Tetrahedron xxx (2014) 1–8

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of protected α-alkyl lanthionine derivatives

Thibaut Denoël, Astrid Zervosen *, Christian Lemaire, Alain Plenevaux, André Luxen

Cyclotron Research Center, University of Liège, B30 Sart-Tilman, 4000 Liège, Belgium

ARTICLE INFO

Article history:
Received 11 March 2014
Received in revised form 30 April 2014
Accepted 2 May 2014
Available online xxx

Keywords:
Lanthionine
Sulfamidate
α-Alkyl amino acid
Peptidoglycan
Protected amino acid

ABSTRACT

Protected α-alkyl lanthionine derivatives were synthesized in five steps starting from a known phenyl-oxazoline precursor. This approach involved the synthesis of a family of substituted cyclic sulfamidates and their regioselective opening by nucleophilic attack with a protected cysteine. This efficient multistep strategy affords various α-alkylated lanthionine derivatives in high yields.

1. Introduction

Lanthionine is a non-proteinogenic diamino diacid, the mono-sulfur analogue of diaminopimelic acid (Fig. 1). Since its discovery by Horn[1] and synthesis by Du Vigneaud,[2] it has been found to play the role of crosslinker in the peptidoglycan of several *Fusobacterium* species.[3] It has also become an important fragment in a family of polypeptidic antibiotics known as lantibiotics.[4]

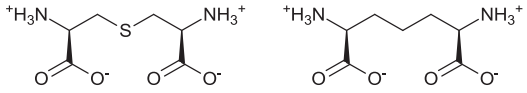


Fig. 1. *meso*-Lanthionine and *meso*-diaminopimelic acid.

The aim of this work was to synthesize protected lanthionines **11a**–**d** (Scheme 3) bearing an α-alkyl group useful for the preparation of peptidoglycan building block analogues. Although several methods are known to produce protected lanthionines,[4–8] most are plagued with various side reactions or defects. In particular, racemization due to β-elimination[9] and subsequent Michael addition,[10–12] or regioisomerization through formation of an aziridine intermediate[13,14] have been reported. Other competing side reactions are thioester formation through *O*-acyl fission,[15,16] or homocoupling after disulfide exchange.[17,18] In addition, sluggish reaction[14] or lack of reactivity due to a sterically hindered α-carbon[16] have also been described. In contrast to the natural β-methyl lanthionine, the α-methyl lanthionine has been much less covered in the literature.[16] A synthetic study aiming to produce labionin, an α-alkyl lanthionine, was described but did not include the crucial thioether functionalization step.[19] Nevertheless, these interesting molecules have been used in several fields of research, such as lantibiotic chemistry[4,20] and lanthionine enkephalin[16,21] analogue synthesis.

2. Results and discussion

2.1. Retrosynthetic analysis

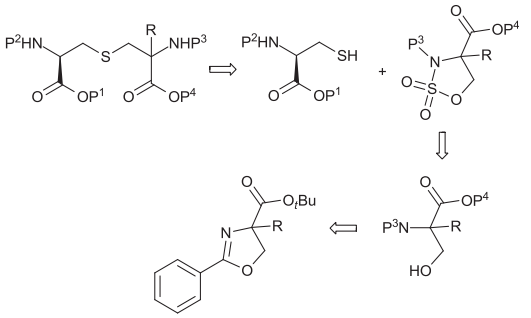
Retrosynthesis hinted that a lanthionine could result from the S_N2 opening of a suitable cyclic sulfamidate precursor with a protected cysteine.[7,22] The sterically crowded sulfamidate can be derived from an α-alkylated serine.[7] This can be obtained from a 4-alkylated oxazoline[23] by reductive[24] opening of the ring (Scheme 1).

2.2. Preparation of precursor

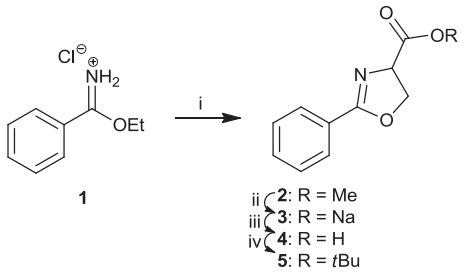
An alternative route to the known[23] 4-unsubstituted phenyl-oxazoline precursor **5** was devised. This compound was obtained in a multigram quantity as follows: first, serine methyl ester hydrochloride[25] was reacted with ethyl benzimidate **1** (Scheme 2). The previously published procedure[26] used CH_2Cl_2 and NEt_3, which gave rise to undesired diketopiperazine by-product. In order to circumvent this problem the reaction was conducted with benzimidate freebase in MeOH. The benzimidate **1** has previously been

* Corresponding author. Tel.: +32 4 366 3383; fax: +32 4 366 2946; e-mail address: azervosen@ulg.ac.be (A. Zervosen).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.05.004



Scheme 1. Retrosynthetic approach to producing α-alkylated lanthionine derivatives. P^1=Me, P^2=Boc, P^3=Bn, P^4=^{t}Bu.



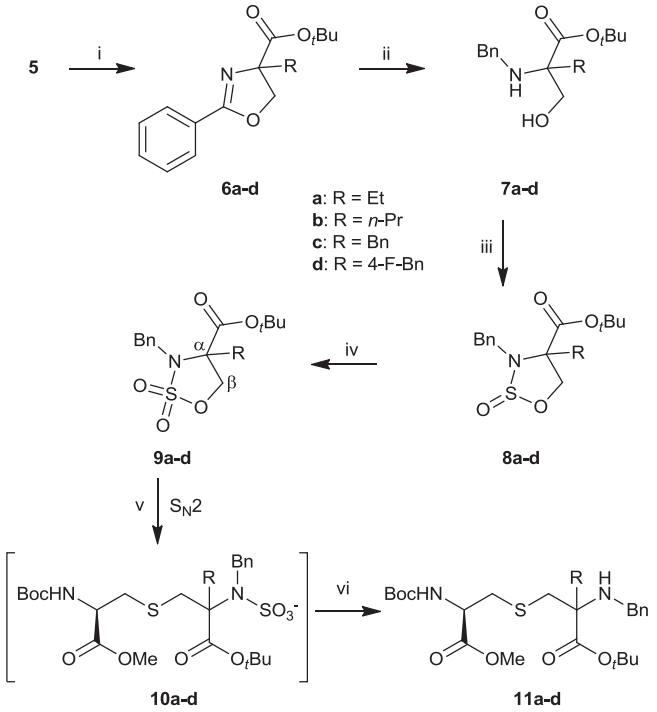
Scheme 2. Synthesis of the oxazoline precursor. Reagents and conditions: (i) (1) Na_2CO_3, CH_2Cl_2, (2) Ser Me ester*HCl, MeOH, reflux, 2 h, 84%; (ii) aq NaOH, MeOH, acetone, rt, 1 h, 92%; (iii) aq HCl, 0 °C, 1 h, 87%; (iv) Boc_2O (2 equiv), DMAP (10 mol %), 1:1 CH_2Cl_2/*tert*-BuOH, reflux, 1 h, 75%.

prepared using the Pinner reaction of EtOH with benzonitrile.[27] In place of gassing the reaction mixture with HCl (g) we chose a more practical approach, involving the use of AcCl and EtOH to generate anhydrous HCl in situ. The methyl ester of oxazoline **2** was then hydrolyzed following the literature method.[28] The sodium salt **3** was converted to oxazolinic acid **4** by using HCl at 0 °C according to Fry's procedure.[28] The crude acid was dried and reacted with Boc_2O and DMAP by applying the protocol reported by Takeda.[29] The poor solubility of the acid **4** was increased in a *tert*-BuOH/CH_2Cl_2 solvent mixture. Other methods, such as DCC/*tert*-BuOH or *tert*-butyl trichloroacetimidate led to extensive side reactions and produced **5** in very low yields. Finally, after five steps from serine and a recrystallization in hexanes **5** was obtained on a multigram scale with a global yield of 50% (Scheme 2).

2.3. *N*-Benzyl lanthionines synthesis from 5

Using the oxazoline precursor **5** various racemic 4-alkylated oxazolines **6a**–**d** were synthesized[23,30] (Scheme 3). In our first approach, tetrabutylammonium bromide (TBAB) was employed as an achiral phase transfer catalyst (PTC) along with solid KOH as a base.[30] Four electrophiles were used: two alkyl bromides (EtBr, *n*-PrBr) and two benzyl bromides (BnBr, 4-F–BnBr). Good yields (79–90%) of the racemic alkylated oxazolines **6a**–**d** (Scheme 3: step i) were obtained.

Next, the reductive[24] opening of the racemic oxazolines was performed. Compounds **6a**–**d** were protonated in acetic acid and reduced at rt with $NaBH_3CN$. Under these mild reaction conditions the cleavage of both the *tert*-butyl ester and the *N*-benzyl groups could be avoided, which is a significant advantage over the harsh hydrolysis conditions (6 N HCl) reported in the literature.[23] Using this method four suitably protected racemic alkylated serines **7a**–**d** were obtained in near quantitative yields (94–98%, Scheme 3: step ii). Transformation of the *N*-benzyl protected serines **7a**–**d** into their respective cyclic sulfamidates[22] was then performed in two steps (Scheme 3: steps iii–iv). Amino alcohols **7a**–**d** were reacted



Scheme 3. Synthesis of α-alkylated lanthionines. Reagents and conditions: (i) RX, KOH (5 equiv), TBAB (10 mol %), 1:1 toluene/CH_2Cl_2; (ii) $NaBH_3CN$ (6 equiv), AcOH, rt, 16 h; (iii) $SOCl_2$, imidazole, NEt_3, −10 °C→rt, 2 h; (iv) $NaIO_4$ (1.2 equiv), $RuCl_3$ (1 mol %), aq CH_3CN, rt, 4 h; (v) Boc L-cysteine Me ester (1.1 equiv), DBU (1.1 equiv), CH_3CN, rt, 1 h; (vi) 10% aq NaH_2PO_4, EtOAc, 50 °C, 2 h.

with thionyl chloride and imidazole[31] to create the cyclic sulfamidites **8a**–**d**. These were isolated as a mixture of diastereomers in 92–99% yield (step iii). The crude products were then oxidized[22] by catalytic $RuCl_3 \cdot xH_2O$ and $NaIO_4$ to give the corresponding sulfamidates **9a**–**d** with good to excellent yields (77–99%, step iv).

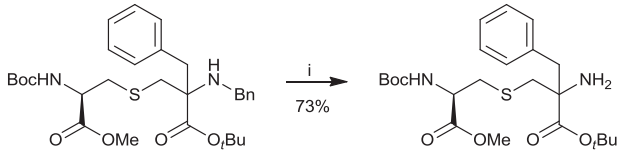
Subsequently, the sulfamidates **9a**–**d** were used in a coupling reaction[22] with the methyl ester of Boc-L-cysteine in CH_3CN and DBU as a base (Scheme 3: steps v). The *N*-sulfamate intermediates **10a**–**d** were subsequently hydrolyzed[32] at 50 °C for 2 h in aqueous 10% NaH_2PO_4 (Scheme 3: steps vi). Interestingly, the cleavage of the sulfamate group failed when the hydrolysis was carried out at rt.[32] It is noteworthy that despite[16] the presence of a sterically hindered α-carbon in compounds **9a**–**d**, the S_N2 reaction at C_β occurred remarkably well, providing protected lanthionines **11a**–**d** in excellent yields (90–99%). The outstanding reactivity[22,33] of cyclic sulfamidates with thiolate nucleophiles in basic conditions is hereby confirmed. It should be noted that an alternative mechanism based on SO_2 extrusion followed by aziridine formation was observed under neutral conditions for isomeric sulfamidates.[34] However, under our basic conditions, the formation of *N*-sulfamate products **10a**–**d** suggests the probable mechanism to be S_N2.

2.4. Debenzylation of 11c

It is known that the deprotection of an *N*-benzyl can be challenging in the presence of a sulfide group.[35] As an example, the debenzylation of the nitrogen atom of lanthionine **11c** (Scheme 4) was explored. Indeed, our initial attempts to deprotect the *N*-benzyl group of the chromatographically purified α-benzyl lanthionine **11c** by hydrogenation with Pd/C as a catalyst were unsuccessful, despite testing several reaction conditions. Furthermore, partially irreproducible *N*-debenzylation was observed when $Pd(OH)_2/C$ (Pearlman's catalyst) was substituted for Pd/C.[35] Fortunately, the use of the more active Pd black in acidic aqueous MeOH at 70 °C[36]

Please cite this article in press as: Denoël, T.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.05.004

(9/1/0.3: MeOH/H_2O/AcOH) gave the *N*-debenzylated protected α-benzyl lanthionine **12** in a good and reproducible yield (Scheme 4).



11c 12

Scheme 4. Hydrogenation of the *N*-benzyl group of **11c**. Reagents and conditions: (i) H_2 (7 bars), Pd black (25% w/w), 9/1/0.3: MeOH/H_2O/AcOH, 70 °C, 16 h.

2.5. Enantioselective alkylation of 5

By using an optically pure PTC developed by the Maruoka's group (Fig. 2) compounds **6a**–**d** were obtained enantioselectively by Jew.[23] This approach was also used for the synthesis of the (*R*)-4-Bn analogue **6c** (entry 1, Table 1). In order to reduce the amount of the electrophilic agent required, the synthesis of which can be difficult, various reaction conditions were investigated. It was found that enantiomeric purity decreased with a smaller excess of electrophile (entries 1 and 2, Table 1). In contrast, higher catalyst loading (entries 2–4), or a decrease in temperature (entries 4–7), increased the enantiomeric excess (ee). At a lower temperature (−10 °C) and at a high catalyst loading (10 mol %) we obtained an excellent ee (97%) by using only 1.5 molar equivalent of the electrophile (entry 7). The high price of the catalyst and high loading was a drawback of this alkylation approach.

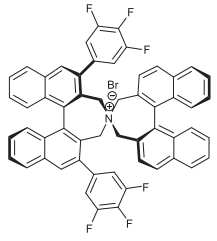


Fig. 2. Maruoka's chiral PTC (*R*,*R*)-3,4,5-trifluorophenyl–NAS bromide used for the alkylation of **5** in Jew's paper[23] and in Table 1 of this work.

Table 1
Enantioselective alkylation of **5** with BnBr to (*R*)-**6c**[a]

Entry	BnBr (equiv)	PTC (mol %)	*T* (°C)	ee (%)	Yield (%)
1	5	2.5	−5	97	85
2	3	2.5	−5	77	75
3	3	5	−5	85	77
4	1.5	10	5	90	82
5	1.5	10	0	92	81
6	1.5	10	−5	94	80
7	1.5	10	−10	97	84

[a] Reaction conditions: **5**, toluene, BnBr, Maruoka's chiral PTC, KOH (5 equiv), 1200 rpm stir under N_2 at the chosen temperature until completion (HPLC).

3. Conclusion

In this paper, a straightforward synthesis of various protected α-alkyl lanthionines **11a**–**d** was developed. This synthetic scheme started with the disclosure of a multigram preparation of the known oxazoline precursor **5**. Alkylation of **5** gave the compounds **6a**–**d** in good yields (79–90%) by using TBAB as an achiral PTC. A smooth reductive cleavage provided protected serines **7a**–**d** in excellent yields (94–98%). Cyclization with $SOCl_2$ and oxidation gave sulfamidates **9a**–**d** in 75–92% yields in two steps. An efficient S_N2 reaction on the cyclic sulfamidates was highly successful, despite the sterically crowded α-carbon, in producing protected lanthionines **11a**–**d** in excellent yields (90–99%). The challenging debenzylation of **11c** was overcome by means of Pd black in warm acidic aqueous MeOH. Finally, for the enantioselective alkylation of **5**, an enantiomeric excess of 97% was obtained with fewer equivalents (1.5 vs 5) of the electrophilic agent. These debenzylated products are excellent starting blocks for peptide synthesis.

4. Experimental section

4.1. Reagents

All solvents and chemicals were of analytical grade and used without further purification. CH_3CN was dried on 3 Å molecular sieves. TLC: Macherey-Nagel Polygram SIL G/UV_{254} using UV light or a stain anisaldehyde/sulfuric acid/AcOH/EtOH: 1/1/0.04/18:v/v/v/v. CC: silica gel Acros, 0.060–0.200 mm, 60 Å. HPLC: Waters system (600 pump, 717 autosampler, 996 PDA detector) with a column XTerra RP18 (4.6×150 mm; 3.5 μm). Chiral HPLC: Chiracel OD-H column (Daicel, 150 mm×4 mm, 5 μm); mobile phase: *n*-Hex/*i*-PrOH:98/2; 0.8 mL/min; 37 °C. Mp: Büchi Melting Point B-545 calibrated on three points (83, 136 and 237 °C). ^1H and ^{13}C NMR: Bruker Avance DRX 400 (^1H at 400 MHz and ^{13}C at 101 MHz) and Bruker AM 250 (^1H at 250 MHz and ^{13}C at 63 MHz) δ in parts per million relative to ^{13}C or the residual proton signal of deuterated solvent, *T*=298 K. MS: Thermoquest Finnigan TSQ 7000 mass spectrometer operating in full scan MS mode with an ESI source. HRMS: ESI-FT-ICR mass spectrometer (SolariX, Bruker) in positive ion mode. For some samples 1 mM LiI was used for adducts. External calibration was done over the range of *m*/*z* 150 to 700 and mean residual error obtained was <1 ppm. Elemental analysis: Flash EA 1112 Series (Thermo Electron Corporation).

4.2. Ethyl benzimidate 1

AcCl (75 mL, 1.05 mol) was added dropwise over 30 min at 0 °C to a solution of dry EtOH (124 mL, 2.1 mol) in dry Et_2O (200 mL) under nitrogen and protected from moisture. The mixture was left to stir for 15 min and benzonitrile (103 g, 1 mol) was added. The solution was poured into a brown glass reagent bottle, which was closed and left at 2 °C for one month. The bottle was shattered and the crystals were suspended in Et_2O and decanted from glass fragments. The product was filtered and dried in vacuo to constant weight to give the *title compound* (101 g, 54%) as colourless crystals. Mp 123–124 °C (lit.[37] 122–123 °C); ^1H NMR (250 MHz, MeOD) δ_H 8.13–8.03 (m, 2H, Ar–H), 7.84–7.76 (m, 1H, Ar–H), 7.71–7.58 (m, 2H, Ar–H), 4.69 (q, *J*=7.0 Hz, 2H, OCH_2), 1.62 (t, *J*=7.0 Hz, 3H, CH_3); ^{13}C NMR (63 MHz, MeOD) δ_C 174.24 (CN), 136.82 (Ar–C), 130.50 (Ar–C), 130.07 (Ar–C), 127.13 (Ar–C), 71.40 (CH_2), 13.91 (CH_3); *m*/*z* (ESI) 150 $[MH]^+$.

4.3. Methyl 2-phenyloxazoline-4-carboxylate 2

The protocol of Huang[26] was modified as follows: The freebase of ethyl benzimidate **1** (37.25 g, 250 mmol), generated from the salt by basification with saturated aqueous Na_2CO_3 and extraction in CH_2Cl_2, was dissolved in 250 mL of MeOH. To this solution serine methyl ester hydrochloride (39 g, 250 mmol) was added and this was heated under reflux for 2 h. The mixture was cooled and diluted with acetone (250 mL). NH_4Cl was filtered and washed with acetone. The solvents were evaporated, the residue was dissolved in CH_2Cl_2 (50 mL) and Et_2O (200 mL) and filtered again. The organic layer was washed twice with water, with brine and dried on $MgSO_4$. After filtration and removal of the solvents in vacuo, the *title*

compound (43 g, 84%) was obtained as a pale pink oil. NMR data were in agreement with the literature;[38] *m*/*z* (ESI) 206 $[MH]^+$.

4.4. Sodium 2-phenyloxazoline-4-carboxylate 3

The synthesis was done by following the protocol described by Fry.[28] A cold solution of NaOH (32 g, 800 mmol) in water (200 mL) was added to the methyl ester **2** (152 g, 741 mmol). The mixture was stirred vigorously with intermittent cooling in an ice bath for 20 min. The suspension was diluted with MeOH (200 mL) and left to stir for 1 h. The suspension was diluted with acetone (2 L) and left at 2 °C for 2 h. The product was filtered on Büchner and washed with acetone (1 L) then dried in vacuo to constant weight. The *title compound* (169 g, 92%) was obtained as pink crystals. ^{1}H NMR (250 MHz, MeOD) δ_H 8.04–7.90 (m, 2H, Ar–H), 7.58–7.36 (m, 3H, Ar–H), 4.76 (dd, *J*=10.4, 8.6 Hz, 1H, H-α), 4.65 (dd, *J*=10.4, 7.9 Hz, 1H, CH_2), 4.53 (dd, *J*=8.6, 7.9 Hz, 1H, CH_2); ^{13}C NMR (63 MHz, MeOD) δ_C 178.83 (CO), 166.68 (CN), 132.73 (Ar–C), 129.43 (Ar–C), 129.41 (Ar–C), 128.71 (Ar–C), 72.54 (C-β), 71.94 (C-α); *m*/*z* (ESI) 190 $[M]^-$.

4.5. 2-Phenyloxazoline-4-carboxylic acid 4

The synthesis was done by following the protocol described by Fry.[28] The sodium salt **3** (169 g, 679 mmol) was suspended in water (1.2 L) and cooled to 0 °C. After cooling to 0 °C, 3 N aqueous HCl solution (220 mL), was added dropwise until pH<3 to precipitate the acid. The product was filtered on Büchner and washed with cold water (500 mL) then dried by repeated suspension in CH_3CN and evaporation in vacuo to constant weight. The *title compound* (112.8 g, 87%) was obtained as pink crystals that were pure enough for the next step. Mp 156–157 °C; ^{1}H NMR (250 MHz, DMSO) δ_H 7.95–7.82 (m, 2H, Ar–H), 7.58–7.42 (m, 3H, Ar–H), 4.88 (t, *J*=9.1 Hz, 1H, H-α), 4.57 (d, *J*=9.1 Hz, 2H, CH_2); ^{13}C NMR (63 MHz, DMSO) δ_C 172.61 (CO), 164.26 (CN), 131.86 (Ar–C), 128.69 (Ar–C), 128.05 (Ar–C), 127.00 (Ar–C), 69.92 (C-β), 68.60 (C-α); *m*/*z* (ESI) 190 $[M]^-$.

4.6. *tert*-Butyl 2-phenyloxazoline-4-carboxylate 5

The esterification was done as proposed by Takeda[29] with special emphasis on the poor solubility of the acid **4**. Compound **4** (19.1 g, 100 mmol), DMAP (2.44 g, 20 mol %), CH_2Cl_2 (125 mL) and *t*-BuOH (125 mL) were placed under nitrogen in a 500 mL round bottom flask equipped with an efficient condenser. The solution was heated at reflux and Boc_2O (43.6 g, 200 mmol) was added via syringe in two portions. *CAUTION*: This step produces substantial gas evolution. The mixture was then heated for 1 h and the solvents were evaporated. The yellow oil was dissolved in CH_2Cl_2 (200 mL) and then filtered through 40 g of silica. The solvent was removed in vacuo, the oil was dissolved in 1:9 (Et_2O/hexanes) and filtered through 40 g of silica then eluted with the same mixture (500 mL). The yellow oil (25 g) that remained after evaporation of the solvents was crystallized from hexanes to give the *title compound* (18.5 g, 75%) as off-white crystals. Mp 42–44 °C (lit.[30] 42–45 °C); Anal. (C,H,N) $C_{14}H_{17}NO_3$; NMR data were in agreement with the literature;[30] *m*/*z* (ESI) 248 $[MH]^+$.

4.7. General method for the preparation of 4-alkyl oxazolines 6a–d

The protocol of Jew[23] was modified as follows: Phenyloxazoline **5** (4.94 g, 20 mmol) was dissolved in toluene (10 mL) and CH_2Cl_2 (10 mL) and the alkyl bromide and TBAB (644 mg, 2 mmol, 10 mol %) were added. The flask was cooled to 0 °C and flushed with nitrogen then finely powdered KOH (6.6 g, 85%, 100 mmol) was added. The flask was capped and the mixture was vigorously stirred at rt until the end of the reaction, which was monitored by TLC (1:4 EtOAc/hexanes, anisaldehyde stain). The suspension was diluted with CH_2Cl_2 (50 mL) and then filtered. The organic layer was washed with water and the solvent was evaporated. The residue was flash chromatographed on 40 g of silica first with hexanes to remove excess electrophile then with 1:4 (EtOAc/hexanes) and the solvent was removed in vacuo to give the product.

4.8. *tert*-Butyl 4-ethyl-2-phenyloxazoline-4-carboxylate 6a (rac)

Following the general method for the preparation of 4-alkyl oxazolines and using EtBr (15 mL, 200 mmol) as an electrophile, the *title compound* was obtained as a pale yellow oil (4.7 g, 85%). NMR data were in agreement with the literature;[30] *m*/*z* (ESI) 276 $[MH]^+$.

4.9. *tert*-Butyl 2-phenyl-4-propyloxazoline-4-carboxylate 6b (rac)

Following the general method for the preparation of 4-alkyl oxazolines and using *n*-PrBr (18 mL, 200 mmol) as an electrophile, the *title compound* was obtained as a pale yellow oil (4.7 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.20–7.75 (m, 2H, Ar–H), 7.64–7.28 (m, 3H, Ar–H), 4.70 (d, *J*=8.8 Hz, 1H, CH_2O), 4.21 (d, *J*=8.8 Hz, 1H, CH_2O), 2.03–1.77 (m, 2H, CH_2), 1.49 (s, 9H, $C(CH_3)_3$), 1.42–1.22 (m, 2H, CH_2CH_3), 0.95 (t, *J*=7.3 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 172.17 (CO), 164.12 (CN), 131.59 (Ar–C), 128.66 (Ar–C), 128.32 (Ar–C), 127.61 (Ar–C), 81.84 ($C(CH_3)_3$), 78.64 (C-α), 73.89 (CH_2O), 40.45 (CH_2), 28.09 ($C(CH_3)_3$), 17.22 (CH_2CH_3), 14.36 (CH_3); *m*/*z* (ESI) 290 $[MH]^+$.

4.10. *tert*-Butyl 4-benzyl-2-phenyloxazoline-4-carboxylate 6c (rac)

Following the general method for the preparation of 4-alkyl oxazolines and using BnBr (7.1 mL, 60 mmol) as an electrophile, the *title compound* was obtained as a pale yellow solid (6.1 g, 90%). This can be recrystallized from 1:4 (Et_2O/hexanes) to give a colourless solid (4.9 g, 73%). Mp 68–69 °C; NMR data were in agreement with the literature;[30] *m*/*z* (ESI) 338 $[MH]^+$.

4.11. *tert*-Butyl 4-(4-fluorobenzyl)-2-phenyloxazoline-4-carboxylate 6d (rac)

Following the general method for the preparation of 4-alkyl oxazolines and using 4-F–BnBr (7.5 mL, 60 mmol) as an electrophile, the *title compound* was obtained as a pale yellow solid (5.6 g, 79%). This can be recrystallized from 1:4 (Et_2O/hexanes) to give a colourless solid (4.1 g, 58%). Mp 69–71 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 8.09–7.97 (m, 2H, Ar–H), 7.64–7.40 (m, 3H, Ar–H), 7.40–7.24 (m, 2H, Ar–H), 7.08–6.94 (m, 2H, Ar–H), 4.74 (d, *J*=8.9 Hz, 1H, CH_2O), 4.36 (d, *J*=8.9 Hz, 1H, CH_2O), 3.34 (d, *J*=13.9 Hz, 1H, CH_2Ar), 3.27 (d, *J*=13.9 Hz, 1H, CH_2Ar), 1.56 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 171.46 (CO), 164.79 (CN), 162.03 (d, $^1J_{C-F}$=245.1 Hz, Ar–C), 132.01 (d, $^3J_{C-F}$=7.9 Hz, Ar–C), 131.70 (Ar–C), 131.52 (d, $^4J_{C-F}$=3.3 Hz, Ar–C), 128.60 (Ar–C), 128.34 (Ar–C), 127.38 (Ar–C), 115.04 (d, $^2J_{C-F}$=21.1 Hz, Ar–C), 82.33 ($C(CH_3)_3$), 78.88 (d, $^6J_{C-F}$=1.2 Hz, C-α), 73.08 (CH_2O), 42.50 (CH_2Ar), 28.04 ($C(CH_3)_3$); *m*/*z* (ESI) 356 $[MH]^+$.

4.12. General method for the reduction of oxazolines 7a–d

The protocol of Reddy[24] was modified as follows: A freshly prepared solution of $NaBH_3CN$ (3.8 g, 60 mmol) in AcOH (60 mL), cooled to 0 °C, was added to the oxazoline **6a–d** (10 mmol) and the

mixture was stirred at rt for 16 h. The solvent was removed in vacuo and the residue was partitioned between EtOAc and an excess of a saturated Na_2CO_3 solution. The pH was adjusted to >12 with 10% NaOH and the organic layer was decanted. The basic aqueous layer was extracted two more times with EtOAc and the pooled fractions were washed twice with brine. The solution was dried on $MgSO_4$, was filtered and the solvent was removed in vacuo to give the product.

4.13. *tert*-Butyl 2-(benzylamino)-2-(hydroxymethyl)butanoate 7a (rac)

Following the general method for the reduction of oxazolines and using **6a** (2.75 g, 10 mmol), the *title compound* was obtained as a colourless solid (2.66 g, 95%). Mp 52–53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.48–7.05 (m, 5H, Ar–H), 3.73 (d, *J*=11.0 Hz, 1H, CH_2O), 3.65 (d, *J*=12.0 Hz, 1H, CH_2Ph), 3.59 (d, *J*=12.0 Hz, 1H, CH_2Ph), 3.58 (d, *J*=11.0 Hz, 1H, CH_2O), 2.30 (b, 2H, NH, OH), 1.75–1.56 (m, 2H, CH_2), 1.49 (s, 9H, $C(CH_3)_3$), 0.88 (t, *J*=7.5 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 173.53 (CO), 140.05 (Ar–C), 128.66 (Ar–C), 128.31 (Ar–C), 127.35 (Ar–C), 81.78 ($C(CH_3)_3$), 66.70 (C-α), 61.85 (CH_2O), 46.90 (CH_2Ph), 28.21 ($C(CH_3)_3$), 26.38 (CH_2), 7.97 (CH_3); *m*/*z* (ESI) 280 $[MH]^+$.

4.14. *tert*-Butyl 2-(benzylamino)-2-(hydroxymethyl)pentanoate 7b (rac)

Following the general method for the reduction of oxazolines and using **6b** (2.89 g, 10 mmol), the *title compound* was obtained as a colourless solid (2.76 g, 94%). Mp 44–46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37–7.29 (m, 4H, Ar–H), 7.29–7.20 (m, 1H, Ar–H), 3.73 (d, *J*=11.0 Hz, 1H, CH_2O), 3.65 (d, *J*=12.0 Hz, 1H, CH_2Ph), 3.60 (d, *J*=12.0 Hz, 1H, CH_2Ph), 3.57 (d, *J*=11.0 Hz, 1H, CH_2O), 2.31 (br, 2H, NH, OH), 1.70–1.51 (m, 2H, CH_2), 1.49 (s, 9H, $C(CH_3)_3$), 1.35–1.23 (m, 2H, CH_2CH_3), 0.92 (t, *J*=7.3 Hz, 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 173.60 (CO), 140.01 (Ar–C), 128.63 (Ar–C), 128.29 (Ar–C), 127.32 (Ar–C), 81.76 ($C(CH_3)_3$), 66.32 (C-α), 62.26 (CH_2O), 46.93 (CH_2Ph), 35.92 (CH_2), 28.20 ($C(CH_3)_3$), 16.98 (CH_2CH_3), 14.51 (CH_3); *m*/*z* (ESI) 294 $[MH]^+$.

4.15. *tert*-Butyl 2-benzyl-2-(benzylamino)-3-hydroxypropanoate 7c (rac)

Following the general method for the reduction of oxazolines and using **6c** (3.37 g, 10 mmol), the *title compound* was obtained as a colourless solid (3.31 g, 97%). Mp 69–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.52–7.25 (m, 10H, Ar–H), 3.87 (d, *J*=11.4 Hz, 1H, CH_2O), 3.86 (d, *J*=12.0 Hz, 1H, CH_2N), 3.80 (d, *J*=12.0 Hz, 1H, CH_2N), 3.74 (d, *J*=11.4 Hz, 1H, CH_2O), 3.15 (d, *J*=13.4 Hz, 1H, CH_2Ph), 3.04 (d, *J*=13.4 Hz, 1H, CH_2Ph), 2.45 (br, 2H, NH, OH), 1.54 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 173.60 (CO), 140.01 (Ar–C), 128.63 (Ar–C), 128.29 (Ar–C), 127.32 (Ar–C), 81.76 ($C(CH_3)_3$), 66.32 (C-α), 62.26 (CH_2O), 46.93 (CH_2Ph), 35.92 (CH_2), 28.20 ($C(CH_3)_3$), 16.98 (CH_2CH_3), 14.51 (CH_3); *m*/*z* (ESI) 342 $[MH]^+$.

4.16. *tert*-Butyl 2-(benzylamino)-2-(4-fluorobenzyl)-3-hydroxy propanoate 7d (rac)

Following the general method for the reduction of oxazolines and using **6d** (3.55 g, 10 mmol), the *title compound* was obtained as a colourless solid (3.52 g, 98%). Mp 67–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38–7.29 (m, 4H, Ar–H), 7.29–7.23 (m, 1H, Ar–H), 7.21–7.15 (m, 2H, Ar–H), 6.99–6.91 (m, 2H, Ar–H), 3.71 (d, *J*=11.5 Hz, 1H, CH_2O), 3.71 (d, *J*=12.0 Hz, 1H, CH_2Ph), 3.66 (d, *J*=12.0 Hz, 1H, CH_2Ph), 3.57 (d, *J*=11.5 Hz, 1H, CH_2O), 2.99 (d, *J*=13.5 Hz, 1H, CH_2Ar), 2.87 (d, *J*=13.5 Hz, 1H, CH_2Ar), 1.42 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 172.78 (CO), 162.09 (d, $^1J_{C-F}$=245.2 Hz, Ar–C), 139.72 (Ar–C), 131.98 (d, $^3J_{C-F}$=7.9 Hz, Ar–C), 131.39 (d, $^4J_{C-F}$=3.3 Hz, Ar–C), 128.79 (Ar–C), 128.28 (Ar–C), 127.54 (Ar–C), 115.15 (d, $^2J_{C-F}$=21.2 Hz, Ar–C), 82.43 ($C(CH_3)_3$), 67.16 (d, $^6J_{C-F}$=1.2 Hz, C-α), 60.67 (CH_2O), 47.59 (CH_2Ph), 39.55 (CH_2Ar), 28.27 ($C(CH_3)_3$); *m*/*z* (ESI) 360 $[MH]^+$.

4.17. General method for the formation of sulfamidites 8a–d

The protocol of Dolence[31] was modified as follows: In a dry round bottom flask under nitrogen *N*-benzyl serine **7a**–**d** (5 mmol), imidazole (1.36 g, 20 mmol), NEt_3 (2.1 mL, 15 mmol) and CH_2Cl_2 (25 mL) were added. The mixture was cooled to −10 °C and then with stirring $SOCl_2$ (0.54 mL, 7.5 mmol) was added dropwise via syringe. The solution was kept for 30 min at −10 °C then allowed to return to rt during 2 h. The mixture was diluted with water (10 mL) and then with 10% aqueous $NaHSO_4$ (30 mL). The organic layer was separated and the aqueous layer was extracted once more with CH_2Cl_2. The pooled fractions were washed four times with water and azeotropically dried by evaporation with CH_3CN in vacuo to give the product.

4.18. *tert*-Butyl 3-benzyl-4-ethyl-2-oxo-1,2,3-oxathiazolidine-4-carboxylate 8a

Following the general method for the formation of sulfamidites and using **7a** (1.40 g, 5 mmol), the *title compound* was obtained as a yellow oil (1.49 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47–7.26 (m, 5H, Ar–H), 5.35 (d, *J*=8.3 Hz, 0.5H, CH_2O), 5.01 (d, *J*=9.0 Hz, 0.5H, CH_2O), 4.71 (d, *J*=9.0 Hz, 0.5H, CH_2O), 4.61 (d, *J*=14.2 Hz, 0.5H, CH_2Ph), 4.47 (d, *J*=14.9 Hz, 0.5H, CH_2Ph), 4.41 (d, *J*=14.9 Hz, 0.5H, CH_2Ph), 4.26 (d, *J*=14.2 Hz, 0.5H, CH_2Ph), 4.14 (d, *J*=8.3 Hz, 0.5H, CH_2O), 2.19–2.01 (m, 1H, CH_2), 1.92–1.81 (m, 0.5H, CH_2), 1.78–1.63 (m, 0.5H, CH_2), 1.53 (s, 4.5H, $C(CH_3)_3$), 1.49 (s, 4.5H, $C(CH_3)_3$), 0.93 (t, *J*=7.5 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.05 (0.5C, CO), 169.98 (0.5C, CO), 137.22 (0.5C, Ar–C), 137.11 (0.5C, Ar–C), 128.92 (Ar–C), 128.83 (Ar–C), 128.72 (Ar–C), 128.66 (Ar–C), 127.97 (Ar–C), 83.18 (0.5C, $C(CH_3)_3$), 82.88 (0.5C, $C(CH_3)_3$), 77.81 (0.5C, CH_2O), 75.60 (0.5C, CH_2O), 71.55 (0.5C, C-α), 69.51 (0.5C, C-α), 46.26 (0.5C, CH_2Ph), 46.20 (0.5C, CH_2Ph), 28.04 (1.5C, $C(CH_3)_3$), 28.00 (1.5C, $C(CH_3)_3$), 27.51 (0.5C, CH_2), 27.07 (0.5C, CH_2), 9.28 (0.5C, CH_3), 8.51 (0.5C, CH_3).

4.19. *tert*-Butyl 3-benzyl-2-oxo-4-propyl-1,2,3-oxathiazolidine-4-carboxylate 8b

Following the general method for the formation of sulfamidites and using **7b** (1.46 g, 5 mmol), the *title compound* was obtained as a yellow oil (1.59 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50–7.27 (m, 5H, Ar–H), 5.34 (d, *J*=8.2 Hz, 0.5H, CH_2O), 5.01 (d, *J*=9.0 Hz, 0.5H, CH_2O), 4.71 (d, *J*=9.0 Hz, 0.5H, CH_2O), 4.61 (d, *J*=14.2 Hz, 0.5H, CH_2Ph), 4.47 (d, *J*=15.0 Hz, 0.5H, CH_2Ph), 4.42 (d, *J*=15.0 Hz, 0.5H, CH_2Ph), 4.26 (d, *J*=14.2 Hz, 0.5H, CH_2Ph), 4.12 (d, *J*=8.2 Hz, 0.5H, CH_2O), 2.14–1.96 (m, 1H, CH_2), 1.82–1.70 (m, 0.5H, CH_2), 1.67–1.58 (m, 0.5H, CH_2), 1.52 (s, 4.5H, $C(CH_3)_3$), 1.48 (s, 4.5H, $C(CH_3)_3$), 1.36–1.23 (m, 2H, CH_2CH_3), 0.94 (t, *J*=7.3 Hz, 1.5H, CH_3), 0.88 (t, *J*=7.3 Hz, 1.5H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.12 (0.5C, CO), 170.01 (0.5C, CO), 137.20 (0.5C, Ar–C), 137.07 (0.5C, Ar–C), 128.92 (Ar–C), 128.83 (Ar–C), 128.71 (Ar–C), 128.65 (Ar–C), 127.97 (Ar–C), 83.15 (0.5C, $C(CH_3)_3$), 82.85 (0.5C, $C(CH_3)_3$), 78.08 (0.5C, CH_2O), 75.73 (0.5C, CH_2O), 71.01 (0.5C, C-α), 68.96 (0.5C, C-α), 46.31 (0.5C, CH_2Ph), 46.21 (0.5C, CH_2Ph), 36.75 (0.5C, CH_2), 36.20 (0.5C, CH_2), 28.04 (1.5C, $C(CH_3)_3$), 27.98 (1.5C, $C(CH_3)_3$), 18.40 (0.5C, CH_2CH_3), 17.67 (0.5C, CH_2CH_3), 14.47 (0.5C, CH_3), 14.42 (0.5C, CH_3).

Please cite this article in press as: Denoël, T.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.05.004

4.20. *tert*-Butyl 3,4-dibenzyl-2-oxo-1,2,3-oxathiazolidine-4-carboxylate 8c

Following the general method for the formation of sulfamidites and using **7c** (1.71 g, 5 mmol), the *title compound* was obtained as a yellow oil (1.94 g, 99%). ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.57–7.11 (m, 10H, Ar–H), 5.10 (d, J=8.5 Hz, 0.5H, CH_2O), 4.90 (d, J=9.2 Hz, 0.5H, CH_2O), 4.83 (d, J=9.2 Hz, 0.5H, CH_2O), 4.75 (d, J=14.2 Hz, 0.5H, CH_2N), 4.63 (d, J=14.9 Hz, 0.5H, CH_2N), 4.52 (d, J=14.9 Hz, 0.5H, CH_2N), 4.44 (d, J=14.2 Hz, 0.5H, CH_2N), 4.34 (d, J=8.5 Hz, 0.5H, CH_2O), 3.61 (d, J=13.3 Hz, 0.5H, CH_2Ph), 3.47 (d, J=13.3 Hz, 0.5H, CH_2Ph), 3.15 (d, J=13.3 Hz, 0.5H, CH_2Ph), 2.87 (d, J=13.3 Hz, 0.5H, CH_2Ph), 1.47 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 168.80 (0.5C, CO), 168.74 (0.5C, CO), 136.97 (0.5C, Ar–C), 136.86 (0.5C, Ar–C), 134.97 (0.5C, Ar–C), 134.21 (0.5C, Ar–C), 129.84 (Ar–C), 129.71 (Ar–C), 128.88 (Ar–C), 128.83 (Ar–C), 128.67 (Ar–C), 127.98 (0.5C, Ar–C), 127.95 (0.5C, Ar–C), 127.63 (0.5C, Ar–C), 127.49 (0.5C, Ar–C), 83.42 (0.5C, $C(CH_3)_3$), 83.22 (0.5C, $C(CH_3)_3$), 77.91 (0.5C, CH_2O), 76.04 (0.5C, CH_2O), 70.73 (0.5C, C-α), 69.36 (0.5C, C-α), 46.27 (0.5C, CH_2N), 46.21 (0.5C, CH_2N), 40.84 (CH_2Ph), 27.90 (1.5C, $C(CH_3)_3$), 27.78 (1.5C, $C(CH_3)_3$).

4.21. *tert*-Butyl 3-benzyl-4-(4-fluorobenzyl)-2-oxo-1,2,3-oxathiazolidine-4-carboxylate 8d

Following the general method for the formation of sulfamidites and using **7d** (1.80 g, 5 mmol), the *title compound* was obtained as a yellow oil (1.99 g, 98%) that was used 'as is' for the next step.

4.22. General method for the formation of sulfamidates 9a–d

The protocol of Boulton[22] was modified as follows: The crude sulfamidite **8a–d** (ca. 5 mmol) was dissolved in CH_3CN (50 mL) and the solution was cooled to 0 °C. Next, $RuCl_3 \cdot xH_2O$ (11 mg, 1 mol %) was added, followed by $NaIO_4$ (1.2 g, 5.6 mmol) and water (25 mL). The greenish-brown solution with a white precipitate was stirred for 15 min at 0 °C and was allowed to return to rt. After 4 h the mixture was diluted with Et_2O (50 mL) and brine (50 mL). The aqueous layer was extracted with Et_2O (3×50 mL) and the pooled fractions were washed twice with saturated $NaHCO_3$ and brine. The organic layer was dried on $MgSO_4$, filtered and the solvents were evaporated in vacuo to yield the crude product. This was flash chromatographed on silica with 1:4 (EtOAc/hexanes) and the solvents were removed in vacuo to give the pure compound.

4.23. *tert*-Butyl 3-benzyl-4-ethyl-2,2-dioxo-1,2,3-oxathiazolidine-4-carboxylate 9a (rac)

Following the general method for the formation of sulfamidates and using **8a** (1.41 g, 4.3 mmol), the *title compound* was obtained as a colourless oil (1.45 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47–7.39 (m, 2H, Ar–H), 7.39–7.27 (m, 3H, Ar–H), 4.92 (d, J=8.7 Hz, 1H, CH_2O), 4.61 (d, J=15.8 Hz, 1H, CH_2Ph), 4.49 (d, J=15.8 Hz, 1H, CH_2Ph), 4.31 (d, J=8.7 Hz, 1H, CH_2O), 2.01–1.90 (m, 1H, CH_2), 1.75–1.63 (m, 1H, CH_2), 1.50 (s, 9H, $C(CH_3)_3$), 0.84 (t, J=7.5 Hz, 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 168.20 (CO), 136.10 (Ar–C), 128.54 (Ar–C), 128.29 (Ar–C), 127.95 (Ar–C), 84.17 ($C(CH_3)_3$), 72.28 (CH_2O), 69.45 (C-α), 46.84 (CH_2Ph), 27.84 ($C(CH_3)_3$), 26.93 (CH_2), 7.46 (CH_3).

4.24. *tert*-Butyl 3-benzyl-2,2-dioxo-4-propyl-1,2,3-oxathiazolidine-4-carboxylate 9b (rac)

Following the general method for the formation of sulfamidates and using **8b** (1.5 g, 4.4 mmol), the *title compound* was obtained as a colourless oil (1.54 g, 98%). ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.50–7.38 (m, 2H, Ar–H), 7.38–7.23 (m, 3H, Ar–H), 4.90 (d, J=8.7 Hz, 1H, CH_2O), 4.60 (d, J=15.9 Hz, 1H, CH_2Ph), 4.48 (d, J=15.9 Hz, 1H, CH_2Ph), 4.31 (d, J=8.7 Hz, 1H, CH_2O), 1.94–1.75 (m, 1H, CH_2), 1.73–1.52 (m, 1H, CH_2), 1.49 (s, 9H), 1.32–1.09 (m, 2H, CH_2CH_3), 0.82 (t, J=7.2 Hz, 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 168.35 (CO), 136.05 (Ar–C), 128.56 (Ar–C), 128.33 (Ar–C), 127.97 (Ar–C), 84.20 ($C(CH_3)_3$), 72.49 (CH_2O), 69.11 (C-α), 46.91 (CH_2Ph), 35.80 (CH_2), 27.87 ($C(CH_3)_3$), 16.60 (CH_2CH_3), 14.04 (CH_3); HRMS m/z (ES^+) Calcd for $C_{17}H_{25}LiNO_5S$ 362.1608, found 362.1607 $[MLi]^+$.

4.25. *tert*-Butyl 3,4-dibenzyl-2,2-dioxo-1,2,3-oxathiazolidine-4-carboxylate 9c (rac)

Following the general method for the formation of sulfamidates and using **8c** (1.94 g, 5 mmol), the *title compound* was obtained as a colourless solid (1.66 g, 82%). Mp 88–90 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.67–7.55 (m, 2H, Ar–H), 7.55–7.29 (m, 6H, Ar–H), 7.29–7.10 (m, 2H, Ar–H), 4.80 (d, J=15.9 Hz, 1H, CH_2N), 4.77 (d, J=8.8 Hz, 1H, CH_2O), 4.73 (d, J=15.9 Hz, 1H, CH_2N), 4.56 (d, J=8.8 Hz, 1H, CH_2O), 3.50 (d, J=13.4 Hz, 1H, CH_2Ph), 2.92 (d, J=13.4 Hz, 1H, CH_2Ph), 1.54 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 167.13 (CO), 136.11 (Ar–C), 132.57 (Ar–C), 130.00 (Ar–C), 128.95 (Ar–C), 128.74 (Ar–C), 128.51 (Ar–C), 128.16 (Ar–C), 128.05 (Ar–C), 84.71 ($C(CH_3)_3$), 72.40 (CH_2O), 69.18 (C-α), 47.01 (CH_2N), 40.10 (CH_2Ph), 27.89 ($C(CH_3)_3$); HRMS m/z (ES^+) Calcd for $C_{21}H_{25}LiNO_5S$ 410.1608, found 410.1607 $[MLi]^+$.

4.26. *tert*-Butyl 3-benzyl-4-(4-fluorobenzyl)-2,2-dioxo-1,2,3-oxathiazolidine-4-carboxylate 9d (rac)

Following the general method for the formation of sulfamidates and using **8d** (1.99 g, 4.9 mmol), the *title compound* was obtained as a colourless solid (1.59 g, 77%). ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.52–7.44 (m, 2H, Ar–H), 7.42–7.30 (m, 3H, Ar–H), 7.09–6.92 (m, 4H, Ar–H), 4.68 (d, J=15.8 Hz, 1H, CH_2Ph), 4.65 (d, J=8.8 Hz, 1H, CH_2O), 4.58 (d, J=15.8 Hz, 1H, CH_2Ph), 4.42 (d, J=8.8 Hz, 1H, CH_2O), 3.36 (d, J=13.6 Hz, 1H, CH_2Ar), 2.80 (d, J=13.6 Hz, 1H, CH_2Ar), 1.44 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 167.06 (CO), 162.51 (d, $^1J_{C-F}$=247.4 Hz, Ar–C), 136.00 (Ar–C), 131.66 (d, $^3J_{C-F}$=8.1 Hz, Ar–C), 128.77 (Ar–C), 128.48 (Ar–C), 128.38 (d, $^4J_{C-F}$=3.4 Hz, Ar–C), 128.21 (Ar–C), 115.90 (d, $^2J_{C-F}$=21.4 Hz, Ar–C), 84.90 ($C(CH_3)_3$), 72.18 (CH_2O), 69.14 (d, $^6J_{C-F}$=1.5 Hz, C-α), 47.03 (CH_2Ph), 39.17 (CH_2Ar), 27.88 ($C(CH_3)_3$); HRMS m/z (ES^+) Calcd for $C_{21}H_{24}FLiNO_5S$ 428.1514, found 428.1513 $[MLi]^+$.

4.27. General method for the formation of lanthionines 11a–d

To a degassed solution of sulfamidate **9a–d** (1 mmol) and Boc cysteine methyl ester (259 mg, 1.1 mmol) in CH_3CN (10 mL), DBU (182 mg, 1.2 mmol) in degassed CH_3CN (1 mL) was added via syringe and the reaction mixture was stirred for 1 h at rt under nitrogen. The solution was diluted with EtOAc (25 mL) and 10% aqueous NaH_2PO_4 (25 mL) and this was heated with stirring at 50 °C for 2 h. The reaction mixture was then basified by pouring in an excess of saturated Na_2CO_3 solution. The organic layer was decanted and the aqueous layer was extracted with EtOAc (3×50 mL). The pooled fractions were washed with brine and dried on $MgSO_4$, were filtered and the solvent was evaporated in vacuo to yield the crude product. This was chromatographed on silica with 1:3 (EtOAc/hexanes) and the solvents were removed in vacuo to give the pure compound.

4.28. *tert*-Butyl 2-benzylamino-3-((*R*)-2-(*tert*-butoxycarbonyl amino)-3-methoxy-3-oxopropylthio)-2-ethyl propanoate 11a

Following the general method for the formation of lanthionines and using **9a** (341 mg, 1 mmol), the *title compound* was obtained as

a colourless oil (495 mg, 99%). ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.45–7.13 (m, 5H, Ar–H), 5.82 (br, 0.5H, NH-Boc), 5.52 (br, 0.5H, NH-Boc), 4.52 (br, 1H, H-α), 3.72 (s, 1.5H, OCH_3), 3.68 (s, 1.5H, OCH_3), 3.68–3.59 (m, 1H, CH_2Ph), 3.59–3.50 (m, 1H, CH_2Ph), 3.04 (d, J=12.9 Hz, 1H, SCH_2C), 3.04–2.94 (m, 2H, $CHCH_2S$), 2.90 (d, J=12.9 Hz, 0.5H, SCH_2C), 2.89 (d, J=12.9 Hz, 0.5H, SCH_2C), 2.17 (br, 1H, NH), 1.90–1.62 (m, 2H, CH_2CH_3), 1.50 (s, 9H, $C(CH_3)_3$), 1.44 (s, 4.5H, $C(CH_3)_3$), 1.43 (s, 4.5H, $C(CH_3)_3$), 0.96–0.80 (m, 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 173.23 (0.5C, CO), 173.16 (0.5C, CO), 171.42 (CO), 155.11 (Boc-CO), 140.00 (0.5C, Ar–C), 139.90 (0.5C, Ar–C), 128.37 (Ar–C), 128.28 (Ar–C), 128.26 (Ar–C), 126.96 (0.5C, Ar–C), 126.93 (0.5C, Ar–C), 81.43 (0.5C, $C(CH_3)_3$), 81.42 (0.5C, $C(CH_3)_3$), 79.82 (0.5C, $C(CH_3)_3$), 79.75 (0.5C, $C(CH_3)_3$), 65.86 (0.5C, C-α), 65.73 (0.5C, C-α), 53.63 (0.5C, CH-α), 53.48 (0.5C, CH-α), 52.30 (0.5C, OCH_3), 52.26 (0.5C, OCH_3), 47.23 (0.5C, CH_2Ph), 47.00 (0.5C, CH_2Ph), 37.79 (0.5C, SCH_2C), 37.55 (0.5C, SCH_2C), 35.70 (0.5C, $CHCH_2S$), 35.49 (0.5C, $CHCH_2S$), 28.21 (1.5C, $C(CH_3)_3$), 28.19 (1.5C, $C(CH_3)_3$), 28.07 (0.5C, CH_2), 27.99 ($C(CH_3)_3$), 27.83 (0.5C, CH_2), 7.89 (0.5C, CH_3), 7.86 (0.5C, CH_3); m/z (ESI) 497 $[MH]^+$; HRMS m/z (ES^+) Calcd for $C_{25}H_{41}N_2O_6S$ 497.2680, found 497.2677 $[MH]^+$.

4.29. *tert*-Butyl 2-benzylamino-3-((*R*)-2-(*tert*-butoxycarbonyl amino)-3-methoxy-3-oxopropylthio)-2-(1-propyl) propanoate 11b

Following the general method for the formation of lanthionines and using **9b** (355 mg, 1 mmol), the *title compound* was obtained as a colourless oil (511 mg, 99%). ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.40–7.17 (m, 5H, Ar–H), 5.79 (br, 0.5H, NH-Boc), 5.44 (br, 0.5H, NH-Boc), 4.51 (br, 1H, H-α), 3.72 (s, 1.5H, OCH_3), 3.67 (s, 1.5H, OCH_3), 3.63 (d, J=11.7 Hz, 1H, CH_2Ph), 3.54 (d, J=11.7 Hz, 1H, CH_2Ph), 3.00 (m, 3H, $CHCH_2S$, SCH_2C), 2.88 (d, J=12.8 Hz, 0.5H, SCH_2C), 2.86 (d, J=12.8 Hz, 0.5H, SCH_2C), 1.92 (br, 1H, NH), 1.81–1.56 (m, 2H, CH_2), 1.48 (s, 9H, $C(CH_3)_3$), 1.43 (s, 4.5H, $C(CH_3)_3$), 1.42 (s, 4.5H, $C(CH_3)_3$), 1.33–1.22 (m, 2H, CH_2CH_3), 0.95–0.85 (m, 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 173.49 (0.5C, CO), 173.42 (0.5C, CO), 171.56 (CO), 155.17 (Boc-CO), 140.15 (0.5C, Ar–C), 140.04 (0.5C, Ar–C), 128.48 (Ar–C), 128.39 (Ar–C), 127.07 (0.5C, Ar–C), 127.04 (0.5C, Ar–C), 81.61 (0.5C, $C(CH_3)_3$), 81.58 (0.5C, $C(CH_3)_3$), 80.03 (0.5C, $C(CH_3)_3$), 79.93 (0.5C, $C(CH_3)_3$), 65.63 (0.5C, C-α), 65.50 (0.5C, C-α), 53.75 (0.5C, CH-α), 53.57 (0.5C, CH-α), 52.46 (0.5C, OCH_3), 52.42 (0.5C, OCH_3), 47.41 (0.5C, CH_2Ph), 47.16 (0.5C, CH_2Ph), 38.43 (0.5C, SCH_2C), 38.15 (0.5C, SCH_2C), 37.76 (0.5C, CH_2), 37.51 (0.5C, CH_2), 35.91 (0.5C, $CHCH_2S$), 35.71 (0.5C, $CHCH_2S$), 28.33 (1.5C, $C(CH_3)_3$), 28.31 (1.5C, $C(CH_3)_3$), 28.12 ($C(CH_3)_3$), 16.98 (0.5C, CH_2CH_3), 16.93 (0.5C, CH_2CH_3), 14.42 (0.5C, CH_3), 14.40 (0.5C, CH_3); m/z (ESI) 511 $[MH]^+$; HRMS m/z (ES^+) Calcd for $C_{26}H_{43}N_2O_6S$ 511.2836, found 511.2834 $[MH]^+$.

4.30. *tert*-Butyl 2-benzyl-2-benzylamino-3-((*R*)-2-(*tert*-butoxy carbonylamino)-3-methoxy-3-oxopropylthio)propanoate 11c

Following the general method for the formation of lanthionines and using **9c** (403 mg, 1 mmol), the *title compound* was obtained as a colourless oil (503 mg, 90%); ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.47–7.15 (m, 10H, Ar–H), 5.57 (br, 0.5H, NH-Boc), 5.43 (br, 0.5H, NH-Boc), 4.55 (br, 1H, H-α), 3.81 (d, J=11.5 Hz, 0.5H, CH_2N), 3.80 (d, J=11.5 Hz, 0.5H, CH_2N), 3.74 (s, 1.5H, OCH_3), 3.71 (s, 1.5H, OCH_3), 3.66 (d, J=11.5 Hz, 0.5H, CH_2N), 3.65 (d, J=11.5 Hz, 0.5H, CH_2N), 3.20–3.04 (m, 3H, SCH_2C, CH_2Ph), 3.04–2.96 (m, 2H, $CHCH_2S$), 2.81 (d, J=12.5 Hz, 0.5H, SCH_2C), 2.79 (d, J=12.7 Hz, 0.5H, SCH_2C), 1.87 (br, 1H, NH), 1.45 (m, 18H, $C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 172.85 (0.5C, CO), 172.79 (0.5C, CO), 171.58 (0.5C, CO), 171.50 (0.5C, CO), 155.16 (Boc-CO), 139.86 (0.5C, Ar–C), 139.79 (0.5C, Ar–C), 136.01 (0.5C, Ar–C), 130.27 (Ar–C), 130.25 (Ar–C), 128.43 (Ar–C), 128.41 (Ar–C), 128.38 (Ar–C), 128.34 (Ar–C), 128.17 (Ar–C), 128.15 (Ar–C), 127.13 (0.5C, Ar–C), 127.09 (0.5C, Ar–C), 126.89 (0.5C, Ar–C), 126.86 (0.5C, Ar–C), 82.08 (0.5C, $C(CH_3)_3$), 82.05 (0.5C, $C(CH_3)_3$), 80.02 ($C(CH_3)_3$), 66.40 (C-α), 53.53 (CH-α), 52.48 (0.5C, OCH_3), 52.44 (0.5C, OCH_3), 47.54 (0.5C, CH_2N), 47.48 (0.5C, CH_2N), 41.39 (CH_2Ph), 37.52 (0.5C, SCH_2C), 37.32 (0.5C, SCH_2C), 35.65 ($CHCH_2S$), 28.31 (1.5C, $C(CH_3)_3$), 28.28 (1.5C, $C(CH_3)_3$), 28.10 ($C(CH_3)_3$); m/z (ESI) 559 $[MH]^+$; HRMS m/z (ES^+) Calcd for $C_{30}H_{43}N_2O_6S$ 559.2836, found 559.2838 $[MH]^+$.

4.31. *tert*-Butyl 2-benzylamino-3-((*R*)-2-(*tert*-butoxycarbonyl amino)-3-methoxy-3-oxopropylthio)-2-(4-fluorobenzyl) propanoate 11d

Following the general method for the formation of lanthionines and using **9d** (421 mg, 1 mmol), the *title compound* was obtained as a colourless oil (564 mg, 98%); ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.44–7.10 (m, 7H, Ar–H), 7.05–6.81 (m, 2H, Ar–H), 5.53 (br, 0.5H, NH-Boc), 5.41 (br, 0.5H, NH-Boc), 4.51 (br, 1H, H-α), 3.77 (d, J=11.4 Hz, 1H, CH_2Ph), 3.72 (s, 1.5H, OCH_3), 3.70 (s, 1.5H, OCH_3), 3.64 (d, J=11.4 Hz, 0.5H, CH_2Ph), 3.62 (d, J=11.4 Hz, 0.5H, CH_2Ph), 3.24–2.83 (m, 5H, $CHCH_2S$, SCH_2C, CH_2Ph), 2.76 (d, J=12.6 Hz, 1H, SCH_2C), 1.88 (br, 1H, NH), 1.48–1.36 (m, 18H, $C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 172.77 (0.5C, CO), 172.72 (0.5C, CO), 171.53 (0.5C, CO), 171.46 (0.5C, CO), 161.90 (d, $^1J_{C-F}$=245.1 Hz, Ar–C), 155.14 (Boc-CO), 139.76 (0.5C, Ar–C), 139.70 (0.5C, Ar–C), 131.77 (d, $^4J_{C-F}$=4.3 Hz, Ar–C), 131.75 (d, $^3J_{C-F}$=7.7 Hz, Ar–C), 128.46 (Ar–C), 128.45 (Ar–C), 128.33 (Ar–C), 128.30 (Ar–C), 127.18 (0.5C, Ar–C), 127.15 (0.5C, Ar–C), 114.95 (d, $^2J_{C-F}$=21.1 Hz, 0.5C, Ar–C), 114.92 (d, $^2J_{C-F}$=21.1 Hz, 0.5C, Ar–C), 82.21 (0.5C, $C(CH_3)_3$), 82.18 (0.5C, $C(CH_3)_3$), 80.04 ($C(CH_3)_3$), 66.34 (C-α), 53.57 (CH-α), 52.49 (0.5C, OCH_3), 52.46 (0.5C, OCH_3), 47.48 (0.5C, CH_2Ph), 47.44 (0.5C, CH_2Ph), 40.35 (0.5C, CH_2Ar), 40.30 (0.5C, CH_2Ar), 37.48 (0.5C, SCH_2C), 37.25 (0.5C, SCH_2C), 35.62 ($CHCH_2S$), 28.29 ($C(CH_3)_3$), 28.10 ($C(CH_3)_3$); m/z (ESI) 577 $[MH]^+$; HRMS m/z (ES^+) Calcd for $C_{30}H_{42}FN_2O_6S$ 577.2742, found 577.2747 $[MH]^+$.

4.32. *tert*-Butyl 2-amino-2-benzyl-3-((*R*)-2-(*tert*-butoxycarbonylamino)-3-methoxy-3-oxopropylthio)propanoate

Compound **11c** (300 mg, 0.54 mmol) was dissolved in MeOH (90 mL) and water (10 mL) and the solution was placed in a hydrogenator containing a magnetic stir bar. Pd black (75 mg, wet with water) was then added cautiously followed by AcOH (3 mL). The reactor was closed and purged four times with H_2 then placed under H_2 pressure (7 bars). The vessel was externally heated to 70 °C and the reaction was allowed to proceed for 16 h with stirring. The vessel was cooled to rt, the H_2 was removed and the reactor was opened. The solution was decanted from palladium and filtered on a fritted funnel. The solvent was evaporated in vacuo and the residue was basified with saturated Na_2CO_3 and extracted twice with CH_2Cl_2. The solvent was removed and the crude oil was purified by column chromatography on silica with 1:1 (EtOAc/hexanes+1% NEt_3) to produce, after evaporation of the solvents in vacuo, the *title compound* as a pale oil (73%). ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 7.23–7.03 (m, 5H, Ar–H), 6.32 (br, 0.5H, NH-Boc), 5.77 (br, 0.5H, NH-Boc), 4.44 (br, 1H, H-α), 3.63 (s, 1.5H, OCH_3), 3.62 (s, 1.5H, OCH_3), 3.09 (d, J=13.0 Hz, 0.5H, SCH_2C), 3.02 (d, J=13.0 Hz, 0.5H, SCH_2C), 3.01–2.89 (m, 3H, $CHCH_2S$, CH_2Ph), 2.71 (d, J=13.1 Hz, 1H, CH_2Ph), 2.63 (d, J=13.0 Hz, 0.5H, SCH_2C), 2.59 (d, J=13.0 Hz, 0.5H, SCH_2C), 1.75 (br, 2H, NH_2), 1.36 (s, 4.5H, $C(CH_3)_3$), 1.35 (s, 4.5H, $C(CH_3)_3$), 1.34 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ_C 173.64 (0.5C, CO), 173.59 (0.5C, CO), 171.14 (0.5C, CO), 171.12 (0.5C, CO), 155.12 (0.5C, Boc-CO), 155.01 (0.5C, Boc-CO), 135.51 (0.5C, Ar–C), 135.48 (0.5C, Ar–C), 129.93 (Ar–C), 129.90 (Ar–C), 128.07 (Ar–C), 128.03 (Ar–C), 126.85 (0.5C, Ar–C), 126.80 (0.5C, Ar–C), 81.71 (0.5C,

$C(CH_3)_3$), 81.69 (0.5C, $C(CH_3)_3$), 79.59 (0.5C, $C(CH_3)_3$), 79.49 (0.5C, $C(CH_3)_3$), 62.78 (0.5C, C-α), 62.66 (0.5C, C-α), 53.85 (0.5C, CH-α), 53.57 (0.5C, CH-α), 52.18 (0.5C, OCH_3), 52.14 (0.5C, OCH_3), 45.26 (0.5C, CH_2Ph), 45.08 (0.5C, CH_2Ph), 43.29 (0.5C, SCH_2C), 43.08 (0.5C, SCH_2C), 36.31 (0.5C, $CHCH_2S$), 36.08 (0.5C, $CHCH_2S$), 28.09 (1.5C, $C(CH_3)_3$), 28.05 (1.5C, $C(CH_3)_3$), 27.70 ($C(CH_3)_3$); *m*/*z* (ESI) 469 $[MH]^+$; HRMS *m*/*z* (ES^+) Calcd for $C_{23}H_{37}N_2O_6S$ 469.2367, found 469.2367 $[MH]^+$.

Acknowledgements

This work was financed by an ARC (grant 03/08-297) of the Belgium French community and by the FP6 *European Integrated Project* EurIntafar (LSHM-CT-2004-512138). We thank Professor Albert Demonceau for insightful discussions and correction of the draft. We thank Erik Ziegler for English support. We thank Dr. Gabriel Mazzucchelli and co-workers at the GIGA MSL for the HRMS determination.

Supplementary data

NMR spectra of the newly synthesized molecules are reproduced. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.05.004.

References and notes

1. Horn, M. J.; Jones, D. B.; Ringel, S. J. *J. Biol. Chem.* **1941**, *138*, 141–149.
2. Du Vigneaud, V.; Brown, G. B. *J. Biol. Chem.* **1941**, *138*, 151–154.
3. Vasstrand, E. N.; Jensen, H. B.; Miron, T.; Hofstad, T. *Infect. Immun.* **1982**, *36*, 114–122.
4. Tabor, A. B. *Org. Biomol. Chem.* **2011**, *9*, 7606–7628.
5. Paul, M.; van der Donk, W. A. *Mini Rev. Org. Chem.* **2005**, *2*, 23–37.
6. Zhu, X.; Schmidt, R. R. *Eur. J. Org. Chem.* **2003**, *2003*, 4069–4072.
7. Cobb, S.; Vederas, J. *Org. Biomol. Chem.* **2007**, *5*, 1031–1038.
8. Aydillo, C.; Avenoza, A.; Busto, J. H.; Jiménez-Osés, G.; Peregrina, J. M.; Zurbano, M. M. *Org. Lett.* **2011**, *14*, 334–337.
9. Narayan, R. S.; VanNieuwenhze, M. S. *Org. Lett.* **2005**, *7*, 2655–2658.
10. Bregant, S.; Tabor, A. B. *J. Org. Chem.* **2005**, *70*, 2430–2438.
11. Martin, N. I. *J. Org. Chem.* **2008**, *74*, 946–949.
12. Probert, J. M.; Rennex, D.; Bradley, M. *Tetrahedron Lett.* **1996**, *37*, 1101–1104.
13. Dugave, C.; Ménez, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1453–1465.
14. Mohd Mustapa, M. F.; Harris, R.; Bulic-Subanovic, N.; Elliott, S. L.; Bregant, S.; Groussier, M. F. A.; Mould, J.; Schultz, D.; Chubb, N. A. L.; Gaffney, P. R. J.; Driscoll, P. C.; Tabor, A. B. *J. Org. Chem.* **2003**, *68*, 8185–8192.
15. Shao, H.; Wang, S. H. H.; Lee, C.-W.; Oesapay, G.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 2956–2957.
16. Smith, N. D.; Goodman, M. *Org. Lett.* **2003**, *5*, 1035–1037.
17. Cavelier-Frontin, F.; Daunis, J.; Jacquier, R. *Tetrahedron: Asymmetry* **1992**, *3*, 85–94.
18. Harpp, D. N.; Gleason, J. G. *J. Org. Chem.* **1971**, *36*, 73–80.
19. Sambeth, G. M.; Süssmuth, R. D. *J. Pept. Sci.* **2011**, *17*, 581–584.
20. Knerr, P. J.; van der Donk, W. A. *J. Am. Chem. Soc.* **2013**, *135*, 7094–7097.
21. Rew, Y.; Malkmus, S.; Svensson, C.; Yaksh, T. L.; Chung, N. N.; Schiller, P. W.; Cassel, J. A.; DeHaven, R. N.; Goodman, M. *J. Med. Chem.* **2002**, *45*, 3746–3754.
22. Boulton, L. T.; Stock, H. T.; Raphy, J.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1421–1430.
23. Jew, S.-S.; Lee, Y.-J.; Lee, J.; Kang, M. J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-H.; Ku, J.-M.; Park, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382–2385.
24. Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230–6231.
25. Dondoni, A.; Perrone, D. *Org. Synth.* **2000**, *77*, 64–77.
26. Huang, Y.; Dalton, D. R.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 372–376.
27. Roger, R.; Neilson, D. G. *Chem. Rev.* **1961**, *61*, 179–211.
28. Fry, E. M. *J. Org. Chem.* **1950**, *15*, 438–447.
29. Takeda, K.; Akiyama, A.; Nakamura, H.; Takizawa, S.-I.; Mizuno, Y.; Takayanagi, H.; Harigaya, Y. *Synthesis* **1994**, 1063–1066.
30. Park, H.-G.; Lee, J.; Kang, M. J.; Lee, Y.-J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-H.; Jew, S.-S. *Tetrahedron* **2004**, *60*, 4243–4249.
31. Dolence, E. K.; Mayer, G.; Kelly, B. D. *Tetrahedron: Asymmetry* **2005**, *16*, 1583–1594.
32. Wei, L.; Lubell, W. D. *Org. Lett.* **2000**, *2*, 2595–2598.
33. Avenoza, A.; Busto, J. H.; Jiménez-Osés, G.; Peregrina, J. M. *J. Org. Chem.* **2006**, *71*, 1692–1695.
34. Jiménez-Osés, G.; Avenoza, A.; Busto, J. H.; Rodríguez, F.; Peregrina, J. M. *Chem.—Eur. J.* **2009**, *15*, 9810–9823.
35. Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549–8552.
36. McNair, R. J. *Aldrich ChemFiles* **2009**, *9* (2), 21–22.
37. Shine, H. J.; Hoque, A. K. M. M. *J. Org. Chem.* **1988**, *53*, 4349–4353.
38. Meyer, F.; Laaziri, A.; Papini, A. M.; Uziel, J.; Jugé, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2229–2238.

Please cite this article in press as: Denoël, T.; et al., Tetrahedron (2014), http://dx.doi.org/10.1016/j.tet.2014.05.004