Stereoselective Addition of Titanium Enolates to Functionalized Acetals: A Novel Approach to the γ-Amino Acid of Bistramides and FR252921

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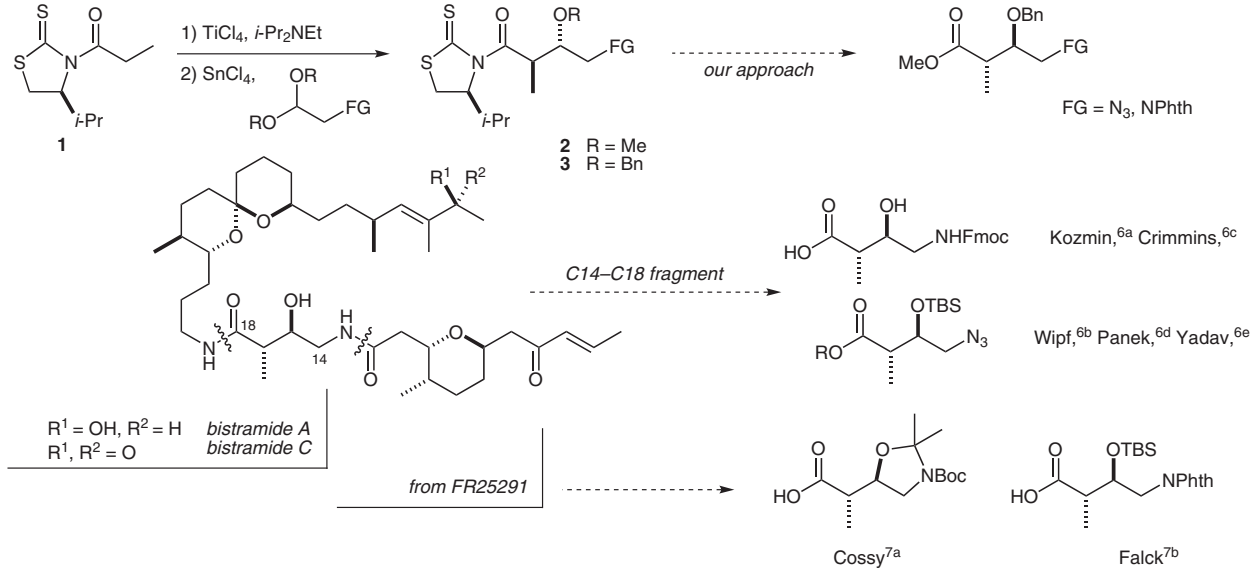
Abstract: Dialkyl acetals containing other functional groups can participate in stereoselective coupling reactions with chiral titanium enolates. Such an approach provides the protected γ-amino acid present in bistramides and FR252921 in a highly efficient manner.

Key words: stereoselective reactions, crossed aldol-like condensation, titanium enolates, acetals, bistramide, FR252921

The widespread presence of β-alkoxy oxygenated relationships in natural products has stimulated the development of a plethora of synthetic approaches to the corresponding β-alkoxy carbonyl compounds,[1] most of them being based on a two-step sequence: (i) stereoselective aldol reaction[2] and (ii) alkylation of the aldol adduct.[3] Considering that the second step is often troublesome, and the integration of a multistep sequence in a single transformation increases the efficiency of a process, we envisaged that the stereoselective addition of chiral enolates to dialkyl acetals might render such β-alkoxy carbonyl compounds in a straightforward manner. In accordance with this approach, we have reported that the Lewis acid mediated addition of titanium enolates of (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione (**1**, Scheme 1) to dimethyl and dibenzyl acetals affords the *anti*-β-alkoxy-α-methyl adducts in good yields and diastereomeric ratios.[4] This methodology has been already applied to the construction of the C9–C21 fragment of debromoaplysiatoxin,[5] but it remained unclear if such a procedure would be compatible with more complex acetals to enable the construction of structurally complex molecular architectures. Herein, we document the use of dimethyl and dibenzyl acetals containing other functional groups in the aforementioned coupling reactions and the successful application of this methodology to the synthesis of a highly functionalized four-carbon fragment present in bistramides and a novel immunosuppressive agent, FR252921 (Scheme 1).[6,7]

Initially, we examined the reaction of **1** with the dimethyl acetals shown in Table 1,[8] which encompass acetals with a heteroatom positioned at C2 or other functional groups that can affect the formation or the reactivity of the putative oxonium intermediate. Preliminary studies with the commercially available bromoacetaldehyde dimethyl acetal (**a**) proved that the experimental conditions established for alkyl acetals provided a synthetically useless yield (see entry 1 in Table 1). After an exhaustive optimization,[9] it was found that the stoichiometry was crucial to improve the yield (compare entries 1–4 in Table 1). Thus, keeping



Scheme 1

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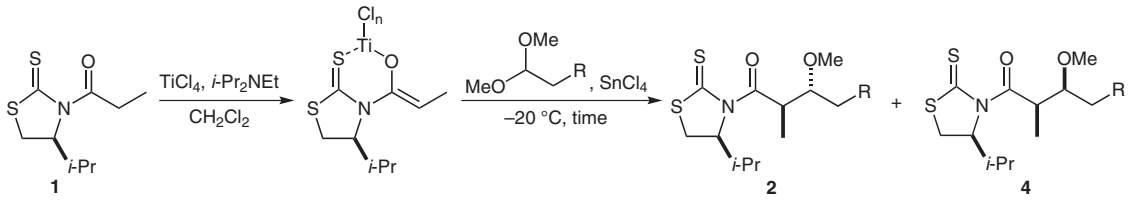
Table 1 Lewis Acid Mediated Addition of the Titanium Enolate from **1** to Dimethyl Acetals



Entry	Acetal	R	$SnCl_4$ (equiv)	Acetal (equiv)	Time (h)	dr (**2**:**4**)[a]	Yield of **2** (%)[b]
1	**a**	Br	1	1	2	90:10	24
2	**a**	Br	1	0.5	2	93:7	27
3	**a**	Br	0.55	0.5	2	92:8	46
4	**a**	Br	0.55	0.5	17	92:8	65
5	**b**	CO_2Me	0.55	0.5	17	92:8	(82)
6	**c**	OBn	0.55	0.5	2	65:35	54 (83)
7	**d**	CH_2OBn	0.55	0.5	2	95:5	82
8	**e**	$(CH_2)_2OBn$	0.55	0.5	2	97:3	73
9	**f**	NPhth	0.55	0.5	17	>97:3	54
10	**f**	NPhth	1	0.5	2	>97:3	80

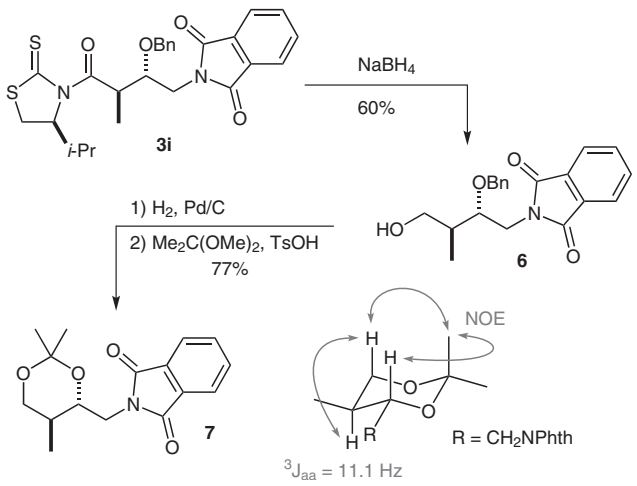
[a] Determined by the HPLC analysis of the reaction mixture.
[b] Isolated yield of **2**. Overall yield is given in parentheses.

at –20 °C a mixture of the titanium enolate from **1** and 0.5 equivalents of $SnCl_4$ and the acetal **a** permitted to isolate the *anti* adduct **2a** in good yield and diastereomeric ratio (dr = 92:8, 65% yield, see entry 4 in Table 1). Parallel results (see entry 5 in Table 1) were obtained with the methyl 3-oxopropanoate dimethyl acetal (**b**). In turn, the diastereoselectivity observed for acetals **c**–**e** containing benzyl ethers was highly dependent on the position of the benzyloxy group. The poorer stereocontrol was obtained for acetal **c** with the OBn group at C2, but it became excellent if such group is placed at C3 or C4 (acetals **d** and **e**, respectively). In all these cases, the reaction proceeded faster and the yield did not increase significantly after two hours (see entries 6–8 in Table 1). Conversely, the acetal **f** possessing a phthalimido group at C2 was much less reactive and required the addition of one equivalent of $SnCl_4$ to attain a high yield of a single diastereomer (compare entries 9 and 10 in Table 1).

Next, we focused our attention on dibenzyl acetals shown in Table 2.[10] As well as their dimethyl counterparts, acetals **g**–**i** emerged as suitable substrates for such coupling reactions and afforded the 2,3-*anti* adducts **3** in high yields. Interestingly, the addition of one equivalent of $SnCl_4$ improved the diastereoselectivity of these reactions, and provided the corresponding adduct as a single diastereomer with the exception of the azidoacetaldehyde dibenzyl acetal **h** (dr = 75:25, see entry 5 in Table 2). The reasons for such low diastereoselectivity are still elusive.

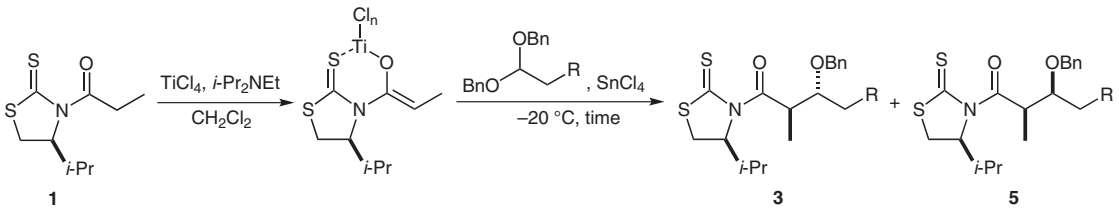
As expected,[4] only two of four possible diastereomers were observed across all the reaction mixtures, which proves the complete control exerted by the chiral auxiliary on the configuration of the α-stereocenter. The 2,3-*anti* relationships on major diastereomers **2** and **3** were assigned through analysis of the $^3J_{2,3}$ coupling constants ($^3J_{2,3} > 7.0$ Hz).[11] Furthermore, it was secured for **3i** by a thorough spectroscopic analysis of the isopropylidene acetal **7** represented in Scheme 2.

The abovementioned synthetic sequence makes clear that the adducts from dibenzyl acetals can be considered as protected *anti*-aldol units. Given that their stereoselective construction is still challenging[12] and the thiazolidinethione chiral auxiliary can be easily removed,[4,5,13] this meth-



Scheme 2

Table 2 Lewis Acid Mediated Addition of the Titanium Enolate from **1** to Dibenzyl Acetals



Entry	Acetal	R	$SnCl_4$ (equiv)	Acetal (equiv)	Time (h)	dr (**3**:**5**)[a]	Yield of **3** (%)[b]
1	**g**	Br	0.55	0.5	17	91:9	69
2	**g**	Br	1	0.5	2	95:5	34
3	**g**	Br	1	0.5	17	95:5	75
4	**h**	N_3	0.55	0.5	17	50:50	(83)
5	**h**	N_3	1	0.5	17	75:25	(87)
6	**i**	NPhth	1	0.5	2	>97:3	79
7	**i**	NPhth	1	0.5	17	>97:3	84

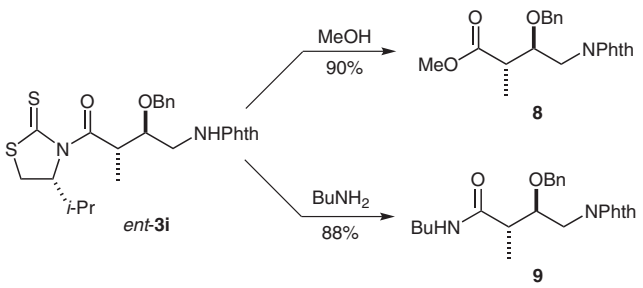
[a] Determined by the HPLC analysis of the reaction mixture.
[b] Isolated yield of **3**. Overall yield is given in parentheses.

odology represents an appealing entry to highly functionalized fragments containing those arrays. To confirm the efficiency of this approach, we undertook the synthesis of the protected γ-amino acid embedded in bistramides and FR252921, as represented in Scheme 1.

Hence, simple stirring of adduct *ent*-**3i**[14] in methanol in the presence of a catalytic amount of DMAP at room temperature for 3.5 hours provided the desired methyl ester **8** in 90% (Scheme 3). This transformation can be carried out with the crude mixture obtained from the coupling reaction. Therefore, the two-step sequence only requires a single chromatographic purification to provide the ester **8** in 77% overall yield.[15]

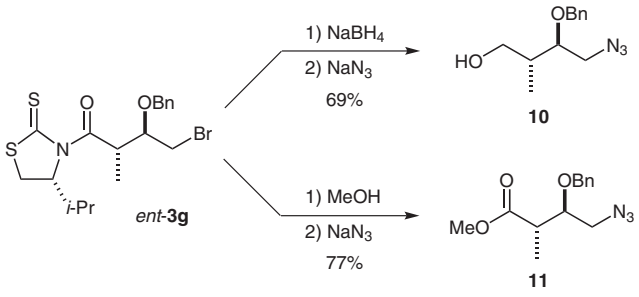
Since the C18 carbon is attached to the spiro fragment of bistramides through an amido link, we speculated about the opportunity of converting *ent*-**3i** into a model amide. Gratifyingly, the treatment of *ent*-**3i** with one equivalent of $BuNH_2$ led to the butyl amide **9** in 88% yield (Scheme 3).

The preparation of the related azido derivatives proved to be troublesome. Since the acetal **h** containing the azido group provided a poorly stereoselective reaction, we took



Scheme 3

advantage of the better results achieved with the bromo acetal **g** (compare entries 3 and 5 in Table 2). Thus, the removal of the chiral auxiliary from the adduct *ent*-**3g** led to the corresponding alcohol and methyl ester, which, in turn, were subsequently treated with NaN_3 to deliver the desired azido derivatives **10** and **11** in good overall yields (Scheme 4).[16,17] This strategy failed in the case of the butyl amide, presumably as a consequence of the cyclization of the bromoamide intermediate.



Scheme 4

In summary, dimethyl and dibenzyl acetals containing different functional groups can participate in highly stereoselective Lewis acid mediated coupling reactions with the titanium enolates from (*S*)-4-isopropyl-*N*-propanoyl-1,3-thiazolidine-2-thione. The resultant *anti*-3-alkoxy-2-methyl adducts can be easily manipulated to deliver densely functionalized synthons. The efficiency of such approach has been proved in the straightforward synthesis of several protected precursors of the γ-amino acid present in bistramides and a novel immunosuppressive agent, FR252921.

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(14) Enantiomeric adducts *ent*-**3** are obtained from *ent*-**1**, which in turn is prepared from the commercially available (*R*)-valinol.

(15) **Preparation of Methyl Ester 8**
Neat $TiCl_4$ (0.12 mL, 1.1 mmol) was added dropwise to a solution of *ent*-**1** (217 mg, 1.0 mmol) in CH_2Cl_2 (8 mL), at 0 °C under N_2. The yellow suspension was stirred for 5 min at 0 °C, cooled at –78 °C, and a solution of *i*-Pr_2NEt (0.19 mL, 1.1 mmol) in CH_2Cl_2 (1 mL) was added. The dark red enolate solution was stirred for 2 h at –50 °C. Then, 1 M $SnCl_4$ in CH_2Cl_2 (1.1 mL, 1.1 mmol), followed by acetal **i** (314 mg, 1.1 mmol) in CH_2Cl_2 (1 mL), was successively added dropwise at –78 °C. The resulting mixture was stirred at –78 °C for 30 min and kept at –20 °C for 2 h. The reaction was cooled at –78 °C and quenched by the addition of sat. NH_4Cl (8 mL) with vigorous stirring. The layers were separated. The aqueous layer was re-extracted with CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4), filtered, concentrated, and analyzed by HPLC. A solution of the residue and a crystal of DMAP in MeOH (8 mL) was stirred for 3.5 h at r.t. under N_2, diluted in Et_2O, and washed with 2 M NaOH, 2 M HCl, sat. $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification of the resultant oil through a pad of SiO_2 (CH_2Cl_2) afforded 141 mg (0.38 mmol, 77% yield) of methyl ester **8**. Colorless oil. R_f = 0.2 (CH_2Cl_2). $[\alpha]_D$ +16.1 (*c* 0.95, $CHCl_3$). IR (film): ν = 2948, 1773, 1715, 1395, 1196, 1071 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.76 (2 H, m, Ar*H*), 7.71–7.67 (2 H, m, Ar*H*), 7.31–7.04 (5 H, m, Ar*H*), 4.57 (1 H, d, *J* = 11.3 Hz, PhCH_xH$_y$), 4.52 (1 H, d, *J* = 11.3 Hz, PhCH$_x$$H_y$), 4.01 (1 H, ddd, *J* = 7.3, 5.8, 4.5 Hz, C*H*OBn), 3.91–3.82 (2 H, m, CH_2N), 3.65 (3 H, s, OCH_3), 2.85–2.76 (1 H, m, COC*H*CH$_3$), 1.33 (3 H, d, *J* = 7.0 Hz, COCHCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.6 (C), 168.2 (C), 137.7 (C), 133.8 (CH), 132.0 (C), 128.1 (2 × CH), 127.5 (CH), 123.2 (CH), 78.3 (CH), 72.7 (CH_2), 51.8 (CH_3), 42.7 (CH), 38.3 (CH_2), 12.6 (CH_3). ESI-HRMS: *m/z* calcd for $C_{21}H_{22}NO_5$ $[M + H]^+$: 368.1492; found: 368.1488.

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(17) **Selected Data for Methyl Ester 11**
$[\alpha]_D$ +34.6 (*c* 1.3, $CHCl_3$). IR (film): ν = 2950, 2101, 1737, 1455, 1285, 1262, 1197, 1172, 1098, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (5 H, m, Ar*H*), 4.65 (1 H, d, *J* = 11.3 Hz, PhCH_xH$_y$), 4.57 (1 H, d, *J* = 11.3 Hz, PhCH$_x$$H_y$), 3.83 (1 H, ddd, *J* = 7.5, 5.7, 3.2 Hz, C*H*OBn), 3.68 (3 H, s, OCH_3), 3.44 (1 H, dd, *J* = 13.2, 3.2 Hz, CH_xH$_y$N$_3$), 3.30 (1 H, dd, *J* = 13.2, 5.7 Hz, CH$_x$$H_yN_3$), 2.92–2.84 (1 H, m, COC*H*CH$_3$), 1.13 (3 H, d, *J* = 7.1 Hz, COCHCH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.6 (C), 137.6 (C), 128.4 (CH), 127.9 (CH), 127.8 (CH), 79.9 (CH), 72.8 (CH_2), 51.8 (CH_3), 51.2 (CH_2), 42.0 (CH), 12.7 (CH_3). ESI-HRMS: *m/z* calcd for $C_{13}H_{17}N_3NaO_3$ $[M + Na]^+$: 286.1162; found: 286.1174.