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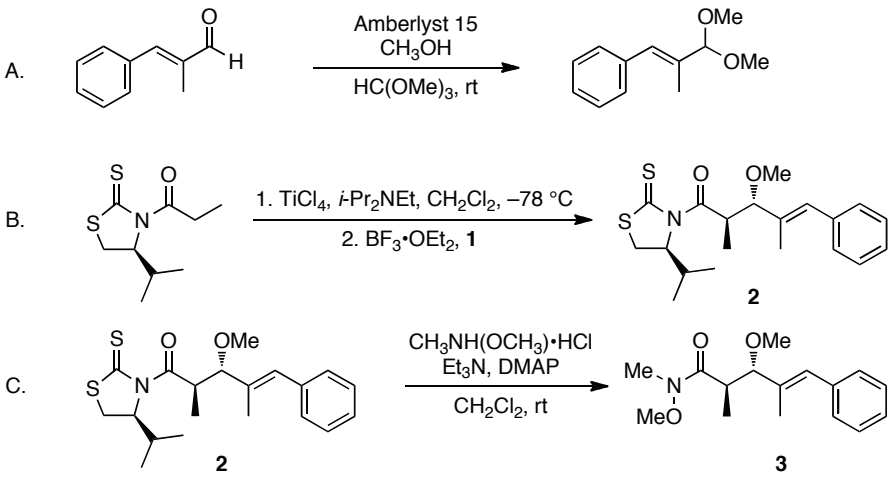
Discussion Addendum for: Stereoselective Synthesis of *anti* α-Methyl-β-Methoxy Carboxylic Compounds



Submitted by Pedro Romea* and Fèlix Urpí.*[1]
Original article: Gálvez E.; Romea P.; Urpí F. *Org. Synth.* **2009**, *86*, 81–91.

Prior and subsequent to our original report in *Organic Syntheses*, we have described a number of highly diastereoselective Lewis acid-mediated additions of titanium enolates from chiral *N*-acyl thiazolidinethiones to acetals.[2] These involve the addition of *N*-propanoyl and *N*-acetyl-4-isopropyl-1,3-thiazolidine-2-thione to dialkyl acetals (eq 1 and 2 in Scheme 1)[3-5] and dimethyl ketals from methyl ketones (eq 3 in Scheme 1).[6] Furthermore, the scope of the acyl groups has been recently expanded to *N*-glycolyl derivatives. Especially, *O*-pivaloyl protected *N*-glycolyl 4-isopropyl-1,3-thiazolidine-2-thione undergoes highly diastereoselective additions to a wide array of dimethyl and dibenzyl acetals (eq 4 in Scheme 1).[7]

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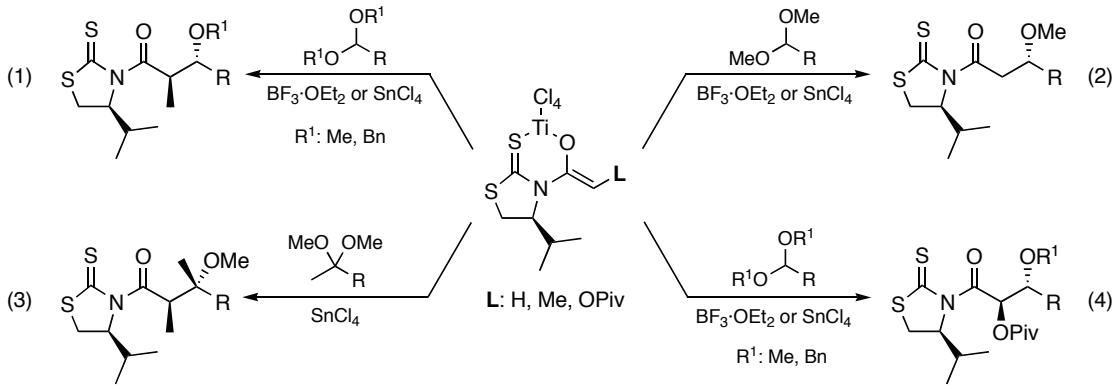
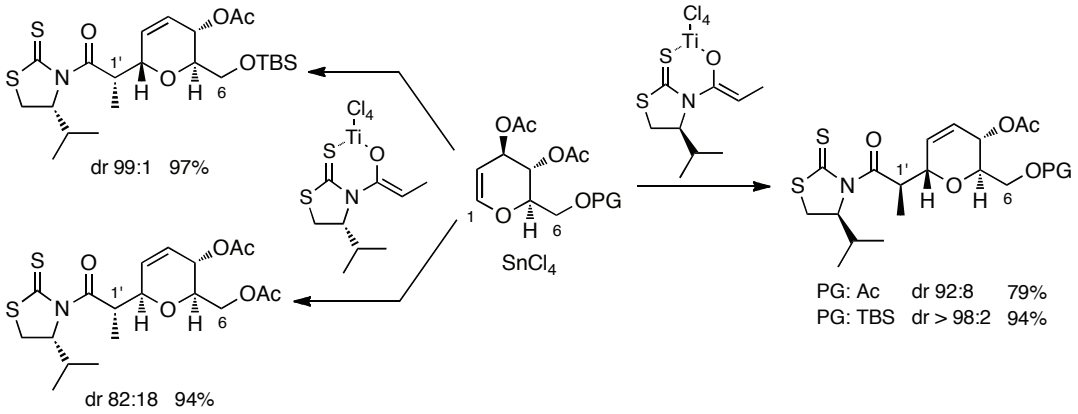
Scheme 1. Stereoselective additions of titanium enolates from *N*-acyl-4-isopropyl-1,3-thiazolidine-2-thione to dialkyl acetals and ketals



These reactions likely proceed through a mechanism in which an oxocarbenium intermediate approaches to the less hindered face of the titanium enolate. Taking advantage of such a picture, this chemistry has been successfully applied to glycals. Thereby, activation of glycals by Lewis acids triggers the formation of cyclic and conjugated oxocarbenium intermediates that may participate in highly diastereoselective α- and β-*C*-glycosidation processes with the abovementioned titanium enolates. Importantly, the appropriate choice of the chiral auxiliary and the C6-protecting group determines the stereochemical outcome of these carbon-carbon bond forming reactions and permits the modular preparation of three of the four possible diastereomers of α- or β-1'-methyl-substituted *C*-glycosides (Scheme 2).[8-10]

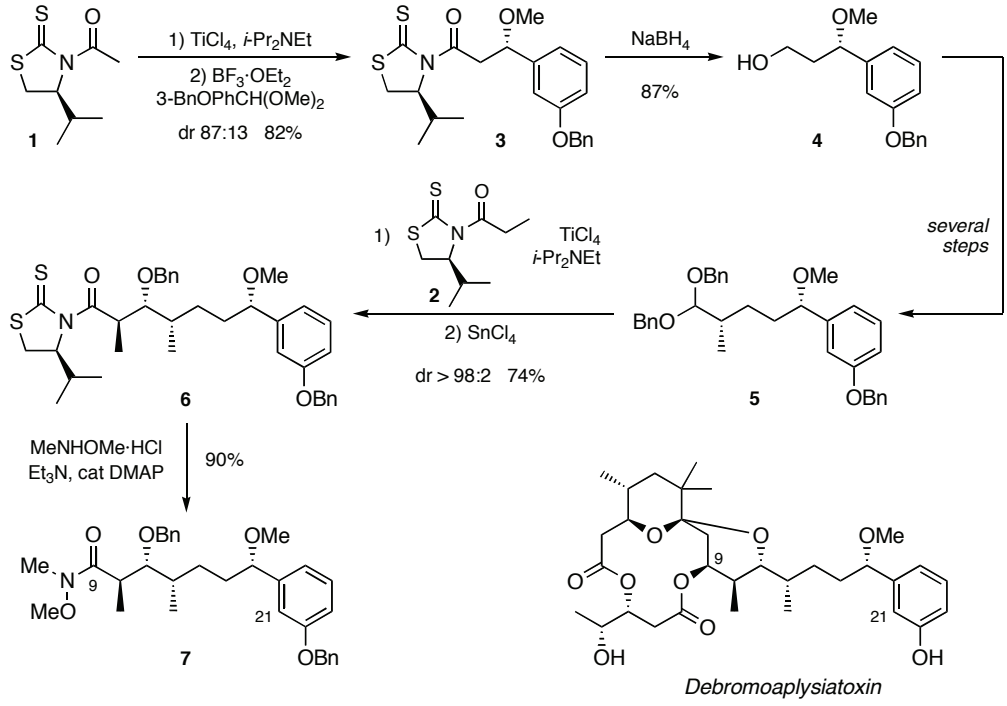
Scheme 2. Stereoselective *C*-glycosidation reactions



Synthetic applications

These methods have been already applied to the synthesis of natural products. For instance, our group took advantage of the Lewis acid-mediated addition of the titanium enolates from (*S*) *N*-acetyl and *N*-propanoyl 4-isopropyl-1,3-thiazolidine-2-thiones (**1** and **2** respectively in Scheme 3) to dialkyl acetals for the construction of the C9–C21 fragment of debromoaplysiatoxin.[11] As shown in Scheme 3, chromatographic purification of the product formed from the reaction between **1** and the dimethyl acetal of an aromatic aldehyde afforded diastereomerically pure adduct **3** in 82% yield. Removal of the chiral auxiliary gave alcohol **4**, which was further elaborated to chiral dibenzyl acetal **5**. Then, the stage was set for the introduction of two new stereocenters. Indeed, the asymmetric induction imparted by the titanium enolate of **2** and the *Felkin* bias of the oxocarbenium cation from **5** provided adduct **6** as a single diastereomer (dr > 98:2) in 74% yield. Finally, treatment of **6** with MeNHOMe furnished Weinreb amide **7** in 90% yield.[12]

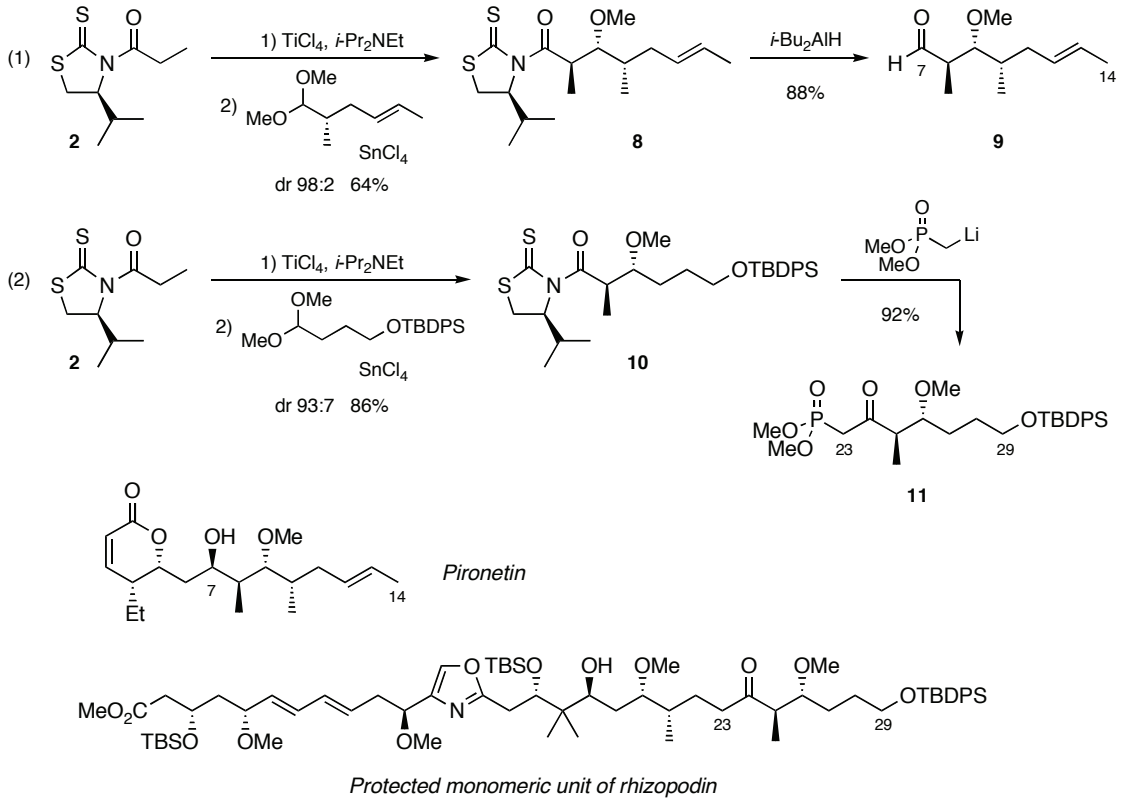
Scheme 3. Stereoselective synthesis of C9–C21 fragment of debromoaplysiatoxin



Crimmins and Chakraborty have also used these transformations in the total syntheses of pironetin and a protected form of the monomeric unit

of rhizopodin respectively (Scheme 4).[13,14] Thereby, Crimmins reported that the addition of **2** to a chiral dimethyl acetal provided adduct **8** as a single diastereomer in 64% yield, which was further converted into aldehyde **9** by treatment with *i*-Bu_2AlH (eq 1 in Scheme 4).[13] In turn, Chakraborty described a similar process involving an achiral dimethyl acetal in which adduct **10** was obtained in an excellent diastereomeric ratio (dr 93:7) and 86% yield (eq 2 in Scheme 4).[14] Interestingly, removal of the chiral auxiliary by the lithium salt of the dimethyl methylphosphonate furnished ketophosphonate **11** ready to participate in an HWE olefination.

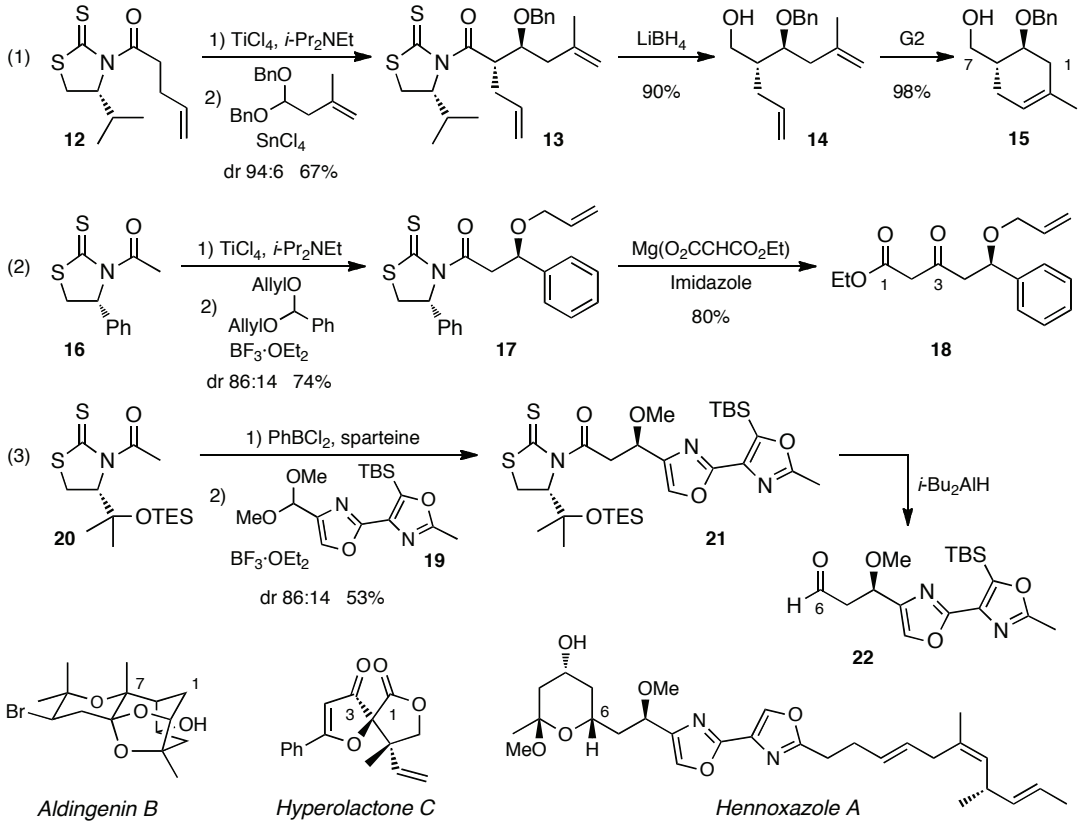
Scheme 4. Total syntheses of pironetin and a monomeric unit of rhizopodin



Other reports have also established that these Lewis acid acid-mediated couplings of *N*-acyl thiazolidinethiones and acetals are flexible enough to be successfully adapted to the synthesis of a broad array of natural products. For instance, Crimmins took advantage of the highly diastereoselective reaction of the titanium enolate from *N*-(4-pentenoyl) thiazolidinethione **12** and a dibenzyl acetal, the mild removal of the chiral auxiliary from adduct **13**, and the RCM of the resultant alcohol **14** to obtain in a few steps the cyclic core **15** of aldigenin B (eq 1 in Scheme 5).[15] In turn, Hodgson reported that the addition of the titanium enolate of (*R*)-

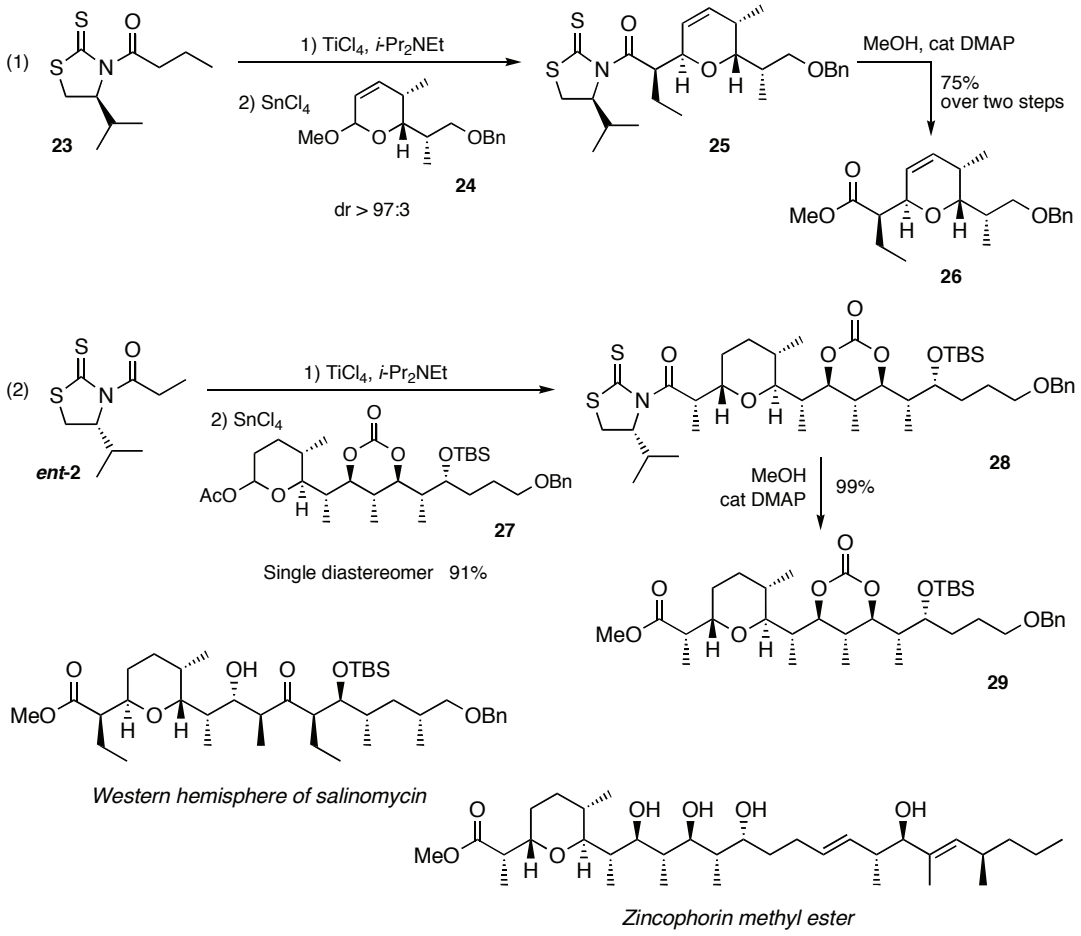
phenylglycine-derived *N*-acetyl thiazolidinethione **16** to the benzaldehyde diallyl acetal provided diastereomerically pure adduct **17** in 74% yield after chromatography. Further treatment of this adduct with magnesium acetoacetate and imidazole led to β-keto ester **18**, a key intermediate in the total synthesis of hyperolactone C (eq 2 in Scheme 5).[16] Finally, the synthesis of hennoxazole A by Smith includes a comprehensive study on the Lewis acid-mediated additions of *N*-acetyl thiazolidinethiones to the dimethyl acetal of bisoxazole **19**.[17] This revealed that the ability of an oxazole nitrogen atom to coordinate with the titanium center altered the stereochemical outcome of such additions and the undesired diastereomer was obtained in 80:20 diastereomeric ratio and 67% yield. Looking for alternative conditions, Smith found that the enolization of *N*-acetyl thiazolidinethione **20** using Sammakia's conditions ($PhBCl_2$/sparteine) followed by the $BF_3{\cdot}OEt_2$-mediated addition of the resultant boron enolate to **19** provided the desired adduct **21** in 86:14 diastereomeric ratio and 53% yield (eq 3 in Scheme 5). Eventually, reduction of **21** with *i*-Bu_2AlH gave aldehyde **22**, which was immediately used in the next step.

Scheme 5. Total syntheses of aldigenin B, hyperolactone C, and hennoxazole



Dialkyl acetals are not the only suitable substrates for these transformations. Certainly, oxocarbenium cations from cyclic hemiacetals and glycals (see Scheme 2) can also undergo highly diastereoselective additions to titanium enolates from *N*-acyl thiazolidinethiones, as was used by our group in the stereoselective synthesis of the western hemisphere of salinomycin. Indeed, the $SnCl_4$-mediated addition of the titanium enolate from *N*-butanoyl thiazolidinethione **23** to hemiacetal **24** afforded α-*C*-glycoside **25** as a single diastereomer (dr > 97:3), which was treated with methanol to obtain methyl ester **26** in 75% overall yield (eq 1 in Scheme 6).[18] More recently, Leighton has reported that the coupling of structurally complex *O*-acetyl hemiacetal **27** with the titanium enolate of ***ent*-2** produced α-*C*-glycoside **28** as a single diastereomer in an outstanding 91% yield (eq 2 in Scheme 6).[19] Methanolysis proceeded exceptionally smoothly to give **29** in quantitative yield, which was finally converted into zincophorin methyl ester in a few steps.

Scheme 6. Syntheses of antibiotic polyethers



In summary, the Lewis acid-mediated addition of titanium enolates from *N*-acyl thiazolidinethiones to dialkyl acetals, hemiacetals, or glycals represents a powerful synthetic tool for the stereoselective construction of carbon-carbon bonds leading to *anti* α-alkyl-β-alkoxy carboxylic derivatives. Importantly, the chiral auxiliary can be easily removed using a number of mild conditions, which confers to these methodologies a remarkable appeal for the synthesis of natural products.

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Pedro Romea completed his BSc in Chemistry in 1984 at the University of Barcelona. That year, he joined the group of Professor Jaume Vilarrasa, at the University of Barcelona, receiving his Master Degree in 1985, and he followed PhD studies in the same group from 1987 to 1991. Then, he joined the group of Professor Ian Paterson at the University of Cambridge (UK), where he participated in the total synthesis of oleandolide. Back to the University of Barcelona, he became Associate Professor in 1993. His research interests have focused on the development of new synthetic methodologies and their application to the stereoselective synthesis of naturally occurring molecular structures

Fèlix Urpí received his BSc in Chemistry in 1980 at the University of Barcelona. In 1981, he joined the group of Professor Jaume Vilarrasa, at the University of Barcelona, receiving his Master Degree in 1981 and PhD in 1988, where he was an Assistant Professor. He then worked as a NATO postdoctoral research associate in titanium enolate chemistry with Professor David A. Evans, at Harvard University (USA). He moved back to the University of Barcelona and he became Associate Professor in 1991. His research interests have focused on the development of new synthetic methodologies and their application to the stereoselective synthesis of naturally occurring molecular structures.