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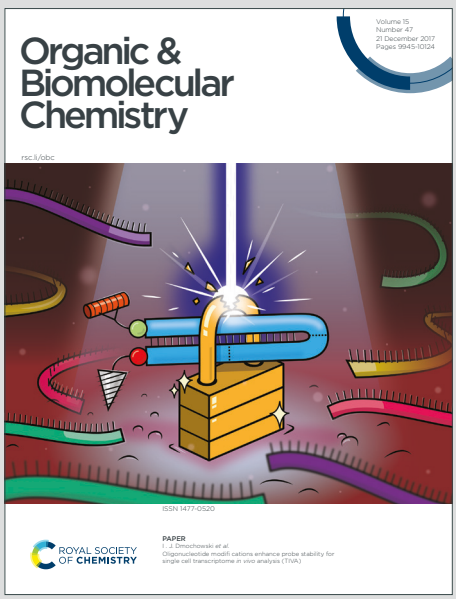

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COMMUNICATION

Synthesis of uniflorol B, a chromanone metabolite of *Calea uniflora*, and investigation of novel analogues as anti-leishmanial agents

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Luana Budny Niero,[a] Daniela Pagliara Lage,[b] Eduardo Antonio Ferraz Coelho,[b] Ricardo Andrez Machado-de-Avila,[a] James W. Barlow,[c] Patricia de Aguiar Amaral[d] and Nicolas Gouault.[*e]

In this work, we report the first synthesis of the anti-leishmanial natural product uniflorol B. Uniflorol B is a chromanone metabolite first isolated from the Brazilian medicinal plant *Calea uniflora* Less., and possesses anti-leishmanial activity. We prepared uniflorol B, the *E* isomer of the natural product, through an 8-step approach featuring Kabbe condensation, regioselective ketone reduction and Morita-Baylis-Hillman elaboration of the side chain. We extended the methodology to four novel analogues and tested all compounds for their activity against various species of *Leishmania*. The most potent activity was seen with compound 22, with an IC_{50} of 64.8 µM against *L. braziliensis*.

Introduction

Chromanones are one of the key divisions of the broader benzopyran class and are defined by the presence of a keto functionality. They occur widely in nature and have found many applications in medicinal chemistry programmes. They have been described as privileged structures and their pharmacological properties and potential have been widely reviewed.[1,2] Among the diverse examples reported, some include chroman-4-one derivatives found to act as a selective inhibitors of Sirtuin-2 (SIRT2) associated with age-related neurodegenerative disease,[3] CDK6 (Cyclin-Dependent Kinase 6) inhibitors for the treatment of chemotherapy-induced myelosuppression,[4] or NO-donor derivatives acting as vasodilators in a search for potential antihypertensive agents (Figure 1).[5]

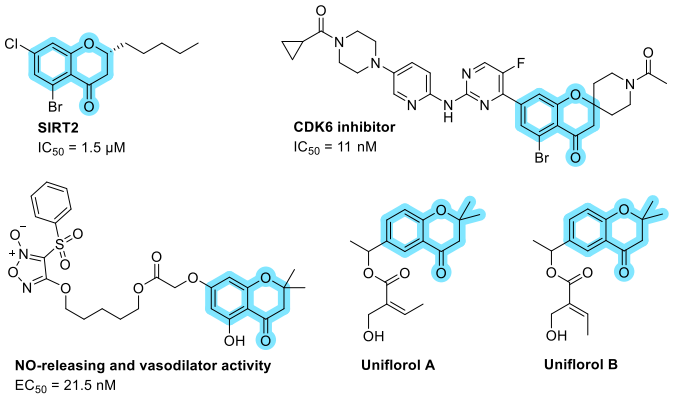
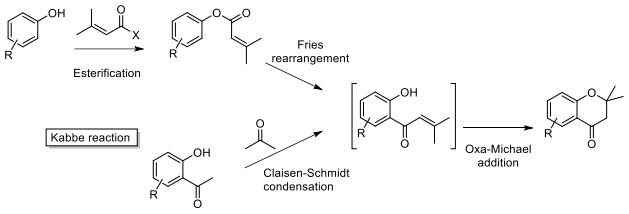


Fig. 1. Examples of biologically active chromanone-containing molecules and structures of Uniflorols A (*Z* isomer) and B (*E* isomer).

A subset of the chromanones is those with a 2,2-dimethyl substitution.



Scheme 1. Synthetic approaches to 2,2-dimethylchromanones.

These compounds may be prepared by various routes,[6] which include the reaction of phenols with 3,3-dimethylacrylic acid or its derivatives (tandem esterification/Fries rearrangement/intramolecular oxa-Michael addition

[a] *Programa de Pos-Graduaçao em Ciências da Saude, Universidade do Extremo Sul Catarinense, Criciuma, Santa Catarina, Brazil.*
[b] *Programa de Pos-Graduaçao em Ciências da Saude : Infectologia e Medicina Tropical, Facultade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.*
[c] *Department of Chemistry, RCSI University of Medicine and Health Sciences, 123 St. Stephen's Green, Dublin 2, Ireland.*
[d] *Programa de Pos-Graduaçao em Ciências Ambientais, Universidade do Extremo Sul Catarinense, Criciuma, Santa Catarina, Brazil.*
[e] *Univ Rennes, CNRS, ISCR – UMR 6226, F-35000 Rennes, France. E-mail: nicolas.gouault@univ-rennes.fr.*

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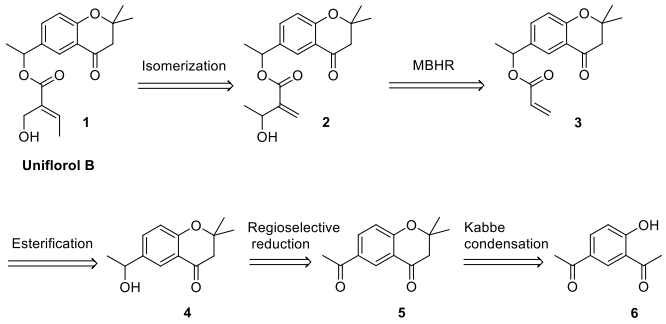
sequence),[7] or Claisen-Schmidt condensation of *o*-hydroxy-acetophenones with acetone (Kabbe reaction)[8,9], the latter approach being perhaps the most convenient and practical method (Scheme 1).We were particularly interested in 6-substituted chromanones, notably the metabolites of various *Calea* species, typified by the diastereomeric uniflorols A and B (Figure 1).[10] These compounds possess a 2,2-dimethylchroman-4-one skeleton with a 2-(hydroxymethyl)but-2-enoate side chain esterified to a hydroxyethyl group at position 6. Both the natural uniflorols[4] and various derivatives[11,12] have demonstrated interesting anti-parasitic activity and prompted our exploration of a route to the natural product uniflorol B.

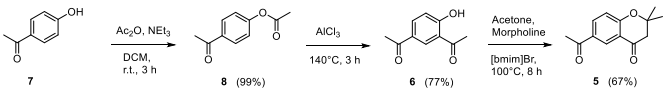
Results and discussion

Our retrosynthetic analysis for the total synthesis of uniflorol B (**1**) is shown in Scheme 2.



Scheme 2. Retrosynthetic analysis of uniflorol B.

It was envisioned that uniflorol B (**1**) could be elaborated from acrylate **3** via Morita-Baylis-Hillman reaction (MBHR) followed by isomerization of allyl alcohol **2**. The acrylate **3** would be obtained from alcohol **4** by reaction with acryloyl chloride. The alcohol **4** in turn could be prepared from chromanone **5** by regioselective reduction of the acetyl moiety. The chromanone core could be elaborated through Fries rearrangement of a suitable phenylacetate to furnish **6**, followed by cyclisation - Claisen-Schmidt condensation of *o*-hydroxyacetophenone **6** with acetone- (Kabbe reaction), as previously reported.[11] Scheme 3 depicts the synthetic route towards the chromanone core of uniflorol B.

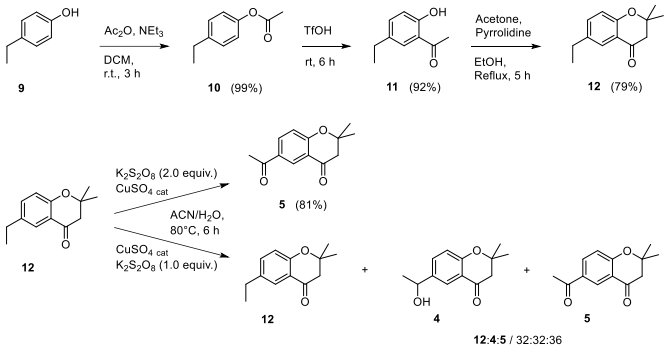


Scheme 3. Access to the acetylated chromanone core from *p*-hydroxyacetophenone.

Commercial *p*-hydroxyacetophenone **7** was acetylated to **8** in excellent yield and subjected to Fries rearrangement in an aluminium chloride melt. Kabbe condensation in the ionic liquid [bmim]Br afforded chromanone **5** in 67% yield. This reaction was also performed in ethanol in place of the ionic liquid, which resulted in the obtention of **5** in 61% yield.

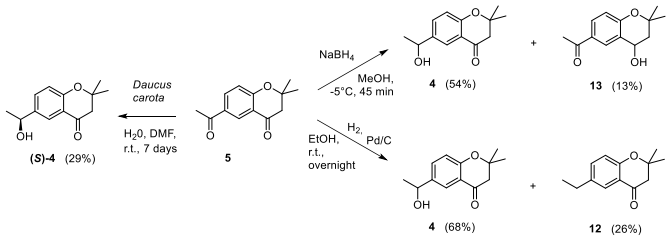
As the acetyl electron-withdrawing group disfavoured the Fries rearrangement and cyclization, we also investigated the use of *p*-ethylphenol as starting material (Scheme 4).

Commercial *p*-ethylphenol **9** was acetylated as previously described to **10** in excellent yield and subjected to Fries rearrangement in triflic acid (conditions easier to manage than aluminium chloride melt on multigram scale) to afford **11** in good yield. It is also interesting to mention that this intermediate (**11**) is commercially available and cheap. Kabbe condensation in refluxing ethanol afforded chromanone **12** in 79% yield. Finally, oxidation of intermediate **11** in its benzylic position was accomplished using an excess of potassium persulfate and a catalytic amount of Cu(II) salt to furnish **5** in 81% yield. Attempts using a stoichiometric amount of oxidizing agent were made in order to obtain alcohol **4**. However, this resulted in the obtention of a mixture of starting material, alcohol **4** and ketone **5** respectively, in a ratio of 32:32:36.



Scheme 4. Access to the acetylated chromanone core from *p*-ethylphenol.

With **5** in hand, the regioselective reduction of the methylketone was then investigated (Scheme 5).



Scheme 5. Regioselective reduction to alcohol **4**.

Enantioselective bioreduction of the prochiral methylketone **5** was already reported, and therefore, both *R* and *S* enantiomers are accessible depending on the selected biocatalyst.[13-15] However, this transformation is slow, inefficient on a multigram scale, and the yield is low (29%). As the absolute configuration of the natural product uniflorol has not yet been determined, we turned our attention towards more conventional reduction procedures of ketones. In this way, we showed that methylketone **5** could be reduced using sodium borohydride to a separable mixture of the desired alcohol **4** and its regioisomer **13**, and furthermore, via hydrogenation over Pd/C to furnish **4** in an improved yield (68%), along with side product **12**.

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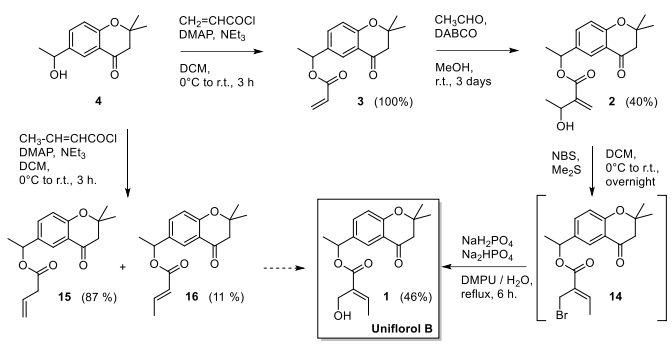
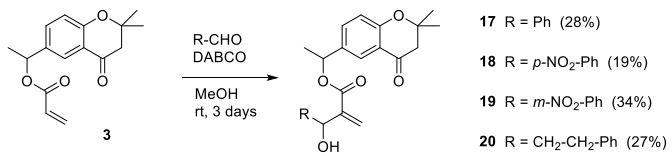
Next, with alcohol **4** in hand, we focused on the synthesis of the side chain via a Morita-Baylis-Hillman approach from the corresponding acrylate (Scheme 6).



Scheme 6. Synthetic approach to the side chain of uniflorol B **1**.

Thus, esterification using acryloyl chloride in the presence of triethylamine and a catalytic amount of DMAP quantitatively furnished intermediate **3**, which was submitted to Morita-Baylis-Hillman reaction with acetaldehyde to give allylic alcohol **2** in moderate yield (40%). Finally, we completed the synthesis of the natural product uniflorol **1** by brominative allylic transposition of **2** using *N*-bromosuccinimide and Me_2S, affording **14** regioselectively and stereoselectively as the (*Z*)-isomer as a result of an S_N2' substitution of a bromide ion.[16] Subsequent hydrolysis of **14** in buffered conditions (NaH_2PO_4/Na_2HPO_4) to prevent any ester hydrolysis gave uniflorol B **1** (as a mix with less than 5% of its diastereomer uniflorol A).[17] Its ^1H and ^{13}C NMR data are consistent with those reported for the natural uniflorol B in reference 10.

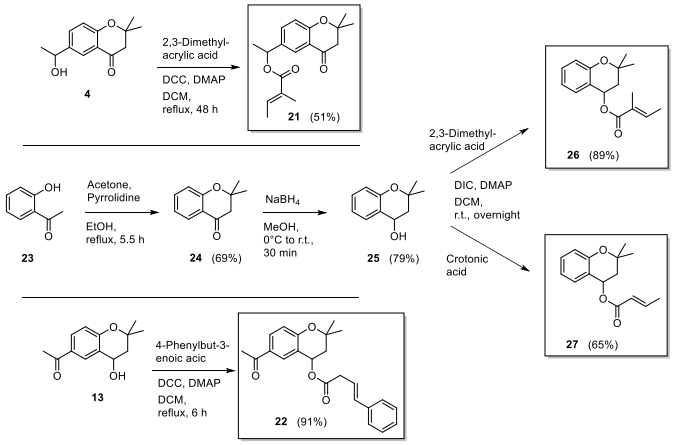
Further, in attempts to decrease the number of required steps, esterification of **4** with crotonyl chloride was attempted, in order to avoid isomerization during the last step. Unfortunately, intermediate **15**, resulting from isomerization of the double bond, was obtained as the major product instead of the desired intermediate **16**. Such deconjugation of α,β-unsaturated acid chlorides in the presence of triethylamine and benzyl alcohol to afford β,γ-unsaturated benzylic esters and proceeding *via* the formation of an intermediate ketene was already reported.[18] Using the strategy developed to afford **2**, some analogues were also synthesised from acrylate intermediate **3** (Scheme 7). Thus, upon MBH reaction using various aldehydes, analogues **17**-**20** were obtained in low to moderate yields.



Scheme 7. Synthetic approach to analogues **17**-**20** derived from the same synthetic route.

As this reaction is proceeding with difficulty, a late-stage esterification strategy was also envisioned. The Baylis-Hillman carboxylic acid adducts are easily accessible on the gram-scale. However, their esterification with chromanol under Steglich conditions revealed inefficient. In fact, such reaction is poorly mentioned in the literature. Esterification of Baylis-Hillman carboxylic acid adducts is performed from halogenated partners *via* an SN_2 mechanism. The few experiments carried out on spiranic analogues have resulted in the formation of the elimination product rather than the esterification product.

Finally, some analogues were also synthesized from alcohols **4** and **13** (Scheme 8).



Scheme 8. Synthetic approach to analogues **21**, **22** and **26**, **27** derived from alcohol intermediates **4**, **13** and **25**.

Thus, esterification using catalysed coupling conditions afforded esters **21** and **22**. In an analogous manner, compounds **26** and **27** were obtained from commercially available 2'-hydroxyacetophenone **23** through Kabbe condensation in the presence of pyrrolidine and acetone, followed by reduction to **25** prior to esterification to the final analogues **26** and **27**.

Some of these compounds were evaluated for anti-leishmanial activity against promastigote cultures of *Leishmania amazonensis*, *L. braziliensis* and *L. infantum*, with activity expressed as inhibition of 50% growth (IC_{50}) (Table 1).[19,20]

Table 1. Anti-leishmanial activity of synthesised compounds

Compound	MW (g/mol)	Anti-leishmanial activity IC_{50} (µM)		
		Leishmania amazonensis	*Leishmania braziliensis*	*Leishmania infantum*
1	318.4	-	-	-
2	318.4	286.7	122.7	352.1
21	302.4	-	-	-
22	364.4	536.4	64.8	149.5
26	258.4	137.6	135.4	121.1
27	246.3	454.3	320.6	338.4
AMB	924.1	0.23	0.33	0.19

MW: Molecular Weight.

Amphotericin B (AMB) was used as positive control. Among the compounds tested, uniflorol B analogue **26** showed the greatest activity against *L. amazonensis*, with an IC_{50} of 137.6 µM, while **22** showed the greatest activity against *L. braziliensis* with an IC_{50} of 64.8 µM and **26** against *L. infantum* (IC_{50} 121.1 µM).

Conclusions

In conclusion, the first total synthesis of uniflorol B was completed in 8 steps from the commercially available 4'-hydroxyacetophenone **7** in 6.4% overall yield and 7 steps from the commercially available 4'-ethyl-2'-hydroxyacetophenone **11** in 8.0% overall yield. The synthetic method involved esterification of a secondary benzylic alcohol with acryloyl chloride followed by Morita-Baylis–Hillman reaction and alcohol transposition to achieve the target molecule. This synthetic strategy could be applied to the synthesis of further analogues to better understand structure-activity relationships.

Author contributions

Luana Budny Niero: Investigation (lead); Writing- review and editing (equal). **Daniela Pagliara Lage**: Biological evaluation (lead). **Eduardo Antonio Ferraz Coelho**: Biological evaluation (lead). **Ricardo Andrez Machado-de-Avila**: Biological evaluation (lead). **James W. Barlow**: Conceptualization (supporting); Methodology (supporting); Writing – original draft (lead); Writing – review and editing (equal). **Patricia de Aguiar Amaral**: Conceptualization (supporting); Supervision (lead); Methodology (supporting); Writing – review and editing (equal). **Nicolas Gouault**: Conceptualization (lead); Methodology (lead); Writing – review and editing (equal).

Conflicts of interest

There are no conflicts to declare.

Data availability

The Supplementary information file contains experimental details and characterisation data (including NMR spectra. See DOI: https://doi.org/xxxxx.

Acknowledgements

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