

Mukaiyama diastereoisomers pattern by computational studies

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INTRODUCTION

Ring-closing reaction is a critical step in the synthesis of macrocyclic compounds due to entropic and enthalpic factors, associated with transition states direct cyclization in generally is not possible without activation.¹ Our efforts to obtain zearalenone analogues from anacardic acid, have led us to explore some classical macrocyclization methods.

RESULTS AND DISCUSSION

As outlined in our synthetic approach, the advanced intermediate **1** was treated under Mukaiyama's protocol (carboxyl activation), resulting the group of stereoisomer **2** (42% yield). Alcohol activation by Mitsunobu method yielded 66% of **2** (Figure 1).

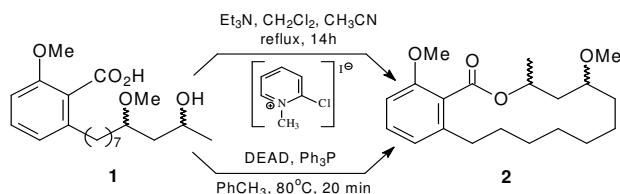


Figure 1. Macrolactonization protocols.

According to ¹H NMR spectra data, in the Mitsunobu's product was observed the expected inversion of ratio comparing to the precursors, whereas the Mukaiyama's product exhibited a discriminatory diastereoisomeric pattern, around 2 parts to 1 (Figure 2).

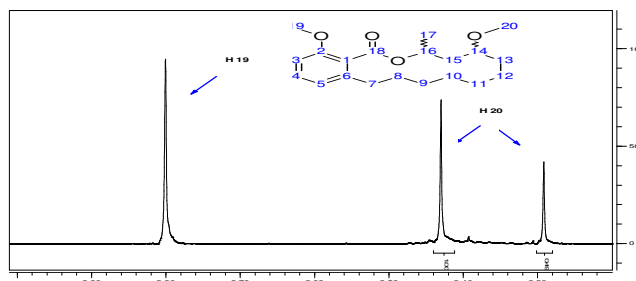


Figure 2. ¹H NMR (300MHz) of the Mukaiyama product.

In order to rationalize these results and determining the favourable diastereoisomer groups from Mukaiyama's protocol, a conformational study on the products was performed by two distinct methods (MM+ force field in HyperChem 5.1 program to windows and MM2 force field in CAChe program). As shown in Table 1, the difference of energy

between diastereoisomers was comparable in both methods.

Force field	Energy (kJ.mol ⁻¹) <i>trans</i> isomer	Energy (kJ.mol ⁻¹) <i>cis</i> isomer	ΔE (kJ.mol ⁻¹)
MM+	158.0225	160.5296	2.5070
MM2	91.3735	94.1770	2.8035

Table 1. Energy profile of conformational study.

The correlation between the number of particles in the discrete states using Boltzmann distribution law, at 40 °C and ΔE equal to 2.8035 kJ.mol⁻¹, gave the ratio of 3 parts to 1 between *trans* and *cis* isomers. The ¹³C NMR chemical shifts assignments are in accordance with the structure of more stable *trans* isomer (Figure 3).

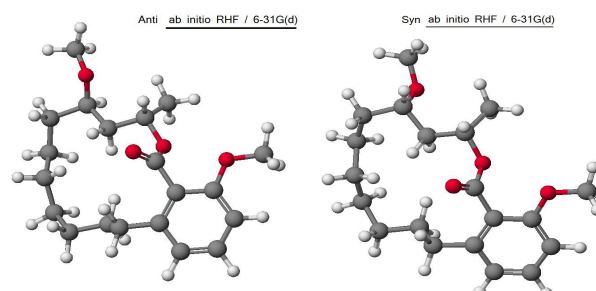


Figure 3. Stable conformations of *trans* and *cis* isomers.

CONCLUSION

A mixture of macrocyclic diastereoisomers was accessible by both applied macrocyclization methods. The conformational study on Mukaiyama's product suggests that the *trans* isomer is more favorable, corroborating the spectroscopy properties. However the estimated grade of stereoselectivity must be based on relative energy of competitive transition states, these computational data can provide qualitative information about ratio of the products, since the reaction was performed under thermodynamic control.

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REFERENCES

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