SYNTHESIS OF MINOR CANNABINOID ANALOGUES RELATED TO ANTIPROLIFERATIVE NATURAL PRODUCTS

Lucía Gurgone, Tonino G. Adessi and Martín J. Riveira

Rosario Chemistry Institute (IQUIR-CONICET), Faculty of Biochemical and Pharmaceutical Sciences, National University of Rosario (FCByF - UNR), Suipacha 531, S2002LRK, Rosario, Argentina.
gurgone@iquir-conicet.gov.ar; adessicofre@iquir-conicet.gov.ar; riveira@iquir-conicet.gov.ar

ABSTRACT

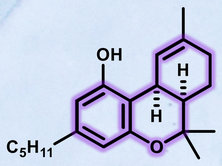
The *cis*-fused tetrahydro-6*H*-benzo[*c*]chromene structural arrangement, found in natural products with promising biological activities, including antiproliferative effects, remains underexplored in synthetic methodologies. This work introduces a methodology to access *cis*-enriched octahydro-6*H*-benzo[*c*]chromenes using $FeCl_3$ as catalyst under environmentally friendly conditions, including the use of ethyl acetate as solvent. The approach demonstrates versatility across multiple starting materials and achieves gram-scale reproducibility. In addition, preliminary studies on oxidation conditions for cyclohexenone ring aromatization have shown promising progress toward the synthesis of *cis*-cannabinoids.

INTRODUCTION

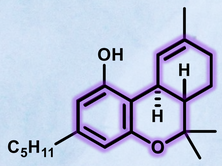
Throughout history, **natural products** have consistently proven to be invaluable sources of solutions for humanity, particularly regarding the development of treatments for diseases.[1]

If only small molecules are taken into consideration, almost half of the approved **anti-cancer drugs** since mid-last century are either natural products or compounds related to them in some way.

***Cannabis sativa* L.**[2]
Plant

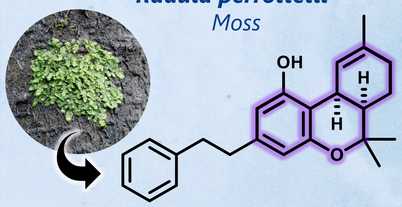


1a, *cis*-tetrahydrocannabinol
Less potent than *trans*-THC (**2a**) in CB1 receptor activation in mice. Mild CNS depressant.



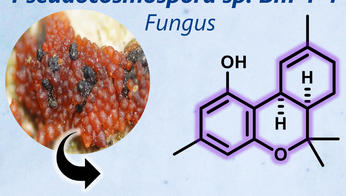
2a, *trans*-tetrahydrocannabinol
Main psychoactive component of Marijuana. In low doses it has beneficial therapeutic effects

***Radula perrottetii*[3]**
Moss



1b, *cis*-perrottetinene
CB1 receptor-dependent inhibition of prostaglandin biosynthesis.

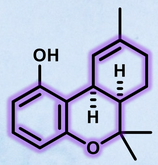
***Pseudocosmospora sp. Bm-1-1*[4]**
Fungus



1c, *cis*-tetrahydrocannabiorcol
Significant cytotoxic activity against HL60 cells (human promyelocytic leukemia).

The ***cis*-fused tetrahydro-6*H*-benzo[*c*]chromene** structural arrangement, is widely distributed in nature, being found in natural products isolated from both marine and terrestrial sources.

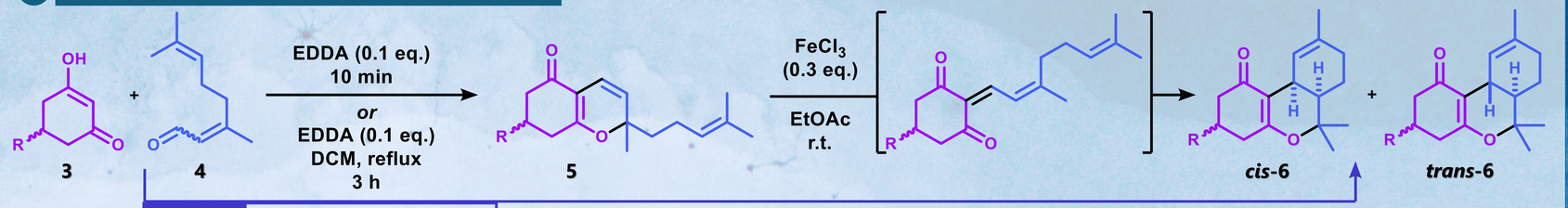
Objectives



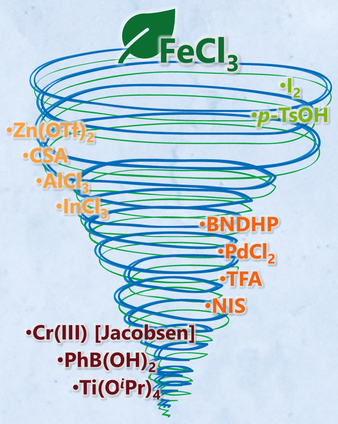
The objective of this research is to develop a methodology to access these systems that is operationally simple, environmentally friendly, and employs catalytic conditions. Additionally, this methodology aims to be applicable to the efficient synthesis of *cis*-cannabinoids.[5]

RESULTS

Cycloisomerization reaction of 2-prenylated-2*H*-pyrans



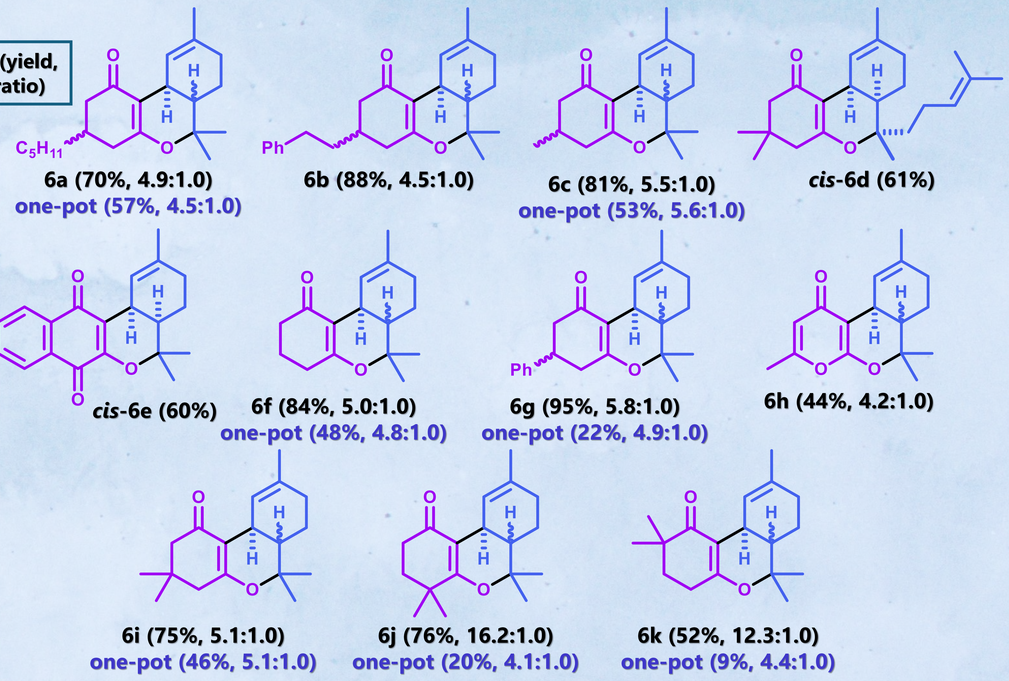
Acid promoter



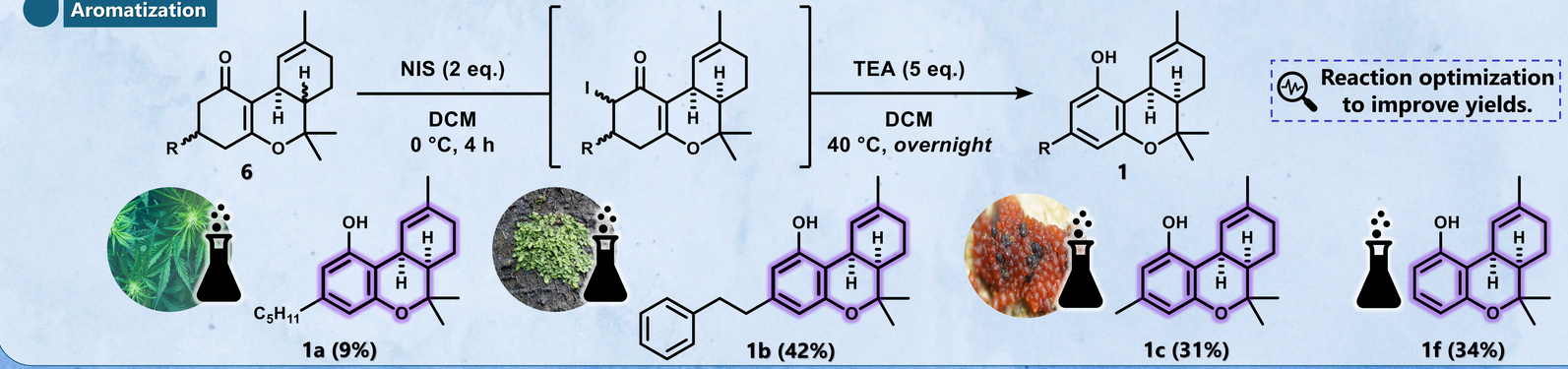
Promoter efficiency

- Complete transformations
- Good diastereomeric ratios and yields
- Incomplete transformations
- Poor diastereomeric ratios
- Only traces of product
- No reaction

Products (yield, *cis*:*trans* ratio)



Aromatization



CONCLUSIONS

- The method enabled the synthesis of multiple *cis*-enriched octahydro-6*H*-benzo[*c*]chromenes with high yields.
- Demonstrated robustness with reproducibility on a gram scale, even using non-anhydrous $FeCl_3$.
- Provided a simple and efficient protocol with readily available reagents and few reaction steps.
- Established environmentally friendly conditions, including $FeCl_3$ as promoter and ethyl acetate as solvent.
- **Future work**: optimize aromatization conditions and evaluate the compounds' anticancer activity.

Acknowledgments

We thank the UNR (BIO 580, 80020220600206UR and 80020210200028UR), the National Agency for the Promotion of Science and Technology (ANPCyT, PICT-2021-353) and the National Scientific and Technical Research Council (CONICET, PUE-2016) for funding. **LG** thanks CIN for the grant awarded (period 09/2022-03/2023). **LG** and **TGA** thank CONICET for the doctoral and postdoctoral fellowships awarded, respectively.

References

1- Newman, D. J.; Cragg, G. M., *J. Nat. Prod.* **2020**, *83*, 770. **2- a)** Gurgone, L.; La-Venia, A.; Caprioglio, D.; Riveira, M. J., *Front. Nat. Prod.* **2023**, *2*. **b)** Uliss, D. B.; Dalzell, H. C.; Handrick, G. R.; Howes, J. F.; Razdan, R. K., *J. Med. Chem.* **1975**, *18*, 213. **3-** Toyota, M.; Kinugawa, T.; Asakawa, Y., *Phytochemistry* **1994**, *37*, 859. **4-**Nakamura, T. et al., *Phytochem. Lett.* **2019**, *31*, 85-91. **5- a)** Schafroth, M. A. et al., *J. Nat. Prod.* **2021**, *84*, 2502. **b)** Gurgone, L., Adessi, T. G., La-Venia, A., Gandon, V., Riveira, M. J., *Eur. J. Org. Chem.* **2024**, e202400608.