Strategies for Total Synthesis of Pyrenophorin

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INTRODUCTION

Molecules belonging to the medium and large size rings lactones have attracted considerable attention from synthetic chemists due to their interesting biological properties. Due these structural features and importance, we have accepted the challenging to prepare Pyrenophorin **1** (Figure 1), a symmetric sixteen-membered diolide isolated from *Pyrenophora avenae*¹ which displays potent antifungal activity. In our synthetic strategy to obtain a half-part of this molecule, we did testing by using some methods of coupling between fragments **3** and **4** for reach the ester **2**. Further early experiments to obtain a ring intermediate have been made by using Nozaki-Hiyama-Kishi reaction. This work shows our results in this direction.

RESULTS AND DISCUSSION

Our efforts began with the choice of best silyl-protecting group of (+/-)-1,4-pentanediol. Among protected agent that were tested the best results were reached at lower temperature reaction (0 °C) performed with TIPSCl as silylating agent and was obtained 85% yield.

Figure 1. Retrosynthetic analysis.

After preparation of 1-O-protected diols, we decided to investigate a suitable methodology to coupling the monosilylated alcohols **4** and *E*-iodo acrylic acid (**3**). Among strategies that were tested, those which reached more promising results were: Yamaguchi reaction and Mitsunobu reaction.

We tested 2 different methodologies with Yamaguchi chloride: a classical procedure² where a mixed anhydride was isolated before addition of alcohol; and a one-pot procedure, without isolation of intermediate³. The best result obtained was one-pot Yamaguchi methodology that was by using DIPEA

as base, toluene during 72h at room temperature obtained 48% yield.

Scheme 1. Coupling- **A**: Yamaguchi chloride, DIPEA, toluene, 0°-rt, 48%. **B**: DIAD, PPh₃, THF, 0°-r.t, 32%.

And then was tested the Mitsunobu methodology⁴ by using DIAD, PPh₃ in THF during 72h at room temperature obtained 32% yield.

Scheme 2. Coupling- 1)TBAF, THF, 3h. r.t. 2) PCC, CH₂Cl₂, 4h, r.t. 3) CrCl₂/Ni, DMF, 48h, r.t.

After obtained the ester intermediate **2'** was desprotected with TBAF in THF during 3h to formed the alcohol with 75% yield. In sequence the alcohol was oxidized with PCC in DCM to obtained the aldehyde.

Immediately from aldehyde crude was made early tests by using Nozaki-Hiyama-Kishi reaction with 5% total yield, and then observed evidence of the formation of an alcohol through infrared spectrum.

CONCLUSION

Then until now the best methodology to coupling **4** and **3** was Yamaguchi; one-pot with 48% yield, but more investigations will be made. Early test to formation of ring intermediate were promising.

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REFERENCES

- ¹ Ishibashi, K.; *Agric. Chem. Soc.* **1961**, 35, 257.
- ² Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M.; *Bull. Chem. Soc. Jpn.* **1979**, 52, 1989.
- ³ Navarro, I.; Basset, J.-F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Brackow, J.; Barrett, A. G. M.; *J. Am. Chem. Soc.* **2008**, 130, 10293.
- ⁴ Lee, D.; Yun, S.-Y.; Hansen, E.C.; Vochkov, I.; Cho, E.J.; Lo, W.-Y. *Angew. Chem. Int. Ed.* **2010**, 49, 4263.