (s, 0.5H, H-1' rotamer-2), 7.38 (t, 1H, *J* =7.7, H-7), 7.07 (d, 1H, *J* = 7.7, H-8), 7.00 (d, 1H, *J* = 7.7, H-6), 3.66 (t, 2H, *J* = 6.2, H-7'), 3.55 (q, 2H, *J* = 6.5, H-3'), 2.79 (s, 3H, Me), 1.69-1.82 (m, 2H, H-4'), 1.55-1.67 (m, 2H, H-6') and 1.43-1.55 (m, 2H, H-5'). ^{13}C NMR δ: 180.6 (C-4), 164.1 (C-2), 160.8 (C-1'), 156.1 (C-8a), 141.6 (C-5), 133.0 (C-7),

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127.5 (C-6), 118.9 (C-4a), 115.6 (C-8), 97.5 (C-3), 62.3 (C-7'), 50.7 (C-3'), 31.9 (C-6'), 30.0 (C-4'), 22.8 (C-5')* and 22.7 (Me-5).* HRMS *m/z* calcd for $C_{16}H_{19}NNaO_4$ 312.1206 $[M + Na]^+$; found: 312.1206.

2-Acetyl-9-methyl-4*H*-furo[3,2-*c*]chromen-4-one (4b, pterophyllin 4)

Brockmann I activated basic alumina (2000 mg, 19.50 mmol) was added to a solution of the aldehyde **8** (200 mg, 0.98 mmol) in anhydrous CH_2Cl_2 (10 mL) and the stirred suspension was treated with $ClCH_2COMe$ (0.790 mL, 9.80 mmol). The reaction was further stirred for 24 h at room temperature, when the reaction was filtered off through Celite to separate the solid promoter, and the Celite was washed with CH_2Cl_2 (5 mL). The combined filtrates were concentrated under reduced pressure and the residue was chromatographed, furnishing **4b** (209 mg, 88%) as a yellow solid, mp.: 161-163 °C (dec.); Lit.: 60-62 °C.[5e] IR (KBr, ῡ): 2922, 2850, 1749, 1674, 1539, 1464, 1194 and 781 cm^{-1}. ^1H NMR δ: 7.67 (s, 1H, H-1'), 7.47 (t, 1H, *J* = 8.0, H-7), 7.30 (d, 1H, *J* = 8.0, H-8), 7.19 (d, 1H, *J* = 8.0, H-6), 2.86 (s, 3H, H-9) and 2.60 (s, 3H, H-5'). ^{13}C NMR δ: 185.9 (C-3'), 160.2 (C-4), 157.4 (C-2), 154.4 (C-8a), 153.2 (C-2'), 135.3 (C-5), 131.8 (C-7), 127.0 (C-6), 115.3 (C-8), 114.5 (C-1'), 111.8 (C-3), 111.3 (C-4a), 26.4 (C-5') and 21.0 (C-9). Except for the signals marked in Table 1, the NMR spectroscopic data of synthetic **4b** were in full agreement with those of the literature for the natural pterophyllin 4.[5e]

9-Methyl-2-(1-methylethenyl)-4*H*-furo[3,2-*c*]chromen-4-one (4a, pterophyllin 2)

A suspension of methyl(triphenyl)phosphonium iodide (80 mg, 0.20 mmol) in THF (0.4 mL), was treated with K^{t}BuO (21 mg, 0.18 mmol) and the mixture was stirred for 45 minutes. LiCl (4 mg, 0.09 mmol) and a solution of **4b** (20 mg, 0.08 mmol) in THF (0.4 mL) were successively added to the so obtained yellow suspension, and the reaction was stirred at room temperature for 1 h. The reaction system was diluted with brine (10 mL), and the products were extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure, leaving a residue which was chromatographed to furnish **4a** (12 mg, 58%) as a colourless solid, mp.: 142-144 °C; Lit.: 57-59 °C.[5e] In addition, part of the starting material was recovered (5 mg), increasing the yield to 78%. IR (KBr, ῡ): 2922, 1741, 1597, 1545, 1325, 1194, 1061 and 791 cm^{-1}. ^1H NMR δ: 7.37 (dd, 1H, *J* = 8.3 and 7.4, H-7), 7.27 (d, 1H, *J* = 8.3, H-8), 7.13 (d, 1H, *J* = 7.4, H-6), 6.83 (s, 1H, H-1'), 5.71 (br s, 3H, H-4a'), 5.23 (t, 3H, *J* = 1.3, H-4b'), 2.80 (s, 3H, H-9) and 2.12 (s, 3H, H-5'). ^{13}C NMR δ: 158.4 (C-2), 157.9 (C-4), 157.3 (C-2'), 153.4 (C-8a), 134.0 (C-5), 131.7 (C-3'), 130.0 (C-7), 126.5 (C-6), 115.1 (C-8), 113.4 (C-4'), 112.2 (C-3), 112.0 (C-4a), 103.7 (C-1'), 21.0 (C-9) and 19.1 (C-5'). Except for the signals marked in Table 1, the NMR spectroscopic data of synthetic **4a** were in full agreement with those informed in the literature for the natural pterophyllin 2.[5e]

Conclusions

In conclusion, the total syntheses of the natural products gerberinol I (**6d**, 4 steps, 29% yield), pterophyllin 4 (**4b**, 5 steps, 30% yield) and pterophyllin 2 (**4a**, 6 steps, 17% yield) have been achieved in short and straightforward synthetic sequences from crotonaldehyde and acetylacetone through the 4-hydroxy coumarin derivative **9** as their common synthetic intermediate, and without the use of protecting groups nor endangered metal-based catalysts.

Other key features of the synthesis include the original access to the heterocycle **9**, which was efficiently performed from inexpensive and readily available starting materials. In addition, the Casnati-Skattebøl reaction was used for the first time to functionalize the C-3 position of coumarins. Further, under different temperature conditions and with compound **9** as a suitable common precursor, this transformation granted facile access to either gerberinol I or to the pterophyllins 2 and 4.

In addition, the syntheses of the pterophyllins also entailed the first *O*-alkylation of the unstable and highly reactive 3-formyl-4-hydroxycoumarin tricarbonylic system. Finally, NMR studies provided the complete sets of ^{13}C NMR signals of the natural products and their unequivocal assignments, suggesting that some of the original data should be revised.

Conflicts of interest

There are no conflicts of interest to declare.

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Total syntheses of gerberinol I and the pterophyllins 2 and 4 using the Casnati-Skattebøl reaction under different conditions

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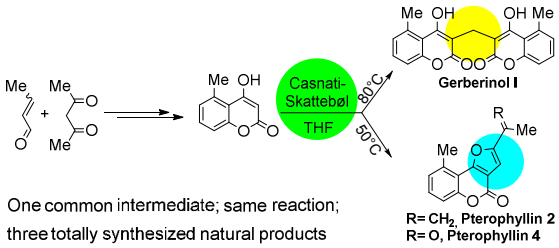
The total syntheses of the title compounds were achieved from a single coumarin precursor, taking advantage of the temperature-dependent divergent outcomes of the Casnati-Skattebøl reaction.



One common intermediate; same reaction;
three totally synthesized natural products