Synthetic studies towards the elucidation of the stereochemistry of compounds of the Cryptomoscatone D family

Roberta L. Drekener* and Ronaldo A. Pilli

Instituto de Química, UNICAMP, P.O. Box 6154, CEP 13083-970, Campinas, SP, Brazil

**drekener@iqm.unicamp.br*

Keywords: cryptomoscatone, Keck's allylation, 1,5-anti aldol

INTRODUCTION

Natural compounds of the 5,6-dihydropyranone family, isolated from the genus *Cryptocarya* (*Laureacae*), have attracted scientific interest due to their biological activities.[1] Among these compounds, we highlight Cryptomoscatone D1 and D2, isolated from *C. mandiocanna*,[2] for which a definitive proof of structure is still lacking. In this work, we describe our synthetic efforts toward compounds 1 and 2 in order to contribute to the elucidation of the stereochemistry of Criptomoscatones D1 and D2 (Figure 1).

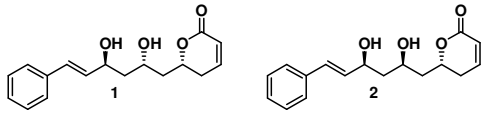
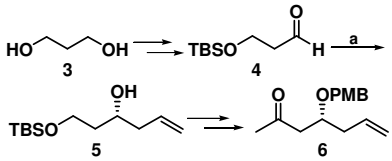


Figure 1. Compounds isolated from *C. mandiocanna* with our proposed stereochemistry.

RESULTS AND DISCUSSION

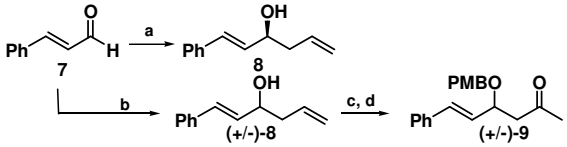
The synthetic strategy proposed for the syntheses of isomers **1** and **2** were based on a key aldol reaction with 1,5-*anti* remote induction. The first approach involved the synthesis of methyl ketone (*R*)-**6** in 8 steps, however in low overall yield (4.2%) (Scheme 1).



a) $Ti(OiPr)_4$, $CH_2CHCH_2SnBu_3$, M.S., DCM, -78 °C- -20 °C, 60 h. 75%, 90 % ee.

Scheme 1. Synthesis of methyl ketone **6**.

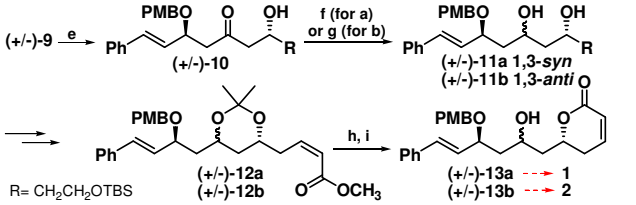
The second synthetic approach led to the synthesis of methyl ketone (+/-)-**9**, in three steps and 54% overall yield (Scheme 2).



a) 80%, 88% ee; b) CH_2CHCH_2MgBr, ether, 0 °C - r.t. 95%;
c) PMBCl, NaH, DMF, r.t., 18 h, 95%;
d) $PdCl_2$ (cat), CuCl, O_2, DMF/H_2O, r.t. 24 h, 60%.

Scheme 2. Synthesis of methyl ketone **(+/-)-10**.

The 1,5-anti aldol reaction involving methyl ketone **(+/-)-9** successfully led to the formation of the diastereoisomer **(+/-)-10** (Scheme 3). The stereogenic center at C2' in **(+/-)-11a** was established via Narasaka's[3] 1,3-*syn* reduction while Evans[4] 1,3-*anti* reduction afforded **(+/-)-11b**. After manipulation of the protecting and functional groups, α,β-unsaturated esters **(+/-)-12a** and **(+/-)-12b** were obtained with the desired *Z* double bond via the Still-Gennari modification of the Horner-Wadsworth-Emmons olefination reaction. Cleavage of the acetonide leading to the α,β-unsaturated δ-hydroxyesters was achieved under mild acidic conditions, and cyclization was performed in the presence of dibutyltin oxide, in excellent yields for both steps, affording **(+/-)-13a** and **(+/-)-13b**. Removal of the *p*-methoxybenzyl ether failed using DDQ or $ZrCl_4$ methodologies.



e) $(c\text{-}Hex)_2BCl$, Et_3N, DCM, -78 °C, 5 h; 55%; f) $(nBu)_3B$, THF, synthetic air, r.t., 2h, 74%; g) $Me_4NBH(OAc)_3$, CH_3CN/AcOH, -78 °C, 4h, 85%; h) HCl 4%, CH_3CN, 0 °C, 8h, 98% for a and 97% for b ; i) Bu_2SnO, CH_3CN, reflux, 8h, 95% for a and b.

Scheme 3. Synthesis of **(+/-)-13a** and **b**.

CONCLUSION

This work shows an approach allowing the formation of compound **(+/-)-13a** in 6.7% yield and compound **(+/-)-13b** in 7.6% yield, from *trans*-cinnamaldehyde. Although our studies did not elucidate the structures of Cryptomoscatone D1 (**1**) and D2 (**2**), they are a valuable contribution for future efforts aimed to unambiguously establish the structure of these natural products.

ACKNOWLEDGEMENTS

The autors thank IQ-Unicamp, FAPESP for fellowship (R.L.D) and FAPESP and CNPq for financial support.

REFERENCES

[1] Cossy, J.; BouzBouz, S. *Org. Lett.* **2003**, *5*, 1995.
[2] Cavalheiro, A. J.; Yoshida, M. Phytochemistry **2000**, *53*, 811.
[3] Narasaka, K.; Pai, F. -C. *Tetrahedron* **1984**, *40*, 2233.
[4] Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939.