ORGANIC LETTERS

2004
Vol. 6, No. 25
4787−4789

γ-Lactone-Tethered Ring-Closing Metathesis. A Route to Enantiomerically Enriched γ-Lactones α,β-Fused to Medium-Sized Rings

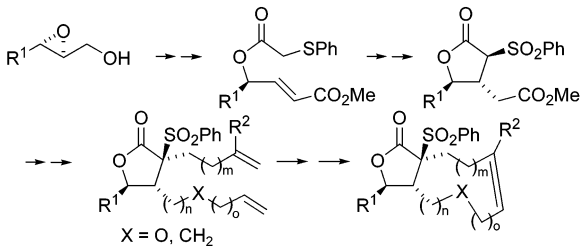
Carmen M. Rodríguez, José Luis Ravelo, and Víctor S. Martín*

Instituto Universitario de Bio-Orgánica "Antonio González", Universidad de La Laguna, C/Astrofísico Francisco Sánchez, 2, 38206 La Laguna, Tenerife, Spain

vmartin@ull.es

Received October 14, 2004

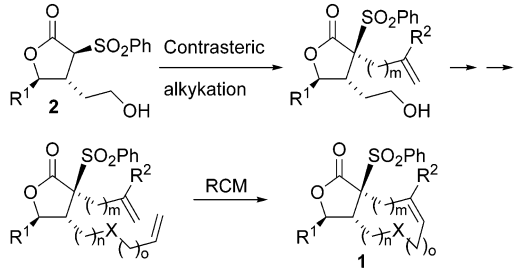
ABSTRACT



The stereoselective alkylation of α-(phenylsulfonyl)-β-[(methoxycarbonyl)methyl]-γ-lactones obtained by the base-induced cyclization of enantiomerically enriched α-[(phenylthio)acyl]-α,β-unsaturated esters and ring-closing olefin metathesis (RCM) are the basis of a new approach for gaining access to γ-lactones that are α,β-fused to medium-sized carbocycles and cyclic ethers.

γ-Lactones are widely distributed in nature in many biologically important natural products.[1] This structural unit is often found fused to medium-sized rings.[2] In addition, γ-lactone chemistry plays a very important role in the synthesis of biologically active natural products.[3] Direct approaches to the stereocontrolled synthesis of such complex systems are highly desirable.[4] The alkylation of α-(phenylsulfonyl)-β-[(methoxycarbonyl)methyl]-γ-lactones obtained by the base-induced cyclization of enantiomerically enriched α-[(phenylthio)acyl]-α,β-unsaturated esters produces highly substituted butyrolactones with a high degree of stereocontrol.[5] On the other hand, ring-closing metathesis (RCM) has been extensively utilized in the synthesis of various organic frameworks.[4,6] Merging both methodologies, we describe in

Scheme 1. Synthesis of Fused Oxa- and Carbocycles to γ-Lactones



(1) *The Merck Index*, 13th ed.; Merck & Co., Inc.: Whitehouse Station, NY, 2001.

(2) *Dictionary of Organic Compounds*, 6th ed.; Chapman & Hall/CRC: England, 1995.

(3) (a) Corey, E. J.; Cheng, X. M. In *The Logic of Chemical Synthesis*; John Wiley & Sons: New York, 1989. (b) Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599−1600. (c) Hayakawa, K.; Nagatsugi, F.; Kanematsu, K. *J. Org. Chem.* **1988**, *53*, 860−863. (d) Mitsuhashi, H.; Muramatsu, T. *Tetrahedron* **1964**, *20*, 1971−1982.

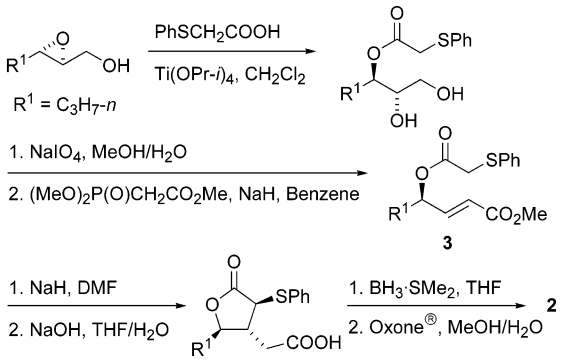
(4) For a precedent in the synthesis of carbocycles β,γ-fused to γ-lactones using RCM, see: Paquette, L. A.; Méndez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301−4304.

10.1021/ol0478739 CCC: $27.50
Published on Web 11/09/2004

this communication a new, general, and stereoselective methodology for accessing highly substituted oxa- and carbocycles fused to γ-lactones **1** (Scheme 1).

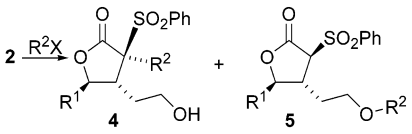
Previous work in our laboratory was directed to the synthesis of **2** in accordance with Scheme 2. Key steps in the said work are the regioselective opening of 2,3-epoxy alcohols using thiophenyl acetic acid and the stereoselective intramolecular Michael addition of the α,β-unsaturated ester **3**.[7]

Scheme 2. Stereoselective Synthesis of Trisubstituted γ-Lactones



The alkylation of **2** with a series of alkylating agents (alkyl halides) proceeded in most cases chemo- and stereoselectively leading to the contrasteric alkylation product **4** as the only isolated stereoisomer (Table 1).[8] Surprisingly, small

Table 1. Contrasteric Alkylation of β-Hydroxyalkyl-α-sulfonyl γ-Lactones



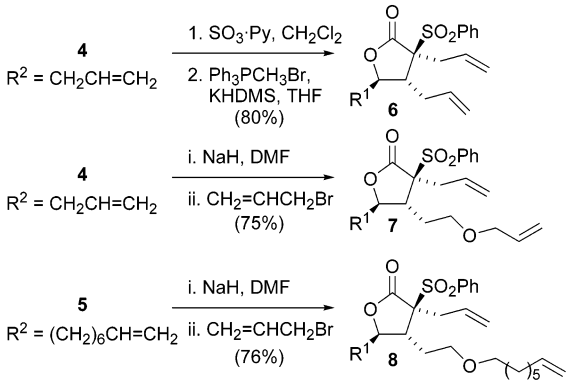
entry	R^2X	time[a] (h)	**4/5**	yield (%)
1	$CH_2{=}CHCH_2Br$	4	100:0	75
2	$CH_2{=}CH(CH_2)_2Br$	8	100:0	60
3	$CH_2{=}CH(CH_2)_3Br$	8	100:0	58
4	$CH_2{=}CH(CH_2)_4Br$	12	0:100	58
5	$CH_2{=}CH(CH_2)_6Br$	12	0:100	42
6	$CH_2{=}C(CH_3)CH_2Cl$	4	100:0	60

[a] NaH, R^2X, DMF, 0 °C to rt.

structural changes in the used halides were critical since the simple use of reagents under the same reaction conditions with slightly longer chains produced the O-alkylation **5** as the preferred product (entries 4 and 5). In these cases also the reaction times were longer.

To introduce the necessary terminal olefin at the β-chain relative to the carbonyl of the γ-lactone, two major approaches were used depending on whether the final oxa- or carbocycles were the desired products. For the preparation of the carbon-unsaturated chain, a protocol consisting in oxidation of the primary alcohol and a Wittig reaction with $Ph_3P{=}CH_2$ provided the desired diene **6**. For the ether, simple alkylation under Williamson conditions of the β-hydroxyalkyl group at **4** provided the desired linear ether **7** (Scheme 3).[9] In a similar manner, the alkylation of **5** yielded also the dialkylated lactone **8**.

Scheme 3. Representative Syntheses of the Diene Precursors for RCM



With the double-unsaturated systems in our hands, we performed ring-closing metathesis (RCM) using second-generation Grubbs' catalysts **9**.[10] The results summarized in Table 2 show that cyclic compounds were obtained in all attempted cases, with yields depending on the ring size to be formed.

Depending on the ring size, the reaction occurred in most cases with acceptable yields. Maximum yields and rates were achieved for the seven-membered ring formations. The internal coupling between geminal disubstituted olefins with terminal alkenes proceeded with excellent yield providing the trisubstituted cycloalkene (entry 6). For the larger rings a competition between intra- and intermolecular reaction appeared, lowering the yield of the monomeric species (entries 4 and 5).[11] In our opinion, such competition is more the cause of low yields than the presence of oxygen or methylene in the unsaturated chains.[12]

Another interesting feature of the presented methodology is that further manipulations of the created double bond

(5) (a) Rodriguez, C. M.; Martín, T.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **1994**, *59*, 4461−4472. (b) Rodriguez, C. M.; Martín, T.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **1994**, *59*, 8081−8091.

(6) (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (b) Nicolaou, K. C.; Snyder, S. A. In *Classics in Total Synthesis II*; Wiley-VCH: Weinheim 2003. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3007.

(7) See the Supporting Information for experimental details.

(8) For a rationalization of the stereochemical course of this reaction see ref 5b.

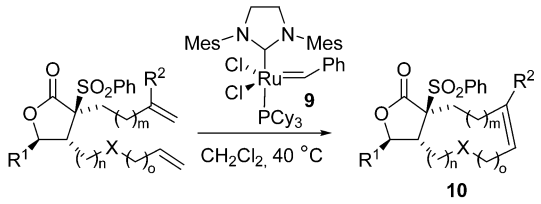
(9) Feuer, H.; Hooz, J. in Patai, S. *The Chemistry of the Ether Linkage*; Wiley: New York, 1967; pp 446−450, 460−468.

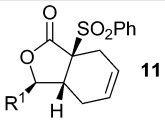
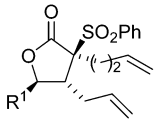
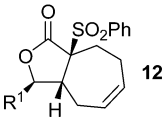
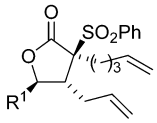
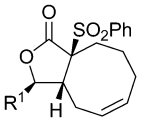
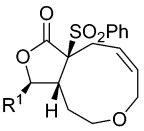
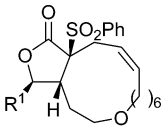
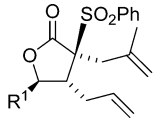
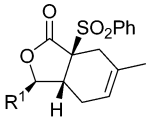
(10) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753.

(11) We were unable to characterize the polymeric products.

(12) Delgado, M.; Martín, J. D. *J. Org. Chem.* **1999**, *64*, 4798−4816.

Table 2. RCM of γ-Lactone-Tethered Dienes

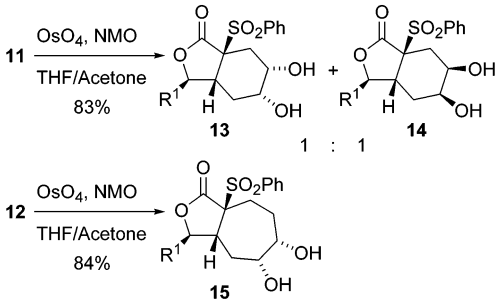


entry	diene	10	yield (%)
1	**6**	 **11**	85
2		 **12**	85
3			45
4	**7**		21[a]
5	**8**		15
6			85

[a] The product was contaminated with unidentified polymeric substances.

permit the introduction of additional substituents (Scheme 4). However, in such reactions the stereochemistry is strongly dependent on ring size. Thus, while the *cis*-dihydroxylation of the cyclohexene **11**, using standard conditions (OsO_4, NMO), provided a 1:1 mixture of diols (**13**, **14**), a similar procedure over the cycloheptene **12** yielded cleanly the diol **15** as the sole isomer.[13] It seems that depending on the ring size, preferred conformations and steric interactions are responsible for the stereochemical outcome.

Scheme 4. Influence of Ring Size in the Stereoselective *cis*-Hydroxylation of Cycloalkenes Fused to Sulfonyl γ-Lactones



In summary, a general protocol for accessing enantiomerically enriched γ-lactones fused to a cyclic system is reported.[14] The method is tunable in terms of the kind of cyclic system to be obtained. In addition, the double bond created during the RCM process permits further synthetic transformations. The development of a related methodology for accessing fused systems at different positions in the γ-lactone unit is under way.

Acknowledgment. This research was supported by the Ministerio de Ciencia y Tecnología of Spain (PPQ2002-04361-C04-02) and the Canary Islands Government.

Supporting Information Available: Preparation of the compounds of Scheme 2, ^1H and ^{13}C NMR spectra for the new compounds, and NOE studies of acetonides of **13**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0478739

(13) The stereochemistry was determined by NOE studies over the corresponding acetonides (see Supporting Information).

(14) For the stereoselective cleavage of the α-benzenesulfonyl group in fused γ-lactones, see: Martín, T.; Rodríguez, C. M.; Martín, V. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1151−1164.