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Highly Diastereoselective Synthesis of *trans*-2,5-Disubstituted Tetrahydrofurans

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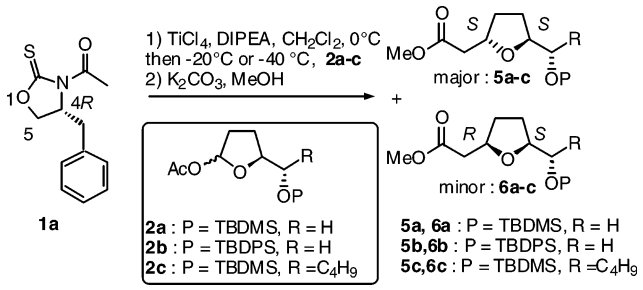
Abstract: *trans*-2,5-Disubstituted tetrahydrofurans were obtained as major diastereomers (*trans*/*cis* ratio 90:10−100:0) when acetylated γ-lactols derived from (*S*)-glutamic acid were treated with titanium enolates of *N*-acetyl (*R*)-oxazolidin-2-thiones. A simple transesterification allowed us to obtain the corresponding methyl esters and recover the chiral auxiliary.

During our work on the total synthesis of annonaceous acetogenins,[1] we were interested in preparing 2,5-disubstituted tetrahydrofurans of *trans* relationship with high diastereoselectivity. Recently, we reported that Grignard reagents add to acetyl γ-lactols derived from (*S*)-glutamic acid in good yields and moderate *trans*/*cis* ratios (e.g., 65:35−78:22).[2] These diastereomeric ratios are, nevertheless, usually obtained whatever the nucleophiles are (e.g., alkylsilanes[3] and enolates[4]). To our best knowledge, the best *trans*/*cis* ratio reported so far concerns the addition of trimethylsilyloxyfuran on an acetyl γ-lactol possessing a long aliphatic chain, derived from (*S*)-glutamic acid, in the presence of trityl perchlorate.[5] Since 2,5-disubstituted tetrahydrofurans are also found in many natural products such as polyethers,[6] we would like to report herein the preparation of such building blocks.[7] Recently, Pilli reported the interesting reaction of the titanium enolate of *N*-acyl (*R*)-4-benzyloxazolidin-2-one with a γ-lactol derived from (*S*)-glutamic acid, leading to the *trans*/*cis* expected adduct mixtures but in a low distereomeric 2:1 ratio for the *N*-acetyl compound and 10:1 ratio for the *N*-bromoacetyl derivative.[8] It is interesting to note that the *N*-acetyloxazolidin-2-ones give also low asymmetric induction in the aldol reactions.[9] We thus decided to study the addition of the titanium enolate of *N*-acetyl chiral oxazolidin-2-thiones to the same γ-lactol derivatives because these oxazolidin-2-thiones were reported to give better diastereoselectivity in aldol reactions.[10]

SCHEME 1. Diastereoselective Addition of the Titanium Enolate of 1a (1.5 equiv) to Lactol Acetates 2a−c (for Clarity, Only (*R*)-1a Is Represented)



Therefore, *N*-acetyl (*R*)-4-benzyloxazolidin-2-thione **1a** was prepared as previously reported.[10b] Its chlorotitanium enolate was generated by sequential addition of 1 equiv of $TiCl_4$ and 1 equiv of diisopropylethylamine (DIPEA) to a cold (0 °C) solution of the oxazolidin-2-thione **1a** in CH_2Cl_2. Then to the solution containing 1.5 equiv of chlorotitanium enolate of **1a** was added dropwise a CH_2Cl_2 solution of acetate **2a**, **2b**, or **2c** at −20 °C (Scheme 1). After 30 min, usual workup gave the corresponding adducts which were directly trans-esterified to the methyl esters by basic methanol treatment (K_2CO_3 in MeOH), giving the nonseparable mixtures of *trans*/*cis* esters **5a−c**/**6a−c** (the chiral auxiliary was recovered at this stage in typical 70−80% yield, after two steps, in a pure optical form). The configurations were determined on **5a−c** and **6a−c** by NMR methods (NOESY, COSY). It is worth noting that in our case the lactols were unreactive.[8] Interestingly, the oxazolidin-2-thione (*R*)-**1a** gave both a better *trans*/*cis* ratio and a better yield than the corresponding oxazolidinone.[8] The reaction of chlorotitanium enolate of (*S*)-**1a**, with **2c** under the same reaction conditions, gave the expected adducts methyl esters **5c** and **6c** in lower overall yield (40%) and lower diastereoselectivity (60:40 dr) (entry 4, Table 1). Interestingly, 1.2 equiv of chlorotitanium enolate of (*R*)-**1a** also reacts with a methoxy lactol to give the adducts in 62% yield and 85/15 dr (results not shown).

These first results are encouraging and show that the chiral *N*-acetyl 4-benzyloxazolidin-2-thione **1a** adds onto an intermediate oxocarbenium (generated in situ from the lactol acetates **2a−c**) with a good diastereoselectivity.

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TABLE 1. Diastereoselective Addition of the Titanium Enolate of 1a (1.5 equiv) to Lactol Acetates 2a−c, Followed by Methanolysis

chiral auxiliary	lactol acetate	*T* (°C)	yield (%) (two steps)	dr (trans/cis)
(*R*)-**1a**	**2a**	−20	52 (**5a** + **6a**)	70:30
(*R*)-**1a**	**2b**	−20	55 (**5b** + **6b**)	77:23
(*R*)-**1a**	**2c**	−40	77 (**5c** + **6c**)	90:10
(*S*)-**1a**	**2c**	−40	40 (**5c** + **6c**)	60:40

SCHEME 2. Addition of the Titanium Enolate of 1b (1.5 equiv) to Lactol Acetates 2a−c (for Clarity, Only (*R*)-1b Is Represented)

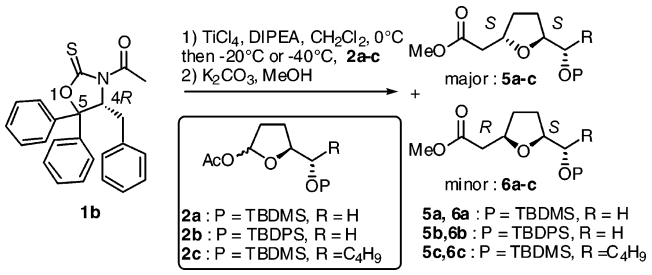


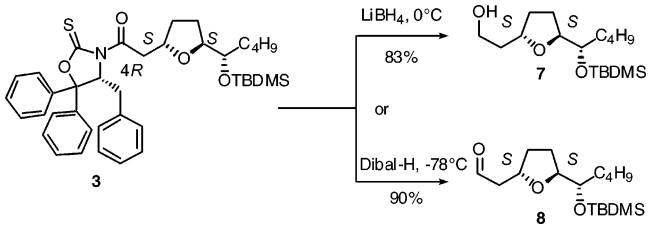
TABLE 2. Diastereoselective Addition of the Titanium Enolate of 1b (1.5 equiv) to Lactol Acetates 2a−c, Followed by Methanolysis

chiral auxiliary	lactol acetate	*T* (°C)	yield (%) (two steps)	dr (trans/cis)
(*R*)-**1b**	**2a**	−20	51 (**5a** + **6a**)	90:10
(*S*)-**1b**	**2a**	−20	51 (**5a** + **6a**)	75:25
(*R*)-**1b**	**2b**	−20	56 (**5b** + **6b**)	100:0
(*R*)-**1b**	**2c**	−40	75 (**5c** + **6c**)	100:0
(*S*)-**1b**	**2c**	−40	48 (**5c** + **6c**)	90:10

However both enantiomers of **1a** gave the same major *trans* diastereomer (with (*R*)-**1a** leading to a better diastereoselectivity and higher yields than (*S*)-**1a**). This means that the reaction is not auxiliary but substrate controlled and that the oxazolidin-2-thione **1a** acts mainly via its bulk and not only via its absolute configuration. We thus decided to prepare a more bulky oxazolidin-2-thione and synthesized for the first time the *N*-acetyl (*R*)-5,5-diphenyl-4-benzyloxazolidin-2-thione **1b**, and its enantiomer (*S*)-**1b**, and studied their reactivity with the lactol acetates **2a−c** (Scheme 2 and Table 2). (*R*)-**1b** and (*S*)-**1b** were prepared from the corresponding chiral (*R*)- and (*S*)-α-amino acid methyl esters of phenylalanine by double phenyl Grignard addition, followed by cyclization of the 1,2-amino alcohols so obtained with thiophosgene.[10c] Acetylation of the oxazolidin-2-thiones was then performed by treatment with acetyl chloride in the presence of NaH, leading to (*R*)-**1b** and (*S*)-**1b** in 55% overall yield (three steps).

When 1.5 equiv of the chlorotitanium enolate of (*R*)-**1b** (generated by 1 equiv of $TiCl_4$ and 1 equiv of DIPEA) reacted at −20 °C with lactol acetate **2a** (1 equiv), the adducts were obtained and directly transesterified to the methyl esters **5a** and **6a** in 51% yield (two steps) and in 90:10 dr (Scheme 2, Table 2). Reaction of the chlorotitanium enolate of (*S*)-**1b**, with **2a**, under the same reaction conditions gave the methyl esters **5a** and **6a** in 51% yield (in two steps) and 75:25 dr. With lactol acetate **2b**, which possesses the more bulky TBDPS protecting group, the chlorotitanium enolate of (*R*)-**1b** gave the methyl esters

SCHEME 3



5b and **6b** in 56% yield (in two steps) and 100:0 dr (Table 2). It is important to note that this is the first time that such a diastereoselectivity has been observed with this lactol derivative. Finally, when the reaction was performed at lower temperature (−40 °C), yields were lower (not shown). In the case of lactol acetates **2c**, with more sterical demands due to the $CH(OTBDMS)C_4H_9$ side chain, both chlorotitanium enolates of (*R*)-**1b** and (*S*)-**1b** (generated as described above) gave the *trans* esters **5c** as the major diastereomer (100:0 and 90:10, respectively) and in 75 and 48% yield, respectively, when the reactions were run at −40 °C. In these cases, higher temperatures gave lower diastereoselectivities (results not shown). These results highlight again the substrate control of the reaction.

It is important to note that the *trans*/*cis* intermediate adducts **3** and **4** could also be isolated and further transformed into the primary alcohols and aldehydes. For instance, the $LiBH_4$ reduction[8] of the *trans* adduct **3**, obtained from addition of the titanium enolate of (*R*)-**1b** to lactol acetates **2c**, afforded the single primary alcohol **7** in 83% yield with 91% recovery of the chiral auxiliary. The corresponding aldehyde **8** could also be prepared in high yield (90%) from the same adduct **3** by Dibal-H reduction,[11] with recovery of the chiral auxiliary in 93% yield (Scheme 3).

In conclusion, this study shows that chiral *N*-acetyloxazolidin-2-thiones are much better nucleophiles than their *N*-acetyloxazolidin-2-one counterparts, and the diastereoselective addition of their chlorotitanium enolates to 2-acetoxytetrahydrofurans allows one to prepare the *trans* compounds in good yields and excellent diastereomeric ratios (up to 100:0). The adducts so obtained may be used in the asymmetric synthesis of 2,5-*trans*-disubstituted tetrahydrofurans with excellent recovery of the chiral auxiliary.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **1b**, *des*-acetyl **1b**, **3**, **5b**,**c**, **7**, and **8**. Experimental procedures and characterization data for *des*-acetyl **1b**, **1b**, **3**, **5b**,**c**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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