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ORIGINAL ARTICLE

# (*L*)-(Trimethylsilyl)alanine synthesis exploiting hydroxypinanone-induced diastereoselective alkylation

**A. René · N. Vanthuyne · J. Martinez · F. Cavelier**

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**Abstract** A new and efficient synthesis of (*L*)-(trimethylsilyl)alanine (TMSAla) with suitable protection for use in Solid Phase Peptide Synthesis (SPPS) has been accomplished starting from glycine *tert*-butyl ester and using hydroxypinanone as chiral inductor. The silylated side chain was introduced by alkylation of the Schiff base intermediate with iodomethyl(trimethylsilane) at −78 °C. Among the different synthetic routes that were tested including several chiral inductors and different Schiff bases, this strategy was selected and afforded (*L*)-TMSAla in good chemical overall yield with 98 % ee.

**Keywords** (Trimethylsilyl)alanine · Diastereoselectivity · Schiff base · Sulfinamide · (1*R*,2*R*,5*R*)Hydroxy-3-pinanone · Chiral HPLC

## Introduction

For several decades, silicon was known to confer physical and chemical properties to the compounds in which it was incorporated, offering non-polar and hydrophobic properties. Physical studies showed that silicon has a smaller electronegativity (Si 1.74; C 2.5) along with a larger steric volume (Si 117 pm; C 77 pm) than carbon (Meanwell 2011). Despite these differences, silicon proved its behavior as a carbon isostere in bioactive compounds. This property has been recently exploited in drug design (Meanwell 2011; Gately and West 2007; Franz and Wilson 2012).

In this domain, unnatural amino acids are of great importance, and silylated amino acids have attracted synthetic efforts. Their incorporation into bioactive peptides can modulate conformational flexibility and structure (Tacke et al. 2000; Vivet et al. 2000b; Cavelier et al. 2006), modify biological properties (Cavelier et al. 2002, 2004), induce enzymatic resistance and facilitate membrane crossing (Pujals et al. 2006).

Despite interest in silicon-containing amino acids, they are still limited in number and diversity, as shown in a recent review (Mortensen et al. 2009). Since then, other synthetic approaches have been reported to obtain chiral silylated α-amino acids and α,α′-dialkylated α-amino acids, through a hydrosilylation reaction on unsaturated substrates (Marchand et al. 2008; Cavelier et al. 2008), or from diethylmalonate (Falgner et al. 2009a, b, 2010). A new silylated amino acid carrying a 1-(4-dihydroxymethylsilyl)butyl side chain was also prepared and showed efficiency as an inhibitor of a specific enzyme (Kim and Sieburth 2012). Recently, the silylated proline surrogate 4,4-dimethylsilaproline (Vivet et al. 2000a; Handmann et al. 2000) has been produced on a gram scale (Martin et al. 2012).

TMSAla is probably the most reviewed silylated amino acid in the literature. It has been first synthesized as a racemate in 1968 (Porter and Shive 1968). Twenty years later, the first synthesis of the (*L*)-enantiomer was described using imidazolinone glycine derivatives (Fitzi and Seebach 1988), and other auxiliaries have been later tested as chiral inductors (Weidmann 1989, 1992; Walkup et al.

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1995). Enzymatic syntheses were also employed (Yamanaka et al. 1996; Pietzsch et al. 2000; Smith et al. 2001), as well as kinetic resolution (Chen et al. 2002). Synthetic routes starting from (*l*)-serine derivatives proved also to be efficient (Sibi et al. 1998; Kenworthy et al. 2004). Surprisingly, the most recent synthesis of TMSAla resulted in a racemic mixture, and the structure of the racemate was characterized by single-crystal X-ray diffraction (Falgner et al. 2009b).

## Materials and methods

All reactions involving air-sensitive reagents were performed under nitrogen or argon. Purifications were performed with column chromatographies using silica gel (Merck 60, 230–400 mesh) or with a Biotage instrument Isolera 4 using SNAP KP-SIL flash cartridges. Proton nuclear magnetic resonance $^{1}$H-NMR and carbon nuclear magnetic resonance $^{13}$C-NMR spectra were recorded on a Bruker spectrometer avance 300 at 300 and 75 MHz, a Bruker spectrometer avance 400 at 400 and 100 MHz or a Bruker spectrometer 600 at 600 and 150 MHz, respectively. All chemical shifts were recorded as values (ppm) relative to internal tetramethylsilane when $CDCl_3$ was used as solvent. Low-resolution electrospray ionization (ESI) mass spectra were recorded on a micromass platform electrospray mass spectrometer. Spectra were recorded in the positive mode ($ESI^+$). Optical rotation values were measured on a Perkin-Elmer 341 (20 °C, sodium ray). The analytical chiral HPLC experiments were performed on a unit composed of a Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven, Merck-Lachrom L-7400 UV-detector, and on-line Jasco OR-1590 polarimeter. Hexane, ethanol and isopropanol, HPLC grade, were degassed and filtered on a 0.45-μm membrane before use. Chiral columns (250 × 4.6 mm) tested are Chiralcel OD-H, OJ, OC, OB-H, Chiralpak AS-H, IC and AD-H from Chiral Technologies Europe (Illkirch, France), Whelk O1 (*S,S*) and Ulmo (*S,S*) from Regis Technologies (Morton Grove, USA), Sumichiral OA-2500 from Sumika (Japan) and Lux-Cellulose-2 from Phenomenex.

### *Para*-tolylsulfiniminoacetate (**2**)

In a 500-mL round-bottom flask under argon atmosphere was placed ethyl glyoxalate (50 % solution in toluene, 1.279 mL; 6.45 mmol). The flask was heated with a heat gun to about 50 °C for 1 min to depolymerize the reagent and then, allowed to cool to room temperature and $CH_2Cl_2$ (160 mL) was introduced. To this rapidly stirred solution was added (*S*)-(+)-*N*-*para*-toluenesulfinamide **1** (1 g; 6.45 mmol) and then 4 Å molecular sieves (activated overnight at 100 °C). After 24 h, the reaction mixture was filtered through Celite® and the residue washed with $CH_2Cl_2$ (3 × 50 mL). Organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give colorless oil. Flash chromatography through a short frit ($SiO_2$, $CH_2Cl_2$) afforded (+)-(*para*-toluenesulfinyl)-iminoacetate **2** (1.11 g; 72 %) as a colorless oil, which solidified on storage at 5 °C.

NMR $^{1}$H ($CDCl_3$, 300 MHz): $\delta$ (ppm) 1.33 (t, 2H, $^{3}J = 6$ Hz, $CH_2CH_3$); 2.39 (s, 3H, $CH_3$Ph); 4.3–4.32 (q, 3H, $^{3}J = 6$ Hz, $CH_2CH_3$); 7.3 (d, 2H, $^{3}J = 9$ Hz, $CH_o$SO); 7.57 (d, 2H, $^{3}J = 9$ Hz, $CH_m$SO); 8.13 (s, 1H, $CHCO_2$Et).

NMR $^{13}$C ($CDCl_3$, 75 MHz): $\delta$ (ppm) 13.8 ($CH_2CH_3$); 21.2 ($CH_3$Ph); 62.4 ($CH_2CH_3$); 124.5 (*C*SO); 129.9 ($C_m$SO); 138.9 ($C_o$SO); 142.3 ($C_p$SO); 152.9 (*C*HCO$_2$Et); 161.0 ($CO_2$Et).

### Alkylation procedure to obtain (**3**)

Magnesium turnings (250 mg, 10.3 mmol) were placed in a high-dry three-neck round-bottom flask equipped with an addition funnel and a cooling system. Ether was added (10 mL) through the addition funnel. Then, the chloromethyl(trimethylsilane) (1.436 mL, 10.3 mmol) was diluted in ether (10 mL) in the addition funnel. Few drops were added and the mixture was heated to weak reflux. Di-bromoethane (a few drops) was added as an Mg activator. The reaction mixture trouble shows that the reaction started. Then, the rest of chloride derivative diluted in ether was added dropwise and heating was maintained. After addition, reaction mixture was diluted with ether (20 mL). Heating was continued for 10 min.

In a second three-necked round-bottom flask under argon atmosphere was placed imino-ester **2** (350 mg, 1.255 mmol) in $CH_2Cl_2$ (10 mL) and a few drops of boron trifluoride diethyl ether were added. After cooling to −78 °C, the Grignard derivative (5 equiv.) was transferred and the reaction mixture was stirred at −78 °C for 1 h and a half. The reaction was quenched with a saturated solution of ammonium chloride. Aqueous layer was separated and extracted with $CH_2Cl_2$ (3 × 20 mL). Organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The diastereoisomers were separated with a chromatography separation on silica flash (cyclohexane/ethyl acetate; from 0 to 30 %). The desired diastereoisomer **3** was obtained in 17 % yield (70.7 mg, 0.216 mmol).

m.p. 56 °C; NMR $^{1}$H ($CDCl_3$, 600 MHz): $\delta$ (ppm) −0.12 (s, 9H, Si($CH_3$)$_3$); 0.83–0.92 (m, 2H, $^{3}J = 54$ Hz, $CH_2$Si(CH$_3$)$_3$); 1.30 (t, 2H, $^{3}J = 6$ Hz, $CH_2CH_3$); 2.41 (s, 3H, $CH_3$Ph); 3.72–3.77 (m, 1H, $^{3}J = 30$ Hz, $CH_2CH_3$); 4.13–4.18 (m, 1H, $^{3}J = 30$ Hz, $CH_2CH_3$); 4.21–4.26 (m, 1H, $^{3}J = 30$ Hz, SiCH$_2$C$H_\alpha$); 4.75–4.76 (d, 1H, N*H*); 7.3 (d, 2H, $^{3}J = 9$ Hz, $CH_o$SO); 7.59 (d, 2H, $^{3}J = 9$ Hz, $CH_m$SO).

NMR $^{13}$C ($CDCl_3$, 150 MHz): $\delta$ (ppm) 1.10 (Si($CH_3$)$_3$); 14.1 ($CH_2CH_3$); 21.5 ($CH_3$Ph); 22.9 ($CH_2$Si); 50.8 ($CHCH_2$Si); 61.5 ($CH_2CH_3$); 126.1 ($C_m$SO); 129.6 ($C_o$SO); 141.0 ($C_p$SO); 141.6 (*C*SO); 174.8 ($CO_2$Et).

Compound **5**: NMR $^1$H ($CDCl_3$, 300 MHz): $\delta$ (ppm) 0.01 (s, 9H, Si($CH_3$)$_3$); 2.39 (s, 3H, $CH_3$Ph); 3.30 (dd, 2H, AB, $^2J$ = 12 Hz; $^3J$ = 304 Hz, $CH_2$Si($CH_3$)$_3$); 7.29 (d, 2H, $J$ = 12 Hz, $CH_3CH_o$); 7.52 (d, 2H, $J$ = 12 Hz, $CH_3CH_m$)NMR $^{13}$C ($CDCl_3$, 150 MHz): $\delta$ (ppm) 3.13 (Si($CH_3$)$_3$); 21.6 ($CH_2$Si); 53.7 (*C*SO); 125.7 (C*Ho*CSO); 129.7 ($CH_m$CSO); 141.3 ($CH_o$CSO); 142.6 ($CH_3C$).

(+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone Schiff base **(10)**

A suspension of glycine *tert*-butyl ester hydrochloride **9** (1.68 g, 10 mmol, 1.5 equiv.) in dry toluene (30 mL) was stirred in the presence of triethylamine (1.4 mL, 1.5 equiv.) for 1 h. After triethylammonium chloride filtration, (1*R*,2*R*,5*R*)hydroxy-3-pinanone (1.12 g, 6.67 mmol) was added to the free amine. The mixture was heated to reflux for 4 h in the presence of boron trifluoride diethyl ether (100 µL). Water, formed during the reaction, was removed with a Dean-Stark trap. After cooling, the mixture was concentrated. The crude product was purified by chromatography separation on silica flash (cyclohexane 7/ethyl acetate 3; 1 % TEA). The Schiff base **10** (1.76 g, 6.24 mmol) was obtained in 94 % yield.

$R_f$ = 0.3 (cyclohexane 7/ethyl acetate 3); MS-ESI [MH$^+$] = 282; NMR $^1$H ($CDCl_3$, 300 MHz): $\delta$ (ppm) 0.85 (s, 3H, $CH_{3\ bridge}$); 1.30 (s, 3H, $CH_{3\ bridge}$); 1.46 (s, 9H, O*tBu*); 1.5 (s, 3H, C(OH)$CH_3$); 2.02–2.06 (m, 3H, $CH_2CHC$(OH)$CH_3$); 2.25–2.35 (m, 1H, $CHCH_2CN$); 2.45 (m, 2H, $CH_2CN$); 4.07 (s, 2H, $CNCH_2$).

Obtention of (**11**)

To a solution of diisopropylamine (1.38 mL, 2.5 equiv.) in dry THF (24 mL) was added very slowly a solution of *n*-butyllithium 2.5 M in hexane (3.78 mL, 2.4 equiv.) at −10 °C. After 30 min, the mixture was cooled to −78 °C and the Schiff base **10** (1.11 g, 3.94 mmol) dissolved in THF (2.5 mL) was added. After 40 min, the iodomethyl(trimethylsilane) (1.05 mL, 1.8 equiv.) was added. The mixture was stirred at −78 °C for 8 h. Then, the mixture was allowed to cool to −10 °C overnight. The reaction was quenched with a saturated solution of ammonium chloride (40 mL). Then, THF was concentrated. The aqueous phase was extracted three times with ethyl acetate (3 × 20 mL). The organic phase was dried over $MgSO_4$. After concentration, the crude product was purified on silica flash (cyclohexane 8/ethyl acetate 2; 1 % TEA). The alkylated Schiff base **11** (1.58 g, 2.83 mmol) was obtained in 72 % yield.

$R_f$ = 0.4 (cyclohexane 8/ethyl acetate 2); MS-ESI [MH$^+$] = 368; NMR $^1$H ($CDCl_3$, 400 MHz): $\delta$ (ppm) 0.008 (s, 9H, Si($CH_3$)$_3$); 0.83 (s, 3H, $CH_{3\ bridge}$); 1.19–1.21 (m, 2H, $CH_2$Si); 1.30 (s, 3H, $CH_{3\ bridge}$); 1.41 (s, 9H, O*tBu*); 1.45 (s, 3H, C(OH)$CH_3$); 1.99–2.05 (m, 1H, $CHC(CH_3)_2$; 2.48–2.49 (m, 2H, $CH_2CHC$(OH)$CH_3$); 2.54–2.57 (m, 2H, $CH_2CN$); 4.14 (m, 1H, $SiCH_2CH_\alpha$).

NMR $^{13}$C ($CDCl_3$, 75 MHz): $\delta$ (ppm) 0.66 (Si($CH_3$)$_3$); 21.3 ($CH_2CN$); 22.9 ($CH_2$Si); 27.4 ($CO_2tBu$); 33.5 ($CH_{3\ bridge}$); 38.3 (C(OH)$CH_3$); 38.4 ($CH_2C$(OH)$CH_3$); 50.2 ($CHCH_2$Si); 60.5 ($CC$(OH)$CH_3$); 81.1 ($C$(OH)$CH_3$); 172.2 (*C*N); 177.6 ($CO_2$tBu).

Synthesis of Fmoc-(*L*)-(trimethylsilyl)alanine-OH **(12)** from **(11)**

To a solution of the alkylated Schiff base **11** (0.63 g, 1.72 mmol) in THF (3.5 mL) was added a solution of citric acid 15 % (10 mL). The mixture was stirred at room temperature for 3 days. After removing THF in vacuo, the aqueous layer was extracted with diethyl ether (15 mL) in order to remove the chiral inductor. Then, the pH was increased to 8–9 with potassium carbonate addition. The free amine was then extracted with ethyl acetate (3 × 30 mL). The organic layer was concentrated at room temperature due to the amine volatility. The (trimethylsilyl)alanine *tert*-butylester was then dissolved in ethyl acetate (10 mL) and Fmoc-OSu (753 mg, 1.3 equiv.) was added. The pH was adjusted to 8–9 with triethylamine addition. The mixture was stirred for 6 h. After TLC monitoring, the solvent was removed. The organic layer was washed with a solution of potassium hydrogenosulfate (3 × 20 mL) and saturated solution of sodium hydrogenocarbonate (3 × 20 mL). Then, organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified on silica flash (cyclohexane 9/ethyl acetate 1). The Fmoc-trimethyl(silylalanine) *tert*-butyl ester (646 mg, 1.47 mmol) was obtained in 86 % yield.

$R_f$ = 0.4 (cyclohexane 9/ethyl acetate 1); MS-ESI [MH$^+$] = 440; [M + Na] = 462.

The Fmoc-(trimethylsilyl)alanine *tert*-butyl ester (646 mg; 1.47 mmol) was dissolved in trifluoroacetic acid (6 mL). The mixture was stirred for 1 h at room temperature. The reaction solvent is concentrated and the acid excess is removed by coevaporation with cyclohexane. The Fmoc silylated amino acid **12** is obtained as foam.

MS-ESI$^+$: [M + H] = 384; [M + Na] = 406; [M + K] = 422; $[\alpha]_{20}^{D}$ −13° (c 1, $CH_2Cl_2$); NMR $^1$H ($CDCl_3$, 300 MHz): $\delta$ (ppm) 0.05 (s, 9H, Si($CH_3$)$_3$); 0.94–1.24 (m, 2H, $CH_2$Si); 4.21 (m, 1H, $SiCH_2CH_\alpha$); 4.39–4.41 (m, 2H, $CH_2CO_2$); 5.07–5.09 (m, 1H, $CHCH_2CO_2$); 7.28–7.38 (m, 4H, $H_{m\ and\ p}$); 7.55–7.57 (dd, 2H, $H_o$); 7.73–7.75 (dd, 2H, $H_{m'}$).

NMR $^{13}C$ ($CDCl_3$, 150 MHz): $\delta$ (ppm) 1.07 ($Si(CH_3)_3$); 21.05 ($CH_2Si$); 47.3 ($CO_2CH_2CH$); 51.2 ($CHCH_2Si$); 67.2 ($CO_2CH_2$); 120.1 ($CH_o$); 125.1 ($CH_m$); 127.2 ($CH_{m'}$); 127.9 ($CH_p$); 141.5 ($CH_{o'}$); 143.9 ($CO_2CH_2CHC$); 155.9 ($CO_2NH$); 178.9 ($CO_2H$).

Obtention of **(13)**

Using the same procedure as to obtain **11** but with iodopropyl(trimethylsilane) (1.93 g, 8 mmol, 1.5 equiv.), the alkylated Schiff base was obtained in 65 % yield. Following the same cleavage/protection procedure, the amino acid **13** was obtained in 88 % yield.

MS-ESI$^+$: [M + H] = 468; [M + Na] = 490; [2M + $H^+$] = 935; NMR $^1H$ ($CDCl_3$, 300 MHz): $\delta$ (ppm) 0.00 (s, 9H, $Si(CH_3)_3$); 0.50–0.65 (m, 2H, $CH_2Si$); 1.30–1.40 (m, 2H, $SiCH_2CH_2CH_2$); 1.45 (s, 9H, O*tBu*); 1.7–1.90 (m, 2H, $SiCH_2CH_2CH_2$); 4.20–4.50 (m, 4H, $CH_\alpha$ and $CHCH_{2\ Fmoc}$); 5.35 (d, 1H, $J$ = 9.49 Hz, N*H*); 7.20–7.80 (m, 8H, *fluorenyle*).

Obtention of **(14)**

Using the same procedure as to obtain **11** but with iodomethyl(dimethylmethylphenylsilane) (1.7 g, 8 mmol, 1.5 equiv.), the alkylated Schiff base was obtained in 68 % yield. Following the same cleavage/protection procedure, the amino acid **14** was obtained in 76 % yield.

MS-ESI$^+$: [M + H] = 502; [M + Na] = 524; NMR $^1H$ ($CDCl_3$, 300 MHz): $\delta$ (ppm) 0.35 (s, 6H, $Si(CH_3)_2$); 1.15–1.45 (m, 2H, $Ph(CH_3)_2SiCH_2$); 1.45 (s, 9H, O*tBu*); 4.15–4.25 (m, 1H, $SiCH_2CH_\alpha$); 4.25–4.40 (m, 3H, $CHCH_{2\ Fmoc}$); 5.00 (d, $J$ = 9.2 Hz, 1H, N*H*); 7.25–7.80 (m, 13H, *fluorenyle* and *SiPh*).

## Results and discussion

In this study, we present different new routes for the synthesis of (*L*)-TMSAla, with a comparison of their efficiency in term of chimio- and stereoselectivities.

Starting from several chiral Schiff bases, the key alkylation reaction permitted to evaluate the chiral induction of each auxiliary.

At first, we tested a *N*-sulfinyl auxiliary resulting from the (*S*)-(+)-*p*-tolylsulfinamide **1** and ethyl glyoxalate condensation. The chiral sulfonamide group is known to activate the C=N bond for nucleophilic addition (Davis and McCoull 1999) and to induce a good diastereoselectivity (Davis et al. 1998). In the reaction with the appropriate alkyl magnesium chloride, we obtained a moderate diastereoselectivity (76:24 diastereomer ratio) of the desired compound obtained in 30 % yield. These diastereomers were separable by column chromatography affording **3** in 17 % yield (Scheme 1). In addition, we observed formation of a side product **5** resulting from sulfoxide nucleophilic attack (*p*-tolylSOCH$_2$SiMe$_3$) obtained in 30 % yield. In the step from **2** to **3**, the nucleophilic agent was issued from a classic Grignard reaction using Mg turnings and chloromethyl(trimethylsilane). The halogen–metal exchange between iPrMgBr and iodomethyl(trimethylsilane) leading to the corresponding bromide Grignard intermediate did not afford the desired compound.

To prevent the side reaction leading to **5**, we envisaged to use a bulkier group, the *tert*-butyl sulfinamide auxiliary **6** (Liu et al. 1997; Ellman et al. 2002; Robak et al. 2010).

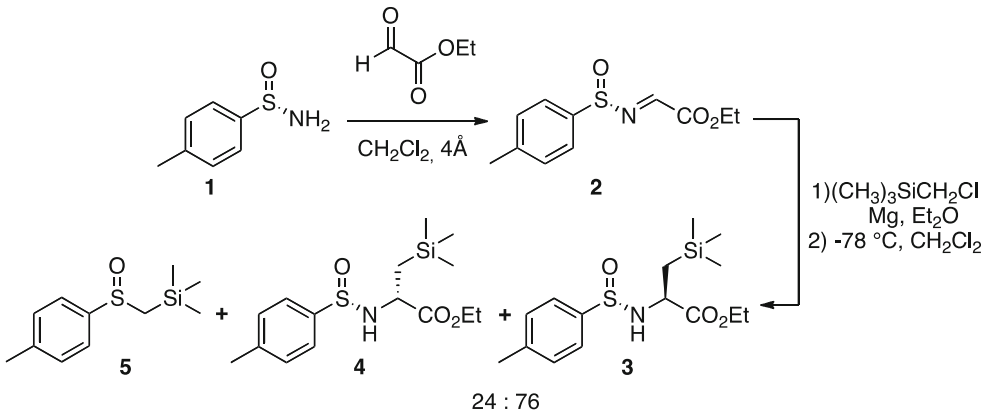
In this route, we started from *(S)-tert*-butyl sulfinamide **6** as chiral inductor. After the *tert*-butylsulfiniminoacetate **7** synthesis, the methyl(trimethylsilyl)magnesium chloride was first synthesized as previously described, but the alkylation step failed. Then, the magnesium bromide derivative was synthesized. Unfortunately, only the ester function attack was observed in this case. Even using the Zn intermediate instead of the Mg intermediate, this alkylation key step experimented at lower temperature (−78 °C) failed. We only observed a partial alkylation of the *tert*-butylsulfiniminoacetate **7** by the Zn intermediate (Scheme 2). We could hypothesize that the methyl(trimethylsilyl) group hindrance, combined with the low temperature, hampered a good access to the imine function. At −50 °C, the nucleophilic attack with the Zn reagent occurred on the ester function.

Finally, we tested (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone as the chiral part of the Schiff base. This commercially available chiral inductor was first used (Yamada et al. 1976) and further proved its efficiency (Tabcheh et al. 1991; Solladie-Cavallo and Nsenda 1998).

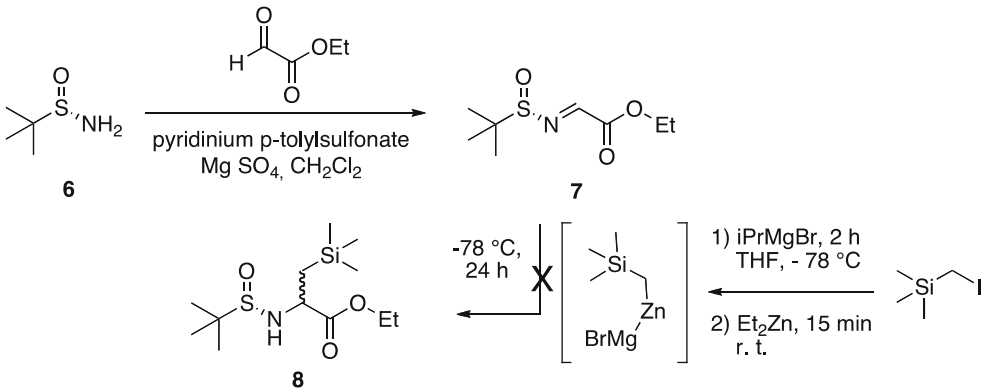
The starting glycinate *tert*-butyl ester hydrochloride **9** was neutralized with triethylamine in toluene and condensed with the hydroxypinanone. The synthesis of the Schiff base **10** was performed in the presence of boron trifluoride diethyl ether using a Dean-Stark trap. A 94 % yield of product was obtained after purification of the amine excess. The alkylation step was achieved using LDA, followed by iodomethyl(trimethylsilane) addition. The reaction was initiated at low temperature (−78 °C) to control the diastereoselectivity, then allowed to reach −10 °C overnight, thus affording **11** in 72 % yield after purification by column chromatography. NMR spectra displayed one diastereoisomer only, thus assuming that the induction was beyond NMR precision. The chiral auxiliary was disconnected by acid hydrolysis. The amine function was then protected with a Fmoc group and the *tert*-butyl ester was removed with trifluoroacetic acid (Scheme 3).

Compound **12** was obtained in 86 % yield over these three steps. Afterwards, chirality was analyzed by chiral HPLC

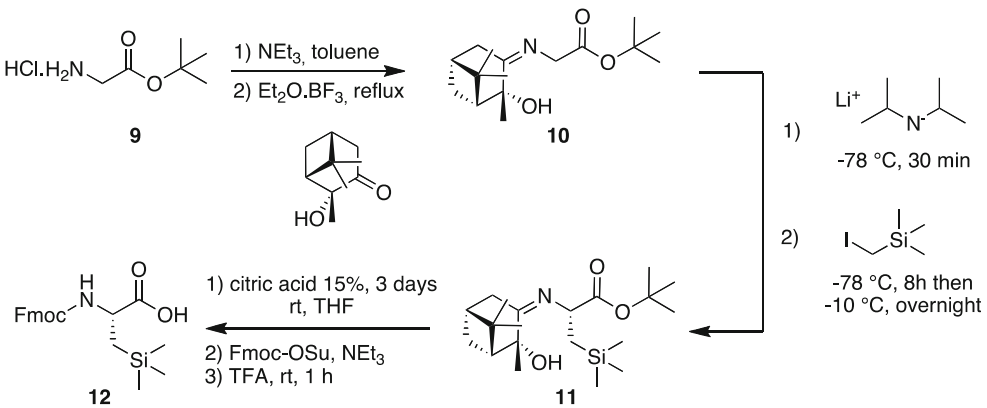
**Scheme 1** *p*-Tolylsulfiniminoacetate induction




**Scheme 2** *Tert*-butylsulfiniminoacetate induction




**Scheme 3** (1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone induction




and showed an ee superior to 98 %. It is worth to note that Fmoc-(*L*)-TMSAla-OH has a (*R*) configuration while all natural (*L*) amino acids have a (*S*) configuration, the silicium atom inverting the priority in Cahn–Ingold–Prelog rules.

Fmoc-(*D/L*)-TMSAla-OtBu and Fmoc-(*L*)-TMSAla-OtBu resulting from the diastereoselective synthesis using the (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone induction were injected into a Chiralcel OD-3 column and elution were performed with hexane/ethanol (80/20). Chromatogram b showed that Fmoc-(*L*)-TMSAla-OtBu was almost the only formed enantiomer with a positive sign on the circular dichroism spectra at 220 nm. Thus for the racemic mixture of Fmoc-TMSAla-OtBu (chromatogram a), the first eluted enantiomer was Fmoc-(*D*)-TMSAla-OtBu with a negative sign, the second eluted enantiomer was Fmoc-(*L*)-TMSAla-OtBu with a positive sign (Fig. 1).

After acidic deprotection of the *tert*-butyl group with trifluoroacetic acid, racemic and Fmoc-(*L*)-TMSAla-OH were injected to evaluate the chiral purity of the final product **12** ready for solid-phase peptide synthesis. Moreover, the value of its specific optical rotation was measured $[\alpha]_{20}^{D} = -13°$ ($c = 1$, $CH_2Cl_2$) and confirmed the formation of the (*L*) enantiomer (lit. $[\alpha]_{20}^{D} = -8.7°$, $c$ 1 $CH_2Cl_2$) (Weidmann 1992).

To explore the scope of this reaction, the Schiff base **10** was subjected to alkylation with 3-iodopropyl

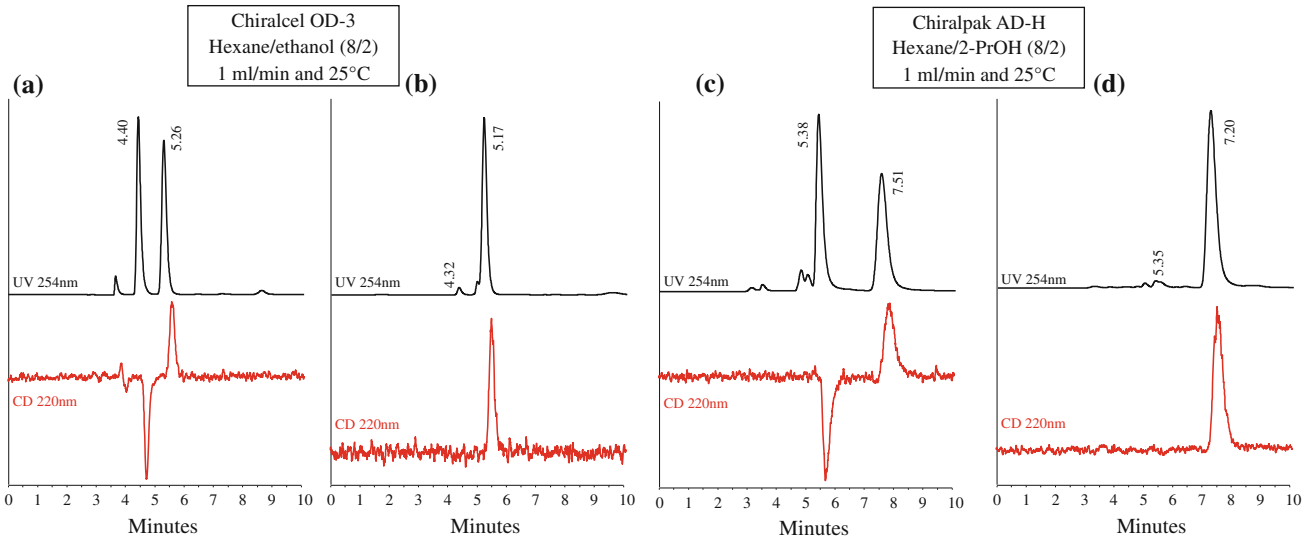
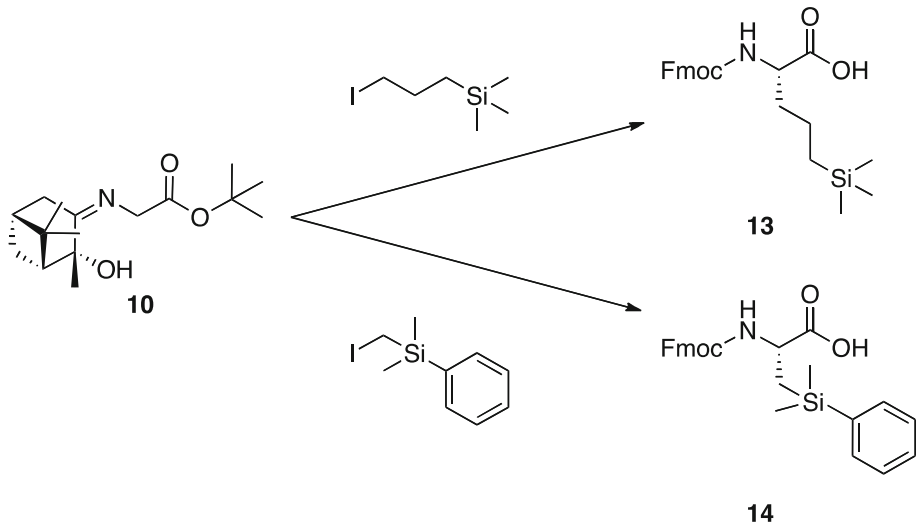



**Fig. 1** Chiral HPLC analyses of TMS-alanine resulting from (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone induction: **a** Fmoc-(*D*/*L*)-TMSAla-OtBu, **b** Fmoc-(*L*)-TMSAla-OtBu, **c** Fmoc-(*D*/*L*)-TMSAla-OH and **d** Fmoc-(*L*)-TMSAla-OH

**Scheme 4** Extension of the strategy




(trimethylsilane) and iodomethyl(dimethylphenylsilane), leading to amino acids **13** and **14**, respectively (Scheme 4).

## Conclusion

In conclusion, we compared the diastereoselectivity induced by chiral Schiff bases involving different mechanisms. On the one hand, we used *p*-tolylsulfinamide Schiff base as an electrophile, which was subjected to a nucleophilic attack. On the other hand, the Schiff base derived from hydroxypinanone was used as equivalent nucleophile of the glycine to stabilize an enolate. According to our results, the use of (+)-(1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone as chiral inductor with electronegative properties permitted to develop a new diastereoselective synthesis of Fmoc-(*L*)-TMSAla-OH in 58 % overall yield in 5 steps with 98 % ee. Two other silylated amino acids were obtained applying the same strategy. These silylated amino acids could be incorporated into bioactive molecules to bring lipophily and potentially enzymatic resistance.

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