Stereoselective synthesis of *β,γ-cis-β*-acyl- *γ*-hydroxymethylene-butyrolactones via chiral nitroalkanes

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INTRODUCTION

Butyrolactones make part of a class of substances with high occurrence in nature. They have different biological profile such as potent antibiotics, antivirals, antifungal[1] among others. Because of these important biological activities various synthetic methodologies capable of producing the butyrolactone ring *β,γ*-disubstituted are available in literature[2], however, few methods allow the introduction of the *cis* relative stereochemistry between C3-C4 and an acyl group at position C3 .[3,4]

This study aims to develop a new synthetic route to obtain enantiopure cis β,γ-disubstituted γ-butyrolactone rings, using nitroalkanes as nucleophiles in diastereoselective Michael additions.

RESULTS AND DISCUSSION

The enoate ***Z*-1** was prepared from D-(+)-mannitol in 3 steps in mixture of isomers *Z*/*E* 10:1 ratio. Different nitroalkanes were added in the presence of TBAF or DBU as base, yield ranging from 63 to 78% with good to excellent diastereoselectivity *syn/anti* (12 to 22:1). This stereoselectivity was independent of the base used. No addition products were detected in the reaction with **2f**, **2g** and **2h**. (Scheme 1).

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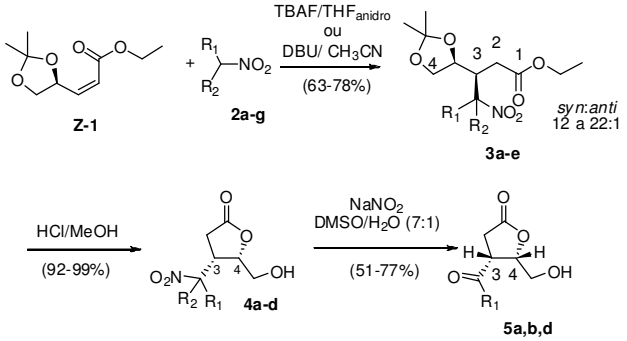

Esquema 1. synthetic route to obtaining β-acyl-β,γ-cis-butyrolactones. **2a**, $R_1 = R_2 = H$; **b**, $R_1 = CH_2CH_3$, $R_2 =$; H; **c**, $R_1 = R_2 = CH_3$; **d**, $R_1 = CH_2(CH_2)_9CH_3$, $R_2 = H$; **e**, $R_1 = CH_2COOEt$, $R_2 = H$; **f**, $R_1 = CH_2CH_2OH$, $R_2 = H$; **g**, $R_1 = CH_2Br$, $R_2 = H$; **h**, $R_1 = CH_2CH_2COOEt$, $R_2 = H$.

The lactonization of Michael adducts was accomplished in acid medium and methanol, providing the desired lactone in high yield (92-99%), except to the **3c** adduct gave a mixture of Five- and six-members lactones on a 1:1 ratio and the adduct **3e** in which the substrate degraded in the presence of acid medium.

The determination of the stereochemistry of the Michael adducts was confirmed by ^{1}H NMR analysis, by measuring coupling constants $^3JH_3$-H_4 = 8.0 Hz (**4a**), $^3JH_3$-H_4 = 7.8 Hz (**4b** and **4d**) and $^3JH_3$ -H_4 = 7.4 Hz (**4c**). These coupling constants indicated a *cis* relationship between H3 and H4 lactone confirming the *syn* stereoselectivity in the addition of alkyl nitronates anions to enoate *Z*-1.

The conversion of the nitro group to ketone was accomplished using the Gissot protocol.[5] Nef reaction of **5b** was obtained in 51%, along with the formation of the corresponding oxime as byproduct (20%). With the increasing amount of $NaNO_2$, the reaction (2 equivalent to 6 equivalent), a higher chemical yield of **5d** (77%) was obtained without detection of the corresponding oxime as byproduct. Besides good performance, this methodology uses a neutral condition avoiding epimerization in C3 position.

CONCLUSION

This work describes a simple and fast methodology, highly *cis*-stereoselective, to obtain *β*-acyl-hydroxymethylene-*γ*-butyrolactone, in just three steps from commercial enoate 1. By this methodology it was possible to synthesize the *cis* lactone **5**, synthetic intermediate used in the formal synthesis of (+)-nephrosteranic acid.[6] Studies are being carried out to inclusion of others functionalized nitroalkenes in *γ*-lactones.

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REFERENCES

1. Huneck, S. Fortschr.Chem.Org.Naturst. 2001, 81, 1-276.
2. Seitz, M.; Reiser, O. Current Opinion in Chemical Biology 2005, 9, 285-292.
3. Dias, L. C.; de Castro, I. B. D.; Steil, L. J.; Augusto, T. Tetrahedron Lett. 2006, 47, 213-216.
4. Donate, P. M.; Frederico, D.; da Silva, R.; Constantino, M. G.; Del Ponte, G.; Bonatto, P. S. Tetrahedron-Asymmetry 2003, 14, 3253-3256.
5. Gissot, A.; N'Gouela, S.; Matt, C.; Wagner, A.; Mioskowski, C. J.Org.Chem. 2004, 69, 8997-9001.
6. Barreto-Junior, C. B.; Pereira, V. L. P. Tetrahedron Lett. 2009, 50, 6389-6392