Asymmetric Synthesis of 2,4,5-Trisubstituted Δ²-Thiazolines

Christoffer Bengtsson,[a] Hanna Nelander,[b] and Fredrik Almqvist*[a, c, d]

Abstract: Δ²-Thiazolines are interesting heterocycles that display a wide variety of biological characteristics. They are also common in chiral ligands used for asymmetric syntheses and as synthetic intermediates. Herein, we present asymmetric routes to 2,4,5-trisubstituted Δ²-thiazolines. These Δ²-thiazolines were synthesized from readily accessible/commercially available α,β-unsaturated methyl esters through a Sharpless asymmetric dihydroxylation and an O→N acyl migration reaction as key steps. The final products were obtained in good yields with up to 97% enantiomeric excess.

Introduction

Δ²-Thiazolines constitute a class of compounds with diverse applications. They possess interesting properties as flavoring agents[1] and pheromones,[2] are present in the structures of many natural products (e.g., Pulicatin B[3] and micacocidin[4]), and are useful as chiral ligands in asymmetric synthesis[5] (Figure 1). As ligands, they have proven successful in a variety of reactions, including Pd-catalyzed allylic substitutions,[5a,6] Diels–Alder reactions,[7] Friedel–Crafts alkylations of indoles[8] and alkylzinc additions to aldehydes.[9] Many ways to construct the Δ²-thiazoline heterocycles have been developed, and they normally involve the use of a dehydrating reagent. Among the known methods are reactions with triethylamine (TEA)/MsCl (Ms = mesityl),[5a,6] SOCl₂/pyridine,[10] the Lawesson reagent,[7b,11] the Burgess reagent,[4c,10] the Hendrickson reagent,[12] TiCl₄,[13] PCl₅,[4a] P₂S₅,[14] diethylaminosulfur trifluoride (DAST),[15] [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor),[9a,16] PPh₃/diisopropyl
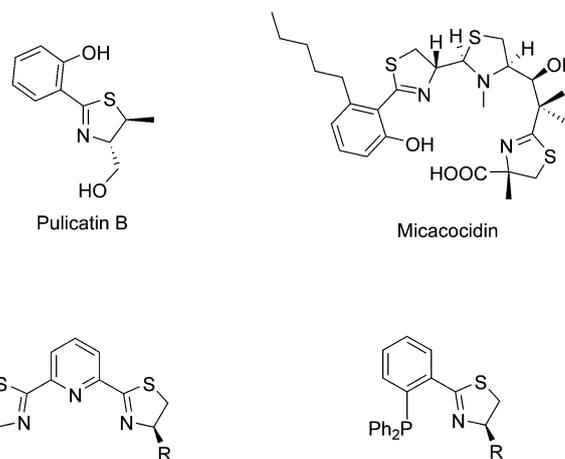

Figure 1. Examples of Δ²-thiazoline-containing natural products and chiral ligands.

azodicharboxylate (DIAD),[17] 3-nitrophenylboronic acid,[18] and Ru/*tert*-butyl hydroperoxide (TBHP).[19] These processes normally lead to 2,4-disubstituted Δ²-thiazolines, with less attention given to the asymmetric synthesis of their 2,4,5-trisubstituted analogues.

In our research group, we are interested in Δ²-thiazolines as intermediates in the synthesis of thiazolo/thiazolino ring-fused 2-pyridones,[20,21] which are constructed through a ketene/imine cyclocondensation reaction between a Δ²-thiazoline and an acyl Meldrum's acid derivative.[22] In the case of 2-substituted thiazolino ring-fused 2-pyridones, only racemates have previously been synthesized (Figure 2), through a conjugate addition reaction with a higher order cuprate onto the corresponding α,β-unsaturated methyl esters.[20b] The intriguing biological activity demonstrated by these compounds as novel antibacterial agents[20c,23] encouraged us to develop asymmetric synthetic pathways to the enantiomers of these compounds. The previously developed cuprate addition has proven hard to perform on a larger scale, and

[a] Dr. C. Bengtsson, Prof. Dr. F. Almqvist
Department of Chemistry
Umeå University, 90187 Umeå (Sweden)
Fax: (+46) 907867655
E-mail: fredrik.almqvist@chem.umu.se

[b] H. Nelander
AstraZeneca R&D Mölndal
Medicinal Chemistry, 43183 Mölndal (Sweden)

[c] Prof. Dr. F. Almqvist
Laboratories for Chemical Biology Umeå
LCBU, Umeå University, 90187 Umeå (Sweden)

[d] Prof. Dr. F. Almqvist
Umeå Center for Microbial Research
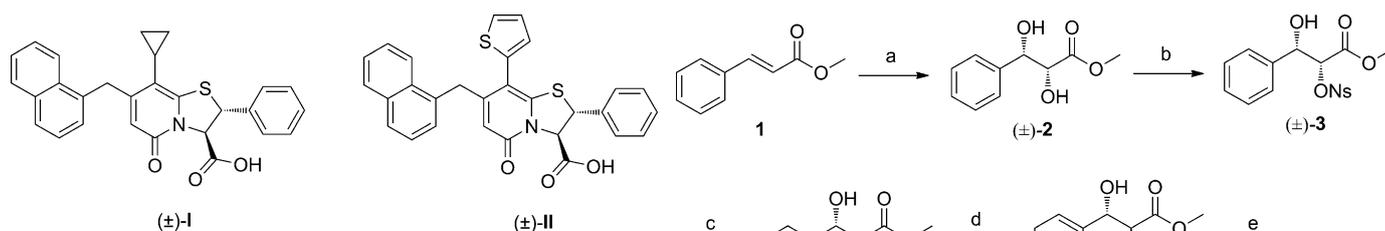UCMR, Umeå University, 90187 Umeå (Sweden)

Figure 2. Previously synthesized racemic 2-substituted thiazolino ring-fused 2-pyridones.

also required very fresh organolithium reagents to proceed in satisfactory yields. Consequently, development of an asymmetric version of that method was not an attractive option. Initially, we also considered the Sharpless amino hydroxylation reaction in the synthesis of (±)-**5**. However, that route would give the *syn*-diastereomer of (±)-**5** when performed on the commercially available *trans*-methyl cinnamate **1** and eventually give the *cis*-configured Δ^2-thiazoline. Additionally, this reaction is known to give mixtures of regioisomers and, in some cases, poor conversions.[24]

We envisioned instead a synthetic pathway starting with a Sharpless asymmetric dihydroxylation of commercially available methyl cinnamate, followed by the selective conversion of the α-hydroxy group into an azide. Subsequently, this azide could be reduced and protected in a two-step one-pot reaction to give the *tert*-butoxycarbonyl (Boc)-protected amino alcohol,[15b] and the remaining benzylic hydroxy group could then be converted to a thiol through simple functional-group interconversion (FGI). Finally, we envisioned that deprotection followed by a thioamine/imino ether condensation[22] would give the 5-substituted Δ^2-thiazoline (Figure 3).
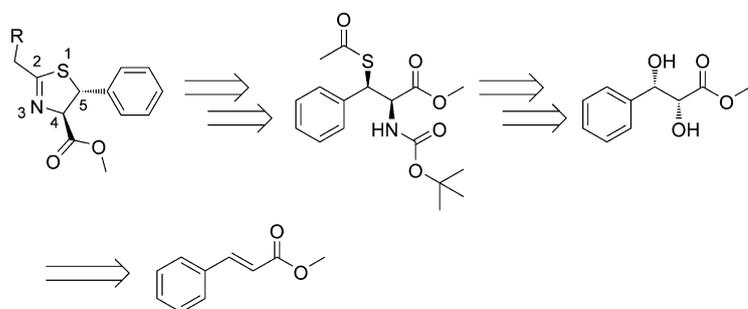

Figure 3. Retrosynthetic analysis of the 5-phenyl-substituted Δ^2-thiazolines.

Results and Discussion

To test our synthetic strategy, we initially performed the dihydroxylation reaction under racemic conditions. Commercially available methyl cinnamate **1** was converted into the corresponding Boc-protected amino alcohol (±)-**5** via diol (±)-**2**, nosylate (±)-**3**, and azide (±)-**4** by following to published procedures for the corresponding ethyl ester (Scheme 1).[15b] The excellent selectivity for the α-hydroxy group in the nosylation reaction can be attributed to the difference
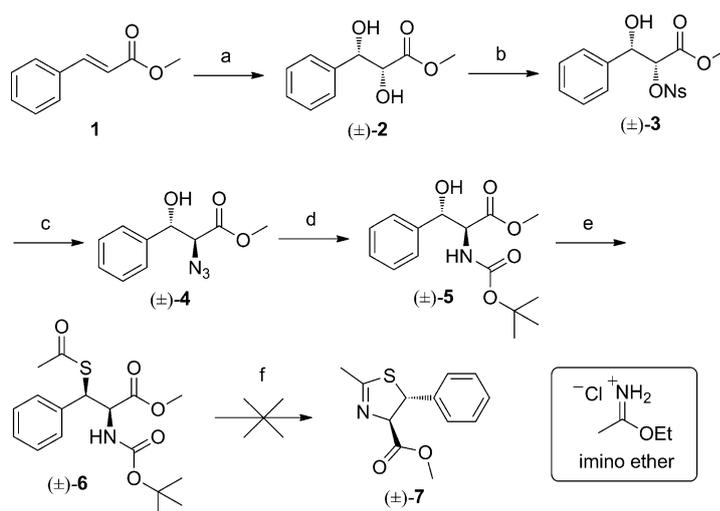
Scheme 1. a) K$_2$OsO$_4$·2H$_2$O, NMO, MeCN/acetone/H$_2$O (1:1:1), RT, 81%; b) NsCl, TEA, CH$_2$Cl$_2$, 0°C, 75%; c) NaN$_3$, DMF, 40°C, 70%; d) i) SnCl$_2$·2H$_2$O, RT; ii) NaHCO$_3$, Boc$_2$O, 1,4-dioxane/H$_2$O, RT, 93%; e) i) Ms$_2$O, TEA, CH$_2$Cl$_2$; ii) KSAc, DMF, RT, 60%; f) i) K$_2$CO$_3$ or NaOMe, MeOH; ii) TFA or HCl; iii) Imino ether, TEA, CH$_2$Cl$_2$.

in pK_a value between the α- and β-hydroxyl groups.[25] The conversion of the Boc-protected amino alcohol (±)-**5** into the S-acyl/N-Boc-protected amino thiol (±)-**6** went smoothly with mesyl anhydride and potassium thioacetate in 60% yield over two steps. Mesyl anhydride was used instead of MsCl to prevent possible scrambling of the sterogenic center due to displacement of the mesyl sulfonate by the nucleophilic chloride ion. However, all attempts to deprotect and then cyclize this compound with the imino ether to generate the 5-substituted Δ^2-thiazoline (±)-**7** failed to work and afforded complex mixtures (Scheme 1).

Amido alcohols are known to be suitable precursors for the synthesis of Δ^2-thiazolines,[11] and consequently our next method was to prepare the amido alcohol of (±)-**5**. Unfortunately, neither Boc-deprotection followed by *N,N,N′,N′*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate (TBTU)/*N,N*-diisopropylethylamine (DIPEA)-mediated coupling nor direct coupling of the amine with acid chloride/TEA proved successful.

In our next attempt to synthesize the amido alcohols, we envisioned making the ester of azido alcohol (±)-**4**, which could then undergo a tandem azide reduction/O→N acyl migration reaction. Of the esterification conditions examined for (±)-**4** (TBTU/acid chloride or *N,N*-dicyclohexylcarbodiimide (DCC)/4-dimethylaminopyridine (DMAP; Steglich conditions)), DCC/DMAP proved more effective.[26] To our delight, the SnCl$_2$·2H$_2$O-induced azide reduction/O→N acyl migration reaction worked well (Table 1) for all substituted (i.e., R≠H) acyl azido esters (±)-**8** (Table 1, entries 2–5), with the corresponding amido alcohols (±)-**9** isolated in 70–84% yields (Table 1). In addition, this synthetic route remained efficient when performed on a gram scale.

An initial attempt to prepare the corresponding thiol amide of (±)-**9c** was performed with 0.6 equivalents of the Lawesson reagent (LR) in toluene at reflux (Table 2). Grati-

Table 1. Synthesis of (±)-**9**: a) RCH₂COOH, DCC, DMAP, CH₂Cl₂, RT; b) i) SnCl₂·2H₂O, RT; ii) NaHCO₃, MeOH/H₂O or 1,4-dioxane/H₂O, RT.
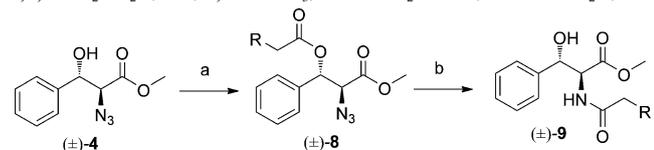
Entry	R	8	Yield [%]	9	Yield [%]
1	H	(±)-**8a**[a]	96	(±)-**9a**	–
2	c-Pr	(±)-**8b**	95	(±)-**9b**[b]	71
3	Ph	(±)-**8c**	95	(±)-**9c**[b]	70
4	m-CF₃Ph	(±)-**8d**	90	(±)-**9d**[b]	80
5	2-thienyl	(±)-**8e**	91	(±)-**9e**[c]	84

[a] Ac₂O/DMAP was used. [b] Use of 1,4-dioxane/H₂O instead of MeOH/H₂O gave a lower yield [c] 1,4-Dioxane/H₂O was used, MeOH/H₂O gave only a 50 % yield.

Table 2. Synthesis of (±)-**10**: a) The Lawesson reagent (0.6 equiv), toluene, reflux.
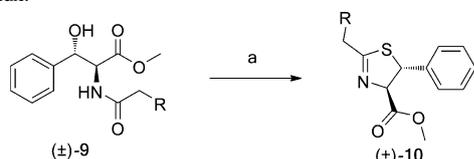

Entry	R	9	10	Yield [%]
1	c-Pr	(±)-**9b**	(±)-**10a**	71
2	Ph	(±)-**9c**	(±)-**10b**	80
3	m-CF₃Ph	(±)-**9d**	(±)-**10c**	72
4	2-thienyl	(±)-**9e**	(±)-**10d**	74

fyingly, we observed only thiazoline formation, with (±)-**10b** isolated in 80 % yield.

To investigate the scope and limitations of this reaction, a series of cinnamate analogues (**11**) were synthesized by the Horner–Wadsworth–Emmons olefination reaction in excellent yields and *trans* selectivities (Table 3). The cinnamate analogues (**11**) were subsequently converted into the corre-

Table 3. Synthesis of (±)-**14**: a) NaH, THF, RT; b) K₂OsO₄·2H₂O, *N*-methylmorpholine *N*-oxide (NMO), MeCN/acetone/H₂O (1:1:1), RT; c) NsCl, TEA, CH₂Cl₂, 0 °C; d) NaN₃, DMF, 40 °C.
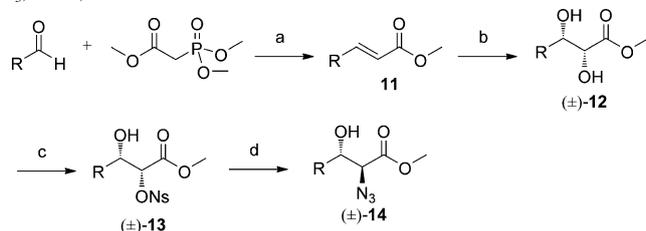

Entry	R	11	Yield [%]	12	Yield [%]	13	Yield [%]	14	Yield [%]
1	p-FPh	**11a**	98	(±)-**12a**	65	(±)-**13a**	63	(±)-**14a**	65
2	m-MeOPh	**11b**	96	(±)-**12b**	75	(±)-**13b**	70	(±)-**14b**	82
3	Bn	**11c**[a]	62	(±)-**12c**	80	(±)-**13c**	62	(±)-**14c**	79
4	2-thienyl	**11d**	98	(±)-**12d**	73	(±)-**13d**	54	(±)-**14d**	78

[a] The aldehyde was freshly distilled prior to use.

sponding azido alcohols (±)-**14** through K₂OsO₄·2H₂O-catalyzed dihydroxylation and selective α-hydroxy nosylation ((±)-**13**). The nosylates (±)-**13** were then substituted with NaN₃ to give the corresponding azido alcohols (±)-**14**.

The azido alcohols (±)-**14** were then reacted with cyclopropylacetic acid under Steglich esterification conditions to furnish the azido esters (±)-**15** in 75–94 % yields (Table 4).

Table 4. Synthesis of (±)-**17**: a) Cyclopropylacetic acid, DCC, DMAP, CH₂Cl₂, RT; b) i) SnCl₂·2H₂O, RT; ii) NaHCO₃, MeOH/H₂O; c) the Lawesson reagent, toluene, reflux.
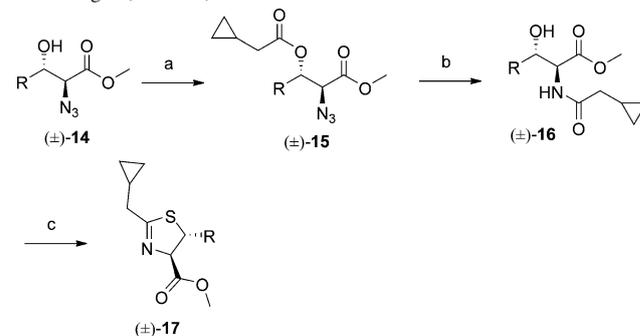

Entry	R	15	Yield [%]	16	Yield [%]	17	Yield [%]
1	p-FPh	(±)-**15a**	85	(±)-**16a**	83	(±)-**17a**	71
2	m-MeOPh	(±)-**15b**	94	(±)-**16b**	80	(±)-**17b**	80
3	Bn	(±)-**15c**	75	(±)-**16c**	77	(±)-**17c**	24
4	2-thienyl	(±)-**15d**	81	(±)-**16d**	78	(±)-**17d**	65

The azide reduction/O→N acyl migration reaction was effective for these azido esters, and the corresponding amido alcohols (±)-**16** were isolated in 77–83 % yield (Table 4). Treatment of aryl/heteroaryl-substituted amido alcohols (±)-**16a,b,d** with LR proceeded efficiently to form the desired Δ²-thiazolines (±)-**17** (Table 4, entries 1, 2, and 4). However, the reaction to form benzyl substituted (±)-**17c**, which was only isolated in 24 % yield (Table 4, entry 3), was less effective.

After establishing the synthetic route required to access the target Δ²-thiazolines racemically, we prepared the enantioselective synthesis. Methyl cinnamate was first oxidized by Sharpless asymmetric dihydroxylation using commercially available AD α- or β-mixes (Scheme 2). Treatment of the enantiomerically pure dihydroxy compounds (−)-**2** and (+)-**2** with NsCl and TEA followed by NaN₃ displacement gave the enantiomerically pure azido alcohols (+)-**4** and (−)-**4**, respectively (Scheme 2).

Azido alcohols (+)-**4** and (−)-**4** were converted into the azido esters (−)-**8b,e** and (+)-**8b,e**, respectively, by the Steglich esterification procedure. This was followed by a SnCl₂·2H₂O-induced azide reduction/O→N acyl migration reaction to give amido alcohols (−)-**9b,e** and (+)-**9b,e** in 72–82 % yield and excellent enantiomeric excess (99 %; Scheme 3). After LR-induced ring-closure, the 5-phenyl-substituted Δ²-thiazolines (−)-**10a,d** and (+)-**10a,d** were
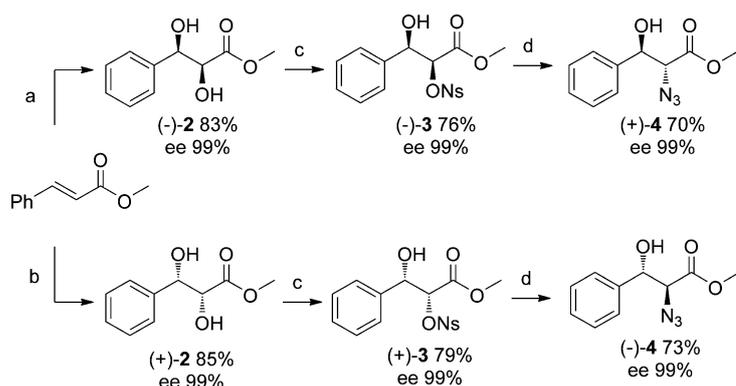
Scheme 2. a) AD-mix-β, MeSO$_2$NH$_2$, *t*BuOH/H$_2$O (1:1), RT; b) AD-mix-α, MeSO$_2$NH$_2$, *t*BuOH/H$_2$O (1:1), RT; c) NsCl, TEA, CH$_2$Cl$_2$, 0°C; d) NaN$_3$, DMF, 40°C.

isolated in 71–80% yields and 71–88% *ee* (Scheme 3).

We used the enantiomerically enriched thiazolines (+)-**10a,d** and (−)-**10a,d** to synthesize the previously mentioned biologically active 2-pyridones (Structures **I** and **II**, Figure 2) by an acyl/ketene cyclocondensation reaction with the acyl Meldrum's acid derivative **19**[22] (Scheme 4). This gave the enantiomerically enriched 2-phenyl-substituted thiazolino ring-fused 2-pyridones (+)-**18a,b** and (−)-**18a,b** in 80–85% yields and 70–88% *ee* (Scheme 4). Hydrol-
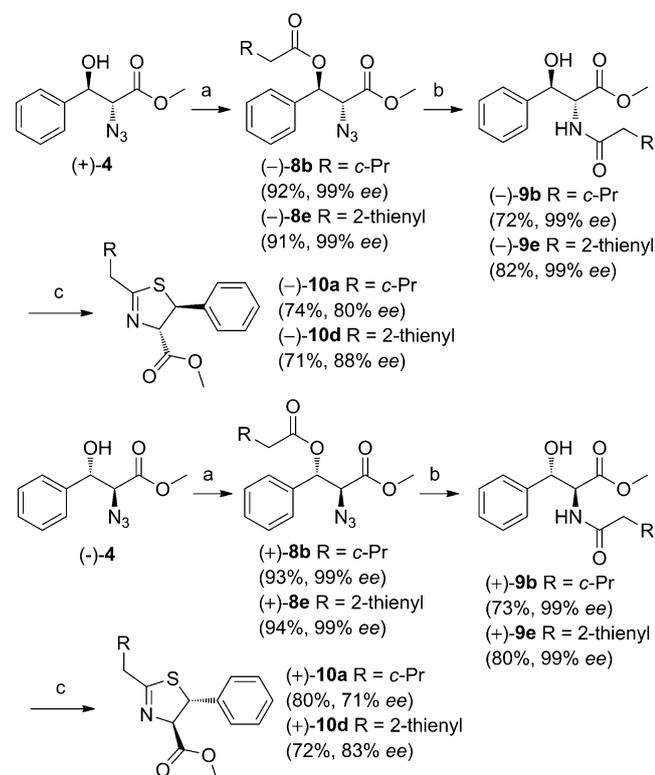
Scheme 3. a) RCH$_2$COOH, DCC, DMAP, CH$_2$Cl$_2$, RT; b) i) SnCl$_2$·2H$_2$O, RT, 2 h; ii) NaHCO$_3$, MeOH/H$_2$O or 1,4-dioxane/H$_2$O, RT, 18 h; c) the Lawesson reagent, toluene, reflux; the *ee* was determined by chiral chromatography.

yses of compounds **18a,b** have previously been reported by our group.[20c,23]

Epimerization of the stereochemistry occurred in the ring-closing reaction with LR (e.g., Scheme 3, (−)-**9b**, 99% *ee*→(−)-**10a**, 80% *ee*). A series of experiments to investigate the influence of LR stoichiometry on the reaction yield and *ee* was therefore performed. Use of less LR resulted in a decreased yield and *ee* of the product (Table 5,

Table 5. Effect of varying the amount of the Lawesson reagent.

| Entry	Amount LR [equiv]	*T*	Yield [%]	*ee* [%][a]
1	0.5	reflux[b]	50	65
2	0.6	RT–reflux[c]	75	73
3	0.6	reflux[b]	78	75
4	1.0	reflux[b]	90	97

[a] Determined by chiral HPLC on a Whelk-O1 column. [b] The oil bath was preheated before the reaction was started. [c] The reaction was heated to reflux starting from RT; the reflux was then continued for 1 h.

entry 1). Conversely, increasing the amount of LR to 1 equivalent significantly improved both the yield (90%) and the *ee* of the reaction (Table 5, entry 4). Reports on this type of 2,4,5-trisubstituted Δ^2-thiazoline containing an ester substituent in the 4-position are scarce in the literature.[11c,15a,17] To the best of our knowledge, this is the first reported direct cyclization of amido alcohols to Δ^2-thiazolines containing an ester in the 4-position and an aryl/heteroaryl in the 5-position with LR.

In addition, these data support the proposed mechanism for the formation of Δ^2-thiazolines with LR published by Nishio,[11b] in which the initial thiolation of the hydroxy compound is known to occur with retention of configuration (Scheme 5).[27] The resultant thiol amide can either undergo a second thiolation reaction of the amide with another equivalent of LR (to form the enantiomerically pure thiol thio amide) or a *syn*-elimination facilitated by compound **B** (Scheme 5). In the latter case, a Michael acceptor is formed that can react further with a sulfur nucleophile (i.e., compound **C**, Scheme 5) through conjugate addition and form the racemic thiol amide. Conjugate addition reactions of thiols to trisubstituted α,β-unsaturated carbonyl compounds are known to precede in high diastereoselectivities with (*E*)-olefins even at elevated temperatures.[28] This selectivity is explained by the selective protonation of the enolate intermediate (shown in the inset in Scheme 5) due to stereoelectronic effects of the sulfur substituent.[28] The α,β-unsaturated ester formed may also undergo a thiolation reaction with LR, and subsequent cyclization to the racemic *trans*-5-substituted 2-thiazoline. Although this 5-*endo*-trig cyclization is disfavored for oxygen and nitrogen nucleophiles, it is known
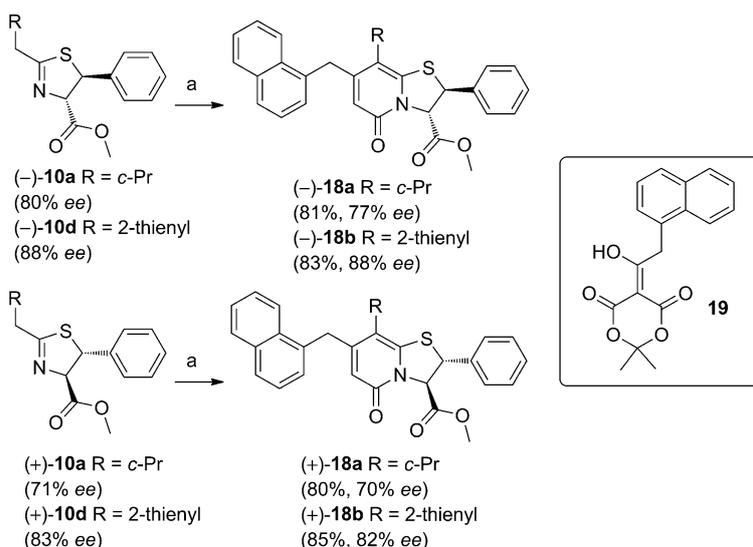
Scheme 4. a) Trifluoroacetic acid (TFA), **19**, microwave irradiation, 140 °C, 2 min, dichloroethene (DCE); the *ee* was determined by chiral chromatography.
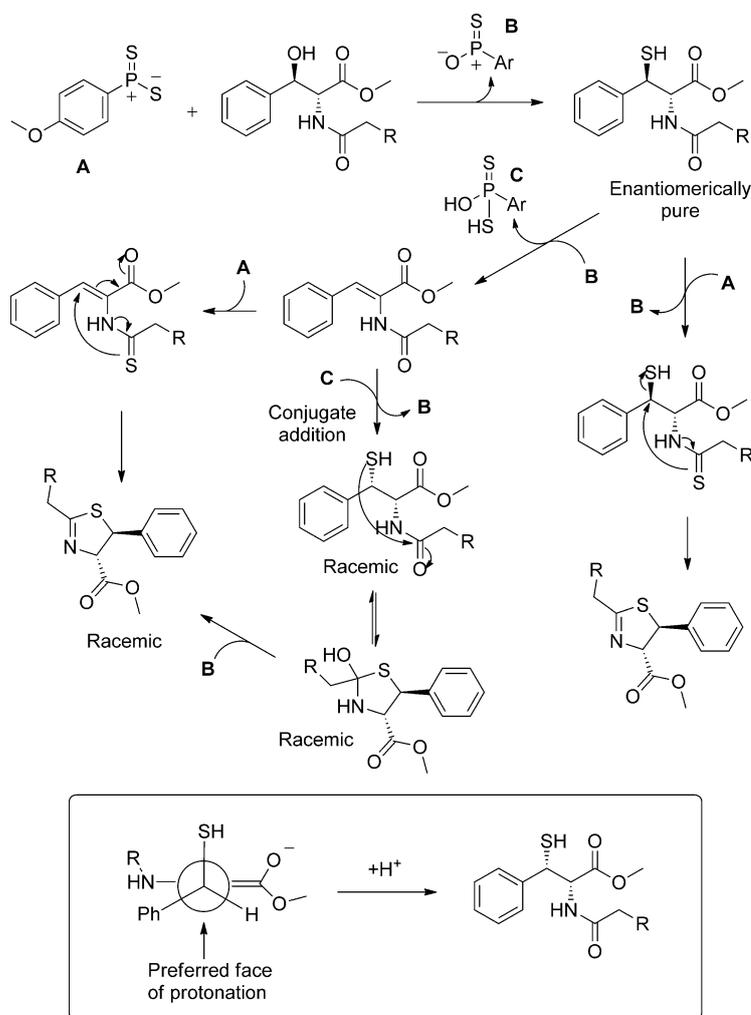
Scheme 5. Possible mechanism for Δ²-thiazoline formation with the Lawesson reagent.

to proceed for sulfur-based nucleophiles.[29] Carbocationic intermediates have also been reported with LR and amido alcohols, but only in the presence of the strongly cation-stabilizing ferrocene group.[11c,30]

Conclusion

We have developed scalable and robust synthetic pathways to highly enantiomerically enriched 5-substituted Δ²-thiazolines, which can be used in a ketene/imine cyclocondensation reaction to yield 2-substituted ring-fused 2-pyridones. The absolute stereochemistry was initially set through a Sharpless asymmetric dihydroxylation of methyl cinnamate. The subsequent nosylation, NaN₃ displacement, esterification, and azide reduction/O→N acyl migration reactions all proceeded in good yields and without detectable epimerization on a gram scale. The final ring-closure of the amido alcohols proceeded in good yields with only 0.6 equivalents of LR, albeit with some epimerization. Increasing the amount of LR to 1 equivalent in this reaction ameliorated this problem, and afforded Δ²-thiazolines in excellent yield and stereochemical purity. The established route proved effective in the synthesis of aryl/heteroaryl 5-substituted Δ²-thiazolines and provides facile access to interesting unnatural analogues of cysteine and serine. Ultimately, this methodology also opens up synthetic possibilities for making asymmetric 5-substituted Δ²-thiazoline-containing ligands, as well as analogues of Δ²-thiazoline based natural products.

Experimental Section

brated by using the residual peak of the solvent as the internal standard (CDCl₃: CHCl₃ $\delta_H = 7.26$ ppm, CDCl₃ $\delta_C = 77.16$ ppm; [D₆]DMSO: [D₅]DMSO $\delta_H = 2.5$ ppm, [D₆]DMSO $\delta_C = 39.5$ ppm). HRMS was performed by using a mass spectrometer with electrospray ionization (ES⁺); sodium formate was used as the calibration chemical.

Representative procedures

(±)-(2S,3R)-2,3-Dihydroxy-3-phenylpropionic acid methyl ester ((±)-2): Methyl cinnamate (30.83 mmol, 5 g), K₂OsO₄·2H₂O (0.62 mmol, 228 mg), and 4-methylmorpholine *N*-oxide (46.25 mmol, 5.42 g) were mixed in acetone/MeCN/H₂O (1:1:1, 140 mL) and the reaction was stirred at RT for 16 h. The volatile solvents were removed by evaporation and the remaining mixture was diluted with saturated aqueous NaHCO₃ and extracted with EtOAc. The organic phase was dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20→50:50) to give (±)-2 as a colorless oil (4.9 g, 81%). Spectral data agreed with published results.[31]

(±)-(2S,3R)-3-Hydroxy-2-(4-nitrobenzenesulfonyloxy)-3-phenylpropionic acid methyl ester ((±)-3): Compound (±)-2 (26.25 mmol, 5.15 g) was dissolved in CH₂Cl₂ (250 mL) and cooled to 0°C in an ice bath. 4-Nitrobenzenesulfonyl chloride (26.25 mmol, 5.82 g) followed by TEA (26.25 mmol, 3.66 mL) were added and the reaction was stirred at 0°C for 1 h. The reaction mixture was acidified and then washed with 1 M aqueous HCl (pH≈1), dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 90:10→60:40) to give (±)-3 as a colorless solid (7.5 g, 75%). Spectral data agreed with published results.[25]

(±)-(2R,3R)-2-Azido-3-phenyl-3-hydroxypropionic acid methyl ester ((±)-4): Compound (±)-3 (7.55 mmol, 2.88 g) and NaN₃ (45.3 mmol, 2.94 g) were mixed in dry DMF (13 mL) and the reaction was heated to 40°C for 48 h. The reaction mixture was diluted with brine and extracted with EtOAc, the organic phase was dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 90:10→60:40) to give (±)-4 as a colorless noncrystalline solid (1.17 g, 70%). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.42$–7.31 (m, 5H), 5.00 (d, $J = 7.2$ Hz, 1H), 4.10 (d, $J = 7.2$ Hz, 1H), 3.77 (s, 3H), 3.02 ppm (br s, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 169.5$, 139.0, 128.9, 128.7 (2C), 126.7 (2C), 74.2, 66.9, 52.9 ppm; IR: $\tilde{v} = 3426$, 2117, 1738 cm⁻¹; HRMS (ES) calcd for C₁₀H₁₁N₃NaO₃: 244.0698 $[M+Na]^+$; found: 224.0701.

(±)-(2R,3R)-2-tert-Butoxycarbonylamino-3-hydroxy-3-phenylpropionic acid methyl ester ((±)-5): SnCl₂·2H₂O (22.6 mmol, 5.1 g) was dissolved in 1,4-dioxane/H₂O (1:4, 20 mL) and (±)-4 (4.52 mmol, 1 g) dissolved in 1,4-dioxane (20 mL) was added. The reaction was stirred at RT for 4 h. NaHCO₃ (4.6 mmol, 386 mg) was added, followed by Boc₂O (0.35 mmol, 76 mg), and the reaction was stirred at RT for an additional 16 h. The reaction mixture was filtered through Celite, and washed with EtOAc. The organic phase was washed with saturated NaHCO₃, dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 90:10→60:40) to give (±)-5 as a colorless noncrystalline solid (1.24 g, 93%). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.39$–7.24 (m, 5H), 5.34 (d, $J = 7.2$ Hz, 1H), 5.18 (d, $J = 2.8$ Hz, 1H), 4.77–4.66 (m, 1H), 3.70 (s, 3H), 1.45 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 170.5$, 156.4, 139.3, 128.4 (2C), 128.1, 126.1 (2C), 80.7, 75.1, 59.8, 52.5, 28.3 ppm (3C); IR: $\tilde{v} = 3425$, 1744, 1713, 1502, 1368 cm⁻¹; HRMS (ES) calcd for C₁₅H₂₁NNaO₅: 318.1317 $[M+Na]^+$; found: 318.1318.

(±)-(2S,3S)-3-Acetylsulfanyl-2-tert-butoxycarbonylamino-3-phenylpropionic acid methyl ester ((±)-6): Compound (±)-5 (0.68 mmol, 200 mg) was dissolved in CH₂Cl₂ (8 mL) and cooled to 0°C in an ice bath. Ms₂O (0.75 mmol, 131 mg) followed by TEA (1.02 mmol, 0.14 mL) were added and the reaction was stirred at 0°C for 2 h. The reaction mixture was diluted with CH₂Cl₂ and washed with saturated aqueous NH₄Cl. The organic phase was dried (Na₂SO₄), filtered, and concentrated. The crude material was dissolved in dry DMF (8 mL) and potassium thioacetate (3.4 mmol, 388 mg) was added; the reaction was stirred at RT for 15 h. The reaction mixture was quenched with 1 M aqueous HCl and acidified to pH≈1, then extracted with EtOAc. The organic phase was dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by

column chromatography on silica gel (heptane/EtOAc 95:5→80:20) to give (±)-6 as a yellow noncrystalline solid (145 mg, 60%). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.34$–7.22 (m, 5H), 5.27 (d, $J = 9.2$ Hz, 1H), 5.00 (d, $J = 7.2$ Hz, 1H), 4.75 (dd, $J = 9.2$, 7.2 Hz, 1H), 3.59 (s, 3H), 2.33 (s, 3H), 1.41 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 194.0$, 170.8, 155.2, 137.6, 128.8 (2C), 128.3 (2C), 128.2, 80.4, 58.2, 52.5, 50.4, 30.5, 28.4 ppm (3C); IR: $\tilde{v} = 3368$, 1747, 1718, 1498, 1164 cm⁻¹; HRMS (ES) calcd for C₁₇H₂₃NNaO₅S: 376.1195 $[M+Na]^+$; found: 376.1196.

(±)-(2R,3R)-2-Azido-3-(2-cyclopropylacetoxy)-3-phenylpropionic acid methyl ester ((±)-8b): Compound (±)-4 (0.90 mmol, 200 mg), cyclopropylacetic acid (1.18 mmol, 0.11 mL), and dicyclohexylcarbodiimide (1.18 mmol, 242 mg) were mixed in CH₂Cl₂ (8 mL) and DMAP (1.18 mmol, 144 mg) was added; the reaction was stirred at RT for 1 h. The reaction mixture was diluted with CH₂Cl₂ and washed with 2% aqueous KHSO₄. The organic phase was dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 95:5→85:15) to give (±)-8b as a colorless oil (258 mg, 95%). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.41$–7.32 (m, 5H), 6.16 (d, $J = 6.4$ Hz, 1H), 4.35 (d, $J = 6.4$ Hz, 1H), 3.76 (s, 3H), 2.28 (d, $J = 7.2$ Hz, 2H), 1.11–0.98 (m, 1H), 0.59–0.51 (m, 2H), 0.20–0.13 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 171.5$, 167.8, 135.4, 129.2, 128.7 (2C), 127.2 (2C), 74.5, 65.4, 52.8, 39.4, 6.8, 4.5 ppm (2C); IR: $\tilde{v} = 2118$, 1750 cm⁻¹; HRMS (ES) calcd for C₁₅H₁₇N₃NaO₄: 326.1117 $[M+Na]^+$; found: 326.1115.

(±)-(2R,3R)-2-(2-Cyclopropylacetylamino)-3-hydroxy-3-phenylpropionic acid methyl ester ((±)-9b): SnCl₂·2H₂O (2.25 mmol, 508 mg) was dissolved in MeOH/H₂O 1:4 (2.5 mL) and (±)-8b (0.45 mmol, 135 mg) dissolved in MeOH (2.5 mL) was added and the reaction was stirred at RT for 2 h. NaHCO₃ (9 mmol, 756 mg) was added in portions to the reaction mixture and the reaction was stirred at RT for an additional 18 h. The reaction mixture was filtered through Celite and the Celite was carefully washed with EtOAc. The organic phase was washed with saturated NaHCO₃, dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20→50:50) to give (±)-9b as a colorless noncrystalline solid (89 mg, 71%). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.27$–7.19 (m, 3H), 7.18–7.13 (m, 2H), 6.66–6.58 (m, 1H), 5.18 (d, $J = 3.6$ Hz, 1H), 4.97–4.92 (m, 1H), 4.45 (br s, 1H), 3.65 (s, 3H), 2.07 (d, $J = 7.6$ Hz, 1H), 0.86–0.76 (m, 1H), 0.52–0.42 (m, 2H), 0.09–0.00 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 174.2$, 170.1, 139.2, 128.3 (2C), 128.1, 126.0 (2C), 75.1, 59.1, 52.6, 41.0, 6.9, 4.6 ppm (split, 2C); IR: $\tilde{v} = 3419$, 1743, 1656, 1521 cm⁻¹; HRMS (ES) calcd for C₁₅H₁₉NNaO₄: 300.1212 $[M+Na]^+$; found: 300.1211.

(±)-(4S,5S)-2-Cyclopropylmethyl-5-phenyl-4,5-dihydrothiazole-4-carboxylic acid methyl ester ((±)-10a): Compound (±)-9b (0.46 mmol, 126 mg) and 0.6 (0.28 mmol, 113 mg) or 1 equivalent (0.46 mmol, 186 mg) of the Lawesson reagent were mixed in toluene (3 mL) and the reaction was heated at reflux with an oil bath for 1 h. The reaction mixture was diluted with EtOAc and washed with saturated aqueous NaHCO₃. The organic phase was dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20→50:50) to give (±)-10a as a colorless oil (with 0.6 equivalents of the Lawesson reagent: 90 mg, 71%; with 1 equivalent of the Lawesson reagent: 114 mg, 90%). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.26$–7.13 (m, 5H), 5.21 (d, $J = 6.8$ Hz, 1H), 5.05–5.01 (m, 1H), 3.68 (s, 3H), 2.45–2.40 (m, 2H), 1.00–0.88 (m, 1H), 0.53–0.45 (m, 2H), 0.20–0.12 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 174.9$, 170.9, 140.6, 129.0 (2C), 128.2, 127.6 (2C), 85.9, 56.6, 52.9, 39.4, 9.4, 5.2, 5.1 ppm; IR: $\tilde{v} = 1744$, 1619, 1266 cm⁻¹; HRMS (ES) calcd for C₁₅H₁₇NNaO₂S: 298.0878 $[M+Na]^+$; found: 298.0875.

trans-3-(3-Methoxyphenyl)acrylic acid methyl ester (11b): Trimethyl phosphonoacetate (8.20 mmol, 1.33 mL) was dissolved in dry THF (40 mL) and NaH (9.02 mmol, 216 mg) was added; the reaction was stirred at RT for 5 min before 3-methoxybenzaldehyde (4.10 mmol, 0.5 mL) was added. The stirring continued at RT for a further 15 h. THF was evaporated and the crude mixture was diluted with saturated aqueous NaHCO₃ and extracted with EtOAc. The organic phase was dried (Na₂SO₄), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 95:5→70:30) to

give **11b** as a colorless oil (755 mg, 96%). Spectral data agreed with published results.[32]

*(2S,3R)-2,3-Dihydroxy-3-phenylpropionic acid methyl ester ((−)-**2**)*: Methyl cinnamate (12.32 mmol, 2 g), AD-mix-β (16.48 g) and methylsulfonamide (12.32 mmol, 1.17 g) were mixed in *t*BuOH/H$_2$O (1:1, 40 mL) and the reaction was stirred at RT for 18 h. The reaction mixture was diluted with water, extracted with EtOAc, and the combined organic phases were dried (Na$_2$SO$_4$), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 80:20→50:50) to give (−)-**2** as a colorless solid (2 g, 83%). $[\alpha]_D^{25\,°C} = −10$ (*c* = 4.0 in CHCl$_3$); spectral data agreed with published results.[31]

*(2S,3S)-7-Naphthalen-1-ylmethyl-5-oxo-2-phenyl-8-thiophen-2-yl-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid methyl ester ((−)-**18b**)*: Compound (−)-**10d** (0.23 mmol, 72 mg), **19** (0.58 mmol, 181 mg), and trifluoroacetic acid (TFA, 0.23 mmol, 18 µL) were mixed in 1,2-dichloroethane (1 mL) and the reaction was heated in a microwave oven at 140°C for 2 min. The reaction mixture was diluted with CH$_2$Cl$_2$ and washed with saturated aqueous NaHCO$_3$. The organic phase was dried (Na$_2$SO$_4$), filtered, and concentrated. The crude material was purified by column chromatography on silica gel (heptane/EtOAc 90:10→50:50) to give (−)-**18b** as a yellow foam (97 mg, 83%). $[\alpha]_D^{25\,°C} = −113$ (*c* = 2.0 in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.88–7.82 (m, 1H), 7.79–7.69 (m, 2H), 7.49–7.43 (m 2H), 7.43–7.30 (m, 7H), 7.28–7.23 (m, 1H), 7.09–7.05 (m, 2H), 5.82 (s, 1H), 5.60 (d, *J* = 3.2 Hz, 1H), 5.00 (d, *J* = 3.2 Hz, 1H), 4.19–4.07 (m, 2H), 3.84 ppm (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 168.2, 161.2, 155.6, 149.0, 138.4, 136.5, 134.0, 133.7, 131.9, 129.4 (2C), 129.3, 129.0, 128.8, 128.0, 127.9, 127.5 (2C), 126.8 (2C), 126.3, 125.8, 125.6, 123.9, 115.5, 108.1, 71.2, 53.5, 50.9, 37.0 ppm; IR: $\tilde{\nu}$ = 1752, 1656, 1265 cm^{-1}; HRMS (ES) calcd for C$_{30}$H$_{23}$NNaO$_3$S$_2$: 532.1017 [*M*+Na]$^+$; found: 532.1020.

Acknowledgements

[1] a) R. Bel Rhlid, Y. Fleury, I. Blank, L. B. Fay, D. H. Welti, F. A. Vera, M. A. Juillerat, *J. Agric. Food Chem.* **2002**, *50*, 2350–2355; b) A. Adams, N. De Kimpe, *Chem. Rev.* **2006**, *106*, 2299–2319.

[2] a) S. D. Sharrow, M. V. Novotny, M. J. Stone, *Biochemistry* **2003**, *42*, 6302–6309; b) J. Brechbühl, F. Moine, M. Klaey, M. Nenniger-Tosato, N. Hurni, F. Sporkert, C. Giroud, M.-C. Broillet, *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 4762–4767.

[3] Z. Lin, R. R. Antemano, R. W. Hughen, M. D. B. Tianero, O. Peraud, M. G. Haygood, G. P. Concepcion, B. M. Olivera, A. Light, E. W. Schmidt, *J. Nat. Prod.* **2010**, *73*, 1922–1926.

[4] a) A. Ino, A. Murabayashi, *Tetrahedron* **1999**, *55*, 10271–10282; b) A. Ino, Y. Hasegawa, A. Murabayashi, *Tetrahedron* **1999**, *55*, 10283–10294; c) A. Ino, A. Murabayashi, *Tetrahedron* **2001**, *57*, 1897–1902.

[5] a) I. Abrunhosa, M. Gulea, J. Levillain, S. Masson, *Tetrahedron: Asymmetry* **2001**, *12*, 2851–2859; b) A.-C. Gaumont, M. Gulea, J. Levillain, *Chem. Rev.* **2009**, *109*, 1371–1401.

[6] I. Abrunhosa, L. Delain-Bioton, A.-C. Gaumont, M. Gulea, S. Masson, *Tetrahedron* **2004**, *60*, 9263–9272.

[7] a) M. Yamakuchi, H. Matsunaga, R. Tokuda, T. Ishizuka, M. Nakajima, T. Kunieda, *Tetrahedron Lett.* **2005**, *46*, 4019–4022; b) T. Nishio, Y. Kodama, Y. Tsurumi, *Phosphorus Sulfur Silicon Relat. Elem.* **2005**, *180*, 1449–1450.

[8] Y. Jia, W. Yang, D.-M. Du, *Org. Biomol. Chem.* **2012**, *10*, 4739–4746.

[9] a) P. Wipf, X. Wang, *Org. Lett.* **2002**, *4*, 1197–1200; b) Z. Gong, Q. Liu, P. Xue, K. Li, Z. Song, Z. Liu, Y. Jin, *Appl. Organomet. Chem.* **2012**, *26*, 121–129.

[10] P. Wipf, P. C. Fritch, *Tetrahedron Lett.* **1994**, *35*, 5397–5400.

[11] a) T. Nishio, *Tetrahedron Lett.* **1995**, *36*, 6113–6116; b) T. Nishio, *J. Org. Chem.* **1997**, *62*, 1106–1111; c) M. Ori, T. Nishio, *Heterocycles* **2001**, *54*, 201–208; d) A. Tárraga, P. Molina, D. Curiel, D. Bautista, *Tetrahedron: Asymmetry* **2002**, *13*, 1621–1628; e) for a review on the Lawesson reagent, see: M. Jesberger, T. P. Davis, L. Barner, *Synthesis* **2003**, 1929–1958.

[12] a) S.-L. You, H. Razavi, J. W. Kelly, *Angew. Chem.* **2003**, *115*, 87–89; *Angew. Chem. Int. Ed.* **2003**, *42*, 83–85; b) Y. Numajiri, T. Takahashi, T. Doi, *Chem. Asian J.* **2009**, *4*, 111–125.

[13] P. Raman, H. Razavi, J. W. Kelly, *Org. Lett.* **2000**, *2*, 3289–3292.

[14] H. Wenker, *J. Am. Chem. Soc.* **1935**, *57*, 1079–1080.

[15] a) P. Lafargue, P. Guenot, J.-P. Lellouche, *Synlett* **1995**, 171–172; b) K. C. Nicolaou, D. H. Dethe, G. Y. C. Leung, B. Zou, D. Y.-K. Chen, *Chem. Asian J.* **2008**, *3*, 413–429.

[16] S. G. Mahler, G. L. Serra, D. Antonow, E. Manta, *Tetrahedron Lett.* **2001**, *42*, 8143–8146.

[17] a) N. Galéotti, C. Montagne, J. Poncet, P. Jouin, *Tetrahedron Lett.* **1992**, *33*, 2807–2810; b) P. Wipf, C. P. Miller, *Tetrahedron Lett.* **1992**, *33*, 6267–6270.

[18] P. Wipf, X. Wang, *J. Comb. Chem.* **2002**, *4*, 656–660.

[19] X. Fernández, R. Fellous, E. Duñach, *Tetrahedron Lett.* **2000**, *41*, 3381–3384.

[20] a) J. S. Pinkner, H. Remaut, F. Buelens, E. Miller, V. Åberg, N. Pemberton, M. Hedenström, A. Larsson, P. Seed, G. Waksman, S. J. Hultgren, F. Almqvist, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 17897–17902; b) E. Chorell, P. Das, F. Almqvist, *J. Org. Chem.* **2007**, *72*, 4917–4924; c) E. Chorell, J. S. Pinkner, G. Phan, S. Edvinsson, F. Buelens, H. Remaut, G. Waksman, S. J. Hultgren, F. Almqvist, *J. Med. Chem.* **2010**, *53*, 5690–5695; d) C. Bengtsson, A. E. G. Lindgren, H. Uvell, F. Almqvist, *Eur. J. Med. Chem.* **2012**, *54*, 637–646.

[21] a) L. Cegelski, J. S. Pinkner, N. D. Hammer, C. K. Cusumano, C. S. Hung, E. Chorell, V. Åberg, J. N. Walker, P. C. Seed, F. Almqvist, M. R. Chapman, S. J. Hultgren, *Nat. Chem. Biol.* **2009**, *5*, 913–919; b) E. Chorell, J. S. Pinkner, C. Bengtsson, S. Edvinsson, C. K. Cusumano, E. Rosenbaum, L. B. Å. Johansson, S. J. Hultgren, F. Almqvist, *Chem. Eur. J.* **2012**, *18*, 4522–4532.

[22] a) H. Emtenäs, L. Alderin, F. Almqvist, *J. Org. Chem.* **2001**, *66*, 6756–6761; b) H. Emtenäs, K. Åhlin, J. S. Pinkner, S. J. Hultgren, F. Almqvist, *J. Comb. Chem.* **2002**, *4*, 630–639; c) H. Emtenäs, C. Taflin, F. Almqvist, *Mol. Diversity* **2003**, *7*, 165–169.

[23] E. Chorell, J. S. Pinkner, C. Bengtsson, T. Sainte-Luce Banchelin, S. Edvinsson, A. Linusson, S. J. Hultgren, F. Almqvist, *Bioorg. Med. Chem.* **2012**, *20*, 3128–3142.

[24] B. Tao, G. Schlingloff, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *39*, 2507–2510.

[25] P. R. Fleming, K. B. Sharpless, *J. Org. Chem.* **1991**, *56*, 2869–2875.

[26] B. Neises, W. Steglich, *Angew. Chem.* **1978**, *90*, 556–557; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522–524.

[27] a) T. Nishio, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1113–1117; b) T. Nishio, Y. Konno, M. Ori, M. Sakamoto, *Eur. J. Org. Chem.* **2001**, 3553–3557.

[28] O. Miyata, T. Shinada, I. Ninomiya, T. Naito, K. Okamura, S. Inagaki, *J. Org. Chem.* **1991**, *56*, 6556–6564.

[29] a) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, R. C. Thomas, *J. Chem. Soc. Chem. Commun.* **1976**, 736–738; b) M. E. M. Baggs, B. Gregory, *Can. J. Chem.* **1980**, *58*, 794–802.

[30] a) G. W. Gokel, P. Hoffmann, M. Klusacek, D. Marquarding, E. Rush, I. Ugi, *Angew. Chem.* **1970**, *82*, 77–78; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 64–65; b) G. W. Gokel, D. Marquarding, I. Ugi, *J. Org. Chem.* **1972**, *37*, 3052–3058.

[31] X. Lu, Z. Xu, G. Yang, *Org. Process Res. Dev.* **2000**, *4*, 575–576.

[32] V. R. Chintareddy, A. Ellern, J. G. Verkade, *J. Org. Chem.* **2010**, *75*, 7166–7174.