DIASTEREOSELECTIVE ADDITION OF ORGANOTITANIUM REAGENTS TO CHIRAL γ-HYDROXYBUTENOLIDES

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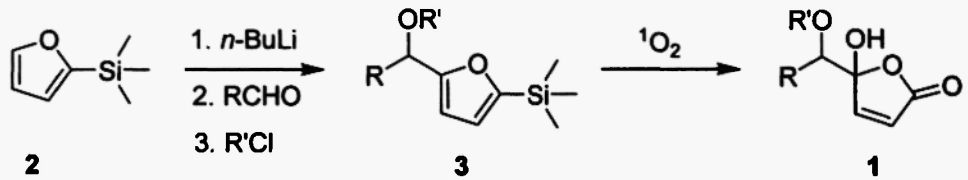
Abstract: The addition of $(i\text{-PrO})_3TiCH_3$ to γ-hydroxybutenolides having a chiral center with an alkoxy group adjacent to the ketone functionality (of the open chain form) gave γ-lactones in good yields and high diastereoselectivity.

Introduction

The γ-hydroxybutenolide moiety is a readily accessible but underutilized functional group.[1-10] The reaction of γ-hydroxybutenolides with carbon nucleophiles gives γ-lactones,[1-9] an important functional group in many natural products as well as an intermediate in natural product synthesis. There are only a handful of reports, however, that describe γ-hydroxybutenolides as intermediates in asymmetric syntheses.[5-10] In considering possible chiral γ-hydroxybutenolides for this study, we felt γ-hydroxybutenolides **1** possessing a chiral center with an alkoxy group adjacent to the ketone functionality (of the open chain form) would be ideal, since there is ample literature precedent for diastereoselective control in the addition of nucleophiles to α-alkoxyketones.[11] In particular, the addition of a methyl group to γ-hydroxybutenolides is a potential synthetic route to 5,5'-disubstituted oxygen-containing heterocyclic natural products, such as eleuthoside A and B,[12] and microtubilin inhibitor eleutherobin.[13]

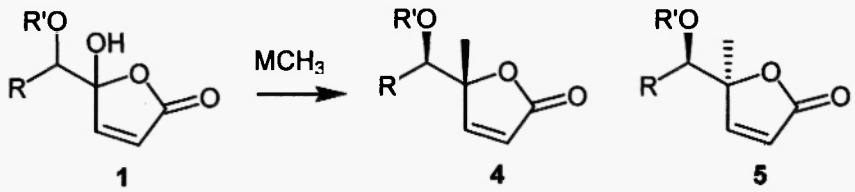
Results

The required racemic γ-hydroxybutenolides (**1**) were readily available in three steps from 2-trimethylsilylfuran (**2**)[14] based on literature procedures (Scheme-1). Lithiation of **2** with *n*-BuLi, followed by the addition of the appropriate aldehyde gave the corresponding alcohols, which were protected as a TBDMS (*tert*-butyldimethylsilyl) or MEM ((2-methoxyethoxy)methyl) (**3**). Singlet oxygen oxidation[15] of **3** gave **I**.



Scheme-1

We examined a variety of conditions (a representative selection listed in Table 1) for the addition of the methyl group to γ-hydroxybutenolides **1** (Scheme-2). The addition of Grignard or lithium reagents to **1** (entries 1 and 2) gave low diastereoselectivity and typically low yields of γ-lactones **4/5** due to 1,4-addition and other unidentified side reactions. Although we were successful in obtaining good yields and high diastereoselectivity for the addition of an organocerium reagent to chiral cyclic γ-hydroxybutenolides in our Vitamin D studies,[8] we were unsuccessful in applying these reaction conditions for the conversion of acyclic γ-hydroxybutenolides **1** to **4/5** (entry 3). The addition of $(i\text{-PrO})_3TiCH_3$,[16] however, offered a solution to this problem, giving fair to good yields (entries 4-8) and excellent diastereoselectivity (entries 5-8) for γ-lactones **4b-e**. Methylene chloride was the preferred solvent, with slightly lower yields and diastereoselectivity observed in diethyl ether. The most convenient procedure leading to optimal yields employed distilled $(i\text{-PrO})_3TiCH_3$[17] rather than the generation of the titanium reagent in situ from $(i\text{-PrO})_3TiCl$ and CH_3Li.



Scheme-2

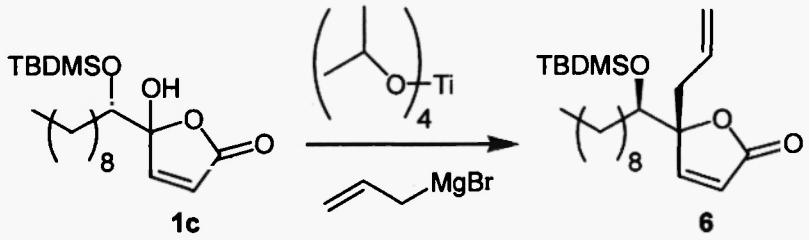
Table-1 : Reaction of 1 with MCH_3.

Entry	1	R	R'	Reagent	Conditions	%Yield; 4:5
1	**1a**	$CH_2C_6H_5$	MEM[a]	$LiCH_3$	THF/Et_2O; -78→0°C	70; 1:1
2	**1a**	$CH_2C_6H_5$	MEM	CH_3MgBr	Et_2O, -78→0°C	24; 1:2
3	**1a**	$CH_2C_6H_5$	MEM	$LiCH_3/CeCl_3$	THF; -78→0°C	20; 1:3
4	**1a**	$CH_2C_6H_5$	MEM	$(i\text{-PrO})_3TiCH_3$	CH_2Cl_2; 22°C; 20 h	50; 4:1
5	**1b**	$CH_2C_6H_5$	TBDMS[b]	$(i\text{-PrO})_3TiCH_3$	CH_2Cl_2; 22°C; 18 h	**72; 30:1**
6	**1c**	$(CH_2)_8CH_3$	TBDMS	$(i\text{-PrO})_3TiCH_3$	CH_2Cl_2; 22°C; 20 h	**87; >50:1**
7	**1d**	$CH_2CH_2OTBDMS$	TBDMS	$(i\text{-PrO})_3TiCH_3$	CH_2Cl_2; 22°C; 20 h	**63; 19:1**
8	**1e**	$CH(CH_3)_2$	MEM	$(i\text{-PrO})_3TiCH_3$	CH_2Cl_2; 22°C; 20 h	**34; >50:1**

[a] MEM = $CH_2OCH_2CH_2OCH_3$. [b] TBDMS = $(CH_3)_3C(CH_3)_2Si$.

The successful addition of the methyl group stands in contrast to our further studies for the addition of other carbon nucleophiles to **1**. In examining the addition of other carbon nucleophiles (*p*-tolyl, *n*-butyl, ethyl, methylltrimethylsilyl) to **1** under a variety of reaction conditions, we have observed poor yields and/or diastereoselectivity of γ-lactones. We achieved modest success (46% yield, > 96% de) in the addition of the allyl group to **1c** using the titanium allyl "ate" complex[16] to give **6** (Scheme-3). The addition of other allyl metal reagents such as

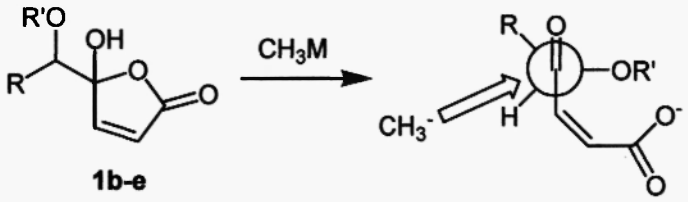
allyltris(isopropoxy)titanium (generated in situ from allyl magnesium chloride and chloro(tris-isopropoxy)titanium) to **1** gave modest yields but poor selectivity.



Scheme-3

Discussion

γ-Lactones **4b** and **5b** are known compounds,[13] so a definitive assignment for the major product as *syn* in the reaction of **1b** with $(i\text{-PrO})_3TiCH_3$ was firmly established. Deprotection of MEM-protected γ-lactones **4a** and **5a** gave the known corresponding alcohols,[12,13] which allowed the definitive assignment for them, too. The assignment of stereochemistry for γ-lactones **4c/5c**, **4d/5d**, **4e/5e** and **6** was established by comparing their ^1H NMRs with the ^1H NMRs of γ-lactones **4a**, **4b**, **5a**, and **5b**. The addition of the titanium reagents to **1b-e** can be explained by the polar Felkin-Anh model (Scheme-4); both the TBDMS protecting group and organotitanium reagents with isopropoxy ligands are known to favor Felkin-Anh addition.[11] The lack of chelation control in the addition of Grignard reagents to MEM-protected **1a** (and **1e**) and the poor Felkin-Ahn selectivity for the TBS-protected ethers **1b** (and **1c**, **1d**) may be due to interference by the nearby carboxylate.



Scheme-4

Conclusions

We have developed reaction conditions for the addition of a methyl group to chiral γ-hydroxybutenolides **1** to give good yields and diastereoselectivity of the corresponding γ-lactones. The synthesis of γ-lactones **4b-e** provides a convenient starting point for the synthesis of complex natural products.[12,13] Since there are several methods for the synthesis of enantiopure furanyl alcohols **3** (either by asymmetric alkylation of 2-furaldehyde or asymmetric reduction of furanyl ketones), this synthetic approach should be applicable to the synthesis of non-racemic γ-lactones. We are continuing to explore further synthetic methods for the addition of other carbon nucleophiles to chiral γ-hydroxybutenolides **1** in order to develop a truly general synthesis of chiral γ-lactones and we will present a full report at the successful conclusion of these studies.

Experimental

To a solution of **1b** (0.250 g, 0.75 mmol) in dry CH_2Cl_2 (5 mL) under Ar was added $(i\text{-PrO})_3TiCH_3$ (0.60 mL, 0.60 g, 2.5 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred 18 h. The reaction mixture was poured into 0.1 M HCl (100 mL), stirred for 5 min, and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated on the rotary evaporator. The crude product was purified by flash chromatography (25 g silica gel; 5% EtOAc in hexanes) to give **4b** and **5b** (0.180 g, 72%; 30:1 **4b**:**5b**) as a clear oil.[13] For **4b**: IR (neat) 1757, 1603 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, J = 5.5 Hz, 1H), 7.18-7.28 (m, 3H), 7.13 (d, J = 7.0 Hz, 2H), 6.04 (d, J = 5.5 Hz, 1H), 3.93 (dd, J = 3.6, 8.8 Hz, 1H), 2.84 (dd, J = 3.6, 13.9 Hz, 1H), 2.57 (dd, J = 8.8, 13.9 Hz, 1H), 1.50 (s, 3H), 0.80 (s, 9H), 0.01 (s, 3H), -0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 158.6, 138.1, 129.8, 128.6, 126.8, 121.8, 91.5, 77.5, 40.2, 26.0, 20.2, 18.2, -4.2, -5.4.

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References

1. F. W. Machado-Araujo, J. Gore *Tetrahedron Lett.* **22**, 1969-1972 (1981)
2. J. Zhang, P. G. Blazecka, H. Berven, D. Belmont *Tetrahedron Lett.* **44**, 5579-5582 (2003)
3. P. Angell, J. Zhang, D. Belmont, T. Curran, J. G. Davidson *Tetrahedron Lett.* **46**, 2029-2032 (2005)
4. E. Lattmann, W. O. Ayuko, D. Kinchinaton, C. A. Langley, H. Singh, L. Karimi, M. J. Tisdale *J. Pharm. Pharmacol.* **55**, 1259-1265 (2003)
5. Y. Nagao, W. Dai, M. Ochiai, M. Shiro *J. Org. Chem.* **54**, 5211-5217 (1989)
6. P. Canonne, M. Akssira *Tetrahedron Lett.* **25**, 3453-3456 (1984)
7. P. Canonne, J. Plamondon, M. Akssira *Tetrahedron* **44**, 2903-2912 (1988)
8. W. H. Miles, K. B. Connell *Tetrahedron Lett.* **44**, 1161-1163 (2003)
9. T. Y. R. Tsai, K. Wiesner *Heterocycles* **22**, 1683-1686 (1984)
10. M. Teijeira, P. L. Suárez, G. Gómez, C. Terán, Y. Fall *Tetrahedron Lett.* **46**, 5889-5892 (2005)
11. A. Mengel, O. Reiser *Chem. Rev.* 99, 1191-1223 (1999)
12. E. Redero, C. Sandoval, F. Bermejo *Tetrahedron* **57**, 9597-9605 (2001)
13. H. Bruyere, S. Ballereau, M. Selkti, J. Royer *Tetrahedron* **59**, 5879-5886 (2003)
14. R. A. Benkeser, R. B. Currie *J. Am. Chem. Soc.* **70**, 1780-1782 (1948)
15. G. C. M. Lee, E. T. Syage, D. A. Harcourt, J. M. Holmes, M. E. Garst *J. Org. Chem.* **56**, 7007-7014 (1991)
16. M. T. Reetz, R. Steinbach, J. Westermann, R. Peter, B. Wenderoth *Chem. Ber.* **118**, 1441-1454 (1985)
17. A de Meijere, H. Winsel, B. Stecker *Org. Synth.* **81**, 14-25 (2005)

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