

Synthesis and Use of Achiral Oxazolidine-2-thiones in Selective Preparation of *trans* 2,5-Disubstituted Tetrahydrofurans

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Dedicated to Professor André Cavé on the occasion of his 75th birthday

Keywords: Titanium / Diastereoselectivity / Natural products / Lactols / Furans / Glycosylation

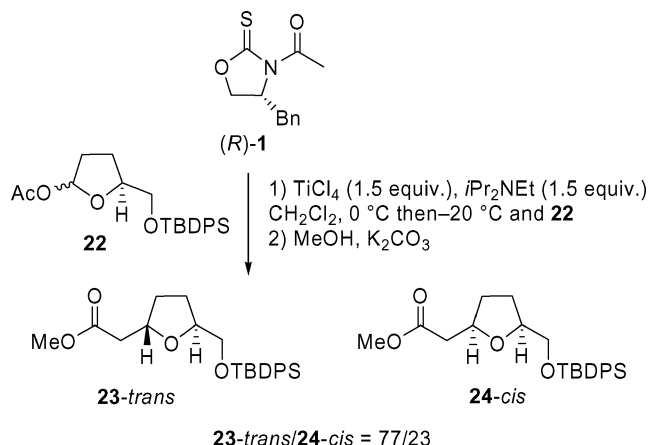
The use of achiral *N*-acetyloxazolidine-2-thiones in the *C*-glycosylation of lactol acetates has allowed us to prepare with high diastereoselectivity the expected *trans* 2,5-disubstituted tetrahydrofurans. A study based on the role of the

steric hindrance of the *N*-acetyloxazolidine-2-thiones is reported.

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Introduction

2,5-Disubstituted tetrahydrofurans are found in many natural products as well as in pharmacologically active products.^[1] Access to this class of compounds has been reviewed^[2] and recently we published a report on the preparation of 2,5-disubstituted tetrahydrofurans based on a highly diastereoselective *C*-glycosylation of lactol acetates with the titanium enolates of chiral *N*-acetyl-4-benzyloxazolidine-2-thione (**1**; Scheme 1).^[3]

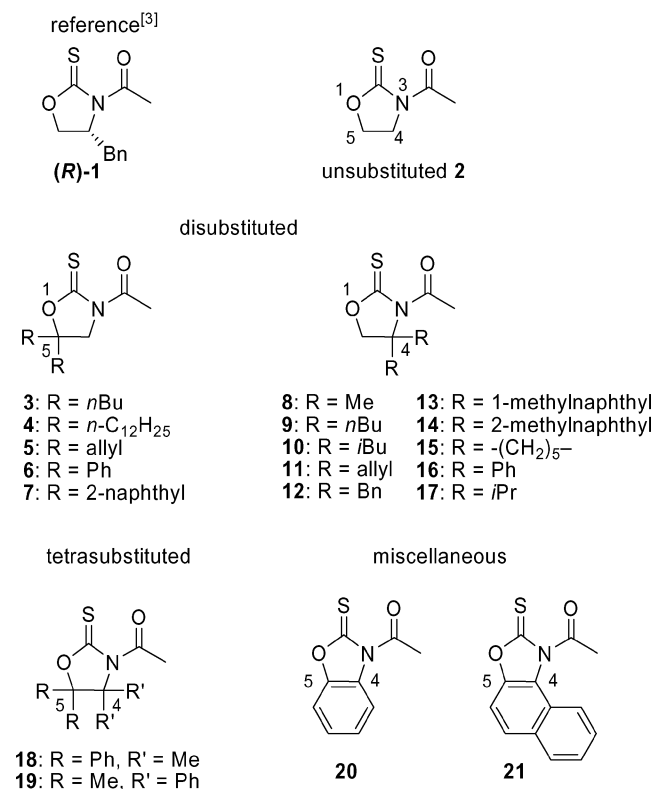


Scheme 1.

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Achiral *N*-acetyloxazolidin-2-thiones



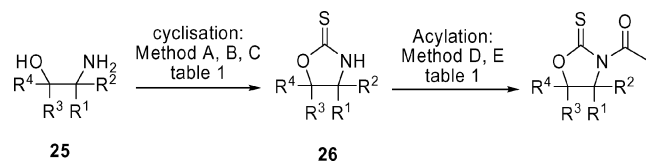
Scheme 2.

steric hindrance of achiral oxazolidine-2-thiones on the course of the reaction and prepared unsubstituted as well as 4,4- or 5,5-disubstituted, and 4,4,5,5-tetrasubstituted oxazolidine-2-thiones (Scheme 2).

To compare the diastereoselectivity after the *C*-glycosylation of compound **22**, all adducts were transesterified to the *trans* and *cis* methyl esters **23** and **24**.

Results and Discussion

The oxazolidine-2-thiones synthesized in this work are represented in Scheme 2 and were prepared from a common intermediate, amino alcohol **25** (Scheme 3, Table 1).

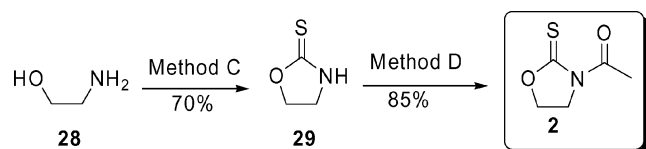


Scheme 3.

All the amino alcohols **25** were cyclized to the corresponding oxazolidine-2-thiones **26** through one of the methods A–C and then acetylated to the corresponding *N*-acetyloxazolidine-2-thiones **2–21** by using methods D–E (Scheme 3, Table 1). *N*-Acetyloxazolidine-2-thione **19** was prepared differently (see below).

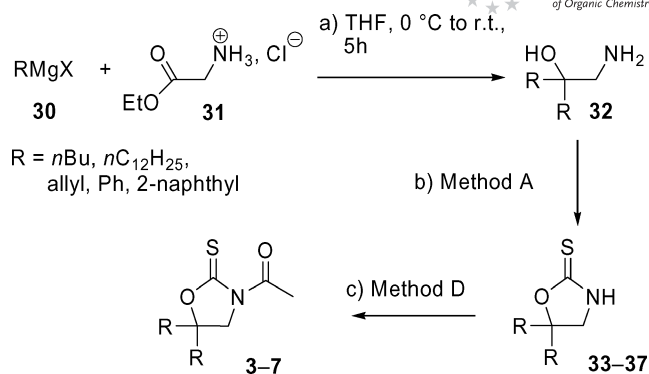
Preparation of Oxazolidine-2-thiones 2–21

Unsubstituted *N*-acetyloxazolidine-2-thione (**2**), without any substituents at the 4- or 5- position, was obtained from commercially available ethanolamine **28** in two steps^[7] and an overall yield of 60% (Scheme 4).



Scheme 4.

The strategy used for the preparation of *N*-acetyloxazolidine-2-thiones **3–7** was based on the double addition of the alkyl or aryl substituent of a Grignard reagent to the chloride salt of ethyl glycinate **31** (Scheme 5, Table 2).



Scheme 5.

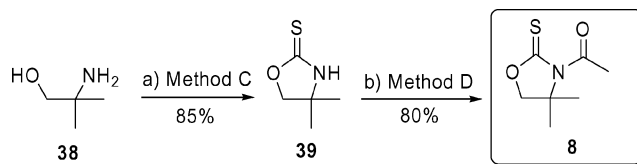
Table 2. Yields of the oxazolidine-2-thiones **33–37** and the corresponding *N*-acetyloxazolidine-2-thiones **3–7**.

Entry	R	Oxazolidine-2-thione, % yield ^[a]	<i>N</i> -Acetyl-oxazolidine-2-thione, % yield
1	<i>n</i> Bu	33 , 40	3 , 80
2	<i>n</i> -C ₁₂ H ₂₅	34 , 30	4 , 83
3	allyl	35 , 44	5 , 90
4	Ph	36 ^[b] , 44	6 , 80
5	2-naphthyl	37 , 20	7 , 90

[a] Yield from two steps. [b] See ref.^[8].

The corresponding amino alcohols thus obtained were cyclized and acetylated by using either method A or D (Table 1).

N-Acetyloxazolidine-2-thione **8** was obtained from commercially available amino alcohol **38** in two steps^[9] and an overall yield of 68% (Scheme 6).



Scheme 6.

N-Acetyloxazolidine-2-thiones **9–14**, possessing two substituents at the 4-position, were synthesized starting from the bis-alkylation of imine **40**, obtained from the chloride salt of ethyl glycinate **31**, with 2 equiv. of bromo- or iodoalkane (Scheme 6, Table 3). Thus, when 2.5 equiv. of *t*BuOK was added at 0 °C to a solution of 1 equiv. of **40** and 2.5 equiv. of halogenoalkane in THF, the bis-alkylated adduct intermediate was obtained after only 1 h. A molar aqueous solution of hydrochloric acid was then directly

Table 1. Methods used for the cyclization of amino alcohols and acetylation of the resulting oxazolidine-2-thiones.

Cyclization	Method A: ^[a] Cl ₂ CS (1 equiv.), Et ₃ N (2.5 equiv.), THF, 0 °C, 30 min
	Method B: ^[b] CS ₂ (1.2 equiv.), Et ₃ N (1.2 equiv.), CH ₂ Cl ₂ , reflux, 16 h
	Method C: ^[c] CS ₂ (2 equiv.), K ₂ CO ₃ (0.5 equiv.), H ₂ O ₂ (1.5 equiv.), EtOH, reflux, 30 min
Acetylation	Method D: NaH (1.5 equiv.), CH ₃ COCl (1.5 equiv.), THF, 0 °C to room temp., 3 h
	Method E: BuLi (1.5 equiv.), CH ₃ COCl (1.5 equiv.), THF, –78 °C to room temp., 3 h

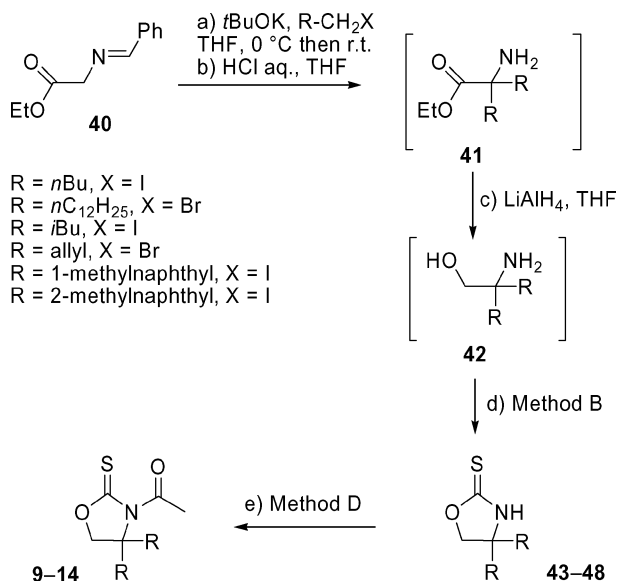
[a] See Crimmins et al.^[4] [b] See Delaunay et al.^[5] [c] See Wu et al.^[6]

added to afford after 4 h, in excellent yield, the expected amino ester **41**. Reduction of the latter with 4 equiv. of LiAlH_4 in THF at room temp. gave the corresponding amino alcohol **42**, which was directly cyclized to oxazolidine-2-thiones **43–48** by using method **B** in yields ranging from 8 to 50% after four steps (Scheme 7, Table 3).

Table 3. Yields of the oxazolidine-2-thiones **43–48** and the corresponding *N*-acetyloxazolidine-2-thiones **9–14**.

Entry	R	Oxazolidin-2-thione, % yield ^[a]	<i>N</i> -Acetyloxazolidine-2-thione, % yield
1	<i>n</i> Bu	43 , 27	9 , 80
2	<i>i</i> Bu	44 , 20	10 , 70
3	allyl	45 , 48	11 , 80
4	Bn	46 , 50	12 , 58
5	1-methylnaphthyl	47 , 8	13 , 53
6	2-methylnaphthyl	48 , 27	14 , 53

[a] Yield from four steps.

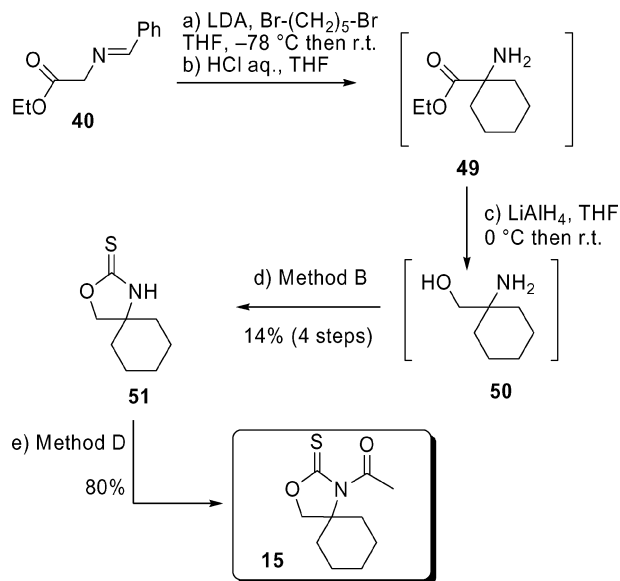


Scheme 7.

Acetylation of oxazolidine-2-thiones **43–48** through method **D** gave the *N*-acetyloxazolidine-2-thiones **9–14** with good-to-excellent yields (53–80%).

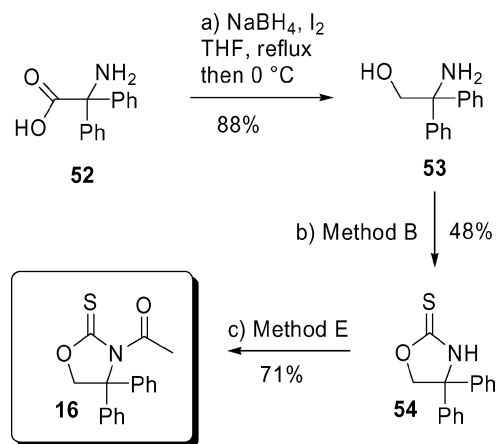
N-Acetyloxazolidine-2-thione **15** was prepared as reported previously.^[10] Imine **40** in THF was treated at -78°C with 2.2 equiv. of LDA followed by 1,5-dibromopentane (0.9 equiv.). After 3 h at room temp. a molar aqueous solution of hydrochloric acid was added. Amino ester **49**, thus obtained, was directly reduced by LiAlH_4 and the resulting amino alcohol was cyclized, using method **B**, to oxazolidine-2-thione **51**^[10] in an overall yield of 14% in four steps. Acetylation of the latter by method **D** gave *N*-acetyloxazolidine-2-thione **15** in 80% yield (Scheme 8).

N-Acetyloxazolidine-2-thione **16** was prepared by reduction of the commercially available α,α' -diphenylglycine **52** to amino alcohol **53** in 88% yield by NaBH_4/I_2 treatment (Scheme 9). When amino alcohol **53** was cyclized, using method **B**, the oxazolidine-2-thione **54** was obtained in a low yield (10%). But when carbon disulfide and triethyl-



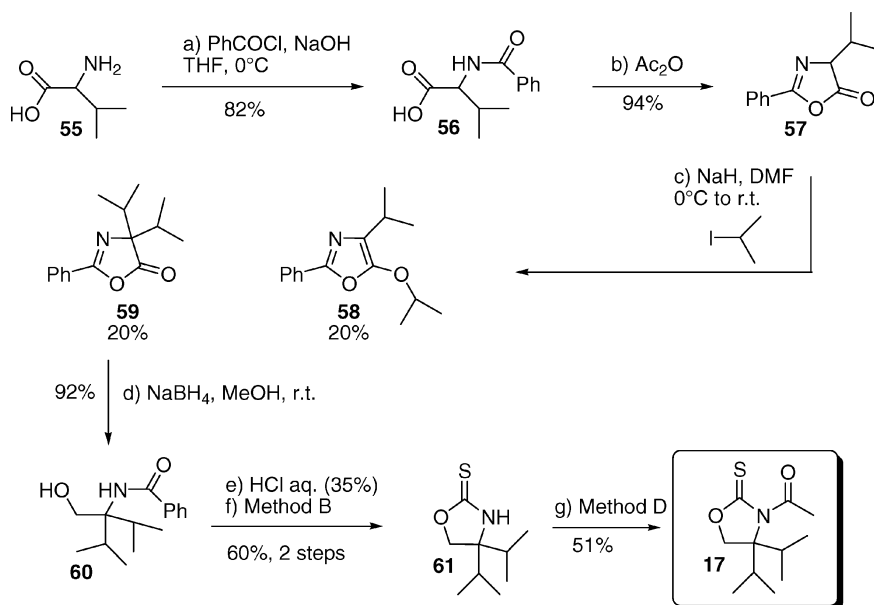
Scheme 8.

amine were used in large excess (5 and 4 equiv., respectively), oxazolidine-2-thione **54** was obtained in 48% yield. Acetylation of the latter through method **E** gave *N*-acetyl-oxazolidine-2-thione **16** in 71% yield.



Scheme 9.

The preparation of oxazolidine-2-thione **17** required another approach because the diisopropyl groups could not be introduced by the procedures described above. We thus decided to prepare azalactone **57**, derived from valine (**55**). First, *N*-benzoylvaline (**56**) was prepared from valine in 82% yield (Scheme 10). Cyclization of *N*-benzoylvaline (**56**) to azalactone **57** was performed under reflux in acetic anhydride to afford the expected azalactone **57** in 94%. Then, azalactone **57** was treated with sodium hydride (1.5 equiv.) and isopropyl iodide (1.5 equiv.) in DMF at 0°C to afford a 1:1 mixture of the desired bis-alkylated azalactone **59** along with the *O*-alkylated oxazole **58** in 40% overall yield (Scheme 10). The following step required the reduction of azalactone **59** to alcohol **60** by treatment with sodium borohydride in methanol. The benzoyl group was then re-



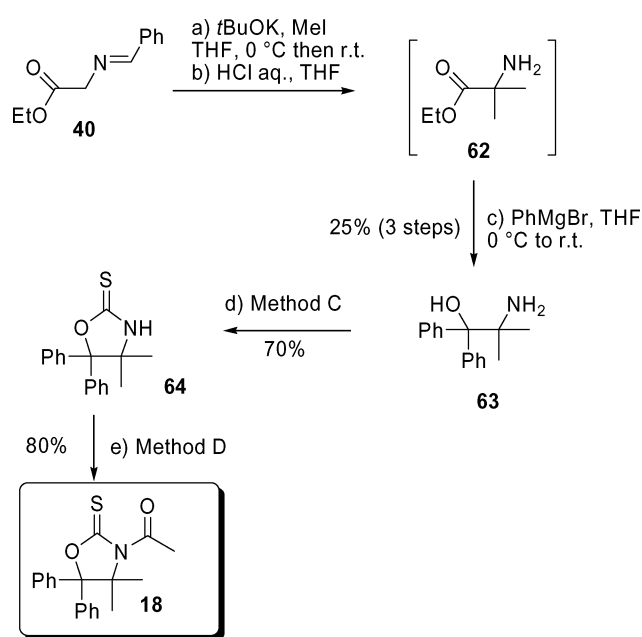
Scheme 10.

moved by acid treatment (aqueous solution of 6 M hydrochloric acid). The amino alcohol thus obtained was directly cyclized to oxazolidine-2-thione **61** in 60% yield after two steps by using method **B**. Acetylation of oxazolidine-2-thione **61** by method **D** gave the expected *N*-acetyloxazolidine-2-thione **17** in 51% yield.

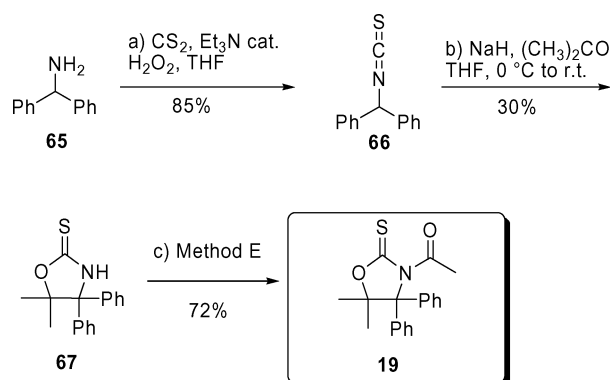
N-Acetyloxazolidine-2-thione **18** was synthesized starting with the bis-methylation of imine **40** under the standard reaction conditions (*t*BuOK and methyl iodide in THF at room temp., Scheme 11). After hydrolysis, amino ester **62** was directly treated with 5 equiv. of phenylmagnesium bromide to give amino alcohol **63** in 25% yield after three steps. The latter was cyclized, using method **C**, to oxazolidine-2-thione **64** in 70% yield. Acetylation of oxazolidine-2-thione **64**, using method **D**, gave *N*-acetyloxazolidine-2-thione **18** in 80% yield.

N-Acetyloxazolidine-2-thione **19**, a positional isomer of **18**, was prepared by a different strategy. Isothiocyanate **66** was first prepared by condensation of benzhydrylamine (**65**) and carbon disulfide in the presence of a catalytic amount of triethylamine and hydrogen peroxide in THF (Scheme 12). Then it was treated with sodium hydride and acetone in THF to afford after 16 h at room temp. the expected oxazolidine-2-thione **67**^[11] in 30% yield. Acetylation of the latter through method **E** gave *N*-acetyloxazolidine-2-thione **19** in 72% yield.

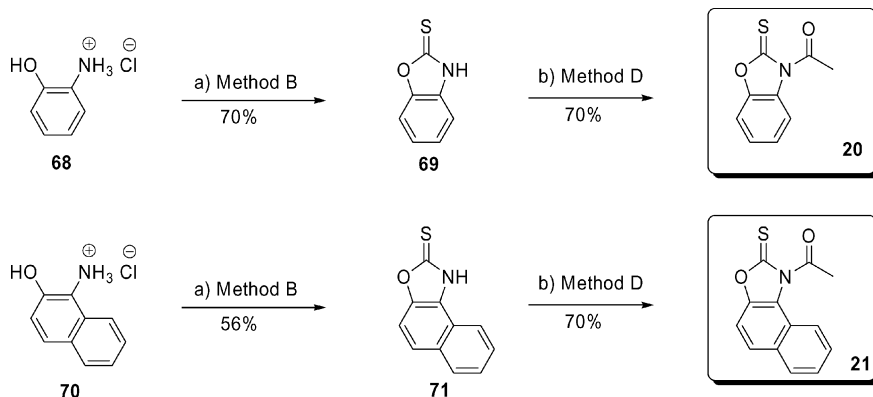
Achiral *N*-acetyloxazolidine-2-thiones **20** and **21** were prepared because the stereoelectronic effects of the aromatic rings were expected to play a role in the conformation of the titanium enolate reactive species, and thus the diastereoselectivity of the condensation reaction should be modified in comparison with the unsubstituted *N*-acetyloxazolidine-2-thione. Both oxazolidine-2-thiones **20** and **21** were obtained from the chloride salts of the corresponding commercially available amino alcohols **68** and **71** in two steps (Scheme 13). Cyclization of these amino alcohols to oxazol-



Scheme 11.



Scheme 12.



Scheme 13.

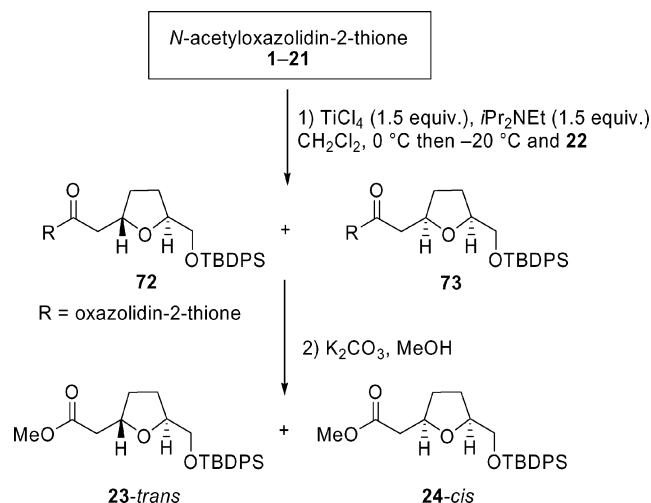
idine-2-thiones **69**^[12] and **71** through method **B**, followed by acetylation using method **D**, gave *N*-acetyloxazolidine-2-thiones **20** and **21** both in 70% yield.

C-Glycosylation of Oxazolidine-2-thiones 2–21 with Lactol Acetate 22

The reactions of the titanium enolates obtained from the *N*-acetyloxazolidine-2-thiones **2–21** with lactol acetate **22** were then studied. To avoid time-consuming determination of the diastereoselectivity of the reactions of the 21 adducts, they were directly transesterified to the common methyl esters **23** and **24**, which have already been obtained and characterized in our previous study;^[3] the corresponding oxazolidine-2-thiones were recovered typically in 65–90% yield.^[13] Thus, when the chlorotitanium enolate of *N*-acetyloxazolidine-2-thione (**2**) was treated with γ -lactol **22** followed by methanolysis of the intermediates **72** and **73**, the nonseparable methyl esters **23** and **24** were obtained in 91% overall yield and with a diastereoselective ratio (*dr*) of 77:23 in favor of the *trans* compound **23** (Scheme 14, entry 2, Table 4). Again the diastereoselectivity was unambiguously determined by ¹H NMR analysis of the mixture of methyl esters **23** and **24** by comparison with the pure methyl ester **23** obtained in our previous study.^[3] This diastereoselectivity was surprisingly identical to that observed when the chiral (*R*)-4-benzyloxazolidine-2-thione (**1**) was used (Scheme 1, entry 1, Table 4).

The achiral *N*-acetyloxazolidine-2-thiones **3–7**, without any substituent at the 4-position, but possessing two identical groups at the 5-position, gave a slightly better diastereoselectivity in favor of the *trans* isomer **23** than both the unsubstituted oxazolidine-2-thione **2** and the chiral oxazolidine-2-thione **1** (entries 3–7, Table 4), except for oxazolidine-2-thione **4**, where the *dr* was lower (70:30). As the 4-position of the oxazolidine-2-thiones is closer to the *N*-acetyl group, it was expected that the steric hindrance of this position might increase the *trans/cis* ratio in favor of the *trans* isomer **23** (Scheme 14, Table 4). Thus, the reactions of oxazolidine-2-thiones **8–17** were studied.

The chlorotitanium enolates of the *N*-acetyloxazolidine-2-thiones **8** and **9**, after methanolysis of the intermediates,



Scheme 14.

gave the expected methyl esters **23** and **24** in 70 and 61% yields, respectively, with *dr* values of 88:12 and 80:20, respectively, in favor of the *trans* isomer **23**, slightly better than the *dr* obtained with the unsubstituted oxazolidine-2-thione **2** (entries 8 and 9, Table 4).

N-Acetyloxazolidine-2-thiones **11** and **15**, substituted, respectively, by two allyl groups and a spirocyclohexyl group, gave, after methanolysis of the intermediates, esters **23** and **24** in 55 and 53% yields and *dr* values of 77:23 and 75:25, respectively, in favor of the *trans* ester **23** (entries 11 and 15, Table 4).

N-Acetyloxazolidine-2-thione **12**, possessing two benzyl group at the 4-position, gave methyl esters **23** and **24** in 69% yield and in a surprisingly low diastereoselectivity (*dr* = 60:40) in favor of the *trans* ester **23** (entry 12, Table 4), whereas (*4R*)-*N*-acetyl-4-benzyloxazolidine-2-thione (**1**), possessing a single benzyl group, gave the same esters **23** and **24** with a *dr* of 77:23 (Scheme 1).^[3] The second benzyl group seems to be prejudicial to the formation of *trans* **23**.

N-Acetyloxazolidine-2-thiones **13** and **14**, substituted at the 4-position by 1-methyl- and 2-methylnaphthyl groups, gave esters **23** and **24** with *dr* values of 77:23 and 70:30, respectively, in favor of the *trans* isomer **23** (entries 13 and

Table 4. Yields^[a] and diastereoselectivities for the preparation of **23** and **24** from oxazolidine-2-thiones **1–21**.

Entry	<i>N</i> -Acetyloxazolidine-2-thione	<i>T</i> [°C]	% Yield ^[a] of 23 + 24	<i>dr</i> (<i>trans/cis</i>)	Efficacy
Unsubstituted					
1	1	–20	55	77:23	
2	2	–20	60	77:23	=
Disubstituted at the 5-position					
3	3	–20	62	87:13	+
4	4	–20	66	70:30	–
5	5	–20	68	80:20	=
6	6	0	83	85:15	+
7	7	0	54	82:18	+
Disubstituted at the 4-position					
8	8	–20	70	88:12	++
9	9	–20	61	80:20	=
10	10	–20	65	93:7	++
11	11	0	55	77:23	=
12	12	–20	69	60:40	--
13	13	–20	67	77:23	=
14	14	0	90	70:30	–
15	15	–20	53	75:25	=
16	16	–20	68	72:28	–
17	17	–20	45	58:42	--
Tetrasubstituted at the 4- and 5-positions and miscellaneous					
18	18	0	70	84:16	+
19	19	–20	54	60:40	--
20	20	–20	73	79:21	=
21	21	0	0	n.r. ^[b]	

[a] Yields from two steps. [b] n.r.: no reaction.

14, Table 4). These results show that replacement of the two benzyl groups by the more bulky 1-methyl- or 2-methylnaphthyl substituent increases the observed diastereoselectivity in favor of the *trans* ester **23**, however, does not give a higher selectivity than the unsubstituted oxazolidine-2-thione **2** (*dr* = 77:23).

N-Acetyloxazolidine-2-thione **16**, substituted at the 4-position by two phenyl groups, gave a better selectivity in favor of the *trans* ester **23**, with a *dr* = 72:28, than oxazolidine-2-thione **12** with two benzyl groups (*dr* = 60:40, entries 12 and 16, Table 4). This diastereoselectivity still remains lower than the selectivity observed with oxazolidine-2-thione **2** (*dr* = 77:23).

N-Acetyloxazolidine-2-thione **10**, substituted at the 4-position by two isobutyl groups, gave esters **23** and **24** in 65% yield and a *dr* of 93:7 in favor of the *trans* ester **23** (entry 10, Table 4). This remarkable increase in diastereoselectivity could be due to the steric repulsion of these two bulky substituents.

To increase further the diastereoselectivity in favor of the *trans* ester **23**, the bulkier *N*-acetyloxazolidine-2-thione **17**, substituted at the 4-position by two isopropyl groups, was synthesized. Thus, when *N*-acetyloxazolidine-2-thione **17** was used, esters **23** and **24** were obtained in an overall yield of 45% and with an unexpectedly low diastereoselectivity (*dr* = 58:42) in favor of the *trans* ester **23** (entry 10, Table 4).

The effect of double substitution at the 4- and 5-positions of the *N*-acetyloxazolidine-2-thiones **18–21** on the diastereoselectivity of the reaction has also been investigated.

N-Acetyloxazolidine-2-thione **18**, substituted at the 4-position by two methyl groups and at the 5-position by two phenyl groups, afforded esters **23** and **24** in 70% yield and with a *dr* of 84:16 in favor of the *trans* ester **23** (entry 18, Table 4).

Interchange of the substituents at the 4- and 5-positions of *N*-acetyloxazolidine-2-thione **18**, that is, *N*-acetyloxazolidine-2-thione **19**, gave, after reaction with lactol acetate **22**, esters **23** and **24** in 54% yield with a *dr* of 60:40 in favor of the *trans* ester **23** (entry 19, Table 4). These last two results show that there was no significant increase in the diastereoselectivity in favor of the *trans* ester **23** as expected compared with *N*-acetyloxazolidine-2-thiones **6** (*dr* = 85:15) or **8** (*dr* = 88:12). When two phenyl groups are at the 4-position of the *N*-acetyloxazolidine-2-thione **8** a strong reduction in the diastereoselectivity in favor of the *trans* ester **23** was unexpectedly observed.^[14]

Aromatic *N*-acetyloxazolidine-2-thione **20** gave esters **23** and **24** in 73% yield and with a *dr* of 79:21 in favor of the *trans* ester **23** (entry 20, Table 4), slightly better than what was observed with unsubstituted oxazolidine-2-thione **2**. Unexpectedly, aromatic *N*-acetyloxazolidine-2-thione **21** did not react under our reaction conditions (entry 21, Table 4).

Conclusions

Among the differently substituted achiral *N*-acetyloxazolidine-2-thiones **2–21** studied herein, the best diastereoselectivity (*dr* = 93:7) in favor of the *trans* ester **23** was observed with *N*-acetyloxazolidine-2-thione **10**, substituted at the 4-position by two bulky isobutyl groups. Note that the diastereoselectivity is better than that observed with the chiral (*R*)-*N*-acetyl-4-benzylloxazolidine-2-thione (**1**; *dr* = 77:23). These results emphasize the difficulty of rationalizing steric effects and reveal that achiral auxiliaries may sometimes give a better diastereoselectivity than chiral ones.^[15] Furthermore, this method is an attractive and complementary method to the diastereoselective additions of chiral oxazolidinethiones^[3] and oxazolidinones^[16] as they do not require the preparation and handling of chiral reagents. This method also offers one of the best diastereoselectivities obtained so far for the addition of achiral acyl equivalents to cyclic oxocarbenium ions, leading to 2,5-disubstituted tetrahydrofurans.^[17]

Experimental Section

General Remarks

Method A: Triethylamine (2.5 equiv.) and then a solution of Cl₂CS (1 equiv.) in dichloromethane were added to a solution of amino alcohol (1 equiv.) in dichloromethane under N₂ at 0 °C. After 30 min of stirring, an aqueous solution of NaHSO₃ (10%) was added and the crude product was extracted with ethyl acetate (three

times). The combined organic phases were dried with MgSO_4 , filtered, then concentrated under vacuum, and the crude product purified by flash chromatography.

Method B: CS_2 (1.2 equiv.) and then triethylamine (1.2 equiv.) were added to a solution of amino alcohol (1 equiv.) in dichloromethane under N_2 at 0°C . The reaction mixture was then heated at reflux for 16 h, then cooled to 0°C , and an aqueous solution of hydrochloric acid (1 M) was added. The crude product was extracted with ethyl acetate (three times). The combined organic phases were dried with MgSO_4 , filtered, then concentrated under vacuum, and the crude product purified by flash chromatography.

Method C: K_2CO_3 (0.5 equiv.) was added to a solution of amino alcohol (1 equiv.) in ethanol at room temp., followed by CS_2 (2 equiv.). The reaction mixture was then heated at 50°C and an aqueous solution of H_2O_2 (50%, 1.5 equiv.) was slowly added (30 min). After stirring for a further 30 min at 50°C , the reaction mixture was cooled to room temp. and then filtered through Celite®. An aqueous saturated solution of NH_4Cl was added to the filtrate and the crude product was extracted with ethyl acetate (three times). The combined organic phases were dried with MgSO_4 , filtered, then concentrated under vacuum, and the crude product purified by flash chromatography.

Method D: A solution of oxazolidine-2-thione (1 equiv.) in THF was slowly added to a suspension of NaH (60%, 1.5 equiv.) in anhydrous THF under N_2 at 0°C . The temperature was then allowed to reach room temp. for 40 min and then cooled again to 0°C before the addition of acetyl chloride (1.5 equiv.). After 3 h of stirring at room temp., an aqueous saturated solution of NH_4Cl was added and the crude product was extracted with ethyl acetate (three times). The combined organic phases were dried with MgSO_4 , filtered, then concentrated under vacuum, and the crude product purified by flash chromatography.

Method E: $n\text{BuLi}$ (2.5 M in hexanes, 1.5 equiv.) was added to a solution of oxazolidine-2-thione (1 equiv.) in anhydrous THF cooled to -78°C under N_2 . Stirring was maintained for 45 min at -78°C and then acetyl chloride (1.5 equiv.) was slowly added. After 3 h of stirring, an aqueous saturated solution of NH_4Cl was added and the crude product was extracted with ethyl acetate (three times). The combined organic phases were dried with MgSO_4 , filtered, then concentrated under vacuum, and the crude product purified by flash chromatography.

General Procedure for the C-Glycosylation Reactions: TiCl_4 (0.16 mL, 1.5 mmol, 1.5 equiv.) was added dropwise to a solution of oxazolidine-2-thione **2–21** (1.50 mmol, 1.5 equiv.) in dichloromethane (5 mL) under N_2 at 0°C . After 5 min of stirring at 0°C , diisopropylethylamine (0.26 mL, 1.50 mmol, 1.5 equiv.) was added dropwise. After 20 min of stirring at 0°C , the temperature was brought to either 0 or -20°C (see Table 4) and a solution of lactol acetate **22** (0.398 g, 1.0 mmol, 1 equiv.) in dichloromethane (5 mL) was added to -20°C (or 0°C) was added dropwise. After 30 min of stirring at -20°C , an aqueous saturated solution of NH_4Cl (5 mL) was added and the reaction mixture was extracted with ethyl acetate (three times). The combined organic phases were dried with MgSO_4 , filtered, and concentrated under vacuum. The crude reaction mixture was poured into methanol (5 mL) and K_2CO_3 (0.497 g, 3.6 mmol, 3.6 equiv.) was added at room temp. Stirring was maintained for 20 min and the reaction mixture was filtered through Celite®. Water (5 mL) was added to the filtrate and the reaction mixture was extracted with ethyl acetate (three times). The combined organic phases were dried with MgSO_4 , filtered, and concentrated under vacuum. After purification by flash chromatog-

raphy on silica gel (eluent: cyclohexane/ethyl acetate, 8:2 then 7:3) the oily methyl ester **23** was obtained (for the yields, see Table 4).

N-Acetyloxazolidine-2-thione (2): ^1H NMR (200 MHz, CDCl_3): δ = 2.83 (s, 3 H, 7-H), 4.21 (t, J = 8.6 Hz, 2 H), 4.54 (t, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ = 25.5, 46.6, 66.3, 170.8, 185.7 ppm. IR (CHCl_3): $\tilde{\nu}$ = 1690, 1460, 1415, 1380, 1365, 1330, 1245, 1170, 1010, 965, 945 cm^{-1} . MS (ESI): m/z (%) = 168 (100) $[\text{M} + \text{Na}]^+$. HRMS (ESI): calcd. for $\text{C}_{13}\text{H}_{23}\text{NSO}_2\text{Na}$ $[\text{M} + \text{Na}]$ 280.1347; found 280.1337.

N-Acetyl-5,5-dibutyloxazolidine-2-thione (3): ^1H NMR (200 MHz, CDCl_3): δ = 0.89 (t, J = 6.3 Hz, 6 H), 1.30 (m, 8 H), 1.72 (m, 4 H), 2.81 (s, 3 H), 3.88 (s, 2 H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ = 13.7, 22.6, 25.0, 26.0, 37.7, 54.6, 88.3, 171.6, 185.4 ppm. IR (CHCl_3): $\tilde{\nu}$ = 2955, 2935, 2870, 1700, 1415, 1380, 1370, 1340, 1245, 1205, 1130, 1090, 1040, 965 cm^{-1} . MS (ESI): m/z (%) = 280 (100) $[\text{M} + \text{Na}]^+$.

N-Acetyl-5,5-didodecyloxazolidine-2-thione (4): ^1H NMR (200 MHz, CDCl_3): δ = 0.87 (t, J = 6.0 Hz, 6 H), 1.25 (br. s, 40 H), 1.66 (m, 4 H), 2.51 (s, 3 H), 3.68 (s, 2 H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ = 14.0, 22.7, 23.0, 26.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 38.0, 54.7, 88.4, 153.1, 170.7, 185.1 ppm. IR (CHCl_3): $\tilde{\nu}$ = 2920, 2850, 1700, 1470, 1415, 1380, 1370, 1335, 1255, 1230, 1200, 1180, 970 cm^{-1} . MS (ESI): m/z (%) = 504 (91) $[\text{M} + \text{Na}]^+$, 413 (100), 301 (59), 245 (65). HRMS (ESI): calcd. for $\text{C}_{29}\text{H}_{55}\text{NSO}_2\text{Na}$ $[\text{M} + \text{Na}]$ 504.3851; found 504.3853.

N-Acetyl-5,5-diallyloxazolidine-2-thione (5): ^1H NMR (200 MHz, CDCl_3): δ = 2.41 (dd, J = 14.4, 6.7 Hz, 2 H), 2.54 (dd, J = 14.3, 6.9 Hz, 2 H), 2.76 (s, 3 H), 3.90 (s, 2 H), 5.17 (dd, J = 6.3, 1.3 Hz, 2 H), 5.24 (br. s, 2 H), 5.72 (m, 2 H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ = 25.9, 42.4, 53.2, 86.4, 121.3, 129.9, 171.2, 185.1 ppm. IR (CHCl_3): $\tilde{\nu}$ = 1700, 1415, 1380, 1370, 1355, 1325, 1250, 1195, 1090, 990 cm^{-1} . MS (ESI): m/z (%) = 248 (91) $[\text{M} + \text{Na}]^+$.

N-Acetyl-5,5-diphenyloxazolidine-2-thione (6): ^1H NMR (200 MHz, CDCl_3): δ = 2.81 (s, 3 H), 4.78 (s, 2 H), 7.39 (m, 10 H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ = 25.9, 58.4, 88.8, 125.5, 128.7, 128.8, 140.6, 171.3, 184.2 ppm. IR (CHCl_3): $\tilde{\nu}$ = 1700, 1415, 1380, 1365, 1335, 1275, 1225, 1200, 1170, 965 cm^{-1} . MS (ESI): m/z (%) = 320 (45) $[\text{M} + \text{Na}]^+$, 238 (53).

N-Acetyl-5,5-di(2-naphthyl)oxazolidine-2-thione (7): ^1H NMR (200 MHz, CDCl_3): δ = 2.91 (s, 3 H), 4.99 (s, 2 H), 7.54 (m, 6 H), 7.86 (m, 6 H), 8.06 (br. s, 2 H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ = 25.2, 57.2, 88.4, 122.7, 123.9, 126.2, 126.3, 126.9, 127.3, 128.4, 132.0, 132.7, 136.8, 170.6, 183.6 ppm. IR (CHCl_3): $\tilde{\nu}$ = 1700, 1470, 1370, 1290, 1255, 1190, 1105, 910, 860, 810 cm^{-1} .

N-Acetyl-4,4-dimethyloxazolidine-2-thione (8): ^1H NMR (200 MHz, CDCl_3): δ = 1.57 (s, 6 H), 2.77 (s, 3 H), 4.16 (s, 2 H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ = 24.0, 27.7, 65.4, 79.1, 172.2, 186.8 ppm. IR (CHCl_3): $\tilde{\nu}$ = 2970, 1710, 1370, 1340, 1310, 1230, 1155, 1000 cm^{-1} . MS (ESI): m/z (%) = 196 (45) $[\text{M} + \text{Na}]^+$.

N-Acetyl-4,4-dibutyloxazolidine-2-thione (9): ^1H NMR (400 MHz, CDCl_3): δ = 0.89 (t, J = 7.1 Hz, 6 H), 1.07 (m, 2 H), 1.29 (m, 6 H), 1.60 (m, 2 H), 2.18 (m, 2 H), 2.81 (s, 3 H), 4.25 (s, 2 H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ = 13.8, 22.6, 25.4, 27.9, 36.6, 71.3, 75.0, 172.6, 187.8 ppm. IR (CHCl_3): $\tilde{\nu}$ = 2960, 2930, 2860, 1705, 1680, 1365, 1330, 1280, 1230, 1200, 1155, 975, 910 cm^{-1} . MS (ESI): m/z (%) = 280 (8) $[\text{M} + \text{Na}]^+$, 216 (100).

N-Acetyl-4,4-diisobutyloxazolidine-2-thione (10): ^1H NMR (200 MHz, CDCl_3): δ = 0.88 (d, J = 6.5 Hz, 6 H), 0.96 (d, J = 6.5 Hz, 6 H), 1.61 (m, 4 H), 2.14 (m, 2 H), 2.79 (s, 3 H), 4.36 (s, 2 H) ppm. ^{13}C NMR (50 MHz, CDCl_3): δ = 23.7, 24.2, 24.6, 28.4,

45.8, 71.3, 75.7, 173.0, 187.8 ppm. IR (CHCl₃): $\tilde{\nu}$ = 2960, 2875, 1705, 1570, 1415, 1370, 1335, 1315, 1250, 1205, 1160, 1055, 1005, 980, 910, 730 cm⁻¹.

N-Acetyl-4,4-diallyloxazolidine-2-thione (11): ¹H NMR (200 MHz, CDCl₃): δ = 2.40 (dd, *J* = 14.2, 7.2 Hz, 2 H), 2.76 (s, 3 H), 2.99 (dd, *J* = 14.2, 7.4 Hz, 2 H), 4.31 (s, 2 H), 5.12–5.22 (m, 4 H), 5.54–5.75 (m, 2 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 27.8, 40.4, 70.2, 73.7, 121.2, 130.5, 172.6, 187.4 ppm. IR (CHCl₃): $\tilde{\nu}$ = 1705, 1415, 1335, 1240, 1200, 1150, 1000, 980, 925 cm⁻¹. MS (ESI): *m/z* (%) = 248 (25) [M + Na]⁺, 206 (100) [M – Ac]⁺.

N-Acetyl-4,4-dibenzylloxazolidine-2-thione (12): ¹H NMR (200 MHz, CDCl₃): δ = 2.81 (s, 3 H), 3.06 (d, *J* = 14.0 Hz, 2 H), 3.71 (d, *J* = 13.9 Hz, 2 H), 4.42 (s, 2 H), 7.12 (m, 4 H), 7.32 (m, 6 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 28.5, 41.6, 71.9, 72.8, 127.5, 128.7, 130.1, 134.5, 174.1, 186.8 ppm. IR (CHCl₃): $\tilde{\nu}$ = 1700, 1410, 1365, 1335, 1288, 1225, 1195, 1125, 980, 910 cm⁻¹. MS (ESI): *m/z* = 348 (100) [M + Na]⁺, 326 (30) [M + H]⁺.

N-Acetyl-4,4-bis(1-methylnaphthyl)oxazolidine-2-thione (13): ¹H NMR (200 MHz, CDCl₃): δ = 2.93 (s, 3 H), 3.91 (d, *J* = 14.7 Hz, 2 H), 4.04 (d, *J* = 14.6 Hz, 2 H), 4.22 (s, 2 H), 7.33–7.49 (m, 8 H), 7.76–7.89 (m, 6 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 29.4, 36.2, 73.5, 74.8, 123.8, 126.0, 126.4, 127.3, 129.1, 129.2, 129.8, 131.8, 133.5, 134.7, 174.3, 194.3 ppm. IR (CHCl₃): $\tilde{\nu}$ = 1700, 1365, 1335, 1315, 1245, 1225, 1020, 980, 910, 800 cm⁻¹. MS (ESI): *m/z* (%) = 448 (100) [M + Na]⁺.

N-Acetyl-4,4-bis(2-methylnaphthyl)oxazolidine-2-thione (14): ¹H NMR (200 MHz, CDCl₃): δ = 2.86 (s, 3 H), 3.31 (d, *J* = 14.0 Hz, 2 H), 3.91 (d, *J* = 13.9 Hz, 2 H), 4.52 (s, 2 H), 7.26 (m, 2 H), 7.85 (m, 4 H), 7.61 (m, 2 H), 7.81 (m, 7 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 28.6, 41.7, 72.4, 72.8, 126.2, 126.5, 127.6, 127.7, 128.0, 128.6, 129.5, 132.1, 132.6, 133.4, 174.5, 194.2 ppm. IR (CHCl₃): $\tilde{\nu}$ = 1700, 1510, 1415, 1365, 1335, 1235, 1195, 1125, 1025, 980, 905 cm⁻¹. MS (ESI): *m/z* (%) = 448 (30) [M + Na]⁺, 426 (12) [M + H]⁺, 342 (54), 186 (100). HRMS (ESI): calcd. for C₂₇H₂₃NSO₂Na [M + Na] 448.1347; found 448.1364.

N-Acetyl-4,4-spirocyclohexyloxazolidine-2-thione (15): ¹³C NMR (50 MHz, CDCl₃): δ = 23.4, 24.1, 28.3, 31.7, 69.9, 76.2, 172.9, 187.5 ppm. IR (CHCl₃): $\tilde{\nu}$ = 2935, 2860, 1710, 1455, 1420, 1365, 1335, 1320, 1255, 1240, 1190, 1555, 1035, 1005, 990, 960 cm⁻¹. MS (ESI): *m/z* (%) = 236 (100) [M + Na]⁺.

N-Acetyl-4,4-diphenyloxazolidine-2-thione (16): ¹H NMR (200 MHz, CDCl₃): δ = 2.78 (s, 3 H), 4.90 (s, 2 H), 7.36 (m, 10 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 27.6, 76.2, 82.6, 127.7, 128.3, 128.4, 138.1, 171.0, 186.5 ppm. IR (CHCl₃): $\tilde{\nu}$ = 1715, 1365, 1330, 1260, 1190, 1170, 1050, 1000, 960, 805 cm⁻¹. MS (ESI): *m/z* (%) = 320 (100) [M + Na]⁺.

N-Acetyl-4,4-diisopropylloxazolidine-2-thione (17): ¹³C NMR (50 MHz, CDCl₃): δ = 17.4, 18.2, 28.1, 32.9, 73.0, 77.9, 173.2, 188.6 ppm. IR (CHCl₃): $\tilde{\nu}$ = 2970, 2930, 1710, 1415, 1365, 1325, 1265, 1235, 1210, 1180, 1165, 1150, 1025, 1005, 985, 965 cm⁻¹.

N-Acetyl-4,4-dimethyl-5,5-diphenyloxazolidine-2-thione (18): ¹H NMR (200 MHz, CDCl₃): δ = 1.50 (s, 6 H), 2.80 (s, 3 H), 7.36 (m, 6 H), 7.48 (m, 4 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 23.8, 27.9, 72.7, 95.3, 126.7, 128.3, 137.7, 172.7, 185.7 ppm. IR (CHCl₃): $\tilde{\nu}$ = 1710, 1495, 1450, 1345, 1290, 1245, 1200, 1170, 1150, 1020, 975 cm⁻¹. MS (ESI): *m/z* (%) = 348 (67) [M + Na]⁺, 250 (100).

N-Acetyl-5,5-dimethyl-4,4-diphenyloxazolidine-2-thione (19): ¹H NMR (200 MHz, CDCl₃): δ = 1.23 (s, 6 H), 2.85 (s, 3 H), 7.35 (br. s, 10 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 25.0, 28.5, 80.9, 90.9, 127.8, 128.0, 128.7, 136.3, 171.8, 186.8 ppm. IR (CHCl₃): $\tilde{\nu}$ =

1720, 1495, 1445, 1415, 1365, 1330, 1260, 1230, 1200, 1130, 740 cm⁻¹. MS (ESI): *m/z* (%) = 348 (100) [M + Na]⁺.

N-Acetylbenzoxazole-2(3H)-thione (20): ¹H NMR (200 MHz, CDCl₃): δ = 3.05 (s, 3 H), 7.31 (m, 3 H), 8.10 (m, 1 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 27.6, 109.5, 116.3, 125.4, 126.0, 129.7, 146.3, 170.8, 179.0 ppm. IR (CHCl₃): $\tilde{\nu}$ = 1720, 1475, 1465, 1410, 1375, 1335, 1300, 1255, 1185, 1140, 1090, 1030, 990, 750 cm⁻¹. MS (ESI): *m/z* (%) = 152 (100) [M – Ac]⁺. C₉H₇NO₂S·0.125H₂O (195.48): C 55.30, H 3.74, N 7.17; found C 55.26, H 3.51, N 7.81.

N-Acetylaphtho[1,2-d]oxazole-2(1H)-thione (21): ¹H NMR (400 MHz, CDCl₃): δ = 2.55 (s, 3 H), 7.58 (m, 1 H), 7.69 (t, *J* = 7.8 Hz, 1 H), 7.71 (d, *J* = 9.0 Hz, 1 H), 7.86 (d, *J* = 9.0 Hz, 1 H), 7.97 (d, *J* = 8.0 Hz, 1 H), 8.52 (d, *J* = 8.2 Hz, 1 H) ppm. IR (CHCl₃): $\tilde{\nu}$ = 1725, 1490, 1385, 1350, 1335, 1130, 1110, 1080, 1025, 1005, 960, 810, 750 cm⁻¹. MS (ESI): *m/z* (%) = 266 (100) [M + Na]⁺.

Methyl (3S,6S)-3,6-Epoxy-7-(tert-butylidiphenylsilyloxy)heptanoate (23): ¹H NMR (400 MHz, CDCl₃): δ = 1.07 (s, 9 H), 1.61 (m, 1 H), 1.91 (m, 1 H), 2.03 (m, 1 H), 2.15 (m, 1 H), 2.48 (dd, *J* = 15.0, 6.1 Hz, 1 H), 2.62 (dd, *J* = 15.0, 7.2 Hz, 1 H), 3.66 (m, 2 H), 3.69 (s, 3 H), 4.18 (m, 1 H), 4.40 (quint., *J* = 7.0 Hz, 1 H), 7.40 (m, 6 H), 7.70 (m, 4 H) ppm. ¹³C NMR (50 MHz, CDCl₃): δ = 19.2, 26.8, 27.8, 31.7, 40.6, 51.5, 66.3, 75.6, 79.2, 127.6, 129.5, 133.6, 135.6, 171.6 ppm. IR (CHCl₃): $\tilde{\nu}$ = 1740, 1430, 1110, 1075, 1005, 825, 740, 700 cm⁻¹. [α]_D = +7 (*c* = 3, CHCl₃). MS (ESI): *m/z* (%) = 435 (100) [M + Na]⁺, 615 (100).

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